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Antimicrobial resistance: An emerging threat for one health - solutions and way forward

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Abstract

The spread of infections that are resistant to antimicrobial medicines has emerged as a threat to public health globally. This is promoted by human actions such as inappropriate prescribing and use of antibiotics prescribing and use of antimicrobials, insufficient hospital hygiene, inappropriate use of antibiotics in livestock sector, misuse of antibiotics in agriculture and humans, irresponsible manufacturing of antibiotics including uncontrolled release of active antibiotics into the environment. Antibiotics resistance can be more prevalent where antibiotic consumption is found to be higher. Lack of monitoring and control in using antibiotics is prominent and need to be targeted at country level. India is at the greatest risk looking to low process of antibiotics, easy availability and unnecessary use of antibiotics.

For containing antimicrobial resistance there is a need to promote and protect human health within the framework of a One health approach through coherent, comprehensive and integrated multi- sectoral cooperation and actions as human, animal and environment health are interconnected. In India, various actions have been taken including setting up of a National Task Force on AMR Containment (2010), "Chennai Declaration" by a consortium of the Indian Medical Societies (2012), Setting of Indian Council of Medical Research national surveillance network of laboratories, "Redline" campaign for educating public and National Action Plan on AMR 2017. There is a need integrating AMR education in medical education.

Keywords: Antibiotic, antimicrobial resistance, global action plan, India, National Action Plan, AMR Spread

Introduction

Resistance is a means whereby a naturally susceptible microorganism acquires ways of not being affected by the drug. Microbial resistance to antimicrobial agents is not a new phenomenon; it has been going on in soil microorganisms since the dawn of time, as competitive/survival mechanisms by microorganisms against other microorganisms. Understanding the mechanisms of resistance is important in order to define better ways to keep existing agents useful for a little longer but also to help in the design of better antimicrobial agents that are not affected by the currently known, predicted, or unknown mechanisms of resistance.

Although antimicrobial resistance is a natural biological phenomenon, it often enhanced as a consequence of infectious agents' adaptation to exposure to antimicrobials used in humans or agriculture and the widespread use of disinfectants at the farm and the household levels. It is now accepted that antimicrobial use is the single most important factor responsible for increased antimicrobial resistance. (Dennis Scott)

What are antibiotics and uses of antibiotics

For the last 70 years, doctors have prescribed drugs known as antimicrobial agents to treat infectious diseases. These are diseases that occur due to microbes, such as bacteria, viruses, and parasites. Some of these diseases can be life-threatening. However, the use of these drugs is now so common that some microbes have adapted and started to resist them. This is potentially dangerous because it could result in a lack of effective treatments for some diseases.

Use of antibiotics as growth promoters is becoming an easy tool for some of the food producing animals for prevention and control of disease and to meet the increased demand of food for the rapidly increasing human population. This irrational use of antibiotics uses in food producing animals has resulted in the occurrence of their residues in livestock products and also contributes to the development of AMR in microorganisms.

Why antibiotics are used in animals?

There are three main reasons why antibiotics are used by farmers:

1. As treatment for animals that show clinical signs of an infectious disease.
2. As metaphylaxis to treat a group of clinically healthy animals and minimise an expected outbreak of a disease or as prophylaxis to prevent those at risk from being infected.
3. As growth promoter to boost the weight of the animals. (Reference: National Pharmaceutical Regulatory Agency (NPRA) http://vam.org. my/home/wp-content/ uploads/2017/11/Pn Asnida_V)

Antimicrobial Resistance – introduction and spread

Antimicrobial resistance occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infectious becomes ineffective. When the microorganisms become resistant to most antimicrobials they are often referred to as superbugs. This is a major concern because a resistant infection may kill, can spread to other, and imposes huge cost to individuals and society

The overuse and abuse of antibiotics have contributed to the global epidemic of antibiotic resistance. Current evidence suggests that widespread dependency on antibiotics and complex interactions between human health, animal husbandry and veterinary medicine, have contributed to the propagation and spread of resistant organisms. The lack of information on pathogens of major public health importance, limited surveillance, and paucity of standards for a harmonised and coordinated approach, further complicates the issue. Despite the widespread nature of antimicrobial resistance, limited focus has been placed on the role of environmental factors in propagating resistance. There are limited studies that examine the role of the environment, specifically water, sanitation and hygiene factors that contribute to the development of resistant pathogens. Understanding these elements is necessary to identify any modifiable interactions to reduce or interrupt the spread of resistance from the environment into clinical settings. (Udakis Laura, 2017) [1].

