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Review Article

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Growing burden of antimicrobial resistance and the need for effective stewardship: An Indian perspective

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ABSTRACT

History of antimicrobial resistance (AMR) dates back to the time from the discovery of antibiotics and has emerged as a significant public health problem. The recent COVID-19 pandemic saw the widespread and irrational use of antibiotics on a large scale. In this review on AMR we have compared the burden and impact of AMR in terms of morbidity, mortality and expenditure. Multiple strategies and action plans have been laid out by global leaders, and also in India to tackle the pervasive issue of AMR. There are a number of factors driving AMR, and recently major humanitarian crises around the world have come up as significant drivers and pose challenges to curbing AMR, which requires collaborative, multisectoral and dedicated efforts from all sides to bring down AMR. Like any other public health issue, attempts to control AMR are plagued with hurdles thwarting our efforts.

KEYWORDS: Antimicrobial resistance; One Health; Antimicrobial stewardship

1. Introduction

Antimicrobials have dramatically transformed medicine and were pivotal in increasing life expectancy from 32 years in the early 20th century to 71 years by 2021, primarily by reducing mortality from infectious diseases like pneumonia and meningitis[1,2]. However, a significant challenge that has emerged is antimicrobial resistance (AMR). AMR is the phenomenon where bacteria, viruses, fungi and parasites no longer respond to antimicrobial medicines. AMR is a major public health challenge, making infections increasingly difficult to treat and increasing the risk of transmission of disease and death. Such resistance naturally develops over time due to genetic changes in microbes. However, the misuse and overuse of antimicrobials in humans, animals, and agriculture are speeding up this process[3].

Recognizing the importance of this issue, the World Health Organization (WHO) listed AMR among the top 10 global health threats in 2019. It is alongside other critical issues like HIV and climate change[4]. This narrative review focuses on the rising problem of AMR in India, its drivers, and measures taken by the Indian government, emphasizing the urgency of implementing Antimicrobial Stewardship Programs (AMSP) to address this critical public health threat.

2. History of AMR

The history of AMR began with the discovery of penicillin by Alexander Fleming. The widespread use of penicillin, following its purification by Ernst Chain and Howard Florey, marked a milestone, empowering our fight against infectious diseases[5]. The era from the 1940s to the 1960s is celebrated as the golden age of antibiotic discovery, as several new antimicrobials like aminoglycosides, cephalosporins, and macrolides were discovered, which are vital even in the current age in combating infectious diseases. However, the pace of discovering new antibiotics has significantly slowed down[5].

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Shortly after the introduction of antibiotics, Fleming cautioned against their overuse, understanding the potential for misuse and abuse of antibiotics due to public pressure[6]. His concerns were quickly proven true as pathogens began developing resistance. Just one year after methicillin was introduced in 1960 as the first semi-synthetic penicillinase-resistant penicillin, methicillin-resistant Staphylococcus aureus (MRSA) was identified, highlighting the rapid emergence of AMR. MRSA has since become notorious for its association with high mortality rates globally every year[7–9].

Severe infections, such as bloodstream infections resistant to third and fourth-generation cephalosporins, require carbapenems, considered "last resort" drugs for effective treatment. However, using carbapenems irrationally can lead to the selection of resistant strains, resulting in multidrug-resistant isolates often associated with treatment failure. COVID-19, in its wake, led to the widespread overuse of antibiotics to save lives, which in turn has exacerbated the problem of AMR[10–12].

Over time, many antibiotics have fallen prey to resistance, leading to the emergence of "superbugs" — microbes resistant to the antimicrobials meant to treat them. Notable examples include vancomycin-resistant enterococcus, multidrug-resistant (MDR) Pseudomonas aeruginosa, MDR Acinetobacter, and carbapenem-resistant Enterobacteriaceae and Klebsiella pneumoniae, besides MRSA[13]. Realising the gravity of the situation, the WHO updated its Bacterial Priority Pathogens list in May 2024, featuring 24 critical pathogens spread across 15 antibiotic-resistant microbe families, grouped into critical, high, and medium categories[14].

2.1. Burden and impact of AMR

AMR has a significant impact in terms of healthcare expenses, morbidity, and mortality. AMR results in more extended hospital stays, the need for isolation beds to prevent the spread of infections, and increased ICU admissions. Outbreaks of resistant pathogens in healthcare settings may lead to the closure of hospital wings and elective surgeries can be canceled, leading to a delay in care. Data from 2022 on global AMR rates showed that the median resistance of *Escherichia (E.) coli* bloodstream infections to third-generation cephalosporins was 41.8% (ranging from 8.4% to 92.9%). The median methicillin resistance in *Staphylococcus (S.) aureus* was 34.7%. Additionally, *Klebsiella (K.) pneumoniae* showed high resistance levels to third-generation (median: 59.0% to 64.7%, depending on the specific antibiotic) and fourth-generation (57.4%) cephalosporins[10,15].

