Mechanisms Of Evolution and Spread of Antimicrobial Resistance in Hospital-Acquired Pathogens: Consequences for Public Health Policy

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A THESIS

Presented to the Department of
Microbiology
program at Selinus University

Faculty of Life and Earth Science
in fulfilment of the requirements
for the degree of Doctor of Philosophy
in Microbiology

2025

Abstract

Antimicrobial resistance (AMR) is a global health crisis of increasing importance that drives the development and use of antibiotics and increases the burden of hospital acquired infections (HAIs), most notably in resource limited settings. In this review, we examine mechanisms for the emergence of AMR such as genetic mutations, horizontal gene transfer, biofilm formation and the involvement of environmental reservoirs for spread of resistant pathogens. A case is made in the article and a list of key contributors to AMR that exist in healthcare environments: inadequate infection controls, overuse of antibiotics, and unhealthy healthcare worker compliance. It explores AMR's economic and public health costs and unique impact on mortality rates, length of hospital stays, health care procedures and health equity particularly within low- and middle-income countries (LMICs). The paper points to the need for antimicrobial stewardship programs, infection prevention and control measures and innovations in diagnostic and treatment technologies like bacteriophage therapy and CRISPR Cas systems in holding back AMR. It also examines why one health must be taken to examine the drivers of resistance in the environment, human, and animal health. Finally, the article concludes that in order to tackle the hydra-like AMR a greater level of global collaboration and policy development, alongside sustainable economic incentives must be leveraged.

Keywords: AMR, CRISPR, LMIC

DEDICATION

I dedicate this research to everyone who offered unwavering guidance, encouragement, and support along my educational journey.

ACKNOWLEDGEMENTS

I would like to express my profound gratitude to all the teachers and lecturers who guided me on my educational journey.

To my extended family, friends, congregation and colleagues, I say thank you for your unwavering support, prayers and motivation throughout my educational journey.

I would like to thank my parents for their gentle but firm direction throughout my life. Their confidence in my abilities helped me to reach for the stars.

To my partner of life, Enoc, thank you for being my rock, cheerleader, confidante, best friend and mentor.

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List of ABBREVIATIONS

AMR - Antimicrobial Resistance

HAIs - Hospital Acquired Infections

MRSA - Methicillin-Resistant Staphylococcus aureus

VRE - Vancomycin-Resistant Enterococcus

CRE - Carbapenem-Resistant Enterobacteriaceae

HGT - Horizontal Gene Transfer

WGS - Whole Genome Sequencing

ASPs - Antimicrobial Stewardship Programs

IPC - Infection Prevention and Control

LMICs - Low- and Middle-Income Countries

AI - Artificial Intelligence

CRISPR-Cas - Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated System

One Health - A holistic approach integrating human, animal, and environmental health

WHO - World Health Organization

GARDP - Global Antibiotic Research and Development Partnership

MALDI-TOF - Matrix-Assisted Laser Desorption/Ionization Time-of-Flight

RLS - Resource-Limited Settings

GDP - Gross Domestic Product

WGS - Whole Genome Sequencing

MALDI-TOF - Matrix-Assisted Laser Desorption/Ionization Time-of-Flight

GAP - Global Action Plan

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats

GARDP - Global Antibiotic Research and Development Partnership.

LIST OF GLOSSARIES

1. Antimicrobial Resistance (AMR): An ability of microorganisms, including bacteria, viruses, fungi and parasites, to resist the effects of drugs once used to kill them or slow their growth, making infections harder to treat.

2. Hospital Acquired Infections (HAIs): Patients that get infections while in a healthcare facility that aren't there or already incubating when they are admitted. A lot of these infections are caused by resistant pathogens.

3. Multidrug-Resistant Pathogens: Bacteria that are antibiotic resistant, meaning they're not killed off by several types of antibiotics. Some examples of such antibiotics are Methicillin-Resistant Staphylococcus aureus (MRSA) and Vancomycin-Resistant Enterococcus (VRE).

4. Horizontal Gene Transfer (HGT): A way in which bacteria exchange genetic material, including genes that cause resistance to antibiotics, between species or strains to widen the spread of AMR.

5. Biofilm Formation: It is a group of bacteria that stick together to make what is essentially a 3D protective coat on the surface where they grow, which becomes more resistant to antibiotic treatment. Catheters, for example, are often latently infected with a biofilm.

6. Antimicrobial Stewardship Programs (ASPs): A systematized efforts within healthcare settings aimed to maximize the usage of antimicrobial agents, decrease needless use and enhance affected person outcomes without compromising the advancement of AMR.

7. Infection Prevention and Control (IPC): Healthcare setting infections can be prevented by hygiene protocols, isolation of infected patients, environmental cleaning, etc.

8. Low- and Middle-Income Countries (LMICs): One special feature of AMR is that countries where GNI per capita is lower and middle levels are often struggling with the fundamentals of health care infrastructure and access to required medical procedures, which further the effect of AMR.

9. Whole Genome Sequencing (WGS): The technique used to sequence the entire DNA of a pathogen, in order to track spread of resistant strains and identify resistance genes.

10. Artificial Intelligence (AI): The application of human intelligence simulation in machines, programmed to think and to learn, to machine intelligence simulation in the prediction of resistance patterns, the optimization of treatments and to the aid of real time surveillance in AMR.

11. CRISPR-Cas: A cutting-edge gene editing technology that enables scientists to manipulate with precision DNA. In the context of AMR, CRISPR-Cas systems may be used to target, and then edit, genes conferring pathogen resistance.

12. One Health Approach: Health involves an integrated approach to human and animal, as well as environmental health, including control of the spread of infectious diseases such as AMR.

13. Vancomycin-Resistant Enterococcus (VRE): A bacterium that has become resistant to the antibiotic vancomycin, a relatively common cause of hospital and health care acquired infections.

14. Methicillin-Resistant Staphylococcus aureus (MRSA): Bacteria that is resistant to methicillin and other antibiotics, causing troublesome skin infections and sometimes more intense ones: pneumonia, or even bloodstream infections.

15. Carbapenem-Resistant Enterobacteriaceae (CRE): Carbapenem resistant bacteria, often including Pseudomonas aeruginosa, a type of common bacteria that can cause life threatening lung infections, bloodstream infections and urinary tract infections.

16. Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF): A rapid microorganism identification (RIM) mass spectrometry technique that is used to diagnose infections and to identify resistant strains.

17. Global Action Plan (GAP): An initiative of the World Health Organization (WHO) aimed at reducing AMR incidence, maximizing antimicrobial usage, enhancing surveillance, and generating research and innovation.

18. Global Antibiotic Research and Development Partnership (GARDP): It involves a public private partnership developing new antibiotics and diagnostic tool to fight resistant infections, in particular neglected diseases.

19. Bacteriophage Therapy: As an alternative to traditional antibiotics, the potential use of viruses which specifically attack and kill bacteria (bacteriophages) in the treatment of resistant infections.

20. Antimicrobial Peptides: Proteins that are short and do have the ability to kill or inhibit the growth of microorganisms. Such bugs are being tried as possible replacements for antibiotics to treat resistant infections.

21. Antibiotic Stewardship: A program designed to drive appropriate antibiotic use, prevent excessive use, prevent AMR by evidence based prescribing practices.

22. Environmental Reservoirs: A source of environmental antimicrobial resistant organisms (such as wastewater, hospital surfaces, or soil).

23. CRISPR: The CRISPR-Cas gene editing technology, using a family of DNA sequences found in bacteria and archaea that form the basis, is being explored as a way to combat AMR, and is also being used to carry out genetic manipulation.

24. Empirical Antibiotic Use: Administration of antibiotics based on anticipated or likely pathogens rather than specific causative organism, before the causative organism is determined.

25. Carbapenemase-Producing Enterobacteriaceae (CPE): A type of bacteria that results in infections that are difficult to treat when the bacteria produce an enzyme that breaks down carbapenem antibiotics, called carbapenemase bacteria

Chapter 1

Introduction

Background of the Study

Antimicrobial resistance (AMR) is a rapidly escalating global public health threat, as defined by the World Health Organization (WHO), where microbes such as bacteria, viruses, fungi, and parasites develop resistance to antimicrobial agents used to treat infections (Ahmed et al., 2024). This resistance diminishes treatment efficacy, leading to prolonged illnesses, higher mortality rates, and increased healthcare costs. WHO identifies AMR as one of the top ten global health threats, with hospital-acquired infections (HAIs) significantly contributing to its spread (Coque, 2023). Hospitals, marked by rapid patient turnover, vulnerable populations, and extensive antibiotic use, act as hotspots for resistant pathogens such as Methicillin-resistant Staphylococcus aureus (MRSA), Carbapenem-resistant Enterobacteriaceae (CRE), and multidrug-resistant Acinetobacter baumannii. These pathogens contribute to significant morbidity, mortality, and economic costs, posing challenges to global healthcare systems. AMR arises from genetic, ecological, and epidemiological factors, including horizontal gene transfer, mutations, antibiotic-driven selective pressure, and biofilm formation, which promote pathogen persistence and transmission in healthcare environments (Prestinaci, 2015). Combating AMR demands coordinated microbiological, clinical, epidemiological, and public health approaches to limit its emergence and spread.

Statement of the Problem

AMR compromises the efficacy of antimicrobial agents vital for treating severe infections like pneumonia, meningitis, and sepsis. Hospital-acquired infections (HAIs), frequently caused by resistant pathogens, worsen this problem by restricting treatment options and escalating healthcare costs (Ho, 2024). The swift rise and spread of AMR in hospitals, fuelled by antibiotic misuse, inadequate infection control, and pathogen adaptability (e.g., biofilm formation and horizontal gene transfer), present major hurdles. These resistant pathogens jeopardize critical medical procedures, such as surgeries, cancer therapies, and organ transplants, by increasing infection risks. Despite progress in understanding AMR's genetic and epidemiological drivers, gaps persist in grasping how resistance mechanisms affect clinical outcomes and the sustained effectiveness of interventions like antimicrobial stewardship and infection prevention and control (IPC) measures (Graham, 2019). The global scope of AMR, intensified by international travel and trade, highlights the need for comprehensive, multifaceted strategies to address its impact on public health and healthcare systems.

Research Objectives /Aim

The main goal of this study is to clarify the mechanisms driving the development and spread of antimicrobial resistance in hospital-acquired pathogens and to assess their implications for clinical practice and global health policy.

Specific Objectives

1. To examine the genetic, ecological, and epidemiological factors contributing to the emergence and spread of AMR in hospital-acquired pathogens.

2. To evaluate the influence of AMR on public health policymaking, emphasizing its socio-economic and behavioural aspects.
3. To identify effective approaches for reducing AMR's impact in healthcare settings, including antimicrobial stewardship and IPC measures.

Research Questions

1. What are the primary genetic, ecological, and epidemiological mechanisms contributing to the development and spread of AMR in hospital-acquired pathogens?
2. How does AMR influence public health policymaking, particularly in terms of socio-economic and behavioural factors?
3. What are the most effective strategies for reducing the impact of AMR in healthcare settings, and how can they be implemented to ensure long-term efficacy?

Significance of the Study

The study is significant as it addresses the critical global health challenge of AMR, particularly in hospital settings where HAIs are prevalent. By elucidating the mechanisms of AMR development and spread, the research will inform evidence-based strategies to enhance antimicrobial stewardship and IPC measures. The findings will benefit healthcare practitioners, policymakers, and scholars by providing insights into bridging the science-policy-practice gap, ensuring the continued efficacy of antimicrobial agents (Adebisi, 2023). Additionally, the study's policy recommendations will support local, national, and international efforts to combat AMR, addressing its impact on healthcare systems, economic burdens, and health inequalities. The research will contribute to sustaining the effectiveness of critical medical interventions, such as surgeries and transplants, thereby fulfilling both clinical and societal needs.

Scope of the Study

The study focuses on AMR in hospital-acquired pathogens, examining the genetic, ecological, and epidemiological mechanisms driving resistance. It explores the impact of AMR on public health policy and evaluates strategies like antimicrobial stewardship and IPC measures to mitigate its effects. The research is limited to healthcare settings, with an emphasis on hospitals as key environments for AMR development and spread. While acknowledging the global nature of AMR, the study primarily draws on microbiological, epidemiological, and policy analysis, incorporating insights from existing literature and WHO frameworks. It does not cover AMR in non-hospital settings (e.g., agriculture or community environments) in depth, though it recognizes their relevance through the One Health approach.

Organization of the Study

The study is structured as follows: Chapter 1 provides the background, problem statement, objectives, research questions, significance, and scope. Chapter 2 reviews existing literature on AMR mechanisms, focusing on genetic, ecological, and epidemiological factors in hospital settings. Chapter 3 outlines the methodology, including the interdisciplinary approach combining microbiology, epidemiology, and policy analysis. Chapter 4 presents the findings on AMR mechanisms, their impact on public health policy, and effective mitigation strategies. Chapter 5 discusses the implications of these findings, offering policy recommendations and identifying areas for future research. Chapter 6 concludes the study, summarizing key insights and emphasizing the need for coordinated global action against AMR.

