MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Journal of Quality in Health care & Economics
ISSN: 2642-6250

Antibiotic Armageddon: Navigating the Resistance Crisis

Maqbool M[1] and Willie MM[2]*

[1]Department of Pharmaceutical Sciences, University Of Kashmir, India

[2]Council for Medical Schemes, Policy Research and Monitoring, South Africa

***Corresponding author:** Michael Mncedisi Willie, Council for Medical Schemes, Policy Research and Monitoring, Pretoria, South Africa, Email: m.willie@medicalschemes.co.za

Review Article
Volume 7 Issue 1
Received Date: December 11, 2023
Published Date: February 23, 2024
DOI: 10.23880/jqhe-16000363

Abstract

The emergence of antibiotic resistance presents a serious worldwide health challenge, rendering previously effective treatments ineffective and imposing significant hurdles on global healthcare systems. This comprehensive examination delves deeply into the intricate realm of antibiotic resistance, investigating its mechanisms, catalysts, and repercussions, while also delving into innovative therapeutic methodologies that propose potential remedies. The mechanisms that underlie antibiotic resistance encompass genetic mutations, horizontal gene transfer, and efflux pumps, enabling bacteria to adapt and persevere when exposed to antibiotics. These mechanisms, when combined with the widespread mishandling and overuse of antibiotics in both human and animal contexts, have facilitated the rapid proliferation of pathogens resistant to multiple drugs. The global reverberations of antibiotic resistance are extensive, encompassing amplified mortality rates, prolonged hospitalizations, and escalated healthcare expenses. Elements such as subpar infection control protocols and international travel contribute to the dissemination of these resistant strains, extending beyond geographic and healthcare boundaries. Given the scarcity of novel antibiotic advancements, addressing antibiotic resistance necessitates novel therapeutic methodologies. This multifaceted challenge requires immediate action. Employing pioneering therapeutic methods alongside judicious antibiotic application can counteract antibiotic resistance and ensure the availability of effective treatments for generations to come.

Keywords: Antibiotic; Resistance; Novel Therapy; Gene Transfer

Introduction

Antibiotic resistance stands as a pivotal global health concern wherein bacteria evolve to withstand antibiotics, rendering these crucial medications ineffective. This phenomenon arises from diverse factors, including the excessive and inappropriate use of antibiotics across clinical and agricultural domains. Bacteria that survive antibiotic treatment seize the opportunity to proliferate, potentially transferring their resistance traits to subsequent generations through mechanisms like horizontal gene transfer. The ramifications of antibiotic resistance are profound, causing once easily treatable infections to become arduous to manage [1]. This results in protracted illness, escalated healthcare expenses, and heightened mortality rates. Conventional medical procedures such as surgeries and chemotherapy carry augmented risks due to the potential emergence of antibiotic-resistant infections. Furthermore, the paucity of novel antibiotics exacerbates the quandary, with limited innovative drugs being developed to supplant those that have lost efficacy [1,2].

The combat against antibiotic resistance demands a multifaceted approach. Healthcare practitioners must prioritize judicious antibiotic prescription practices, administering these medications only when necessary and in appropriate dosages. Elevated infection control measures can curb the proliferation of resistant bacteria within healthcare facilities. Moreover, public awareness campaigns can disseminate knowledge about the significance of completing prescribed antibiotic courses and refraining from sharing these medications [3]. Research and innovation are also pivotal to combating antibiotic resistance. The creation of novel antibiotic alternative therapies such as bacteriophage therapy, and precision strategies that target specific bacterial mechanisms exhibit potential. Government policies and international collaborations play a critical role in incentivizing antibiotic research, regulating their usage, and instating global surveillance systems to monitor resistance patterns. Antibiotic resistance jeopardizes the core of contemporary medicine and public health. Through the implementation of prudent antibiotic use, the improvement of infection control measures, and the progress of research into innovative treatment approaches, we can collaboratively confront this urgent challenge and ensure the continued effectiveness of antibiotics in the treatment of bacterial infections [4-7].

Mechanisms of Antibiotic Resistance

Antibiotic resistance mechanisms are intricate processes through which bacteria evolve to evade the impact of antibiotics, rendering these medications ineffective in addressing infections. These mechanisms involve various genetic, biochemical, and structural alterations within bacterial cells. Grasping these mechanisms is pivotal for devising strategies to counter antibiotic resistance [8,9]. The following table provides a comprehensive overview of the diverse mechanisms through which antibiotic resistance emerges. Each mechanism is accompanied by a detailed description and pertinent examples to elucidate its practical implications. This comprehensive presentation not only highlights the complexity of antibiotic resistance but also underscores the significance of understanding these mechanisms in the context of addressing this pressing issue effectively.

A profound comprehension of these mechanisms illuminates the intricate landscape of antibiotic resistance, underscoring the imperative for a multifaceted and all-encompassing strategy to address this formidable challenge. Effectively combating antibiotic resistance necessitates a multifarious approach, which may encompass the creation of innovative antibiotics engineered to bypass these resistance mechanisms. Furthermore, combination therapies, integrating multiple antibiotics or auxiliary compounds, may hold potential to circumvent resistance and expand the arsenal of effective treatments. Exploring alternative therapeutic avenues, including phage therapy and the harnessing of antimicrobial peptides, stands as an imperative frontier in the ongoing battle against antibiotic resistance. These diversified approaches collectively present promising prospects for addressing this pressing concern and preserving the efficacy of antibiotic treatment [17,18].

Mechanisms of Antibiotic Resistance	Description	Examples	References
1. Mutation of Target Sites	Bacteria can undergo mutations that alter the structure of antibiotic target sites, reducing the affinity of antibiotics for these sites and diminishing their effectiveness. For example, mutations in bacterial ribosomal RNA can lead to resistance against antibiotic classes such as macrolides and tetracyclines.	Macrolides, Tetracyclines	Luo J, et al. [10]
2. Enzymatic Inactivation	Certain bacteria produce enzymes that modify or degrade antibiotics before they can take effect. β-lactamase enzymes can cleave the β-lactam ring in β-lactam antibiotics, rendering them inactive. This mechanism is common in bacteria resistant to penicillins and cephalosporins.	β-lactam antibiotics	Zhang L, et al. [11]
3. Efflux Pumps	Bacteria can possess efflux pumps, proteins that actively transport antibiotics out of bacterial cells, reducing intracellular antibiotic concentration. This makes it challenging for drugs to reach their targets effectively and contributes to resistance against antibiotic classes like fluoroquinolones.	Fluoroquinolones	Cascioferro S, et al. [12]

4. Alteration of Cell Permeability	Some bacteria modify their outer membrane structure to resist antibiotic penetration, hindering access to their intended targets. This is evident in Gram-negative bacteria, which have an outer membrane that acts as a barrier against antibiotics.	Gram-negative bacteria	Cascioferro S, et al. [12], Wilson DN, et al. [13]
5. Biofilm Formation	Bacteria within biofilms, organized communities enclosed in a protective matrix, exhibit heightened antibiotic resistance. The matrix acts as a physical barrier, preventing antibiotics from effectively reaching bacterial cells within the biofilm.	Biofilms	Zhu T-T, et al. [14]
6. Horizontal Gene Transfer	Bacteria can acquire resistance genes from other bacteria through mechanisms like conjugation, transformation, and transduction. This rapid exchange of genetic information facilitates the spread of resistance traits among bacterial populations, even across different species.	Genetic transfer mechanisms	Mancuso G, al. [2], Colclough AL, et al. [15]
7. Reduced Antibiotic Uptake	Bacteria can develop mechanisms to decrease antibiotic intake into their cells. This may involve alterations in porin proteins that serve as gateways for antibiotic entry, restricting the amount of drug that enters bacterial cells.	Porin proteins	Colclough AL, et al. [15], Pachori P, et al. [16]
8. Altered Dihydropteroate Synthase (DHPS) in Sulfonamide	Certain bacteria possess modified versions of the DHPS enzyme targeted by sulfonamide antibiotics. These altered forms have reduced affinity for sulfonamides, leading to decreased drug efficacy. Resistance	Sulfonamides	Pachori P, et al. [16], Guo Y, et al. [17]

Table 1: Mechanisms of Antibiotic Resistance.

