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Antimicrobial resistance in the environment: The Indian scenario

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Antimicrobial resistance (AMR) continues to pose a significant public health problem in terms of mortality and economic loss. Health authorities of several countries including India have formulated action plans for its containment. In this fight against AMR, it is important to realize the contribution by all the following four spheres: humans, animals, food and environment. This review incorporates all the spheres of One Health concept from the Indian perspective. India has one of the highest rates of resistance to antimicrobial agents used both in humans and food animals. The environment, especially the water bodies, have also reported the presence of resistant organisms or their genes. Specific socio-economic and cultural factors prevalent in India make the containment of resistance more challenging. Injudicious use of antimicrobials and inadequate treatment of waste waters are important drivers of AMR in India. Use of sludge in agriculture, improper discard of livestock animals and aquaculture industry are considered AMR contributors in other countries but Indian data regarding these are lacking. Efforts to combat AMR have been initiated by the Indian health authorities but are still at preliminary stages. Keeping in view the challenges unique to India, future directions are proposed.

Key words Antimicrobial resistance - combating antimicrobial resistance - food animals - National action plan on antimicrobial resistance - one health concept

Introduction

With 700,000 people losing battle to antimicrobial resistance (AMR) per year and another 10 million projected to die from it by 2050, AMR alone is killing more people than cancer and road traffic accidents combined together[1]. Economic projections suggest that by 2050, AMR would decrease gross domestic product (GDP) by 2-3.5 per cent with a fall in livestock by 3-8 per cent, costing USD100 trillion to the world[2]. The global rise of AMR has attracted the attention of World Health Organization (WHO) and several other stakeholders. With WHO announcing AMR as an urgent priority area[3] and several world leaders from Europe framing their Action Plans for the containment of AMR[4,5]. It is obvious that sincere efforts are being directed against this common enemy. India has also framed its National Action Plan (NAP) for AMR[6].

It is important to realize that AMR is a multi-faceted problem and its containment requires multi-pronged approach. The One Health concept highlights the inter-relatedness among human health, animal health, food and environment and fosters collaborative efforts on the part of the health authorities dealing with these spheres[7]. For the effective control of AMR, it is imperative that due consideration is given to each of these contributors. Unfortunately, while injudicious use of antimicrobial agents for human and animal health has been the focus of most of the reports[1,3,8], AMR engendered from the environment has largely remained neglected so far. What makes the situation more complex is the fact that among the drivers of AMR, it is the contribution by environment that varies significantly among different geographical regions of the world and hence estimations and directions laid out by any developed nation (for example England[9]) may not be applicable for the rest of the world. India has recently framed its NAP on AMR in April 2017[6] enumerating the proposed efforts for the coming five years. We present here the current situation of AMR in India, challenges unique to this part of the world and the drivers of environmental AMR.

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[10]. 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 nation-wide 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 miscellaneous[11].

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)'[11], 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[11]. 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 antimicrobial[11]. 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*[12], 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[11].

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[13]. Further, the poultry consumption in India is expected to rise by 577 per cent between year 2000 and 2030[14]. 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 × 10^3 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 analyzing 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)[16]. Among the Gram-positive organisms isolated from these milk samples, 2.4 per cent of *S. aureus* were vancomycin resistant (West Bengal)[17] while the rate of methicillin resistance was 21.4 per cent for *S. aureus* and 5.6 per cent for coagulase-negative Staphylococci (Karnataka)[18]. India, where 9579×10^3 tonnes of fish is produced in a year[15], 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[19]. *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[20]. In the poultry industry of India, 1,916×10^3 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%)[15]. Among the seven studies available on AMR in poultry[11], 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[11].

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[21]. 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[22] with detection of resistance genes like bla_{NDM-1} and bla_{OXA48}[23]. Of the 283 *E. coli* isolates from the south Indian river Cauvery in Karnataka, 100 per cent were resistant to third generation cephalosporin[24]. 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[25], seven per cent in north India (Kashmir)[26], 50 per cent in east India (Sikkim)[27] and 100 per cent in south India (Hyderabad)[28]. 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'[29]. 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[30]. Lack of awareness about infectious diseases in the general masses and inaccessibility to healthcare often preclude them from seeking medical advice[31]. This, more often than not, leads to self-prescription of antimicrobial agents without any professional knowledge regarding the dose and duration of treatment[32]. 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[30,33]. Easy availability of over-the-counter (OTC) drugs[34], 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[33,35]. 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[36]. 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*[37], 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 co-factors 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 total consumption of antibiotics for human use. A total of 12.9×10^9 units of antibiotics with 10.7 units per individual were consumed in India in 2010 alone[38]. There was a 23 per cent increase in the volume of antibiotic retail sale from 2000 to 2010[38]. The rate of consumption is feared to be on a rise ever since. These figures, though threatening, are not surprising for India where antibiotics are used day in and day out[39,40]. While the lack of adequate knowledge regarding the rational use of antibiotics including fixed-drug combinations was found among medical practitioners[41], the wide availability of illegitimate antimicrobials[34] shows inadequacy in the working of health authorities. According to a review by Kelesidis and Falagas[42], India was the leading country in manufacture and usage of substandard and counterfeited antimicrobial agents where as many as 39 per cent of the tested agents were found substandard. Approximately half of the consumed antibiotic is eliminated unchanged from the body via faeces and urine. The practice of defecating in the open, as prevalent in India for decades[43], causes seeping of antibiotics or their residues into the environment via soil and water. With nearly 35 per cent population being exposed to faeces-contaminated drinking water[44], this part of environment contributes significantly to development of AMR.