Reported rate of AMR in India

The problem statement The One Health concept highlights the importance of inter-dependence of human, animal and environmental parameters for the containment of AMR. The same holds true for India wherein the rates of AMR in all these three sectors have been rising disproportionately in the past decades. Another issue is the lack of sufficient research and paucity of data that not only hampers the estimation of exact rise and extent of AMR in India but also prevents a nationwide comparison. Of the 2152 studies published by Indian institutions on AMR, 1,040 (48.3%) were on humans, while only 70 (3.3%) on animals, 90 (4.2%) on environment and 11 (0.5%) on One Health. The rest were based on novel agents, diagnostics, editorials and miscellaneous11. The current magnitude of the problem in India is as follows:

AMR in man

As per the ‘scoping report on antimicrobial resistance in India (2017)’ (Joshi *et al.*), under the aegis of government of India, among the Gram-negative bacteria, more than 70 per cent isolates of Escherichia coli, Klebsiella pneumoniae and Acinetobacter baumannii and nearly half of all Pseudomonas aeruginosa were resistant to fluoroquinolones and third generation cephalosporins. Although the resistance to drug combination of piperacillin-tazobactum was still <35 per cent for E. coli and P. aeruginosa, the presence of multiple resistance genes including carbapenemases made 65 per cent K. pneumoniae resistant ((Joshi *et al.*). Increasing rates of carbapenem resistance to the tune of 71 per cent in A. baumannii led to frequent use of colistin as the last resort antimicrobial11. The resistance to colistin has also emerged in India. Although the rate of colistin resistance was <1 per cent, except for 4.1 per cent reported by Gandra *et al.*, 2008, high mortality of 70 per cent was associated with colistin resistant K. pneumoniae. Among the Gram-positive organisms, 42.6 per cent of Staphylococcus aureus were methicillin-resistant and 10.5 per cent of Enterococcus faecium were vancomycin-resistant. The rates of resistance among Salmonella Typhi and Shigella species were 28 and 82 per cent, respectively, for ciprofloxacin, 0.6 and 12 per cent for ceftriaxone and 2.3 and 80 per cent for co-trimoxazole. For Vibrio cholerae, resistance rates to tetracycline varied from 17 to 75 per cent in different parts of the country (Joshi. *et al*. 2017) [15].

AMR in food animals

According to the statistics of 2015, India was the largest producer of milk and the second largest producer of fish in the world (GOI, 2015). Further, the poultry consumption in India is expected to rise by 577 per cent between year 2000 and 2030. With such a huge potential of food animal industry, antimicrobial agents are being used in abundance to increase the productivity. India produced 137,685.8 × 103 tonnes of milk in 2013-2014 with major contributions from States of Uttar Pradesh (17.6%), Rajasthan (10.6%) and Andhra Pradesh (9.4%)15. On analysing milk samples for the estimation of AMR in livestock, 48 per cent of Gram-negative bacilli detected in cow and buffalo milk were extended-spectrum β-lactamases (ESBL) producers (West Bengal) and 47.5 per cent were resistant to oxytetracycline (Gujarat). Among the Gram-positive organisms isolated from these milk samples, 2.4 per cent of S. aureus were vancomycin resistant (West Bengal) while the rate of methicillin resistance was 21.4 per cent for S. aureus and 5.6 per cent for coagulase-negative Staphylococci (Karnataka). India, where 9579×103 tonnes of fish is produced in a year, is becoming an important hub of aquaculture industry. In the common Tilapia fish found in the lakes of Maharashtra, 48 per cent Enterobacteriaceae isolated from the gut were ESBL producers. Vibrio cholera and V. parahaemolyticus, isolated from the retail markets of shrimps, shellfish and crabs in Kerala were 100 per cent resistant to ampicillin, 100 per cent susceptible to chloramphenicol while resistance to ceftazidime ranged from 67 to 96 per cent. In the poultry industry of India, 1,916×103 tonnes of broiler meat is produced each year with maximum production by States of Haryana (18.4%), West Bengal (17.1%) and Uttar Pradesh (14.1%). Among the seven studies available on AMR in poultry, three studying ESBL producing Enterobacteriaceae have documented the rate of ESBL producers to vary from 9.4 per cent in Odisha to 33.5 per cent in Madhya Pradesh to 87 per cent in Punjab. Other four studies reported the presence of Salmonella species in broilers to vary from 3.3 per cent in Uttar Pradesh to 23.7 per cent in Bihar with 100 per cent isolates being resistant to ciprofloxacin, gentamicin and tetracycline in Bihar and West Bengal. (Taneja and Sharma, 2018) [19].

