ZIMONCZYK, Mariusz, ZAWÓŁ, Monika, NOJEK, Paweł, PAWLIK, Wiktoria, BŁASZCZYŃSKI, Gustaw and NOWOTARSKA, Agnieszka. The Impact of prolonged antibiotic use on the development of bacterial resistance - a literature review. Journal of Education, Health and Sport. 2024;71:56137. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.71.56137
https://apcz.umk.pl/JEHS/article/view/56137

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 12.11.2024. Revised: 20.11.2024. Accepted: 27.11.2024. Published: 27.11.2024.

The Impact of prolonged antibiotic use on the development of bacterial resistance - a literature review

Mariusz Zimonczyk [MZ],
Muncipal Hospital in Zabrze, ul. Zamkowa 4, 41-803 Zabrze, Poland
ORCID: https://orcid.org/0009-0004-9256-3798
e-mail: mariusz.zimonczyk1@gmail.com

Monika Zawół [MZA],
Lower Silesian Center for Oncology, Pulmonology, and Hematology in Wrocław, plac Hirszfelda 12, 53-413 Wroclaw, Poland
ORCID: https://orcid.org/0009-0003-9854-5083
e-mail: monikazawol315@gmail.com

Paweł Nojek [PN],
Muncipal Hospital in Siemianowice Śląskie, ul. 1 maja 9, 41-100 Siemianowice Sląskie, Poland
ORCID: https://orcid.org/0009-0005-4460-3406
e-mail: pawel.nojek98@gmail.com

Wiktoria Pawlik [WP],
Muncipal Hospital in Siemianowice Śląskie, ul. 1 maja 9, 41-100 Siemianowice Sląskie, Poland
ORCID: https://orcid.org/0009-0006-8756-5398,
e-mail: wikipawlik@gmail.com

Gustaw Błaszczyński [GB],
Muncipal Hospital in Siemianowice Śląskie, ul. 1 maja 9, 41-100 Siemianowice Sląskie, Poland
ORCID: https://orcid.org/0009-0001-3017-3514,
e-maul: gustawblaszczynski@gmail.com
Agnieszka Nowotarska [AN],
Katowice Oncology Center, Katowice, Poland
ORCID: https://orcid.org/0009-0009-2698-9519,
e-mail: nowotarska.agnieszka@o2.pl

Abstract

Introduction and Objective. Antimicrobial resistance (AMR) arises when pathogens no longer respond to antimicrobials, including antibiotics, making infections harder to treat and increasing the risks of severe illness and death. Although AMR is a natural evolutionary process, human activities, especially the misuse of antimicrobials in healthcare, agriculture, and animal care, accelerate its spread. This review examines the impact of prolonged antibiotic use on bacterial resistance and analyzes global trends and strategies to combat AMR.

Methods. A literature review was conducted using PubMed and Google Scholar with search terms like "antimicrobial resistance," "antibiotic-resistant bacteria," and "overuse of antibiotics." Articles from the last five years were prioritized.

State of Knowledge. AMR poses a major global health threat due to excessive and improper antibiotic use, resulting in resistant infections and higher healthcare costs. Addressing AMR requires limiting antibiotic use, implementing rapid diagnostics, and exploring alternatives like bacteriophage therapy.

Conclusions. Innovative treatments, such as bacteriophages, and rapid diagnostics show promise, while public education on responsible antibiotic use is essential. Combating AMR will require coordinated international efforts, research support, and global standards to maintain effective treatments in the future.

Keywords: antimicrobial resistance (AMR); antibiotic-resistant bacteria; overuse of antibiotics; mechanisms of bacterial resistance;

Introduction

1. Introduction to the issue

Antimicrobial resistance (AMR) refers to the phenomenon in which bacteria develop the ability to survive despite the presence of antibiotics that previously effectively eradicated them. This process is a natural microbial response to exposure to antimicrobial agents; however, it has been accelerated by human factors such as overuse and misuse of antibiotics. [1] Antibiotics are indispensable in medicine, but their excessive and unconsidered use leads to resistance, which threatens the efficacy of future therapies and public health. [2]

The main issues arise from the excessive exposure of bacteria to antibiotics, often through improper dosing or unjustified prescriptions for viral infections, against which antibiotics are ineffective.[3] In long-term healthcare facilities, where antibiotic use is routine, this phenomenon becomes even more pronounced, contributing to the development of particularly resistant strains, such as MRSA and VRE. [1]

The long-term use of antibiotics triggers a variety of mechanisms of bacterial resistance, including changes in bacterial cell membrane structures, active efflux of the antibiotic from the cell, and enzymatic mutations that degrade the drug's structure.[4]

An example of such adaptation is resistance to β-lactam antibiotics, which are widely used in the treatment of bacterial infections, including hospital-acquired infections. [5]

Improper use of antibiotics not only has health consequences but also ecological implications—pharmaceutical waste and wastewater containing antibiotics contribute to the spread of resistance genes to environmental bacteria, which can serve as sources of human infection.[3] In countries with limited access to antibiotics, the problem of overuse exacerbates the widespread dissemination of resistance and impacts treatment costs and the availability of effective healthcare.[6]

