medical sciences forum

MDPI

Proceeding Paper

Antibiotics in a Changing World: Resistance, Ecology, and Public Health Conundrums †

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† Presented at the 3rd International Electronic Conference on Antibiotics (ECA 2023), 1–15 December 2023; Available online: https://eca2023.sciforum.net/.

Abstract: The world of antibiotics is undergoing a significant transformation, driven by the dual challenges of antimicrobial resistance and ecological ramifications associated with their use. This thesis provides a comprehensive examination of the intricate relationship between antibiotics, public health, and the environment, shedding light on the multifaceted problems that this interplay creates. The research scrutinizes the global crisis of antibiotic resistance, investigating its origins, underlying mechanisms, and its alarming proliferation. Antibiotic-resistant bacteria pose a serious threat to the effectiveness of these crucial drugs in the fight against infectious diseases. This necessitates a reevaluation of antibiotic use and the development of innovative strategies to curb resistance also focusing on the ecological consequences of antibiotic utilization. While antibiotics are designed to target specific pathogens, their impact extends to the broader microbial communities they encounter. The research delves into the effects of antibiotics on ecosystem balance, with a particular emphasis on their contribution to the growing problem of environmental antibiotic resistance. This thesis offers a holistic perspective on the evolving landscape of antibiotics through a comprehensive analysis of these interconnected aspects. It emphasizes the urgent need for a global response to address resistance, advocates for a balanced approach to antibiotic usage, and underscores the pivotal role of public health strategies in managing these intricate challenges

Keywords: antibiotics; resentence; medicine

Citation: Hasan, M.M.; Rana, M.M.; Tithy, T.A. Antibiotics in a Changing World: Resistance, Ecology, and Public Health Conundrums. *Med. Sci. Forum* **2023**, *24*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 1 December 2023

1. Introduction

Antibiotics have long been hailed as one of the greatest medical advancements in human history, revolutionizing the treatment of infectious diseases and saving countless lives. However, the world of antibiotics is now facing a critical crossroads. The dual challenges of antimicrobial resistance and the ecological consequences associated with their use have initiated a transformation that demands our immediate attention and a comprehensive reevaluation of our approach to these life-saving drugs [1].

In this era of antibiotic evolution, this thesis seeks to provide an in-depth exploration of the intricate relationship between antibiotics, public health, and the environment. We aim to illuminate the multifaceted problems arising from the interplay between these domains and to underscore the urgency of finding solutions [2]. Our investigation commences with an in-depth analysis of the global crisis of antibiotic resistance. The origins, underlying mechanisms, and the alarming proliferation of antibiotic-resistant bacteria have thrown into sharp relief the very real threat they pose to the effectiveness of these crucial drugs in the fight against infectious diseases. The gravity of antibiotic resistance necessitates not only a reevaluation of antibiotic use but also the development of innovative strategies to curb its relentless advance. This thesis will emphasize the need for a paradigm shift in the way we perceive and employ antibiotics [3], recognizing that they are a finite and precious resource that should be preserved for future generations.

Beyond the realm of public health, the impact of antibiotics extends into the environment, and this aspect remains a critical and often overlooked concern. Antibiotics, designed to target specific pathogens, cast a broader net when it comes to their ecological effects [4]. These drugs disrupt the delicate balance of microbial communities, with far-reaching consequences. This research delves into the effects of antibiotics on ecosystem equilibrium, paying particular attention to their contribution to the growing problem of environmental antibiotic resistance. The consequences of this ecological disruption are not confined to the natural world but have ripple effects on human health and well-being [5].

In sum, this thesis endeavors to provide a holistic perspective on the evolving landscape of antibiotics by analyzing the interconnected aspects of resistance, ecology, and public health. It serves as a clarion call, emphasizing the urgent need for a global response to address antibiotic resistance, advocating for a balanced approach to antibiotic usage, and underscoring the pivotal role of public health strategies in managing these intricate and pressing challenges. It is our hope that the insights and findings within these pages will contribute to the ongoing dialogue on antibiotics in a changing world and serve as a foundation for addressing these pressing global conundrums.

