Antibiotic Resistance and Sanitation in India: Current Situation and Future Perspectives

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Contents

Abstract Antimicrobial resistance (AMR) is a global threat as the existing health care may become ineffective. Antibiotics, antibiotic-resistant bacteria (ARB), and antibiotic resistance genes (ARGs) considered as emerging contaminants are the three major components of AMR. India is one of the largest consumers of antibiotics with defined daily dose (DDD) of 4,950 per 1,000 population in 2015. By 2030, therapeutic and nontherapeutic use of antibiotics in veterinary animals is projected to increase by 18%. Antibiotics, ARB, and ARGs in the solid and liquid waste generated enter the environment via different pathways. The major sources of antibiotics, ARB, and ARG include domestic, hospital, and pharmaceutical industry wastewater apart from the solid/liquid waste generated from veterinary and food animals. Existing conventional wastewater treatment technologies like activated

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sludge process (ASP) do not ensure complete removal of antibiotics, ARB, and ARGs from wastewater. Similarly, the sludge generated find its way to agriculture land and eventually spread resistance in the environment. Once introduced in the environment, elimination of these contaminants is difficult. India's action plan on AMR in 2017 regulates antibiotic use for human and animal and addresses environment AMR spread from all possible sources and containment. In 2020, the Government of India introduced discharge standard for 121 antibiotics in the effluents of bulk drug manufacturing industries, formulation industries, and common effluent treatment plant (CETP) receiving pharmaceutical wastewater.

Keywords AMR, Antibiotics, ARB, ARG, Discharge standards, Environment, India, Nontherapeutic, Solid and liquid waste, Therapeutic, Wastewater treatment

1 Introduction

Antibiotic resistance is a major public health concern at the global level as the existing health-care services may become ineffective. To exemplify, chloramphenicol is no longer a preferred choice for treating patients with antibiotic-resistant bacterial infections [1]. By 2050, two million deaths are projected to occur in India because of antibiotic resistance [2]. In developing countries like India urbanization and population growth are in increasing trend and this could lead to high consumption of antibiotics. In 2010, India was one of the top 5 countries with the largest shares of global antibiotic consumption. According to the Center for Disease Dynamics, Economics, & Policy (CDDEP), the antibiotic consumption was 2,645 DDD per 1,000 population in the year 2000 and has increased to 4,950 DDD per 1,000 population in the year 2015 [3]. Increase in antibiotic consumption could increase the antibiotic resistance burden and failure of treatment [4]. Hence, containment of antibiotic resistance spread is important. However, it is important to understand that AMR containment is not specific to only health-care services but also to the environment.

Antibiotics, ARB, and ARGs are the three major components of antibiotic resistance. The major sources of antibiotics, ARB, and ARGs in environment are wastewater from hospital, domestic use, and pharmaceutical industries [5–7]. Apart from wastewater and solid/liquid waste generated from animals, nontherapeutic use also introduce antibiotics, ARB, and ARGs into the environment [5, 6]. The western part of India has 47% of nation's pharmaceutical manufacturing units, but the effluent characteristic data including antibiotics from the manufacturing unit is scarcely available for this zone. While southern India hosts 18% of the pharmaceutical manufacturing units, concentration of the pharmaceutical compounds in the effluent is well reported compared to other zones [8]. The data is very important to understand the contribution of manufacturing units in polluting the environment

with antibiotics. However, the data on contribution from animal and nontherapeutic use is limited due to lack of strict rules and stringent monitoring. Similarly, quantitative data on ARB and ARGs entering environment due to anthropogenic activities are also limited in India.

To frame policies and treatment standards for an emerging concern like antibiotics, ARB, and ARG contamination, a holistic study approach is required. The study may include data on (1) antibiotics use in hospital, veterinary antibiotics in farms, and in other nontherapeutic applications; (2) source, pathway, or fate and transport of antibiotics, ARB, and ARGs; (3) occurrences of antibiotics, ARB, and ARGs in different environment matrices; (4) efficiency of current wastewater treatment practices in removing antibiotics, ARB, and ARGs; (5) national policies and plans implemented by the Government to contain AMR spread; and (6) current status and future recommendations. This book chapter attempts at presenting the Indian scenario of the abovementioned holistic approach.

2 Antibiotic Consumption for Therapeutics Purpose

Antibiotic use is one of the major determining factors of resistance gain and transfer. In India, antibiotics are prescribed in excess [9], and consumption is increasing steadily [10]. The most commonly consumed antibiotics are β-lactams while commonly prescribed includes fluoroquinolones, macrolides, cephalosporins, tetracyclines, and co-trimoxazole apart from penicillins [11]. It was reported that global antibiotic consumption has increased by 36% of which Brazil, Russia, India, China, and South Africa (BRICS) countries contribute 76%. About 23% of overall retail sales in BRICS countries was attributed to India. Between 2010 and 2015, there was a substantial increase in consumption of cephalosporins, broad-spectrum penicillins, and macrolides [3]. Cephalosporin and broad-spectrum penicillin consumption have significantly increased from 330 and 691 to 1822 and 1,055 DDD per 1,000 population between 2000 and 2015, respectively. Similarly, the consumption of macrolides has increased from 247 in 2000 to 469 DDD per 1,000 population in 2015 (Fig. 1). The consumption of trimethoprim has dropped from 332 to 186 DDD per 1,000 population between 2000 and 2015. However, consumption of the fluoroquinolones in 2000 was 492 and increased to 1,033 DDD per 1,000 population in 2006 and has dropped to 762 DDD per 1,000 population in 2015 (Fig. 1). Pattern change in antibiotic use could be attributed to rapid economic growth, rising income, and easy availability of antibiotics.

