Growing Concerns on Antimicrobial Resistance – Past, Present, and Future Trends

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Abstract

Antimicrobial resistance [AMR] is a global problem that affects multiple domains including healthcare, agriculture, aquaculture, and many more. Every year, 700,000 people die from it. AMR is predicted to claim 10 million lives by 2050 if immediate action is not taken. Thus, to halt the spread of AMR it is important to understand what contributes to its emergence and transmission across borders and domains. The burden is disproportionately higher in Low middle income countries (LMICs) due to multiple factors such as environmental, social, healthcare, and cultural barriers. This review paper describes the comprehensive analysis of the past, present, and future trends in AMR, focusing on the complex interconnectedness of the factors contributing to this issue. Historical trends reveal antibiotic discoveries, resistance periods, resistance genes, and multidrug-resistant pathogens, providing insights into crisis evolution and the emergence of multidrug-resistant pathogens. The present trends reflect the current state of AMR in India and emphasize the negative consequences of AMR for clinical medicine and healthcare systems. It identifies the factors driving the global pandemic surge and examines current global and country-level policies and actions to mitigate its impact. The future trends anticipate the trajectories of AMR and discuss innovative approaches to combat resistance, including the exploration of alternative therapies and the implementation of stewardship programs. Thus, by synthesizing existing knowledge and identifying emerging gaps, this review paper presents a holistic perspective on the evolution of AMR.

Keywords: AMR future threat, AMR in India, antimicrobial resistance, global health, health system factors for AMR, one health, public concern, strategies to mitigate AMR

Introduction

Antimicrobial resistance [AMR] has grown as a global challenge with far-reaching implications for healthcare, agriculture, aquaculture, and the economy. Its emergence and spread in the past few decades eroded the effectiveness of antibiotics, which were once hailed as a revolution in the medical practice and cure infectious disease.[1]

In 2019, there were 1.27 million deaths directly attributed to bacterial AMR out of an estimated 4.95 million deaths linked to bacterial AMR. The six leading pathogens for deaths associated with resistance are *Escherichia coli*, followed by Staphylococcus aureus, Klebsiella pneumoniae, *Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa*.[2]

The global resurgence of AMR is a complex crisis, not limited to human health. Excessive antibiotic use in agriculture and global interconnectedness have enabled the transmission of resistant genes, highlighting the need for a comprehensive "One Health" approach.

It is a particular challenge in India due to various reasons like high burden of communicable diseases, overburdened public health system, limited laboratory capacity for specific diagnosis of diseases and appropriately targeted treatment, inexpensive and readily available antibiotics without prescriptions, inconsistent infection control practices, and the lack of standardized effective surveillance system that monitor healthcare-associated infections.[2]

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Antibiotic resistance in Southeast Asian nations is poorly understood, despite WHO and national action plans [NAPs] raising awareness. Practitioners need to address this community gap to maintain drug efficiency.[3] The study explores historical patterns of AMR including assessment of its present conditions and speculating on its future potential trajectories.

Historical Perspective

Early era of antibiotics

Bartolomeo discovered mycophenolic acid in 1893, while Paul Ehrlich discovered Salvarsan in 1909, the first synthetic arsenic-derived antibiotic effective against Treponema pallidum, the causative pathogen of Syphilis.

In 1913, the second and more effective drug for Syphilis was discovered, which is Neosalvarsan. However, both of these drugs had elevated risk due to the presence of arsenic and were replaced by Prontosil – broad-spectrum antibacterial sulphonamide drug discovered by a German bacteriologist Gerhard Domagk in 1930.[4] Initially, this was used by soldiers in World War I. This discovery set a benchmark in the history of antibiotic research. However, due to the occurrence of mutations in the DHPS- dihydropteroate synthase (DHPS) enzyme, bacteria became resistant to Prontosil.

In 1928, Scottish Alexander Fleming discovered a fungus, Penicillium notatum, that inhibited *Staphylococcus aureus* growth [Refer Table 1].

