Editorial

A Silent Pandemic of Antimicrobial Resistance: Challenges and Strategy for Preparedness in India

Yogendra Kumar Gupta[1,2] Subasree Srinivasan[2]

[1] Former Dean and HOD Pharmacology, All India Institute of Medical Sciences, New Delhi, India
[2] Global Antibiotics Research and Development Partnership, Switzerland

Ann Natl Acad Med Sci (India) 2022;58:55–59.

In the face of growing resistance against existing antibiotics and a dried-up pipeline of newer agents, the world is heading toward a silent pandemic. Globally, an estimated 4.95 million deaths occurred in 2019 due to drug-resistant infections including 1.27 million deaths attributable directly to bacterial antimicrobial resistance (AMR).[1] As per projected estimates, by 2050, AMR would cause approximately 10 million deaths worldwide and 2 million deaths in India.[1,2] Recently (2019), in World Health Organization's (WHO) list of 10 threats to global health, AMR stands on fifth place.[3] In the preantibiotic era, infectious diseases were the primary cause of mortality worldwide. Today, if AMR left unchecked, treatable infections will lead to huge increases in fatality from bacterial infections worldwide. The resistance to first line of empirical therapy (β-lactam antibiotics and fluroquinolones) against six priority pathogens (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas. aeruginosa*) accounted for more than 70% deaths globally.[1] This continued escalation puts at risk the very practice of modern medicine, unless drastic measures are taken today to counter this threat.

Paradigm of Antimicrobial Development and Resistance

The discovery of penicillin by Sir Alexander Fleming (1928) and its first use (1940) to treat serious infection brought modern era of antibiotics. While receiving the Nobel Prize (1945), Fleming warned about the beginning of an era of antibiotic abuse and evolution of resistance. His prediction came true when penicillin resistance became a substantial clinical problem in 1950s leading to development and use of newer beta lactam antibiotics. The first case of methicillin-resistant *Staphylococcus aureus* (MRSA) resistant to all available antibiotics emerged in 1962. Vancomycin (1959) was used sparingly to treat select cases of MRSA infection, until its use increased dramatically in the 1980s when MRSA became much more common. Between 1960 and 1980, pharmaceutical industry was flooded with newer antibiotics, and there were many descriptions of emergence of antibiotic resistant strains for various pathogens. The industry was able to innovate and introduce new agents and new classes of drugs that could counter these resistant infections. However, eventually the pipeline began to dry up and only few antibiotics have been developed in the twenty-first century, despite the continued evolution of AMR.

Etiology of Antimicrobial Resistance

AMR is a natural process of evolution for bacterial species; however, several factors have led to accelerated and more pronounced emergence of progressively resistant strains of pathological bacteria. The antibiotics have been overprescribed worldwide for syndromes not likely to be caused by bacteria, for example, viral upper respiratory tract infections. A direct link between antibiotic consumption and emergence and dissemination of resistant bacterial strains has been demonstrated by various epidemiological studies. The empirical use by clinicians is mainly attributed to nonavailability of rapid and accurate diagnostics required for management of life-threatening conditions.[4] Serial empiric use of antimicrobials by general practitioners is also widespread.[5] Although the use of antimicrobials has improved overall health and yield of crops and stocks in agriculture and livestock, increasingly abundant and diverse AMR genes in agricultural naïve environment suggest disturbed microbial ecology.[6] Further, the effluent produced by pharmaceutical antimicrobial

Address for correspondence Yogendra Kumar Gupta, MD, Principal Advisor India Strategy Development, Global Antibiotics Research and Development Partnership (GARDP) & Former Dean & HOD Pharmacology, All India Institute of Medical Sciences, New Delhi, India (e-mail: yk.ykgupta@gmail.com).