The use of antibiotics varies due to different reasons ranging from availability [12] to self-medication. Antibiotics consumption also varies with season, and in India, the average consumption was reported to peak during September, the end of the monsoon [13]. Inappropriate consumption of antibiotics for acute diarrhea [13], viral dengue fever [14], and acute respiratory infections [12] is widely reported in India. Poor sanitation practice [13], unregulated over-the-counter private pharmacy sales [14, 15], inappropriate prescription by medical practitioners for incentives [16],

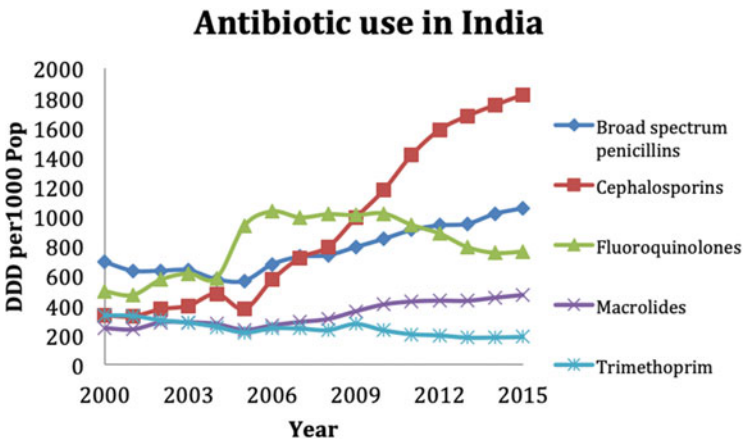

Fig. 1 Pattern change in antibiotic consumption in India, 2000–2015 [3]

and pharmacy sales in hospitals [17] are also reported in India. Over 50% of antibiotics consumed for presumed tuberculosis in Nagpur were dispensed without prescription over the counter [14]. A study conducted by Peripi et al. in Vijayawada reported that broad-spectrum antibiotics are highly prescribed by private practitioners compared to the public doctors [9], while Kumari Indira et al. observed high antibiotic prescription by rural practitioners compared to urban practitioners [12]. The prescription pattern also depends on nonclinical factors such as drug availability, type of hospital and department, and patients' request. Drugs available in the reserve (for specific treatments) are commonly prescribed in private hospitals, while in public/government hospitals, availability at the pharmacy is the deciding factor of prescription [12]. In some situations, antibiotics are prescribed based on patients' request. About 11–35% of doctors prescribed antibiotics due to patient pressure in a study conducted in Tamil Nadu [18]. However, irrational prescription of antibiotics is quite common in private and public sector hospitals across India [19]. Nevertheless, education on rational use of antibiotics is mandatory for both medical practitioners and patients.

3 Antibiotics Use in the Animal Food Industry

Over the years, the purpose of antibiotics use in livestock industry has changed. The antibiotics are used in animal farms as therapeutic agents, growth promoters, and prophylactic agents [20]. Antibiotics and antimicrobials constitute more than 70% of veterinary medicine [21]. Global consumption of antibiotics in 2013 in animal food industries was estimated to be 131,109 tons and is expected to increase more than 50% by the year 2030 [22]. In 2010, India was the fourth largest consumer of

antibiotics in food animal, which accounts for about 3% of the global consumption. By 2030, antimicrobial consumption for animals is expected to grow by 99% in BRICS countries [23].

Antibiotics are mixed in the feed to make animals resistant against disease and to gain more weight in a short time, which increases productivity. India is one of the largest producers of milk, producing 165.4 million tons in the year 2016–2017 primarily from smallholders [24]. An easy way for a smallholder to increase the yield is to make use of uncontrolled availability of antibiotics for therapeutics and to promote growth as it is economical [25]. This could result in high concentration of antibiotics in milk products and meat and animal wastes exceeding the maximum residue limits. Lack of regulatory framework to curb the use of antibiotics in livestock and food animals is one of the reasons for resistance spread in India. It is also estimated that in 2030, the antibiotics consumption in livestock in India may increase by 18% [23]. Chicken consumption in India is rapidly increasing. To meet the growing demand addition of unregulated quantity of antibiotics to animal feed as a growth promoter in poultry is practiced. The chicken meat was reported to have antibiotic residues such as tetracyclines (sum of oxytetracycline, chlortetracycline, doxycycline) and fluoroquinolones (sum of enrofloxacin and ciprofloxacin). Concentration of tetracyclines and fluoroquinolones was in the range of 16.01 to 46.02 μg/kg and 3.37 to 196.34 μg/kg, respectively [26]. In European countries, food quality controls on chemicals including antibiotics are in place. In India, the tolerance limit for antibiotics is set for seafood under Food Safety and Standards Regulation 2011, but no such regulation is put in place for chicken meat. The chicken meat that is exported has to comply with EU standards, while the domestic consumption has no regulation [26].

Nontherapeutic use of antibiotics in food preservation, apiary, aquaculture, agriculture, poultry, and pig farming is one of the sources of antibiotic resistance gain, and it spreads to the larger environment [22, 23]. 90% of the antibiotics are administered to farm animals at subtherapeutic concentration, of which 30% constitute growth promoters. Over-the-counter sale of veterinary antibiotics as growth promoters is quite common in India [27]. Antibiotics at sublethal concentration could increase the chance of resistance acquisition and transfer in animal gut bacteria [28]. Up to 90% of the antibiotics are excreted via urine and animal feces either unchanged or as active metabolized products [29]. Apart from the antibiotic residues and ARB in animal products, animal waste in all forms (carcasses, urine, feces) serves as a medium for AMR spread in the environment.