In the fight against AMR, new approaches are necessary, including the implementation of stricter regulations on antibiotic prescriptions and monitoring their use in healthcare facilities.[4] Moreover, increasing emphasis is being placed on the development of diagnostic tools that allow for faster and more accurate identification of bacteria and the selection of more effective, narrow-spectrum drugs.[5] In recent years, intensive research has also been conducted into alternatives to antibiotics, such as phage therapy, which uses viruses that target bacteria and may prove to be an effective weapon against drug-resistant bacteria. [2]

Implementing stringent antibiotic use standards in animal farming is crucial, as excessive drug use in agriculture contributes to the transfer of resistance genes to human populations.[3] Another modern strategy is public education regarding the dangers of overusing antibiotics and promoting their responsible use.[6] Global cooperation is vital, as bacterial resistance knows no borders, and its development in one region can quickly affect the epidemiological situation in another. [4]

Ultimately, a comprehensive approach involving science, policy, and education must be adopted to reduce the risk of resistance development and ensure the continued effectiveness of antibiotics for future generations.

2. The importance of antibiotics in medicine

The history of antibiotic use began with the discovery of penicillin in 1928 by Alexander Fleming, who observed that the mold *Penicillium notatum* produced a substance inhibiting bacterial growth.[7] This discovery initiated a revolution in medicine, with penicillin becoming the first widely used antibiotic, saving millions of lives during World War II.[8] The widespread introduction of antibiotics opened new possibilities in the treatment of infections that were once often fatal. Over the following decades, the development of antibacterial therapies led to the emergence of additional classes of drugs, such as streptomycin, tetracyclines, and cephalosporins, which enabled the treatment of a broad range of infections. [9]

Antibiotics quickly became the cornerstone of modern medicine, facilitating the performance of complex surgeries and the treatment of infections that were previously untreatable. The introduction of antibiotics contributed to a significant reduction in mortality from bacterial infections and an increase in average life expectancy.[7] Thanks to antibiotics, diseases such as pneumonia, tuberculosis, sepsis, and many other infectious diseases, which were once considered incurable, could now be effectively treated.

The positive effects of antibiotic use are particularly evident in the treatment of surgical infections, where antibiotics help prevent infections in surgical wounds, significantly reducing the risk of complications.[9]

In emergency medicine, antibiotics play a critical role in the treatment of sepsis, allowing for the rapid containment of bacterial spread in the body and preventing life-threatening conditions. [10]

In the case of urinary tract infections, which are among the most common bacterial infections, antibiotics allow for rapid and effective treatment, reducing patient discomfort and preventing severe complications such as kidney infections.[11] Antibiotics are also often used for long-term treatment, for example, in patients with chronic infections, to halt the progression of the infection and improve quality of life. [12]

As a result of the widespread use of antibiotics, mortality associated with bacterial infections has significantly decreased, contributing to the improvement of public health worldwide.[7] The introduction of antibiotics has also enabled the advancement of complex medical procedures, such as organ transplants and chemotherapy, which require intensive antibacterial prophylaxis.[8]

II. Long-term use of antibiotics and the development of bacterial resistance

1. Mechanisms of bacterial resistance development

Antibiotic resistance in microorganisms is both a natural and acquired process, and its development poses a significant threat to public health. Natural resistance mechanisms are inherent to bacterial organisms and may stem from their physiological characteristics. For instance, some bacteria possess a protective barrier in the form of an outer cell membrane, which impedes the penetration of antibiotics into the cell.[13] Additionally, bacteria may produce enzymes, such as β-lactamases, that degrade antibiotics and neutralize the action of many β-lactam drugs.[14]

Alongside natural resistance, bacteria can acquire new resistance mechanisms through genetic mutations or horizontal gene transfer. These mutations may alter the target structures of antibiotics within the bacterial cell, rendering the drug ineffective.[15] For example, changes to the ribosomal structure may lead to a loss of efficacy of antibiotics that inhibit protein synthesis, such as tetracyclines.[16] Another way of acquiring resistance is the transfer of resistance genes, which can occur between different bacteria via plasmids, transposons, or bacteriophages—referred to as horizontal gene transfer.[18] An example of this is *Acinetobacter baumannii*, which transfers resistance genes to carbapenems, potent antibiotics used in the treatment of multidrug-resistant infections.[17]

Prolonged use of antibiotics exerts strong selective pressure, favoring the development and dominance of resistant strains. When antibiotics are used over extended periods, bacteria with inherent or acquired resistance survive, while susceptible strains are eliminated. This process

leads to the emergence of bacterial populations resistant to specific antibiotics, rendering treatment less effective. The selection of resistant strains can have particularly pronounced effects in hospitals, where patients are intensively treated with antibiotics, creating an ideal environment for the development of multidrug-resistant pathogens. [20]
This phenomenon also leads to co-selection, whereby the use of one type of drug results in an increase in resistance not only to that drug but also to other classes of substances, such as preservatives or heavy metals.