DOI https://doi.org/10.1055/s-0042-1756285.
ISSN 0379-038X.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

manufacturing units have contaminated the water and food sources in the vicinity. Recently, presence of ciprofloxacin in river Cauvery water is one such example.[7] Uncensored accessibility of antimicrobials outside of clinical oversight is another reason for rising AMR. In India, although the use of antimicrobials is regulated, their easy over the counter accessibility without prescription, abundance, and affordability has promoted misuse. Recently, despite guidelines issued by health ministry in India, antibiotic use has increased during first and second wave of coronavirus disease 2019 (COVID-19). A total of 16.29 billion doses of antibiotics were sold in India in 2020 and adult dose usage has increased from 72.6% in 2018 to 76.8% in 2020. The sales of azithromycin have increased from 4% in 2018 to 5.9% in 2020. Approximately, 216 million excess doses of antibiotics for adults and 38 million excess doses of azithromycin were sold between June and September 2020. On the other hand, adult antibiotic use has decreased in developed countries.[8] Tackling AMR will require a multipronged approach that addresses these root causes.

Challenges to Healthcare Workers

With rapidly evolving AMR, it has become a challenging task for healthcare workers to treat once treatable infections. Covering the issues faced in all specialities is out of scope for this article but in the following section we will illustrate the issues, with examples, faced by practitioners in few specialities to highlight the rising threat and vast impact of AMR on the very practice of medicine.

Globally, multidrug-resistant infections in pediatric populations vary from 20% in United States to 30% in Europe. In Sub-Saharan Africa, 66% of neonatal meningitis and sepsis were caused by resistant bacteria, 83% of children from South East Asia had resistant infections, whereas in Middle East 90% of new born hospitalized with sepsis had resistant bacteria.[9] In India, as per Centre for Disease Dynamic, Economics and Policy report, antibiotic-resistant infections kill approximately 58,000 children every year. Among hospitalized children across India, *S. aureus* and *K. pneumoniae* were the most commonly reported pathogens, from 2000 to 2015, with almost half being caused by MRSA and two-thirds of *K. pneumoniae* infections resistant to third generation cephalosporins.[10]

India is home to world's second largest geriatric population and projected approximately 320 million by 2050. Aging population poses various healthcare challenges including increased susceptibility to acquire various infections. Influenza and pneumonia are fifth leading cause of death among elderly patients with approximately 20% incidence of nosocomial infections; hence, there are lots of instances of empirical use of antibiotics. Senthilkumar et al reported 53.8% of empirical antibiotic use in a tertiary care hospital in India, among geriatric patients admitted between November 2018 and April 2019, with two thirds not having bacteriological investigations.[11] Moreover, 54.4% of the prescribed antibiotics were from WHO Watch category including cefotaxime and ceftriaxone, which goes against WHO stewardship guidance. The WHO in 2017 created the AWaRe (Access, Watch and Reserve) classification for antibiotics to prevent inappropriate use and restricting the newer class for resistant infections and recommends less than 40% of antibiotic usage to be from Watch and Reserve categories.

Surgical Site Infections

It is the second most common postoperative complication with incidence varying from 2 to 40% in developing countries.[12] The mortality rate increases from 2 to 11 times in patients who develop surgical site infection (SSI). Almost a decade back, Rajput et al showed that in Indian populations most common SSI were caused by S. *aureus* (43.18%), *E. coli* (22.72%), *Klebsiella* (15.9%), and *Pseudomonas* (4.54%). Almost 50% of the S. *aureus* were methicillin resistance and 22% of *E. coli* and 15.9% of *Klebsiella* were extended-spectrum beta-lactamases producing strains.[13] Similarly, Patel et al also documented increasing emergence of MRSA in 54.8% surgical infections in India.[14]

Cancer is the fifth leading cause of death in India and incidence of cancer is likely to increase in view of increasing aging population. Approximately one in five cancer patients require antibiotics during their course of cancer therapy. The Gram-negative sepsis among cancer patients at the Tata Memorial Hospital has shown a high level of resistance to cephalosporins, fluoroquinolones, and beta-lactam—beta lactamase inhibitor combinations, particularly in *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and Acinetobacter spp making the use of carbapenems and polymyxins routine in this group. This is alarming, as the emergence of strains resistant to all known antibiotics is a possibility.

