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Antimicrobial Resistance and its Impact on Public Health

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Aim of the Study: The current study addresses the increasing threat of AMR and its direct impact on global public health. It aims to contribute to the existing knowledge about the key challenges of AMR, bringing attention to the need for further research and creating a combined effort in the battle with antimicrobial resistance.

Background and Methods: Antimicrobial resistance (AMR) has been considered one of the key problems that humankind has come across, showing a massive impact on public health globally. The continuous emergence of new microbial strains complicates it further by reducing the efficacy of the available antimicrobial drugs. For the current study, various scientific journals were studied from multiple resources. Furthermore, the websites of policymakers and agencies associated with this cause were studied and referred to.

Results and Conclusions: The study has revealed a concerning trend of a steep increase in resistance of pathogens to antimicrobial agents. The major contributing factors which were identified during this study include misuse and overuse in the healthcare sector, inadequate prevention of infections and disease control, overuse in agriculture and the lack of novel antimicrobial agents. Several policies like the "One Health" approach by the Centers for Disease Control and Prevention (CDC) and the United Nations Sustainable Development Goals (SDGs) have been put in place as a means to combat the global public health problem. The study also highlights the need for policymakers, stakeholders and researchers to work in unison to combat the global issue.

Keywords: Antimicrobial Resistance, AMR, Healthcare, Public Health, Resistance

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Introduction

Antimicrobial resistance (AMR) is one of the most critical challenges faced by modern scientists and healthcare professionals which has a direct impact on global public health[1], [2]. The emergence, continuous and consistent evolution of resistant pathogenic microorganisms reduces the efficacy of available antimicrobial agents. This has reduced the ability to treat even the common infections and manage diseases increasingly difficult. The treatment of cancer, for example, is affected adversely due to the resistance to cytotoxic drugs[3].

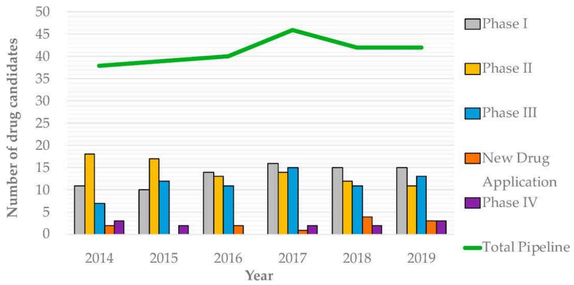

Figure 1 Evolution of the total antibiotic pipeline and the antibiotic pipeline by stage of development[4]. *The graph includes the clinical trials (phase I-IV) and a comparison with the total pipeline of novel antibiotics. Although the number of antimicrobial candidates is high, the candidates which make it to the phase IV trials are significantly low*.

The World Health Organisation (WHO) has already identified the misuse of antimicrobials as the driving force for AMR[5]. Studies have revealed that in 2019 alone, out of 4.95 million global deaths, 1.27 million deaths were due to AMR[6]. According to the report of The World Bank, it is estimated that AMR could add 1 trillion U.S. dollars to healthcare costs by 2050. They have also reported that the gross domestic product (GDP) would reach 3.4 trillion U.S. dollars by the year 2030[7]. The misuse of antimicrobials has not only fueled the emergence of novel strains but has also resulted in an increase in the severity of diseases along with their associated complications. It has led to longer hospital stays and increased chances of mortality[8]. It, therefore, undermines the basic cornerstone of medicine which is to control infections and secure the public health system.

AMR is not limited to just bacterial strains; fungi, viruses and parasites have also shown resistance to antimicrobial agents[9],[10]. The evolution of the resistant species is a natural biological process. AMR is often accelerated by human activities which include, overprescribing of antibiotics, and suboptimal infection control practices. It is predicted that the "post-antibiotic era", where even the common infections would be frequently untreatable, is not far away[11]. Another contributing factor to AMR is the uncontrolled and extensive use of antimicrobial therapeutic agents in agricultural practices and livestock production. The study revolves around understanding the means of acquiring resistance and analysing the various determinants leading to AMR. This study, therefore, aims to provide insights, anticipate future plausible challenges, and thereby contribute to the global fight to attenuate the threat to global health security.

