PRIORITIES FOR THE ENVIRONMENTAL DIMENSION OF ANTIMICROBIAL RESISTANCE IN INDIA



















ICMR-National Institute of Cholera and Enteric Diseases (ICMR-NICED)

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Priorities for the Environmental Dimension of Antimicrobial Resistance in India





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FOREWORD

Antimicrobial resistance (AMR) has been recognized as a serious health concern for both humans and animals. Various sectors contribute to development of AMR in different environmental pathways involving air, soil and water, and subsequently transmitted to humans and animals. This environmental component of AMR has been acknowledged as critical globally. Therefore, understanding the environmental dimension of AMR is imperative towards reducing the incidence of AMR in a country like India burdened with infectious diseases.

In the present report, ICMR-National Institute of Cholera and Enteric Diseases has correlated the development of AMR in humans, animals, involving different environmental dimensions, within the concept of 'One health'. Through explanatory sequential design, the report has assessed the present state of AMR incidence in India and identified the scopes for improvement in policy, institutions, research and innovation to tackle the environmental dimension of AMR in the country.

This report highlights sector specific roadmap emphasizing the key actions that may be considered to address the identified policy, institutional, and capacity gaps as medium to long term goals. I believe these recommendations will be effective in containing AMR in the various sectors as well as for the suitable improvements of the existing policies, as may be necessary.

I sincerely thank the United Nations Environment Programme (UNEP) for funding the project and congratulate the entire research team from ICMR-NICED for preparing such an effective document to enable future research, policymaking, developing India's leadership in AMR containment and AMR stewardship.

Prof. (Dr.) Balram Bhargava

Balran Brango





UN Environment Programme Country Office, India

Message

Antimicrobial resistance (AMR) is a multi-faceted, complex global public health issue and has been recognized as a 'One Health' concern owing to its significant linkages with human health, animals, and the environment. Failing to address the global burden of AMR, may cause up to 10 million global deaths annually by 2050 – more than currently die from cancer and diabetes combined.

While aspects addressing AMR from the human health perspective have received much attention, focus on the environmental dimensions of AMR has been limited. The United Nations Environment Assembly (UNEA) has recognized that AMR is an increasing threat to global health, food security and sustainable development, and has underlined the need to further understand the transmission channels in the development, transmission and spread of AMR in the environment. These range from poor sanitation to waste from pharmaceutical manufacturing and healthcare facilities to releases in animal production. The United Nations Environment Programme (UNEP) is working to provide evidence that can inform national and global strategies and prevent millions of deaths.

As the world enters the third year of the COVID-19 pandemic, there is broad recognition that the environment matters to One Health more than ever. Globally, the work to tackle the challenges of human, animal and ecosystem health using a more integrated approach has seen significant progress in recent years. Earlier this year, UNEP joined the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) in a Strategic Framework for collaboration on AMR. The framework sets out for the first time what these organizations will do jointly to support countries' efforts to scale up national responses to AMR. The approach mobilizes multiple sectors, disciplines, and communities at varying levels to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, acting on climate change, and contributing to sustainable development.

India has made a historic endeavor to address the environmental dimensions of AMR with the development of the National Action Plan on AMR (2017-2021) soon after the Global Action Plan on AMR came into action in 2015. India has also constituted the Inter-Ministerial Steering Committee on Environment and Health, where UNEP and WHO are members, with the aim to promote research, action, and awareness on issues at the interface of environment and health, including AMR.

This report, commissioned by UNEP with funding support from the Government of Norway, aims to collate and analyze the available evidence from India on environmental factors that contribute to AMR risks and spread of resistance in the environment. We hope this understanding will inform the National Action Plan on AMR, as well as related policy and interventions more broadly.

I thank and congratulate the Indian Council of Medical Research and the entire research team at the National Institute for Cholera and Enteric Diseases for taking up this study and for leading the way in addressing the environmental priorities of AMR in India.

Shri. Atul Bagai

Head of Country Office, UNEP, India



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WHO COLLABORATING CENTRE FOR RESEARCH AND TRAINING ON DIARRHOEAL DISEASES

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Dated: 27th May, 2022

PREFACE

It is my privilege to be the lead investigator of the UNEP funded project "Priorities for the environmental dimensions of Antimicrobial Resistance (AMR) in India" which focuses on an important global health concern and has indirect effect on the development and transmission of AMR. Addressing the environmental dimension for developing antimicrobial resistance (AMR) should be the foremost priority today for taking appropriate actions at the program or policy implementation level and optimizing the incidence of AMR. Environment plays a vital role in the transmission of AMR genes among bacteria residing in the humans, animals and environment. Most of the studies on AMR in India reported the resistance patterns of bacterial strains of either animal or human origin, few studies have shown presence of resistant bacteria in environmental samples like water, soil, sediment, etc. Through the current activity, we have the opportunity to synthesize a state-of-the-art report documenting the environmental dimensions of AMR, which includes important facts/information from most of the major stakeholders contributing to the environmental origin of AMR. The report also presented an in-depth understanding of the scenario of environmental impact on AMR and identified the knowledge gaps inviting sector-specific suitable policy recommendations. This report has been developed through systematic review and meta-analysis and also through key informants' interviews (KII) of relevant stakeholders such as medical/veterinary practitioners, farmers and policy implementing officials form different sectors across the country. Besides, the sector-specific recommendations, the report has many short-term and long-term action points and strategic priorities for India's National Action Plan (NAP) on AMR, which may be of use to the policymakers to design the future plan of action.

I sincerely thank the United Nations Environment Programme (UNEP) for supporting this important study with generous funding and extending constant support throughout the study period. I would like to congratulate the project staff at ICMR-NICED for successfully conducting the research despite the challenges posed by the COVID-19 pandemic, especially for conducting the KIIs via meetings in both virtual and physical mode. I do believe that this report would be useful for drafting the revised NAP of AMR and would strongly encourage more researchers to focus their research on the environmental aspects of AMR to address the existing knowledge gaps.

I take this opportunity to acknowledge the continuous support and cooperation extended by the experts of the review committee in every step of planning and execution of this document. The support of ICMR for administrative clearance is gratefully acknowledged.

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Shanta Dutta

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Acknowledgment

A state-of-art report on the "Priorities for the Environmental Dimension of Antimicrobial Resistance (AMR) in India" through Scoping Review and Key Informant Interview was prepared by ICMR-National Institute of Cholera and Enteric Diseases (NICED). The project was funded by United Nations Environment Programme (UNEP). Indeed, it was a wonderful journey during the entire study. We take great pleasure in thanking all those people who made this report possible.

