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Perspective

Combating antimicrobial resistance in India: Technical challenges & opportunities

In the last five years antimicrobial resistance (AMR) has gained greater importance and climbed up higher on the global health and development agenda. In 2011, an initiative by India was culminated in the Jaipur Declaration on AMR by the 11 countries of the World Health Organization's (WHO) South-East Asia region[1]. In response to request by the 68th Session of the World Health Assembly (WHA), the WHO coordinated the development of a global action plan (GAP) against AMR through extensive process of consultation[2]. This global plan was endorsed by the WHA in May 2015 as well as by the Food and Agriculture Organization (FAO) of the United Nations and World Organisation for Animal Health (OIE) during the same year[3-5].

Several international political platforms, *viz*. G7[6], G20[7] and G77[8], and World Economic Forum[9] have also recognized importance of AMR and given calls to mitigate its impact. UN sustainable development goals (SDGs) clearly articulate commitment to contain AMR[10]. The United Nations General Assembly, in 2016, called for concerted global efforts to halt the emergence and spread of AMR[11].

Antimicrobial resistance and economy

Studies undertaken in European Union, Thailand and the United States of America have revealed annual loss of more than USD 2 billion each attributed to the infections due to resistant pathogens[12]. The review on antimicrobial resistance chaired by Jim O'Neill has projected a global loss of almost USD 100 trillion by 2050 equivalent to a decrease in about 3.5 per cent of global gross domestic product (GDP)[13]. Macroeconomic studies have projected the current loss of GDP from AMR ranging from 0.4 to 1.6 per cent[14].

Antimicrobial resistance and human health

The global initiatives against AMR are the results of known and established impact of AMR on human health and global development. Estimated current annual mortality associated with AMR is around 700,000[15]. Inaction in containing this menace is likely to cause, by 2050, more than 10 million deaths every year[13], more than the deaths caused by cancers and road accidents. Most of these deaths will be in developing countries of Asia and Africa.

AMR will impede efforts to achieve universal health coverage (UHC), since medicines, especially antibiotics, are an essential component of UHC. AMR can make existing antibiotics ineffective and new ones unaffordable. AMR shall also negate the achievements made through global efforts against HIV, tuberculosis and malaria. If the current trends continue, sophisticated interventions, such as organ transplantation, joint replacements, cancer chemotherapy, and care of preterm infants, will become more difficult or even too dangerous to undertake.

Antimicrobial resistance and food

Impact of AMR will also come on the growing demand of safe nutritious food of animal origin. Overall meat consumption increased by almost 60 per cent between 1990 and 2009[16]. This trend is expected to continue, driven in particular by income growth in countries in Asia, Latin America and the Middle East[16]. It is also expected that between 1997 and 2020, the quantity of meat consumed in developing countries will double[17]. In India, the Indian Council of Agriculture Research (ICAR) projects increase in meat consumption from 4.3 kg in 2000 to 10.1 kg by 2030 and 18 kg by 2050, two-third of which shall be from poultry[18]. Within a span of 25 yr, the egg production in India has gone up to 70 billion from a few millions and the broiler production has gone to around 42 million tons in 2016. Growing nutritionally important poultry sector is at risk due to burgeoning AMR[18].

Widespread resistant bacteria have harmful effects on animals, including those raised for food. Mortality,

morbidity and cost of care in animals will increase when infected with resistant pathogens. This will primarily affect resource-poor communities pushing them further into poverty.

Global action plan (GAP) for antimicrobial resistance

To overcome these critical challenges to development, the global community has now joined hands. GAP[2] is the framework to guide countries in developing respective national action plans (NAP) and assiduously implementing the following broad objectives of GAP:

(*i*) Improve awareness and understanding of AMR.

(*ii*) Strengthen the knowledge and evidence base through research and surveillance, thus enhancing awareness.

(*iii*) Reduce the incidence of infectious diseases and cross-colonization of multidrug-resistant organisms in healthcare settings and in the community.

(*iv*) Optimize the use of antimicrobials in human and animal health.

(*v*) Ensure sustainable funding for programme implementation and development of new medicines, diagnostic tools, vaccines and other interventions.

India's National Action Plan (NAP)

India's NAP is well aligned with GAP and also voices the need for India's leadership role in the field of AMR. Three committees that deal with inter-sectoral coordination, technical oversight and drafting of NAP were charged with finalization of NAP within the stipulated period. NAP has been developed and submitted to the WHA in May 2017 as committed in 2015 in the WHA[3]. However, its implementation shall demand substantial efforts. Major challenges would include earmarking funds to initiate activities proposed under NAP, sustained funding, creating mechanisms for efficient inter-sectoral coordination, effective implementation of regulations and providing technical stewardship across the country. Success of NAP will also depend upon soundness of technical support to overcome plethora of technical challenges that India faces.

Technical and coordination challenges

AMR is the culmination of a variety of factors. In settings with high burden of infectious diseases with concomitant greater use of broad-spectrum antimicrobial agents, there is proportionately higher possibility of selection of resistant strains and their propagation. To combat AMR, one has to address all these issues especially those that reduce the burden of infectious diseases which continue to be a major challenge in India.

In addition, quality of antimicrobial used, dosage, appropriate indications and utilization by the patient for the recommended duration are of equal importance in assuring proper interaction between the microorganisms and the antimicrobial agents. Rational use of antibiotics, hence, in addition to excessive use is critical to minimize AMR. The logical and right approach to reduce emergence of AMR is to optimize the therapy through (*i*) a good indication, (*ii*) timely initiation of therapy, (*iii*) avoidance of too long therapy, and (*iv*) adequate dosing.