2. Overview of the Related Work

In 1958, the world of medicine welcomed vancomycin, a glycopeptide, with open arms as a potent tool to combat infections caused by methicillin-resistant Staphylococci. However, the enthusiasm was short-lived as, just two decades later, in 1979, vancomycin-resistant strains of coagulase-negative Staphylococci (CoNS) began to emerge. A decade further, vancomycin-resistant Enterococcus (VRE) made its disquieting debut. The efficacy of vancomycin against Staphylococcus aureus began to erode, giving rise to vancomycin-intermediate Staphylococcus aureus (VISA) in 1997, followed by the arrival of vancomycin-resistant Staphylococcus aureus (VRSA) in 2002 [6].

Cephalosporin, a β-lactam antibiotic discovered in the mid-1940s, entered clinical practice in 1964 as a solution for penicillin-resistant cases. Subsequent generations of cephalosporins followed, with the fifth generation being the most recent. Its initial efficacy, particularly against extended beta-lactamases (ESBLs) [7] producing gram-negative bacteria, was commendable. Nevertheless, as generations progressed, resistance steadily became a growing concern.

Tetracycline, unveiled in 1950, initially exhibited promise in addressing common infections, including gastrointestinal diseases [8]. However, within a decade of its discovery, its effectiveness against Shigella strains came into question in 1959. In 1996, levofloxacin, a third-generation fluoroquinolone, entered the antibiotic arsenal. Regrettably, in the same year, levofloxacin-resistant Pneumococcus reared its head [9].

In 1980, carbapenem, a β-lactam variant, was introduced as a last line of defense for treating infections caused by members of the enterobacterales family, particularly in cases resistant to cephalosporin. As its use increased during the 1990s and 2000s, carbapenem-resistant enterobacterales (CRE) began cropping up in various regions, with reports dating back to 2006 [10].

A close examination of the antibiotic discovery timeline reveals a disconcerting pattern. New classes of antibiotics were brought into existence by pharmaceutical industries for just a fleeting two decades, spanning from 1960 to 1980. Thereafter, the pace of discovery slowed dramatically, a concerning trend that persisted until recent times [11]. This stark contrast between the rising tide of drug-resistant pathogens and the limited number of available antibiotics has led critics to predict the looming onset of a post-antibiotic era. The timeline of major antibiotic discoveries and their corresponding struggles with resistance is graphically depicted in Figure 1 below.

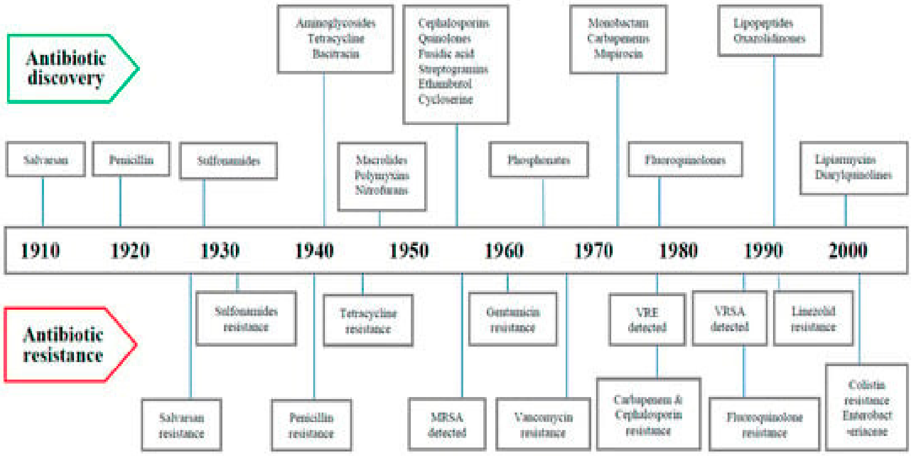

Figure 1. Timeline of discovery of major antibiotics and antibiotic resistance [22].

Here's a brief overview of the related work for each of the topics you've identified in your thesis:

2.1. Antibiotic Resistance

Historical Perspective: Review the historical development and use of antibiotics, dating back to the discovery of penicillin. Discuss the initial optimism and the gradual emergence of resistance [12].

Mechanisms of Resistance: Summarize the known mechanisms of antibiotic resistance, including genetic mutations, horizontal gene transfer, and the role of plasmids.