We express our sincere gratitude to Prof (Dr.) Balram Bhargava, Secretary, Dept of Health Research (DHR) and Director General, Indian Council of Medical Research (ICMR) for his overall guidance and continuous encouragement to develop this state of art report; We would like to sincerely thank Dr. V. M. Katoch, Former Secretary, DHR & Director General - Indian Council of Medical Research (ICMR); Shri. Lav Agarwal, Joint Secretary, Ministry of Health & Family Welfare (MoH&FW); Mr. Atul Bagai, Head of Country Office, United Nations Environment Programme (UNEP), India; Dr. Samiran Panda, Additional Director-General and Head-ECD, Indian Council of Medical Research (ICMR), New Delhi; Dr. Kamini Walia, Scientist-F and programme officer on AMR, Indian Council of Medical Research (ICMR), New Delhi; Dr. Rajnarayan Tiwari, Director & Scientist- G. ICMR-National Institute for Research in Environmental Health (NIREH), Bhopal; Dr. Lata Kapoor, Joint Director, National Centre for Disease Control (NCDC), Delhi; Dr. Jyoti Misri, Principal Scientist and Nodal Coordinator, INFAAR, Indian Council of Agricultural Research (ICAR), New Delhi; Dr. Ravishankar C. N., Former Director, ICAR-Central Institute of Fisheries Technology (CIFT), Kochi; Dr. Gaurav Rathore, Coordinator Fisheries component of INFAAR, ICAR-National Bureau of Fish Genetic Resources (NBFGR), Lucknow; Dr. Murugadas Vaiyapuri, ICAR-Central Institute of Fisheries Technology (CIFT), Kochi; Dr. J. K. Jena, Deputy Director-General (Fisheries), Indian Council of Agricultural Research (ICAR), Krishi Bhavan, New Delhi; Dr. Kuldeep K. Lal, Director, ICAR-National Bureau of Fish Genetic Resources (NBFGR), Lucknow; Dr. Anuj Sharma, Program Officer, World Health Organization (WHO) Country Office for India, Delhi; Mr. Manjeet Saluja, Program Officer, WHO Country Office for India, Delhi; Dr. Chandra Bhushan, President & CEO, International Forum for Environment, Sustainability and Technology (iFOREST), Delhi; Dr. Prasad Thomas, Scientist, ICAR-Indian Veterinary Research Institute (IVRI), Izatnagar, Uttar Pradesh for their constant support during the entire venture.

We are extremely grateful to all the members of the technical resource group for constantly guiding us to the proper direction for making this project a success.

We are extremely thankful to Dr. Divya Datt, Programme Manager, UNEP; Dr. Sonia Devi Henam, Programme Officer, UNEP for their huge effort to facilitate the funding and cooperating all along the project period for its smooth accomplishment. We specially thank the Government of Norway for funding this all important report.

We also expand our wholehearted thanks to all the anonymous experts from different organizations, medical practitioners, farmers for their cooperation and suggestions during the key informants' interview.

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Abbreviations and Acronyms

AGISAR Advisory group on Integrated Surveillance of Antimicrobial Resistance

AMR Antimicrobial Resistance

AMRRSN Antimicrobial Resistance research and Surveillance network

AMSP Antimicrobial Stewardship Program

AOP Advanced Oxidation Process

API Active Pharmaceutical Ingredient

ASP Antibiotic Stewardship Program

ARB Antibiotic resistant bacteria

ARG Antibiotic resistant genes

BMW Biomedical waste

BMWM Biomedical waste management
BOD Biological oxygen demand
BIS Bureau of Indian Standards
CAA Coastal Aquaculture Authority

CBMWTF Common biomedical waste treatment facility

CDDEP Centre for Disease Dynamics & Policy
CETP Combined effluent treatment plant
CIL Central Insecticide Laboratory
CME Continuing Medical Education
COD Chemical oxygen demand

CoNSCoagulase-negative staphylococciCPCBCentral pollution control boardCSECentre for Science and Environment

DBT Department of Biotechnology

DDD Daily defined dose
DNA Deoxyribonucleic acid

EHI Environment and Health Initiative

EIC Export Inspection Council

ESBL Environmental management system
ESBL Extended-spectrum beta-lactamases

ETP Effluent treatment plant

EU European Union

FAO Food and Agriculture Organization

FSSAI Food Safety and Standards Authority of India

GAP Global Action Plan

GMP Good manufacturing Practices
HAA Hospital associated areas
HAI Hospital-acquired infection

HCF Healthcare facilities

HCWM Healthcare waste management

HQ Hazardous quotient

ICAR Indian Council of Agricultural Research

ICAR - National Institute of Veterinary Epidemiology and Disease Informatics

ICMR Indian Council of Medical Research

IEC Information Education and Communication

IIT Indian Institute of Technology

INFAAR Indian Network of Fisheries & Animal Antimicrobial Resistance

IPC Infection prevention and control

KAP Knowledge, attitude and practice survey

KII Key informant interview

MAR Multiple Antibiotic Resistance

MDR Multi drug resistance

MOU Memorandum of Understanding

MRSA Methicillin resistant Staphylococcus aureus

MoEF & CC Ministry of Environment, Forest and Climate Change

MoH & FW Ministry of Health and Family Welfare

MPEDA Marine Products Export Development Authority **NADCP** National Animal Disease Control Programme **NADRES** National Animal Disease Referral Expert System

NAP National Action Plan

NDM-1 New Delhi Metallo beta lactamase-1 **NRCP** National Residue Control Plan **NLEM** National List of Essential Medicines OIE World Organization for Animal Health **PAH**

PH Power of hydrogen **PDR** Pan drug resistance

PGPR Plant Growth Promoting Rhizobacteria

PICO Population-Intervention-Comparison -Outcomes

Polycyclic aromatic hydrocarbons

PK-PD Pharmacokinetics-Pharmacodynamics

PPCP Pharmaceutical and Personal care products

PPE Personal Protective Equipment

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RAMP Responsible Antibiotic Manufacturing Platform

RQ Risk quotient

SPTL State Pesticide Testing Laboratory

STP Sewage treatment plant **TSS** Total suspended solids **TDS** Total dissolved solids

UNEP United Nations Environment Programme

USAID United States Agency for International Development

VCIA Veterinary Critically Important Antimicrobials **VHIA** Veterinary Highly Important Antimicrobials

VRSA Vancomycin-resistant S. aureus **WASH** Water, Sanitation and Hygiene **WBE** Wastewater based epidemiology

WHO World Health Organization **WWTP** Wastewater treatment plant **XDR** Extensively drug resistance

ZLD Zero liquid discharge

Executive Summary

Antimicrobial resistance (AMR) is an evolving 'One Health' issue affecting human and animal mortality and environmental health, and causing global economic losses. The issue is becoming even more serious as the development of novel antimicrobials is slowing down. The environmental dimension of AMR not only includes human health but also animal health and environmental (water, soil, and, increasingly, air) health, and their interactions with each other. Therefore, a multisectoral engagement is always required for the containment of environmental AMR. In view of the seriousness of the problem of AMR, the sixty-eighth World Health Assembly (WHA) came up with Global Action Plan on AMR (GAP-AMR) in 2015. This action plan streamlined the major objectives and outlined the activities to be adopted by the nations. In addition, the WHA also urged the member-states to develop their National Action Plan on AMR (NAP-AMR) in line with the GAP-AMR. In keeping the same, India developed the National Action Plan on AMR in April 2017, that focused on six strategic priorities -(i) improving awareness and understanding of AMR through effective communication, education and training; (ii) strengthening knowledge and evidence through surveillance; (iii) reducing the incidence of infection through effective infection prevention and control; (iv) optimizing the use of antimicrobial agents in health, animals and food; (v) promoting investments for AMR activities, research and innovations; and (vi) strengthening India's leadership on AMR.

Environmental AMR in India

The 'One Health' approach to AMR recognizes the interlinkages between human health, animal health and the environment. This is pertinent to India where incidences of antimicrobial resistance are gradually increasing in all three sectors. However, limited research on AMR, and the absence of sufficient data are major barriers to develop an understanding of the actual magnitude of AMR in the different sectors in the country.