Global Impact of Antibiotic Resistance

The global implications of antibiotic resistance encompass a complex and far-reaching crisis that exerts a profound influence on healthcare systems, economies, and the overall well-being of populations across the world. This predicament presents substantial challenges in the realm of healthcare, significantly impacting patient treatment and outcomes while also casting a shadow on the overall welfare of diverse global communities [19-21]. In the subsequent discussion, we undertake an in-depth exploration of the extensive and far-reaching consequences brought about by antibiotic resistance.

Consequences of Antibiotic Resistance	Description	References
1. Heightened Morbidity and Mortality	Infections resistant to antibiotics are more challenging to treat, leading to prolonged illnesses, increased hospitalizations, and higher rates of complications. Severe cases can turn once manageable infections into life-threatening conditions, resulting in	Hernando-Amado S, et al. [4], Hernando-Amado S, et al. [22]
	elevated morbidity and mortality rates, especially among vulnerable groups such as the elderly, immunocompromised individuals, and those undergoing medical procedures.	
2. Extended Hospital Stays	Antibiotic-resistant infections often require more complex medical interventions and longer hospitalizations, placing additional strain on healthcare resources, increasing healthcare costs, and reducing the capacity of medical facilities to address other healthcare needs.	Yadav S, et al. [23], Ara I, et al. [24]

3. Escalated Healthcare Expenses	Managing antibiotic-resistant infections results in higher healthcare expenditures due to prolonged hospital stays, extended treatment durations, and the use of more expensive antibiotics. These costs burden both individuals and healthcare systems, diverting resources from other essential healthcare services.	Yadav S, et al. [23], Romandini A, et al. [25]
4. Disruption of Medical Interventions	Antibiotic-resistant infections can complicate surgical procedures, chemotherapy, and other medical treatments, increasing the risk of postoperative complications and treatment delays, which impact patients' overall health and recovery.	Chen H, et al. [26], Zehravi M, et al. [27]
5. Reduced Effectiveness of Vital Medications	Antibiotics are vital in critical medical practices such as organ transplants, cancer therapies, and surgeries. The loss of effective antibiotics places these treatments at risk, making once-routine medical procedures more precarious.	Uddin TM, et al. [28]
6. Economic Implications	Antibiotic resistance has significant economic consequences, affecting individual economies and the global economy. The increased healthcare costs, reduced workforce productivity due to illness, and losses in agricultural output (since antibiotics are essential in livestock farming) contribute to economic instability.	Jit M, et al. [29]
7. Threat to Food Security	Antibiotics play a crucial role in ensuring animal health and food safety in agriculture. Antibiotic-resistant bacteria can transmit from animals to humans through the consumption of food, potentially compromising food security and safety standards.	Rezasoltani S, et al. [30]
8. Global Health Vulnerability	The rise in antibiotic resistance poses a threat to global health security by diminishing the effectiveness of responses to infectious disease outbreaks. Resistant pathogens can spread swiftly across borders, undermining international health interventions and preparedness efforts.	Aslam B, et al. [31]
9. Challenges in Developing Nations	Developing countries often bear a heavier burden of infectious diseases and have limited access to healthcare resources. Antibiotic resistance exacerbates these challenges, making it more challenging to manage infectious disease outbreaks and healthcare infrastructure, thereby impacting public health in these regions.	Zhang Z, et al. [6], Serwecińska L [32]

Table 2: Consequences of Antibiotic Resistance.

To effectively combat resistance, it is imperative to promote the judicious use of antibiotics, enhance infection control measures, allocate resources to support research for the development of novel antibiotics and alternative treatment methods, and establish global surveillance systems aimed at monitoring patterns of resistance [33]. By pooling our collective efforts and working in unison to confront this pressing challenge, we possess the potential to safeguard the efficacy of antibiotics, thereby ensuring the long-term health and overall well-being of populations on a global scale. This collective endeavour is indispensable in preserving the potency of antibiotics and securing the continued health and prosperity of communities worldwide, as underscored in previous research [34].

Factors Contributing to Antibiotic Resistance

Antibiotic resistance represents a multifaceted challenge, stemming from a intricate interplay of biological, environmental, social, and behavioural factors. These intricate components interact in nuanced ways, creating an environment conducive to the emergence and widespread dissemination of bacteria that exhibit resistance to antibiotics. It is imperative to grasp the intricacies of these contributory factors to develop and implement effective strategies aimed at mitigating antibiotic resistance [27,35]. The subsequent table offers a detailed exploration of each of these elements that collectively contribute to the complex issue of antibiotic resistance.

Factors Contributing to Antibiotic Resistance	Description	References
1. Excessive and Improper Antibiotic Usage	Widespread antibiotic use in healthcare and animal farming increases selective pressure on antibiotic-resistant bacteria. Overuse and misuse, such as	Chokshi A, et al. [36]
	prescribing antibiotics for viral infections or using low doses, promote the dominance of resilient bacteria.	
2. Inadequate Infection Control Measures	Substandard hygiene practices in healthcare settings can facilitate the spread of resistant infections. Poor hand hygiene, inadequate equipment sterilization, and insufficient patient isolation contribute to bacterial transmission, including drug-resistant strains.	Uruén C, et al. [37]
3. Global Mobility and Migration	The movement of individuals across borders accelerates the dissemination of antibiotic-resistant bacteria. Resistant variants can be introduced to new regions by travellers or migrants, leading to localized outbreaks and contributing to	Stracy M, et al. [5]
	global resistance.	
4. Antibiotic Use in Agriculture	Antibiotic use in animal husbandry for growth promotion and infection prevention in agriculture provides opportunities for resistance development in animals. This resistance can transmit to humans through the food chain or direct contact.	Gebreyohannes G, et al. [38]
5. Limited Development of New Antibiotics	The pace of antibiotic discovery has slowed significantly, while resistant	Gebreyohannes G, et al. [38], Xu H, et al. [39]
	strains continue to emerge. This imbalance results in bacterial resistance outpacing the creation of novel drugs, limiting treatment options.	
6. Horizontal Transfer of Genetic Material	Bacteria have evolved mechanisms for horizontal gene transfer, enabling the exchange of resistance genes between different species. This accelerates the spread of resistance traits across bacterial populations, even among formerly non-resistant species.	Chokshi A, et al. [36], Hayat K, et al. [40]
7. Inadequate Sanitation and Clean Water Access	Insufficient sanitation and lack of access to clean water create favorable conditions for bacterial growth. Resistant strains can contaminate water sources, food supplies, and communities, exacerbating resistance spread.	Kanneppady SS, et al. [41]
8. Economic and Commercial Influences	Economic factors and commercial interests can influence antibiotic use,	Van TTH, et al. [42]
	potentially leading to improper applications for growth promotion in agriculture or hastening drug resistance development in patients.	
9. Public Awareness and Patient Expectations	Patient demands for antibiotics, even when unnecessary, can result in their	Das B, et al. [43]
	overprescription. Raising public awareness through campaigns is crucial for educating patients about prudent antibiotic use and resistance consequences.	
10. Healthcare Infrastructure and Access to Medical Care	Inadequate healthcare infrastructure, especially in resource-limited settings, can contribute to improper antibiotic use. Lack of access to diagnostics or trained medical professionals may lead to broad-spectrum antibiotic prescriptions	Dadgostar P [44], Maqbool M, et al. [45]
	when more targeted treatments are appropriate.	