AMR contributed by antimicrobial use in animals: India is an important producer of food animals for the global market in the form of meat, meat products and farmed seafood and a rise by 312 per cent in this market is expected by 2030[14]. Antimicrobial agents are widely used to prevent diseases in these farmed animals and to increase productivity[45]. India is the world's fourth largest consumer of antimicrobials for animal use, after China, USA and Brazil[38]. Bayesian projections show that at this pace, India will contribute to the largest relative increase in antimicrobial consumption for use in livestock between 2010 and 2030[14]. Antibiotic residues have been reported from food animal products in India like chicken meat and milk[29,46]. Since there are no data available to represent the national picture, future studies investigating the same are urgently required. The International Food Safety and Quality Network standards have laid down strict regulations for the use of antimicrobials in food animals[33,47]. Though this has curtailed excess use of antimicrobial agents in animal products for export, no such guidelines are currently in effect for domestic consumption of animal products in India. Even the Food Safety and Standard Regulations did not encompass use of antimicrobial agents in poultry till early 2017[29].

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[9]. Sub-lethal concentrations of biocides can increase the pool of resistant organisms in the environment[48]. Use of nitrogen-based fertilizers has shown to alter the soil content selecting out *van*A gene and thus contributing to clinical vancomycin resistance[36]. 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[49]. The global biocide market showed a 40 per cent growth between 1992 and 2007[9] and although the data regarding biocide consumption in India are largely lacking but it is feared to be high in magnitude. The European Commission[4] 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 India[6] and prospective studies analyzing 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[50]. 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[51]. 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[52]. Both the types of drugs are widely present in the wastewaters of Indian pharmaceutical companies which pollute the neighbouring rivers, ponds and sea coasts[14,53]. Lübbert *et al*[28] 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[37], the adequate treatment of this wastewater in developed countries decreases the overall associated risk while the lack of optimal wastewater treatment increases its overall risk in India. The high cost associated with regular monitoring of antimicrobial levels in pharmaceutical waste water makes it a low-priority objective for India[35]. With the antibiotic factories in India and China being the largest contributors in global rise of AMR[54], a strict vigilance on the effluent produced is needed.

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[35]. 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[55]. 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[56].

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[57] 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[58]. 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[59]. Unfortunately, <45 per cent of healthcare facilities in India have adequate waste water treatment systems in place[60].

Other sources of AMR

(*i*) Livestock discard: Animal excreta can contaminate the environment directly with resistant organisms or indirectly with antimicrobials[61]. In a study from Netherlands[62], more than one-third of the samples collected from faeces of pig and cattle contained more than one antibiotic or its residue, with three different antibiotics recovered from pig faeces and eight different antibiotics from cattle faeces. Although no such studies have been conducted in India, one can speculate the situation to be worse as overcrowded shelter houses and improper disposal of animal waste and carcasses are rampant among Indian livestock farms. A definite link was observed between consumption of antibiotic in animals and development of resistance in humans[1].

(*ii*) Agricultural manure and sludge: While manure is the natural or synthetic growth-promoter for crops, sludge is the undissolved slurry that is generated from biological treatment of waste water and is rich in micro-organisms and un-degraded pharmaceuticals[63]. Owing to different sources of generation, the antimicrobial content of both is different. While manure has abundance of drugs like oxytetracycline, doxycycline and sulphadiazine[62], sludge mainly contains drugs that are less water-soluble like ofloxacin, ciprofloxacin, norfloxacin and trimethoprim[64]. The 'resistome' or the collection of genes capable of conferring resistance has been found to persist long after the manure or sludge is decomposed[65,66]. In absence of Indian data, the magnitude of problem can be inferred from a study in China[67]. wherein 156 new antimicrobial-resistant genes and mobile genetic elements were identified in the composted manure and sludge.

(*iii*) Heavy metals: Metals can have similar mechanisms of resistance, structurally or functionally, as that of antimicrobials like decreased membrane permeability, efflux pumps, target alterations, intracellular sequestration and the presence on the same plasmid[68]. Also bacteria carrying metal-resistance genes are more likely to harbour drug-resistance genes[49]. Although a few studies have addressed the effect of changing metal concentrations and toxicities in soil and water environment[69], there is not much information on its contribution to selection of resistant genes.