Chapter 2

Systematic Literature Review

Table 1. Literature Review

Aut hor(s)	ear	Findings	Research Gaps
Salam	2023	Hospital-acquired infections (HAIs) due to multidrug-resistant pathogens (MRSA, VRE, CRE) increase mortality, hospital stays, and costs.	Strategies to reduce HAIs and optimize treatment protocols for multidrug-resistant pathogens.
Merker	2020	AMR evolves through genetic mutations and horizontal gene transfer (HGT), facilitated by antibiotic use in healthcare settings.	Better understanding of HGT mechanisms and their mitigation in clinical settings.
UruÃ©n	2021	Biofilms on medical devices create barriers to antibiotics and enhance resistance through efflux pump expression.	Methods to disrupt biofilm formation and enhance antibiotic penetration.

Endale	2023	AMR is transmitted via patients, healthcare workers, and shared medical equipment, especially in resource-limited settings.	Effective interventions for AMR control in low-resource settings and healthcare worker compliance.
Hamerlinck	2023	Environmental reservoirs, such as hospital wastewater, are significant contributors to AMR spread.	Improved methods for decontaminating environmental reservoirs in healthcare settings.
Naghavi	2024	AMR increases mortality and threatens major medical procedures (surgery, chemotherapy) due to diminished treatment efficacy.	More studies on long-term economic and clinical impacts of AMR interventions.
Ahmed	2024	AMR imposes significant economic burdens, with resistant infections requiring longer hospital stays and costly therapies.	Cost-effective strategies for AMR mitigation in LMICs to reduce economic disparities.

Sharma	2022	Antimicrobial stewardship programs (ASPs) optimize antibiotic use but face challenges like resource constraints and training gaps.	Sustainable ASP implementation strategies in resource-limited settings.
Ackers et al.	2020	Hand hygiene, environmental cleaning, and genomic surveillance (e.g., WGS) are crucial for tracking and controlling AMR.	Broader adoption of genomic surveillance techniques and their cost-effectiveness analysis.
Ribes-MartÃnez	2024	Bacteriophage therapy and antimicrobial peptides offer alternative treatments; rapid diagnostics improve treatment outcomes.	Clinical trials to validate the efficacy of alternative therapies like bacteriophage therapy.
Moo et al.	2019	Public awareness campaigns and rational antibiotic use are essential, especially in LMICs with limited diagnostic access.	Behavioural studies to enhance public compliance with rational antibiotic use policies.

Muteeb	2023	Socioeconomic factors and inappropriate antibiotic use drive AMR; healthcare infrastructure investments are needed.	Innovative diagnostic tools for low-cost, rapid identification of resistant pathogens in LMICs.
Krockow	2019	Economic incentives are required to stimulate antibiotic development due to low profitability for pharmaceutical companies.	Strategies to make antibiotic development financially viable for pharmaceutical companies.
Chua	2021	WHO's Global Action Plan emphasizes reducing infection incidence, optimizing antimicrobial use, and strengthening surveillance.	Implementation challenges and monitoring of WHO's Global Action Plan in LMICs.
Littmann	2015	Ethical considerations in AMR include balancing individual patient needs with long-term social benefits.	Ethical frameworks for equitable AMR interventions, particularly in vulnerable populations.

The literature review examines the interaction of AMR and HAI, pointing to the drivers of resistance in hospital environments, key resistance mechanisms among the pathogens that establish themselves in hospitals, and the implications for public health generally. This review looks at recent studies and findings and tries to bring attention to the urgent requirement for coordinated strategies to control AMR within healthcare systems and beyond.

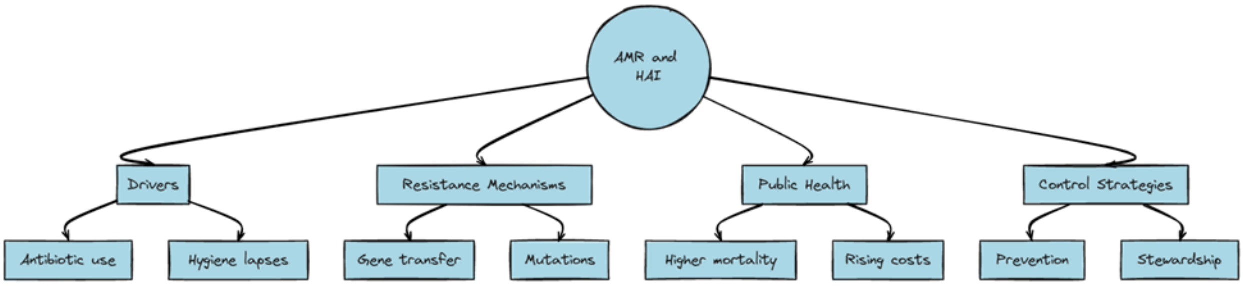


Figure 1. ***AMR and HAI***

Antimicrobial Resistance (AMR)

According to Salam (2023), hospital-acquired infections (HAIs) pose a significant threat due to antimicrobial resistance (AMR), driven by multidrug-resistant pathogens such as Methicillin-Resistant Staphylococcus aureus (MRSA), Vancomycin-Resistant Enterococcus (VRE), and Carbapenem-Resistant Enterobacteriaceae (CRE). These pathogens contribute to higher mortality rates, prolonged hospital stays, and increased treatment costs, placing substantial burdens on healthcare systems. The study explores the genetic, environmental, and behavioural factors fuelling AMR mechanisms, emphasizing their role in HAIs and implications for public health policy (Salam, 2023).

The convergence of HAIs and AMR represents a critical public health challenge, as noted by Salam (2023), with multidrug-resistant pathogens increasingly threatening global health systems. The rise of resistant strains like MRSA, VRE, and

CRE exacerbates clinical management difficulties and heightens global health security risks. Hospitals, where immunocompromised patients receive care, often serve as breeding grounds for these resistant organisms, amplifying the problem. HAIs led to severe outcomes beyond patient discomfort, with multidrug-resistant infections driving elevated mortality rates.

The resistance mechanisms of these pathogens render standard treatments ineffective, forcing reliance on stronger, often toxic, antibiotics with greater side effects, complicating clinical outcomes. Patients with multidrug-resistant infections face extended hospital stays, increased need for intensive care, and more invasive treatments, all of which inflate healthcare costs. These prolonged hospitalizations strain healthcare resources, diverting funds from other critical medical needs and perpetuating a cycle of overburdened systems and rising pathogen resistance. This financial toll not only impacts healthcare providers but also places a broader economic strain. The burden is particularly acute in developing countries, where limited access to advanced antibiotics and basic infection control measures intensifies the devastating effects of AMR. It is built up by complex interchanges among hereditary, environmental and human conductive variables. In particular, HAIs require us to understand these mechanisms to combat resistant pathogens. The genetic evolution of the pathogen is at the heart of antimicrobial resistance. Bacteria and other microorganisms have the inherent ability to evolve and do so, for the most part, in response to selective pressures including antibiotics. Resistant to specific types of antibiotics can be due to mutations in the microbial genome. Often these mutations occur spontaneously but they are more likely to appear in bacteria experiencing suboptimal levels of antibiotics. One example is that if you're not given the right form of medication, or you don't complete all the prescribed treatment courses, some bacteria can survive and continue to breed and may even become more resistant. In addition, bacteria become resistant by horizontal gene transfer that is, they can give off genetic material, including resistance genes, to other bacteria. Molecular transfer of this gene can happen by conjugation, transformation, or transduction. Bacteria acquire resistance genes, which then disseminate this resistance rapidly across different populations and the spread of resistant strains can occur in hospitals and communities.

A major important factor contributing to AMR propagation is also environmental conditions in the health care settings. Says schools of hygiene, hospitals with their high patient turnover and intensive medical procedures offer ideal conditions for resistant pathogen transmission. These bacteria can reside on surfaces, medical equipment and even air systems, creating reservoirs reinfecting patients and health care workers as well, lending credence to the need for improved practices around hand hygiene. Environmental persistence of these pathogens is caused by inadequate sterilization practice, poor hygiene and overuse of antibiotics. Add to that, these organisms can be spread environmentally from contaminated water sources, poorly disposed pharmaceuticals and the overuse of antibiotics in agriculture. An example of this would be taking antibiotics on livestock creating resistance in animals which can be passed on from animal to animal and from there consumed by humans. This environmental cross contamination has led to AMR becoming a global issue that has transcended the boundaries of hospitals encompassing entire ecosystems.

Another critical factor in spreading and amassing AMR is human behaviour. Certainly, among the most obvious illustrations of human actions that have contributed to the rise of resistant pathogens are the over prescription and misuse of antibiotics. Viruses are often targeted with antibiotics that do not help or used to treat health conditions that are capable of resolving themselves. Meanwhile, patients also fail to finish prescribed antibiotic courses, lending some survivors of such courses with partially resistant bacteria. As well as their patients, healthcare professionals may themselves contribute to the dissemination of AMR if they misuse, for example, prescribe inappropriately or fail to follow good infection control procedures. The misuse of antibiotics without proper diagnostic testing can lead to the overuse of broad-spectrum antibiotics, of which the more we use, the greater chance we have of resistance developing. On part, care givers that do not adhere to the rigorous hygiene and sanitation etiquette might inadvertently spread resistance germs from one show to another, including in the cycle of infection.

AMR implications are wide and wide range for public health. Unless they are stopped, the emergence of multidrug resistant infections could take down antibiotics that have made even routine surgical procedures risky. If antimicrobials (antibiotics) were to collapse, then the effective treatments that support organ transplants, cancer therapies, chronic condition management would bear an immense amount of pressure. The direct clinical impacts of AMR are in addition to its possible threat to roll back decades of progress in global health. But the most serious of these diseases were once controllable, such as tuberculosis and gonorrhoea, and infectious diseases are now less and less controllable and the burden of infectious disease may escalate further. Additional complicating factors are the spread of resistant pathogens across borders, leaving healthcare systems in low- and middle-income countries in a position to neither detect nor counter such emerging threats.

Figure 2. AMR Effects and Causes

AMR Evolution Mechanisms Amphiregulin (AR)

Antimicrobial resistance evolution is an extremely complex genetic process, the result of both mutations and horizontal gene transfer. By alters the target sites of antibiotics that are used to kill the target bugs, that can confer resistance in a spontaneous manner. For example, an association with resistance to fluoroquinolones and to rifampin has been shown with mutations in genes like gyrA and rpoB, respectively. Arising from the further problem of HGT facilitating the exchange of resistance genes between bacteria, HGT exacerbates this problem. Bacterial transfer of mobile genetic elements, plasmids, transposons that are often multi resistant, occurs by mechanisms including conjugation, transformation, and transduction. Such genetic exchanges are important in health care environments, where the selective pressures of antibiotic use increase the likelihood of survival of resistant strains (Merker, 2020).

Another important mechanism that increases AMR is biofilm formation. Bacterial aggregates, commonly called biofilms, are common on medical devices such as catheters and implants. These structures serve as a physical barrier that limits antibiotic penetration and help bacteria thrive metabolically dormant, better protected from treatment. Not only do biofilms increase resistance, but biofilms often increase resistance by increasing the expression of efflux pumps that actively expel antibiotics from bacterial cells. Antibacterial resistance further accelerates its' development, due to the overuse and misuse of antibiotics within hospital settings, which puts the selective pressure there (Uruén, 2021).

Antimicrobial resistance (AMR) is a complex evolutionary process driven by genetic adaptations in bacteria. The rise of resistant pathogens primarily results from spontaneous mutations and horizontal gene transfer (HGT), which work in concert to enable bacterial adaptations. These mechanisms allow bacteria to develop resistance to antibiotics, posing significant challenges to effective treatment.

One primary way bacteria develop resistance is through mutations in genes targeted by antibiotics. These mutations alter the molecular structure of bacterial components, preventing antibiotics from binding effectively or functioning properly. For example, mutations in the gyrA gene can confer resistance to fluoroquinolones, while mutations in the rpoB gene may lead to resistance against rifampin. Such spontaneous mutations can rapidly enable bacteria to resist specific antibiotics, contributing to the emergence of antibiotic-resistant strains (Merker, 2020).

The full scope of AMR extends beyond spontaneous mutations, with HGT playing a critical role in the rapid spread of resistance. Through HGT, bacteria exchange genetic material, including antibiotic resistance genes, via conjugation, transduction, or transformation. Conjugation involves direct cell-to-cell transfer of plasmids—circular DNA molecules often carrying resistance genes. Transformation occurs when bacteria take up naked DNA from their environment, while transduction involves the transfer of genetic material via bacteriophages, viruses that infect bacteria. Mobile genetic elements, such as plasmids and transposons, enable bacteria to acquire resistance to multiple antibiotics simultaneously, accelerating the spread of AMR.