In practice, this means that the use of antibiotics can influence the development of resistance to other antimicrobial agents, further complicating the fight against infections.[19] This process is particularly dangerous in aquatic environments, where resistance genes can freely spread between bacteria, creating a reservoir of resistance. [17]
Effective management of resistance requires the rational use of antibiotics and the implementation of strategies to monitor the spread of resistance genes. To reduce selective pressure, antibiotics must be used only when absolutely necessary, and the narrowest possible spectrum should be selected. Such an approach can limit the potential for the development of resistant strains and preserve the effectiveness of available drugs.[18]

2. Types of superbugs and their global significance

Superbugs, or multidrug-resistant (MDR) bacteria, pose an increasingly serious threat to global public health. Among the most dangerous of these are bacteria such as *Staphylococcus aureus* resistant to methicillin (MRSA), *Enterococcus faecium* resistant to vancomycin (VRE), and bacteria producing extended-spectrum beta-lactamases (ESBLs). MRSA is a bacterial strain that does not respond to treatment with standard β-lactam antibiotics, making the treatment of skin, respiratory, and blood infections caused by this pathogen much more difficult.[21] VRE refers to *Enterococcus* species that have developed resistance to vancomycin, a drug commonly used to treat serious hospital-acquired infections, rendering these infections challenging to control.[23] Meanwhile, ESBL-producing bacteria are capable of neutralizing a broad range of antibiotics, including penicillins and cephalosporins, significantly limiting treatment options for urinary, respiratory, and gastrointestinal infections. [22]
The rise in infections caused by multidrug-resistant bacteria can be attributed to several factors, including the overuse of antibiotics and inadequate hygiene and infection control in healthcare settings. MDR infections are particularly dangerous in hospitals, where patients are often immunocompromised, and the risk of transmission between patients is high.[24] The increase in MDR infections in Europe, as evidenced by data, leads to thousands of deaths and millions of years of life lost (DALY) annually, representing a significant burden on healthcare systems. [23]
Antibiotic resistance significantly complicates the treatment of many infectious diseases, forcing physicians to resort to more expensive, more toxic, or less effective therapies. In cases where infections do not respond to conventional antibiotics, treatment options are severely limited, which can lead to prolonged hospitalizations, higher treatment costs, and increased mortality. [25]

In a global context, infections caused by multidrug-resistant (MDR) bacteria have serious social and economic consequences. High mortality rates, extended hospital stays, and increased transmission risks mean that the problem of resistance is not only a medical issue but also an economic one. Effective management of MDR requires international cooperation, which includes monitoring resistance patterns, promoting rational antibiotic use, and implementing effective infection control strategies.[22]Additionally, there is a critical need for new research into antibiotics and alternative therapies that could help mitigate the impact of superbugs on public health.

3. Global data on antimicrobial resistance

Antimicrobial resistance (AMR) is a global public health threat that is reaching alarming proportions in many regions of the world. According to the World Health Organization (WHO), the issue of AMR is particularly severe in low- and middle-income countries, where access to antibiotics is limited, and misuse is more common. The WHO has published a list of priority pathogens, which includes the most dangerous multidrug-resistant bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. [26]

Statistics show that approximately 700,000 people die each year globally due to infections caused by antibiotic-resistant bacteria, and this number continues to rise. It is estimated that, if no effective actions are taken, the annual death toll from AMR could exceed 10 million by 2050.[29] Antibiotic resistance affects different regions of the world in varying ways—for instance, in developing countries, where there is a lack of effective infection control and AMR monitoring systems, resistance rates are particularly high. In developed countries, although better control measures help reduce resistance, the problem is still growing due to excessive and inappropriate antibiotic use in both medicine and agriculture. [28]

AMR also represents a significant economic burden. The treatment costs for infections caused by antibiotic-resistant bacteria can be several times higher than for infections that are susceptible to standard treatments. These costs not only include the direct expenses of medications but also extend to prolonged hospitalizations, diagnostic testing, and isolation measures. The global economic losses caused by AMR could amount to billions of dollars annually, posing a severe challenge to healthcare systems, particularly in resource-limited countries. [27]

The increase in deaths related to antibiotic resistance presents a major challenge for the treatment of infectious diseases, especially in hospitals, where patients are more vulnerable to hospital-acquired infections caused by multidrug-resistant bacteria. Pathogens such as MRSA and ESBL-producing bacteria are particularly dangerous in medical settings, where their transmission can lead to outbreaks of epidemic proportions. AMR forces the use of more expensive and toxic antibiotics, which increases the risk of complications and prolonged hospitalizations. [30]

Different sectors, including human health, veterinary medicine, and agriculture, have a significant impact on the development and spread of antimicrobial resistance (AMR). The use of antibiotics in livestock production, such as in poultry farming, contributes to the development of resistance in bacteria such as *E. coli*, which can then transfer to humans.[28] The World Health Organization (WHO) emphasizes the importance of the "One Health" approach, which integrates actions across human health, animal health, and the environment to effectively control AMR. [26]

III. Modern approaches to combating the development of bacterial resistance

1. Strategies for reducing antibiotic use

Strategies to reduce antibiotic use are critical in the fight against increasing bacterial resistance, and the One Health approach forms the foundation of effective actions in this area. This concept takes into account the interconnectedness between human health, animal health, and the environment, enabling a holistic approach to the issue of antimicrobial resistance (AMR).