It has been estimated that bacterial AMR contributed to 4.95 million deaths and directly caused 1.27 million deaths globally in 2019. More than 1.5 million deaths resulting from lower respiratory tract infections in 2019 were due to AMR. The resistance associated with six major pathogens (*E. coli*, *S. aureus*, *K. pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter (A.) baumannii*, and *Pseudomonas aeruginosa*) was responsible for nearly 1 million deaths[16]. It is predicted that by 2050, 10 million deaths will be caused every year by AMR, equalling the predicted mortality by cancer[17].

Infections associated with AMR can be life-threatening after surgery, organ transplantations, or in patients undergoing chemotherapy or in other immunosuppressed conditions. The persistent trends of AMR will reduce the effectiveness of antibiotics, making classes of medications such as carbapenems and polymyxins, which are used as a last resort, less effective. It is also important to note that these medications may not be readily available in developing countries. Also, these medicines are expensive and have many adverse effects[18].

AMR has undermined decades of global efforts to combat infectious diseases such as tuberculosis (TB), HIV, and malaria. As per 2018 data, 3.5% of active and 18% of previously treated TB cases are MDR TB, and there is growing concern about extensively drug-resistant TB[19]. The number of HIV cases resistant to drugs is also increasing, with 60% of HIV patients in sub-Saharan Africa developing resistance. This increases the risk of patients developing acquired immunodeficiency syndrome and increases mortality[20]. *Plasmodium falciparum* has become resistant to antimalarial drugs over the past 50 years, particularly in the Southeast Asia Region[21].

The Centers for Disease Control (CDC) calculates that AMR will cost the United States 55 billion USD in healthcare expenses annually, with 20 billion spent on healthcare and 35 billion due to lost productivity from extended hospital stays[22]. According to a World Bank report, by 2050, AMR will lead to a 3.8% annual reduction in GDP, with shortfalls in economic output potentially reaching 6.1 trillion USD annually. The impact of AMR on poverty is more significant in low-income countries, as they are more reliant on labor income. The income will decrease with a high prevalence of infectious diseases, potentially pushing nearly 28 million people into poverty by 2050[23]. Similarly, just like humans, animals are prone to increased illness and mortality due to AMR, which impacts livestock production. By 2050, low- and middle-income countries will experience an 11% decrease in livestock production, further adding to their economic burden[24].

In a comprehensive study conducted by the Indian Council of Medical Research (ICMR) in 2023 regarding AMR, a total of 99492 culture-positive isolates were analyzed. *E. coli* emerged as the predominant pathogen, demonstrating a decline in imipenem susceptibility from 81% in 2017 to 63% in 2023. Additionally, imipenem susceptibility in K. pneumoniae decreased from 59% in 2017 to 36% in 2023. The study also highlighted that A. baumannii showed susceptibility only to minocycline and colistin[25]. MRSA rates had increased from 28.4% in 2016 to 42.6% in 2021, as per the previous reports[26]. The current report found MRSA among 50% ICU and 35% OPD isolates. Meanwhile, Salmonella typhi and Salmonella paratyphi showed good susceptibility to cephalosporins and azithromycin[25]. The 2021 report revealed an 11.4% terbinafine resistance rate among dermatophytes[26].

Moreover, in 2019, AMR was responsible for 297 000 direct deaths and contributed to 1 042 500 deaths. The mortalities due to AMR surpassed those caused by critical diseases such as neoplasms, respiratory infections including tuberculosis, enteric infections, diabetes, kidney diseases, and complications related to maternal and neonatal illnesses. The leading pathogens responsible for the high mortality rate in India include *E. coli*, *K. pneumoniae*, *S. aureus*, *A.*

baumannii, and *Mycobacterium tuberculosis*[27]. Furthermore, India experiences an increased burden of bacterial infections, notably with an estimated 410 000 children under five years of age succumbing to pneumonia annually, contributing to approximately a quarter of all child mortality. The crude mortality rate from infectious diseases stood at 417 per 100 000 individuals in 2016, placing AMR as a pressing public health concern in the country[28].

Additionally, the financial implications of AMR are profound in India, where out-of-pocket health expenditures account for approximately 47.1% of the total health expenditure, one of the highest in the world[29]. Such high out-of-pocket health expenditures have a significant impact, pushing families into poverty. According to a study by Chandy *et al.*, the median cost of treating resistant bacterial infections far exceeds that of treating susceptible counterparts, significantly burdening individuals in terms of overall costs, antibiotics, and pharmacy costs[30]. This economic aspect emphasizes the critical need for targeted interventions to alleviate financial and health impacts of AMR in India.