(*iv*) Aquaculture: With aquaculture becoming a fast growing industry in India and neighbouring countries, the injudicious use of antimicrobial agents to increase the productivity of farmed seafood can serve as an emerging source of environmental AMR. As described by Henriksson *et al*[70], the disturbing fact is that unlike soil and waste water which are geographically more confined, AMR in the aquatic environment has the maximum propensity of international spread through international waters. Although the exact extent is yet not known, antimicrobial residues have been reported from aquaculture shrimps of India[71].

Steps taken to curb AMR in the environment

Political commitments

(*i*) International efforts: AMR was recognized as a serious public health threat by WHO in 2011[3]. The South East Asian Regional Office (SEARO) conducted several meetings to plan and adopt means of tackling AMR in the Region. One such landmark meeting was held in 2011 in Jaipur, India, wherein the Health Ministers of all the Member countries, including India, committed to adopt the Jaipur Declaration[3] by taking intensive measures on AMR. With the 2014 Report of WHO[72], the extraordinary rates of AMR prevalent in India came into focus. After this Report, joint efforts were made by India and the WHO. While WHO labelled AMR as the Flagship Priority area for SEARO[8], the Indian Medical Association launched an awareness programme[73] to train the physicians and sensitize the general public. In 2015, the 68th World Health Assembly decided to incorporate the concept of One Health in the fight against AMR and a Global Action Plan was initiated[74]. All Member countries, including India, agreed to frame their own NAPs for AMR by 2017.

(*ii*) National efforts: The Government of India formulated a Core Working Group on AMR that drafted a NAP for the country. Six strategic priorities have been listed in NAP, all of which have incorporated considerations for AMR in the environment, directly or indirectly[6,75]. Further, each strategic priority has defined interventions, activities and outputs, the fulfilment of which is delineated by a timeline projected for the next five years. The NAP, although promising, has not yet come into full action in any of the Indian States so far. To curtail the prevalent malpractice of OTC sale of drugs, the Central Drugs Standard Control Organization implemented Schedule H1 in India in 2014. It, however, encompasses only a few selected antimicrobial groups[33]. In June 2017, the Food Safety and Standards Authority of India (FSSAI) published the list of maximum residue levels for antimicrobials in foods prepared from animal, poultry and fish[76].

Health organizations of India

To know the near-exact extent of AMR, AMR surveillance networks were initiated by the Indian Council of Medical Research and the National Centre for Disease Control in 2013 and 2014, respectively[30]. In 2015, these two organizations along with support from Centers for Disease Control and Prevention (CDC), USA, started a systematic assessment of the prevailing IPC practices in India with the aim of formulating new guidelines for preventing hospital-acquired infections. These activities, however, cater basically to the emerging AMR in the healthcare settings and do not include special provisions for AMR in the environment. Similarly, the National Health Mission's National Health Systems Resource Centre and the National Accreditation Board deal with IPC practices and strengthening of laboratories/hospitals and not with the AMR in the environment *per se*[30]. The importance of AMR in the environment has been realized recently by the national health authorities[77] and The National Health Policy 2017[75] calls for 'a rapid standardization of guidelines regarding antibiotic use, limiting the use of antibiotics as OTC medications, banning or restricting the use of antibiotics as growth promoters in animal livestock, and pharmacovigilance including prescription audits inclusive of antibiotic usage - in the hospital and community'.

Innovative ideas

The National Health Mission of India started the *Swachh Bharat Abhiyan*[78] or the Clean India Mission to improve the basic hygiene and sanitation in all spheres of life. As a part of this massive programme, education was imparted through mass media on the health hazards of open defecation. UNICEF data shows that out of one billion openly-defecating people in the world, 60 per cent reside in India[79]. It is further argued that it is a behavioural problem with the Indians as other poverty-struck nations of Africa and South East Asia did not have the problem of open defecation to this an extent[10]. To deal with such sociocultural issues, innovative ideas along with mass media are needed in India. We propose the following future directions for containment of AMR in India (Box).

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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Box. Future directions for India

1. Promoting further research on the drivers of AMR with due importance to components other than antimicrobial use for human health alone

2. Framing of antibiotic stewardship plans for healthcare settings to monitor and ensure judicious use of antimicrobials, including all tiers of healthcare-primary health centres, secondary and tertiary hospitals

3. Strict vigilance and control over sale of antimicrobial agents. Prescription audit to bring down the over the counter (OTC) sale

4. Disciplinary control over the functioning of hospital effluent plants with periodic assessment and reporting of antimicrobial residue in the discharge

5. Regulation of waste water discharges from pharmaceutical companies with regular monitoring of antimicrobial residues in them along with provision of legislative support to punish offenders

6. Framing and implementing rules and regulations for the use of antimicrobial agents in food animals including farmed seafood

7. Improving agricultural practices by ensuring use of environment-friendly manure and fertilizers

8. Educating the masses at the community level regarding AMR and formulating educational bodies/non-governmental organizations for continued dissipation of information.

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