Antibiotic-resistant bacteria can spread not only among humans but also among farm animals and within the environment, where antibiotics are used in agriculture, potentially contaminating water, soil, and food. Therefore, effective strategies for reducing antibiotic use must involve collaboration across various sectors—human medicine, veterinary medicine, and environmental protection. For example, in animal farming, the use of antibiotics should be limited in prophylactic treatments, with their application strictly based on bacterial infection diagnosis. Additionally, improving management practices and quality control in animal production is recommended to minimize the need for antibiotics. [32]

Responsible prescribing of antibiotics is a key element in strategies for reducing their use. Diagnosis is the first step in this process—before prescribing antibiotics, it must be established whether the infection is bacterial, as antibiotics are ineffective against viral infections. In this context, susceptibility testing is highly valuable, as it allows for the identification of which antibiotics will be effective against a specific bacterial strain. These tests enable more precise drug selection, which helps avoid the use of broad-spectrum antibiotics that may contribute to the development of resistance. [31] A further step involves therapy de-escalation, which means reducing the scope of antibiotic use as diagnostics progress and susceptibility test results are obtained. It is also important to note that effective antibiotic therapy requires appropriate supervision and monitoring to prevent unnecessary prolongation of treatment and the risk of adverse side effects.

Antimicrobial stewardship programs (ASPs) are one of the most important tools for curbing the irresponsible use of antibiotics. These programs aim to improve the quality of antibiotic use through monitoring, education for healthcare staff, and the implementation of best practices in therapy. Research shows that successful implementation of ASPs leads to a significant reduction in antibiotic consumption, thus lowering the risk of resistance development. [33] An essential aspect of these programs is the systematic evaluation of treatment effectiveness, which allows for the rapid adjustment of therapy based on the changing clinical conditions of the patient. ASPs are also particularly effective in pediatric hospitals, where their implementation allows for better management of antibiotics in the pediatric population, which may be especially vulnerable to the side effects of therapy. [34] It is worth noting that these programs must be tailored to the specific needs of local communities and healthcare systems, and their success depends on the engagement of all stakeholders—from physicians to hospital administration and patients. [35]

Through responsible antibiotic prescribing, susceptibility testing, therapy de-escalation, and effective antimicrobial stewardship, it is possible to significantly reduce the use of these drugs, which is crucial in the fight against bacterial resistance. However, the effectiveness of these strategies requires collaboration across various sectors and full integration of actions at the local, national, and international levels, in line with the One Health philosophy. [32]

2. New therapies and alternative approaches

New therapies and alternative approaches are a critical component in combating the rising challenge of bacterial resistance, especially in the face of the development of so-called "superbugs" that are resistant to most available antibiotics. One of the most promising areas in this field is phage therapy, which uses viruses, called bacteriophages, to combat bacterial infections. Bacteriophages exhibit specificity for particular bacteria, thereby reducing the risk of resistance development. This therapy is particularly effective in treating infections caused by antibiotic-resistant bacteria, such as *Pseudomonas aeruginosa*, which form biofilms that are resistant to pharmacological treatment. Numerous studies have demonstrated the effectiveness of bacteriophages in fighting such biofilms, which act as protective barriers for bacteria, making them difficult to eradicate with traditional antibiotics. [37] Moreover, bacteriophages can act synergistically with antibiotics, enhancing their efficacy and reducing the need for high doses of conventional drugs, which in turn may slow down the development of resistance. [37]

Another modern strategy in the fight against antibiotic resistance is the development of antibacterial compounds outside traditional drug classes. An example of such approaches includes new antibiotics based on alternative mechanisms that attack bacteria in ways different from conventional antibiotics, for instance by disrupting metabolic processes or interacting with bacterial proteins responsible for maintaining the structural integrity of the cell. These new drug classes, such as antimicrobial peptides that act on bacterial cell membranes, show promise in treating infections caused by bacteria resistant to traditional drugs. [36] These therapies have the ability to bypass resistance mechanisms, such as antibiotic-degrading enzymes, and are less susceptible to mutations in bacteria that lead to resistance development.

Immunological therapies also provide an alternative approach, such as the use of monoclonal antibodies designed to neutralize bacterial toxins or block bacterial-host cell interactions. Such approaches offer a promising option, particularly in the treatment of diseases caused by pathogens that develop resistance to conventional antibiotics. [38] Furthermore, gene therapies, which involve modifying the bacterial genotype to make them less capable of developing resistance or restoring sensitivity to existing antibiotics, represent an emerging avenue. Research on the use of CRISPR-Cas9 technology in treating bacterial infections, as well as in precisely targeting genes responsible for resistance, may open new possibilities for treating infections caused by resistant strains. [39]

New approaches also include supporting the microbiome, which plays a crucial role in protecting against bacterial infections. Therapy aimed at restoring microbial balance in humans and animals through probiotics or microbiota transplants may help reduce the need for antibiotics by naturally combating pathogens and enhancing the body’s defenses against infections. [40]

In the face of growing antibiotic resistance, new therapies and alternative approaches not only represent promising avenues for treating resistant infections, but also offer a way to reduce reliance on conventional antibacterial drugs. In the long term, this could contribute to delaying the development of antibiotic resistance. [40] The effective implementation of these innovative therapies, considering their synergy with currently used drugs, could become a critical element of the global strategy to combat the superbug pandemic.

