Review Article

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Addressing Antimicrobial Resistance in India: A 2 Stewardship Roadmap

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Abstract:

Antimicrobial resistance (AMR) poses a critical challenge in India, driven by the widespread misuse of antibiotics across human, animal, and environmental dimensions and exacerbated by the rapid expansion of the pharmaceutical industry. Despite progress in combating AMR, challenges persist. A holistic approach is necessary, encompassing awareness, education and stringent regulations to optimize patient outcomes. This review emphasizes the ongoing AMR challenge in India and proposes strategic solutions through the implementation of antimicrobial stewardship (AMS).

Keywords: antibiotic misuse, antimicrobial resistance, antimicrobial stewardship, india, public health

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Introduction

Antimicrobial resistance (AMR) poses a major public health challenge; especially in developing nations where widespread access to and extensive use of medications results in higher AMR incidences than in developed countries[1]. In India, infectious disease rates are among the world's highest, driven by irrational use of antimicrobials, contributing to increased AMR. India saw 297,000 deaths attributed to AMR, with an additional 1,042,500 deaths associated with AMR, in 2019[2]. Resistance primarily develops due to the inappropriate and excessive utilization of antimicrobial agents in humans, animals, the environment and food[3]. The rapid expansion of the Indian pharmaceutical industry has intensified selective pressure, leading to the significant release of waste-containing antibiotics into the environment and the convenient availability of non-prescription antimicrobials for both humans and livestock[4]. Globally, India is the largest consumer of antibiotics with respect to absolute volume[5], combined with extensive misuse in healthcare and agriculture, this has led to the widespread emergence of multidrug-resistant organisms (MROs) characterized by resistance to all available antibiotics[6,7]. Despite this, there is a notable scarcity of social analysis regarding the intricacies of resistance in everyday life and limited exploration of its impact on the practices of health professionals[8].

Recent strains of pathogens; especially those classified as gram-negative bacteria, have demonstrated intricate resistance mechanisms against conventional antibiotics. The molecular targets of antibiotics have undergone rapid evolutionary changes within a limited timeframe and over a few successive generations. Bacteria have developed adaptive strategies to counteract the impact of antibiotics commonly employed in healthcare systems. Noteworthy alterations in penicillin-binding proteins, upregulation of efflux pumps, and increased beta-lactamase production have collectively contributed to a notable reduction in the efficacy of a broad spectrum of antimicrobials[9]. In addressing this growing challenge, carbapenems were introduced to provide partial protection against beta-lactamases. Initially celebrated as the preferred empirical therapy for patients with sepsis or severe infections, the rate of carbapenem resistance is now escalating at an alarming pace[10].

Despite considerable research and development efforts by pharmaceutical companies, there has been an absence of novel and significant antibiotics entering the market. Mindful utilization of existing antibiotic options is crucial to prevent the strain on healthcare systems from escalating due to the widespread prevalence of resistant and recurrent infections. Strategic use of existing antibiotics is crucial to mitigate the imminent threat of overwhelming healthcare infrastructure due to antibiotic resistance and recurrent infections[11].

India allocates a mere 4.7% of its gross domestic product (GDP) to healthcare, with the government contributing only 1.15%[12]. Addressing a bacterial infection that is resistant to treatment incurs a cost exceeding the annual wages of a rural worker. Elements such as inadequate public health infrastructure, a substantial disease burden, and unregulated antibiotic sales collectively contribute to a swift rise in resistant infections in India. This, in turn, leads to notable socioeconomic repercussions; including elevated mortality rates, heightened healthcare expenses, and a loss in productivity[13].

In this review, we highlight the current AMR challenge in India and address it by implementing antimicrobial stewardship (AMS).

Origin and evolution of a health crisis

India's combat with AMR gained worldwide attention in 2008 when a new multidrug-resistant strain was isolated in a Swedish traveller[14]. The bacteria harboured a drug-resistant gene capable of transmission across various species. To the frustration of Indian authorities, the pathogen was named: "New Delhi Metallo-beta-lactamase-1" (NDM-1)[15]. This nomenclature marked a pivotal, albeit challenging, moment in India's emergence as a significant player in the growing AMR crisis[16]. NDM-1 then rapidly spread to other countries as well[17].

After the emergence of NDM-1, there was a growing number of reports in India about infants succumbing to drug-resistant bacterial infections. These infections proved untreatable, even with the use of last resort antibiotics[18]. The presence of NDM-1 highlighted how countries with lower incomes and resources play a significant role in the emergence of new types of drug resistance. India, in particular, was described as having ideal conditions that contribute to the worsening of this issue[19].