AMR bacteria in the environment

Soil and water are the major environmental reservoirs and modes of transmission of AMR bacteria in humans and animals. Water (ground and surface water), especially, is getting more attention for spreading antibiotic-resistant bacteria (ARBs) and antibiotic-resistant genes (ARGs). However, only a few studies have reported the presence of AMR bacteria/genes in the environmental samples. AMR bacteria from various sources like pharmaceutical effluents, biomedical waste and effluents, waste and litter from poultry and livestock farms, and slaughterhouse waste either directly contaminate the aguatic environments or contaminate the soil. AMR bacteria are eventually transferred to surface water through runoff or to groundwater through leaching. Some studies have also reported the presence of AMR bacteria in hospital wastewater and in water bodies adjoining the hospitals. The presence of AMR bacteria was also reported in the river waters of Cauvery and Yamuna, where third-generation cephalosporin-resistant E. coli and extendedspectrum β-lactamase (ESBL) producing gramnegative bacteria were detected. Third-generation cephalosporin-resistant E. coli bacteria were detected in groundwater and surface water samples from three places (Kashmir, Sikkim and Hyderabad) in the country. Existing literature on environmental AMR in India also reports the application of antibiotics along with pesticides in plant agriculture. The use of antibiotics alongside pesticides, in the production of cotton, rice, fruits, vegetables, cereals, oilseeds and pulses in the states of Haryana, Uttar Pradesh, and Punjab is mostly frequently reflected in literature.

AMR in human health

The scoping review conducted for this study revealed that several gram-positive and gram-negative bacteria that cause serious public health issues are resistant to a varied group of antimicrobials. Among gram-positive bacteria, isolates of *Escherichia coli*,

Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa were found to be resistant to fluroquinolones and third-generation cephalosporins. Carbapenem resistance reported in Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, and E. coli. As A. baumannii is resistant to carbapenem, another last-resort antibiotic called colistin is often used for treatment. Thus, resistance to colistin has also emerged. The mortality among Indian patients from exposure to both carbapenem and colistinresistant K. pneumoniae is quite high. Among the gram-positive bacteria, Staphylococcus aureus and Enterococcus faecium were found to be resistant to methicillin and vancomycin, respectively. Salmonella sp. and Shigella sp. also exhibited resistance to ciprofloxacin, ceftriaxone, and co-trimoxazole, while Vibrio cholerae exhibited resistance to tetracycline.

AMR in the poultry, livestock and aquaculture sectors

Antibiotic use in the poultry and livestock sectors are a very common practice in India. Many critically important antimicrobials used in human medicine are also applied for the treatment of animal diseases. In poultry, evidence of resistant bacteria is available from all over the country. Most of the studies reviewed have reported that the resistant bacteria came from chicken meat. Only a few studies have found AMR bacteria from the environment surrounding poultry production. The major resistant bacteria that were reported are E. coli, Salmonella spp., S. aureus, Campylobacter jejuni, K. pneumoniae. These bacterial isolates exhibited resistance to various antibiotics, such as chloramphenicol, tetracycline, ciprofloxacin, erythromycin, gentamicin, azithromycin, trimoxazole, trimethoprim, amikacin, meropenem, cefotaxime, and ceftriaxone.

Clinical and subclinical bovine mastitis is one of the major problems plaguing the dairy sector. Studies have reported *Staphylococcus aureus* as the major etiological agent of bovine mastitis. Researchers have also found other resistant bacterial strains like *E. coli, Listeria sp., Proteus sp.,* and *Candida sp.* in the environment surrounding dairy production. All these bacterial isolates from the dairy sector showed resistance against ceftriaxone, oxytetracycline, chloramphenicol, penicillin G, piperacillin, oxacillin, ceftriaxone, ampicillin, amoxicillin–clavulanic acid, and nalidixic acid. Studies have also reported the

prevalence of ESBL producing *E. coli* isolates in the fecal samples taken from healthy pigs.

Many studies on the aquaculture sector have reported the prevalence of AMR bacteria and their resistance pattern. Bacterial isolates collected from fishes and other aquaculture products from the aquaculture environment, such as water, soil, and sediment, were found to contain E. coli, Vibrio cholerae, V. parahaemolyticus, V. vulnificus, Klebsiella pneumoniae, Salmonella spp., Aeromonas hydrophila, A. caviae, A. enteropelogenes, A. punctata, A. aquarorium, Pseudomonas spp., Edwardsiella tarda, Enterococcus faecalis, Staphylococci aureus, S. haemolyticus, S. epidermidis, S. saprophytics, S. intermedius, and W. Resistance against several antibiotics like tetracycline, co-trimoxazole, rifampicin amoxiclav, ampicillin, erythromycin, gentamicin, kanamycin, nitrofurantoin, penicillin G, streptomycin, sulphafurazole, ceftazidime, and nalidixic acid were found.

Programmatic approach, initiatives, and national capacity to address environmental AMR

Before the NAP-AMR came into action in 2017, several guidelines such as amendments of the Drug and Cosmetics Rules, the banning of certain antibiotics in aquaculture by the Coastal Aquaculture Authority (CAA), the Bureau of Indian Standards (BIS) specification for poultry feed, and advisory of the Department of Animal Husbandry, Dairying, and Fisheries, already existed, either setting a permissible limit for antibiotic residues in discharges or recommending the prudent use of antibiotics in different sectors. The Indian Council of Medical Research (ICMR) had also initiated the Antimicrobial Resistance Surveillance and Research Network (AMRSN) in 2013, before GAP-AMR had even come into existence.

After the introduction of NAP-AMR, the Government of India became more proactive in formulating guidelines and laws, and initiating surveillance programmes in public and animal health for optimizing antibiotic-use as well as containing environmental AMR. In the public health sector, several initiatives to contain AMR, such as the National Programme on AMR Containment, developed by the National Centre for Disease Control (NCDC) in 2012, the Antimicrobial Stewardship Programme (AMSP) in 2018, Treatment Guidelines for Antimicrobial Use in

Common Syndromes in 2019, National Guidelines for Infection Prevention and Control in Healthcare Facilities in 2020, were introduced. Likewise, in the animal health sector, several programmes were initiated and guidelines were implemented, like the National Animal Disease Control Programme in 2019, the gazette notification of Ministry of Health and Family Welfare (MoH&FW) to stop using colistin and its formulations for food-producing animals, poultry, aquafarming, and animal feed supplements, the revised list of antibiotics for veterinary use issued by the Food Safety and Standards Authority of India (FSSAI) in 2019, the National Residue Control Plan (NRCP) issued by the Marine Products Export Development Authority (MPEDA) for exportable aquaculture products to EU countries, a ban on the use of certain antibiotics, issued the by Coastal Aguaculture Authority, and the establishment of the Indian Network of Fisheries & Animal Antimicrobial Resistance (INFAAR) for documenting AMR and resistance patterns in different sectors. However, in the human and animal health sectors, very few guidelines for reducing antimicrobial pollution in the environment, like the biomedical waste management rules issued in 2019, and the gazette notification of the Ministry of Environment, Forest and Climate Change (MoEF&CC) in 2020, that set the permissible limit for antibiotic residues in the effluents discharged by the pharmaceutical industry. Recently, a new collaborative platform has been launched in India by the joint venture of Stockholm International Water Institute (SIWI) and Shawview Consulting. The platform is called 'Responsible Antibiotic Manufacturing Platform (RAMP)' which aims to combat environmental AMR by reducing antibiotic emission from the manufacturers.