3. Raising awareness and public education

Increasing public awareness of the threats associated with antibiotic resistance and promoting the responsible use of these medications are fundamental in the fight against the superbug pandemic. Educational campaigns targeting both patients and healthcare workers play a pivotal role in reducing inappropriate antibiotic use. For patients, it is essential to understand that antibiotics are only effective for bacterial infections, not viral ones, which helps prevent their misuse for conditions such as the common cold or flu. For healthcare professionals, education should focus on principles of responsible prescribing, including accurate diagnostics, susceptibility testing, and therapy de-escalation. [41] These campaigns should also promote the use of alternative treatment methods and the restoration of microbial balance through probiotics or other supportive therapies.

Education on antibiotic resistance also aims to raise awareness about how the irresponsible use of antibiotics contributes to the development of resistant bacterial strains. Studies indicate that education levels directly impact patients' awareness and their tendency to misuse antibiotics. [42] Unfortunately, in many countries, particularly those with low- and middle-income economies, there is a high prevalence of inappropriate antibiotic use, stemming from a lack of knowledge about how antibiotics work and easy access to over-the-counter medications. [44] In such cases, education becomes crucial, not only to raise awareness but also to promote responsible prescribing and the judicious use of antibiotics.

The success of educational campaigns depends on their effectiveness in reaching broad segments of society, including those with lower levels of education, who often exhibit higher rates of antibiotic misuse. [42] In this context, research suggests that educational strategies should be adapted to the cultural, linguistic, and socioeconomic specifics of different regions to maximize their impact. [43] In developing countries, where the resistance problem is particularly severe, education on antibiotic resistance should include widespread informational campaigns that highlight not only the health effects but also the social and economic consequences of excessive antibiotic use. [44] Engaging community leaders and non-governmental organizations is also crucial, as they can support these efforts at the local level.

In addition, training for healthcare professionals aims to enhance doctors' competencies in the responsible prescribing of antibiotics. Medical personnel must be aware of modern diagnostic methods, such as rapid susceptibility testing, which allow for precise determination of which drugs will be effective. This, in turn, can significantly reduce unnecessary use of broad-spectrum antibiotics, which contribute to the development of resistance. [41] It is also important to emphasize the need for education on alternative therapies that can be used in the treatment of infections, thereby reducing dependence on antibiotics. Educational programs that engage both patients and healthcare staff have the potential to substantially reduce the global problem of antibiotic resistance.

IV. Examples of actions at the international and national levels

Actions at the international and national levels play a pivotal role in combating antibiotic resistance (AMR). The World Health Organization (WHO) plays a central role in this effort, developing global strategies and action plans aimed at curbing the spread of resistance.

One such key document is the WHO Global Action Plan on Antimicrobial Resistance, which outlines specific goals and recommendations for member states, such as strengthening antibiotic surveillance, promoting responsible prescribing, and fostering the development of new therapies. The plan also emphasizes education and public awareness to minimize the inappropriate use of antibiotics in the treatment of infectious diseases, particularly in low- and middle-income countries. [45] Additionally, WHO has launched the AWaRe (Access, Watch, Reserve) initiative, aimed at improving access to essential antibiotics while promoting the restriction of broad-spectrum antibiotics, which are more susceptible to the development of resistance. [45]

International collaboration in research and information exchange is also an essential component of the global strategy. Programs such as the Global Antimicrobial Resistance Surveillance System (GLASS) organize the collection of data on antimicrobial resistance, enabling the exchange of information between countries regarding the spread of resistant bacterial strains. These efforts make it possible to monitor changes in the epidemiology of AMR and effectively identify regions where resistance is particularly concerning. Such global systems allow for more rapid responses to critical situations, such as the emergence of new resistant pathogens. [46]

At the national level, many countries are implementing health policies aimed at curbing the spread of AMR. In Poland, as in other European countries, the government has launched the National Program for Combating Antimicrobial Resistance, which includes a broad range of measures, from public education to improving the oversight of antibiotic sales and prescriptions. This program emphasizes the importance of rapid diagnostics and susceptibility testing to ensure the precise selection of appropriate treatments. Non-governmental organizations also play a significant role in these efforts, engaging in educational campaigns directed at citizens, promoting responsible antibiotic use, and raising awareness of the consequences of misuse. [47]

An example of governmental actions in other countries is the Antimicrobial Stewardship strategy in the United States, which ensures the responsible use of antibiotics in healthcare facilities by establishing dedicated teams responsible for monitoring their usage. The aim of these initiatives is not only to reduce the number of prescribed antibiotics but also to improve the quality of patient care [48]. Furthermore, initiatives such as the European Antimicrobial Resistance Initiative engage European Union member states in a coordinated effort to combat AMR, promoting the exchange of best practices and joint actions to reduce antibiotic use.

However, the implementation of strategies to combat AMR is fraught with numerous challenges. One of these challenges is the barrier to access to modern therapies in developing countries, where there is often a lack of financial and technological resources to purchase expensive medications or introduce advanced diagnostic methods. Moreover, in many of these countries, restrictive regulations on the use of antibiotics encounter resistance both from healthcare workers and patients, who expect quick and effective solutions. In some cases, lack of access to basic healthcare, as well as illegal antibiotic trade, further hinder the effective implementation of policies. [48]

Despite these challenges, international cooperation, public education, and strengthening national health policies are critical tools in the fight against the rising threat of antibiotic resistance. In the future, greater integration of actions at both the global and national levels, as well as continued development of new therapies, may help slow the development of AMR, thus minimizing the threats posed by the rise of superbugs.