Previous research on Antimicrobial Resistance (AMR)

Evolution is a natural, continuous, consistent process shown by all living organisms. Evolution, in the case of microorganisms, is largely influenced by human practices, which not only leads to the development of new strains but also helps them adapt to their new environment. The phenomenon of adaptation of microorganisms, which helps them to tolerate antimicrobial agents and thrive in their presence, is known as antimicrobial resistance (AMR). The property of resistance has been seen to arise via various mechanisms, which provide them with the means to survive.

Mechanisms of AMR

Mutation of the genetic material is one of the primary means of evolution and forms the basis of natural selection. Gene mutations are random, and spontaneous, and often take place during the replication of their genetic material[12]. β lactams, for example, are the most widely used antibiotics. To increase their spectrum of activity, however, several new classes of these drugs have been developed. Bacteria have developed mechanisms with which they can produce β lactamase, an enzyme which hydrolyses the β lactam ring and renders it ineffective[13]. Horizontal gene transfer (HGT) is another method which plays a pivotal

Role in conferring resistance to microorganisms. There are three main modes of HGT, i.e. conjugation, transformation and transduction, which allows the bacteria to exchange part or the entire genetic material to its mating partner[14],[15]. Table 1 provides examples of organisms, who they are resistant to and their mechanisms of providing resistance. Table 2 summarises the mode of action of various antimicrobial agents on a microorganism.

Table 1 Examples of intrinsic resistance and their respective mechanisms[16]

Resistance Mechanism	Observed Resistance	Mechanism Involved
Mutations	*Mycobacterium tuberculosis* to Rifamycins	Point Mutation in the Rifampin binding region
	Resistance to Fluoroquinolones	Mutation of the Quinolone Resistance Determining Region (QRDR)
	Escherichia coli, Haemophilus influenzae to Trimethoprim	Mutations in the gene specifying Dihydrofolate Reductase
Horizontal Gene Transfer (HGT)	*Staphylococcus aureus* to Methicillin (MRSA)	Acquisition of mecA gene
	Resistance to Sulfonamides	Mediated by horizontal transfer if foreign genes or parts of it
	Enterococcus faecium and *Enterococcus faecalis* to Vancomycin	Acquisition of VancomycinA and VancomycinB gene clusters which code for enzymes which can modify peptidoglycan precursor and hamper binding of Vancomycin

AMR is a dynamic and evolutionary process governed largely by the interaction of microorganisms with their environment. When microorganisms are exposed to the various external environmental pressures created by antimicrobial agents, they can change their overall genetic makeup to thrive and proliferate[18],[19]. In due course, the development of multidrug-resistant strains become prevalent[20]. AMR is a complex episode largely influenced by several factors. The key contributors include the inappropriate usage of antibiotics, poor infection management and control of the spreading of the infection. The unavailability of clean drinking water also contributes to this[21]. The key contributing factors leading to AMR are summarised in Figure 2. Factors which result in a susceptible strain becoming resistant are the rate of mutation, the frequency of horizontal gene transfer, the intensity of selective pressure and other ecological factors which include the population density, level of host immunity and the diversity of microbial community[22].

Table 2 Mode of Actions of different Antimicrobial Agents and their Target Sites[17]