In healthcare environments, the frequent and often inappropriate use of antibiotics creates significant selective pressure, favouring the survival and proliferation of resistant bacterial strains. High antibiotic usage, combined with patient turnover, provides ideal conditions for the spread of resistant pathogens. Close proximity, invasive procedures, and recurring antibiotic therapy in hospitals facilitate the exchange of resistance genes among bacteria, amplifying AMR prevalence (Merker, 2020). This selective pressure increases the likelihood of resistant bacteria thriving, particularly among vulnerable patients with infections.

Biofilm formation presents a significant challenge in treating AMR infections. Biofilms are bacterial aggregates encased in a protective extracellular matrix, often forming on medical devices like central venous catheters, implants, and ventilators. Bacteria within biofilms are more resistant to antibiotics than free-floating (planktonic) bacteria due to the physical barrier provided by the biofilm matrix, which shields antibiotics from reaching the bacteria. Additionally, bacteria in biofilms can enter a metabolically dormant state, rendering them less susceptible to antibiotics that target actively dividing cells. Dormant bacteria can survive antibiotic treatment and later cause recurrent infections when antibiotic pressure decreases.

The expression of efflux pumps further enhances bacterial resistance, particularly in biofilms. Efflux pumps are proteins that actively expel antibiotics from bacterial cells, reducing the intracellular concentration of the drug and diminishing its effectiveness. Overexpression of efflux pumps is often associated with resistance to multiple antibiotic classes, complicating treatment efforts. This mechanism significantly contributes to the persistence and spread of AMR, especially in chronic infections or those associated with implanted medical devices (Uruén, 2021).

Overuse and misuse of antibiotics in hospitals are major drivers of AMR. Antibiotics are often prescribed unnecessarily, such as for viral infections where they are ineffective, or for mild conditions that do not require them. Incomplete antibiotic courses, where patients fail to complete the prescribed regimen, allow partially resistant bacteria to survive and proliferate. Inadequate infection control practices, crowded hospital conditions, and frequent use of invasive devices further promote the spread of resistant bacteria. These factors create an environment conducive to the transmission of resistant pathogens, particularly among immunocompromised patients, leading to healthcare-associated infections (HAIs) with increased morbidity, mortality, and costs.

The evolution of AMR results from a complex interplay of genetic mechanisms, environmental factors, and human behaviour. Spontaneous mutations, horizontal gene transfer, biofilm formation, and antibiotic overuse all contribute to the emergence and spread of resistant bacteria. Addressing AMR requires a comprehensive strategy, including reducing unnecessary antibiotic use, improving infection control practices, and developing new antibiotics and alternative therapies. Additionally, mitigating environmental factors, such as antibiotic overuse in agriculture and poor sanitation, is critical to preventing further AMR development.

Resistant Pathogen Dissemination in Healthcare

In the healthcare settings, AMR is spread through different pathways, including patient to patient transmission, healthcare workers and environmental reservoirs. In crowded or resource-limited facilities, vector transmission is usually facilitated by shared medical equipment, while direct transmission is often through shared medical equipment or inadequate isolation measures. Cross contamination between patients, however, can occur when healthcare workers fail to comply with hand hygiene protocols, and healthcare workers themselves act as an important bridge in the dissemination of resistant pathogens (Endale, 2023).

Significant contributors to persistence and spread of AMR include environmental reservoirs, such as hospital surfaces, water systems and medical devices. Fittingly, hospital wastewater has been studied to be contaminated with multidrug resistant organisms, including carbapenemase producer Enterobacteriaceae highlighting the rationale for eradicating these pathogens. Factors that further influence outbreak of resistant pathogens include patient movement, usage patterns of antibiotics and lapses in infection control. Also, because of limited access to diagnostic tools, suboptimal infection prevention, and a higher prevalence of empirical antibiotic use, which has increased precisions and therefore the resistance, low- and middle-income countries (LMICs) in particular face difficulties in controlling AMR (Hamerlinck, 2023).

Vector transmission of antimicrobial resistance (AMR) is a significant concern in healthcare settings, particularly in crowded or resource-limited facilities. Shared medical equipment, such as catheters, ventilators, and surgical instruments, often becomes contaminated, facilitating the spread of resistant bacteria between patients. Inadequate sterilization of medical devices or insufficient infection control measures can create direct conduits for multidrug-resistant organisms to spread across multiple patients. Contaminated surfaces or equipment further exacerbate direct transmission of AMR pathogens, underscoring the critical need for robust sterilization and disinfection protocols to mitigate risks.

Resistant pathogens are not only transmitted patient-to-patient but are also significantly disseminated by healthcare workers. Close contact between patients and healthcare workers in healthcare settings positions workers as key vectors for AMR transmission, especially when hygiene protocols, such as hand washing, are not strictly followed. Common practices leading to cross-contamination include healthcare workers failing to wash their hands thoroughly between patient interactions or improperly handling complex equipment. Strict adherence to infection control protocols is vital, as the movement of healthcare workers between patients increases the likelihood of transferring resistant pathogens within a facility. Healthcare workers serve as a critical bridge in the transmission of resistant organisms, and studies indicate that failure to follow standard infection prevention guidelines—such as hand washing, wearing appropriate personal protective equipment (PPE), and disinfecting surfaces between patient encounters—greatly facilitates the spread of AMR pathogens (Endale, 2023).

Environmental reservoirs in healthcare settings, particularly in high-risk areas like intensive care units (ICUs), contribute significantly to the persistence and spread of AMR. Surfaces such as countertops, doorknobs, bedrails, and other high-contact areas can harbour resistant pathogens, maintaining their presence between contamination and patient infection. Hospital water systems, including sinks, faucets, and showerheads, are also potential reservoirs, with studies identifying contamination by carbapenem-producing Enterobacteriaceae (CPE), a family of resistant pathogens capable of overcoming powerful antibiotics like carbapenem (Hamerlinck, 2023). Additionally, medical devices, particularly invasive ones like catheters and endotracheal tubes, can become colonized by resistant bacteria if not properly sterilized. These devices are prone to biofilm formation, which makes bacteria more difficult to eliminate, compounding the risk of device-related infections.

The movement of patients within and between healthcare facilities is another key factor in the persistence and spread of AMR. Resistant pathogens can be transferred through shared equipment or by healthcare workers moving between units, leading to cross-contamination. High patient turnover or prolonged hospital stays, particularly in ICUs or long-term care facilities, exacerbate this issue. The failure to isolate infected patients or properly clean medical devices further amplifies the risk of outbreaks, especially in high-workload settings where infection prevention training may be inadequate (Endale, 2023).

Antibiotic usage patterns significantly influence the evolution and spread of AMR. Overuse and misuse of antibiotics, particularly in hospitals, create selective pressure that fosters the development of resistant organisms. Empirical antibiotic use—prescribing broad-spectrum antibiotics based on symptoms rather than a specific diagnosis—can accelerate resistance, as these antibiotics may not effectively target the causative pathogen, allowing resistant bacteria to survive and proliferate. Inadequate diagnostic tools further complicate accurate pathogen identification, leading to inappropriate antibiotic selection and increased resistance.

The spread of AMR is particularly challenging in resource-limited settings, such as low- and middle-income countries (LMICs). Limited access to diagnostic tools delays the identification of resistant pathogens, often resulting in reliance on empirical antibiotic treatments. This practice, coupled with overuse due to a lack of alternatives or accurate diagnostics, promotes resistance. Suboptimal infection prevention measures, including poor hand hygiene, inadequate sanitation, and insufficient use of PPE, create environments where AMR thrives. Additionally, limited access to care in these settings can lead to delayed or inappropriate treatment, further driving resistance. The lack of regulatory oversight over antibiotic sales and use, combined with poor infection control measures in both community and healthcare settings, accelerates the spread of AMR in LMICs (Hamerlinck, 2023).

Public Health Policy Consequences of AMR

AMR has far reached clinical implications that increase morbidity and mortality along with diminished treatment efficacy. Mortality rates for infections caused by resistant pathogens, including bloodstream infections resulting from CRE, exceed 50%. Moreover, AMR threatens the success of major medical procedures such as surgery, organ transplants and cancer chemotherapy, which rely on prophylactic antibiotics to prevent infections (Naghavi, 2024).

AMR is equally large in terms of economic burden. In particular, resistant infections are not easily cured and dependent on additional diagnostics tests, more extended hospital stays and expensive second line therapies. Left unchecked, the AMR crisis would cost the global economy well over 4 percent of its GDP by 2050, according to a World Bank report. In addition, AMR worsens health inequalities globally, particularly in LMICs. Where healthcare infrastructure is limited and antibiotic stewardship not rate, resistant infections tend to be higher than elsewhere and over burden healthcare systems which are already stretched (Ahmed, 2024).

Prevention of AMR in Hospital Settings

AMR in the hospital setting requires addressing a multifaceted approach: antimicrobial stewardship programs (ASPs), infection prevention and control (IPC) measures and robust surveillance. ASPs are intended optimizing antibiotic use by reducing selective pressure on resistance and improving patient outcomes. These programs contain core components of implementing evidence-based guidelines for prescribing antibiotic and conducting audits to give prescribers feedback. Although challenges such as resource constraints, lack of training, and professional resistance to ASPs are among the challenges that hinder the effectiveness of ASPs (Sharma, 2022),

Just as important as IPC measures are in controlling the spread of resistant pathogens. Hand hygiene procedures have been shown to be successful techniques in reducing nosocomial transmission when the number of procedures is rigid and environmental cleaning and isolation of infected patients are accomplished. Studies suggest that their compliance with hand hygiene protocols is drastically decreasing rates of infection in their healthcare facilities. Because of their importance in tracking trends of AMR and informing public health strategies, surveillance and monitoring systems are essential. Thanks to advances in genomic surveillance, such as whole genome sequencing (WGS), we've increased our understanding of resistance mechanisms and transmission pathways and have been able to target interventions (Ackers et al., 2020).

Completely AMR combating also requires research and innovation. As antidrug resistant infection is on rise bacteriophage therapy and antimicrobial peptides emerged as alternative therapies. Timely identification of resistant pathogens is enabled with rapid diagnostic tools, including matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, improving treatment outcomes and reducing the use of broad-spectrum antibiotics without benefit. Addressing the root causes of AMR requires policy innovations, for example, regulating antibiotic use in agriculture, and incentives to develop new antibiotics (Ribes-Martínez, 2024).

Antimicrobial resistance (AMR) in hospital settings poses a significant global threat, requiring a holistic and multi-faceted approach. Hospitals, as high-risk environments with intensive antimicrobial use, provide an ideal breeding ground for the emergence and spread of resistant pathogens. Effective strategies to combat AMR include antimicrobial stewardship programs (ASPs), robust infection prevention and control (IPC) programs, surveillance systems, new treatment interventions, and policy changes addressing the root causes of resistance. Combining these interventions is essential to mitigate the threat of AMR and preserve the efficacy of antibiotics for future generations.

Antimicrobial stewardship programs (ASPs) are a cornerstone of efforts to combat AMR. These programs aim to reduce unnecessary antibiotic exposure in clinical settings, thereby decreasing the development of resistance. The goal of ASPs is to enhance patient outcomes by promoting sensible antibiotic use, minimizing side effects, and reducing the frequency of resistant infections. ASPs implement evidence-based guidelines for prescribing antibiotics, ensuring they are used only when necessary and selecting the optimal drug, dose, and duration to reduce selective pressure on pathogens—a major driver of AMR. Regular audits with feedback to prescribers, reviewing antibiotic prescriptions for adherence to clinical guidelines, and promoting specific antibiotics further support appropriate prescribing practices and improve patient outcomes.

Despite their proven benefits, ASPs face significant challenges in hospital environments. Resource constraints, particularly in low-resource settings, can limit their implementation. Additionally, a lack of training for healthcare providers in antimicrobial stewardship and resistance management diminishes the impact of these programs. Resistance from prescribers, concerns about clinical autonomy, and limitations in prescribing practices can also hamper success. Addressing these challenges requires continuous education, institutional support, and strong leadership from clinicians championing practices aligned with antimicrobial stewardship goals.

Infection prevention and control (IPC) is critical in limiting the spread of AMR in hospitals. Effective IPC practices reduce the transmission of resistant pathogens, particularly in facilities with high patient turnover or frequent invasive procedures. Hand hygiene, including the use of alcohol-based sanitizers or soap and water, is a fundamental and proven IPC measure to prevent the spread of microorganisms, including antibiotic-resistant bacteria. Studies consistently show that compliance with hand hygiene protocols correlates with reduced healthcare-associated infections (HAIs), including those caused by resistant pathogens. However, achieving high compliance rates remains challenging, especially in crowded or understaffed settings. Increased awareness, regular training, and audit systems can improve hand hygiene practices among healthcare workers.

Beyond hand hygiene, effective IPC strategies include environmental cleaning and patient isolation. Thorough cleaning of high-touch areas, such as patient rooms, operating theatres, and ICU units, is essential to reduce the environmental load of resistant bacteria. Effective cleaning protocols focusing on disinfecting surfaces, equipment, and medical devices help minimize cross-contamination risks. Isolating patients infected with resistant pathogens, such as Methicillin-resistant Staphylococcus aureus (MRSA) or Vancomycin-resistant Enterococcus (VRE), is another critical strategy to prevent transmission to other patients.