Table 3: Factors Contributing to Antibiotic Resistance.

Effectively addressing antibiotic resistance necessitates a comprehensive strategy that tackles each of these factors. This entails promoting responsible antibiotic use, bolstering infection control protocols, supporting research into new antibiotics and alternative treatments, and fostering international cooperation to exchange knowledge and resources. Ultimately, a multifaceted endeavour is essential to preserve the continued efficacy of antibiotics in treating bacterial infections [46-48].

Current Therapeutic Challenges

The current state of antibiotic resistance poses numerous significant therapeutic obstacles that have extensive implications for patient well-being, public health, and the medical field. These challenges emphasize the critical need to address antibiotic resistance through inventive strategies and all-encompassing approaches [48-50]. Table 4 below depicts some of the noteworthy therapeutic challenges.

Challenges of Antibiotic Resistance	Description	References
1. Emergence of Multi-Resistant Pathogens	Increased prevalence of bacteria resistant to multiple antibiotics, limiting treatment options and requiring last-resort antibiotics, which are also at risk of losing effectiveness.	Ward RA, et al. [51]
2. Depleted Pipeline of New Antibiotics	Decreased interest from the pharmaceutical industry in antibiotic research, coupled with the complexity of discovering new compounds, results in a scarcity of effective drugs to combat resistant infections.	Mulani MS, et al. [52]
3. Lack of Innovative Mechanisms	Many new antibiotics operate through mechanisms similar to existing drugs, reducing their efficacy against resistant strains with similar mechanisms.	Wang X, et al. [53]
4. Treatment Setbacks and Complexities	Antibiotic-resistant infections lead to treatment delays, prolonged illnesses, and an increased risk of complications, necessitating more aggressive therapies, longer hospital stays, and additional medical interventions.	Löscher W, et al. [54]
5. Cross-Resistance and Unintended Consequences	Resistance mechanisms can cause cross-resistance, where resistance to one antibiotic results in resistance to others. Certain antibiotics can unintentionally promote resistance to other antibiotic classes, leading to unintended consequences in the microbial environment.	Bergogne-Berezin [55]
6. Challenges in Battling Biofilms	Bacteria within biofilms, structured communities encased in a protective matrix, exhibit heightened resistance to antibiotics. Treating biofilm-related infections is challenging due to the protective matrix that shields bacteria from antibiotics and the immune response.	Eleraky NE, et al. [56]
7. Global Propagation of Resistance	Antibiotic-resistant bacteria can spread rapidly across geographical boundaries, increasing global resistance. This complicates surveillance, response strategies, and international collaboration.	Mahizan NA, et al. [57], Ara I, et al. [58]
8. Elderly and Immunocompromised Patients	Vulnerable groups, such as the elderly and immunocompromised individuals, are at higher risk of antibiotic-resistant infections due to weakened immune systems, increasing the risk of adverse outcomes from difficult-to-treat infections.	Sundaram DNM, et al. [59]
9. Substantial Economic Load	Managing antibiotic-resistant infections leads to higher healthcare costs, longer hospitalizations, and extended treatment, straining both individuals and healthcare systems and diverting resources from essential medical services.	Theuretzbacher U, et al. [60]

10. Antibiotic Stewardship Hurdles	Implementing antibiotic stewardship programs effectively, ensuring judicious antibiotic use, presents challenges in balancing patient care with the need to reduce unwarranted antibiotic prescriptions, requiring complex decision-making.	Annunziato G [61]

Table 4: Challenges associated with Antibiotic Resistance.

Confronting these therapeutic hurdles mandates an all-inclusive strategy encompassing research, policy transformations, medical practices, and public awareness initiatives. Approaches may encompass promoting responsible antibiotic use, incentivizing research and development of fresh antibiotics, fostering collaborations between healthcare and research realms, and investigating alternative treatment avenues like phage therapy, antimicrobial peptides, and innovative combination therapies. The pressing need to tackle these obstacles is paramount for upholding the potency of antibiotics and ensuring optimal patient outcomes [62,63].

Novel Therapeutic Approaches

In the face of the escalating menace of antibiotic resistance, fresh therapeutic methodologies are imperative. With conventional antibiotics losing effectiveness, scientists and medical professionals are delving into inventive strategies to confront this challenge. These approaches tap into cutting-edge technologies and alternative treatment paradigms [64,65]. The list of innovative strategies depicted in table 5 below are key in mitigating antibiotic resistance demonstrates considerable potential; however, many of these approaches remain in the investigational phase, lacking comprehensive clinical validation and safety assessments. Furthermore, a deeper understanding of the ecological and environmental ramifications, along with a thorough evaluation of cost-effectiveness, especially within resource-constrained settings, is imperative. To establish the viability of these innovative strategies in effectively addressing the global antibiotic resistance challenge, additional research and extensive clinical trials are warranted.

Innovative Antibiotic Treatment Approaches	Description	References
1. Bacteriophage Therapy	Bacteriophages, viruses that selectively attack bacteria, are employed in phage therapy. This approach identifies and utilizes bacteriophages that target antibiotic- resistant bacteria, offering a tailored solution with the potential to combat infections while preserving beneficial microbiota.	Morrisette T, et al. [66], Mohd M, et al. [67]
2. Antibiotic Adjuvants	Antibiotic adjuvants are compounds that enhance antibiotic efficacy by disrupting bacterial resistance mechanisms, restoring susceptibility. They may also modify bacterial environments, strengthening antibiotic potency and potentially extending	Lawson JH, et al. [68]
	the effectiveness of existing antibiotics.	
3. Antimicrobial Peptides (AMPs)	Antimicrobial peptides (AMPs), natural molecules with potent antimicrobial properties, utilize various mechanisms to target bacteria, hindering resistance	Wu SC, et al. [69]
	development. Ongoing research explores AMPs as potential therapeutic agents against antibiotic-resistant infections.	
4. CRISPR-Cas Systems	The precise gene-editing tool CRISPR-Cas can be repurposed to combat antibiotic resistance. Researchers investigate CRISPR-Cas systems to selectively	Jalal K, et al. [70]
	incapacitate antibiotic-resistant genes in bacteria, rendering them susceptible to antibiotics once more.	
5. Combination Therapies	Combining different antibiotics or pairing antibiotics with non-antibiotic agents produces synergistic effects, enhancing overall treatment efficacy. Combination therapies can overcome resistance mechanisms and broaden the antibacterial spectrum.	Mubeen B, et al. [71], Bashir R, et al. [72]

6. Targeting Virulence Factors	Instead of eradicating bacteria, some strategies focus on neutralizing virulence factors driving disease. By reducing bacteria's ability to cause harm, these approaches minimize the evolutionary pressure for resistance.	Cho SX, et al. [73]
7. Repurposing Existing Drugs	Certain non-antibiotic drugs possess antimicrobial properties. Researchers explore these agents as potential treatments for antibiotic-resistant infections, offering a faster path to clinical application compared to developing entirely new compounds.	Nombela P, et al. [74]
8. Synthetic Biology and Engineered Microbes	Synthetic biology enables the engineering of bacteria to produce antimicrobial molecules or enzymes that can degrade resistance mechanisms. Engineered probiotics or "living antibiotics" are investigated for targeted treatments at infection sites.	Wang CH, et al. [75], Ara I, et al. [76]
9. Pharmacokinetic and Pharmacodynamic Optimization	Innovative dosing strategies optimize antibiotic distribution within the body and interactions with bacteria, enhancing their effectiveness against resistant strains.	Sharma D, et al. [77]
10. Precision Medicine Approaches	Precision medicine tailors antibiotic treatment based on an individual's genetic makeup and the genetic profile of the infecting bacteria. This increases the likelihood of selecting the most suitable antibiotic for a specific infection.	Huemer M, et al. [3]

Table 5: Innovative Antibiotic Treatment Approaches.