2.2. Factors driving AMR

Most disease-causing microorganisms can become resistant to various antimicrobial drugs. The primary resistance mechanisms include reducing drug uptake, changing the drug's target, inactivating the drug, and expelling the drug. Microorganisms can either inherit these resistance strategies or acquire them from other microorganisms[31]. Several factors listed below lead to the development and spread of AMR.

2.2.1. Irrational use of antimicrobials

From 2000 to 2015, global antibiotic consumption increased by 65%[32]. Over-prescription due to patient expectations and liability concerns contribute to drug resistance. Inappropriate use of broad-spectrum antibiotics, often due to a delayed or incorrect diagnosis, is also an important factor that exacerbates AMR[33–35].

2.2.2. Substandard drugs and over–the–counter availability

Substandard drugs, which contain incorrect doses of active ingredients, allow bacteria to survive and adapt, increasing the risk of resistance. The availability of antibiotics without prescriptions leads to misuse and overuse, with patients often self-medicating without proper diagnosis and using incorrect dosages[36,37].

2.2.3. Patients' non–compliance

When patients do not complete their treatment or use subtherapeutic doses, they fail to achieve optimal drug concentrations, facilitating the development of antimicrobial resistance[38,39].

2.2.4. Inadequate sanitation and hygiene

Poor sanitation promotes the spread of resistant bacteria through contaminated water and food. This results in more frequent infections and increased antibiotic use, which, in turn, selects for and proliferates resistant bacterial strains[40–41].

2.2.5. Misuse of antimicrobials in livestock

Excessive or inappropriate use of antimicrobials in animal farming, often for growth promotion or disease prevention without proper veterinary oversight, exposes bacteria to subtherapeutic doses, which fosters resistance. These resistant bacteria spread to humans through contaminated food or environmental pathways like soil and water[42–44].

2.2.6. Use of biocides in agriculture

Biocides, used as disinfectants, antiseptics, and preservatives in agriculture, can exert selective pressure on microbial populations, leading to the survival and proliferation of resistant strains. This resistance can arise through cross-resistance, co-selection, and horizontal gene transfer, amplifying resistance within microbial communities[43–45].

2.2.7. Travel and recreation

Globalization has facilitated the ease of travel, spreading infections, and AMR by allowing rapid movement of people, animals, and goods. Resistant strains can migrate from regions with high antibiotic misuse to those with stricter controls, worsening the global AMR problem. Notable examples include the international spread of drug-resistant strains of *E. coli* and *Salmonella*[46].

2.2.8. Humanitarian conflicts

Humanitarian conflicts present significant obstacles to AMR surveillance and control, including the absence of functional microbiology laboratories, inadequate antibiotic stewardship, weak infection prevention and control programs, and poor biohazard regulation. Direct attacks on health systems lead to the loss of trained professionals, resulting in mass casualties that increase reliance on empirical antibiotics and may necessitate the use of reserve antibiotics. Also, the availability and quality of antibiotics are compromised by disrupted supply chains and sanctions, both during and after conflicts[47,48].

3. Tackling AMR – current scenario

3.1. Global scenario

The global threat of antimicrobial resistance has led to a coordinated international response, manifesting in various strategic initiatives and programs. The "Global Action Plan on Antimicrobial Resistance" (GAP-AMR) is a comprehensive strategy developed by WHO in collaboration with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (WOAH) and was adopted by the World Health Assembly in May 2015. The main goal of this plan is to "ensure the continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality assured, used in a responsible way and accessible to all who need them." It also provides a framework for developing national action plans aligned with the global strategy[18].

GAP-AMR emphasizes the need for a "One Health" approach,

an integrated and unifying strategy to balance and improve the health of people, animals, and the environment. This approach involves mobilizing various sectors, disciplines, and communities at different levels of society to collaborate[49,50]. This facilitates the development and implementation of coordinated interventions that simultaneously address AMR in human healthcare practices, animal husbandry, and the environment, leading to more effective and sustainable solutions[51].

The WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015, the first global collaborative effort to standardize AMR surveillance. GLASS standardizes global AMR data collection, supports capacity building, and informs public health actions. It publishes annual reports summarizing global AMR trends, highlighting areas of concern[52]. By 2021, 116 countries had enrolled in GLASS, establishing it as one of the most comprehensive global AMR surveillance systems[53].