V. Conclusions

Antibiotic resistance has become one of the most serious global health issues, jeopardizing the effectiveness of treatments for many infections. As the number of so-called "superbugs" increases, which are resistant to standard therapies, it becomes crucial to understand the underlying problems leading to this situation and to develop innovative solutions in both therapy and diagnostics. International collaboration and education on the responsible use of antibiotics also play a key role in addressing this phenomenon.

One of the most significant challenges in the context of antibiotic resistance is the rising number of superbugs. These organisms, which develop resistance to multiple classes of antibiotics, are becoming increasingly prevalent, leading to difficulties in treating infections. The improper use of antibiotics, both in human medicine and veterinary practices, is a major contributing factor to this issue. Overuse of these drugs promotes the emergence of strains resistant to standard treatments.

Additionally, the pharmaceutical industry is struggling to keep pace with the production of new antibiotics, putting patients and healthcare providers in a difficult position, as many bacteria are becoming resistant to available drugs. There is an urgent need to develop new therapies and innovative treatment methods.

In the face of the growing problem of antibiotic resistance, modern therapies and advanced diagnostics play a pivotal role. Innovative treatment methods, such as bacteriophage therapy and gene therapies, offer new possibilities for combating resistant bacterial strains. Additionally, the development of modern diagnostic tests, such as molecular assays, enables faster and more accurate identification of pathogens and their resistance profiles, which allows for more targeted and effective treatment.

Equally important is education. It is crucial to educate both healthcare professionals and patients about the responsible use of antibiotics and infection prevention strategies. Raising awareness of the issue of antibiotic resistance is essential to implementing behavioral changes related to their use.

The fight against antibiotic resistance requires coordinated efforts at the international level. Global initiatives and collaboration between countries are vital for the exchange of information, research, and best practices in preventing and treating antibiotic-resistant infections. Establishing and implementing international standards for antibiotic use in medicine and veterinary practice can help curb their misuse.

The future of combating antibiotic resistance presents both opportunities and challenges. Continued investment in research on new antibiotics and alternative treatment methods is essential to ensuring the effectiveness of therapies. Increasing public awareness of antibiotic resistance is necessary to change behaviors related to their use. Furthermore, the implementation of resistance monitoring systems and epidemiological studies is crucial to understanding and effectively addressing this issue.

Fighting antibiotic resistance requires an integrated approach that combines innovative therapies, advanced diagnostics, education, and international cooperation. Only through collective action can we slow the development of antibiotic resistance and ensure effective treatment for future generations.

Disclosures

Author's contribution:
Conceptualization: MZ, AN, GB
Methodology: MZA
Software PN, WP
Check: GB, AN, MZA
Formal analysis: WP, MZ
Investigation: AN, PN
Resources: GB
Data curation: WP, GB
Writing-roughpreparation: MZA, MZ
Writing review and editing: AN, PN
Visualization: MZ, WP, MZA
Project administration: PN, GB

Supplementary Materials:

They have not been provided.

Funding Statement:

This research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of interest:

The authors declare no conflict of interest.

All authors have read and agrees to the published version of the manuscript.

References

1. van Buul LW, van der Steen JT, Veenhuizen RB, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc*. 2012;13(6):. doi.org/10.1016/j.jamda.2012.04.004
2. Development of Bacterial Resistance to Antibiotics. *JAMA*. 2022;328(20):2074. doi.org/10.1001/jama.2021.17225
3. Mutuku C, Gazdag Z, Melegh S. Occurrence of antibiotics and bacterial resistance genes in wastewater: resistance mechanisms and antimicrobial resistance control approaches. *World J Microbiol Biotechnol*. 2022;38(9):152. Published 2022 Jul 4. doi.org/10.1007/s11274-022-03334-0
4. Li T, Wang Z, Guo J, et al. Bacterial resistance to antibacterial agents: Mechanisms, control strategies, and implications for global health. *Sci Total Environ*. 2023;860:160461. doi.org/10.1016/j.scitotenv.2022.160461
5. Baran A, Kwiatkowska A, Potocki L. Antibiotics and Bacterial Resistance-A Short Story of an Endless Arms Race. *Int J Mol Sci*. 2023;24(6):5777. Published 2023 Mar 17. doi.org/10.3390/ijms24065777
6. Islam MM. Bacterial resistance to antibiotics: access, excess, and awareness in Bangladesh. *Expert Rev Anti Infect Ther*. 2021;19(8):973-981. doi.org/10.1080/14787210.2021.1865804
7. Uddin TM, Chakraborty AJ, Khusro A, et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *J Infect Public Health*. 2021;14(12):1750-1766. doi.org/10.1016/j.jiph.2021.10.020
8. Lewis K. The Science of Antibiotic Discovery. *Cell*. 2020;181(1):29-45. doi.org/10.1016/j.cell.2020.02.056
9. Duquette E, Bhatti P, Sur S, Felbaum DR, Dowlati E. History and Use of Antibiotic Irrigation for Preventing Surgical Site Infection in Neurosurgery: A Scoping Review. *World Neurosurg*. 2022;160:76-83. doi.org/10.1016/j.wneu.2022.01.098
10. Babiker A, Li X, Lai YL, et al. Effectiveness of adjunctive clindamycin in β-lactam antibiotic-treated patients with invasive β-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study [published correction appears in Lancet Infect Dis. 2021 May;21(5):e122. doi: 10.1016/S1473-3099(21)00228-0]. *Lancet Infect Dis*. 2021;21(5):697-710. doi.org/10.1016/S1473-3099(20)30523-5
11. Frimodt-Møller N, Bjerrum L. Treating urinary tract infections in the era of antibiotic resistance. *Expert Rev Anti Infect Ther*. 2023;21(12):1301-1308. doi.org/10.1080/14787210.2023.2279104
12. Horne M, Woolley I, Lau JSY. The Use of Long-term Antibiotics for Suppression of Bacterial Infections. *Clin Infect Dis*. 2024;79(4):848-854. doi.org/10.1093/cid/ciae302
13. Stefan KL, Kim MV, Iwasaki A, Kasper DL. Commensal Microbiota Modulation of Natural Resistance to Virus Infection. *Cell*. 2020;183(5):1312-1324.e10. Stefan KL, Kim MV, Iwasaki A, Kasper DL. Commensal Microbiota Modulation of Natural Resistance to Virus Infection. *Cell*. 2020;183(5):1312-1324.e10. doi.org/10.1016/j.cell.2020.10.047
14. Netea MG, Domínguez-Andrés J, van de Veerdonk FL, van Crevel R, Pulendran B,