AMR in environment

Antimicrobial-resistant bacteria and their genes have been reported from different water sources of India. The major sources are the pharmaceutical waste waters and hospital effluents that are released into the nearby water bodies without adequate treatment. The rate of isolation of E. coli resistant to third generation cephalosporin was 25, 70 and 95 per cent when the inlet to the treatment plant was domestic water alone, domestic waste along with hospital effluent and hospital effluent alone, respectively. The two largest rivers of India, Ganges and Yamuna, span across a massive area of land and receives multiple inlets with varying concentration of drug-resistant bacteria. The rate of ESBL producers was 17.4 per cent among Gram-negative bacteria isolated from these north Indian rivers with detection of resistance genes like blaNDM-1 and blaOXA4823. Of the 283 E. coli isolates from the south Indian river Cauvery in Karnataka, 100 per cent were resistant to third generation cephalosporin. The groundwater and surface water that are used for drinking and recreational purposes have been reported with 17 per cent rate of E. coli, resistant to third generation cephalosporin, in central India, seven per cent in north India (Kashmir), 50 per cent in east India (Sikkim) and 100 per cent in south India (Hyderabad). The samples in these studies were collected from water sources like rivers, ponds, lakes, springs, hand pumps and tube-wells**.**

Challenges of AMR in India

India has been referred to as ‘the AMR capital of the world’ (Chaudhary *et al.*, 2017) [18]. While on one hand, emergence of newer multi-drug resistant (MDR) organisms pose newer diagnostic and therapeutic challenges, on the other hand India is still striving to combat old enemies such as tuberculosis, malaria and cholera pathogens, which are becoming more and more drug resistant. Factors such as poverty, illiteracy, overcrowding and malnutrition further compound the situation. Lack of awareness about infectious diseases in the general masses and inaccessibility to healthcare often preclude them from seeking medical advice. This, more often than not, leads to self-prescription of antimicrobial agents without any professional knowledge regarding the dose and duration of treatment. Among those who seek medical advice, many end up receiving broad-spectrum high-end antimicrobials owing to lack of proper diagnostic modalities for identifying the pathogen and its drug susceptibility. Low doctor to patient and nurse to patient ratios along with lack of infection prevention and control (IPC) guidelines favour the spread of MDR organisms in the hospital settings. Easy availability of over-the-counter (OTC) drugs, further contributes to AMR. The rise in the pharmaceutical sector has caused parallel rise in the amount of waste generated from these companies. With the lack of strict supervisory and legal actions, this waste reaches the water bodies and serves as a continuous source of AMR in the environment. Another important challenge could be the use of antimicrobial agents as pesticides and insecticides in the agriculture industry, although the evidence for the same is currently lacking. India has vast agricultural lands and farmers already face a lot of adversities at the hands of harsh weather, difficult terrain and natural calamities. They fall an easy prey to the lure of protecting their hard-earned field from pests and rodents by using antimicrobial agents without considering the future consequences. This large reservoir of antimicrobial agents forms a favourable niche for the emergence of MDR pathogens who then drift into the water bodies with rains and floods. The paucity of data on the extent of AMR, especially in animals and environment, presents hurdles to framing and implementation of policies on the control of AMR.

Drivers of environmental AMR in India

Chereau *et al.*, in their evaluation of risk assessment for AMR, have shown that while AMR originating from environmental sources may be contributing a low proportion in developed countries, it poses a moderate to high-risk in developing countries of South East Asia including India due to several cofactors associated with the overall event. The following drivers of AMR in the environment are noteworthy: Excess use or misuse of antimicrobial agents AMR contributed by antimicrobial use in humans: India ranks first among all countries of the world in the environment are noteworthy:

Excess use or misuse of antimicrobial agents

AMR contributed by biocides: Biocide is an umbrella term encompassing agents directed to kill the offending pathogen or microbe. It includes insecticides, pesticides, fertilizers and disinfectants. Sub-lethal concentrations of biocides can increase the pool of resistant organisms in the environment. Use of nitrogen-based fertilizers has shown to alter the soil content selecting out vanA gene and thus contributing to clinical vancomycin resistance. Another important aspect is the sharing of resistance mechanisms between biocides and antimicrobial agents, thus facilitating their co-selection. Resistance of S. aureus to biocide benzalkonium chloride confers eight-fold higher tolerance to oxacillin due to the co-location of both the resistant genes on the plasmid. The global biocide market showed a 40 per cent growth between 1992 and 2007 and although the data regarding biocide consumption in India are largely lacking but it is feared to be high in magnitude. The European Commission4 has incorporated the assessment of AMR generated by biocides and has also formulated regulation for use and disposal of biocides. Biocides as a route of AMR, however, have not been listed in the NAP on AMR of India6 and prospective studies analysing the contribution of biocides towards AMR in Indian context should be undertaken.

Contaminated water as a source of AMR

Pharmaceutical waste water: India is one of the leading producers of pharmaceuticals in the world (Rehman *et al.*, 2015). In the effluent of one of the Indian pharmaceutical plants, the levels of ciprofloxacin were found to be 28 and 31 mg/l on two consecutive days. Extrapolating these figures to the total volume of effluent generated, several kilograms of antibiotic are being released in to the waste water every day. Antimicrobial classes such as fluoroquinolones and sulphonamides produce stable residues while beta-lactam group of drugs degrade relatively faster from the environment. While the former constitute an ever-growing pool of AMR, the latter indicates recent contamination of wastewater. Both the types of drugs are widely present in the wastewaters of Indian pharmaceutical companies which pollute the neighbouring rivers, ponds and sea coasts. Lübbert *et al.*, 2017 [21] found antibiotic residues from 28 environmental sampling sites in the sewers of industrial area in Hyderabad, India. Wastewater is generated by every pharmaceutical company of the world, but as per the risk assessment, the adequate treatment of this wastewater in developed countries decreases the overall associated risk while the lack total consumption of antibiotics for human use.

Municipal waste water: With 30-90 per cent fraction of all antimicrobials being excreted unchanged via human faeces and urine, municipal waste water becomes an important dumping ground of resistant organisms or genes. It is estimated that only 20-30 per cent of municipal waste water is treated in treatment plants and that too is not effective enough to eliminate the resistant organisms. This potentially 'AMR-rich' municipal waste water is discharged into the nearby water bodies. Antibiotic-resistant genes even to high-end antibiotics were detected in Mutha river flowing through Pune, India, with 30-times higher concentration in the sediments near the city, originating from domestic and municipal sewage waste (https://outbreakwatch.blogspot.com/2017/09/proahedr-antibioticresistance- 08-india.html,). While isolation of enterococci, a normal commensal of human gut, was possible from river sources at several places, the rate of vancomycin-resistant enterococci ranged between 22 and 100 per cent from banks of Indian river Gomti

Hospital effluent: Hospitals and all other healthcare facilities are important sources of generation of antimicrobial waste indirectly via patient secretions or directly as unused discarded medicines. Mutiyar and Mittal have reported the worrisome extent to which residues of fluoroquinilones, sulphonamides and tinidazoles were recovered from one of the hospital effluents in India. Since hospitals are the places with highest level of antimicrobial consumption, their effluent waters are expected to be the richest source of resistant bacteria and their genes. The concentrations of antimicrobials from effluent plants of Indian hospitals were high enough to cause genotoxic alterations and modify bacterial strains (Diwan *et al.*, 2010) [13]. It has been shown that 80-85 per cent of antimicrobial residues can be effectively removed if hospital effluent undergoes proper treatment before final disposal (Duong *et al.*, 2008) [14]. Unfortunately, <45 per cent of healthcare facilities in India have adequate waste water treatment systems in place.

Consequences of antibiotic resistance

Antibiotic resistance poses great threat to food safety and public health when the resistant bacteria spread from food animals to humans through the food chain. Antibiotics used in the first line treatment are no longer effective to eradicate common food-borne disease-causing bacteria such as Salmonella and Campylobacter.

