

India's National Action Plan for antimicrobial resistance – An overview of the context, status, and way ahead

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ABSTRACT

Antimicrobial resistance (AMR) is a multifaceted complex problem with momentous consequences for individuals as well as health-care systems. Understanding the gravity of the problem, the World Health Assembly has adopted the Global Action Plan on AMR in the year 2015 as a part of the tripartite collaboration with World Health Organization, Food and Agricultural Organization, and World Organization for Animal Health. India's National Action Plan (NAP) for AMR was released in April 2017 by the Union Ministry of Health and Family Welfare. The objectives of the NAP include improving awareness, enhancing surveillance measures, strengthening infection prevention and control, research and development, promoting investments, and collaborative activities to control AMR. On the basis of the NAP, various states have begun the process of initiating their State Action Plans. The aim of this article is to highlight some of the main components of the NAP and to make family physicians, general practitioners, and other stakeholders aware of the issue of AMR and its factors and what can be done. The article also discusses some of the challenges in implementation of NAP such as varied perceptions about antibiotic use and AMR among key stakeholders, inappropriate antibiotic use owing to a number of reasons, lack of diagnostic facilities, widespread use of antibiotics in various sectors, environmental contamination because of pharmaceutical industry, agricultural and hospital waste, gaps in infection prevention and control, and difficulty in enforcing regulations. Similar to other low-middle income countries (LMICs), lack of sufficient finances remains a major challenge in NAP implementation in India as well. Overall, a strong political will, inter-sectoral co-ordination between public and private sectors and comprehensive strengthening of the healthcare systems are necessary to achieve the desired forward momentum.

Keywords: AMR, antibiotic use, challenges

Introduction

Antimicrobial resistance (AMR) is a critical public health problem, which can shake the foundation of modern health-care.^[1] Infections caused by drug-resistant organisms could lead to increased mortality and prolonged duration of hospitalization, causing a huge financial burden to the affected persons, health-care systems, and hinder the goals of sustainable development.^[2] Understanding the gravity of the situation and the threat posed by AMR on health-care, the World Health Assembly (WHA) adopted the

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Global Action Plan (GAP) on AMR in 2015.^[3] Following this, many countries have formulated their own National action plans (NAPs). The Indian Ministry of Health and Family Welfare published the National Action Plan for containing AMR in April 2017.^[4] It was submitted at the 70th WHA in Geneva in May 2017. This 5 year NAP on AMR (2017–2021) outlines the priorities and implementation strategies for curbing AMR in India.^[4] In the present article, we have briefly reviewed the NAP in relation to the status and challenges of AMR in India with the aim of sensitizing primary physicians, other healthcare professionals, and other stakeholders toward the various components of the NAP and the areas where they can support the NAP. Although the NAP focuses equally on human, environment, and food-animal

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sectors to encompass a one health approach, this article's focus is mainly on the human sector.

Overview of Antimicrobial Resistance in India

Although development of resistance is a natural phenomenon, selection of resistant bacterial strains is driven by antimicrobial use in human and animal sectors.^[5,6] Antibiotic-resistant strains have emerged among both Gram-positive and Gram-negative species. Examples include *Staphylococcus aureus*, *Enterococcus* species, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Escherichia coli*, *Klebsiella pneumoniae*, and *Neisseria gonorrhoeae*.^[7] Antibiotic resistance in *Mycobacterium tuberculosis* has led to the emergence of multi-drug resistant tuberculosis and extensively drug-resistant (XDR) strains causing tuberculosis (XDR-TB).^[8]

Bacteria differ in terms of the mechanisms by which they develop antibiotic resistance. Over the last couple of decades, novel mechanisms and dissemination of antibiotic resistance have been identified. Examples include the New Delhi metallo-beta-lactamases in Gram-negative bacteria, AmpC (a type of beta-lactamase)-mediated drug resistance in *Enterobacteriaceae*, Vancomycin-resistant Enterococci (VRE), and XDR *Mycobacterium tuberculosis*. Of late, drug-resistant mechanisms for carbapenems and colistin (which are important last resort antibiotics) have been identified among Gram-negative organisms, and cases of colistin resistance are being reported.^[9] The rise of “superbugs” is another cause for alarm. They denote multi-drug resistant organisms that can be treated only with the use of high-end antibiotics; examples of superbugs include the “ESKAPE” group of organisms i.e. *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species.^[10] Studies from India are limited, and a scaling up is essential to identify patterns of resistance as well as to quantify the nationwide mortality burden owing to AMR.