These innovative approaches underscore the dynamic domain of antibiotic research and the promise they hold for innovative solutions against resistance. While challenges and regulatory considerations persist for many of these methods, they hold the potential to reshape the landscape of infection management and treatment. Persistent research, clinical trials, and collaborations between researchers, clinicians, and regulatory bodies are essential to ushering these approaches into clinical prominence [78,79].

CRISPR-Cas Systems for Antibiotic Resistance

CRISPR-Cas systems, initially renowned for their revolutionary gene-editing capabilities, have emerged as a promising asset in the battle against antibiotic resistance. These systems, found in bacteria and archaea, act as defence mechanisms against viral infections by capturing fragments of viral DNA and integrating them into the host's genetic material [80]. This stored genetic data serves as a "memory" that recognizes and targets specific sequences in invading DNA. In the context of antibiotic resistance, CRISPR-Cas systems provide a distinct approach to tackle the issue of drug-resistant bacteria [81,82]. Researchers are exploring various applications of CRISPR-Cas technology in the context of combating antibiotic resistance. First, CRISPR-Cas is utilized to identify antibiotic resistance genes within bacterial genomes by designing guide RNA sequences matching known resistance gene sequences. This enables the detection of specific resistance traits in clinical samples [83]. Additionally, CRISPR-Cas-based diagnostic tools are employed to swiftly detect antibiotic-resistant pathogens in patient samples. These tests use the CRISPR-Cas system to target and cleave the DNA of the resistant pathogen, generating a detectable signal for rapid and precise diagnosis, guiding appropriate treatment decisions [84,85].

Furthermore, CRISPR-Cas holds potential for editing or deactivating antibiotic resistance genes in bacteria, allowing for the precise disruption of genetic components responsible for resistance, rendering bacteria responsive to treatment once more [86]. Moreover, CRISPR-Cas systems can be engineered to modify bacterial behaviour by targeting virulence or essential genes, potentially making infections more manageable and decreasing the drive for resistance [87]. Bacteriophage therapy can also benefit from CRISPR-Cas technology by preventing bacteria from developing resistance to phages through the deactivation of the bacterial CRISPR-Cas system [88]. Additionally, these systems could hinder bacteria from acquiring antibiotic resistance genes through horizontal gene transfer by targeting and degrading mobile genetic elements carrying resistance genes [89,90].

However, there are challenges when applying CRISPR-Cas systems for antibiotic resistance. These challenges include the need for precise targeting of resistance genes to avoid affecting essential bacterial genes, the development of effective delivery methods for CRISPR components into bacterial cells, potential bacterial evolution of resistance to CRISPR-Cas targeting, and ethical considerations surrounding the therapeutic application of CRISPR-Cas, particularly when editing bacterial genomes within the human body [91-94]. As research in this domain advances CRISPR- Cas systems exhibit promise as versatile tools to tackle antibiotic resistance. They offer inventive strategies for detection, treatment, and management of drug-resistant infections, potentially reshaping the landscape of infectious disease control [95-97].

Regulatory and Policy Implications

Regulatory and policy considerations play a pivotal role in the progression, endorsement, and prudent application of antibiotics. Given the urgent imperative to counter antibiotic resistance, regulatory structures and policies are crafted to strike a balance between ensuring the availability of efficacious antibiotics and safeguarding their sustained potency [98,99]. Regulations and policies in the realm of antibiotic development hold significant implications for addressing the pressing issue of antibiotic resistance. Antibiotic stewardship initiatives are at the forefront, with regulatory bodies and medical institutions advocating for judicious antibiotic use, optimized dosages, and suitable treatment durations to reduce the selective pressure that drives resistance formation [100]. Vigorous surveillance systems are indispensable for monitoring global antibiotic resistance trends, and regulatory agencies collaborate to analyse data on resistance patterns, enabling timely responses to emerging resistant strains [36].

To incentivize research and development, governments and entities provide grants, tax advantages, priority review status, and extended exclusive periods, encouraging investment in new antibiotic creation [4]. Furthermore, expedited approval pathways prioritize antibiotics addressing unmet medical needs, particularly in life-threatening infections, and prioritize medications with the potential to significantly impact patient outcomes [101]. The complex nature of resistant infections requires bespoke clinical trial designs, where regulatory entities collaborate with researchers to consider factors like smaller patient cohorts and rapidly evolving resistance patterns [102].

Regulatory agencies may offer priority reviews and focused approvals for antibiotics serving public health needs, expediting access to medications designed to combat specific resistant pathogens [44]. Some antibiotics necessitate companion diagnostics to identify specific resistant genes, ensuring prescription based on the genetic characteristics of infecting bacteria [103]. Recognizing the global scope of antibiotic resistance, regulatory authorities collaborate to standardize norms, share data, and harmonize regulations, ensuring uniform approaches to antibiotic development and authorization [104]. Post- market surveillance is indispensable for evaluating antibiotic safety and efficacy, with regulatory agencies continuously assessing for adverse events, monitoring emerging resistance trends, and updating recommendations based on new data [47]. In advocating for alternative therapies like phage therapy or antimicrobial peptides, regulatory bodies establish pathways for their evaluation and endorsement, diversifying the arsenal against antibiotic resistance [105]. Finally, educational campaigns and initiatives play a vital role in raising public awareness about the importance of antibiotic stewardship, responsible usage, and the repercussions of antibiotic resistance, thus promoting informed decision-making among healthcare practitioners and the general population [96,106].

These comprehensive measures underscore the multi-faceted approach required to combat antibiotic resistance on a global scale, with regulation and policy playing a pivotal role in driving progress. Striking a balance between expeditious access to efficacious antibiotics and the imperative of safeguarding their efficacy necessitates a nuanced and adaptable regulatory approach. Collaboration among regulatory bodies, researchers, medical professionals, and policymakers is indispensable to guarantee that regulatory frameworks and policies remain adaptive to the evolving landscape of antibiotic development and resistance [107].

Future Directions

The future trajectory of antibiotic advancement is being molded by the urgent necessity to combat antibiotic resistance while also ensuring a sustainable stream of effective treatments. Scientists, pharmaceutical companies, policymakers, and medical practitioners are exploring a variety of inventive strategies to confront these issues and lay the groundwork for the upcoming generation of antibiotics [108]. The future of antibiotic development is intricately intertwined with a myriad of influential pathways that promise to transform the landscape of healthcare. Precision medicine and genomics hold the potential to usher in an era of highly personalized antibiotic treatments, where therapy decisions are based on the genetic profiles of both the patient and the infecting bacteria. This tailored approach not only optimizes treatment outcomes but also stands as a bulwark against the emergence of resistance, redefining the way we combat infections in a more precise and effective manner [109].