4 Source and Pathways of Antibiotics, ARB, and ARGs in the Environment

Figure 2 represents the source and pathway of antibiotics, ARB, and ARGs into the environment. Direct contamination of surface and groundwater with components of AMR is due to direct and indirect discharge of treated/untreated wastewater from

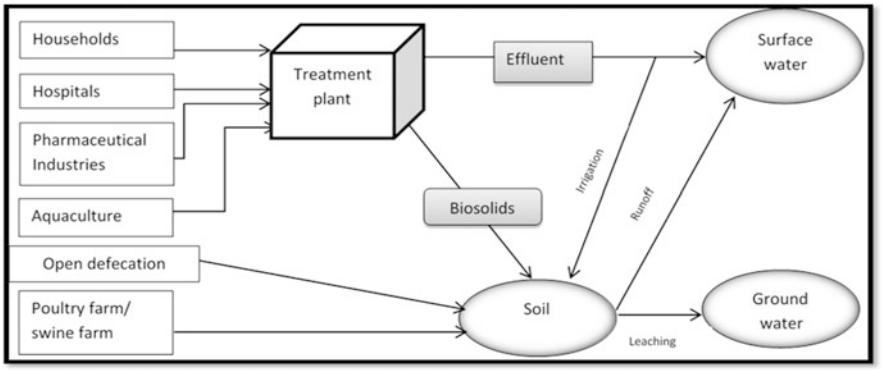

Fig. 2 Source and pathway of antibiotics into the environment

residence, industries, and solid/liquid waste generated from livestock farms, aquaculture, etc. In recent years, rapid urbanization has led to the implementation of decentralized treatment plants, and the treated effluent from such plants is commonly used for landscaping, watering lawns, gardening, and irrigation. The application of treated effluent for irrigation and recreational activities could contaminate the soil and indirectly contaminate the surface and groundwater [29, 30]. The sludge generated from wastewater treatment plant (WWTP) or sewage treatment plant (STP) and solid/liquid waste from livestock farms containing antibiotics, ARB, and ARGs are widely used as soil amendment to improve the nutrient content of the agriculture soil [31, 32]. Leaching of antibiotics, ARB, and ARGs over time from amended soil may reach groundwater and contaminate it indirectly [33]. Poor sanitation practice is also reported as one of the reasons for AMR and spread [34]. According to the UNICEF monitoring data 2012, 59% of 1.1 billion people who practice open defecation in the world reside in India [35]. Open defecation contaminates the soil, surface water, and groundwater directly and indirectly.

In India, surface water serves as the source of drinking and irrigation of agriculture fields. Contamination of the water sources with antibiotics, ARB, and ARGs can disseminate resistance genes to the environment [36]. Direct and indirect human exposure to contaminated environment such as water and soil is risky. Similarly, the prevalence of antibiotic resistance in the environment can be life-threatening when there is a disease outbreak making treatment of the resistant organism's infection difficult.

5 Antibiotics in Different Environmental Matrices

Lack of sufficient infrastructure and proper waste management practices are the main reasons for introduction of antibiotics into natural streams. The concentration of each antibiotic in different environmental matrices vary due to properties of antibiotics

such as octanol-water partition coefficient, biodegradability, bioavailability, etc. (Table 1). The direct source of antibiotics in surface water results from the discharge of untreated or partially treated wastewater from hospitals, industries, and WWTPs [37]. The concentration of antibiotics in sewage is directly proportional to prescription quantity [38]. In India, antibiotics are sold as nonprescription drug with a frequency of 18% [18]. Hence, there is no control over the residual concentration ending up in sewage. High concentration of fluoroquinolones was detected in hospital effluents and in river water samples especially ciprofloxacin [38, 39]. The concentration of ciprofloxacin found in effluent from a CETP that treats wastewater from bulk drug manufacturing units was 31,000 μg/L [6].

The Yamuna River is polluted with antibiotics including ampicillin, ciprofloxacin, gatifloxacin, sparfloxacin, and cefuroxime and is continuing to receive effluents from 17 STPs and 17 storm water drains [40]. Cochin estuaries receive 250 m^3 of domestic sewage because of improper waste management. This estuary is reported to have antibiotic-resistant *E. coli* counts higher than that reported in estuaries in France and Portugal [41, 42]. Sediments collected from Mutha River immediately after discharge point of treated wastewater from major hospitals and residential zone are enriched with genes conferring resistance to last resort antibiotics like carbapenems as well as metals and biocides [37, 43]. Contamination of Mutha River is due to the malfunctioning of WWTPs in Pune city and 50% of city's untreated sewage being discharged into the river [38].

The discharge of conventionally treated wastewater into streams has a significant effect on all forms of surface water. Efficient tertiary treatment of wastewater, proper management of sludge, and changes in disposal ways could control antibiotic resistance transmission to different environmental matrices.

6 Seasonal and Spatial Variation of Antibiotics in the Environment Matrices

Antibiotic concentration in the environment is reported to vary with seasons. Antibiotics concentration is reported to be highest during winter season, less during summer, and least during monsoon in River Yamuna [40]. Kshipra River water was found to have high concentration of sulfamethoxazole during autumn (2.75 μg/L) and winter (2.15 μg/L) compared to summer (1.39 μg/L) and rainy season (0.04 μg/L) [48]. The change in antibiotic residue concentration could be due to change in pH. pH of the water bodies can influence the solubility of the antibiotics [50]. Sulfamethoxazole concentration in Kshipra river sediments is reported to be influenced by solubility, which in turn is influenced by pH [48]. High concentration of antibiotics in river water during winter could be due to low biodegradation rate, which is influenced by temperature and other operational parameters of the treatment plant [45]. The lower concentrations of antibiotics observed during monsoon could be due to the dilution effect of rainwater. During summer, photo degradation, temperature,