Organism	Target Site	Antimicrobial Agent
Bacterial Spores	Core	- Formaldehyde - Glutaraldehyde - Hydrogen Peroxide
	Cortex	- Glutaraldehyde - Lysozyme - Nitrous Acid
	Coat	- Alkali
Vegetative Bacteria	Membrane	- Anilides - Hexachlorophene - Parabens - Phenols
	Cell Wall	- Formaldehyde - Mercury (II) Salts - Organic Mercurials - Phenols
	Cytoplasm	- Chlorhexidine - Copper (II) Salts - Glutaraldehyde - Hexachlorophene - Hydrogen Peroxide - Mercury (II) Slats - Organic Mercurials - Phenols - Quaternary Ammonium Compounds - Silver Salts
	Leakage of Intracellular Components	- Chlorhexidine - Quaternary Ammonium Compounds
Fungus	Ribosomes	- Hydrogen Peroxide - Iodine
	Plasma Membrane	- Alcohols - Chlorhexidine - Esters - Organic Acids - Quaternary Ammonium Compounds
	Cell Wall	- Glutaraldehyde
	DNA	- Acridine - Dyes
	Amino Groups	- Ethylene Oxide - Formaldehyde - Glutaraldehyde - β-Propiolactone - Sulphur Di-oxides - Sulphites
Virus	Envelope	- Alcohols - Quaternary Ammonium Compounds - Chlorhexidine
	Nucleic Acids	- Peracetic Acid

Capsid	- Alcohols
	- Glutaraldehyde
	- Iodine
	- Peracetic Acid
	- Phenols
	- Quaternary Ammonium Compounds
Thiol Groups	- Bronopol
	- Copper (II) Salts
	- Ethylene Oxide
	- Glutaraldehyde
	- Hydrogen Peroxide
	- Iodine
	- Mercury (II) Salts
	- Organic Mercurials
	- Silver Salts
	- β-Propiolactone

Effect on Public Health

The immediate and tangible consequence of antimicrobial resistance is the effect it has on human health[23],. It undermines our ability to have an effective treatment plan to cure infectious diseases and decrease mortality and morbidity rates. It also reduces the chances of complications that may arise from the infection. It is predicted that the morbidity rate will rise nearly to 10 million by 2050[24]. A patient infected with a multidrug-resistant strain is likely to have a prolonged illness with delayed recovery. The rate of treatment failure is higher in comparison to a patient who is infected with a less resistant strain. Furthermore, AMR poses a threat to the management of healthcare-associated infections (HAIs) or nosocomial infections in vulnerable groups of people who might be immunocompromised[25]. Additionally, AMR complicates the treatment regime of chronic diseases which require long-term antimicrobial therapy, such as in the case of malaria, tuberculosis (TB) and HIV/AIDS[26]. Table 3 comprises the list of countries which are potentially at risk.

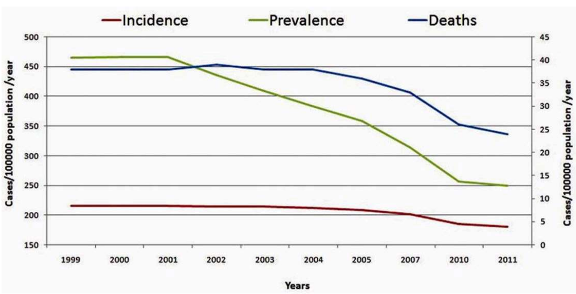

Figure 3 TB cases in India from 1999 to 2011[27]. *Comparison of MDR TB cases reported against the total TB cases reported from the year 2005 to 2011 in India. It shows a significant rise in mortality rates from 2001-2004. Although the mortality rates have seen a decline, the statistics of mortality and prevalence are still alarming.*

Table 4 Key Determinants of AMR. *Three major determinants are identified and listed along with the reasons for misuse/overuse associated with them.*

Determinant	Reasons for Misuse/Overuse
Consumption of Antimicrobial Drugs[36],[37],[38],[39]	- Lack of laboratory testing protocols - Use of broad spectrum antibiotics - Generation of cross immunity for treatment of viral infections using drugs other than antivirals
Overuse in Agriculture and Livestock[40],[41],[42]	- Self Medication for Infections - Growth Promotion
Environmental Contamination[43],[44]	- Untreated healthcare wastes - Industry contamination