Strategy and Preparedness to Tackle Antimicrobial Resistance

World Health Assembly (WHA, 2015) adopted a Global Action Plans (GAP) and accordingly countries developed their own National Action Plans (NAP) against AMR.[15] The measures taken globally and in India to strengthen the action plans, their implementation, and potential elements are necessary to move these forward in the near future.

GAP and NAP hand in Hand: Indian Perspective!

Lower middle-income countries are going to be the hardest hit due to high burden of infectious diseases, poor status of sanitation, lower access to healthcare facilities, inadequate diagnostic infrastructure, difficulty in procuring costly alternative of antibiotics, and suboptimal preventive measures in communities and hospitals. The WHA initiative on formulating the GAP was in line with these needs. India formulated NAP in line with the GAP detailing a 5-year program to contain AMR. The overall goal of these action plans is to enable the continuity of the ability of antimicrobial agents in preventing and treating infectious diseases.[16]

GAP identified five strategic objectives that are also adopted by the NAP (►**Table 1**).

NAP (India) additionally added a *sixth objective* to emphasize strengthening India's leadership on AMR by collaborations at international, national, and subnational levels.

Table 1 Strategic objectives adopted by the National Action Plan

Objective 1	Improve awareness and understanding of antimicrobial resistance through effective communication, education, and training
Objective 2	Strengthen the knowledge and evidence base through surveillance and research
Objective 3	Reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures
Objective 4	Optimize the use of antimicrobial medicines in human and animal health
Objective 5	Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines, and other interventions

India has gone ahead with the implementation of the NAP and has made strides into the initiation to combat AMR. Enrolment in WHO Global Antimicrobial Resistance Surveillance System, release of "antibiotic residues limits" in food from animal origin by Food Safety and Standards Authority of India, launch of Antibiotic Stewardship initiative and release of guidelines for antimicrobial use in common and hospital acquired infections by Indian Council of Medical Research and also Central Pollution Control Board drafted standards for antibiotic residues in pharmaceutical industrial effluent and common effluent treatment plants, and establishment of AMR surveillance laboratory networks are a few such measures. The plan to control AMR is comprehensive and promising; however, the implementation requires extensive teamwork of various stakeholders.[17] India's NAP followed the "One Health approach" focused equally on human and nonhuman sectors including environment and food-animal sectors. One Health recognizes the complex link between humans, animals, and environment to achieve better community health and well-being. It is an interdisciplinary and holistic concept, which takes into consideration the interdependent human and animal health in association with the ecosystem. The spilling and dissemination of resistant pathogens in between this chain lead to widespread transfer of AMR. The major domains of One Health in context with AMR include surveillance and reporting AMR, keeping track on transmission of multidrug-resistant pathogens among human-animal-environment, community awareness and education, policy making, and preparing a technical workforce to keep track on AMR. India has made great progress in beginning to implement most of the objectives of the GAP. But more needs to be done.

Strengthening the NAP: Focus on Diagnostic Stewardship and New Antibiotic Development

Diagnostic Stewardship

The right antibiotic for right patient at right time and in correct dose is essential to prevent resistance. Diagnostic capabilities are a must to understand susceptibility patterns and guide appropriate antibiotics. Developing better laboratories including newer diagnostics is important. Minimizing the duration of inappropriate empiric antibiotics is key to averting bad consequences of AMR-related infections and contain AMR. This needs systematic sampling for all patients with infections, laboratory diagnosis in a timely manner, and antibiotics to target highly drug-resistant pathogens. The key criteria of good diagnostics are accessibility, affordability, and ease of operation. The diagnostics should be patient centric and less time consuming. Often prescribing an antibiotic empirically is considered cheaper than going for an expensive and time-consuming diagnostic tool. The current methods for antibiotic susceptibility testing require several days to provide results. Newer genetically based methods may fail to differentiate between multiplying and nonmultiplying organisms, between colonization versus true infection. This challenge can be combated with innovation that requires an eagle approach. Biomarkers based on metabolomics/proteomics can give results in a very short span of time and could be an approach that helps with these barriers to care.