The exploration of targeted therapies represents a paradigm shift, moving away from the indiscriminate killing of bacteria to a more focused approach. Crafting antibiotics with precise targeting of bacterial components or virulence factors offers a substantial reduction in the selective pressure for the emergence of resistance.is approach offers the promise of innovative treatments that could revolutionize the field of antibiotic development, making it more sustainable and effective [110]. Combination therapies represent another facet of the evolving landscape, where innovative combinations of antibiotics or the pairing of antibiotics with non-antibiotic agents amplify treatment effectiveness and reduce the likelihood of resistance emerging. By targeting multiple bacterial pathways simultaneously, we enhance our ability to combat even the most resilient infections [111,112]. Repurposing existing drugs offers a faster route to new treatment development. This strategy involves exploring non-antibiotic drugs with inherent antimicrobial qualities, potentially providing solutions for infections that have become resistant to traditional antibiotics [113]. Antibiotic adjuvants, which enhance the potency of antibiotics or disrupt mechanisms of resistance, present a means of restoring the effectiveness of current antibiotics, thereby extending their usefulness in the face of evolving resistance patterns [114]. The investigation into engineered enzymes and peptides opens doors to novel treatment avenues, targeting bacterial membranes, biofilms, and virulence factors with precision and offering fresh strategies to combat infections [115,116]. Phage therapy, an age-old concept, is experiencing a renaissance with advances in phage discovery, characterization, and delivery methods. This approach, which utilizes viruses to target and eliminate bacteria, is poised to become more accessible and effective in the fight against infections [117,118]. Antibiotic alternatives, such as antimicrobial peptides, nanomaterials, and immune-modulating therapies, offer new avenues to combat infections, alleviating the pressure on conventional antibiotics and expanding our arsenal of treatment options [119].

In addition to these scientific advancements, the healthcare landscape is also embracing the power of digital health, artificial intelligence, and machine learning to enhance diagnostics, predict antibiotic resistance, and optimize treatment plans. These digital tools promise more effective and personalized therapies [120,121].

As the scientific community and regulatory bodies adapt to these changes, flexible regulatory pathways are emerging to accommodate innovative antibiotics and alternative therapies, acknowledging the unique challenges posed by antibiotic resistance [122]. International collaboration is paramount in the fight against antibiotic resistance, necessitating the exchange of data, resources, and knowledge among researchers, medical professionals, governments, and regulatory agencies [123,124]. The One Health approach recognizes the interconnectedness of human, animal, and environmental health and advocates for a comprehensive response to antibiotic resistance [125]. Economic incentives, such as rewards upon market entry, are being explored to stimulate the development of antibiotics that address unmet medical needs, ensuring that this critical area of healthcare receives the attention and investment it requires [126, 127].

And finally, continuous public awareness and education campaigns play a pivotal role in promoting responsible antibiotic use and raising awareness about the global threat of antibiotic resistance. These educational initiatives inform healthcare practitioners and the general population, fostering informed decision-making in the battle against antibiotic-resistant infections [128]. These multifaceted pathways collectively shape the trajectory of antibiotic development, promising a future where we can address infectious diseases with greater precision, efficacy, and sustainability. The journey ahead in antibiotic development necessitates a collaborative and multidisciplinary endeavour to ensure the effective development, approval, and deployment of innovative treatments. Through a blend of scientific innovation, adaptive regulations, and responsible antibiotic management, we can confront the challenge of antibiotic resistance and guarantee the sustained effectiveness of antibiotics in preserving public health [126-128].

Conclusion

The fight against antibiotic resistance has reached a crucial point, demanding an immediate and coordinated response from the worldwide medical community, scientists, policymakers, and the general population. The rise of antibiotic resistance presents a major challenge to modern medicine. Processes like genetic changes, sharing of genes between bacteria, and mechanisms that pump out antibiotics enable bacteria to adapt and survive when exposed to these drugs. These mechanisms, combined with the widespread incorrect use of antibiotics, have led to the rapid spread of bacteria that are resistant to multiple drugs. The global effects of antibiotic resistance go beyond borders and medical environments, causing higher death rates, longer hospital stays, and increased healthcare expenses.

Elements such as insufficient infection control methods and international travel contribute to the spread of these resistant strains. Given the diminishing number of new antibiotics being developed, addressing antibiotic resistance requires a shift towards new and creative treatment strategies. The review highlights various innovative methods that have the potential to change the landscape of infectious disease treatment. Bacteriophage therapy, which uses viruses to infect and eliminate bacteria, has shown promise in clinical tests. Substances that enhance the effectiveness of existing antibiotics by disrupting resistance mechanisms, known as antibiotic adjuvants, are being explored. Antimicrobial peptides, gene editing using CRISPR-Cas, combinations of therapies, and alternative treatments such as engineered probiotics provide diverse options to combat resistance. Nonetheless, implementing these strategies encounters challenges from different angles. Regulatory frameworks need to adapt to accommodate these novel approaches while ensuring their safety and efficacy.

The responsible use of antibiotics remains crucial, demanding a collective effort from healthcare providers and patients to follow appropriate prescription practices. Furthermore, continuous research and innovation are vital to refine these methods, improve their outcomes, and address any unexpected consequences. Collaborative efforts that bridge the gap between medical research, public health policies, industry, and patient advocacy are essential. Tackling antibiotic resistance requires a comprehensive approach that acknowledges the interdependence of human health, animal health, and the environment. Additionally, public awareness plays a significant role. Educating the public about the implications of misusing antibiotics, the emergence of resistance, and the importance of using antibiotics responsibly is essential for creating lasting change. Despite the complexity of this challenge, the review emphasizes human resourcefulness. While antibiotic resistance is a serious threat, the determination to combat it is equally strong. By adopting innovative treatment strategies, promoting responsible antibiotic use, and fostering global collaboration, we can steer toward a future where effective treatments overcome resistance. At this critical moment, the review acts as a call to action, urging stakeholders at all levels to come together in the battle against antibiotic resistance and to shape a healthier and more resilient future for generations to come.

References

1. Larsson DJ, Flach C-FJNRM (2022) Antibiotic resistance in the environment. Nature Reviews Microbiology 20: 257-269.
2. Mancuso G, Midiri A, Gerace E, Biondo CJP (2021) Bacterial antibiotic resistance: The most critical pathogens. Pathogens 10(10): 1310.
3. Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS (2020) Antibiotic resistance and persistence—Implications for human health and treatment perspectives EMBO Rep 21(12): e51034.
4. Hernando-Amado S, Coque TM, Baquero F, Martínez JL (2019) Defining and combating antibiotic resistance from One Health and Global Health perspectives. Nature Microbiology 4: 1432-1442.
5. Stracy M, Snitser O, Yelin I, Amer Y, Parizade M, et al. (2022) Minimizing treatment-induced emergence of antibiotic resistance in bacterial infections. Science 375(6583): 889-894.
6. Zhang Z, Zhang Q, Wang T, Xu N, Lu T, et al. (2022) Assessment of global health risk of antibiotic resistance genes. Nature Communications 13: 1553.
7. Wang J, Chu L, Wojnárovits L, Takács E (2020) Occurrence and fate of antibiotics, antibiotic resistant genes (ARGs) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: An overview. Sci Total Environ 744: 140997.
8. Chaudhari R, Singh K, Kodgire P (2023) Biochemical and molecular mechanisms of antibiotic resistance in Salmonella spp. Res Microbiol 174(1-2): 103985.
9. Amyes S, Young H-K (2020) Mechanisms of antibiotic resistance in Acinetobacter spp. genetics of resistance, pp: 185-223.
10. Luo J, Zhang L, Du W, Cheng X, Fang F, et al. (2021) Cao J, Wu Y, Su YJBT: Metagenomic approach reveals the fates and mechanisms of antibiotic resistance genes exposed to allicins during waste activated sludge fermentation: insight of the microbial community, cellular status and gene regulation. Bioresour Technol 342: 125998.
11. Zhang L, Ji L, Liu X, Zhu X, Ning K, et al. (2022) Wang ZJWR: Linkage and driving mechanisms of antibiotic resistome in surface and ground water: their responses to land use and seasonal variation. Water Res 215: 118279.
12. Cascioferro S, Parrino B, Carbone D, Schillaci D, Giovannetti E, et al. (2020) Thiazoles, their benzofused systems, and thiazolidinone derivatives: versatile and promising tools to combat antibiotic resistance. J Med Chem 63: 7923-7956.
13. Wilson DN, Hauryliuk V, Atkinson GC, O'Neill AJ (2020) Target protection as a key antibiotic resistance mechanism. Nature Reviews Microbiology 18: 637-648.
14. Zhu T-T, Su Z-X, Lai W-X, Zhang Y-B, Liu Y-W (2021) Insights into the fate and removal of antibiotics and antibiotic resistance genes using biological wastewater treatment technology. Science of the Total Environment 776: 145906.
15. Colclough AL, Alav I, Whittle EE, Pugh HL, Darby EM, et al. (2020) RND efflux pumps in Gram-negative bacteria; regulation, structure and role in antibiotic resistance. Future Microbiol 15: 143-157.
16. Pachori P, Gothalwal R, Gandhi P (2019) Emergence of antibiotic resistance Pseudomonas aeruginosa in

intensive care unit: A critical review. Genes Dis 6(2): 109-119.