Use of Antibiotics

Studies have shown that resistance to antibiotics is directly linked to their usage.^[5] It would therefore be important to briefly review the patterns of antibiotic use. In 2010, India recorded a staggering 12.9 billion units of antibiotic consumption, which was the highest among all the countries.^[11] In addition, an increased consumption rate of carbapenems, lincosamides, glycopeptides, linezolid, and daptomycin has been reported in one study.^[12] The reasons leading to such situations are multiple, as explained here under^[13-18]:

1. Easy access to medicines over-the-counter in medical stores (chemist/pharmacy outlets);
2. Self-medication through hearsay or information gathered from the internet or upon the advice of the shop-keeper;
3. Non-availability and non-utilization of the laboratory service for cultures and antibiotic susceptibility testing;
4. Varying approach of treating doctors – owing to the anxiety of missing a bacterial infection or covering for secondary

bacterial infection, lack of up-to-date knowledge on the current revised guidelines and algorithms for antibiotic usage;

5. Empirical but incorrect use of antibiotics, simultaneous use of more than a single antibiotic when actually not necessary, not de-escalating when possible, inefficiency in the review of the response to antibiotics;
6. Regulatory issues – Lack of strict implementation of policies (such as schedule H1) and control by the regulatory authorities;
7. Varied perceptions such as perceived demand and expectations among key stakeholders and ethical challenges among healthcare professionals;
8. Unethical commercial practices to promote the sale of antibiotics in large quantities; and
9. Use of antibiotics by other non-medical and informal healthcare providers.

Not only misuse and overuse, but underuse due to lack of access is common in India. Lack of access to good quality, affordable antibiotics leads to significant mortality (especially in children), and hence, there is an urgent need to maximize access and limit excess antibiotic use.^[19] Besides the healthcare sector, antibiotics are also used in livestock such as in animal husbandry, fisheries, and agricultural sectors for therapeutic purposes as well as growth promotion.^[20] Environmental pollution by means of pharmaceutical waste, waste from livestock, and hospitals is another dimension contributing to the crisis of antibiotic resistance.^[21]

National Plan for Antimicrobial Resistance

The current NAP is comprehensive and aligns well with the World Health Organization's (WHO's) GAP for AMR.^[3] The plan covers all the five major objectives as listed in the GAP and adds an additional objective related to strengthening India's leadership on AMR.^[4] The plan proposes to target several key aspects of AMR in both human and non-human sectors (such as agriculture, fisheries, animal husbandry, and environment) incorporating the ‘one health approach’.^[22] The target periods for the components of various objectives have been listed as short-term (within 1 year), medium-term (from 1 to 3 years), and long-term (more than 3 years). The strategic priorities are mentioned below in Table 1. Similarly, Table 2 provides a list of key initiatives undertaken in India towards tackling AMR.

Strategic priority 1

This strategic priority focuses on the measures to increase awareness, design, and communication for the “Information, Education and Training” material, and implementation of communication programs for the public and other stakeholders involved in antibiotic use. It also proposes to revise the professional curriculum of students (medical, veterinary, and schools) and develop modules for promoting awareness. Besides, it proposes to offer training courses for people

Table 1: Priorities outlined in the National Action Plan for antimicrobial resistance in India

Priority	Main objective
Strategic priority 1	Improve awareness and understanding of AMR through effective communication, education, and training
Strategic priority 2	Strengthen knowledge and evidence through surveillance
Strategic priority 3	Reduce the incidence of infection through effective infection, prevention, and control
Strategic priority 4	Optimize the use of antimicrobial agents in all sectors
Strategic priority 5	Promote investments for AMR activities, research, and innovations
Strategic priority 6	Strengthen India's leadership on AMR by means of collaborations on AMR at international, national, and sub-national levels

Table 2: Some key initiatives by India to contain AMR before and after NAP adoption*