Major gaps identified from the scoping review on containing environmental AMR in India

Containing environmental AMR in India is quite a challenging endeavor as the healthcare facilities are insufficient in comparison to the burden of infection. The major gaps identified through the scoping review are – (1) AMR is insufficiently addressed in the national health agenda, even though the incidences of antimicrobial-resistant infections in India are quite high; (2) there is insufficient research on the environmental aspects of AMR in the different sectors; (3) the implementation of the existing guidelines and policies for AMR containment has so far been inadequate; (4) there is irrational use

of antibiotics in the health sector; (5) laboratory-based strong surveillance for AMR is inadequate; (6) Water Sanitation and Hygiene (WASH) system within the communities is poor and there is a lack of proper knowledge on infection prevention; (7) there is a huge risk of financial loss in the livestock sector if antibiotic-use in that sector is prohibited overnight; (8) there is a lack of sufficient research and technological innovation on developing alternatives to antibiotic growth promoters; (9) there is an absence of research and technological intervention for the monitoring and containment of environmental AMR; and (10) there is a lack of multi sectoral coordination for the tracking and collection of AMR database.

The way forward and specific action points

As the health system comes under the purview of the state government, it is often difficult to allocate funds separately for the implementation of national policies managing many other schemes. Therefore, a liaison between the authorities at the state and national levels is the primary requisite for addressing AMR. Specific committees that include representatives from the different governmental departments, practitioners, farmers' associations, and institutes must be constituted to make concerted efforts to address the knowledge gaps from the lower level (practitioners and farmers) to the higher level (policymakers). Such a system will also ensure that policies formulated at the higher level can percolate to the lower level. As the 'One Health' approach calls for the interlinking of the sectorspecific issues of human, animal, and environmental health, a steering committee governed by a nationallevel administrator, with representation from the sector-specific committees, to address their issues and to come up with suitable policy intervention and governance, must be established. However, the policies should focus on short-term and long-term action points, some of which have been detailed below. The short-term action points include:

- Institutional and regulatory strengthening for improved effluent treatment and handling in sectors.
- Inclusion of residual antibiotic management in environmental policies and guidelines from the perspective of both manufacturing and use of antibiotics.
- Provision of subsidy or incentives to farmers

for encouraging them to adopt alternatives to antibiotic growth promoters

 Enhanced participation of pharmaceutical companies towards sustainable antibiotic manufacturing practices

On the other hand, the long-term action points include:

- Rational use of antibiotics in both humans and animals
- Multisectoral engagement for tracking and collection of AMR data from human health, animal health and the environment, applying the 'One health' approach
- Development of strong surveillance to monitor antibiotic residues and transmission of AMR bacteria from healthcare facilities,

- pharmaceutical effluents, food animals, water etc.
- Promotion of more research and technological innovation to optimize the use of antibiotics in certain sectors as well as to reduce the incidence of AMR
- Making the engagement of microbiologists and environmental specialists in the sectors contributing to environmental AMR mandatory, for time-to-time monitoring and reporting of the resistance pattern of the different bacteria in the environmental samples

Collectively, these approaches can enable us to strengthen India's leadership in containing environmental AMR as well as achieving AMR stewardship.











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Scope and Objectives

1 Scope of the report

1.1 Purpose, objectives and scope of this report

Antimicrobial Resistance (AMR) is a rapidly emerging global concern as antimicrobial agents (commonly called antibiotics in this report) are becoming increasingly ineffective against disease-causing microorganisms. AMR has been recognized as a 'One Health' issue owing to its linkages with human and animal health and the environment, and requiring a multisectoral involvement and holistic approach for its mitigation. Since the 1940s, the large-scale commercial availability of antibiotics revolutionized the health care system with significant improvement of human and animal health in terms of treating and preventing serious infections. Gradually, the use of antibiotics expanded from preventing infections to promoting in the livestock-rearing sector. However, this widespread use of antimicrobials has selected resistance in several bacterial organisms. Some bacteria have developed resistance to not only multiple antibiotics but also to and even last-resort antibiotics such as colistin.

There are several sources of antimicrobial pollution to the environment. These sources can be direct or indirect. Direct sources include effluents from the pharmaceutical industry, biomedical wastes from hospitals and healthcare facilities, expired medicines that are improperly disposed, and antibiotics used in soil or water for agriculture and aquaculture activities. Indirect sources include the antibiotics passed through treated humans or animals. The presence of antibiotics in the environment can exert selective pressure on bacteria that promote the spread of AMR by horizontal gene transfer.

Considering the gravity of this public health issue, the World Health Organization (WHO) has constituted a dedicated advisory group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) in 2008, to support the WHO in monitoring the use of antimicrobials in food-producing animals and in mitigating the impact of AMR on public health. Later in May 2018, the WHO, the Food and Agriculture Organization of the United Nations (FAO), and the World Organization for Animal Health (OIE) signed a

Memorandum of Understanding (MOU) agreeing to step up with joint advocacy to strengthen cooperation on work related to the human-animal-environment interface, including AMR. The WHO, in collaboration with the OIE and FAO, developed a Global Action Plan (GAP) on AMR. This tripartite coordination with the United Nations Environment Programme (UNEP) is also strengthening the capacity of the countries to establish linkages with the environmental dimensions of the 'One Health' approach, and augmenting multistakeholder involvement to collectively combat AMR.

Following the Global Action Plan on AMR, India has also formulated the National Action Plan for containing AMR in 2017. This national-level endeavor for containing AMR became more intense when the UNEP and the WHO launched an Environment and Health Initiative (EHI) to set up a high-level working group/steeringcommitteeundertheco-chairmanship of the Ministry of Environment, Forest and Climate Change (MoEF&CC) and the Ministry of Health and Family Welfare (MoH&FW), the Government of India. Subsequently, MoH&FW has constituted a steering committee comprising members from the various ministries, departments, and international bodies like the UNEP and the WHO. The responsibility of this committee is to propose activities to be executed to tackle AMR and to establish its linkages with the environment. ICMR-National Institute of Cholera and Enteric Diseases has been functioning as an Antimicrobial Resistance Hub since 2019, with a broader objective of generating evidence on public health impacts of AMR in India, and providing appropriate directives to tackle it through the integration of AMR-specific programs within the ongoing national disease surveillance program. This collaborative study with the UNEP will enable the identification of knowledge gaps and the scope of future studies on AMR in the environment in the Indian context, thus contributing not only towards developing the next version of India's NAP-AMR for India (2022 - 2026) but also towards developing a regional document on AMR linkages with the environment for the Asia-Pacific.

1.2 Rationale for considering sectoral contribution to antibiotic pollution in the environment

The sources of antibiotic pollution can be broadly categorized as (1) manufacturing sector, and (2) application sectors. The Pharmaceutical sector, especially bulk drug manufacturers, is one of the major sources of antibiotic pollution in the environment (Gothwal & Shashidhar, 2014). Other sources such as the biomedical or healthcare sectors, livestock sector, aquaculture, agriculture and households are application sectors of antibiotics that also contribute to significant antibiotic pollution in the environment (Figure 1.1) (Kraemer et al., 2019). Effluents containing antibiotic residues from pharmaceuticals and healthcare systems, expired drugs from households, and manure and litter from livestock sector contaminate the environment (water and soil) through various modes. In addition, the application of antibiotics in aquaculture and plant agriculture directly pollutes water and soil. All these sources of antibiotic pollution result in the development of antibiotic resistance among different bacteria in the environment. These resistant bacteria present in the environment are transmitted to humans through

contaminated food, drinking water or recreational water, and cause serious health issues which may prove to be lethal owing to the failure of administered antibiotics. Therefore, the present scoping review has focused on these sectors to explore their role in developing environmental AMR in India as well as possible interventions to counter their impacts.