17. Guo Y, Song G, Sun M, Wang J, Wang Y (2020) Prevalence and therapies of antibiotic-resistance in Staphylococcus aureus. Front Cell Infect Microbiol 10: 107.
18. Botelho J, Grosso F, Peixe L (2019) Antibiotic resistance in Pseudomonas aeruginosa– Mechanisms, epidemiology and evolution. Drug Resist Updat 44: 100640.
19. Ahmad M, Khan AU (2019) Global economic impact of antibiotic resistance: A review. J Glob Antimicrob Resist 19: 313-316.
20. Zainab SM, Junaid M, Xu N, Malik RN (2020) Antibiotics and antibiotic resistant genes (ARGs) in groundwater: A global review on dissemination, sources, interactions, environmental and human health risks. Water Res 187: 116455.
21. Dar MA, Maqbool M, Gani I, Ara I (2023) Menstruation hygiene and related issues in adolescent girls: A brief commentary. International Journal of Current Research in Physiology and Pharmacology 7(1): 1-5.
22. Hernando-Amado S, Coque TM, Baquero F, Martínez JL (2020) Antibiotic resistance: Moving from individual health norms to social norms in one health and global health. Front Microbiol 11: 1914.
23. Yadav S, Kapley A (2021) Antibiotic resistance: Global health crisis and metagenomics. Biotechnol Rep Amst 29: e00604.
24. Ara I, Maqbool M, Gani I (2022) Specificity and Personalized medicine: a novel approach to Cancer management. International Journal of Current Research in Physiology and Pharmacology 6(4): 11-20.
25. Romandini A, Pani A, Schenardi PA, Pattarino GAC, Scaglione F, et al. (2021) Antibiotic resistance in pediatric infections: global emerging threats, predicting the near future. Antibiotics Basel 10(4): 393.
26. Chen H, Jing L, Yao Z, Meng F, Teng Y, et al. (2019) Prevalence, source and risk of antibiotic resistance genes in the sediments of Lake Tai (China) deciphered by metagenomic assembly: a comparison with other global lakes. Environ Int 127: 267-275.
27. Zehravi M, Maqbool R, Maqbool M, Ara I (2021) To Identify Patterns of Drug Usage among Patients Who Seek Care in Psychiatry Outpatient Department of a Tertiary Care Hospital in Srinagar, Jammu and Kashmir, India. Journal of Pharmaceutical Research International 33(31): 135-140.
28. Uddin TM, Chakraborty AJ, Khusro A, Zidan BRM, Mitra S, et al. (2021) Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. J Infect Public Health 14(12): 1750-1766.
29. Jit M, Ng DHL, Luangasanatip N, Sandmann F, Atkins KE, et al. (2020) Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies. BMC Med 18(1): 38.
30. Rezasoltani S, Yadegar A, Hatami B, Aghdaei HA, Zali MR, et al. (2020) Antimicrobial resistance as a hidden menace lurking behind the COVID-19 outbreak: the global impacts of too much hygiene on AMR. Front Microbiol 11: 590683.
31. Aslam B, Khurshid M, Arshad MI, Muzammil S, Rasool M, et al. (2021) Antibiotic resistance: one health one world outlook. Front Cell Infect Microbiol 11: 771510.
32. Serwecińska L (2020) Antimicrobials and antibiotic-resistant bacteria: a risk to the environment and to public health. Water 12(12): 3313.
33. Chin KW, Michelle THL, Luang-In V, Ma NL (2022) An overview of antibiotic and antibiotic resistance. Environmental Advances 11: 100331.
34. Morel CM, Lindahl O, Harbarth S, Kraker ME, Edwards S, et al. (2020) Industry incentives and antibiotic resistance: an introduction to the antibiotic susceptibility bonus. J Antibiot Tokyo 73(7): 421- 428.
35. Nguyen AQ, Vu HP, Nguyen LN, Wang Q, Djordjevic SP, et al. (2021) Monitoring antibiotic resistance genes in wastewater treatment: Current strategies and future challenges. Science of The Total Environment 783: 146964.
36. Chokshi A, Sifri Z, Cennimo D, Horng H (2019) Global contributors to antibiotic resistance. J Glob Infect Dis 11(1): 36-42.
37. Uruén C, Chopo-Escuin G, Tommassen J, Mainar-Jaime RC, Arenas J, et al. (2020) Biofilms as promoters of bacterial antibiotic resistance and tolerance. Antibiotics Basel 10(1): 3.
38. Gebreyohannes G, Nyerere A, Bii C, Sbhatu DB (2019) Challenges of intervention, treatment, and antibiotic resistance of biofilm-forming microorganisms. Heliyon 5(8): e02192.
39. Xu H, Li H (2019) Acne, the skin microbiome, and antibiotic treatment. Am J Clin Dermatol 20(3): 335-344.

40. Hayat K, Jamshed S, Rosenthal M, Haq NU, Chang J, et al. (2021) Understanding of pharmacy students towards antibiotic use, antibiotic resistance and antibiotic stewardship programs: a cross-sectional study from Punjab, Pakistan. Antibiotics Basel 10(1): 66.

41. Kanneppady SS, Oo AM, Lwin OM, Al-Abed A-AAA, Kanneppady SK, et al. (2019) Knowledge, attitude, and awareness of antibiotic resistance among medical students. AM&HS 7(1): 57-60.

42. Van TTH, Yidana Z, Smooker PM, Coloe PJ (2020) Antibiotic use in food animals worldwide, with a focus on Africa: Pluses and minuses. J Glob Antimicrob Resist 20: 170-177.

43. Das B, Verma J, Kumar P, Ghosh A, Ramamurthy T (2020) Antibiotic resistance in Vibrio cholerae: understanding the ecology of resistance genes and mechanisms. Vaccine 38(suppl 1): A83-A92.

44. Dadgostar P (2019) Antimicrobial resistance: implications and costs. Infect Drug Resist 12: 3903-3910.

45. Maqbool M, Zehravi M (2021) Neuroprotective role of polyphenols in treatment of neurological disorders: A review. Neuromodulation 1(1): e117170.

46. Konstantinidis T, Tsigalou C, Karvelas A, Stavropoulou E, Voidarou C, et al. (2020) Effects of antibiotics upon the gut microbiome: a review of the literature. Biomedicines 8(11): 502.

47. Roope LS, Smith RD, Pouwels KB, Buchanan J, Abel L, et al. (2019) The challenge of antimicrobial resistance: what economics can contribute. Science 364(6435): eaau4679.

48. Ukuhor HO (2021) The interrelationships between antimicrobial resistance, COVID- 19, past, and future pandemics. J Infect Public Health 14(1): 53-60.

49. Streicher LM (2021) Exploring the future of infectious disease treatment in a post-antibiotic era: A comparative review of alternative therapeutics. J Glob Antimicrob Resist 24: 285-295.

50. Ara I, Maqbool M, Gani I (2022) Neuroprotective Activity of Herbal Medicinal Products: A Review. IJCRP& Pharmacology 6(4): 1-10.