Golden era of antibiotics

In 1939, French microbiologist René Dubos isolated tyrothricin from Bacillus brevis, inhibiting gram-positive bacteria. Selman Waksman, in the 1940s, discovered numerous antibiotics and antifungals, including actinomycin, neomycin, streptomycin, clavacin, and fumigacin marking the beginning of the antibiotic discovery era from the 1940s to 1970s.[5]

Few new antibiotic groups have been detected: Nitrofuran in 1953, macrolides in 1952, tetracyclines in 1948, quinolones in 1960, and oxazolidinones in 1987.[4,5]

Table 1: APA format

Timeline of Antibiotic Discoveries

Year	Drug Development	Effective Against
1893	*Mycophenolic acid*	*Bacillus anthracis*
1909	*Salvarsan [Arsphenamine]*	*Treponema pallidum- Syphilis*
1913	*Neosalvarsan.*	*A broad-spectrum antibacterial sulphonamide*
1930	*Prontosil*	*Gram-positive bacteria*
1928-1939	*Penicillin*	
1940-1970s	*Actinomycin, neomycin, streptomycin, clavacin, and fumigacin*	

Resistance period and discovery dropped

Following the golden era, there was a sudden reduction in the rate of discovery of novel drug classes in the 1970s because of the strategy of modification of existing antimicrobials due to overuse of the above-discovered medicines in a short period.[6] However, before penicillin was widely used, several observations suggested that bacteria may degrade it enzymatically.[7] The range is so extended that few bacteria like Enterobacteriaceae have become resistant not only to the original penicillin but also to semisynthetic penicillin, cephalosporins, and newer carbapenems.[8]

Present State of AMR in India

India is facing one of the largest burdens of drug-resistant pathogens in the globe, including the highest burden of multidrug-resistant tuberculosis and a rapid increase of resistance among gram-positive and gram-negative bacteria. Among the gram-negative bacteria, more than 70% of isolates of *Escherichia coli, Klebsiella pneumoniae,* and *Acinetobacter baumannii* and nearly half of all *Pseudomonas aeruginosa* were resistant to fluoroquinolones and third-generation cephalosporins.[9] Resistance to the drug combination of piperacillin-tazobactam was less than 35% for *E. coli* and *P. aeruginosa*, but due to the presence of resistant gene carbapenems, the combination became resistant to K. pneumonia up to 65%.[10] Colistin-resistant K. pneumonia has a low resistance rate of less than 1%, but a high mortality of about 70%.

Among the gram-positive organisms, in 2008, about 29% of isolates of *Staphylococcus aureus* were methicillin-resistant, and by 2014, this had risen to 47%.[10] The rates of resistance among *Salmonella* Typhi and *Shigella* species were 28 and 82%, respectively, for ciprofloxacin – an antibiotic commonly used to treat urinary tract infections 0.6 and 12% for ceftriaxone and 2.3 and 80% for cotrimoxazole.[9] These high resistance rates are attributable to the high use of antibiotics,[11] and antibiotic sales continue to rise rapidly despite the reduction of communicable diseases. The use of broad-spectrum penicillin has increased by almost double unit per 1000 population in the past 2 decades.

This resulted in a huge socioeconomic impact, increased costs due to prolonged stay in the hospital, additional and repeated laboratory investigations, and loss of work for treating these bacterial infections. There is a lack of estimates on the economic impacts of AMR in India. However, according to one study, the median cost of treatment of a resistant bacterial infection is more than a year's wages for a rural worker[12] [Refer Figure 1].

Factors Contributing to AMR

Health system factors

It includes healthcare practices, policies, and infrastructure. Pharmaceutical firms and pharmacists frequently compensate doctors in exchange for antibiotic prescriptions.[13] Private practitioner prescribes unnecessary and frequently compensated antibiotics that cause overuse and resistance in the community.

Patients have started approaching "Over-the-counter medicines" in the last few years because of easy availability, affordability, and increased awareness among patients. Many nations consider OTC medications as a distinct class of drugs and have developed regulations for their usage, but India does not have any specific guidelines for licensing OTC medicines. A study reported the prevalence of self-medication in the rural population of Maharashtra in India to be 81.5%,[14] urban Delhi to be 92.8%, and thus overall, 52% of Indians were estimated to self-medicate in India according to a web portal-based survey of 2000 people across 10 cities. The reasons were lack of time, the need to avoid doctors' fees, and dependence on the Internet[15] OTC drugs need to be appropriately labelled and proper regulations are need of hour for their distribution and delivery.

About 5% of India's GDP is allocated to the health sector, of which 0.9% is provided by the public health system and the majority by the commercial health sector. In the private sector, lack of knowledge regarding AMR, inadequate training, patient demands, and fear of losing patients are contributing factors. On the other hand, in the public sector, due to the heavy patient load, there is less time for counselling on the prudent use of antibiotics, nonavailability of essential medicines, and pressure to use short-dated medicine are major causes of inappropriate antibiotic prescription.