India is a diverse country with a large difference in availability of healthcare facilities at primary, secondary, and tertiary care centers along with government and private hospitals settings. So, developing diagnostics need a multifaceted collaborative approach. Microbiologists, clinicians, and government should work hand-in-hand keeping in view the public health prominence.

New Antibiotics Development

The pipeline of new antibiotic development should run in step to the speed of resistance. The time elapsed between introduction of a new antibiotic and the development of resistance is variable. Vancomycin had 16 years (longest) without resistance, penicillin developed resistance within 2 years, while recently developed daptomycin and ceftaroline developed resistance within a year.[9] Hence, it is essential to maintain investment in the development of newer antibiotics with a collaborative approach.

Currently, antibiotic development shows a failing market due to costs of drug development with relatively low volume of target infections. As a result, normal market forces cannot by itself drive sales; indeed it is these very forces that will accelerate emergence of resistance. Hence, innovation in the discovery and development of new antibiotics has slowed tremendously. Although there have been quite a few approvals in the past 10 years, most of these are modifications of older agents rather than new classes of drugs. In the past two decades, three new classes of antibiotics against Gram-positive pathogens have been approved, while there have been no new classes approved for Gram-negative infections. The newly established India Innovation Hub and the establishment of Centre for Cellular and Molecular Platform as an innovation incubator are significant steps in the right direction.

There is a need to potentiate the antibiotic development process through push and pull incentives. Push incentives include grants, tax incentives, or subsidies to lower antibiotic drug development cost. Examples of global initiatives include CARBx, Global Antibiotic Research and Development Partnership (GARDP), and Innovative Medicines Initiative (IMI). Pull incentives include economic models that provide rewards, patent extension, and exclusivity. For example, Generating Antibiotic Incentives Now act of US government extends market exclusivity for additional 5 years for licensed product to promote development of antifungal and antibacterial drugs for serious or life-threatening infections.

In low- and middle-income countries, rigid and lengthy process of regulatory approval, multilayered decision-making processes, limited financial, and human resources prevent the timely approval of drugs. Further lack of harmonization between countries leading to duplication of work and increased cost makes the drug development process inefficient. In India, Central Drugs Standard Control Organization is the apex body regulating the drug development process. Ministry of Health and Family Welfare constitutes Subject Expert Committee (SEC) to oversee drug development and for antimicrobial development, currently there are two committees (SEC Antiviral and SEC Antimicrobial) that oversee the novel antimicrobial development. To expedite antimicrobial innovation in India, regulatory authorities recommended to create a separate category for antimicrobials required in treating life threatening infection so that the clinical trial framework and regulatory approval process can be expedited. Further, it is recommended to create a committee of regulatory experts who can focus on issue related to AMR and can improve coordination among various stakeholders.

Multisectoral Coordination and International Collaboration

Health is a state subject in India and a few states have been able to launch their own action plans. However, setting an agenda and providing a toolbox of solutions would go a long way in implementation of plans at the local level. Moreover, there is a need for bringing together various factors that are currently working on AMR across the many sectors of the government, given the complex nature of AMR control. Appointing a central coordinating authority that can help create the AMR agenda for the next 5 years would be critical to continue the progress made thus far.

In order to strengthen India's leadership through international collaborations, it is recommended to create an antibiotic clinical trial network that can help in promoting collaboration with various national and international stakeholders and to support the conduct of complex clinical trials. India is strategically placed as the next chair of the G20 to play an influential and leadership role in elevating the issue of AMR in the region and globally.