Clinical Studies: Explore studies and case reports that highlight the growing challenges of antibiotic resistance in clinical settings, including hospitals and healthcare-associated infections [13]. Epidemiology: Examine research on the prevalence and distribution of antibiotic-resistant pathogens on a global scale. Highlight regions or specific pathogens that pose significant threats [14].

2.2. Ecological Consequences

Microbiome Studies: Discuss research related to the human and environmental microbiome, and how antibiotics disrupt the balance of microbial communities. Emphasize studies that show how antibiotic use affects non-target species [15].

Environmental Impact: Review studies that investigate the presence of antibiotics in the environment, including soil, water, and food. Discuss how this exposure can lead to environmental antibiotic resistance.

One Health Approach: Explore research that embraces the "One Health" approach, which recognizes the interconnectedness of human, animal, and environmental health. Highlight studies that investigate the ecological impact of antibiotic use in agriculture and livestock [16].

Wastewater and Resistance: Examine studies on the presence of antibiotics and antibiotic-resistant bacteria in wastewater systems and their potential contribution to environmental antibiotic resistance [17].

2.3. Public Health Conundrums

Antibiotic Stewardship: Discuss strategies and studies related to antibiotic stewardship programs in healthcare settings. These programs aim to optimize antibiotic use and combat resistance [18].

Policy and Regulation: Review the policies and regulations in place to address antibiotic use and resistance at the national and international levels. Discuss the challenges in implementing and enforcing these measures.

Health Economics: Explore research on the economic impact of antibiotic resistance on healthcare systems, including increased treatment costs and hospitalization.

Global Initiatives: Discuss international efforts and collaborations to combat antibiotic resistance, such as the World Health Organization's Global Action Plan on Antimicrobial Resistance (AMR) [19].

When conducting your literature review, be sure to select key studies, research articles, and reports that are most relevant to your thesis and its specific research questions. Additionally, consider the latest developments and research findings, as the field of antibiotic resistance is dynamic and constantly evolving.

3. Antibiotic Resistance Unveiled

Antibiotic resistance is the intricate evolutionary response of bacteria to the continuous challenge posed by therapeutic antibiotics. Clinically speaking, when a new antibiotic is introduced, all targeted pathogens initially exhibit susceptibility. However, as time progresses and these antibiotics are employed consistently, bacteria adapt, rendering the antibiotics less effective [20]. This adaptation is viewed from an evolutionary perspective, where bacteria fine-tune their interactions with antibiotics by either (1) undergoing mutations in chromosomal genes or (2) acquiring external genetic material through horizontal gene transfer (HGT) [21] that harbors the coveted resistance determinants.

These mutations primarily revolve around three distinct types of genes: those responsible for encoding the antibiotic targets, genes connected to the transportation of antibiotics, and regulators controlling the expression of transporters. This dynamic alteration can give rise to antibiotic resistance and involve mechanisms such as the development of antibiotic-altering enzymes and multidrug efflux pumps [22].

Fascinatingly, compelling evidence substantiates the concept that commensal or environmental bacteria act as reservoirs for antibiotic resistance genes. These genes are subsequently transmitted to human pathogenic bacteria through the process of HGT. It's a well-acknowledged fact that the natural world is teeming with microorganisms that synthesize antibiotics [23]. To ensure their survival in the face of these self-produced antibiotics, these microorganisms must possess their own arsenal of antibiotic-resistant genes; without them, they would be defenseless against their own chemical creations

3.1. Antibiotics for the 21st centurys

Antibiotics in the 21st century continue to play a crucial role in modern medicine and healthcare, but their landscape has evolved significantly compared to their early counterparts from the 20th century. In this century, antibiotic development and usage are characterized by both exciting advancements and formidable challenges [24]. This introduction will provide an overview of antibiotics in the 21st century.