The high AMR burden in India is driven by different factors: antibiotic over prescription due to inadequate understanding by providers and patients, dispensing without prescriptions by pharmacists and insufficient monitoring of antibiotic use in hospitals. Faulty health systems have also included doctors receiving compensation for antibiotic prescriptions from pharmaceutical companies; additionally alarming resistance rates in animal isolates of human pathogens are reported; however, national estimates are lacking[20,21]. Available data has shown rising AMR rates in India. In 2008, 29% of *Staphylococcus aureus* isolates were methicillin-resistant; increasing to 47% by 2014. In contrast, countries with effective antibiotic stewardship and infection control have seen a decrease in methicillin resistant *S. aureus* (MRSA) isolates[22].

A recent systematic review has highlighted a wide spectrum of multidrug resistant tuberculosis (MDR-TB) rates in India: ranging from 0.85% to 9.9% among new cases and 4.5% to 20.6% among previously treated cases; wherein, the pooled prevalence of MDR-TB stands at 3.9% among new cases, 13.4% among previously treated cases, and 6.7% overall, showing consistently high heterogeneity across all cases[23]. Additionally, the current prevalence of MRSA in India is alarmingly high; reaching 37%[24].

Moreover, antimicrobial resistant microbes have been identified in various animal species and water sources across the nation, a topic that will be further explored in subsequent sections of this review.

AMR's deep-rooted presence in India

AMR is a complex issue requiring a multifaceted containment approach. Grace and colleagues have established a strong link between poverty, livestock keepers, and zoonotic diseases, disproportionately affecting both humans and animals; particularly in impoverished and marginalized communities[25]. One health, emphasizing collaboration among human health, animal health and environmental partners, addresses the interdependence of these factors in tackling AMR[26,27]. In India, rising AMR rates lack comprehensive research and data. Out of 2,152 studies, 48.3% focused on humans, 3.3% on animals, 4.2% on the environment, and 0.5% on one health, with the remaining studies covering various topics. Effectively controlling AMR requires due consideration for each contributor[28]. The prevailing extent of AMR in India is delineated below.

AMR in humans

According to the Indian government's report on AMR, over 70% of gram-negative bacteria exhibited resistance to cephalosporins (third-generation) and Fluoroquinolones, while nearly half of *Pseudomonas aeruginosa* demonstrated similar resistance[28]. The resistance to Piperacillin-Tazobactam was below 35% for *Escherichia coli* and *Pseudomonas aeruginosa*; however, *Klebsiella pneumoniae* showed a higher resistance rate of 65% due to the presence of carbapenemases. The surge in carbapenem resistance in

Acinetobacter baumannii to 71% in India has prompted an increased utilization of colistin as a last-line antimicrobial. Although colistin resistance has generally stayed below 1%, it is associated with a significant 70% mortality rate in cases of *K. pneumoniae* that are colistin-resistant. In Gram-positive organisms, 42.6% of *Staphylococcus aureus* exhibit methicillin resistance, and 10.5% of Enterococcus faecium show resistance to vancomycin. Resistance rates of 28% to ciprofloxacin for *Salmonella typhi* and 82% for *Shigella species*, along with rates of 0.6% and 12% to ceftriaxone and 2.3% and 80% to co-trimoxazole, respectively, are observed. For *Vibrio cholerae*, tetracycline resistance varies from 17% to 75% across different regions of the country[28].

AMR in the food chain

Food plays a crucial role as a carrier of AMR, hosting both spoilage and pathogenic bacteria. Elevated levels of AMR bacteria in food can have detrimental effects on human health, and it's possible that the true extent of AMR spread through the food supply is underestimated globally[29]. Resistant bacteria can infiltrate the food supply at any stage, from farm to consumption; thriving particularly on raw and undercooked foods. Exposure to these resistant bacteria can occur indirectly through food consumption or directly through contact with infected animals or their biological constituents (e.g., blood, urine, feces, saliva and semen)[30,31].

Poultry: In Asia, where 56% of the world's pigs and 54% of chickens are located, there is a noteworthy rise in AMR among animals[32]. This is particularly pronounced in China and India, where the usage of antibiotics in livestock exceeds rates of human consumption[32]. Globally, 73% of antibiotics are dedicated to food-producing livestock, which is in response to the increased demand for protein-rich food[32]. This amplified antibiotic use in both clinical and livestock sectors creates potential hotspots for the emergence of antibiotic-resistance genes, acting as crucial entry points into the food chain and subsequent ecosystem circulation[33]. The consumption of poultry in India is expected to surge by 577% from 2000 to 2030. Out of the seven studies available on AMR in poultry, three specifically addressed extended spectrum beta-lactamases (ESBL) producing *Enterobacteriaceae*, uncovering diverse rates of ESBL producers: 9.4% in Odisha[34], 33.5% in Madhya Pradesh[35] and 87% in Punjab[36]. The remaining four studies documented the occurrence of *Salmonella species* in broilers, with prevalence ranging from: 3.3% in Uttar Pradesh[37] to 23.7% in Bihar[38]. Notably, all isolates found in Bihar and West Bengal exhibited complete resistance to ciprofloxacin, gentamicin, and tetracycline[39,40].