Table 1 Occurrence of antibiotics in various environmental matrices

Type of sample	Location	Antibiotics	Concentration (μg/L)	Analytical instrument	Reference
Wastewater	Hospital wastewater, Madhya Pradesh	Ofloxacin	4.5	LC-MS/MS	[44]
		Ciprofloxacin	218.3		
		Norfloxacin	6.4		
		Levofloxacin	5		
	CETP for pharmaceutical wastewater, Andhra Pradesh	Ofloxacin	150–160	HPLC	[6]
		Ciprofloxacin	28,000–31,000		
		Norfloxacin	390–420		
		Enrofloxacin	780–900		
		Lomefloxacin	150–300		
		Enoxacin	150–300		
	Okhla STP, Delhi	Ciprofloxacin	8	HPLC-PDA	[40]
		Gatifloxacin	1.22		
		Sparfloxacin	0.14		
		Cefuroxime	0.22		
		Ampicillin	12.68		
	STPs, South India	Chloramphenicol	<0.01	HPLC-MS	[10]
		Trimethoprim	0.04–0.29		
		Sulfamethoxazole	0.40–0.64		
		Ofloxacin	0.21–2.47		
	WWTP influent from Metropolitan city, Western India	Levofloxacin	150	HR-LC-MS/MS	[45]
		Norfloxacin	20		
		Azithromycin	300		
River	Yamuna River, Delhi	Ciprofloxacin	1.44	HPLC-PDA	[40]
		Gatifloxacin	0.48		
		Sparfloxacin	2.09		
		Cefuroxime	1.7		
		Ampicillin	13.75		
		Ofloxacin	1.51	LC-ESI-MS/MS	[46]
		Erythromycin	0.10		
		Azithromycin	0.16		
		Norfloxacin	0.20		
		Ciprofloxacin	4.88		
		Moxifloxacin	0.16		
		Amoxicillin	0.18		
	Musi River, Telangana	Ofloxacin	1.55–318.1	LC-MS/MS	[47]
		Ciprofloxacin	6.59–5,528		
		Norfloxacin	16.14–217.5		
		Pefloxacin	0.74–44.34		
		Enrofloxacin	2.57–123.4		
		Difloxacin	0.47–37.74		

(continued)

Table 1 (continued)

Type of sample	Location	Antibiotics	Concentration (μg/L)	Analytical instrument	Reference
		Lomefloxacin	3.59–10.32		
	Kshipra River, Madhya Pradesh	Norfloxacin	0.66	LC-MS/MS	[48]
		Ofloxacin	0.99		
		Sulfamethoxazole	0.04–2.75		
	Cauvery River, Tamil Nadu	Carbamazepine	0.13	GC-MS	[49]
	Tamraparni River, Tamil Nadu		0.01		
	Vellar River, Tamil Nadu		<0.01		
River sediments	Kshipra River, Madhya Pradesh	Ofloxacin	0–9.74	LC-MS/MS	[48]
		Sulfamethoxazole	0–8.23		
Aquifer	Delhi	Ofloxacin	4.34	LC-ESI-MS/MS	[46]
		Erythromycin	0.11		
		Azithromycin	0.17		
		Norfloxacin	0.05		
		Ciprofloxacin	5.90		
		Moxifloxacin	0.21		
		Amoxicillin	0.18		

and microbial activity play important role in reducing the antibiotic concentration [48].

In India, the concentration of antibiotics is comparatively more in river tributaries than in the main river because the tributaries are the immediate discharge points of wastewater. The antibiotics concentration reduces due to dilution effect when it reaches the main river [47]. Also, the contamination level of antibiotics in surface water such as river is positively correlated with land use pattern [39, 43]. This could be due to discharge of treated/untreated wastewater containing high concentration of antibiotics resulting from high domestic consumption. High concentrations of antibiotics are reported near the discharge points in surface water [51] and in rivers traversing through urbanized area as the infusion of sewage and industrial effluent are inevitable in densely populated areas [52]. There are several other physic-chemical properties such as photosensitivity, co-metabolism, nature of active metabolites/by-products, etc. that determines the spatial distribution and concentration of antibiotics in different environments. However, reports available on seasonal and spatial variation of antibiotics in different Indian environment are limited. Antibiotics in any environment could increase the chance of resistance spread, disease burden, and treatment failure from direct and indirect human exposure to resistant pathogens [36].

7 Antibiotic-Resistant Bacteria in the Environment

ARB are inherently present in the environment. ARB and antibiotics enter the environment from different sources [44] such as human and animal excreta, discharge form wastewater treatment plant, and direct sewage discharge. It is supposed that antibiotic residues that enter aquatic environment can promote resistance in aquatic microbial communities [53]. High concentration of antibiotics may select ARB in the environment [54]. Reports suggest that antibiotics at low and subminimum inhibitory concentration can also select ARB [55]. ARB mutants selected at low and subinhibitory concentrations exhibit higher stability than the ones selected at high antibiotic concentration [56].

WWTP acts as a connecting bridge between wastewater generated and aquatic environments. WWTP provides the right environment for mutation and exchange of genes resulting in resistance spread because a large number of bacteria constantly encounter antibiotics at subinhibitory concentration [56, 57]. Proportion of ARB may increase during course of wastewater treatment mainly when treatment processes involve one or more biological methods [54]. Akiba et al. reported that increased prevalence of resistant bacteria in the STPs was due to inflow of hospital wastewater. Also, the strains isolated were resistant to antibiotics quantified in the STP samples [10]. Partially treated or untreated wastewater is usually discharged into surface water leading to contamination of aquatic environment with ARB. ARB could share resistant genes with environmental bacteria. When antibiotic resistance genes are shared, the environmental ARB (eARB) could become pathogenic ARB (pARB) if the eARB carries virulence traits [58, 59]. This signifies that inadequate wastewater treatment and poor maintenance of STPs in hospitals could contribute to the spread of AMR in the environment [60, 61]. ARB are reported in different environments including hospital wastewater, untreated sewage, STPs, drinking water, river water and sediments, coastal waters, marine water, and sediments (Table 2). Bacteria exhibiting different levels of resistance are widely reported in various environments across India (Table 2). However, distribution of ARB in environment varies with season [48], and elimination of ARB from any environment can be difficult [5]. Hence, ARB introduced into the environment through anthropogenic activities are of concern.