Surveillance systems are vital for tracking the spread of AMR and identifying trends in resistance patterns to inform targeted interventions and public health strategies. Without effective surveillance, detecting emerging resistant pathogens or assessing the impact of infection control measures is impossible. Advances in genomic surveillance, particularly whole-genome sequencing (WGS), have revolutionized the understanding of resistance mechanisms by identifying resistant genes, mutation hotspots, and transmission pathways. Real-time surveillance data enable healthcare providers to target infections with specific interventions, tailor treatment strategies, and implement effective infection control measures. Additionally, surveillance data guide public health policies and decisions on antibiotic use and infection control practices, helping detect local outbreaks or the spread of specific resistant strains for rapid containment.

As AMR continues to rise, traditional antibiotics are becoming less effective, necessitating the development of alternative therapies. Bacteriophage therapy, which uses viruses that target specific bacteria, is a promising area of research. Bacteriophages offer advantages over traditional antibiotics, including bacterial strain specificity and a lower likelihood of resistance development. Antimicrobial peptides (AMPs), naturally occurring substances that disrupt bacterial cell membranes, are another potential therapeutic avenue. Alongside new therapies, advanced diagnostic technologies, such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, enable rapid identification of pathogens and their resistance profiles, allowing for more targeted treatments. These technologies help clinicians quickly detect resistant infections, reduce reliance on broad-spectrum antibiotics, and improve therapeutic outcomes.

AMR Mitigation—Future Directions

With growing knowledge about antimicrobial resistance (AMR), there are many roads to innovative solutions. Yet, there is still much work to be done in closing knowledge gaps and turning research into actionable strategies. The successful integration of mechanistic understanding into molecular biology, healthcare delivery, and global policy will be the focus of future directions.

Genomic technologies have recently advanced the fight against AMR. Whole genome sequencing (WGS) has transformed how we identify and track resistance genes and has improved our ability to understand how these genes spread between pathogen hosts. By analysing the genetic makeup of resistant bacteria, researchers can identify which mutations or mobile genetic elements are responsible for resistance. This data is crucial for the targeted development of antimicrobial agents and diagnostics. CRISPR-Cas systems also offer great promise in combating AMR. In experiments, this gene-editing technology has been used to "disrupt" resistance genes in certain bacteria, making them susceptible to antibiotics again. Although CRISPR-based therapies are still in early development, they hold potential for clinical applications targeting multidrug-resistant pathogens. Additionally, research into synthetic biology aims to engineer bacteria with antimicrobial properties, which could lead to new tools for infection control.

The environmental dimension of AMR is increasingly recognized as a critical factor in its global spread, presenting new challenges for understanding and addressing resistance. Resistance genes, found in agricultural runoff, untreated industrial effluents, and wastewater, act as reservoirs that can transfer to human pathogens. Addressing these challenges requires a One Health approach that integrates human, animal, and environmental health. Effective management of waste from healthcare and pharmaceutical industries, along with strategies like membrane bioreactors and ozonation, has shown promise in removing antibiotics and resistant bacteria from effluents. Policies should enforce stricter disposal regulations for antimicrobial agents and promote sustainable practices in agriculture and industry to mitigate environmental AMR.

Human behaviour significantly contributes to the development and spread of AMR, particularly through the misuse of antibiotics, such as over-the-counter purchases without prescriptions, which is especially prevalent in low- and middle-income countries (LMICs). To promote rational antibiotic use, public awareness campaigns targeting patients, healthcare workers, and policymakers are essential (Moo et al., 2019). These efforts aim to address behavioural and socioeconomic factors driving AMR and foster more responsible antibiotic use globally.

What educational initiatives should focus on is that unnecessary antibiotic use is risky and that courses designed are to be finished (that means no stopping mid-course). Indeed, AMR interventions are also dependent on socioeconomic factors (Muteeb, 2023).

Empirical and somewhat inappropriate antibiotic use is common in resource constrained settings that often do not have access to the essential diagnostic component. Investments in healthcare infrastructure, especially in LMICs, are essential to allow a correct diagnosis and evidence-based treatment. Funding for capacity building programs related to AMR should be prioritized by international organizations including the World Health Organization (WHO) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Antibiotic development Economic Incentives A stagnant pipeline of new drugs has been defined by the economic model for antibiotic development which for so long has been unattractive to the pharmaceutical companies (Krockow, 2019).

By using antibiotics sparingly to preserve their efficacy, they get lower financial returns compared to chronic disease medications. An innovative set of economic incentives will be needed to drive investment in antibiotic research and development to address this market failure. Proposals to push and pull antibiotic innovation have been made. Grants and subsidies, for example, make it cost cheaper to do research and development. Financial incentives for bringing new antibiotics to market come from pull mechanisms such as market entry rewards, advanced purchase commitments, or other reward mechanisms. There are examples of public-private partnership like the Global Antibiotic Research and Development Partnership (GARDP) showing the benefits of mixed approach in fighting AMR. Artificial Intelligence and Big Data integration AI and big data analytics' integration into AMR research and management have strongly demonstrated its promise. Using large genomic sequences, clinical records, and epidemiological data, AI algorithm can also be used to predict the resistance patterns and optimized treatment regimens. For example, to find potential candidate resistance genes in bacterial genomes and predict evolutions from resistant mechanisms. Real time surveillance of the AMR trends also facilitated by big data platforms, which make public health interventions better. Data from many sources, e.g. hospital electronic medical records, environmental monitoring systems and global AMR databases can be integrative to identify hotspots and guide resource allocation. Data sharing and interoperability are highlighted as critical ingredients for the global AMR surveillance work of collaborative initiatives like the Fleming Fund and Antimicrobial Resistance Alliance. Enhancing Global Policy Framework Another obvious area for global collaboration involves the transnational nature of AMR. Coordinating efforts across countries and sectors are largely dependent on international agreements and frameworks.

The Global Action Plan on Antimicrobial Resistance, launched by the WHO in 2015, provides a roadmap for AMR mitigation through five strategic objectives: By reducing infection incidence, improving antimicrobial use, strengthening surveillance and research, improving awareness and understanding of AMR, reducing antimicrobial use, optimizing antimicrobial use and ensuring sustainable investment. To implement these objectives, sustained political commitment and resource allocation is required. LMICs must rely on high income countries to develop their capacity in AMR management by macro infrastructure development, macro workforce training, and macro technology transfer. Politicians should also look at the overuse of antibiotics in agriculture, the main driver of resistance that remains, and reform trade and regulatory policies to deal with that (Chua, 2021).

AMR Management – Ethical considerations.

Although, the ethical dimensions of AMR management are often ignored, but they are important elements creating effective and equitable interventions. These ethical dilemmas arise because clinicians have to worry about their hands on patient care and their goals for antimicrobial efficacy over the long term. For example, denying antibiotics to people with suspected but unproven bacterial infections can harm individual patients themselves despite being socially beneficial by decreasing selective pressure. Access to cheap and efficient antibiotics for vulnerable sections of the population and addressing disparities in the sphere of healthcare infrastructure and diagnostic equipment, is a matter of morality. Impact of AMR Interventions Evaluated The effectiveness of AMR interventions and smart decisions for future strategies will be evaluated in robust evaluation frameworks. Clinical indicators as measures of outcome should include infection rates, prevalence of resistance, treatment success and economic and social outcomes. High quality evidence from longitudinal studies and randomized controlled trials can be provided on the impact of some of such interventions like antimicrobial stewardship programs or rapid diagnostic tools (Littmann, 2015).

Chapter 3

Data and Methodology

Analysis

Antimicrobial resistance (AMR) is one of the world's most pressing public health threats, with the potential to reverse decades of medical progress. The research comprehensively reviews AMR factors, their influence on healthcare systems, and the urgent need for systemic solutions. It illuminates biological, clinical, and socioeconomic aspects of AMR, though some areas could benefit from deeper exploration or clarification.

The research highlights how AMR evolves through genetic mutations and horizontal gene transfer (HGT). While HGT is noted as a key facilitator of AMR in hospital settings, the discussion could delve deeper into its mechanisms across different bacterial species. For instance, the genetic and behavioural differences between hospital-acquired pathogens and those in the wider community underscore the need for tailored public health responses. Further exploration of HGT in specific contexts, such as hospital-acquired infections, would strengthen the analysis.

Biofilm formation is correctly identified as a critical contributor to AMR in healthcare settings. However, biofilms also play a significant role in chronic infections outside hospitals, such as in cystic fibrosis or chronic wound infections. A more refined discussion of biofilms, considering their impact across diverse patient populations, is necessary to fully address their contribution to AMR.

The study thoroughly covers AMR spread in hospitals, particularly through patient-to-patient transmission and deficient infection control measures. It notes that healthcare workers can act as vectors for resistant pathogens. However, the paper falls short in exploring psychological and organizational factors—such as time pressures, understaffing, and insufficient training—that lead to lapses in hand hygiene and infection control protocols. Addressing these barriers beyond mere lack of knowledge is critical, especially in resource-limited settings (RLS).

The research could be strengthened by discussing environmental reservoirs, such as hospital wastewater and surfaces, which contribute to AMR spillover into communities. A stronger link between AMR mitigation and environmental management practices would enhance the article's scope, emphasizing the need for integrated strategies to control resistant pathogens beyond healthcare facilities.

The research details the economic and social consequences of AMR, including increased mortality, prolonged hospital stays, and significant burdens on health systems. It compares AMR's impact to air pollution, noting that while air pollution causes an estimated 3.8 million deaths globally, AMR accounts for 0.1 million deaths in advanced countries, with a disproportionate impact in low- and middle-income countries (LMICs). The interplay between non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotic stewardship is highlighted, but underdeveloped infrastructure in LMICs exacerbates health inequalities. A deeper analysis of policy interventions, such as the World Health Organization's Global Action Plan on AMR, and case studies of successful or failed interventions would provide more granular insights.

Antimicrobial Stewardship Programs (ASPs) and Infection Prevention and Control (IPC) measures are discussed as key strategies to optimize antibiotic use and reduce resistant pathogen transmission. However, the article does not fully address the challenges of implementing these programs in resource-constrained settings, where access to rapid diagnostics and genomic sequencing is limited. A focused discussion on how international organizations like the WHO can support LMICs in enacting ASPs and IPC measures would add value. Additionally, the integration of technologies like AI and big data for real-time AMR surveillance and trend prediction is underexplored but holds transformative potential.

The research highlights promising alternatives to traditional antibiotics, such as bacteriophage therapy and antimicrobial peptides. While experimental results are encouraging, the paper could provide more detail on the clinical development of these therapies, including regulatory, safety, and efficacy challenges. Similarly, CRISPR-Cas systems are noted as a potential tool to combat AMR, but their real-world implementation raises ethical and logistical concerns that warrant further discussion.

Environmental factors, such as antibiotic use in agriculture and contamination of water sources, are significant drivers of AMR. The article could elaborate on the One Health approach, which integrates human, animal, and environmental health to address resistance holistically. Strategies to reduce antibiotic use in agriculture, alongside healthcare interventions, deserve greater attention.

In LMICs, widespread over-the-counter antibiotic use and cultural attitudes toward antibiotics contribute to AMR. The article could expand on the role of public awareness campaigns and the socioeconomic disparities that drive inappropriate antibiotic use. Understanding these structural drivers is critical for designing effective interventions to combat AMR in these settings.

Research Methodology

In the context of this work, a systematic literature review (SLR) is conducted to study hospital pathogens' antimicrobial resistance (AMR). The study seeks to contribute a structured and comprehensive examination of existing research on the mechanisms driving AMR, its prevalence, and the effectiveness of interventions, using the SLR approach. The methodology entails collating and aggregating information from credible and applicable sources to ensure a fair and evidence-informed understanding of AMR in hospital settings.

The research begins with the identification of specific research questions related to key areas of AMR in hospital settings. These questions guide the review process, ensuring alignment with the study's purpose. The questions address the major objectives: understanding the mechanisms of AMR, identifying pathogen profiles, examining prevalence trends, and assessing strategies for controlling AMR. This focused approach ensures a clear and targeted review.

The SLR follows a rigorous methodology to identify relevant studies in established academic databases such as PubMed, Scopus, Web of Science, and Google Scholar. Specific search terms, including antimicrobial resistance, hospital-acquired infections, horizontal gene transfer, multidrug-resistant pathogens, and public health interventions, are carefully selected to capture the multifaceted nature of AMR. Boolean operators are used to enhance the quality and quantity of search results, retrieving relevant studies while minimizing irrelevant ones. The review covers research from the last 15 years to reflect contemporary developments, while foundational studies of historical significance are included for broader context.