1.3 Methodology of the study report

1.3.1 Methodology of the scoping review

In the scoping exercise, we have tried to map the available studies on AMR published in the last 10 years (from 2011 to 2021) in the Indian context. We have also identified the evidence gap and subsequently developed a study tool to address the evidence gap. For this systematic review and meta-analysis, modified PICO (P: Patient or Population, I: Intervention or Phenomena or Interest, C: Comparison or Context, O: Outcome) inclusion or exclusion criteria has been applied, followed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol. The approach

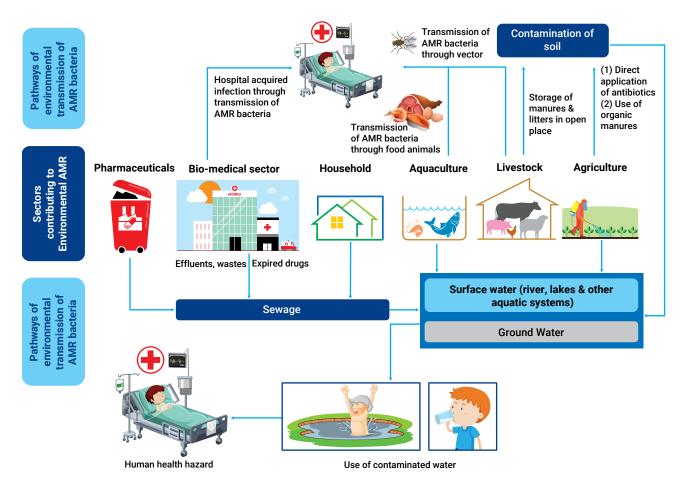


Figure 1.1: Rationale for selecting different domains for searching AMR literature

follows 5 methodological stages as stated below:

- (A) Searching for relevant studies and application of modified PICO inclusion/exclusion criteria
- (B) Selecting studies using PRISMA protocol
- (C) Extracting data
- (D) Collation, summarizing and reporting of the study results
- (E) Undertaking consultations with stakeholders (different domain experts)

Stage A. Searching relevant studies and application of inclusion / exclusion criteria:

The studies which were considered eligible for review fulfilled the following criteria (**Table 1.1**):

Databases:

Relevant studies were retrieved by searching the following electronic databases of published literature: PubMed/Medline, Google Scholar, Scopus, Embase, and Index Medicus. The search strategies are presented in **Table 1.2.**

Table 1.1: Modified PICO inclusion and exclusion criteria (Naylor et al., 2016)

Criteria	Inclusion	Exclusion	
Population	Human Animals Plants Incidence of AMR in all the populations	Not applicable	
Intervention	All the existing interventions Policy documents and guidelines	Not applicable	
Comparison	Not applicable	Not applicable	
Outcomes	 AMR impact on human health AMR impact on animal health Different AMR pathways in the Environment Transmission of AMR through different wastes and effluents 	Not applicable	
Literature types	 Mention of Antibiotic/antimicrobial or AMR must be in place Articles that reported the prevalence of antibiotic resistance among clinical pathogenic bacteria isolated from humans, animals, or the environment 	Articles that reported AMR in humans, animals, and the environment but that did not report any prevalence data will not be included in the meta-analysis.	
	 AMR in all the ecological (plain land, coastal area, dry land, hilly region, forest, industrial area) area will be included. Articles reported the results of the in-vitro study on antimicrobial sensitivity patterns, the novel discovery of antimicrobial-resistant genes. 		
	Studies conducted in India	Studies conducted outside India	
	Original and review articles published in peer-reviewed journals, brief reports, short communications, mini-reports, published thesis	Correspondence, letter to the editors, unpublished documents	
Study period	Publications from the year 2011 onwards	Studies published before 2011	

Table 1.2: Search Strategies of literature from different sectors

Search domain	Search strategy		
AMR in human/ animal health	((((((((antimicrobials) OR antibiotics) AND resistance) OR human health) OR public health) OR animal health) AND environment) AND India [Title]		
AMR in Waste material	((((((((((((((((((((((((((((((((((((((
AMR in Agriculture	((((((((((((((((((((((((((((((((((((((

Stage B. Selecting studies:

We have conducted the review process through 2 layers of screening: (1) a title and abstract review and (2) a full-text review. For the former, the titles and abstracts of articles retrieved in the search were read and analyzed by two independent investigators to identify potentially eligible articles. In the next step, the two investigators independently assessed the full-text articles to determine whether they meet the inclusion/exclusion criteria. Discordant full-text articles were reviewed a second time, and further disagreements about study eligibility at the full-text review stage were resolved through discussion and full consensus. A PRISMA flow diagram was used to organize the study (Figure 1.2).

Stage C. Data extraction, charting and plotting:

A data abstraction method followed the extraction of study attributes, including questions related to the publication (type of publication, journal, author, and year) and the content (title, year and place of the research, methodology including study design, sample size, analysis, the results, and conclusions). Based on a preliminary assessment, we developed parameters and themes for further extraction and mapping of data.

Stage D. Collation, summarization, and reporting of the study results:

In our scoping review, we have described key

PRISMA Flow Diagram

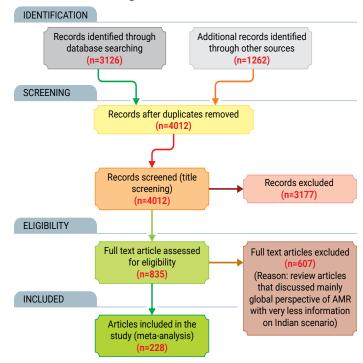


Figure 1.2: PRISMA flow diagram showing the number of documents searched, excluded, and included in the present study

categories, such as AMR in humans, livestock rearing, aquaculture, and other agriculture practices, driving factors of AMR, major sources of antibiotic pollution in the environment, antibiotic-resistant bacteria, and genes in the surrounding environments. This review of the research on environmental AMR has also identified potential gaps and provided directives for future research. All the collected data were digitized in Microsoft Excel to generate a comprehensive database. The results of this study have been presented descriptively through tables and graphs.

Stage E. Consultation with stakeholders (different domain experts):

A literature review on its own would not be able to provide all the information on the AMR and its environmental dimensions, existing policies on antibiotic use, antimicrobial pollution, and transmission chains in the environment. Therefore, in order to make our report more comprehensive and to find the gaps in the existing studies, several domain experts/researchers who have profound knowledge on AMR and its environmental dimensions were consulted through stakeholders' meetings conducted from time to time.

The domains of experts:

- Experts working on AMR in human/public health/animal health
- Experts working on AMR in solid waste/ municipal waste/pharmaceutical waste
- Experts working on AMR in livestock rearing/ food animals/aquaculture
- Experts working on any environmental dimension of AMR
- Experts working on developing novel agents for mitigating AMR

Experts having knowledge on different existing policies/guidelines/regulations

1.3.2 Methodology to Conduct Key Informant Interview (KII)

Key Informant Interviews (KIIs) were conducted with stakeholders from the different sectors which are responsible for environmental AMR - biomedical, pharmaceutical, aquaculture, animal husbandry, and plant agriculture. One stakeholder from each domain, one stakeholder of three different strata; i.e., tier-1 (practitioner), tier-2 (executive or implementing officer and scientists), and tier-3 (policymakers) were randomly selected as interviewees though the interviews were undertaken based on their availability. The process of KII (Figure 1.3) was initiated with the development of an interview schedule for each tier of each domain, based on the findings of scoping review of the impact of environmental determinants on AMR in India. The interview schedule comprised of 3 major divisions such as introduction (including consenting with anonymous identity and essential information of the interviewee), key questions (including probing questions), and closing questions. Informed consent was taken from each stakeholder before conducting the interview, and their identity was anonymized. Questions were asked in the vernacular, and the response of the interviewees was audio-recorded in the same language. Data were organized and transcribed into text data in Bengali, and finally translated to English. Different colors were used to code text data based on the predetermined areas of scoping review. The identified codes were then clubbed under different categories to remove redundancy. The major themes were thereafter derived from the categories. To exhibit the group of codes along with their leading themes in a singlewindow, an Abstraction Matrix was developed from the KII for each dimension.