Cattle: To enhance productivity in the food animal industry, antimicrobial agents are extensively employed due to their significant potential. In 2015, India became the world's top milk producer and the second-largest fish producer. Examining milk samples for AMR in livestock revealed that in West Bengal, 48% of Gram-negative bacilli in cow and buffalo milk were ESBL producers, while in Gujarat, 47.5% exhibited resistance to oxytetracycline[12,41]. Among Gram-positive organisms, West Bengal exhibited a vancomycin-resistant rate of 2.4% for *S. aureus,* whereas Karnataka reported methicillin resistance rates of 21.4% for *S. aureus* and 5.6% for coagulase-negative *Staphylococci*[42].

Aquaculture: In Maharashtra's lakes, Tilapia fish in India showed that 48% of *Enterobacteriaceae* in its gut were ESBL producers[43]. Additionally, *Vibrio cholera* and *Vibrio parahaemolyticus*, isolated from retail markets in Kerala. associated with shrimps, crabs and shellfish, demonstrated complete resistance to ampicillin and full susceptibility to chloramphenicol. However, resistance towards ceftazidime varied from 67% to 96%[44].

AMR in environment

Antibiotics from environmental microorganisms impact primarily on a microscale, with concentrations expected to diminish around the producing organisms; limiting exposure rapidly. In contrast, synthetic antibiotics operate on a macroscale, exerting selection pressures across entire microbial communities[45].

Antibiotics enter the environment through human and animal excretions[46], improper drug disposal[47], direct aquaculture or plant production contamination and waste streams from antibiotic production[48]. The most common and significant source of antibiotic release is usage and subsequent excretion. Exposure levels through this pathway are inherently limited by factors, such as the percentage of the population using the antibiotic, doses administered and metabolic processes in humans or animals[49].

Evidence strongly supports resistance selection in environments with exceptionally high antibiotic levels; particularly in areas polluted by antibiotic manufacturing. These increases are not accompanied by a corresponding rise in fecal contamination[50,41].

In India, antimicrobial-resistant bacteria and genes are found in water sources, primarily originating from untreated pharmaceutical wastewater and hospital effluents. The resistance rate of *Escherichia coli (E. coli)* to third-generation Cephalosporin varied depending on the water sources entering the treatment plant: 25% for domestic water alone, 70% for the combination of domestic waste and hospital effluent, and 95% for hospital effluent alone[52].

India's major, northern rivers: Ganges, and Yamuna, receive varying concentrations of drug-resistant bacteria. Within these rivers, 17.4% of Gram-negative bacteria exhibit ESBL production, and resistance genes; including blaNDM-1 and blaOXA48, have been identified[53,54].

All 283 isolates of *E. coli* from the Cauvery River in Karnataka, South India demonstrated complete resistance, marking a 100% resistance rate to third-generation cephalosporin[55]. In central India water used for drinking and recreation reported a 17% rate of *E. coli* resistance to third-generation cephalosporin[56]. Comparable investigations in North India (Kashmir) revealed a 7% resistance rate, while East India (Sikkim) documented a 50% rate, with South India (Hyderabad) reporting a complete resistance rate of 100%. Samples were collected from springs, ponds, rivers, lakes, hand pumps and tube wells[8,57,58].

Past actions and ongoing initiatives

For nearly a decade, the global concern of AMR lingered on the sidelines of political discourse, despite repeated warnings from the World Health Organization (WHO). It was not until mid-2016 that Indian prime minister Narendra Modi brought this critical issue to the forefront during his radio program. Modi declared AMR a serious crisis, underscoring factors contributing to resistance and urging citizens to change their habits of non-prescribed antibiotic use. The Indian government, recognizing the dangers of self-medication, emphasized the need to avoid antibiotics without prescriptions and complete prescribed courses[59].

Following Modi's declaration, the first inter-ministerial report on AMR in India shed light on the extensive challenges across the health and livestock sectors. Titled: "AMR and its Containment in India", the report proposed methods to enhance awareness and surveillance; outlining regulatory frameworks. Despite addressing structural problems, population vulnerabilities, and weak governance, the report lacked direct qualitative evidence, revealing a gap in social science knowledge that this article aims to fill[60].