The review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and reproducibility. Studies undergo a rigorous inclusion and exclusion process. Peer-reviewed studies on AMR in hospital settings that provide data on resistance mechanisms, pathogen profiles, or intervention outcomes are included. Reports from reputable organizations, such as the World Health Organization (WHO) and the Centres for Disease Control and Prevention (CDC), are also incorporated. Titles and abstracts are reviewed to eliminate duplicates, articles not meeting quality criteria, or those lacking relevance. Full-text articles are then assessed to ensure they meet strict inclusion criteria, excluding studies in non-hospital settings or those with insufficient methodological details.

Data extraction is systematic, using a predesigned form based on a thematic framework aligned with the study's objectives. Extracted data include study titles, authors, publication year, research design, sample size, study location, key findings, and conclusions, as well as specific information on AMR mechanisms, pathogens, prevalence trends, and intervention outcomes. The extracted data are synthesized through thematic analysis, organized into themes of resistance mechanisms, intervention strategies, and prevalence trends. Critical appraisal evaluates the methodological quality, relevance, and contribution of each study, giving more weight to robust designs while critically analysing studies with limitations for potential biases.

Potential biases and limitations are carefully considered to maintain research integrity. For instance, publication bias is mitigated by designing a broad search strategy that includes grey literature and institutional reports not indexed in academic databases. Studies in multiple languages are included if they meet the inclusion criteria. This comprehensive approach ensures a wide and objective collection of evidence.

The findings are presented in a clear and structured manner, organized by themes with detailed descriptions of resistance mechanisms, pathogen profiles, prevalence trends, and intervention outcomes. Key findings are summarized using tables, charts, and diagrams to enhance clarity. The discussion situates the findings within the broader research landscape, highlighting implications for policy and practice. The synthesis identifies patterns, gaps, and areas of consensus, providing a detailed understanding of AMR in hospital settings and offering actionable recommendations to address this global health challenge.

The SLR provides a comprehensive and transparent exploration of AMR in hospital settings, drawing on credible secondary data from peer-reviewed studies and institutional reports. By adhering to rigorous protocols and PRISMA guidelines, the study yields reliable and actionable insights. The findings not only reflect the current state of knowledge but also guide future research and policy development to combat AMR effectively.

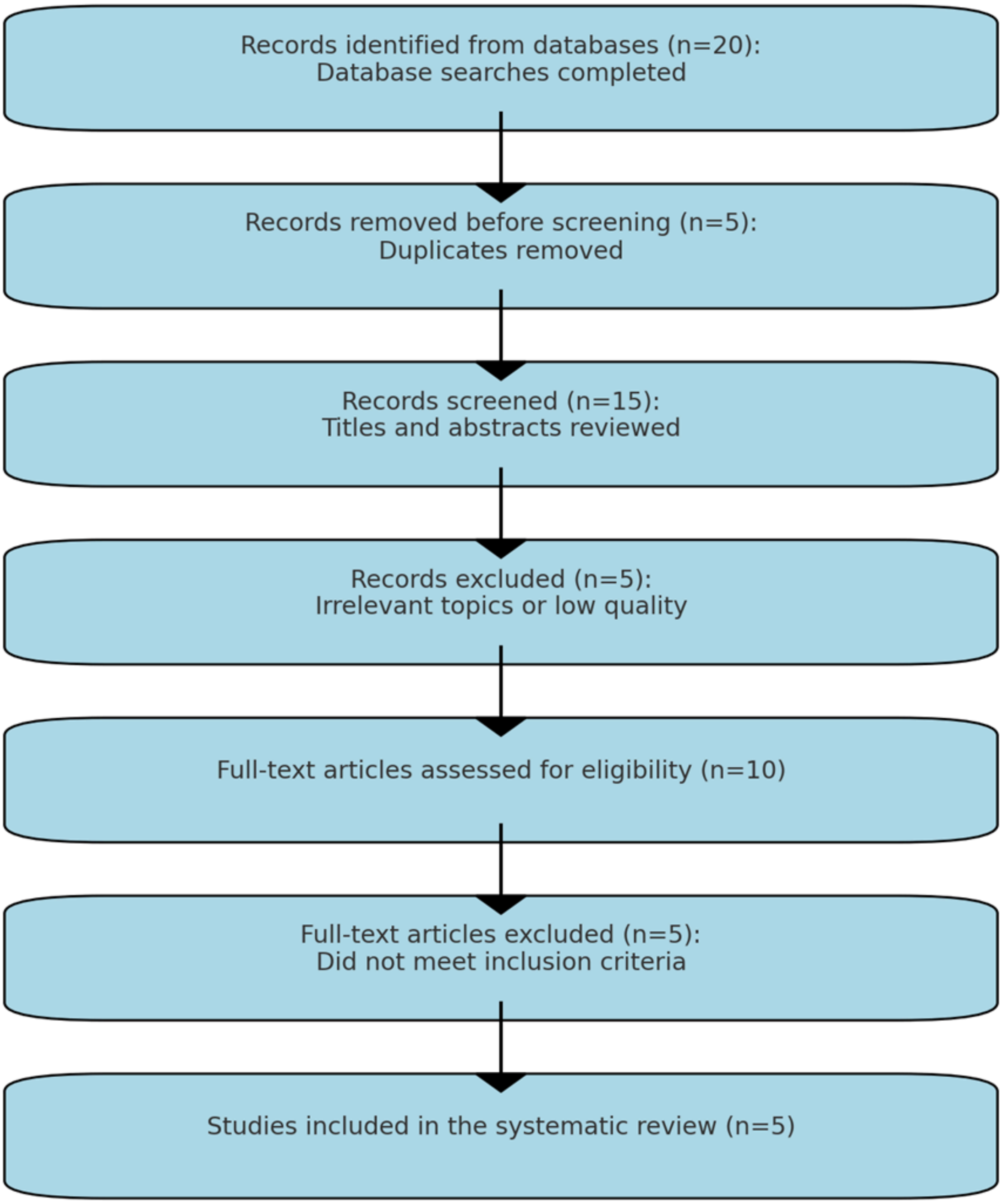


Figure 3*. Systematic Literature Review Process*

Thematic Synthesis

Table 2. ***Key Themes***

Theme	**Sub-theme**	**Key Findings**	**Research Gaps**
Genetic & Mechanistic Factors	Mutation & Horizontal Gene Transfer (HGT)	Mutations in bacterial genes (e.g., *gyrA*, *rpoB*) lead to resistance to antibiotics like fluoroquinolones and rifampin. HGT facilitates the transfer of resistance genes through plasmids, transposons, and other mobile genetic elements, exacerbating AMR.	Need for more research on specific genetic mutations linked to resistance and their global spread.
	Biofilm Formation	Biofilms serve as physical barriers that protect bacteria from antibiotics. They are common on medical devices and contribute to chronic infections. Biofilms increase resistance by enhancing efflux pump activity and reducing antibiotic penetration.	Lack of effective therapies to prevent or disrupt biofilm formation in clinical settings.
	Efflux Pumps	Efflux pumps actively expel antibiotics from bacterial cells, increasing their resistance. This mechanism is enhanced by	Need for innovative drugs or technologies that inhibit efflux pump

		biofilm formation, which further protects bacteria from antibiotics.	activity in resistant pathogens.
Spread in Healthcare Settings	Nosocomial Infections (HAIs)	Hospital-acquired infections (e.g., MRSA, VRE, CRE) are major sources of AMR spread. These infections lead to longer hospital stays, higher treatment costs, and increased mortality.	More research is needed on how to reduce HAIs in resource-limited settings and enhance infection control.
	Transmission Pathways	AMR spreads through patient-to-patient transmission, healthcare workers, and environmental reservoirs. Poor infection control practices, including inadequate hand hygiene and improper isolation of infected patients, facilitate AMR transmission.	Research is needed on effective interventions to break transmission chains in healthcare settings.
Public Health & Economic Impact	Increased Morbidity & Mortality	AMR causes higher mortality rates, particularly from bloodstream infections caused by CRE and other resistant pathogens. Resistant infections lead to more complications and extended hospital stays.	Need for more global data on the true scale of AMR's impact on morbidity and mortality, particularly in LMICs.
	Economic Burden	AMR increases the cost of healthcare due to	More studies on the long-term

		longer hospital stays, the need for expensive second-line treatments, and additional diagnostics. The economic burden is significant and could exceed 4% of global GDP by 2050.	economic impact of AMR on health systems, especially in LMICs.
Mitigation Strategies	Antimicrobial Stewardship Programs (ASPs)	ASPs aim to optimize antibiotic use and reduce selective pressure, improving patient outcomes. Challenges to ASPs include limited resources, lack of training, and resistance from healthcare providers.	Research into the effectiveness of ASPs in LMICs and how to overcome barriers to their implementation.
	Infection Prevention & Control (IPC)	Hand hygiene, environmental cleaning, and patient isolation are effective in controlling the spread of AMR. Non-compliance with IPC measures is a major factor in the spread of resistant pathogens in healthcare settings.	Need for better compliance monitoring and more research on IPC effectiveness in diverse healthcare settings.
	Surveillance & Rapid Diagnostics	Whole genome sequencing (WGS) and rapid diagnostic tools like MALDI-TOF are instrumental in identifying resistant pathogens quickly, enabling more targeted treatments	Expansion of genomic surveillance and the development of low-cost diagnostic tools for AMR detection.

		and reducing unnecessary use of broad-spectrum antibiotics.	
Policy, Regulation, & Global Collaboration	Global Action Plans	The WHO's Global Action Plan aims to reduce AMR by improving infection prevention, optimizing antibiotic use, and strengthening surveillance. International collaboration is essential to address the global spread of AMR.	Need for stronger international frameworks to monitor and regulate AMR at the global level.
	One Health Approach	The One Health approach recognizes the interconnection between human, animal, and environmental health in addressing AMR. Agricultural runoff, wastewater, and industrial effluents are key contributors to the spread of AMR.	More research on the integration of the One Health approach in global AMR management strategies.
Ethical & Social Considerations	Access to Antibiotics	AMR is exacerbated by disparities in access to antibiotics, particularly in LMICs, where misuse and overuse are common. Improving access to diagnostics and rational antibiotic use are crucial in mitigating AMR.	Research into policies to improve access to antibiotics while preventing misuse in under-resourced regions.

	Misuse of Antibiotics	Over-the-counter sales and insufficient regulations contribute to the overuse and misuse of antibiotics, particularly in LMICs. Awareness campaigns are needed to reduce self-medication and misuse.	Studies on the effectiveness of public awareness campaigns on reducing antibiotic misuse in different regions.
	Socioeconomic Factors	Socioeconomic factors such as poverty, poor healthcare infrastructure, and lack of education exacerbate AMR in LMICs. Interventions must address these root causes in addition to antimicrobial use.	Research into cost-effective interventions tailored to different socioeconomic settings to tackle AMR.
Innovative Solutions	New Antibiotics Development & Economic Incentives	The antibiotic development pipeline is stagnant due to economic disincentives for pharmaceutical companies. Financial incentives, such as grants and subsidies, are necessary to stimulate investment in new antibiotics.	Need for innovative economic models that incentivize antibiotic R&D, especially for neglected resistant strains.
	AI & Big Data in AMR	AI and big data analytics can be used to predict resistance patterns, optimize treatment regimens,	More research into integrating AI and big data into

		and improve surveillance. Integration of clinical and genomic data can enhance the fight against AMR.	real-time AMR surveillance and treatment optimization.
AMR Management in Low-Income Settings	Infrastructure & Diagnostic Capacity	In LMICs, limited healthcare infrastructure and diagnostic capacity contribute to empirical and inappropriate antibiotic use. Investments in these areas are critical to reduce AMR.	Research into scalable solutions to improve diagnostic capacity and healthcare infrastructure in LMICs.
	International Support	Funding and capacity-building efforts from international organizations (e.g., WHO, Global Fund) are essential to address AMR in LMICs.	Need for increased funding for AMR-related infrastructure and capacity-building programs in LMICs.

The evolutionary mechanisms of AMR can be categorized into developmental and strategic action mechanisms. A recurring theme in the literature is the focus on evolutionary processes as key contributors to the origins of AMR. AMR primarily arises through genetic mutations, recombination, and horizontal gene transfer (HGT). Studies highlight specific genetic markers, such as gyrA for fluoroquinolone resistance and rpoB for rifampin resistance, as mediators of resistance to first-line drugs (Merker, 2020). Additionally, the exchange of resistance genes via mobile genetic elements like plasmids, transposons, and bacteriophages accelerates AMR proliferation. Despite the selective pressures from antibiotic use in healthcare settings, AMR is not a unidimensional phenomenon, as noted by Salam (2023).

Horizontal gene transfer is particularly prevalent in healthcare environments, facilitating the spread of multidrug-resistant organisms (Uruén, 2021). Biofilm formation on medical devices further exacerbates AMR by limiting antibiotic access, contributing significantly to healthcare-associated infections (HAIs), especially those caused by multidrug-resistant pathogens (Endale, 2023).