From Table 2, it can be seen that in India, domestic/hospital wastewater and effluents from WWTPs/STPs are the widely reported sources of ARB. This is because wastewater and effluents are direct source of ARB introduction. Indirect/neglected sources of ARB include application of STP/WWTP sludge, livestock waste on land as soil amendment, open defecation, and direct dumping of animal waste in the vicinity water sources, which are widely practiced in India [29, 82–84]. The indirect sources ARB are least studied. Runoff water from agriculture lands and places of open defecation also serve as a medium for ARB introduction in the environment [49, 85]. However, not all the reported ARB are clinically significant.

Table 2 Antibiotic-resistant bacteria in different environment matrices

Source	Location	Bacterial group	Type of resistance	Reference
Kshipra River	Ujjain, Madhya Pradesh	*E. coli*	ESBL	[48, 62]
Musi River	Hyderabad, Telangana	Ciprofloxacin resistant bacteria	MDR	[63]
Mula-Mutha River	Pune, Maharashtra	*E. coli*	MDR	[38]
		Thermotolerant fecal coliform	DDR	[43]
		Acinetobacter spp.	MDR	[37]
Yamuna River	Delhi	ESBL and Amp C- producing *E. coli*	MBR	[64]
		ESBL producers	MDR	[65]
		Enterobacteriaceae	Carbapenem resistant	[61]
		ESBL-producing *Klebsiella pneumonia*, *Klebsiella quasipneumoniae*, *Klebsiella variicola*	MDR	[66]
Cauvery River	Karnataka	*E. coli, Enterobacter cloacae*, *Pseudomonas trivialis*, *Shigella sonnei*	MDR	[67]
		Staphylococcus spp. and *Staphylococcus aureus*	Methicillin and vancomycin resistant	
Subarnarekha River, Kharkai River, Dimna Lake, and Hudco Dam	Jamshedpur, Jharkhand	*Pseudomonas*, *Acinetobacter*, *Aeromonas*, *Klebsiella*, *Enterobacter*, and *Proteus* spp.	MDR	[58]
Stream, well water, drinking water, tap water, soil	Wayanad, Kerala	*Vibrio cholerae*	MDR	[68]
Drinking water and wastewater	Ujjain, Madhya Pradesh	*E. coli*	MDR	[69]
5 recreational beaches	Mumbai, Maharashtra	*E. coli* pathotypes (EHEC, ETEC, EPEC, STEC, EAEC, and UPEC)	MDR	[70]
Palk Bay	Tamil Nadu	*Vibrio* spp.	MDR	[71]
Port Blair Bay	Andaman and Nicobar Islands	*Enterococcus faecalis*	DDR	[72]
River, ponds, kunds, hand pumps, piped supply and dug wells	Across India	*Escherichia coli* O157: H7	MDR	[73]

(continued)

Table 2 (continued)

Source	Location	Bacterial group	Type of resistance	Reference
Wetland	Lakhimpur Kheri, Uttar Pradesh	*Citrobacter*, *Aeromonas*, *Curtobacterium*, *Erwinia*, *Providencia*, *Shigella*, *Arthrobacter*, *Chryseobacterium*, *Acinetobacter*, *Enterobacter*, *Pseudomonas*, *Janthinobacterium*, *Bacillus*, *Yersinia*, *Rahnella*, *Rheinheimera*, *Sphingobacterium*, *Micrococcus*, *Vogesella*, and *Kluyvera* spp.	MDR	[74]
Karwar coast (Arabian Sea)	Karnataka	*Bacillus toyonensis* PNTB1, *Lysinibacillus sphaericus* PTB	MDR	[75]
Cochin estuary	Cochin, Kerala	*E. coli*	MDR	[41]
Recycled hospital wastewater	Kanchipuram, Tamil Nadu	*E. coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus mirabilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*	MDR	[76]
Wastewater outfalls of 12 hospitals	Delhi	Gram-negative pathogens	Carbapenem and ESBL	[77]
Wastewater outlets of a rural and an urban hospital	Ujjain, Madhya Pradesh	ESBL-producing *E. coli*	MDR	[78]
WWTP	Jalandhar, Punjab	*Staphylococcus aureus*	MDR	[79]
WWTP	Haridwar, Uttarakhand	Fluoroquinolone- resistant bacteria	Ciprofloxacin, norfloxacin, and ofloxacin	[54]
STPs	Tamil Nadu	*E. coli*	MDR	[10]
STPs	New Delhi	*E. coli*, *Pseudomonas putida*, *Enterobacter cloacae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Aeromonas caviae*	ESBL	[60]
		E. coli, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* subsp.	Carbapenem resistant	

(continued)

Table 2 (continued)

Source	Location	Bacterial group	Type of resistance	Reference
		pneumoniae, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Pseudomonas putida*, *Shigella dysentery*		
Drain sites, hospital waste outfalls, effluents from STPs	New Delhi	*Enterobacteriaceae*	Carbapenem resistant	[61]
Sewage outfalls from hospital to community drains	New Delhi	*Pseudomonas putida*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Klebsiella pneumoniae* subsp. *pneumoniae*	Carbapenem resistant	[77]
		E. coli, *Pseudomonas putida*	ESBL	
Electronic industrial effluent discharges and CETP	Hyderabad, Telangana	*Pseudomonas*, *Bacillus*, *Halomonas*, and *Kocuria* spp.	Chloramphenicol, streptomycin, and ampicillin	[80]
Shrimp (effluent) pond discharge point, Vellar estuary	Parangipettai, Tamil Nadu	*Bacillus pumilus* and *Bacillus flexus*	MDR	[81]

MDR multidrug resistant, *DDR* dual drug resistant, *MBR* multiple β lactam resistant, *ESBL* extended spectrum β-lactams

