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REVIEW ARTICLE

Beyond Infection: The Global Health and Economic Burden of Antimicrobial Resistance

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ABSTRACT

Anti-microbial Resistance (AMR) has become one of the major contributors to mortality and disability globally. After the discovery of antimicrobials, it was believed by the medical industry that the battle against microbes would be conquered. However, the rise in resistance of microbes changed the dynamics of the battle. The numbers of morbidity and mortality are staggering due to AMR in 2021 about 21.36 million people died due sepsis and 4.71 people died due to drug-resistant infections. If this trend continues, it is estimated that 39 million people will be expected to die by 2050. AMR has grown from a clinical issue to a systemic threat that is challenging global health security and economic stability. AMR, if overlooked, can cause critical economic losses according to WHO AMR can cause an additional 1 trillion dollars in healthcare costs by 2050 and GPD loss of about 3.4 trillion per year by 2030. The high-burden pathogens, especially those belonging to the ESKAPE group, are at the centre of HAIs as well as treatment failures. The health burden caused by AMR is not limited to increased mortality rates but also includes increased durations of hospitalization, increased risks of complications during critical medical procedures such as cancer chemotherapy, organ transplantation, and neonatal care, as well as compromised surgical safety. Based on projections by global institutions, unless effective control measures are put in place, AMR is expected to significantly impact global GDP in the coming decades. The global response to AMR, such as antimicrobial stewardship programmes and surveillance, as well as the One Health approach, is critical but needs to be more effectively implemented. The issue of AMR requires urgent, sustained, and multidisciplinary action to reduce its growing health burden as well as economic consequences.

Keywords: Antimicrobial resistance. AMR Health Burden. AMR Economic burden. Antimicrobial Stewardship

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Introduction

Antimicrobial resistance (AMR), which is the ability of microorganisms, especially bacteria, to develop genetic mutations making antimicrobial agents less effective or ineffective, has been identified as one of the biggest health challenges of the 21st century. This is because of the genetic mutations that occur in microorganisms, which make it difficult to manage infectious diseases using conventional antimicrobial drugs.[1] Although antimicrobial resistance is a natural process, the current antimicrobial resistance crisis is man-made and is attributed to the misuse and abuse of antimicrobial drugs in human and animal health as well as in agriculture. The misuse and abuse of antimicrobial drugs are a major factor in the spread of antimicrobial resistance, and this has been identified as one of the biggest health challenges of the 21st century because of its negative effects on the management of infectious diseases in the world. In light of the seriousness of antimicrobial resistance, organizations such as the World Health Organization have identified antimicrobial resistance as one of the biggest health concerns in the world today.[2]

The increase in antimicrobial resistance is mainly as a result of the following factors in addition to the misuse of antibiotics. All these factors are sometimes referred to as the socioeconomic factors. They include poor infection control measures in hospitals and healthcare facilities, poor food handling practices, and poor community hygiene and sanitation.[2] Environmental factors are also important in this context. This includes the accumulation of antibiotic residues in the soil and other environmental systems. In addition, the use of antibiotics in the food industry and in animal husbandry has encouraged the emergence and spread of resistant microorganisms. All these factors contribute to the promotion and development of antimicrobial resistance in the environment and in the community.[3]

In fact, the introduction of antibiotics has in the past led the medical community to conclude that the war against infectious diseases has been won conclusively. However, the rise of bacteria resistant to multiple antimicrobial drugs has changed the dynamics of the war against infectious diseases, and it is now becoming increasingly difficult to fight these diseases as they have escalated from a controlled and manageable threat to a menace in the form of resistant bacteria. Following the widespread clinical introduction of Penicillin in the 1940s, bacteria rapidly began to develop resistance, and this marked the beginning of the contemporary problem of Antimicrobial Resistance. Initial reports highlighted the presence of penicillin-inactivating enzymes, such as penicillinase, in pathogens like Staphylococcus aureus. Interestingly, Alexander Fleming himself highlighted in his Nobel Prize lecture in 1945 that the misuse of antibiotics and under-dosing could give rise to resistant pathogens. These early studies highlighted the adaptability of bacteria and thus marked the beginning of the AMR problem.[4]

However, the majority of the isolates of Staphylococcus aureus have developed resistance to penicillin, which was used to treat these bacterial infections. Methicillin was introduced as a solution to the resistance of S. aureus to penicillin. However, some strains have developed resistance to methicillin through the production of PBP2a, a penicillin-binding protein. This means that MRSA strains have the ability to develop resistance to several antibiotics, thus the need for the discovery of new antibiotics.[5]

Health Burden of AMR:

Global Epidemiology of AMR: Antimicrobial Resistance (AMR) is a major contributor to mortality and morbidity worldwide. In 2021, 21.36 million People died due to sepsis, there were an estimated 4.71 million deaths associated with bacterial AMR, with 1.14 million deaths directly caused by resistant infections. Over the past three decades, there has been an increase in AMR mortality trends among adults 70 years of age or older and a decrease among children under 5 years of age. Methicillin-resistant Staphylococcus aureus and resistance to Gram-negative bacteria, especially carbapenems, are major contributors to AMR mortality. It is estimated that over 8.22 million deaths per year may be associated with AMR worldwide by 2050 if current trends continue and it is estimated that between 2025 and 2050 39 million are expected to die due to AMR.[6]

The burden of AMR varies between regions and income groups. Low- and middle-income countries (LMICs), particularly in South Asia, sub-Saharan Africa, and Latin America, experience higher mortality rates due to AMR. On the contrary, high-income countries (HICs) have lower AMR levels despite high antibiotic use. This is attributed to well-structured health care, effective infection control practices, well-regulated antibiotic use, and access to clean water and sanitation facilities. The social determinants of income inequality, deprivation, and ethnicity are also known to affect AMR levels in HICs. The high-burden pathogens causing AMR worldwide are ESKAPE organisms, which include Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. These organisms are known to cause hospital-acquired infections and severe diseases.[7,8]

Prolonged Hospital Stays: Antimicrobial resistance plays a major part in the prolonging of hospital stays. This has a major impact on increased healthcare utilization and increased patient morbidity. Infections that are resistant to treatment often result in delayed treatment, treatment failure, or the need for second line treatments that are often complex or toxic. This all results in a longer hospital stay. Research has shown that individuals infected by resistant pathogens have a longer hospital stay compared to those infected by drug susceptible pathogens. A retrospective study showed that antimicrobial resistant bacterial pneumonia resulted in a hospital stay of 14 days compared to 8 days for those infected by susceptible pathogens.[9] In addition, population studies suggest that resistant infections can prolong the length of hospitalization by 9 additional days, as well as increase the risk of readmission or mortality.[10,11]

From a system perspective, the aggregate effect of increased hospital stays due to AMR can have a significant impact on the system. Modelling studies have shown that millions of additional hospital bed days can be caused by resistant infections, reflecting the substantial burden that AMR can have on healthcare systems worldwide. The increased hospital stays can also have a significant effect on secondary complications, including hospital-acquired infections or the need for intensive care. The international public health community, including the World Health Organization and the Centers for Disease Control and Prevention, has identified prolonged hospital stays as one of the key contributors to the overall public health burden of antimicrobial resistance. Therefore, it is essential to have appropriate antimicrobial stewardship measures to mitigate the increasing effect of AMR on the system.[12]

Complications in Medical treatment: Antimicrobial resistance is a critical concern in various aspects of critical care medicine. The consequence is a reduction in the efficacy of antimicrobial prophylaxis and treatment. The end result is an increased burden of illness and poor outcomes in specific at-risk populations. In the setting of chemotherapy for malignancy, for instance, a high prevalence of antimicrobial resistance in bacteria such as Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus limits the available antimicrobial agents and is associated with increased healthcare use in this at-risk population. A systematic review and meta-analysis revealed a high prevalence of resistant bacterial pathogens in cancer patients worldwide, especially in those with hematological malignancies.[13]

Similarly, solid organ transplant patients are also at an increased risk of multidrug-resistant organism bloodstream infections, including those caused by carbapenem-resistant Enterobacterales or other Gram-negative pathogens with reduced susceptibilities to antibiotics compared to susceptible pathogens.[14] In the ICU setting, the presence of resistant pathogens complicates patient care, increases the duration of ICU stay for patients with infections caused by such pathogens, and is also associated with poorer clinical outcomes for those patients (e.g., those caused by Gram-negative pathogens). Neonates with sepsis are also increasingly challenged by the presence of resistant pathogens that limit the options for empirical as well as definitive therapy for their infections, resulting in increased complications and risk of poor outcomes for the patients (e.g., trends of resistance in neonatal UTIs or sepsis). All of the above observations point to the various ways in which AMR complicates the provision of routine medical care for patients and increases the burden on them and the healthcare system.[15]

Impact on Surgical safety: Antimicrobial resistance (AMR) has a profound impact on the safety of surgical interventions by contributing to a rise in the incidence and severity of postoperative infections. The prevalence of resistant microbes such as multidrug-resistant Staphylococcus aureus, Klebsiella pneumoniae, and Pseudomonas aeruginosa in surgical site infections (SSIs) is a cause for concern in the safety and efficacy of surgical interventions. The latest study involving a multicentred cohort study observed that over 40 % of SSIs were associated with multidrug-resistant organisms. The study highlights the widespread prevalence of resistant microbes in SSIs and the increased risk of adverse outcomes in such cases.[16] Systemic evidence suggests that the rise in antimicrobial resistance makes the use of antimicrobials in the prevention and treatment of infections in the perioperative period challenging. The increased prevalence of resistant microbes in the perioperative period makes the safety and efficacy of surgical interventions a cause for concern.[17] The rise in antimicrobial resistance in SSIs and the increased risk of adverse outcomes in such cases make the use of antimicrobials in the prevention and treatment of infections in the perioperative period a cause for concern.[18]

Economic Burden of AMR: In addition to morbidity and disability, AMR poses serious economic loss. According to a Report by WHO, AMR could contribute to additional 1 trillion dollars to healthcare costs by 2050 and a staggering GDP loss about 1 trillion to 3.4 trillion per year by 2030.