Hospitals are critical hubs for the amplification of resistant pathogens due to their operational nature. Literature consistently identifies patient-to-patient transmission, healthcare worker (HCW) contact, and fomites as key transmission routes (Endale, 2023). Inadequate hand hygiene among healthcare personnel is a primary driver of resistant organism spread. Environmental sources, such as water, bed linens, and medical equipment, also serve as reservoirs for resistant pathogens, underscoring the importance of infection prevention and control (IPC) measures. AMR is particularly prevalent in underfunded and understaffed healthcare systems, where deficiencies in infection control protocols, diagnostics, and perioperative antibiotic prescribing practices amplify resistant infections (Hamerlinck, 2023).

Socioeconomic and environmental factors significantly contribute to AMR. In low- and middle-income countries (LMICs), limited access to diagnostic testing leads to empirical and inappropriate antibiotic use, increasing resistance risks (Moo et al., 2019). Poverty, restricted healthcare access, and inadequate treatment availability further fuel AMR development (Krockow, 2019). Additionally, antibiotic misuse in animal agriculture and pollution from wastewater systems are global drivers of AMR (Endale, 2023; Naghavi, 2024). Addressing these challenges requires improved waste management, stricter regulations on antibiotic use in agriculture, and enhanced healthcare infrastructure (Ribes-Martínez, 2024).

AMR poses profound challenges to global public health. Resistant pathogens, such as carbapenem-resistant Enterobacteriaceae (CRE) and methicillin-resistant Staphylococcus aureus (MRSA), increase morbidity and mortality, particularly in pulmonary infections and sepsis (Naghavi, 2024). AMR jeopardizes critical interventions like surgeries, organ transplants, and cancer treatments, which rely on effective antibiotics for infection prevention (Sharma, 2022). Economically, AMR drives up healthcare costs through prolonged hospital stays, additional diagnostics, and the need for more expensive second-line treatments. The World Bank estimates that AMR could reduce global GDP by over 4% by 2050, exacerbating healthcare access challenges, particularly in LMICs (Ahmed, 2024).

Effective AMR mitigation requires multifaceted strategies, including hospital-based antibiotic stewardship programs (ASPs), infection control measures, and robust surveillance systems. ASPs aim to reduce selective pressure through responsible antibiotic use, though challenges like training, funding, and provider resistance persist (Sharma, 2022). IPC measures, such as hand hygiene, isolation precautions, and environmental cleaning, are critical for reducing nosocomial infections and resistant pathogen spread (Ackers et al., 2020). Genomic surveillance, including whole-genome sequencing, aids in tracking resistance trends and understanding pathogen spread (Littmann, 2015). Innovative approaches, such as rapid diagnostics and bacteriophage therapy, also show promise in combating AMR (Ribes-Martínez, 2024).

AMR management raises complex ethical and policy challenges. A key ethical issue is balancing individual patient needs for antibiotics with the public health goal of minimizing resistance. Denying antibiotics to patients with suspected bacterial infections may benefit the broader population but can harm individuals (Littmann, 2015). Inequities in access to antibiotics, diagnostics, and healthcare, particularly in LMICs, exacerbate the AMR burden and demand targeted policy solutions (Moo et al., 2019). Global health strategies, such as the WHO Global Action Plan, advocate for international cooperation, including regulations on agricultural antibiotic use, enhanced diagnostic capacity, and public-private partnerships for new antibiotic development (Chua, 2021; Krockow, 2019). Emerging technologies, like artificial intelligence and big data analytics, offer potential for predicting resistance patterns and optimizing public health interventions. The “One Health” approach, integrating human, animal, and environmental health, is increasingly recognized as a comprehensive framework for addressing AMR’s complexity (Ribes-Martínez, 2024).

This thematic approach to antimicrobial resistance (AMR) highlights critical features such as genetic mechanisms, circulation in healthcare settings, public health impacts, control measures, and the social, economic, political, and ethical dimensions of AMR. By examining these aspects and identifying research gaps, we can better understand the multifaceted challenges posed by AMR.

AMR originates from various genetic and mechanistic components, including mutational events and horizontal gene transfer (HGT). Key mechanisms involve alterations in antibiotic target sites, such as the gyrA and rpoB genes, enabling bacteria to survive antibiotic exposure. HGT amplifies resistance by allowing bacteria to share resistance genes via mobile genetic elements like plasmids, transposons, and integrons. Through processes like conjugation, transformation, and transduction, resistance spreads across bacterial species, particularly in high-pressure environments like healthcare facilities. Additionally, biofilm formation on medical devices, such as catheters and implants, complicates treatment by shielding bacteria from antibiotics and host immunity while enhancing efflux pump activity, which expels antibiotics from bacterial cells.

Healthcare-associated infections (HAIs) caused by resistant organisms like Methicillin-Resistant Staphylococcus aureus (MRSA), Vancomycin-Resistant Enterococcus (VRE), and Carbapenem-Resistant Enterobacteriaceae (CRE) are a global concern. These infections increase hospitalization duration, treatment costs, and mortality rates. Resistance spreads in hospitals through patient-to-patient transmission, healthcare workers (HCWs), and environmental carriers. Shared medical equipment, inadequate isolation measures, and poor hand hygiene exacerbate the issue, particularly in low- and middle-income countries (LMICs) where infection control is often weak. Weak diagnostic procedures and empirical antibiotic overuse further contribute to AMR in these settings.

AMR poses significant public health challenges, with resistant infections like CRE-related bloodstream infections carrying mortality rates exceeding 50%. Economically, AMR leads to prolonged hospital stays, costly second-line treatments, and additional diagnostic tests, potentially draining over 4% of global GDP by 2025. LMICs bear a disproportionate burden due to limited resources, weaker health infrastructure, high empirical antibiotic use, and scarce diagnostic facilities, amplifying the effects of AMR.

Effective AMR control relies on Antimicrobial Stewardship Programs (ASPs), Infection Prevention and Control (IPC), and surveillance systems. ASPs optimize antibiotic use to reduce selective pressure, incorporating evidence-based prescribing guidelines and feedback mechanisms. However, challenges like resource scarcity and professional resistance hinder their implementation. IPC practices, including hand hygiene, environmental cleanliness, and isolation precautions, are critical for preventing resistant organism spread, with hand hygiene proven effective against nosocomial infections. Surveillance, including genomic sequencing and MALDI-TOF mass spectrometry, enables rapid identification of resistant pathogens, improving treatment outcomes.

Global initiatives, such as the WHO's Global Action Plan on AMR (launched in 2015), aim to address AMR through five objectives: preventing infections, rationalizing antimicrobial use, strengthening IPC, advancing research, and securing long-term funding. Achieving these goals requires sustained political will and financial support, particularly in LMICs with underdeveloped health systems. The One Health approach, integrating human, animal, and environmental health, tackles AMR's environmental drivers, such as agricultural runoff and wastewater pollution, through international collaboration and capacity-building.

AMR's social and ethical implications highlight inequalities in antibiotic access and use. In LMICs, low-quality antibiotics and non-prescription use, driven by poverty, limited healthcare access, and low awareness, fuel resistance. Public awareness campaigns targeting healthcare workers and communities are essential to promote rational antibiotic use. Addressing socio-economic factors requires investments in diagnostic capabilities and health infrastructure beyond education alone.

Developing new antibiotics is critical to combating AMR, but the economic model for antibiotic research is challenging. Antibiotics are used sparingly and for short courses, making them less profitable than treatments for chronic conditions. Incentives like grants, subsidies, and advance purchase commitments are needed to stimulate research. Organizations like the Global Antibiotic Research and Development Partnership (GARDP) play a vital role in advancing new antibiotic development to address this market failure.

Chapter 4

Contents and Results

The final results of this analysis of Antimicrobial Resistance (AMR), based on a detailed thematic synthesis of various studies, reveal a comprehensive view of AMR's mechanisms, its spread, the public health and economic consequences, and the mitigation strategies required to combat this global health challenge. This synthesis also identifies key research gaps in understanding, preventing, and managing AMR, while offering insights into the impact of AMR on healthcare systems worldwide, particularly in resource-limited settings.

Findings

AMR is driven by complex mechanisms involving genetic mutations and horizontal gene transfer (HGT), which allow bacteria to evolve and survive despite antibiotic treatment. These processes enable the spread of resistance genes across bacterial populations, often facilitated by mobile genetic elements such as plasmids, transposons, and integrons. In healthcare settings, biofilm formation on medical devices like catheters and implants further compounds the issue by limiting antibiotic penetration and promoting the expression of efflux pumps, which actively expel antibiotics from bacterial cells. Together, these genetic and biological factors significantly contribute to the development of multidrug-resistant pathogens, which are associated with hospital-acquired infections (HAIs) such as MRSA, VRE, and CRE.

The spread of AMR is particularly concerning in healthcare environments where patients, healthcare workers, and environmental reservoirs serve as key transmission pathways. Nosocomial infections account for a substantial portion of AMR cases, and poor infection control practices, including inadequate hand hygiene and isolation measures, exacerbate the transmission of resistant bacteria. In low- and middle-income countries (LMICs), where healthcare infrastructure is limited, the lack of diagnostic tools and overuse of antibiotics contribute to the high rates of resistant infections, making AMR particularly difficult to manage.

From a public health perspective, AMR increases morbidity and mortality. Infections caused by resistant pathogens are associated with higher death rates, longer hospital stays, and increased treatment costs. Economic analyses predict that, by 2050, AMR could cost the global economy over 4% of its GDP due to the direct healthcare costs and loss of productivity. The burden of AMR is especially heavy in LMICs, where healthcare systems are already overstretched. The economic burden also includes the costs of second-line therapies, diagnostic tests, and extended hospitalizations, all of which place immense strain on national healthcare budgets.

Mitigation strategies for AMR include Antimicrobial Stewardship Programs (ASPs) aimed at optimizing antibiotic use and reducing resistance through evidence-based prescribing. However, ASPs face several challenges, particularly in resource-limited settings, where the implementation of such programs is often hindered by lack of training, limited resources, and resistance from healthcare professionals. Infection Prevention and Control (IPC) measures, such as hand hygiene protocols, patient isolation, and environmental cleaning, are essential for controlling the spread of AMR in hospitals. Genomic surveillance technologies, including whole genome sequencing (WGS), offer powerful tools for tracking resistance patterns and identifying new resistance mechanisms, providing valuable insights for public health policy and interventions.

At the policy level, the World Health Organization's (WHO) Global Action Plan on AMR (2015) provides a strategic framework for addressing AMR globally. Key policy goals include reducing infection incidence, optimizing antimicrobial use, strengthening surveillance systems, and increasing public awareness. In addition to policy reform, global collaboration is critical to managing AMR. The One Health approach, which integrates human, animal, and environmental health, offers a comprehensive framework for addressing AMR at all levels. Efforts to curb antibiotic misuse in agriculture and improve waste management in healthcare settings are crucial to minimizing environmental sources of resistance.

From an ethical standpoint, AMR poses challenges related to access to antibiotics and the misuse of antibiotics in vulnerable populations. In LMICs, access to essential antibiotics is often limited, while at the same time, over-the-counter sales and self-medication are prevalent. These issues exacerbate the development of resistance and highlight the need for educational initiatives aimed at promoting rational antibiotic use. Behavioural factors, such as lack of public awareness about the risks of unnecessary antibiotic use, also play a role in the spread of AMR.

Finally, innovative solutions are urgently needed to address the stagnant pipeline of new antibiotics. Financial incentives, such as grants and subsidies, could help stimulate investment in antibiotic research and development. Additionally, alternative treatments, such as bacteriophage therapy and antimicrobial peptides, are emerging as promising options to combat resistant infections. AI and big data also offer new possibilities for tracking AMR trends, optimizing treatment regimens, and improving diagnostic capabilities.

Table 3. ***Key Mechanisms***

Mechanism	Key Findings	Research Gaps
Mutation & Horizontal Gene Transfer (HGT)	Mutations in *gyrA* and *rpoB* genes confer resistance. HGT enables the spread of resistance genes through plasmids, transposons, and integrons.	Need for further studies on specific genetic mutations linked to resistance.
Biofilm Formation	Biofilms protect bacteria from antibiotics and immune responses, enhancing resistance mechanisms like efflux pumps.	Lack of therapies that target or disrupt biofilm formation.
Efflux Pumps	Efflux pumps actively expel antibiotics, contributing to resistance, especially in biofilm-forming bacteria.	Need for inhibitors that can block efflux pumps.

Table 4. ***Key Transmission Pathways***

Transmission Pathway	Key Findings	Research Gaps
Nosocomial Infections (HAIs)	MRSA, VRE, CRE are common in hospital settings, leading to longer stays, increased mortality, and higher healthcare costs.	Research on more effective strategies to reduce HAIs in hospitals.
Transmission Routes	AMR spreads through patient-to-patient contact, healthcare workers, and environmental reservoirs.	Need for targeted interventions to prevent cross-contamination.

Table 5. ***Key Impacts***

Impact	Key Findings	Research Gaps

Morbidity & Mortality	Resistant infections, particularly CRE, have high mortality rates (over 50%).	More global data on the burden of AMR on morbidity and mortality.
Economic Burden	AMR could cost the global economy 4% of GDP by 2050 due to longer hospital stays, additional diagnostics, and second-line treatments.	Need for economic models assessing AMR's impact on LMICs.