8 Antibiotic Resistance Genes in the Environment

Some microbes have intrinsic resistance to antibiotics irrespective of antibiotic use [86]. However, excessive use of antibiotics results in resistance acquisition and transfer. Though ARGs are inherent to microbial community, the intensive use of antibiotics for human, animal, and agriculture accelerates ARG mutation and acquisition of new ARGs [53]. ARGs are widely reported in different environment including hospital wastewater, untreated sewage, STPs, drinking water, river water, and sediments (Table 3). ARGs are considered as emerging pollutants, and dissemination of ARGs in the environment is of concern. ARGs can be of genomic or plasmidic origin. However, antibiotic resistance traits are usually associated with horizontally transferable mobile genetic elements [87]. ARGs in genomic DNA are transferred to progeny, while plasmid DNA may also be transferred to different bacteria species via horizontal gene transfer (HGT) through conjugation, transduction, and transformation mechanisms [59]. ARGs are associated with MGE such as

Table 3 ARGs reported in different environment across India

Source	Location	ARGs	Gene abundance (log gene copy mL^{-1})	Resistance	HGT genes/ RDRs	Reference
Mula- Mutha River	Pune, Maharashtra	*qnr*A, *qnr*B, *qnr*S, *oqx*A	–	Quinolone	*int*I1, *int*I2	[37, 38]
		bla_{TEM}, bla_{SHV}, $bla_{CTX\text{-}M\text{-}15}$, $bla_{CTX\text{-}M\text{-}27}$, GES, OXA-1, OXA-2, OXA-10, CAR	–	β-lactam		
		ant(3″)-*la*, *ant*(2″)-*la*, *ant*(6)-*la*, *aph*(3″)-*lb*	–	Aminoglycoside	Integrases ISCR, transposases	[37]
		GES-type, OXA-58, NDM, KPC, IMP, OXA-48 type	–	Carbapenem		
		*cat*A16, *cat*B2, *cat*B3, *cml*A	–	Chloramphenicol		
		ere(A), *ere*(C), *erm*(F)	–	Macrolides		
		*inu*F	–	Lincosamide		
		*sul*1, *sul*2, *sul*3	–	Sulfonamide		
		tet(M), *tet*(Q), *tet*(X), *tet*(32)	–	Tetracycline		
		mcr-1	–	Colistin		
		*dhfr*A1, *dhfr*A15	–	Trimethoprim		
		tet (X)	–	Tigecycline		
Yamuna River	Delhi	$bla_{CTX\text{-}M}$, bla_{TEM}, bla_{SHV}, amp_C	–	β-lactams	–	[64, 65]
		bla_{TEM}, bla_{SHV}, $bla_{CTX\text{-}M}$	–	ESBL	–	[66]
		$bla_{NDM\text{-}1}$	~6 ± 0.25–8 ± 0.5	β-Lactams	*int*1, *int*2, *int*3	[61]
		bla_{OXA}	–			
		$bla_{NDM\text{-}1}$	5.4 ± 0.4	β-Lactams	–	[90]
		bla_{OXA}	–			
		tet(M), *tet*(Q), *tet*(W)	–	Tetracycline	–	

Upper Ganges River	Rishikesh-Haridwar	$bla_{\text{NDM-1}}$, bla_{OXA}	2.1 ± 0.6	β-Lactams	–	[90]
		tet(M), *tet*(Q), *tet*(W)	–	Tetracycline		
Kshipra River	Ujjain, Madhya Pradesh	$bla_{\text{CTX-M-1}}$	–	β-Lactams	–	[48]
		qnr S, *qnr* B	–	Quinolone		
		*sul*1, *sul*2	–	Sulfonamide		
Ganga River	Lucknow, Uttar Pradesh	bla_{TEM}	0.36 ± 0.15–5.32 ± 3.69	β-Lactams	–	[91]
Gomti River	Kanpur, Uttar Pradesh	bla_{TEM}	1.94 ± 0.5–5.96 ± 1.54	β-Lactams	–	
		*gyr*A, *par*C, *qnr*A, *qnr*B, *qnr*S, *aac(6′)-Ib-cr*, *oqx*AB, *qep*A	–	Quinolones		
Cauvery River	Karnataka	bla_{TEM}	–	β-Lactams	–	[67]
		dhfr		Trimethoprim		
Cochin estuary	Cochin, Kerala	bla_{TEM}, $bla_{\text{CTX-M}}$	–	β-Lactams	*int*1, *int*3	[41]
		tet (A), *tet* (B)		Tetracycline		
		*sul*1, *sul*2, *sul*3		Sulfonamide		
		*aph*A2		Gentamicin		
		*cat*1		Chloramphenicol		
		*dhfr*1, *dhfr*7		Trimethoprim		
Drinking water and wastewater	Ujjain, Madhya Pradesh	$bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-9}}$	–	β-Lactams	–	[69]
		*qnr*A, *qnr*S		Quinolone		
Sewage outfalls from hospital to community drains	New Delhi	$bla_{\text{NDM-1}}$	11.29 ± 2.11–8.87 ± 2.15	ESBL	*int*1	[77]
		bla_{CTX}, bla_{OXA}, bla_{TEM}	–			
STPs	New Delhi	bla_{CTX}	~6 ± 1–9 ± 0.1	ESBL	*int*1, *int*2, *int*3	[60]
		bla_{OXA}	~4 ± 0.1–6.5 ± 0.1			

(continued)

Table 3 (continued)

Source	Location	ARGs	Gene abundance (log gene copy mL^{-1})	Resistance	HGT genes/ RDRs	Reference
		bla_{TEM}	~7 ± 0.1–9.75 ± 0.25			
		bla_{NDM-1}	~5 ± 0.25–8 ± 0.1			
Drain sites, hospital waste outfalls, STPs effluent	Delhi	bla_{NDM-1}	~6.5 ± 0.25–8.25 ± 0.25	β-Lactams	*int*1, *int*2, *int*3	[61]
		bla_{OXA}	–			
WWTP	Haridwar, Uttarakhand	*gyrA*	–	Quinolone	–	[54]

RDR resistance-determining regions

plasmids and integrons, and transposons enable easy dissemination of resistance via HGT [88]. ARGs in plasmids are self-transmissible and capable of transferring and replicating in different organisms [89].