CLASS	CLINICALLY INTRODUCED SINCE 2000	IN PHASE II OR III TRIALS
Sulfonamides	None	None
β-lactams	Biapenem (16), ceftaroline (11), doripenem (15), ertapenem	Ceftobiprole, ceftolozane (12), razupenem (17)
Aminoglycosides	None	Plazomicin (29)
Amphenicols	None	None
Macrolides	Telithromycin (35)	Cethromycin (36), solithromycin (37)
Tetracyclines	Tigecycline (4)	Eravacycline (41), omadacycline (34)
Rifamycins	Rifaximin (19)	None

CLASS	CLINICALLY INTRODUCED SINCE 2000	IN PHASE II OR III TRIALS
Glycopeptides	Telavancin (30)	Dalbavancin (36), oritavancin (24), ramoplanin (37)
Quinolones	Balafoxacin, gemifloxacin, pazufloxacin, prulifloxacin	Avarofloxacin (35), delafloxacin (43), finafoxacin (36), JNJ-Q2, levonadifloxacin, nemonoxacin (6)
Streptogramins	None	None
Polymyxins	None	None
Oxazolidinones	Linezolid (14)	AZD5847 (38), radezolid (26), sutezolid (27), tedizolid (25)
Lipopeptides	Daptomycin (39)	Surotomycin (20)

Precision Medicine: The 21st century has seen a shift towards precision medicine, where antibiotics are increasingly tailored to the specific needs of individual patients. Advances in genomics and molecular diagnostics allow for more precise identification of pathogens and their susceptibility to antibiotics. This personalized approach minimizes the overuse of broad-spectrum antibiotics, reducing the risk of antibiotic resistance.

Antibiotic Resistance: One of the most pressing challenges of this century is the rising threat of antibiotic resistance. The misuse and overuse of antibiotics have led to the development of resistant strains of bacteria. To address this issue, researchers are working on novel strategies to combat resistance, such as the development of new antibiotics, combination therapies [42], and alternative treatments.

New Antibiotics: While the discovery and development of new antibiotics had stagnated for some time, there has been a renewed focus on finding novel antibiotic agents. Researchers are exploring new sources, such as soil bacteria, to identify potential candidates. Additionally, advances in synthetic biology and drug design are leading to the creation of antibiotics with unique mechanisms of action.

Antibiotics in the Age of Technology: The 21st century has witnessed significant technological advancements that aid in antibiotic development, including artificial intelligence, machine learning, and high-throughput screening techniques. These tools expedite the discovery process and help identify compounds with antibiotic potential more efficiently [43].

Antibiotics and Global Health: Antibiotics remain vital in the fight against infectious diseases worldwide. They are crucial tools in managing outbreaks and pandemics, as demonstrated during the COVID-19 pandemic [44]. Ensuring access to effective antibiotics in low- and middle-income countries remains a global health priority.

Antibiotic Stewardship: In response to antibiotic resistance, antibiotic stewardship programs have become widespread. These programs promote the responsible and appropriate use of antibiotics in healthcare settings to reduce the emergence of resistance.

Challenges and Ethical Considerations: The 21st century also brings ethical challenges, including the cost and availability of novel antibiotics, potential environmental impacts, and questions about equitable access to these life-saving drugs.

In conclusion, antibiotics in the 21st century continue to be essential tools in healthcare, but they face both exciting opportunities and significant challenges. Advances in precision medicine, new discoveries, and technology-driven approaches hold promise for addressing infectious diseases, while antibiotic resistance and ethical concerns require careful attention to ensure the continued effectiveness and responsible use of these vital medicines.

4. Conclusions

The importance and value of antibiotics cannot be overstated. Our reliance on them for the treatment of infectious diseases is absolute, and they should never be regarded as mere commodities. Moreover, antibiotics are indispensable for the success of complex surgical procedures, including life-saving organ transplants and the implantation of prosthetic devices. The use of antimicrobials in clinical practice represents a relatively recent development in human history, compared to the emergence of bacterial life on our planet. Consequently, the development of antibiotic resistance should be seen as a natural, adaptive response, in line with the principles of evolution put forth by Charles Darwin.

With the expanding knowledge of environmental reservoirs of resistance, it is now possible to anticipate potential resistance mechanisms to new or existing antibiotics, enabling proactive preparation for clinical challenges. It is our responsibility to launch a collective effort that fully leverages our newfound understanding and cutting-edge technologies. Neglecting this duty may lead to a future resembling the preantibiotic era for our descendants.

Acknowledgments: The authors extend their sincere appreciation to the Pharmacy Department of World University of Bangladesh and the ECE Department of HSTU Bangladesh for their consistent encouragement and support in the realm of academic research.

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