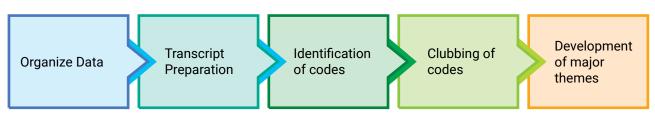
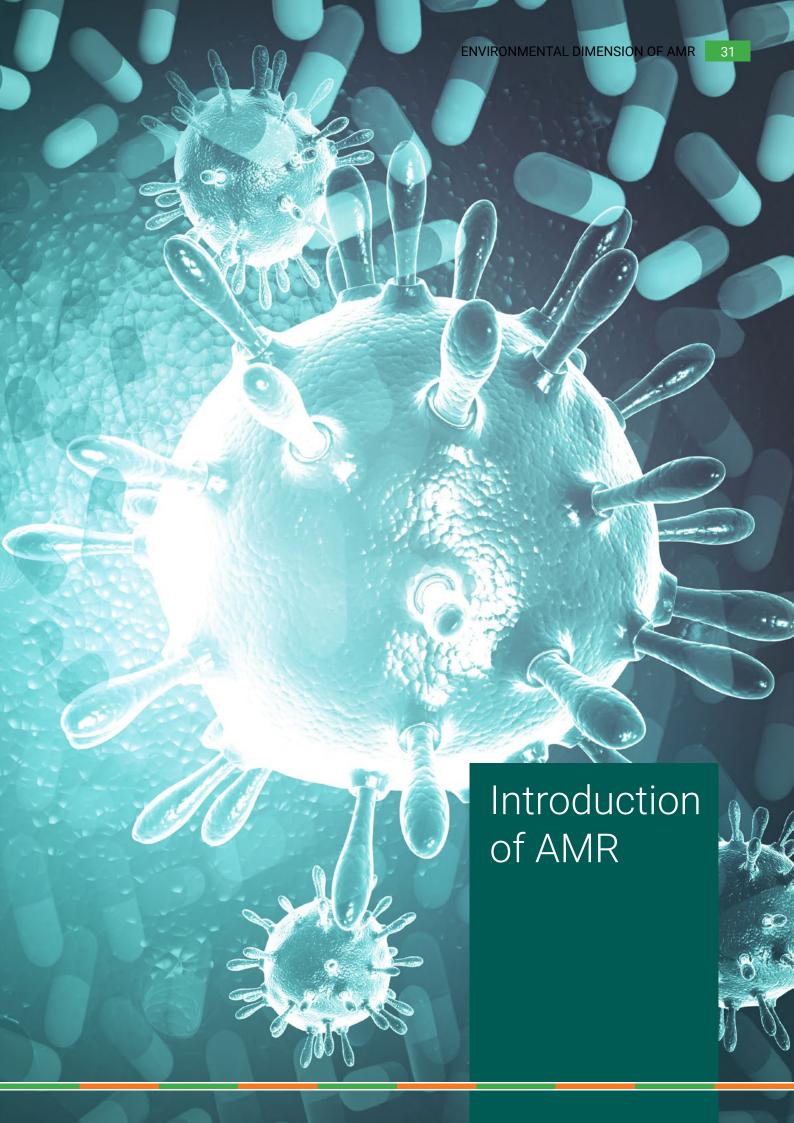


Figure 1.3: Steps followed to develop Abstraction Matrix from KII



2 Introduction of AMR

2.1 Definition

Antimicrobial resistance is the ability of microbes to grow and multiply in the presence of antimicrobial agents that would normally kill them or limit their growth. Antimicrobial resistance is a major challenge impacting human and animal lives and also causing economic losses.

2.2 Mechanism of development of resistance to antibiotics

Some bacteria are naturally resistant to antimicrobials. This phenomenon is called intrinsic resistance. When a bacterium that was previously susceptible to an antibiotic develops resistance, it is called acquired resistance. Antibiotic resistance can be progressed on the basis of one of many mechanisms that can lead to the complete or partial cessation of the antibiotic from reaching its target in the body in one of the following ways (Gupta et al., 2014). The different mechanisms are presented in **Figure 2.1** and in **Table 2.1**.

Efflux of the antibiotic out of the cell: Bacteria can produce pumps, called efflux pumps, that sit in their membrane or cell wall. These efflux pumps are very common in bacteria, and can transport a variety of compounds such as signal molecules and nutrients.

Some of these pumps can also transport antibiotics out of the bacterium, thus lowering the antibiotic concentration inside the bacterial cell. In some cases, mutations in the bacterial DNA can make the bacteria produce more of a certain pump, which in turn increases resistance.

Decreasing permeability of the membrane: Certain changes in the bacterial membrane make it more difficult to pass through it. In this way, less amount of the antibiotic enters the bacteria.

Inactivation of the antibiotic: Certain bacterial enzymes can inactivate antibiotics. One example is β -lactamase which destroys the active component (the β -lactam ring) of penicillins, which are extremely important antibiotics for the treatment of human infections. In later years, bacteria that produce extended-spectrum β -lactamases, called ESBL-producing bacteria, have become a major problem. They can degrade a wide spectrum of β -lactam antibiotics and even last-resort drugs available for infections (Purohit et al., 2017).

Modification of the structure of the antibiotic: Bacteria can sometimes produce enzymes that are capable of adding different chemical groups to antibiotics. This, in turn, prohibits binding between

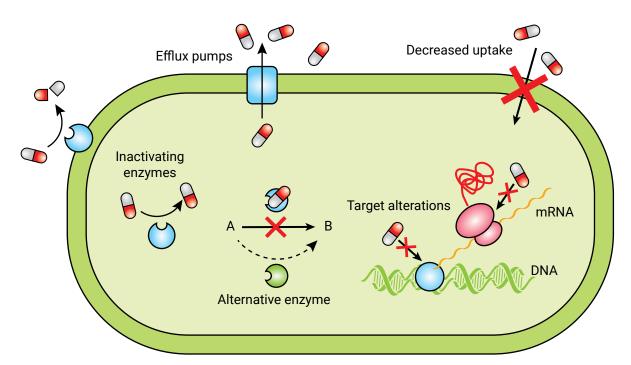


Figure 2.1: Antibiotic resistance strategies in bacteria (Yuen et al., 2017)

Mechanism	Typical example	Antibiotics affected	
Inactivation	Beta lactamases	Beta lactam antibiotics	
	Aminoglycoside modifying enzyme	Aminoglycosides	
Changes in target-binding	Changes in penicillin binding proteins	Beta lactams/ Glycopeptides	
	Ribosomal methylation	Macrolides	
	DNA gyrase mutation	Fluoroquinolones	
Efflux and permeability	Efflux pumps	Pump specific	
alteration	Porin protein loss	Most antibiotics except polymyxins and aminoglycosides	

Table 2.1: Some of the important mechanisms of resistance to antimicrobials (Chandra et al., 2021; Dhawde et al., 2018; Gupta et al., 2014; Kumar et al., 2017; Lübbert et al., 2017; Saha et al., 2019; Saharan et al., 2020)

the antibiotic and its target in the bacterial cell.