Initiative	Description
1	The Health minister of India along with the Health ministers of all member states of the WHO South-East Asia Region adopted the "Jaipur Declaration on Antimicrobial Resistance" in September 2011.
2	The "National Programme on Containment of Antimicrobial Resistance" was launched under the 12th five-year plan (2012-2017), which included Schedule H1.
3	An international conference on AMR - "Combating Antimicrobial Resistance: A Public Health Challenge and Priority" was jointly organized by the Government of India and the WHO in February 2016 and the "Medicines with the Red Line" media campaign was launched.
4	The National Action Plan on AMR was adopted in April 2017
5	To begin the implementation phase of the NAP, a meeting titled "National Consultation to Operationalize Action Plan for AMR Containment" was jointly organized by the Ministry of Health and Family Welfare, National Centre for Disease Control (NCDC), and WHO Country Office for India, State health ministries and other relevant stakeholders during 24 th - 25 th August 2017 in New Delhi.
6	Strengthening AMR surveillance network for key pathogens and enrolment in WHO Global Antimicrobial Resistance Surveillance System (GLASS).
7	Food Safety and Standards Authority of India (FSSAI) released "Antibiotic Residues limits" in food from animal origin.
8	The Indian Network for Fisheries and Animals Antimicrobial Resistance has been established with Food and Agriculture Organization's (FAO's) assistance
9	ICMR launched Antibiotic Stewardship initiative, released treatment guidelines for antimicrobial use in common conditions and the hospital infection control guidelines were made available on the NCDC website, in addition to the NCDC guidelines for antimicrobial use.
10	Draft standards for antibiotic residues in pharmaceutical industrial effluent and common effluent treatment plants were developed by the Central Pollution Control Board.
11	Kerala became the first state to adopt the sub national State Action Plan in October 2018

*The above list is not exhaustive

from various sectors and industries such as human, animal, environment, pharmaceutical, and food.

Studies have clearly shown that many stakeholder groups such as school students, teachers, and pharmacists are not fully aware of AMR and the consequences thereof.^[18,23,24] Awareness has to be improved among health professionals as well as the public. Although campaigns are held every year during the World Antibiotic Awareness Week in November with the aim of raising awareness among the public, sustained involvement of media all-round the year is essential. Mass media campaigns and special programs (in the form of celebrity interviews across print and electronic media) that focus on AMR could be designed, intensified, and combined with other initiatives such as the Revised National Tuberculosis Control Program (RNTCP) for tuberculosis (TB), the Swachh Bharath Abhiyan, India's National Immunization Programme, Redline campaign, etc. Although promoting awareness is the foremost step in this objective, awareness does not always translate into behavioral change, and hence, behavioral change strategies optimized to our cultural context need to be developed and implemented.^[25]

Strategic priority 2

In this strategic priority, the objective is to strengthen microbiology laboratories and establish standards for AMR surveillance in humans, animals, food, and environment. The plan also mentions collecting and publishing surveillance data annually in all the key sectors. In addition, special emphasis is laid on defining the standards for antibiotic residues in industrial effluents, an issue that is gaining ground in India.

Knowing the pathogens and their antibiotic susceptibility patterns through surveillance, and understanding the trends at the national level is of paramount importance for providing a foundation to design and update the treatment guidelines. The Indian Council of Medical Research (ICMR) has initiated the "Antimicrobial Resistance Surveillance Network" to provide surveillance data at the national level, wherein the data on medically indexed microbes is collected from more than twenty state medical college laboratories with a dedicated national co-ordination center. These findings are published annually.^[26] India is also enrolled in the Global AMR Surveillance System program since 2017.

To give a true picture of the resistance patterns across the country, rather than just at a few centers, strengthening of laboratories and generation of data from a wider network of public and private hospitals needs to be initiated. As trained microbiologists and microbiology laboratories are the cornerstones for surveillance, it is necessary to improve the quality of laboratories by ensuring increased availability of trained personnel, availability of adequate infrastructure, reinforced quality controls, and hands-on training support from tertiary care institutions.