Conclusion

AMR is a global and national threat. We need to strengthen the one health approach, implementation of policies to combat resistance, and strengthening of regulatory system by adopting technology driven solutions. This crisis is global and should be dealt with coordinated efforts. Emphasis should be given on building a research infrastructure locally in accordance with Good Laboratory and Clinical Practices for mutual acceptance of data between countries and bolster global and national AMR plans of action. In the words of Tagore—"You can't cross the sea merely by standing and staring at the water." India must confront this daunting and complex problem and show its leadership through innovation, regulation, and global collaboration.

Conflict of Interest
None declared.

References

1 Murray CJ, Ikuta KS, Sharara F, et al; Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399 (10325):629–655
2 Dixit A, Kumar N, Kumar S, Trigun V. Antimicrobial resistance: progress in the decade since emergence of New Delhi metallo-β-lactamase in India. Indian J Community Med 2019;44(01): 4–8
3 Ten threats to global health in 2019. Accessed August 17, 2022 at: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019
4 Kuehn BM. Excessive antibiotic prescribing for sore throat and acute bronchitis remains common. JAMA 2013;310(20): 2135–2136
5 Kuehn BM. IDSA: Better, faster diagnostics for infectious diseases needed to curb overtreatment, antibiotic resistance. JAMA 2013; 310(22):2385–2386
6 Zhu YG, Johnson TA, Su JQ, et al. Diverse and abundant antibiotic resistance genes in Chinese swine farms. Proc Natl Acad Sci U S A 2013;110(09):3435–3440
7 IIT Madras study finds pharmaceutical contaminants in river Cauvery | Mint. Accessed August 17, 2022 at: https://www.livemint.com/news/india/iit-madras-study-finds-pharmaceutical-contaminants-in-river-cauvery-11633609751477.html
8 Sulis G, Batomen B, Kotwani A, Pai M, Gandra S. Sales of antibiotics and hydroxychloroquine in India during the COVID-19 epidemic: an interrupted time series analysis. PLoS Med 2021;18(07): e1003682
9 Romandini A, Pani A, Schenardi PA, Pattarino GAC, De Giacomo C, Scaglione F. Antibiotic resistance in pediatric infections: global emerging threats, predicting the near future. Antibiotics (Basel) 2021;10(04):393
10 Dharmapalan D, Shet A, Yewale V, Sharland M. High reported rates of antimicrobial resistance in Indian neonatal and pediatric blood stream infections. J Pediatric Infect Dis Soc 2017;6(03):e62–e68
11 Senthilkumar S, Raaj ASA, Padmavathi K, Dhanapal CK, Periasamy K. Study on antibiotic use among geriatric patients based on anatomical therapeutic classification or defined daily dose methodology and world health organization-essential medicine list access, watch and reserve concept in tertiary care hospital of South India. Int J Basic Clin Pharmacol 2020;9(07):1106–1113
12 Narula H, Chikara G, Gupta P. A prospective study on bacteriological profile and antibiogram of postoperative wound infections in a tertiary care hospital in Western Rajasthan. J Family Med Prim Care 2020;9(04):1927–1934
13 Rajput RB, Telkar A, Chaudhary A, Chaudhary B. Bacteriological study of post-operative wound infections with special reference to MRSA and ESBL in a tertiary care hospital. Int J Adv Med. 2019;6 (06):1700

14 Patel I, Hussain R, Khan A, Ahmad A, Khan MU, Hassalai MAA. Antimicrobial resistance in India. J Pharm Policy Pract 2017;10(01):27
15 World Health Organization. (2015). Global Action Plan on Antimicrobial Resistance. Accessed August 17, 2022 at: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1&isAllowed=y
16 Sharma A. National Action Plan on Antimicrobial Resistance. 2017 Accessed August 17, 2022 at: https://ncdc.gov.in/WriteReadData/l892s/File645.pdf
17 Ranjalkar J, Chandy SJ. India's National Action Plan for antimicrobial resistance - an overview of the context, status, and way ahead. J Family Med Prim Care 2019;8(06):1828–1834