In 2017, the AWaRe classification of antibiotics was introduced by WHO, which categorizes antibiotics into three groups- Access, Watch, and Reserve- to guide their use and to promote rational prescribing. AWaRe has been widely adopted by healthcare systems and governments around the world as a part of their efforts to manage antibiotic use and prevent AMR[54].

The United Nations established an Interagency Coordination Group on Antimicrobial Resistance (IACG) in 2017 to guide the approach needed to ensure sustained, effective global action to address AMR. The group comprises high-level representatives of relevant UN agencies, other international organizations, and individual experts[55]. Following IACG's initial mandate in 2019, several new structures were also established, which include the Global Leaders Group on Antimicrobial Resistance, launched in 2020 to advocate for action on AMR, and the Independent Panel on Evidence for Action Against Antimicrobial Resistance, established to assess and report on the science and evidence related to AMR[56].

While these global initiatives represent significant strides in combating antimicrobial resistance, the fight against AMR remains an ongoing challenge that requires continued innovation, collaboration, and commitment from all sectors and nations.

3.2. Indian scenario

The Government of India recognizes the significant issue of AMR, and the Ministry of Health and Family Welfare has undertaken various initiatives to address this problem.

The National Action Plan for Containment of Antimicrobial Resistance (NAP-AMR), launched on April 19, 2017, involves stakeholders from multiple ministries and sectors to tackle AMR. The NAP-AMR identified six strategic priorities: 1) improving awareness and understanding of AMR through communication, education, and training; 2) strengthening knowledge and evidence through surveillance; 3) reducing the incidence of infection through effective infection prevention and control; 4) Efficiently using antimicrobial agents in health, animals and food; 5) promoting investments for AMR activities, research and innovations; and 6) strengthening India's leadership on AMR. Within each strategic priority and focus area, strategic interventions, key activities, and outputs have been defined with tentative responsibility and timelines – short (within 1 year), medium (between 1 and 3 years), and long-term (between 3 and 5 years)[57].

The National Programme on Containment of AMR, which was initiated during the 12th Five Year Plan, is under the direction of the National Centre for Disease Control. This program aims to establish a laboratory-based AMR surveillance system, monitor antimicrobial usage in healthcare settings, strengthen infection control practices, promote rational use of antimicrobials through stewardship activities, and raise awareness among healthcare providers and the community. The National Antimicrobial Surveillance Network was established under this program to track the magnitude and trends of AMR across different regions in India, with 35 state medical college labs across 26 states and UTs currently participating. This network generates quality data on AMR for seven priority bacterial pathogens using the WHONET software. The network focuses on seven priority bacterial pathogens: *Klebsiella* spp., *E. coli*, *S. aureus*, *Enterococcus* spp., *Pseudomonas* spp., *Acinetobacter* spp., and *Salmonella* enterica serotypes *typhi* and *paratyphi*[58].

AMSP has been implemented to encourage the rational use of antibiotics among healthcare providers. The program organizes a series of sensitization and training workshops in various healthcare facilities. AMSP is an intervention designed to improve the appropriate use of antimicrobial agents by the selection of optimal antimicrobial drug regimens, including dosing, therapy duration, and route of administration.

The main goal of AMSP is to optimize the safe and appropriate use of antibiotics to improve clinical outcomes and minimize adverse effects. Furthermore, a secondary goal is to reduce healthcare costs without negatively impacting the quality of patient care and to decrease the incidence of antibiotic-induced collateral damage[59]. Strategic approaches to antimicrobial stewardship include ensuring appropriate antimicrobial therapy, optimizing prophylaxis for surgical procedures, and developing antibiotic policies and standard treatment guidelines. Key strategies involve prospective auditing with feedback for timely prescription interventions and formulary restriction or pre-authorization. Educational and administrative improvements also play a crucial role. Active strategies like audit feedback and formulary restrictions are complemented by supplemental strategies such as didactic education, clinical practice guidelines for infectious disease syndromes, antibiotic cycling, combination therapy, and antimicrobial order forms. Switching from parenteral to oral therapy, information technology for surveillance and decision support, microbiology laboratory roles, process monitoring, and assessing antimicrobial consumption and outcomes are critical[59,60].

These government programs improved our ability to detect and fight antibiotic resistance. These efforts include setting up Antimicrobial Resistance - National Reference Laboratories (AMR-NRLs), strengthening labs in medical colleges to detect and notify AMR, and training healthcare workers. Researchers are also analyzing AMR surveillance data to develop local strategies to address the problem. Additionally, various educational activities

have been carried out to raise awareness about antibiotic resistance among healthcare professionals and the general public[61].