Strategic priority 3

This strategic priority is for Infection Prevention and Control (IPC) in health-care, veterinary settings, and animal husbandry. As suggested by the "Chennai Declaration," the

ICP program should move toward being made mandatory for licensing as well as accreditation purposes, both in public and private hospitals, to ensure compliance.^[27] Studies have revealed that lack of infrastructure, shortage of trained staff (coupled with staff turnover), higher workloads, and language difficulties among staff members were the major barriers for implementing effective infection control programs.^[28]

On the community side, measures to improve access to safe water, sanitation, and hygiene are presently in vogue in the form of campaigns such as the “Swachh Bharat Abhiyan” and the “Kayakalp Programme” undertaken by the Government of India. Strong support from top-level relevant stakeholders, diligence of staff members, and active community participation are needed for effective implementation of such programs and campaigns.

Strategic priority 4

This strategic priority mainly focuses on optimizing antibiotic use in all the sectors, developing a regulatory framework for antibiotic use in food and animal industries, formulating regulations in relation to hospital waste and prevention of environmental contamination, surveillance for antibiotic use and antibiotic stewardship in both human and non-human sectors, and strengthening the existing regulatory framework.

To improve the appropriate use of antibiotics, the National Centre for Disease Control has published the National Treatment Guidelines for Antimicrobial Use in infectious diseases in 2016 and the ICMR published its guidelines in 2017. Hospital authorities are expected to disseminate the guidelines to all staff members and ensure compliance by practicing antibiotic stewardship. However, since local antibiograms may vary in different regions and facilities, it is important to adopt these guidelines to local resistance patterns.

Unfortunately, many health centers in India face a lot of challenges such as limited diagnostic services (and hence are forced to rely only on clinical judgment for initiating antibiotic therapy), and there are also issues of patient affordability. The high burden of TB, malaria, dengue, and HIV further complicate the scenario. In addition, in view of a perceived benefit for patients, doctors may start off with antibiotics even before the diagnostic reports arrive.^[14] Hence, developments in the design of rapid diagnostic tools and the improvement of such facilities should be encouraged simultaneously with other measures.

Medical interns and postgraduate registrars manage a considerable number of outpatients (at teaching hospitals attached to medical institutions) often without proper supervision because of the heavy workload. They may not be sufficiently informed about the updated guidelines and/or protocols for the use of an antibiotic. Special efforts should therefore be taken to monitor and guide these interns. Many of these notions are encompassed within the concept of antibiotic stewardship. Antibiotic stewardship refers to “coordinated interventions designed to improve and measure

the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration.”^[29] Some of the interventions used are framing policies and treatment guidelines according to the local antibiogram (both at national level and hospital level), the five D's (5D's viz., right Diagnosis, right Drug, right Dose, right Duration, and De-escalation), pre-authorization for restricting high-end antibiotics and measuring antibiotic use either by days of therapy or defined daily doses, etc.^[30] Studies have shown the beneficial effect of antibiotic stewardship in optimizing and reducing the antibiotic use besides achieving improved patient outcomes.^[31]

In 2012, the ICMR launched the program on Antimicrobial Stewardship Prevention of Infection and Control in collaboration with other institutions.^[32] In a move to encourage antibiotic stewardship and to further highlight the growing crisis of antibiotic resistance, the WHO adopted a new method of classifying antibiotics into three categories; namely Access, Watch, and Reserve in the 20th Essential Medicine list classification.^[33] The Reserve group includes antibiotics such as colistin and some cephalosporins, which should be reserved for use in managing life-threatening multi-drug resistant infections. Access group antibiotics (such as amoxicillin) should be made available at all times and are commonly used to treat many infections. The Watch group includes antibiotics, which are reserved as “Drug of Choice” for certain infections – such as ciprofloxacin for the treatment of cystitis.

Physicians and microbiologists play a key role in initiating antibiotic stewardship measures as well as in framing infectious disease treatment guidelines. For the implementation of antibiotic stewardship, there is a need for physicians, nurses, and clinical pharmacists specialized in infectious diseases, a dedicated team, staff time, and leadership support. However, ensuring the implementation of guidelines by all health-care professionals irrespective of specialties in a given hospital, performing regular audits and providing feedback to higher authorities requires significant human resources. Clinical pharmacologists and pharmacists can contribute by taking part in prescription auditing for ensuring adherence to hospital antibiotic guidelines, measuring antibiotic consumption, implementing antibiotic stewardship measures, and carrying out therapeutic drug monitoring, especially for last resort antibiotics such as meropenem, colistin, vancomycin, etc.^[34]