Economic Burden and Societal Consequences

There is a substantial economic burden that AMR presents. It encompasses healthcare costs directly, and on the management of productivity losses. AMR not only poses a significant financial strain on the healthcare systems, but also requires increased expenditures on following up with an alternative therapy route, and infection control mechanisms, and requires strict surveillance programs[29]. Studies have shown that the economic costs associated with AMR amount to billions of dollars annually in nations both developed and those who are still developing[30],[31]. AMR has significant implications for society. It directly affects the communities, families and individuals in detrimental ways. In healthcare systems, the spread of microorganisms that are resistant to available antimicrobial agents, undermines the safety, security and overall effectiveness of treatment procedures[32],[33]. The patients and their families would experience intensified fear and anxiety and would be frustrated with the prospect of failure to get proper treatment or several other associated complications. The healthcare system is not equal for everybody[34]. Individuals or groups suffering from an infection which is resistant to antimicrobial therapies only complicates the situation.

AMR therefore aggravates disparities and inequalities in this sector and affects largely the marginalised populations who have very limited access to proper treatment, clean drinking water and sanitation practices[35]. On a larger scale, increasing AMR cases would make proper surveillance, control and management practices increasingly difficult.

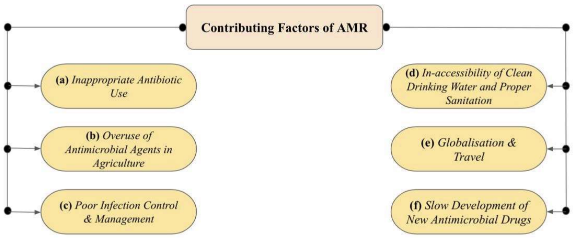

Figure 2 Contributing factors of AMR[21]. *The major contributors of AMR include the inappropriate and overuse of antibiotics in humans (a) and in agriculture (b), poor control and management of infections (c), inaccessibility of clean drinking water and proper sanitation (d), increase in travel and globalisation (e) and the slow development of novel or improved antimicrobial drugs.*

Discussion

To combat a global health crisis like antimicrobial resistance (AMR), coordinated action with strict implementation is a necessity. These strategies aim to address and resolve the multifaceted issues of AMR. It is already predicted that the morbidity rate will rise nearly to 10 million by 2050[24],[45]. From a national point of view, the government plays a key role in the development of policies to combat AMR. The government requires the help and coordination of the agencies to effectively establish and oversee the policies. Furthermore, it is also the role of the government to make the public aware of the ill trends and effects of AMR. On a global level, organisations like the World Health Organisation (WHO), the Food & Agriculture Organisation (FAO) and the World Organisation for Animal Health (OIE) have been developing and updating action plans to address and combat AMR. The United States Agency for International Development (USAID) for example, has made partnerships through their Global Health Security Agenda[46]. The WHO has set up the Global Action Plan[47] in 2019, for healthy lives and well-being for all. Switzerland-based company, the Global Antibiotic Research and Development Partnership (GARDP) works to provide access to treatments for drug-resistant bacterial infections. With several partners, it aims to preserve the efficacy of antibiotics[48].

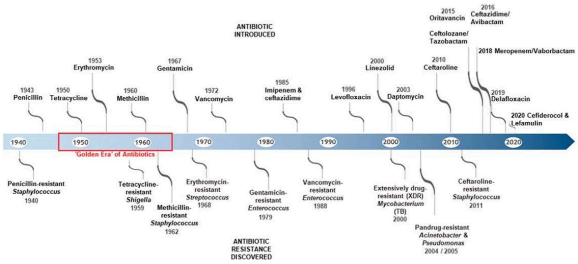

Figure 4 Timeline of discovery of a few antibiotics[23]. *A comparative timeline of the discovery of antibiotics and the development of AMR associated with those antibiotics. Roughly ten years is enough for an organism to develop resistance to a particular antibiotic drug.*

Regulation of the determinants of AMR (table 4) is an essential step in combating AMR. Enforcing the regulatory frameworks to strengthen environmental governance is essential. Furthermore, the development of a national action plan and implementation of it is crucial. Chemical and biological pollutants from the various industries should be closely monitored. That can only be achieved with enhanced surveillance, monitoring and reporting of recorded data. It is essential that innovative research and proper funding are provided to address the issues of AMR[49]. In terms of total volume, India is one of the topmost consumers of antibiotics[49],[50]. The Indian Ministry of Health and Welfare has therefore formed a National Action Plan on AMR (NAP-AMR) for 2017-2022 which addresses six critical points (figure 5). It was presented at the 70th WHA in Geneva in May 2017[51].