Table 6. ***Key Strategies***

Strategy	**Key Findings**	**Research Gaps**
Antimicrobial Stewardship Programs (ASPs)	ASPs optimize antibiotic use and reduce resistance but face challenges such as limited resources and healthcare worker resistance.	Need for more research on ASP implementation in resource-poor settings.
Infection Prevention & Control (IPC)	Hand hygiene, patient isolation, and environmental cleaning are effective in reducing AMR spread in hospitals.	Research on improving IPC adherence in resource-constrained environments.

Table 7. ***Key Policies/ Actions***

Policy/Action	**Key Findings**	**Research Gaps**
Global Action Plans	WHO's Global Action Plan provides a roadmap for AMR mitigation through surveillance, infection control, and antimicrobial use optimization.	Need for strengthened international agreements and frameworks for AMR.
One Health Approach	The One Health approach links human, animal, and environmental health, addressing AMR holistically.	More integration of One Health strategies in global AMR policies.

Table 8. ***Key Considerations***

Consideration	**Key Findings**	**Research Gaps**
Access to Antibiotics	Disparities in access to antibiotics in LMICs, coupled with misuse, exacerbates AMR.	Research into policies to improve access to essential antibiotics.

Misuse of Antibiotics	Over-the-counter sales and self-medication contribute to the development of resistance, particularly in LMICs.	More studies on the effectiveness of public awareness campaigns.

The study also aims to present the results of systematic review analysis.

The systematic literature review looked at a wide variety of articles related to AMR focusing on its causes, how it works, how it spreads, its consequences for public health and notions of how it can be addressed. The key findings are as follows:

Mechanisms of AMR

Genetic Mutation: Research continuously pointed to the fact that genetic mutations played a part in the process that led to resistance. Among these genes, gyrA involved in fluoroquinolone resistance and rpoB involved in rifampin resistance were found to be crucial for antibiotic resistance in pathogens.

Horizontal Gene Transfer (HGT): Development for bacterial conjugation, transduction, and other mobile genetic elements as a primary cause for the expression of AMR were also acknowledged. HGT is common in the health care context especially where there is rampant use of antibiotics.

Biofilm Formation: Biofilm formation on the surface of implanted medical devices was identified as another factor which makes bacteria resistant to antibiotics particularly in HAIs.

AMR in Healthcare Environment

Nosocomial Infections (HAIs): Acquired infections in the hospital setting were as a result considered to be causes of AMR. The types of MRSA, VRE and CRE where other resistant pathogens which posed higher mortality rates and more days averted for patients.

Transmission Pathways: The emergence and dissemination of resistant pathogens were related to infection control failings, including healthcare worker hand touch contamination in their practice, from one patient to another, and surfaces, water systems, respectively.

Transmission in LMICs: Several works from LMICs identified actual antibiotic consumption and low diagnostic tests as the main drivers of AMR.

Economical and Public Health Consequences

Increased Mortality and Morbidity: Disease due to AMR tends to be more dangerous and death rate for patients with bloodstream infection, especially CRE, is very high. This was made worse by the fact that such infections could hardly be managed with regular antibiotics.

Economic Burden: It is estimated that the burden of AMR is going to be more than 4% of the global gross domestic product in the year 2050 due to lengthened duration with hospitalization increase in the cost of second-line antibiotics and more extensive diagnostic procedure. This economic burden is worst in LMICs; most of which are struggling to meet the increased demand for healthcare services.

Mitigation Strategies

Antimicrobial Stewardship Programs (ASPs): The role of ASPs as being useful in enhancing appropriate prescription of antibiotics, avoiding development of prescriptions for resistance, and in overall controlling selective pressure for pathogen resistance was established. However, their effectiveness is typically limited by inadequate resources and subsequent issues of inadequate HCW training.

Infection Prevention and Control (IPC): Hand hygiene and patient isolation measures and environmental cleaning were put forward as critical elements in the fight against AMR in the healthcare facilities. The arguments and evidence showed that targeted interventions to adhere to IPC measures considerably decreased AMR transmission.

Surveillance and Rapid Diagnostics: Some of the best practices that were established related to genomic surveillance work consisted of WGS as significant to monitor development of AMR, and to identify pathogens that exhibit resistance. This fast method such as MALDI-TOF mass spectrometry has been found to accurately fasten the detection of the resistance bacteria and therefore timely treatment.

Chapter 5

Discussion

Antimicrobial resistance (AMR) demands urgent attention across healthcare, policy, research, and public health sectors due to its complex and multifaceted nature. The primary drivers of AMR include genetic mutations in bacteria that enable survival despite antibiotic exposure and horizontal gene transfer (HGT), which accelerates the spread of resistance. Mutations in key bacterial genes, such as gyrA and rpoB, confer resistance to critical antibiotics like fluoroquinolones and rifampin. Additionally, mobile genetic elements (MGEs), particularly plasmids, facilitate the rapid exchange of resistance genes, driving the evolution and dissemination of resistant strains, especially in antibiotic-heavy healthcare settings.

Biofilm formation significantly contributes to AMR by creating a physical barrier that shields bacteria from antibiotics and the host immune system, complicating infection treatment. Within biofilms, bacteria often enhance efflux pump activity, which expels antibiotics from cells, further elevating resistance levels. These mechanisms underscore the urgent need for novel strategies to disrupt biofilm formation, inhibit efflux pumps, and develop new antibiotics to counter resistant strains effectively.

AMR is a critical concern in healthcare settings, where hospital-acquired infections (HAIs) caused by pathogens like Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococcus* (VRE), and Carbapenem-Resistant *Enterobacteriaceae* (CRE) increase mortality, prolong hospital stays, and escalate healthcare costs. Poor infection control practices, such as inadequate hand hygiene, insufficient patient isolation, and environmental contamination, drive the spread of these resistant pathogens. In resource-constrained settings, particularly low- and middle-income countries (LMICs), limited diagnostic capabilities and widespread antibiotic misuse exacerbate resistance rates.

From a public health perspective, AMR threatens to reverse decades of medical progress, particularly for high-risk groups like surgical patients, cancer patients, and organ transplant recipients who rely on effective prophylactic antibiotics. Economically, AMR strains healthcare systems through prolonged treatments, reliance on costly second-line therapies, and increased diagnostic testing. The World Bank estimates that AMR could reduce global GDP by up to 4% by 2050, with LMICs bearing a disproportionate burden due to limited access to care and existing healthcare inequities.

Antimicrobial stewardship programs (ASPs) are essential for promoting rational antibiotic use and reducing selective pressure that fuels AMR. However, resource limitations, inadequate healthcare worker training, and institutional barriers hinder their implementation, particularly in LMICs. Similarly, infection prevention and control (IPC) measures—such as hand hygiene, patient isolation, and environmental cleaning—are critical but inconsistently applied in resource-limited settings, allowing resistant pathogens to spread unchecked.

Advanced surveillance technologies, such as whole-genome sequencing (WGS) and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectrometry, enable tracking of resistance patterns and identification of emerging threats, providing real-time data for decision-making. Additionally, alternative therapies like bacteriophage therapy and antimicrobial peptides show promise but require further research to establish their safety, efficacy, and clinical viability. Artificial intelligence (AI) and big data analytics offer potential for predicting resistance patterns, optimizing treatments, and improving diagnostics by integrating clinical, genomic, and global data.

Global collaboration is vital for addressing AMR comprehensively. The World Health Organization's Global Action Plan on AMR provides a strategic framework, but implementation remains challenging, particularly in LMICs. The One Health approach, which integrates human, animal, and environmental health, emphasizes reducing antibiotic use in agriculture, preventing environmental contamination, and improving waste management. International organizations, governments, and the private sector must collaborate to share resources, research, and best practices to combat AMR effectively.

To combat AMR, future efforts should prioritize strengthening antimicrobial stewardship programs, particularly in high-risk healthcare settings, and adapting these programs for low-resource environments by addressing barriers like inadequate training and infrastructure. Simultaneously, improving access to rapid diagnostic tools, genomic surveillance, and point-of-care technologies in LMICs is critical for accurate pathogen identification and rational antibiotic use. Global cooperation and investment in research, diagnostics, and alternative therapies are essential to mitigate the growing threat of AMR and safeguard global health and economic stability.

Countries must adopt the One Health approach, integrating antimicrobial resistance (AMR) into national health policies to address environmental and agricultural factors contributing to its spread. This requires enhanced coordination between human, animal, and environmental sectors to reduce the overall AMR burden. Global surveillance systems for resistance must be improved to provide timely data on resistance patterns, enabling faster and more effective interventions. International agreements on antibiotic use, particularly in agriculture and environmental management, are critical to curbing AMR at its roots. Additionally, AMR must be framed ethically, focusing on equitable access to antibiotics, especially for vulnerable populations in low- and middle-income countries (LMICs). Policies should ensure access to essential antibiotics without encouraging misuse, while education campaigns for healthcare professionals and the public should address risks of unnecessary antibiotic use, tailored to cultural and social contexts to reduce self-medication and over-the-counter sales.

The urgency of addressing AMR as a global threat, as highlighted in the I AM document, underscores the need for multifaceted recommendations that integrate technological and medical advancements with systemic policy and healthcare changes. These actions are essential to combat the rising AMR threat and preserve antibiotics as a cornerstone of modern medicine. Expanding antimicrobial stewardship programs (ASPs) is a priority, as they optimize antibiotic prescribing and reduce inappropriate use in healthcare settings. However, implementation in LMICs faces challenges like resource constraints, lack of training, and resistance to guideline-based prescribing. Successful ASPs require sustained financial investment, government support, and integration into routine healthcare, with context-specific models tailored to local infrastructure, cultural factors, and prescribing habits. Interdisciplinary collaboration among healthcare workers, pharmacists, and policymakers is also vital for ASP success.

In parallel, global infection prevention and control (IPC) strategies must be strengthened. Poor infection control measures, such as inadequate hand hygiene and faulty isolation protocols, are a primary route of AMR spread in healthcare settings. Simple, evidence-based IPC practices can significantly reduce resistant pathogen transmission, even in resource-limited settings. Developing cost-effective, locally tailored IPC interventions for LMICs and funding rigorous protocols are critical. Additionally, improving environmental decontamination and medical equipment sterilization will minimize contamination and the spread of resistant pathogens.

Advancing diagnostic technologies is key to tackling AMR by enabling faster detection of resistant pathogens and tailored treatments. Current tools, like whole-genome sequencing (WGS) and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF), are expensive and less accessible in LMICs. Future investments should focus on affordable, accessible diagnostic platforms, particularly for point-of-care resistance marker detection and rapid susceptibility testing. Increased use of rapid diagnostic tests (RDTs) for common infections can reduce over-prescription of broad-spectrum antibiotics and minimize treatment delays, ensuring patients receive optimal treatment promptly.

Enhanced research into new antibiotics and alternative therapies is critical, as the pipeline for new antibiotic classes remains underdeveloped. Financial disincentives for pharmaceutical companies, due to short treatment courses and low profitability, must be addressed through incentives like market entry rewards, grants, and subsidies. Alternative therapies, such as bacteriophage therapy, antimicrobial peptides, and CRISPR-based technologies, show promise for multidrug-resistant infections but require further clinical validation for safety, efficacy, and feasibility.

Integrating these alternatives with traditional antibiotics can mitigate AMR's impact in settings lacking new antibiotics.

AMR's global nature necessitates international collaboration due to cross-border movement of people, goods, and animals. The One Health approach, integrating human, animal, and environmental health, recognizes that AMR extends beyond healthcare to include antibiotic use in agriculture and environmental contamination. Policies should regulate antibiotic use in agriculture, particularly for growth promotion and disease prevention in healthy animals and improve wastewater treatment to reduce resistant bacteria spread. Robust regulatory frameworks and oversight are needed to curb antibiotic misuse across sectors.

Global surveillance and data-sharing systems must be advanced to track AMR trends in real time. Countries should collaborate to establish networks for monitoring antibiotic use, AMR prevalence, and treatment outcomes, enabling evidence-based decision-making. Big data analytics and artificial intelligence can analyse clinical, environmental, and genomic data to predict resistance patterns and identify high-risk areas, particularly in regions with limited surveillance. Integrated platforms for cross-border data sharing will enhance hotspot identification and response coordination.

Ethical challenges in AMR policy, particularly in LMICs, centre on ensuring equitable antibiotic access while preventing misuse. Over-the-counter sales and self-medication, driven by lax regulations, fuel resistance. Public health campaigns and educational initiatives must raise awareness about antibiotic overuse risks, tailored to local contexts to curb self-medication. Stricter regulations on antibiotic sales, prioritizing prescription-only access, are essential, alongside ensuring affordable access for vulnerable populations.