Environmental factors

Poor wastewater treatment facilities from India's pharmaceutical industry's antibiotic manufacturing companies cause gene resistance in the human microbiome. Antimicrobial residues have been found in animal products like meat and milk. India lacks regulatory provisions for antimicrobial use in domestic cattle, chickens, and pigs. The expansion of the chicken sector in India alone is expected to grow 312% by 2030. There is no tolerance of antibiotic residues in poultry, although such standards do exist for seafood under the Food Safety and Standards Regulations of 2011 and recently standards for honey were developed.[16,17] Thus, the transmission of resistance genes to human ecosystems and pathogenic bacteria is facilitated by environmental factors.

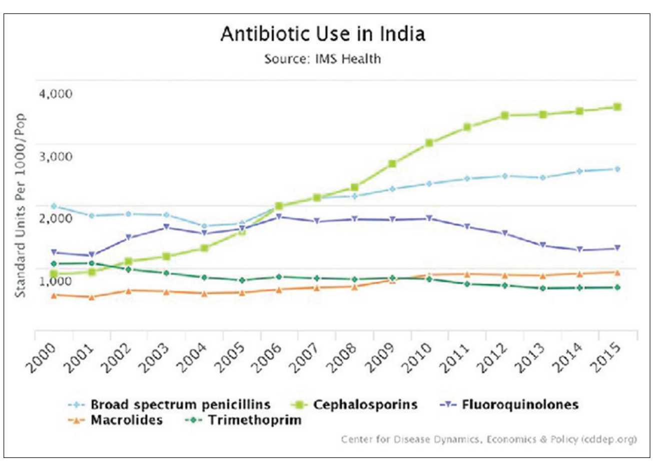

Figure 1: Trend analysis of antibiotic usage

Poor political will and government commitment

AMR is the best example of the iceberg phenomenon of disease with superbugs the visible manifestations of our prolonged failure to preserve antibiotics. It is essential to consider the lack of a strong governmental commitment to a comprehensive and coordinated response, proper regulation and surveillance system, and absence of accountability concerning antimicrobial usage and resistance. Another major issue is that there is a lack of national data on AMR in different pathogens except for those where there are specific national health programs. The networking of Revised National Tuberculosis Control Program (RNTCP) laboratories in the country generated some useful data on drug resistance in tuberculosis and recently a laboratory network has also been established for antimicrobial testing of HIV under the National AIDS Control Organization because of the rapid expansion in access to antiretroviral medicines in recent years.[18] Such sensitized action in major programs would track the usage of antimicrobials – the patient consumption pattern and mutation in the microbes as a reaction to the drug [Refer to Figure 2].

Actions Taken so Far

Global actions

During the 2015, World Health Assembly (WHA) nations made global commitments to the framework outlined in the Global Action Plan1 2015 on AMR for the creation and execution of multisectoral NAPs. It was supported by the governing bodies of the UN and the OIE-World Organization for Animal Health. WHO launched the Global Antimicrobial Resistance and Surveillance System in 2015 to fill the knowledge gaps and to inform strategies at all levels. An extensive platform collects, analyses, interprets, and shares region-representative data by countries, territories, and areas and monitors the status of existing and new national surveillance systems. A tripartite joint secretariat [FAO, OIE, and WHO] has been established and hosted by WHO to drive multistakeholder engagement in AMR.[19]

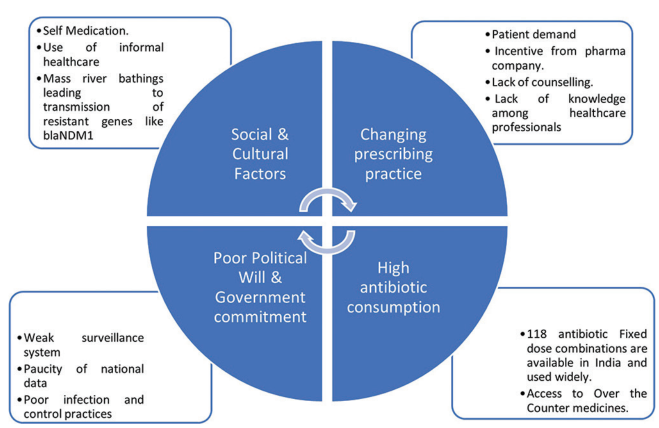

Figure 2: Factors contributing to AMR

Actions taken in India

National Task Force on AMR Containment in 2010 was the first significant move to solve the issue in India. The Jaipur Declaration, the National Policy for Containment of AMR, was followed by the inclusion of antimicrobial containment in the 12th Five-Year Plan in 2011,[20] but this policy did not make much progress.