51. Ward RA, Fawell S, Floc'h N, Flemington V, McKerrecher D, et al. (2020) Challenges and opportunities in cancer drug resistance. Chem Rev 121(6):3297-3351.

52. Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi KR. (2019) Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Front Microbiol 1:10:539.

53. Wang X, Zhang H, Chen X (2019) Drug resistance and combating drug resistance in cancer. Cancer Drug Resist 2(2): 141-160.

54. Löscher W, Potschka H, Sisodiya SM, Vezzani A (2020) Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. Pharmacol Rev 72(3): 606-638.

55. Bergogne-Berezin (2020) Resistance of Acinetobacter spp. to antimicrobials—overview of clinical resistance patterns and therapeutic problems. PP: 133-183.

56. Eleraky NE, Allam A, Hassan SB, Omar MM (2020) Nanomedicine fight against antibacterial resistance: an overview of the recent pharmaceutical innovations. Pharmaceutics 12(2): 142.

57. Mahizan NA, Yang S-K, Moo C-L, Song AA-L, Chong C-M, et al. (2019) Terpene derivatives as a potential agent against antimicrobial resistance (AMR) pathogens. Molecules 24(14): 2631.

58. Ara I, Zehravi M, Maqbool M, Gani I (2022) A review of recent developments and future challenges in the implementation of universal health coverage policy framework in some countries. J Pharma Res Rep 3(2): 1-8.

59. Sundaram DNM, Jiang X, Brandwein JM, Valencia-Serna J, Remant K, et al.(2019) Current outlook on drug resistance in chronic myeloid leukemia (CML) and potential therapeutic options. Drug Discov Today 24(7): 1355-1369.

60. Theuretzbacher U, Outterson K, Engel A, Karlén A (2020) The global preclinical antibacterial pipeline. Nat Rev Microbiol 18(5): 275-285.

61. Annunziato G (2019) Strategies to overcome antimicrobial resistance (AMR) making use of non-essential target inhibitors: A review. Int J Mol Sci 20(23): 5844.

62. Singh R, Dwivedi SP, Gaharwar US, Meena R, Rajamani P, et al. (2020) Recent updates on drug resistance in Mycobacterium tuberculosis.128(6): 1547-1567.

63. Huang M, Lin Y, Wang C, Deng L, Chen M, et al. (2022) New insights into antiangiogenic therapy resistance in cancer: Mechanisms and therapeutic aspects. Drug Resist Updat 64: 100849.

64. Dieterle MG, Rao K, Young VB (2019) Novel therapies

and preventative strategies for primary and recurrent Clostridium difficile infections. Ann N Y Acad Sci 1435(1): 110-138.

65. Pang Z, Raudonis R, Glick BR, Lin T-J, Cheng Z (2019) Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies. Biotechnol Adv 37(1): 177-192.
66. Morrisette T, Kebriaei R, Lev KL, Morales S, Rybak MJ (2020) Bacteriophage therapeutics: a primer for clinicians on phage-antibiotic combinations. Pharmacotherapy 40(2): 153-168.
67. Mohd M, Maqbool M, Dar MA, Mushtaq I (2019) Polycystic ovary syndrome, a modern epidemic: an overview. Therapeutics 9(3): 641-644.
68. Lawson JH, Niklason LE, Roy-Chaudhury P (2020) Challenges and novel therapies for vascular access in haemodialysis. Nat Rev Nephrol 16(10): 586-602.
69. Wu SC, Liu F, Zhu K, Shen JZ (2019) Natural products that target virulence factors in antibiotic-resistant Staphylococcus aureus. J Agric Food Chem 67(48):13195-13211.
70. Jalal K, Khan K, Hayat A, Ahmad D, Alotaibi G, et al. (2023) Mining therapeutic targets from the antibiotic-resistant Campylobacter coli and virtual screening of natural product inhibitors against its riboflavin synthase. Mol Divers 27(2): 793-810.
71. Mubeen B, Ansar AN, Rasool R, Ullah I, Imam SS, et al. (2021) Nanotechnology as a novel approach in combating microbes providing an alternative to antibiotics 10(12): 1473.
72. Bashir R, Maqbool M, Ara I, Zehravi MJC (2021) An Insight into Novel Drug Delivery System: In Situ Gels. 11: 61-67.
73. Cho SX, Rudloff I, Lao JC, Pang MA, Goldberg R, et al. (2020) Characterization of the pathoimmunology of necrotizing enterocolitis reveals novel therapeutic opportunities 11: 5794.
74. Nombela P, Miguel-López B, Blanco SJMc (2021) The role of m6A, m5C and Ψ RNA modifications in cancer: Novel therapeutic opportunities 20: 1-30.
75. Wang CH, Hsieh YH, Powers ZM, Kao C YJIjoms (2020) Defeating antibiotic-resistant bacteria: exploring alternative therapies for a post-antibiotic era. MDPI 21: 1061.
76. Ara I, Maqbool M, Zehravi MJOH (2022) Psychic consequences of infertility on couples: A short commentary 3: 114-119.
77. Sharma D, Misba L, Khan AUJAR (2019) Control I: Antibiotics versus biofilm: an emerging battleground in microbial communities 8: 1-10.
78. Nabavi SF, Sureda A, Sanches-Silva A, Pandima Devi K, Ahmed T, Shahid M, et al. (2019) Novel therapeutic strategies for stroke: The role of autophagy 56: 182-199.
79. Gaurav A, Bakht P, Saini M, Pandey S, Pathania RJM (2023) Role of bacterial efflux pumps in antibiotic resistance, virulence, and strategies to discover novel efflux pump inhibitors 169(5): 001333.
80. Wu Y, Battalapalli D, Hakeem MJ, Selamneni V, Zhang P, et al. (2021) Engineered CRISPR-Cas systems for the detection and control of antibiotic-resistant infections 19: 1-26.
81. Gholizadeh P, Köse Ş, Dao S, Ganbarov K, Tanomand A, Dal T, et al. (2020) CRISPR-Cas system could be used to combat antimicrobial resistance 2020: 1111-1121.
82. Ara I, Maqbool M, Gani (2022) Pharmacology: Reproductive Health of Women: implications and attributes. IJIJo CRiP 2022: 8-18.
83. Kamruzzaman M, Iredell (2020) CRISPR-Cas system in antibiotic resistance plasmids in Klebsiella pneumoniae. JRJFiM 10: 2934.
84. Abavisani M, Khayami R, Hoseinzadeh M, Kodori M, Kesharwani P, et al. (2023) CRISPR- Cas system as a promising player against bacterial infection and antibiotic resistance 68: 100948.
85. Zehravi M, Maqbool M (2022) Healthy lifestyle and dietary approaches to treating polycystic ovary syndrome: a review. Degruyter 3: 60-65.
86. Duan C, Cao H, Zhang LH, (2021) Harnessing the CRISPR-Cas systems to combat antimicrobial resistance. 12: 716064.
87. Aslam B, Rasool M, Idris A, Muzammil S, Alvi RF, et al. (2020) CRISPR-Cas system: a potential alternative tool to cope antibiotic resistance. BMC 9: 1-3.
88. Alduhaidhawi AHM, AlHuchaimi SN, Al-Mayah TA, Al-Ouqaili MT, Alkafaas SS, et al. (2022) Prevalence of CRISPR-cas systems and their possible association with antibiotic resistance in Enterococcus faecalis and Enterococcus faecium collected from hospital wastewater. Infect Drug Resist 15: 1143-1154.

Maqbool M and Willie MM. Antibiotic Armageddon: Navigating the Resistance Crisis. J Qual Healthcare Eco 2024, 7(1): 000363.