Direct Costs:

1-Increased Hospitalization costs: A substantial part of the financial burden of AMR is caused by increased hospital stays for those whose infections do not resolve promptly with conventional antibiotic therapy. The infections that demonstrate resistance are not cleared quickly. Clinicians keep such patients under observation for a longer time and explore alternative treatment options. This results in increased cost burdens. The global modelling studies now suggest that the total cost burden of hospital stays for those with resistant infections is measured in hundreds of billions of dollars. The cost is mainly due to increased hospital stays. A global study published in BMJ Global Health estimated that the cost of multidrug-resistant infections was about US$693 billion for hospital stays worldwide. The cost of hospital bed days was a substantial contributor to the cost burden.[19]

A study conducted in Pakistan indicated that bloodstream infections that were resistant to antibiotics resulted in longer hospital stays, which meant additional costs of around PKR 9483 compared to susceptible ones. The cost of transportation, pharmacy, and lab tests was an additional cost of around PKR 3435 for the patient. The indirect cost, which included food, accommodation, etc, was higher for non-infected controls, which was around PKR 15,588. The cost of resistant ones was around PKR 9186 more than the susceptible ones, which indicates the cost due to longer hospital stays.[20]

2- Expensive second and third line of treatments: The other main direct cost is the actual price of the medication. As a result of the failure of first-line antibiotics, additional and more expensive antibiotics from the second and third lines need to be sought. The increase in drug costs is an important consideration since resistant infections require several treatments before an effective drug can be identified. Recent health economics studies worldwide note that one of the main causes of additional costs in antimicrobial resistance (AMR) is the need for these expensive alternative treatments, especially in severe infections where the initial treatments fail.[12,21]

The alternative treatments not only attract a premium price but can also require additional costs for dosage adjustment and combination therapy.

3-ICU Utilization: When the infections are severe or fail to improve with regular treatment regimens, the patient is likely to require Intensive Care Unit (ICU) treatment. The cost of ICU treatment is high due to nursing care, monitoring, and the need for machines to support respiration and other vital functions. Drug-resistant infections are also more likely to require ICU treatment, which means increased cost. While the actual cost of drug-resistant infections worldwide is subject to some variation depending on the study done, one fact is certain: all serious studies on the economics of healthcare have identified increased ICU treatment as one of the top drivers of increased cost due to AMR.[22]

Indirect Costs:

1-Loss of Productivity: The indirect costs of antimicrobial resistance (AMR) are mainly those of lost productivities, disabilities, and premature deaths from resistant infections. The people infected with AMR will take a longer time to recover from illness than those infected with susceptible bacteria. This will lead to a reduction in workforce participation in a country, thus affecting its overall productivity. A global modelling study found that the costs of lost productivities due to antibiotic-resistant infections amount to almost $194 billion annually. This also shows that there are macroeconomic implications of AMR beyond those of healthcare costs.[19]

2-Disability adjusted life years (DALYs): The resistant infections also cause a great deal of health loss to a country's population in terms of disability-adjusted life years (DALYs), which is a measure of the number of years lost due to premature death from an infection or illness caused by resistant bacteria. This also includes a measure of years lived with a disability. The DALYs lost to resistant infections are millions annually. This also shows that there are macroeconomic implications of AMR beyond those of healthcare costs.

3-Loss in GDP: The macroeconomic implications of AMR are seen in the fact that economic projections by the World Bank indicate that if current trends continue, AMR could cause a reduction in gross domestic product (GDP) by 1.1 to 3.8 percent by 2050. The low- and middle-income countries will be most severely impacted by AMR from an economic perspective. The reduction in workforce productivities due to AMR has also been found to cause billions of dollars in economic costs to OECD countries annually.[12]

Global Action Plan and Policy responses:

WHO Global Action Plan: The international response to AMR has been largely through the World Health Organization's Global Action Plan for Antimicrobial Resistance, which was adopted in 2015 to provide a comprehensive approach to international action against AMR. It has five strategic objectives that include increasing awareness and understanding of AMR, improving surveillance and research, reducing the incidence of infection, using antimicrobial agents in a more optimal manner, and ensuring sustainable investment in new medicines and diagnostics. It is reported that since its adoption, it has been guiding international policy action and encouraging countries to establish a comprehensive national action plan to address AMR, which is consistent with international action. It also recognizes the need to address AMR through a multi-sector approach that involves health, veterinary, and agricultural sectors and the environment. It is reported that progress is being made worldwide to address AMR, and it has helped to expand surveillance networks and antimicrobial stewardship policies and to increase international funding to support AMR mitigation strategies. However, it is also reported that implementation gaps exist, particularly in low- and middle-income countries due to lack of infrastructure and surveillance to effectively execute AMR control strategies.[23,24]

National Action Plan Pakistan Prospective: In the face of the antimicrobial resistance crisis across the globe, the World Health Organization called on its member countries to develop their National Action Plans on antimicrobial resistance in accordance with the Global Action Plan on Antimicrobial Resistance. As a result of this call to action by the World Health Organization, the Government of Pakistan launched its National Action Plan on Antimicrobial Resistance (2017–2022), implemented through the National Institute of Health Pakistan and the Ministry of National Health Services Regulations and Coordination. The plan is designed to address antimicrobial resistance through a One Health approach that brings together the human, animal, and environmental health sectors to combat antimicrobial resistance. Among its major priorities is to strengthen antimicrobial resistance surveillance activities, encourage antimicrobial stewardship, improve infection prevention and control practices, and increase awareness among the population about the improper use of antimicrobial agents. Pakistan is also a contributing country to the Global Antimicrobial Resistance and Use Surveillance System (GLASS), coordinated by the World Health Organization, to monitor antimicrobial resistance trends across the country and globally.[25]

Antimicrobial Stewardship: Antimicrobial stewardship programs are a fundamental part of various antimicrobial resistance mitigation plans worldwide. The programs focus on ensuring optimal antimicrobial use while minimizing resistance. Antimicrobial stewardship programs emphasize evidence-based antimicrobial use, dosing, and treatment duration to prevent excessive antimicrobial use. Various hospitals and healthcare facilities that have implemented antimicrobial stewardship programs have observed a decrease in antimicrobial misuse, positive patient outcomes, and decreased healthcare costs. Antimicrobial stewardship programs require a multidisciplinary approach to antimicrobial use among various medical practitioners, microbiologists, pharmacists, and infection control practitioners. Recent research has also focused on antimicrobial stewardship programs among both human and animal medicine, which is a clear indication of the relationship between antimicrobial use among humans and animals. Antimicrobial stewardship programs are essential in controlling antimicrobial resistance because they ensure optimal antimicrobial use while preserving the effectiveness of various antimicrobial agents.[26,27]

Surveillance Systems: Effective surveillance is crucial in identifying the trends of antimicrobial resistance (AMR) and informing appropriate public health decisions. The World Health Organization has established the Global Antimicrobial Resistance and Use Surveillance System (GLASS) to harmonize the process of collecting data on AMR and facilitate data sharing among nations. Pakistan participates in this system through national reporting to the National Institute of Health Pakistan. This enhances the surveillance of resistance to various pathogens. However, there are various challenges that hinder full spectrum surveillance in Pakistan, including limited capacity in the labs and gaps in diagnostic infrastructure and data reporting. This underscores the need to support investment in labs and effective national surveillance systems.[23]

One Health Approach: The evolution of antimicrobial resistance is embedded in the interconnected patterns of human, animal, and environmental systems. Thus, there is a paradigm shift toward a One Health philosophy. This means that we now recognize that how we use antimicrobials in agriculture and animal husbandry, as well as how we contaminate our environment, all contribute to the development and transmission of antimicrobial resistance. Teamwork is required to address antimicrobial resistance effectively, including public health agencies, animal health agencies, environmental agencies, as well as agricultural agencies. There is a need to address how antimicrobials are used improperly and how resistance genes are disseminated into the environment. Recent research has emphasized that a One Health approach to antimicrobial resistance is essential to address antimicrobial resistance effectively. This includes biosecurity measures, antimicrobial use in animals, as well as environmental surveillance.[26]

Conclusion

Antimicrobial resistance has progressed from being an isolated clinical problem to an overarching threat for global health and economic sustainability. The statistics presented herein illustrate an alarming trend, wherein ESKAPE organisms continue to surge ahead of drug discovery, and the very bedrock of modern medicine, from cancer therapy to neonatal care, is on the cusp of being fundamentally undermined. To effectively counter this threat, there must be an immediate transition from disparate solutions to an overarching One Health approach, wherein robust antimicrobial stewardship is complemented by innovative financing strategies. The disparate economic burden of AMR between LMICs and HICs also serves to illustrate that AMR is not simply an issue of biology, but also of equity. In conclusion, antimicrobial efficacy must be viewed as a global public good, and the cost of continued inaction must be calculated not merely in trillions of dollars of lost GDP, but also in the loss of all the medical progress of the twentieth century.

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