With the ICMR's active participation and approval of the "Chennai Declaration" during Clinical Infectious Disease Society, further advancements were made.[21] This was the first gathering of Indian medical associations on this subject which offered a strategy for overcoming AMR's difficulties from an Indian point of view. The ICMR created a network of tertiary medical academic centers' laboratories for nationwide surveillance.[22]

The issue of antibiotic resistance and the introduction of the "Red Line" campaign were highlighted by the prime minister which put public education in the focus. A red line that appears on antibiotic packaging to alert people to the risks of misusing them has won praise from all over the world.[23]

In 2017, the government passed a NAP on AMR. Under the NAP-AMR, six strategic priorities have been determined that include improving awareness through IEC, efficient infection prevention and control practices, evidence generation through robust surveillance, promoting investments for research and innovations, and strengthening India's leadership in AMR.[24]

One Health Approach

AMR is a health issue affecting people, animals, plants, and the environment. The use of antimicrobials in hospitals and farm makes it more difficult to cure infections in both humans and animals. Currently, there is scientific evidence that the indiscriminate use of antimicrobials in the veterinary field has led to the emergence of resistant bacteria that cause infections in humans, particularly in *Enterococcus* spp., *Campylobacter* spp., *Salmonella* spp., and *E. coli* strains.[25-27] Furthermore, it has been documented that animal excretes a significant percentage [75%–90%] of antimicrobials without being metabolized and dispersed into the environment.[28] Moreover, the use of antibiotics in manure for agriculture practices transfers the antibiotic to various ecological niches such as soil and water.

AMR is ranked first in the most recent One Health approach framework according to the World Bank report. One Health framework offers a variety of strategies to stop the transboundary and zoonotic spread of AMR and maintain the efficient use of antibiotics in both human and animal treatment.

Novel Antimicrobials: Innovations to Combat AMR

There are some potential alternatives to antibiotic treatment such as passive immunization, phage therapy but the mainstream approach still relies on the discovery and development of newer and more efficient antibiotics. The majority of antimicrobial classes that we use today have been isolated mainly from soil actinomyces. So, some possible approaches to tap the novel antimicrobial diversity are the exploration of ecological niches other than soil like the marine environment, borrowing antimicrobial peptides and compounds from animals and plants, mimicking the natural lipopeptides of bacteria and fungi, accessing the uncultivated portion of microbiota through the metagenomic approach, and finally the use of the complete synthetic route.[29]

Future Prospects – Emerging Strategies for Tackling Antibiotic Resistance

Innovation depends on action and collaboration across sectors and healthcare settings.

1. Global nonprofit partnerships [such as CARB-X] are funding early-stage research to develop new treatments, particularly for use in LMICs. It focuses on targeting neglected and underinvested areas of research and development.
2. Pediatric practice needs innovation in particular since, even though drug-resistant illnesses are thought to be responsible for about 214,000 neonatal deaths each year, there has not been much study done on how long antibiotics should be given to patients. Only 53 out of 1,073 projects were explicitly examined for children under the age of five, even though these results in high U5MR.
3. Biochemical approaches to reducing resistance and increasing susceptibility to available antibiotics – The main idea of this approach is to neutralize the natural resistance defense mechanisms of microorganisms, thereby making already available antibiotics more effective and lethal – reactive oxygen species that can severely damage the bacteria's DNA and proteins if not quickly defused.
4. Effective vaccine development for deadly diseases like Hib – Prophylactic vaccines are also highly effective and valuable tools in the tool to fight against AMR. Disease prevention by vaccination lowers antibiotic use and reduces AMR. Both Haemophilus influenzae type B and pneumococcal conjugate vaccines are instructive examples and success stories having demonstrated their effectiveness in reducing antibiotic use and reducing AMR.[30]
5. In India, Star power has been used in numerous effective media efforts including those promoting polio vaccine and tuberculosis screening. For AMR, a new celebrity campaign would be a good start to make aware the public of the appropriateness of treatment when they receive the antibiotics from a prescriber or chemist.

Conclusion

In conclusion, every stakeholder concerned must put in tremendous effort if India has to successfully address the AMR challenge. Although it took a while for this topic to acquire attention, it now controls the public debate. In the recent G20 Summit on health, representatives from all over the world also discussed the global threat of AMR. The lack of a defined implementation plan and research shortages are impeding development despite the adoption of a national policy and the sizeable initiatives that are already underway. We can innovate to protect the future of modern medicine and prevent a postantibiotic apocalypse by working together across sectors and borders.

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