Limitations

This analysis provides a detailed overview of the current state of antimicrobial resistance (AMR) from an environmental perspective. Most AMR studies have been conducted in high-income countries, with limited research exploring AMR dynamics in low- and middle-income countries (LMICs), where the burden of resistance is often most severe. This research gap restricts the generalizability of findings to resource-poor settings with weaker healthcare infrastructure and less regulated antibiotic access. To address this, future investigations should prioritize AMR in LMICs, focusing on resistance spread in community settings and developing interventions tailored to local healthcare challenges.

A key limitation of this analysis is its focus on specific pathogens and hospital settings, with less attention to widespread AMR across broader sectors like agriculture and the environment. The One Health approach, integrating human, animal, and environmental health, remains underexplored. Research is needed to investigate environmental exposures, such as wastewater contamination and antibiotic use in agriculture, which contribute to AMR spread. A holistic understanding of AMR transmission across sectors would support the development of comprehensive strategies to combat resistance.

The affordability and accessibility of surveillance and diagnostic technologies pose significant challenges in managing AMR, particularly in low-resource settings, though these are not the focus of this review. More research is needed to develop affordable diagnostic solutions for routine clinical practice in areas with limited healthcare infrastructure. Additionally, while bacteriophage therapy shows promise as an alternative treatment, it is still in early research stages. These therapies require thorough clinical validation for safety, efficacy, and long-term applicability and should complement, not replace, standard antibiotics, as they are unlikely to fully address the AMR threat alone.

Despite progress in understanding and addressing AMR, significant work remains. This analysis recommends steps to mitigate AMR's impact, emphasizing the need to fill research gaps and address current limitations. The global urgency of AMR, as highlighted in the I AM document, underscores the importance of advancing technological and medical breakthroughs while integrating systemic changes in policy, healthcare, and global collaboration. These efforts are critical to maintaining antibiotics as a cornerstone of modern medicine.

Expanding antimicrobial stewardship programs (ASPs) is a critical recommendation for managing AMR. ASPs optimize antibiotic prescribing and reduce inappropriate use, thereby curbing resistance development. However, their implementation, particularly in LMICs, is hindered by resource constraints, inadequate healthcare worker training, and resistance to guideline-based prescribing. To succeed, ASPs in LMICs require sustained government investment, integration into routine healthcare, and context-specific models tailored to local infrastructure, prescribing habits, and resources. Interdisciplinary collaboration among healthcare workers, pharmacists, and policymakers is also essential.

Globally, infection prevention and control (IPC) strategies must be strengthened to limit AMR spread, particularly in healthcare settings where poor practices, such as inadequate hand hygiene and improper isolation protocols, drive resistance. Evidence shows that simple, effective IPC measures can significantly reduce resistant pathogen transmission, even in resource-limited settings. Developing cost-effective IPC interventions for LMICs, improving environmental decontamination, and enhancing medical equipment sterilization are crucial steps to minimize contamination and pathogen spread.

Diagnostic technologies can accelerate AMR management by enabling rapid detection of resistant pathogens and tailored treatments. However, advanced tools like whole-genome sequencing (WGS) and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) are costly and inaccessible in resource-constrained settings. Future investments should focus on developing affordable, accessible diagnostic platforms for LMICs. Rapid diagnostic tests (RDTs) for common infections could reduce over-prescription of broad-spectrum antibiotics and minimize treatment delays by enabling timely, targeted therapy.

Enhanced research into new antibiotics and alternative therapies is urgently needed, as the antibiotic development pipeline remains limited. The pharmaceutical industry faces financial disincentives due to the short treatment courses and low profitability of antibiotics. Governments, international organizations, and the private sector must provide incentives like market entry rewards, grants, and subsidies to encourage antibiotic research and development. Promising alternatives, such as bacteriophage therapy, antimicrobial peptides, and CRISPR-based technologies, require further clinical validation for safety, efficacy, and feasibility, and should be integrated with traditional antibiotics to address multidrug-resistant infections.

AMR is a global issue requiring international collaboration due to the cross-border movement of people, goods, and animals. The One Health approach, integrating human, animal, and environmental health, is critical to addressing AMR holistically. Antibiotic use in agriculture and veterinary medicine, along with environmental contamination, significantly contributes to resistance. Global and national policies must regulate antibiotic use in agriculture, improve wastewater treatment, and strengthen environmental decontamination to reduce resistance spread. Robust regulatory frameworks and stricter oversight are needed across all sectors.

Strengthening global surveillance and data-sharing systems is essential for tracking AMR trends and informing evidence-based decisions. Real-time global networks for monitoring antibiotic use, AMR prevalence, and treatment outcomes can enhance coordinated responses to emerging resistance threats. Big data analytics and artificial intelligence (AI) offer opportunities to analyse clinical, environmental, and genomic data to predict resistance patterns and identify high-risk areas or populations, enabling more effective interventions.

CHAPTER 6

Conclusions

Global public health faces an extreme and growing threat from antimicrobial resistance (AMR), a public health crisis affecting both developed and developing countries. With antibiotic-resistant infections on the rise, the implications for clinical practice and healthcare systems worldwide are profound. This multifactorial problem arises from genetic mutations, horizontal gene transfer, biofilm formation, and the widespread use and misuse of antibiotics in human healthcare and agriculture. Systemic weaknesses, such as inadequate infection control measures, poor public health infrastructure, limited access to rapid diagnostic tools, and patient-to-patient transmission, exacerbate AMR, particularly in low- and middle-income countries (LMICs), though no region is immune.

The consequences of AMR are far-reaching, leading to increased morbidity, mortality, prolonged hospital stays, and higher treatment costs. It undermines the effectiveness of critical medical procedures, including surgery, cancer treatment, and organ transplants. The financial burden on healthcare systems is immense, particularly in resource-limited settings, where AMR exacerbates existing healthcare inequalities. These disparities highlight that AMR is not merely a clinical or scientific issue but a social and economic disaster disproportionately affecting vulnerable populations.

Addressing AMR requires a multilayered approach. Antimicrobial stewardship programs (ASPs) and robust infection prevention and control (IPC) measures are critical but insufficient alone to reduce the selective pressure driving bacterial resistance. The success of these strategies hinges on global cooperation, substantial funding, and the capacity to implement scientifically grounded approaches across diverse healthcare settings. Local antibiotic stewardship and infection control efforts, especially in resource-constrained environments, will increasingly rely on international support and knowledge transfer.

The development and implementation of innovative diagnostic and therapeutic technologies are equally vital. Progress in genomic surveillance, such as whole-genome sequencing (WGS) and artificial intelligence (AI), holds promise for understanding resistance evolution and tracking resistant pathogens. Emerging technologies like CRISPR-Cas systems and bacteriophage therapy offer hope for new treatment options, but their widespread use requires significant research, development, and regulatory oversight to address ethical, safety, and efficacy concerns.

Addressing the environmental drivers of AMR is an urgent priority. Antibiotic residues in agricultural runoff, wastewater, and other environmental reservoirs contribute to the global spread of resistance. Mitigating these drivers demands a One Health approach, integrating human, animal, and environmental health. This includes limiting antibiotic overuse in agriculture, improving waste management systems, and encouraging industries to adopt sustainable practices.

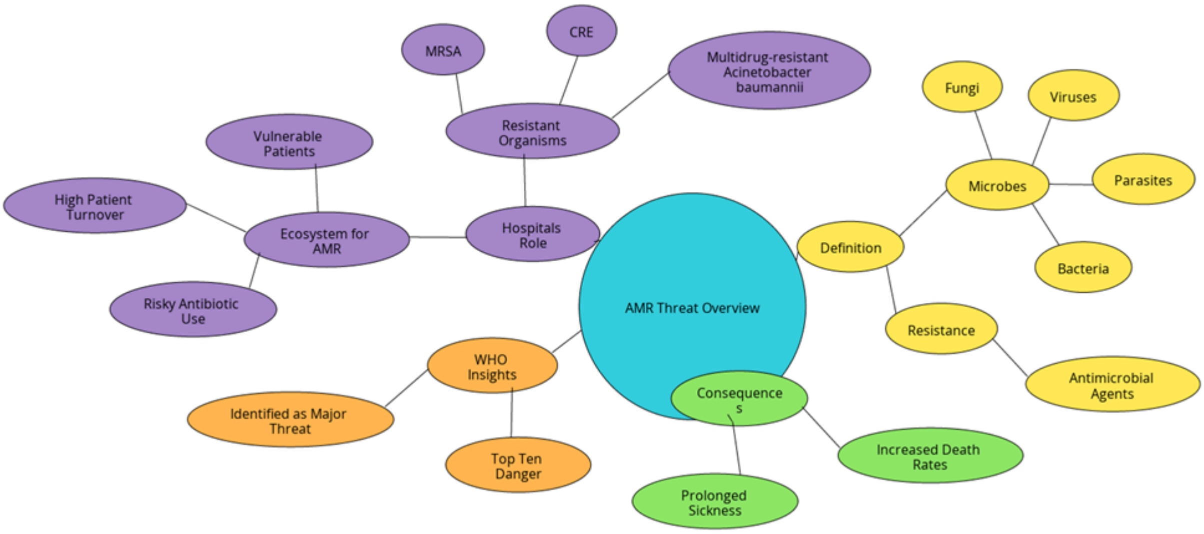
A global policy framework is essential to combat AMR effectively. The WHO Global Action Plan on AMR provides a roadmap for countries to control infections, promote rational antibiotic use, and invest in research and development. However, implementation requires strong political will, robust monitoring systems, and sufficient resources. AMR is not solely a medical challenge but a socio-economic and political one, necessitating collaboration across governments, healthcare workers, the agricultural sector, and the public.

Changing public attitudes toward antibiotic misuse is critical and requires public health campaigns to raise awareness about the dangers of AMR and promote rational antibiotic use. These efforts must be culturally and economically sensitive to address inappropriate antibiotic use effectively. International organizations, such as the WHO and the Global Fund, should fund the development of diagnostics, antibiotics, and vaccines, alongside capacity-building measures to strengthen local healthcare systems, particularly in LMICs.

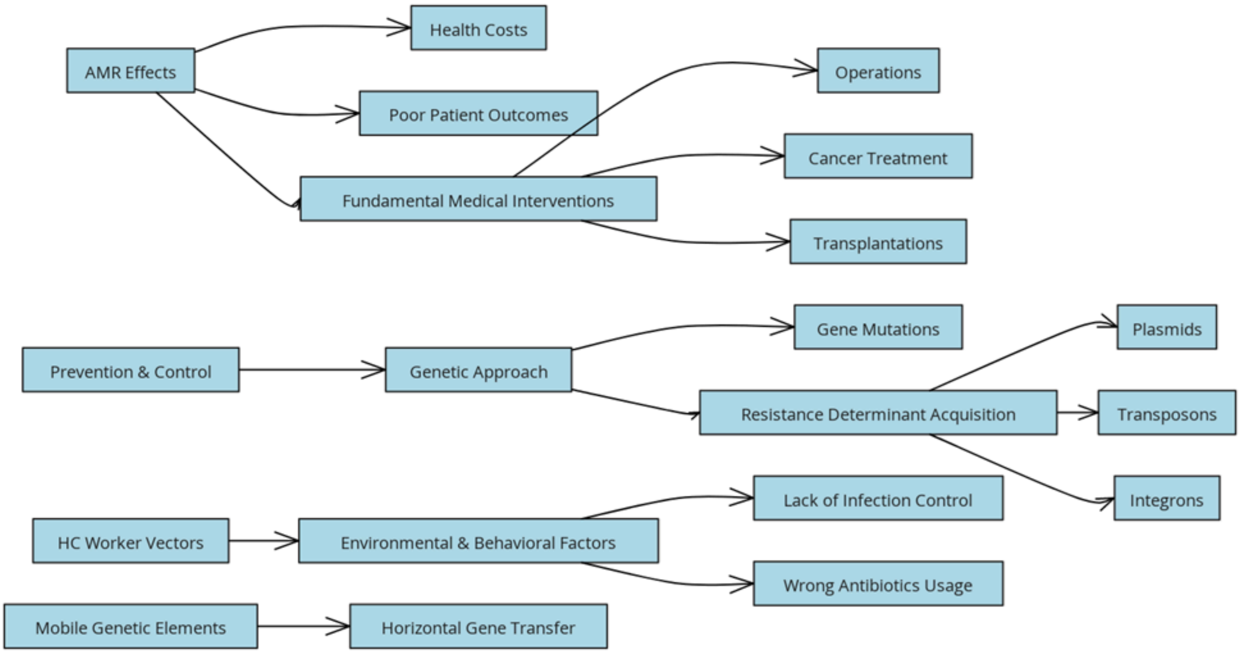
Tackling AMR demands a comprehensive, well-coordinated, and sustained global response. Developing new antibiotics or technologies is insufficient without addressing how antimicrobial use is perceived across society. This involves improving governance, reducing socio-economic disparities, fostering global partnerships, and committing to preserving antibiotic efficacy for future generations. Though the road ahead is challenging, concerted efforts by the global community can curb the spread of AMR and ensure antibiotics remain a cornerstone of modern medicine.

Appendices

Appendix A. AMR Threat Overview



Appendix B. AMR Effects and Related Factors



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