Strategic priority 5 and 6

Strategic priorities 5 and 6 deal broadly with promoting investments for research and innovation, as well as leadership, coordination and inter/intra-country collaboration for AMR related activities. Drug development involving novel antibiotics, unfortunately, does not guarantee a return-on-investment because bacteria may develop resistance to the new antibiotics rapidly, and antibiotics are used for short fixed durations, unlike drugs used for the cases of chronic diseases. In addition, there

is pressure to reserve newer antibiotics as the last resort for critically ill patients. The concept of de-linking the returns from the pharmaceutical volume of sales has been discussed widely but has not yet been fully implemented.^[35] India has a large number of pharmaceutical companies and academia that have the potential to carry out research and development activities on newer classes of antibiotics with encouragement and support from the government. To facilitate drug development, WHO has published a list of priority pathogens for which new antibiotics are urgently needed.^[36] Besides the development of new antibiotics, novel innovations pertaining to probiotics and vaccines are also needed.^[37] Further details on methods of financing could be found in the article on 'AMR and Sustainable Development' by Dag Hammarskjold Foundation and ReAct.^[38]

Role of family physicians in AMR and areas where they should contribute

Symptoms suggestive of infections such as fever, sore throat, cough, and diarrhea account for a significant number of visits to the family physicians (FPs) and general practitioners (GPs). Both groups usually act as the first contact point for patients presenting with any infection faced by the community, especially in rural and semi-urban parts of India where access to higher level healthcare is limited. Antibiotics are a crucial armament for physicians for treating such infections. Unfortunately, antimicrobial use is on the rise owing to inappropriate use. This has led to a situation where these very antibiotics have become less effective owing to AMR. Improving the use of antibiotics through appropriate prescribing has been shown to contain AMR. Hence, FPs and GPs have a very crucial role in containing AMR.

Most of the factors discussed under the section "Use of Antibiotics" are applicable for FPs/GPs as well, though perceived patient expectations and the need to maintain a good relationship with patients is more pronounced in these settings. However, because FPs/GPs share a good relationship with members of the patient's family, they are well placed to educate and explain the natural course of infections to the family members, advise on the proper treatment strategy, and emphasize the limited value of antibiotics in many infections. By virtue of accessibility and familiarity to patients, they could also employ a "delayed prescribing" strategy (where the patient is asked to collect the prescription if symptoms worsen) as part of rationalizing use.

In addition, this article is a timely reminder that FPs/GPs should contribute by:

- A. Spreading awareness on antibiotic use and AMR, the importance of hygiene, conditions where antibiotics have no role, harm due to misuse of antibiotics, etc., through counseling when the opportunity arises, and wider measures such as by displaying posters/short videos in waiting areas.
- B. Overall health promotion, especially the importance of timely vaccinations, in the pediatric and geriatric age group and other high-risk groups.

- C. Incorporating antibiotic stewardship principles in clinical practice i.e. to prescribe antibiotics only when needed with right drug, dose, duration, and considering the AWARE categorization by WHO.

Conclusion and the way ahead

The Indian NAP for AMR is a well-designed comprehensive plan that incorporates all the essential objectives of the GAP, and promises to address the important policy and regulatory issues in relation to antibiotic use according to the "One health approach." However, implementation has been slow and a big push is needed by all stakeholders. Lack of a separate financial allocation remains the greatest challenge for the implementation of NAPs and/or State Action Plans, not only in India but also in other LMICs. Health comes under the purview of state governments. As state governments are usually burdened in managing the finances for many other schemes, the focus and fund allocation toward newer health initiatives is limited. Hence, a separate funding mechanism toward AMR with coordination between central and state governments is needed. Civil society, private sectors, and media have a crucial role to play apart from the industries such as pharmaceuticals, food animal production, and food chains in designing the strategies to contain AMR. Once the NAP is implemented, authorities should lay greater emphasis on monitoring and evaluation of all the objectives, establish appropriate governance mechanisms, and accountability to strategize how well these outcomes can be achieved in the respective settings. Hospital staff and health care professionals should enhance initiatives to promote antibiotic stewardship interventions and infection prevention and control measures as these are strategies that are completely under their control. A strong political commitment and support from many of the private stakeholders are essential for successful implementation of the NAP.

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