Reorienting the target: Changes in the composition or structure of the target in the bacterium (resulting from mutations in the bacterial DNA) can stop the antibiotic from interacting with the target. Alternatively, the bacteria can add different chemical groups to the target structure, thus shielding it from the antibiotic.

Expression of alternative proteins: Some bacteria are able to produce alternative proteins that can be used instead of the ones that are inhibited by the antibiotic. For example, the bacterium $Staphylococcus\ aureus$ can acquire the resistance gene mecA and produce a new penicillin-binding protein. These proteins are needed for bacterial cell wall synthesis and are the targets of β -lactam antibiotics (Nagar et al., 2011). The new penicillin-binding protein has low affinity to β -lactam antibiotics and is, thus, resistant to drugs, helping the bacteria survive treatment. This type of resistance forms the basis of MRSA (methicillin-resistant $Staphylococcus\ aureus$).

Reorienting the target and quorum-sensing: Quorum-sensing is a cell-to-cell communication system that exists widely in the microbiome and is related to cell density. The high-density colony population can generate a sufficient number of small molecule signals and activate a variety of downstream cellular processes.

Horizontal gene transfer: Horizontal gene transfer allows the bacteria to exchange genetic material within diverse species. In this process resistant genes from one bacterial species can be transferred to other species. The transfer of the genetic element

is mediated by three processes — transduction, transformation and conjugation.

2.3 Facilitating factors for development of AMR with emphasis on environmental dimensions

AMR is a multifactorial global challenge, and the environment is a vital melting pot of drug resistance in these pathogens. Hence, it is necessary that all stakeholders across the world, including environmental specialists, become involved in various capacities to find possible solutions to the problem of AMR. Multiple intertwined factors, including high burden of disease, poor public health infrastructure, lack of appropriate diagnostic support, poor infection-control practices, and the tendency of clinicians to continue empirical treatment practices, have amplified the crisis of AMR in India (Barbhuiya & Adak, 2021). Bacteria from clinical and non-clinical settings are becoming increasingly resistant to standard antibiotics. Conventionally, the growing challenge against antibiotic resistant bacterial strain development is a result of practices taking place within the medical community, and the poultry and livestock sectors. However, in recent years, the agricultural sector has also contributed to the rise of AMR. Figure 2.2 depicts antibiotic use in hospitals in India between 2000 and 2015 (indicated in terms of Defined Daily Dose - DDD per 1000 population). Figure 2.3 represents the trends of resistance of the most frequently used classes of antimicrobials in India. The indiscriminate use of antibiotics may additionally correlate with emergence, maintenance and transmission of antibiotic resistant pathogenic traces in the environment (Kumar et al., 2017).

A number of cumulative factors, including poor public fitness infrastructure, rising earning, changing consumption patterns, excessive burden of disease, and reasonably-priced, unregulated sales of antibiotics have cumulatively created fertile conditions for a speedy upward thrust in antibiotic resistant infections in India. In addition to the countrywide Action Plan (2017-2021), India has set up a countrywide Antimicrobial Resistance Research and Surveillance Network (AMRRSN), which is specially focused on the surveillance of diarrheainflicting bacterial pathogens, enteric pathogens, enteric organism-inflicting sepsis, gram-negative non-fermenters and gram-positive methicillinresistant Staphylococcus aureus. River water is considered one of the major sources of AMR bacteria due to the presence of effluents and discharge from healthcare and sources in it.

A study conducted by Sivagami et al. (2018) discussed antimicrobial resistance patterns and trends of strains like *P. stuartii, K. pneumoniae, E. coli, S. typhimurium, S. flexneri* and *P. aeruginosa*. The study indicated that these pathogens were resistant to 22 antimicrobials which belong to 9 distinct classes. In case of *E. coli* and *Salmonella spp.*, the highest resistance (>95%) was observed against streptomycin while for *S. aureus*, the highest

resistance was observed against trimethoprim, among other antibiotics.

The emergence and spread of multi-drug resistance in bacterial pathogens globally constitute an impending threat to public health (Laxminarayan et al., 2013). Sivagami et al. (2018) reported that around 30-80% of antibiotics given to feed animals are excreted due to partial metabolization. It was also reported that, animal feed containing antibiotics that are not consumed by the animals directly reach the soil. Compliance with the WHO Antibiotic Stewardship Program (ASP) in public health sector, help improve the treatment of infections and minimize adverse drug reactions associated with antibiotic use (Dhawde et al., 2018).

2.4 Possible solutions to contain antimicrobial resistance

The following are some of the ways through which antimicrobial resistance can be contained in the environment:

Discovery of new antibiotics: The discovery of newer antimicrobials has been dwindling over the last few decades even as antimicrobial resistance rises. Newer antimicrobials offer more therapeutic options for the treatment of bacterial and fungal infections.

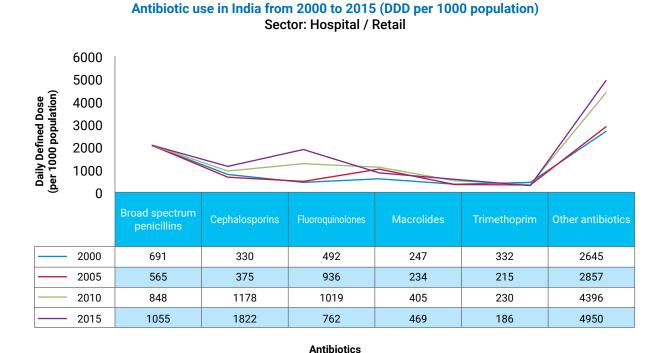


Figure 2.2: Antibiotic use in India between 2000 and 2015 (indicated in terms of DDD per 1000 population)

100 90 80 Percentage of Resistance (isolates) 70 60 50 40 30 20 10 0 12 49 55 Aminopenicilins 13 16 60 84 79 82 89 81 88 Fluoroquinolones

Resistance profile of most frequently used antimicrobials in India

Figure 2.3: Trends of resistance of the most frequently used classes of antimicrobials in India.

Year

- Reduction of disease burden: More advanced therapeutic treatment options must be developed for the reduction of infectious diseases and their burden. Improved Infection prevention and control practices (IPC) are also the need of the hour.
- Vaccination of humans and animals: Vaccination ensures better protection against infectious diseases and minimizes the emergence of antimicrobial resistance.
- Antibiotic stewardship activities: Implementation of an effective AMSP requires a multidisciplinary approach, involving a variety of experts. The major goals are to judiciously prescribe and use antibiotics that are effective in treating critical infections, protect patients from harms caused by unnecessary antibiotic use, and combat antibiotic resistance.



3 AMR: status and initiatives to address it

3.1 Extent of global incidence of AMR and its impacts on human health, the economy, and development

Antimicrobial resistance (AMR) leads to an increase in mortality, morbidity, and healthcare costs. It is a worldwide problem that has become worse in recent decades due to the overuse of antimicrobial medications in human and veterinary treatment. Antibiotic resistance can originate, evolve and spread in several interrelated human, animal and environmental habitats, and the health of these adjoining habitats (the emphasis of the 'One Health' concept) may pose a threat to human health (Amado et al., 2019). Due to the high prevalence of bacterial illnesses in Low- and Middle-Income Countries (LMICs), AMR surveillance is crucial. But conducting AMR surveillance in resource-limited settings is hampered by poorly functioning health systems, limited financial resources, and a lack of competent staff (Gandra et al., 2020). An understanding of the human AMR surveillance efforts and progress in LMICs will be useful in addressing the challenges and providing guidance for other countries that are launching these efforts, as several countries have begun to develop National Action Plans (NAPs) following the WHO Global Action Plan (GAP) for containing AMR.