Antibiotics stress not only selects bacteria but also results in gene mutation in resistance genes [54]. ARGs are persistent and may occur in the environment even in the absence of antibiotic selection pressure [43], and the distribution of different ARGs in environment may vary with season [27, 92]. However, ARGs proliferate irrespective of seasons during wastewater treatment [43]. The gut bacteria especially *E. coli* is a human commensal, antibiotic resistance indicator [69] and a reserve for antibiotic resistance genes, which can be horizontally transferred to pathogenic bacteria [93]. *E. coli* could reach environment matrices such as river due to discharge of partially treated and untreated domestic or hospital wastewater. ARGs encoded by plasmids in *E. coli* may result in resistance gene spread/transfer [69] in such environment. Bajaj et al. demonstrated co-transfer of plasmid-mediated quinolone-resistant (PMQR) gene *qnr*S and plasmid-mediated AmpC β-lactamase genes between *E. coli* strains isolated from River Ganga and quinolone susceptible *E. coli* J53. *E. coli* J53 after gene acquisition exhibited co-resistance to quinolone and β-lactams [94]. This study proves that plasmid-mediated HGT of ARG is possible between an environmental *E. coli* resistant to antibiotics and *E. coli* susceptible to antibiotics.

Mutation in RDR also determines the bacteria's ability to resist antibiotics and may confer cross-resistance to other antibiotics [94]. Hence, it is important to understand the relationship between RDR and ARG. Lamba et al. reported correlation between expression levels of mobile genetic elements *int*1 and *int*3 and $bla_{\text{NDM-1}}$ gene abundance in *Enterobacteriaceae* [61]. The study also reported co-carriage of *int*1 and $bla_{\text{NDM-1}}$ gene in carbapenem -resistant *Enterobacteriaceae* (CRE) isolated from different sources. The co-carriage was reported to be 28%, 45%, 52%, and 57% in CRE isolated from STP, hospital, drain, and river samples, respectively, across New Delhi [61]. Co-occurrence of ARGs is quite common in MDR bacteria. In hospital setting, MDR bacterial infections are difficult to treat and sometimes are life-threatening. Chandran et al. reported co-occurrence of cephalosporin and quinolone resistance genes in *E. coli* isolated from hospital wastewater in Ujjain, Central India [78]. Hospital wastewater is also reported to contain MDR *E. coli* that are genetically diverse [78]. ARGs are inherent to resistant bacteria in the environment. However, anthropogenic activities such as discharging partially treated and untreated wastewater, application of livestock waste as soil amendments, open defection, etc. could increase ARG prevalence in the environment [85]. This could also promote resistance transfer to nonresistant/ pathogenic environmental bacteria [59].

9 Indian WWTPs Status in Eliminating Antibiotics, ARB, and ARG

Wastewater is linked to the natural environment by STPs. In India, the treatment facilities exist only for 31.5% of wastewater generated [95]. The commonly employed treatment technologies include ASP, oxidation pond, upflow anaerobic sludge blanket (UASB), sequential batch reactor, fluidized bed reactor, waste stabilization pond, Karnal Technology, rotating biological rope contactor, chrome recovery pilot plant, and aerated lagoon [96]. In India, the total capacity of treatment plants are 23,277 millions of liters per day, of which 5% is nonoperational, and 11% is under construction [95]. There is a large gap between wastewater generated and wastewater treated.

WWTPs/STPs receiving sewage and sewage mixed with hospital effluents contain antibiotics, ARB, and ARGs. The efficiency of the WWTPs in removing the AMR components decides the quality of the effluent. Hence, it is important to evaluate the performance of existing treatment technologies in removing antibiotics, ARB, and ARGs. The activated sludge process showed good removal efficiency for antibiotics like sparfloxacin and cefuroxime with 99% and 94% removal, respectively [40], and is less effective in case of low concentration antibiotics and recalcitrant antibiotics. The antibiotics removal efficiency is high when extended aeration process is employed for domestic wastewater [97]. Mutiyar and Mittal observed high removal of amoxicillin in STP involving an extended aeration ASP [97]. The antibiotic removal efficiency is also dependent on the influent wastewater quality. Prabhasankar et al. reported high antibiotic concentration in the effluent of the STPs receiving mixed wastewater from hospitals and domestic zone than that treating exclusively the hospital wastewater [1]. The high antibiotic removal rate in the STPs treating exclusively the hospital wastewater could be due to quantity of the influent wastewater and residence time. However, the antibiotics were not completely removed in the effluent of STP treating exclusively hospital wastewater [1]. Proper treatment of hospital wastewater can eliminate antibiotics by 80%, but only 40% of health-care facility has proper wastewater treatment facilities [98]. It is reported that an average of 0.53 kg of sulfamethoxazole is discharged annually from a STP in India serving an average population of 325,000 [21]. The concentrations of antibiotics in effluents from Indian STPs are higher when compared to Europe and North American countries [97]. The effluent of a CETP in Patancheru, Hyderabad, which receives wastewater from 90 drug manufacturing companies, after biological treatment is reported to have high concentration of antibiotics [6].