Over the past eight years, India has demonstrated an increasing commitment to tackling AMR, aligning with Kingdon's policy window model[61]. The formation of a National Task Force, adoption of the Jaipur declaration and inclusion of antimicrobial containment in the 12th 5-year plan marked initial steps[62]. The Indian Council of Medical Research (ICMR) played an important role, leading to the "Chennai Declaration" in 2012, which outlined a roadmap for addressing AMR challenges[63]. Political commitment, notably from the Prime Minister, manifested in public education initiatives; such as the: "Red Line" campaign, launched in 2016 to raise awareness about antibiotic misuse[64].

Following this, in September 2016, the Ministry of Health & Family Welfare of India (MoHFW) put in place three governance mechanisms: the intersectoral coordination committee, Technical advisory group, and core working group on AMR. The core working group took the lead in formulating the National Action Plan on Antimicrobial Resistance (NAP-AMR), which outlines strategic priorities for tackling AMR and reinforcing India's leadership in the global campaign[65].

Aligned with the global action plan to combat AMR (GAP-AMR), endorsed by the 68th World Health Assembly in May 2015, NAP-AMR's strategic objectives mirror international efforts. However, it also emphasizes India's distinctive role by incorporating a specific priority tailored to Indian circumstances, highlighting the country's leadership in combating AMR through diverse partnerships. NAP-AMR delineates six strategic priorities[66]:

Improving awareness and understanding of AMR using efficient communication, education, and training.

Reinforcing knowledge and evidence through the surveillance of AMR. Decreasing infection rates by implementing effective infection prevention and control measures.

Enhancing the prudent use of antimicrobial agents in health, animals, and food.

Encouraging investments in activities, research, and innovations related to AMR.

Bolstering India's role in AMR leadership through collaborations at international, national and sub-national levels.

Each strategic priority has specific focus areas and interventions, with defined responsibilities and timelines spanning short, medium and long-term durations[66].

Role of ICMR

India has implemented key strategies that emphasized public education, rational use of antimicrobials, control of substandard drugs as well as the development of new drugs and vaccines, in response to the challenges posed by AMR[66]. The ICMR significantly contributed by establishing the Antimicrobial Resistance Surveillance and Research Network (AMRSN) in 2013, which reflected the nation's proactive stance in combating this critical global health issue[67].

In 2007, the Infectious Diseases Society of America, coined the term AMS, a comprehensive approach addressing the global health threat of AMR. AMS strategically optimises the selection, dosing, administration route and duration of antimicrobial therapy, so as to positively impact patient outcomes[68]. These coordinated measures significantly improve patient care, reduce infection rates and counter the progression of resistant pathogens[69].

Recognizing the urgency of AMS in healthcare institutions, the ICMR actively supported initiatives; including an AMS curriculum and workshops for awareness and education. Efforts were extended to expanding surveillance of antimicrobial usage and resistance trends, providing vital data for effective national treatment strategies. Despite strides, many Indian hospitals still lack structured AMS processes, emphasizing the need for a multidisciplinary approach. AMS programs enhance patient care quality and safety, resulting in increased infection cure rates, reduced treatment failures and improved precision in prescription for therapy and Prophylaxis[70].

In 2018, the ICMR launched the Antimicrobial Stewardship Program (AMSP) guidelines to assist Indian hospitals in establishing their programs. Section 15 of the guidelines suggests measures for quality improvement, emphasizing the need for a multidisciplinary team of physicians specialised in infectious diseases, a clinical microbiologist, a pharmacist, and infection control personnel comprising of the AMS team. This team secures separate funds within the hospital and focuses on capacity building, including infrastructure development for monitoring, reporting, audit capabilities and robust information systems[71].

Key components of a successful AMS program involve generating antibiograms and formulating an antibiotic policy tailored to specific infection sites. It is essential to mandate approvals for appropriate prescribing, dispensing and selling of certain drugs in addition to implementing comprehensive guidelines for antimicrobial treatment and prophylaxis. Training is mandatory, with periodic certification for hospital staff; particularly prescribers. Meticulous attention is given to monitoring and timely reporting of antibiotic use, encompassing past medical and medication history information collection and the implementation of electronic patient record systems[71].

Concrete objectives and quantifiable results are essential, encompassing adherence to surgical prophylaxis prescriptions, the implementation of: 'care bundles,' and the measurement of outcomes (rates of antimicrobial use, rates of bacterial culture, resistance rates). The audit and feedback processes are pivotal in overseeing implementation by reviewing prescriptions, laboratory results, clinical notes, and performing audits specific to antibiotic use. Interventions within AMS programs centre on aligning therapy with established guidelines and the clinical status of patients, employing strategies like directed therapy, de-escalation of therapy and optimizing dosage[71].