4. Challenges in effective AMR control in India

India is a country with a significant burden of communicable diseases, population migration, and high population density enables the spread of AMR. A resource-limited public health infrastructure in India is forced to rely on the irrational use of antimicrobials due to unavailability and higher patient load[62]. In a study done in two different states in India, researchers found that antibiotics were commonly dispensed over-the-counter at retail pharmacies for typically viral and self-limiting conditions like fever, cough, cold, and acute diarrhea, with pharmacists citing commercial interests and lack of stringent regulations as key drivers of this practice[63]. This excessive and inappropriate use of antibiotics among humans is a major contributor to AMR in India. Public understanding of AMR is generally poor, with the majority unaware of the risks of improper antibiotic use[64]. Antibiotics are readily available for purchase, and their misuse in the animal farming sector compounds the problem. Less than optimum infection control practices in many healthcare facilities lead to drug-resistant HAIs[65]. The country's limited access to clean water and sanitation increases the spread of infectious diseases, driving up antibiotic use and potentially promoting AMR[66].

The lack of an existing legal framework, with limited political commitment, and insufficient funds to support AMR control adds to the woes of controlling the misuse of antibiotics in both humans and animals[36,67]. India, a major producer and consumer of antibiotics, faces continuous challenges due to poor oversight in the production and disposal of pharmaceutical waste. Pharmaceutical industries providing financial incentives for overprescription further exacerbate the problems. Due to the low economic incentives available to the pharmaceutical industries, they hesitate to fund the research and development of newer antibiotics, and diagnostics. Inconsistent implementation of AMR policies across states and deficient human resources in regulatory bodies to enforce them deter progress[62,68].

In India, there are limited laboratories with dedicated infrastructure for AMR surveillance, and existing surveillance systems primarily focus on human health. With the increasing emphasis and the need to embrace the One Health concept, the lack of integration and data sharing between human, environmental, and animal health sectors hinders the effective monitoring of AMR in India[68]. Moreover, India's limited AMR surveillance system makes it hard to grasp the full extent of the problem and implement effective solutions[69]. These interconnected factors collectively hinder India's efforts to combat the growing threat of AMR.

5. Conclusions

Addressing AMR in India is a multifaceted challenge that requires a coordinated and comprehensive approach. This includes enforcement of the Drugs and Cosmetics Act and Schedule H1 regulations to prevent over-the-counter antibiotic sales. Establishing dedicated AMR monitoring cells within state drug regulatory authorities, as well as creating stricter penalties for unauthorized dispensing, is also necessary. Healthcare infrastructure must be expanded to reduce self-medication, with more primary healthcare centers in rural areas equipped with basic diagnostic facilities and appropriate antimicrobials, and enforcement of India-specific treatment guidelines.

Stewardship programs should be implemented with different approaches for urban and rural settings considering literacy levels and healthcare access, and antimicrobial stewardship committees should be established in all hospitals, including smaller district facilities.

Agricultural and environmental factors must be addressed through regulation of antibiotic use in livestock and aquaculture, and promotion of organic farming practices. Monitoring of antibiotic residues near pharmaceutical manufacturing hubs in states like Telangana and Himachal Pradesh needs to be done at frequent intervals, and appropriate effluent treatment measures need to be followed.

Public education campaigns should be developed in multiple languages for India's diverse population. Utilize accredited social health activists to educate rural communities on the appropriate use of antibiotics through targeted training programs, empowering them with accurate knowledge and communication tools to address misconceptions.

In 2018, the South Indian state of Kerala launched the Kerala Antimicrobial Resistance Strategic Action Plan (KARSAP), India's first subnational AMR action plan, aimed to address antimicrobial resistance through a comprehensive "One Health" approach. KARSAP's implementation highlights the importance of state-level initiatives in combating AMR and serves as a model for other states to develop localized strategies aligned with national and global action plans[70].

Surveillance systems need strengthening by expanding ICMR's AMR surveillance network, incorporating private sector data, developing accessible online reporting systems, and enhancing laboratory capacity across district hospitals.

Enhanced funding and support should be allocated to targeted research aimed at discovering new antimicrobials, optimizing existing treatments, and developing innovative diagnostic technologies. In recent studies, the taxation of antibiotics has been modeled as an effective way to curb the empirical and uncontrolled use of antibiotics[71,72]. By adopting these measures, we can effectively combat AMR and safeguard public health.

Conflict of interest statement

The authors claim there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Jayaprakasan AK, Ghosh A, Banerjee B, Singh MM and Solanki HK contributed to the writing, literature review, and editing of the manuscript to ensure clarity, coherence, and scholarly rigor. All authors reviewed and approved the final version of the manuscript.

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