van der Meer JWM. Natural resistance against infections: focus on COVID-19.*TrendsImmunol*.2022;43(2):106-116. doi.org/10.1016/j.it.2021.12.001
15. Panou V, Røe OD. Inherited Genetic Mutations and Polymorphisms in Malignant Mesothelioma: A Comprehensive Review. *Int J Mol Sci*. 2020;21(12):4327. Published 2020 Jun 17. doi.org/10.3390/ijms21124327
16. Lee C, Park SH, Yoon SK. Genetic mutations affecting mitochondrial function in cancer drug resistance. *Genes Genomics*. 2023;45(3):261-270. doi.org/10.1007/s13258-022-01359-1
17. Li W, Zhang G. Detection and various environmental factors of antibiotic resistance gene horizontal transfer. *Environ Res*. 2022;212(Pt B):113267. doi.org/10.1016/j.envres.2022.113267
18. Jeon JH, Jang KM, Lee JH, Kang LW, Lee SH. Transmission of antibiotic resistance genes through mobile genetic elements in Acinetobacter baumannii and gene-transfer prevention. *Sci Total Environ*. 2023;857(Pt 2):159497. doi.org/10.1016/j.scitotenv.2022.159497
19. Jian Z, Zeng L, Xu T, et al. Antibiotic resistance genes in bacteria: Occurrence, spread, and control. *J Basic Microbiol*. 2021;61(12):1049-1070. doi.org/10.1002/jobm.202100201
20. Romero JL, Grande Burgos MJ, Pérez-Pulido R, Gálvez A, Lucas R. Resistance to Antibiotics, Biocides, Preservatives and Metals in Bacteria Isolated from Seafoods: Co-Selection of Strains Resistant or Tolerant to Different Classes of Compounds. *Front Microbiol*. 2017;8:1650. Published 2017 Aug 31. doi.org/10.3389/fmicb.2017.01650
21. Poletajew S, Pawlik K, Bonder-Nowicka A, Pakuszewski A, Nyk Ł, Kryst P. Multi-Drug Resistant Bacteria as Aetiological Factors of Infections in a Tertiary Multidisciplinary Hospital in Poland. *Antibiotics (Basel)*. 2021;10(10):1232. Published 2021 Oct 10. doi.org/10.3390/antibiotics10101232
22. Volgenant CMC, Hoogenkamp MA, Dahlén G, Kalfas S, Petti S, De Soet JJ. Low prevalence of multi-resistant bacteria in undergraduate dental students; an observational case-control multi-centre study in Europe. *J Oral Microbiol*. 2021;13(1):1889898. Published 2021 Feb 21. doi.org/10.1080/20002297.2021.1889898
23. Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. 2019;19(1):56-66. doi.org/10.1016/S1473-3099(18)30605-4
24. Imoto W, Yamada K, Kuwabara G, et al. Impact of coronavirus disease 2019 on infectious disease treatment and infection control at a tertiary hospital in Japan. *J Infect Chemother*. 2022;28(5):616-622. doi.org/10.1016/j.jiac.2022.01.008
25. Kandeel M. The impact of the M184V resistance mutation on treatment outcomes in patients with HIV infection: a systematic review and meta-analysis. *AIDS Rev*. 2023;26(3):136-144. doi.org/10.24875/AIDSRev.23000002
26. Govindaraj Vaithinathan A, Vanitha A. WHO global priority pathogens list on