Education and awareness initiatives are vital, necessitating the integration of AMSP into medical education curricula and creating awareness among healthcare professionals, administrators, governing authorities and patients. Research on AMS is essential in addition to: encouraging studies on novel stewardship strategies, implementation, impact of programs, point prevalent studies, effective interventions and surveillance and management of antimicrobial usage data tailored specifically for Indian settings. This interconnected approach comprehensively addresses the challenges posed by AMR in Indian healthcare settings[71].

The ICMR has led diverse initiatives to advance AMSP practices; including establishing a nationwide network with six nodal centres and 20 regional centres for comprehensive AMR surveillance across India. Academic efforts involve developing an AMSP curriculum and conducting workshops to enhance expertise. Through the antibiotic stewardship and infection control programs, the ICMR trains professionals; such as microbiologists, pharmacologists and physicians. Multidisciplinary collaboration is emphasized, with effective AMSP involving various experts; like clinical pharmacists, infectious disease physicians, clinical microbiologists and informatics professionals. A survey assessed existing AMSP practices in India, providing insights and identifying gaps. Collaborative efforts extend to working with governmental departments and international agencies to establish an AMR network. Notably, the ICMR advocates for antibiotic regulation, aiming to reduce antibiotic usage; such as colistin in therapy and pushing for a ban on its use as a growth promoter in livestock and poultry. These initiatives underscore the ICMR's commitment to advancing and regulating AMSP practices in India[71].

Key advantages

Improved patient outcomes, such as decreased infection and mortality rates, fewer treatment failures and enhanced precision in therapy and prophylaxis prescriptions are some of the advantages of employing AMSP. Additionally, it plays a role in mitigating AMR by advocating for restricted antimicrobial use; thereby, slowing the development and spread of resistant organisms. AMSP also helps in cost savings, as effective stewardship programs have the potential to save 10–30% of antimicrobial costs by reducing unnecessary usage. By focusing on the selection, drug dosage, therapy duration and route of administration, AMSP optimizes antimicrobial utilization, thereby, ensuring the achievement of optimal therapeutic results[72].

Through regular surveillance and monitoring within a healthcare facility, AMSP further improves antimicrobial usage and resistance patterns in microorganisms. AMSP acts as a pivot in educating healthcare professionals about appropriate antimicrobial usage and guides them to make evidence-based and informed decisions. Moreover, AMSP helps to achieve environmental sustainability by curbing improper use and subsequent disposal of antimicrobials; thereby, reducing environmental accumulation of antimicrobials and their ecological footprint. This multifaceted approach is essential for preventing AMR in the environment[72].

Barriers to AMS implementation

AMSP implementation faces several prominent challenges. Firstly, numerous hospitals lack structured AMSP, along with a shortage of trained personnel to lead and participate in AMSP teams. Financial constraints further impede the implementation of effective surveillance systems, thereby, hindering the execution of AMSP. Additionally, a notable limitation exists in the form of insufficient microbiological laboratory capabilities in many healthcare facilities. There is also an absence of a clear antibiotic prescription policy in several hospitals. This leads to the irrationality and overuse of broad-spectrum antibiotics. posing a significant risk of resistance. Self-medication is another huge barrier, facilitated by easy over-the-counter access to antibiotics and a lack of awareness about associated risks. Another overlooked problem is the improper disposal of leftover antibiotics, which can harm the environment and human health; further contributing to the resistance problem. The absence of stringent regulations concerning antibiotic sales and use leads to unchecked access and utilization. Finally, treatment non-compliance among patients, who often do not complete the full treatment course, poses a substantial risk to the development of resistance[73,74].

Conclusion

The challenges of AMR in India demand a multifaceted approach. As the largest consumer of antibiotics globally, India faces dire consequences due to widespread antimicrobial misuse in health and agriculture. This issue has penetrated the food chain, causing AMR in animals; particularly poultry, impacting human health. AMR in the environment, driven by antibiotic-laden waste, further complicates the scenario; necessitating rigorous regulations.

Despite commendable efforts by the Indian government led by the ICMR challenges persist. The lack of structured AMSP in many hospitals, coupled with a shortage of trained personnel, financial constraints, and inadequate laboratory capabilities, hinders the implementation of AMSP. Addressing these challenges requires stringent regulations, enhanced education and promotion of rational antibiotic use. Ongoing collaboration and research are crucial in combating the growing threat of AMR in India's healthcare settings.

Conflict of interest

There are no potential conflicts of interest to declare.

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