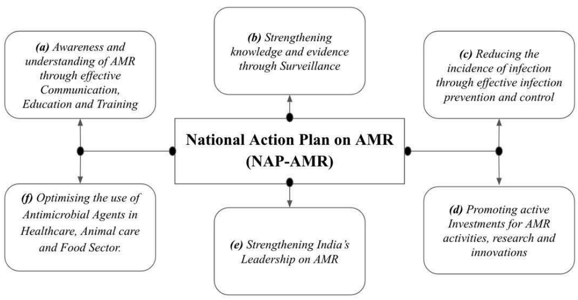

Figure 5 The Indian National Action Plan on AMR (NAP-AMR) for 2017-2022[51]. *The NAP-AMR addresses six critical points (a)-(f)*

To which the various healthcare systems should adhere to control AMR.

Another approach in the battle against AMR is the introduction of Antibiotic Stewardship Programs (ASPs). It is an initiative to promote accurate usage of antimicrobial agents by reducing irrelevant prescriptions and improving the overall outcome of the therapy[52],[53]. The roles of ASPs are summarised in Figure 6[54]. ASPs have not only improved treatment outcomes, but cases show that they have been effective in the management of *Clostridioides difficile* infections[55]. It not only reduces the overall cost of treatment but also has an impact on reducing AMR from healthcare facilities. ASPs, therefore, promote sustainability by optimising the various healthcare practices and act as a barrier to AMR[56]. The number of healthcare systems adopting ASPs has increased over time, however, smaller healthcare systems still have not adopted them. Lack of funds remains a barrier to this program[57].

Figure 6 Roles of ASPs[54]. *The roles of ASPs include the enhancement of infection prevention and its control, prescribing only the necessary and appropriate antibiotics when needed, proper assessment of treatment regimes, selecting the antibiotic for the shortest duration, increasing surveillance for AMR and HAIs and initiating an interdisciplinary approach.*

Besides regulation of the determinants (table 4) and employing ASPs to control AMR, an adaptation of several other approaches might help in combating AMR.

Non-pharmaceutical practices such as maintaining overall hygiene, and sanitation, and enforcing proper vaccination programs can help control the infection and prevent its transmission[58]. Adopting alternative forms of treatment can also be an immense help[59],[60]. Bacteriophage therapy is specific and would work against multidrug-resistant strains. It can also be combined with CRISPR-Cas systems to make it more effective[61],[62]. The use of immunomodulatory agents, which modify host immune responses is an efficient alternative. Modern therapy regimes recommend the use of probiotics and prebiotics. They not only restore the microbial flora of the patient but can also enhance and modulate their immune responses. Some modern therapies also include the use of vitamins as an alternative to antimicrobials[63],[64]. Disrupting the biofilm of a pathogen would make it sensitive to the antimicrobials[65]. Modern technologies, like using nanoparticles as a mode of therapy, are also advised. They can be used as drug carriers and can be used to enhance the effectiveness of antimicrobial agents. However, the extent of toxicity is questionable[66]. An antibiotic combination therapy could also likely solve the issue of AMR[67]. In many cases, combination therapy has shown positive results. A combination of an antibiotic with a bacteriophage has been used in the treatment of MDR infections[68]. Maintaining the safety and efficacy of these forms of treatment is a challenge. The alternative methods need to be tried and tested in clinical settings and undergo due trials before their implementation. Using these methods requires understanding the mechanisms of resistance, pathogenesis and the host-pathogen interactions to optimise the treatment. Research on the threat at hand becomes essential to study. Several techniques like machine learning are being integrated as a mode for translational research[69]. For maximal output, academic researchers, pharmaceutical companies, government and non-government agencies must come together and take a collaborative approach. Collaborative efforts at the global level for research and funding initiatives can bring all the agencies together. Academic personnel, healthcare providers, policymakers and even philanthropic people could work together. Their shared