Mixed or not both domestic and hospital wastewater contain ARB and ARGs [99]. A STP employing UASB followed by ASP and chlorine disinfection scheme was ineffective in removing MDR *E. coli* [100]. Similarly, STPs receiving mixed wastewater and exclusively hospital wastewater employing ASP followed by clarification and chlorine disinfection were not effective in removing MDR *E. coli* [97]. The biological treatment employed in a municipal WWTP in Haridwar, removed 60–80% of fluoroquinolones, and disinfection by chlorine eliminated

96% of fluoroquinolone-resistant bacteria [54]. The effluent of a hospital wastewater treatment plant in Delhi was reported to carry carbapenem-resistant bacteria such as *Pseudomonas* spp., *Klebsiella* spp., *Escherichia* spp., and *Acinetobacter* spp., and ARG $bla_{\text{NDM-1}}$ associated with *int*1 [101]. Similarly, effluents from 12 STPs employing aerobic sludge as treatment process across Delhi were also reported to carry ARB such as carbapenem and ESBL-resistant bacteria and ARGs such as NDM-1, CTX, OXA, and TEM. However, including anaerobic digestion and chlorination as tertiary treatment improved the removal rate of ARB and ARGs [60]. There is no complete removal of antibiotics by the existing treatment plants, and the most common removal mechanism is sorption to sludge particulates [40]. Seasonal changes and type of wastewater treatment process do not have an impact on the prevalence of resistant isolates [10]. ARB and ARGs are also not completely removed during the treatment process, and maximum percentage ends up in the sludge [60].

10 India's Action Plans on AMR and Current Status

Antibiotic resistance is not considered a serious threat in majority of the developing countries due to lack of awareness among public. In India, antibiotic resistance made the news pages in 2010 with report on isolation of New Delhi metallo-ß-lactamase-1 (NDM-1). Ever since the NDM-1 reports in 2010 several clinical studies reporting isolation of antibiotic-resistant pathogens, and genes in clinical samples are increasing, indicating the awareness among research community. Several policies addressing effective antibiotic use and AMR containment are adopted in India since 2011 (Table 4). National antimicrobial policy for containment of AMR in India was adopted in 2011 [102], while Global Action Plan on AMR was adopted in 2014 [103].

Even though India's action plan on AMR was adopted in 2011, the plan considered only human and animal consumption and over-the-counter sale of antibiotics as the main reason for AMR spread. This resulted in inclusion of antibiotics in schedule H1 drug, AMR prevention and containment declaration, guidelines for antimicrobial usage in treating infectious disease, and widespread campaign across India. In August 2016, the Prime Minister of India addressed the antibiotic resistance and launched "Red line campaign" to make the public aware of the importance of antibiotic use and misuse [102]. This was followed by India's National Action Plan on AMR in 2017 that focuses on the use of antibiotics and resistance in human, animal, agriculture, food products, and environment [110]. One of the objectives of India's National Action Plan is to reduce environmental contamination with resistance genes, resistant pathogens, and antibiotic residues arising from solid/liquid waste generated from manufacturing, use, waste treatment, and disposal [110]. Even though antibiotics are classified under schedule H1 drug, antibiotics are still sold over the counter without prescription. However, the frequency has significantly dropped compared to the earlier reported studies [113]. Following

Table 4 India's policies on AMR

Year	Authority	Policy	Reference
2011	Ministry of health and family welfare	National policy for containment of AMR	[104]
2011	Ministry of health and family welfare, WHO	National action plan on AMR (2011–2016)	[104]
2011	Ministry of health and family welfare, WHO	Jaipur declaration	[105]
2012	Directorate general of health services/national centre for disease control	Chennai declaration	[106]
2016	Ministry of health and family welfare, WHO	AMR and its containment in India	[107]
2016	Indian council of medical research (ICMR)	National AMR research and surveillance network (AMRSN) and inclusion of antibiotics in schedule H1 drug	[108]
2016	National centre for disease control (NCDC)	National treatment guidelines for antimicrobial use in infectious diseases	[109]
2017	Ministry of health and family welfare, WHO	National action plan on AMR (2017–2021)	[110]
2017	National centre for disease control (NCDC)	Delhi declaration on AMR	[111]
2017	Food safety and standards authority of India (FSSAI)	Food safety and standards (contaminants, toxins, and residues) regulations in food animals	[102]
2017	Indian council of agriculture research (ICAR)- food and agriculture organization (FAO)	Indian network for fisheries and animal antimicrobial resistance (INFAAR)	[112]

National Action Plan on AMR in 2017, research on environmental AMR in India has significantly increased and is gaining attention. About 61.3% of increase in households with toilet is reported with implementation and funding through Swachh Bharat Mission [114], and open defecation has greatly reduced. In January 2020, Indian government has published a draft comprising discharge standard for 121 antibiotics in the treated effluents of bulk drug and formulation industry and CETP treating pharmaceutical wastewater. The draft also suggests incineration of the sludge containing antibiotics residue [115].

11 Conclusion

Implemented rules and regulations for human consumption, animal use, and disposal of antibiotics must be strictly followed and regularly monitored in India. Public awareness about the importance of antibiotics to treat serious infections and AMR

emergence must be created to avoid misuse of antibiotics. Recall and safe disposal of unused antibiotics from households should be implemented. AMR research in India is majorly focused on contribution of WWTPs of domestic sewage, pharmaceutical industries, and hospital effluents in environment AMR spread. There is little to no data on contribution of environmental AMR by other sources such as sewage sludge, solid/liquid waste generated by poultry, aquaculture, dairy and other livestock, agriculture run off, etc. Also a holistic approach to study the dissemination pathways of ARB and ARGs for better understanding and designing of suitable treatment technology is needed. Standards for treatment and discharge of hospital and domestic wastewater must be introduced. Similarly framing antibiotic discharge standards for sectors like poultry, aquaculture, and dairy wastewater, etc. is also necessary considering the fact that emerging contaminants like antibiotics, ARB, and ARG pose serious threat if disposed/discharged untreated. In a developing country like India, wastewater treatment capacity must be increased to treat the waste generated, and advance treatment technologies may be implemented as tertiary treatment option to ensure safe effluent discharge or reuse. Also existing conventional treatment facilities may be retrofitted with advanced tertiary treatment technologies to eliminate antibiotics, ARBs, ARGs, and the like. Alternatively, standard for reuse of reclaimed water for potable and non-potable purpose could be implemented. Quality of such water should be regularly monitored for emerging contaminants like antibiotics, ARB, and ARGs.

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