Excessive use of antibiotics is considered as the main driver of AMR. India is the leading antibiotic consumer in the world with 12.9×10^9 units consumption every year, closely followed by China at 10.0×10^9 units and the USA at 6.8×10^9 units[19]. In animal health sector also, India is among the top five consumers of antibiotics[20]. However, exact quantum and dynamics of antibiotics used in human health, different sectors of animal health and agriculture remain unknown. Reliable information on irrational usage practices is also not available. National regulatory mechanism has been historically weak in India, primarily because of health being a State subject as per the Constitution of India. The Federal government has to work with all State governments with varying degree of regulatory willingness and capacity in implementation of appropriate actions and monitoring and evaluation (M and E) of national programmes.

The national burden of AMR remains unknown. Existing AMR data are primarily from tertiary healthcare facilities which carry questionable quality and lack of geographical representativeness. Some studies have observed and reported antibiotic use patterns in private and public healthcare facilities. The data though available from such studies are from small settings and fragmented and thus cannot be extrapolated to draw national picture[21-24].

Epidemiological linkages between rampant use of antibiotics in veterinary and environment sectors and AMR are not fully established. Impact of environment on AMR remains an enigma and

demands extensive research; to not only understand the dynamics in environment but also the possible and affordable solutions. There are three pathways by which environment get contaminated with antimicrobial agents. These are animal waste, human waste and manufacturing waste. These environment settings also provide milieu for resistance to metals and biocides along with antibiotics. Evidence is now becoming available to demonstrate co-selection of genes that confer resistance to chemical hazards, biocides, antibiotics and metals[25]. There is an urgent need to target hospital effluent and pharmaceutical manufacturing plants in the context of AMR. This potentially ecologically and clinically important phenomenon must be urgently and comprehensively researched to elucidate better understanding and development of cost-effective interventions.

Rational use of antibiotics by prescribers is one of the critical cornerstones of prevention and control of AMR. Very little research has been done to understand the prescriber and consumer behaviour with respect to prescription practices in Indian settings. Currently, no training plan and material are available to impart training to professionals and workers in health and veterinary sectors. This is one of the weakest links in the country.

Programme M and E are essential to gauge the progress made through activities. SMART (Specific, Measurable, Attainable, Relevant and Timely) indicators and targets shall be established in NAP. Mechanism especially tools, skills and institutional support to undertake M and E and for tracking the indicators needs to be integrated in NAP.

AMR has multifactorial aetiology and therefore, demands multi-sectoral and multidisciplinary response. Coordination with animal health, environment, private and non-governmental organization sectors has been inadequate and poses a complex challenge. Besides, health being a State subject in India gives majority of implementation responsibility to the States/provinces. Efficient coordination and cooperation between State and Federal governments is fundamental to success of NAP.

Way forward

There is an urgent need for accelerating multi-sectoral engagement for development and effective implementation of NAP with focus on a strong and enforceable regulatory mechanism. Poor regulatory mechanisms are the weakest links in chain of actions for combating AMR. Priority needs to be accorded to strengthen and expand regulatory mechanisms for production, sale and use of antibiotics in both human and animal health sectors at federal as well as State levels. Structural and functional systems need to be operationalized from central to peripheral action-areas to comprehensibly implement NAP.

One Health approach is the key to contain AMR. Understanding the current magnitude of AMR is essential to quantify the burden for monitoring its progress and impact of interventions. National network of laboratories that follow uniform protocols and contribute data to central, regional and local agencies for formulating actions for rational usage of antibiotics needs to be established and coordinated by national reference laboratory. Under NAP, studies must be commissioned to quantify use of antibiotics in different settings both in human and animal health sectors along with irrational usage practices being followed. A system for nation-wide data management on AMR from both human health and animal health needs to be established for almost real-time data processing and analyses to assist in programme development and policy formulation.

Training of a large number of professionals and allied workforce will require development of a national training plan customized and tailored as per needs assessment and supported by research carried out within the country. It may not be feasible for government agencies to undertake this task alone. The academic institutes and professional associations/ bodies can be roped in to complement national efforts.

The apex research bodies of India, the Indian Council of Medical Research (ICMR) and ICAR, should assume leadership role in identifying, promoting and supporting innovations and research needs apropos to the needs of India. Research priorities should include, but not restricted to, quantifying the burden of AMR in India, its economic impact, understanding its epidemiological pattern, exploring behaviour patterns of prescribers and users, development and use of new diagnostics, alternatives to antibiotics and identifying the role of environment in emergence and selection of resistant strains.

Conclusion

AMR is a global health emergency that no nation can afford to ignore. It is a cross-sectoral issue that affects developed and developing countries/societies alike and has potential to derail all developmental

activities and achievements. Addressing this challenge requires a proactive and aggressive approach. With increasing global awareness on AMR, this is the best time and opportunity to avert this health crisis. The cost of responding to this crisis will only be a fraction of financial burden any country would incur due to the impact of AMR that may also annul the achievements made in the past 50 years in controlling infectious diseases. This will not only risk the benefits of medicine and associated technological advances made so far but also threaten to put a spanner in the entire global development agenda as enunciated in the SDGs.

***Conflicts of Interest*:** None.

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