antibiotic resistance: an urgent need for action to integrate One Health data. *Perspect Public Health*. 2018;138(2):87-88. doi.org/10.1177/1757913917743881
27. Yang X, Li X, Qiu S, et al. Global antimicrobial resistance and antibiotic use in COVID-19 patients within health facilities: A systematic review and meta-analysis of aggregated participant data. *J Infect*. 2024;89(1):106183. doi.org/10.1016/j.jinf.2024.106183
28. Roth N, Käsbohrer A, Mayrhofer S, Zitz U, Hofacre C, Domig KJ. The application of antibiotics in broiler production and the resulting antibiotic resistance in Escherichia coli: A global overview. *Poult Sci*. 2019;98(4):1791-1804. doi.org/10.3382/ps/pey539
29. Aggarwal R, Mahajan P, Pandiya S, et al. Antibiotic resistance: a global crisis, problems and solutions. *Crit Rev Microbiol*. 2024;50(5):896-921. doi.org/10.1080/1040841X.2024.2313024
30. Tarín-Pelló A, Suay-García B, Pérez-Gracia MT. Antibiotic resistant bacteria: current situation and treatment options to accelerate the development of a new antimicrobial arsenal. *Expert Rev Anti Infect Ther*. 2022;20(8):1095-1108. doi.org/10.1080/14787210.2022.2078308
31. Tang KWK, Millar BC, Moore JE. Antimicrobial Resistance (AMR). *Br J Biomed Sci*. 2023;80:11387. Published 2023 Jun 28. doi:10.3389/bjbs.2023.11387
32. Aslam B, Khurshid M, Arshad MI, et al. Antibiotic Resistance: One Health One World Outlook [published correction appears in Front Cell Infect Microbiol. 2024 Sep 25;14:1488430. doi: 10.3389/fcimb.2024.1488430]. *Front Cell Infect Microbiol*. 2021;11:771510. Published 2021 Nov 25. doi:10.3389/fcimb.2021.771510
33. Cunha CB. Antimicrobial Stewardship Programs: Principles and Practice. *Med Clin North Am*. 2018;102(5):797-803. doi:10.1016/j.mcna.2018.04.003
34. Donà D, Barbieri E, Daverio M, et al. Implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review [published correction appears in Antimicrob Resist Infect Control. 2020 May 7;9(1):59. doi: 10.1186/s13756-020-00720-x]. *Antimicrob Resist Infect Control*. 2020;9(1):3. Published 2020 Jan 3. doi:10.1186/s13756-019-0659-3
35. Lanckohr C, Bracht H. Antimicrobial stewardship. *Curr Opin Crit Care*. 2022;28(5):551-556. doi:10.1097/MCC.0000000000000967
36. Cook MA, Wright GD. The past, present, and future of antibiotics. *Sci Transl Med*. 2022;14(657):eabo7793. doi:10.1126/scitranslmed.abo7793
37. Chegini Z, Khoshbayan A, Taati Moghadam M, Farahani I, Jazireian P, Shariati A. Bacteriophage therapy against Pseudomonas aeruginosa biofilms: a review. *Ann Clin Microbiol Antimicrob*. 2020;19(1):45. Published 2020 Sep 30. doi:10.1186/s12941-020-00389-5
38. MacNair CR, Rutherford ST, Tan MW. Alternative therapeutic strategies to treat antibiotic-resistant pathogens. *Nat Rev Microbiol*. 2024;22(5):262-275. doi:10.1038/s41579-023-00993-0
39. Dai L, Sahin O, Grover M, Zhang Q. New and alternative strategies for the prevention, control, and treatment of antibiotic-resistant Campylobacter. *Transl Res*. 2020;223:76-88. doi:10.1016/j.trsl.2020.04.009
40. Aggarwal R, Mahajan P, Pandiya S, et al. Antibiotic resistance: a global crisis,

problems and solutions. *Crit Rev Microbiol*. 2024;50(5):896-921. doi:10.1080/1040841X.2024.2313024
41. Satterfield J, Miesner AR, Percival KM. The role of education in antimicrobial stewardship. *J Hosp Infect*. 2020;105(2):130-141. doi:10.1016/j.jhin.2020.03.028
42. Mallah N, Orsini N, Figueiras A, Takkouche B. Education level and misuse of antibiotics in the general population: a systematic review and dose-response meta-analysis. *Antimicrob Resist Infect Control*. 2022;11(1):24. Published 2022 Feb 3. doi:10.1186/s13756-022-01063-5
43. Machowska A, Stålsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe. *Int J Environ Res Public Health*. 2018;16(1):27. Published 2018 Dec 23. doi:10.3390/ijerph16010027
44. Sulis G, Sayood S, Gandra S. How can we tackle the overuse of antibiotics in low- and middle-income countries?. *Expert Rev Anti Infect Ther*. 2023;21(11):1189-1201. doi:10.1080/14787210.2023.2263643
45. Moja L, Zanichelli V, Mertz D, et al. WHO's essential medicines and AWaRe: recommendations on first- and second-choice antibiotics for empiric treatment of clinical infections. *Clin Microbiol Infect*. 2024;30 Suppl 2:S1-S51. doi:10.1016/j.cmi.2024.02.003
46. Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS. Antibiotic resistance and persistence-Implications for human health and treatment perspectives. *EMBO Rep*. 2020;21(12):e51034. doi:10.15252/embr.202051034
47. Bhardwaj S, Mehra P, Dhanjal DS, et al. Antibiotics and Antibiotic Resistance-Flipsides of the Same Coin. *Curr Pharm Des*. 2022;28(28):2312-2329. doi:10.2174/1381612828666220608120238
48. Uddin TM, Chakraborty AJ, Khusro A, et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *J Infect Public Health*. 2021;14(12):1750-1766. doi:10.1016/j.jiph.2021.10.020