Efforts and knowledge to address the issues would accelerate progress. The Global Antibiotic Research & Development Partnership (GARDP), for example, works in the segment of development and access to treatment for resistant bacterial infections[48]. Bringing together multidisciplinary research teams can help address the various queries which may arise during the process. Adopting open science initiatives can help in promoting transparency and reproducibility. Sharing research data can therefore be an important tool which can be utilised effectively. An initiative of the Center for Disease Control and Prevention (CDC), which is widely accepted and implemented is the "One Health" approach (figure 6). It integrates human, animal and environmental health points of view. It helps us understand the complex dynamics between the use of antimicrobials, the emergence of resistance and the transmission of resistant species. The foundations of the "One Health" approach are built on communication, coordination and collaboration[70],[71].

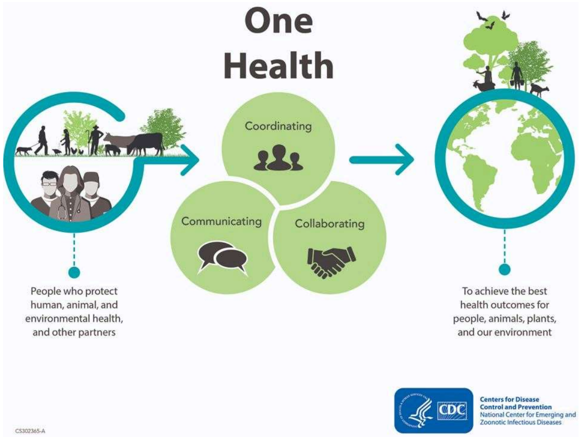

Figure 7 "One Health" initiative of the Center for Disease Control and Prevention (CDC)[70]. *This initiative integrates human, animal and environmental health points of view. It helps us understand the complex dynamics between the use of antimicrobials, the emergence of resistance and the transmission of resistant species. The foundations of the "One Health" approach are built on communication, coordination and collaboration.*

Conclusions

Antimicrobial resistance (AMR) is one of the top global public health issues that the world is dealing with. It threatens the efficacy of antimicrobial agents and thereby has a significant impact on global public health[72]. This study has revealed a concerning trend of a steep increase in resistance of pathogens to antimicrobial agents. A major contributor to AMR is the healthcare sector, through their overuse and misuse of antimicrobial agents[21]. As a result, the inclusion of increased surveillance policies and monitoring efforts in this sector becomes essential. Strict supervision and implementation of the use of antimicrobial agents become necessary for both human consumption and agricultural practices. Scrutiny of the implemented policies, with constant observation, is also key to this. Creating awareness, and educating people would not only help in the control of AMR but also inspire people to come forward for research and thereby help in the process of innovation[75]. In addition, this study has also explored the popular methods of adaptation by microorganisms and highlights the importance of this study[12],[14]. Optimised therapy plans and thereby controlling the spread of these resistant pathogens would significantly improve the quality of public health[59],[60],[73]. As the health outcomes improve, the associated economic burdens would decrease[29],[30],[31]. Several societal implications are associated with AMR. Food security, agricultural productivity and the overall economic development are affected. AMR, therefore, threatens the United Nations Sustainable Development Goals (SDGs). It aims to put an end to poverty, protect the planet and ensure that all lives can prosper[74]. Several initiatives including the "One Health" approach (figure 6) have been initiated to combat AMR[70]. With implementation gaps and resource constraints, the ability to fight AMR is challenging. Planned interventions and innovations like ASPs, and AMR can be controlled[56]. Investigating mechanisms of resistance and identification of novel antimicrobial agents will play a pivotal role in the forthcoming days.

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