89. Shehreen S, Chyou TY, Fineran PC, Brown (2019) Genome-wide correlation analysis suggests different roles of CRISPR-Cas systems in the acquisition of antibiotic resistance genes in diverse species. 374: 20180384.

90. Yeh TK, Jean SS, Lee YL, Lu MC, Ko WC, et al. (2022) Bacteriophages and phage-delivered CRISPR-Cas system as antibacterial therapy 59: 106475.

91. Fage C, Lemire N (2021) Delivery of CRISPR-Cas systems using phage-based vectors. 68: 174-180.

92. Mortensen K, Lam TJ (2021) Comparison of CRISPR–Cas immune systems in healthcare-related pathogens 12: 758782.

93. Roy S, Naha S, Rao A (2021) CRISPR-Cas system, antibiotic resistance and virulence in bacteria: through a common lens. Prog Mol Biol Transl Sci 178: 123-174.

94. Saha U, Gondi R, Patil A, Saroj (2023) CRISPR in modulating antibiotic resistance of ESKAPE pathogens. Mol Biotechnol 65: 1-16.

95. Pursey E, Dimitriu T, Paganelli FL, Westra ER (2022) CRISPR-Cas is associated with fewer antibiotic resistance genes in bacterial pathogens. Philos Trans R Soc Lond B Biol Sci 377: 20200464.

96. Dar MA, Maqbool M, Ara IJJoEoM (2023) Prescription Pattern of Antibiotics in Pulmonary Ward of a Tertiary Care Hospital, Jammu and Kashmir. Journal of Evaluation of Medicine and Dental Science 12(6): 171-175.

97. Maqbool M, Fekadu G, Jiang X, Bekele F, Tolossa T, et al. (2021) An up to date on clinical prospects and management of osteoarthritis. Ann Med Surg (Lond) 72(2): 103077.

98. Lulijwa R, Rupia EJ (2020) Antibiotic use in aquaculture, policies and regulation, health and environmental risks: a review of the top 15 major producers 12: 640-663.

99. Jacobs TG, Robertson J, Van den Ham HA, Iwamoto K, Bak Pedersen H, et al. (2019) Assessing the impact of law enforcement to reduce over-the-counter (OTC) sales of antibiotics in low-and middle-income countries; a systematic literature review. BMC health 19: 1-15.

100. Laxminarayan R, Van Boeckel T, Frost I, Kariuki S, Khan EA, et al. (2020) The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. The Lancet 20: e51-e60.

101. Kraemer SA, Ramachandran A (2019) Antibiotic pollution in the environment: from microbial ecology to public policy. Perron GGJM 7: 180.

102. Iwu CD, Korsten L, Okoh AIJM (2020) The incidence of antibiotic resistance within and beyond the agricultural ecosystem: A concern for public health. Microbiologyopen 9: e1035.

103. Majumder MAA, Rahman S, Cohall D, Bharatha A, Singh K, et al. (2020) Antimicrobial stewardship: Fighting antimicrobial resistance and protecting global public health pp: 4713-4738.

104. Schar D, Klein EY, Laxminarayan R, Gilbert M, Van Boeckel (2020) Global trends in antimicrobial use in aquaculture. 10: 21878.

105. Zhao X, Yu Z, Ding TJM (2020) Quorum-sensing regulation of antimicrobial resistance in bacteria. Microorganisms 8(3): 425.

106. Preena PG, Swaminathan TR, Kumar VJR (2020) Antimicrobial resistance in aquaculture: a crisis for concern. Biologia 75: 1497-1517.

107. Iskandar K, Molinier L, Hallit S, Sartelli M, Hardcastle TC, et al. (2021) Surveillance of antimicrobial resistance in low-and middle- income countries: a scattered picture. Antimicrobial Resistance & Infection Control 10: 1-19.

108. Laws M, Shaaban A, Rahman (2019) Antibiotic resistance breakers: current approaches and future directions. FEMS Microbial Reviewes 43: 490-516.

109. Ramey AM, Ahlstrom CA (2020) Antibiotic resistant bacteria in wildlife: Perspectives on trends, acquisition and dissemination, data gaps, and future directions. J Wild Dis 56(1): 1-15.

110. Boyanova L, Hadzhiyski P, Kandilarov N, Markovska R, Mitov I (2019) Multidrug resistance in Helicobacter pylori: current state and future directions. Expert Rev Clin Pharmacol 12(9): 909-915.

111. Sulis G, Sayood S, Gandra S (2022) Antimicrobial resistance in low-and middle-income countries: current status and future directions. Expert Rev Anti Infect Ther 20(2): 147-160.

112. Amenyogbe E, Chen G, Wang Z, Huang J, Huang B (2020) The exploitation of probiotics, prebiotics and synbiotics in aquaculture: present study, limitations and future directions.: a review. 28: 1017-1041.

113. Gan BH, Gaynord J, Rowe SM, Deingruber T (2021) The multifaceted nature of antimicrobial peptides: Current synthetic chemistry approaches and future directions. 50:7820-7880.

114. Golub LM, Lee H (2020) Periodontal therapeutics: Current host-modulation agents and future directions. Periodontol 82(1): 186-204.

115. Maqbool M, Bekele F, Fekadu G (2022) Treatment strategies against triple-negative breast cancer: an updated review. Breast Cancer (Dove Med Press) 14: 15-24.

116. Bal-Öztürk A, Özkahraman B, Özbaş Z, Yaşayan G, Tamahkar E (2021) Advancements and future directions in the antibacterial wound dressings–A review. 109(5): 703-716.

117. Zehravi M, Maqbool M, Ara I (2021) Polycystic ovary syndrome and infertility: an update. pp: 34: 1-9.

118. Freeman JC, Smith LB, Silva JJ, Fan Y, Sun H, et al. (2021) Fitness studies of insecticide resistant strains: lessons learned and future directions. Pest Management Science 77(9): 3847-3856.

119. Zehravi M, Maqbool M, Ara I (2021) Correlation between obesity, gestational diabetes mellitus, and pregnancy outcomes: an overview. Int J Adolesc Med Health 33(6): 339-345.

120. Kim D-W, Cha C-J (2021) Antibiotic resistome from the One-Health perspective: Understanding and controlling antimicrobial resistance transmission. Experimental & molecular medicine 53: 301-309.

121. Tshibangu-Kabamba E, Yamaoka Y (2021) Helicobacter pylori infection and antibiotic resistance—from biology to clinical implications. Nat Rev Gastroenterol Hepatol 18(9): 613-629.

122. Zehravi M, Maqbool M, Ara I (2021) Depression and anxiety in women with polycystic ovarian syndrome: a literature survey. Int J Adolesc Med Health 33(6): 367-373.

123. Siqueira JF, Rôças IN (2022) Present status and future directions: Microbiology of endodontic infections. Int Endod J 55: 512-530.

124. Sadowska JM, Genoud KJ, Kelly DJ, O'Brien FJ (2021) Bone biomaterials for overcoming antimicrobial resistance: Advances in non-antibiotic antimicrobial approaches for regeneration of infected osseous tissue. Materials Today 46: 136-154.

125. Zehravi M, Maqbool M, Ara I (2021) Polycystic ovary syndrome and reproductive health of women: a curious association. Int J Adolesc Med Health 33(6): 333-337.

126. Kim NM, Sinnott RW, Sandoval NR (2020) Transcription factor-based biosensors and inducible systems in non-model bacteria: current progress and future directions. Current Opinion in Biotechnology 64: 39-46.

127. Zhang G, Li W, Chen S, Zhou W, Chen J (2020) Problems of conventional disinfection and new sterilization methods for antibiotic resistance control. Chemosphere 254: 126831.

128. Zehravi M, Maqbool M, Ara I (2022) Teenage menstrual dysfunction: an overview. Int J Adolesc Med Health 35(1): 15-19.