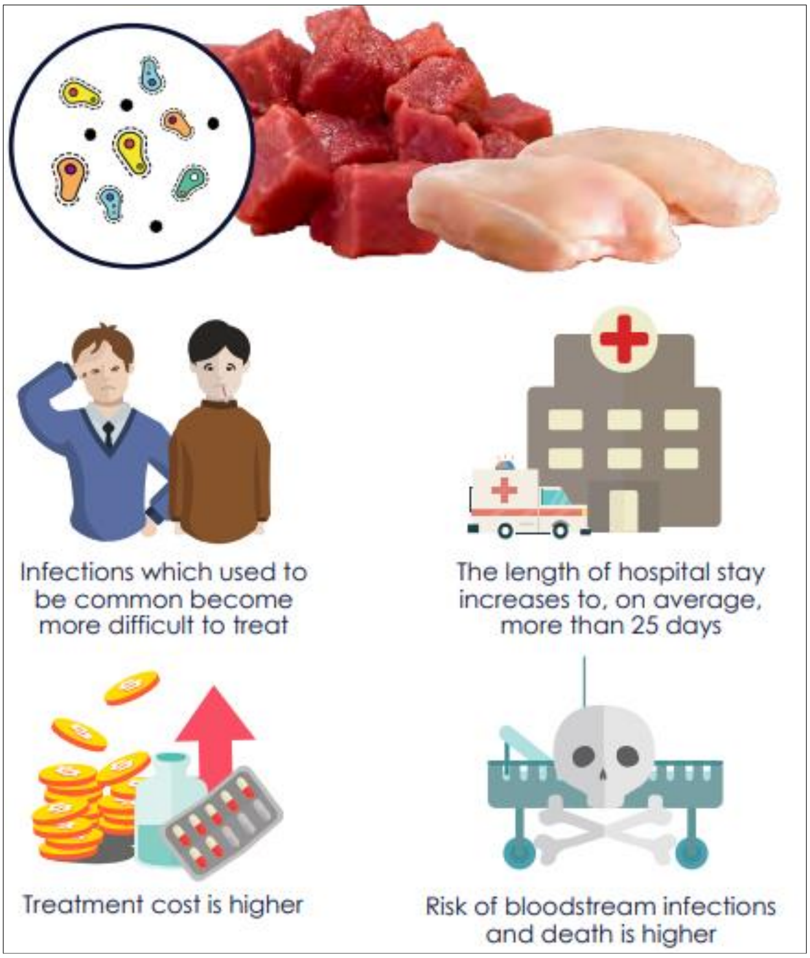

Fig 1: Consequences of AMR (Ref- Self Medication and Antibiotic Resistance: Crisis, current scenario, ScienceDirect.com)

National Action Plan of AMR- strategy for reducing AMR

As one of the countries most affected by antimicrobial resistance (AMR), India is now taking strides to address the growing problem. In 2017, Indian health authorities released their National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017–2021, that outlines the various challenges that need to be tackled to manage the phenomenon. There are six key areas that the NAP-AMR has identified as being strategic priorities for Indian health authorities to take action on.

Table 1: Show the Priority Main objective

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

(Ref- Ranjalkar *et al.*, 2019- Priorities outlined in the National Action Plan for antimicrobial resistance in India)

National Plan for Antimicrobial Resistance

The current NAP is comprehensive and aligns well with the World Health Organization's (WHO's) GAP for AMR (WHO, GAP on AMR 2017) 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 (NAP- AMR).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'(Calistri *et al.*, 2013) [9] 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).

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

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 (Chandy *et al.*, 2013) [10]. 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 behavioural change, and hence, behavioural change strategies optimized to our cultural context need to be developed and implemented

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 centre. These findings are published annually (Annual Report on AMR, Walia, 2017-18). 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 centres, 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 (Gafur A *et al*.,2013). 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 (Barker *et al*., 2017) [4].

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 (Basu *et al*., 2018) [6] 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." 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. (Balram *et al*., 2016) [5]. Studies have shown the beneficial effect of antibiotic stewardship in optimizing and reducing the antibiotic use besides achieving improved patient outcomes (Schuts *et al*., 2016) [28].

In 2012, the ICMR launched the program on Antimicrobial Stewardship Prevention of Infection and Control in collaboration with other institutions (Chandy *et al*., 2014) [11]. 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. 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.

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 (Outterson *et al*., 2016) [25]. 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. Besides the development of new antibiotics, novel innovations pertaining to probiotics and vaccines are also needed. Further details on methods of financing could be found in the article on 'AMR and Sustainable Development' by Dag Hammarskjold Foundation and ReAct.

Conclusion

AMR in the environment has been a neglected topic in India so far. With environment in India posing a continuously increasing threat of AMR, urgent steps are necessary to halt its progress and spread. A multisectoral and multidisciplinary approach with combined efforts and supervision is required to tackle this problem.

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