To establish and strengthen AMR surveillance, several factors, including health system efficacy and resource availability, have played a major role. The WHO estimates that AMR operations, such as cesarean sections, joint surgery and organ transplants, contribute almost 4% to the global GDP. There are inadequate public health facilities and low government spending on health care in a majority of the countries in the world. The health industry has devised a number of strategies and initiatives to tackle AMR. As per a WHO report (2018), around 154 countries around the world have been working on framing and implementing AMR policies and the use of antimicrobials on humans and animals, as recommended in the GAP (2015). Although 100 countries have created their own NAPs to combat AMR, all of them are facing practical difficulties in implementing them due to the complexity and internecine character of the problem (Bhatia, 2018). Following the World Health Assembly's (WHA) approval of the WHO GAP on AMR, measures to combat AMR were launched in numerous member states. Several countries have started developing and implementing initiatives to control AMR in the human, animal, and environmental sectors (Gandra et al., 2020).

According to World Bank Data (2018), the total health expenditure for 8 Asian countries, like, Bangladesh, Cambodia, India, Nepal, Pakistan and Vietnam, ranged from 2.3% (Bangladesh & Cambodia) to 6.3% (Nepal) of the GDP (Gandra et al., 2020) (Figure 3.1). In 2016, the US and the UK allocated 17% and 9.7% of their respective GDPs to healthcare. Limited financial resources, lack of technical capacities and standardized laboratory practices in Asian LMICs may challenge AMR surveillance in these countries. In India, Vietnam and Thailand, each state has its own system of healthcare services, delivered by the private and public sectors. But other abovementioned countries have a Ministry of Health at the national level, which is responsible for providing healthcare facilities. Both Thailand and Vietnam have succeeded in achieving universal health coverage for their citizens (Gandra et al., 2020).

Initial data from AMR surveillance networks in LMICs suggest a significant frequency of AMR, but these data have several flaws, including a lack of representativeness, and use of standardized laboratory methods, and microbiological services consumption. The private sector has an advantage over the public sector in providing better healthcare services, due to better governance and regulation, accreditation of healthcare organizations with adequately-trained and certified healthcare staff, and lower patient load, but it may only be accessible to the wealthier section of the population.

According to a report released by the WHO and the World Bank Group in 2015, 400 million people across the world lack access to vital health treatments, resulting in significant out-of-pocket spending. Estimates of the entire cost of AMR are unknown, and the cost could be far greater than current best estimates. The difficulty of determining the cost of changes in overall resistance levels accounts for much of the uncertainty (Bhatia, 2018).

Countrywise Health Expenditure (2018)

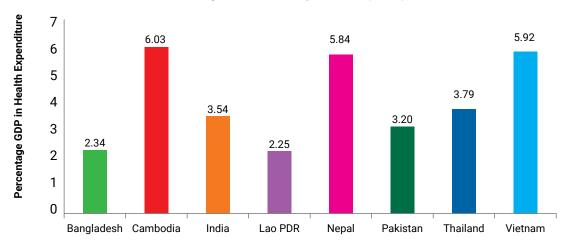


Figure 3.1: Current health expenditure (% of GDP) in 8 countries (2018)

3.2 Global initiatives to combat AMR

Antimicrobial resistance, which causes drugresistant illnesses, and its growing health, social, and economic effects, are increasingly observable on a global scale. According to the Centers for Disease Control and Prevention (CDC), United States collaborative initiatives such as, the rational use of drugs, infection control and prevention, antimicrobial surveillance, ban on over-the-counter (OTC) antibiotics, educating and motivating people, development of new drugs/vaccines, immunization coverage, hand hygiene, standard treatment programmes, new AMR programmes, can combat environmental AMR at the international, national, community, hospital, individual, and patient levels (Uchil et al., 2014). In addition, the CDC has also committed itself to setting goals to resist antibiotic resistance across multiple sectors, including healthcare, food, communities (both at the local and national levels), and the environment Many other leading international organizations such as World Health Organization (WHO), World Organisation for Animal Health (OIE), Food and Agriculture Organization (FAO), United Nations General Assembly (UNGA) also recommended some approaches to contain AMR (Table 3.1).

Table 3.1: Global progress in containing AMR

Organization	Recommended approaches to containing AMR
WHO (2011 & 2018)	 Increased collaboration among governments, non-governmental organizations, professional groups and international agencies New networks that undertake surveillance of antimicrobial use and AMR Incentives for the research and development of new drugs and vaccines Simple diagnosis tests and introduction of newer technologies help to control AMR Training programs for unregistered and unqualified health workers
UNGA (2019)	 Member-states have prepared and begun implementing national antimicrobial resistance action plans based on guidance and instruments produced cooperatively by the WHO, the FAO, and the OIE
OIE (2020)	 Provide a basis for policy recommendation for animal and human health Identify the sources of antimicrobial resistant bacteria Offer data for monitoring antimicrobial prescribing practices and making suggestions for judicious use Assess and determine the effects of antimicrobial resistance-fighting actions
FAO (2018)	 Protect water from contamination with residues Reduce environmental pollution through effective treatment of wastes, and eliminate residual antimicrobials In terms of agricultural sources, lowering the need for antimicrobial usage through better animal health and hygiene measures is the most efficient approach to prevent antibiotic residues and AMR bacteria from contaminating animal wastes
UNEP	The UNEP has been invited to join the tripartite (FAO, IOE, and WHO) to deepen their AMR programme and build global surveillance systems, a worldwide AMR stewardship programme, and a global action plan monitoring and assessment framework

3.3 AMR in India

The development of multi-drug resistant bacteria and antibiotic resistance is a major public health issue in India. Several factors, such as increase in income, uncontrolled access of antibiotics, over-the- counter sales without prescription, and perverse financial incentives for providers to prescribe antibiotics, often driven by patient demand and expectations, has often played a vital role in the development of AMR in India (WHO, 2016). According to several studies, antibiotic residue is increasingly contaminating the environment, with an uncontrolled discharge of antibiotic-laden effluents from the industrial sector and sewage treatment plants. These antibiotic residues become responsible for the formation of antibiotic-resistant bacteria (ARBs) and antibioticresistant genes (ARGs) in the environment, consequently re-contaminating humans and animals through the consumption of contaminated food and water. Ecosystems, in addition to soil and water, are also getting contaminated with an abundance of ARBs/ARGs from different critical sources (viz., household, industry, healthcare, livestock and agriculture) entering through distinct pathways.

3.3.1 Antimicrobial resistance in humans:

Several social and environmental factors, including health system efficacy and resource availability, influence a country's ability to develop and strengthen AMR surveillance. India has the highest antibiotic-resistant rates of disease-causing bacteria in community and healthcare facilities. More than 70% resistance against the broad-spectrum antibiotics

like fluoroquinolones, and cephalosporin was found in Acinetobacter baumannii, Escherichia coli and Klebsialla pneumoniae, while > 30% resistance was found in Pseudomonas aerugenosa (DBT report, 2017). In India, antibacterial resistance among neonates was also discovered after examining blood stream collected from neonates. Results revealed 50% methicilin resistance among S. aureus, and 63% resistance to third-generation cephalosporin among Klebsiella species. Extended spectrum betalactamase (ESBL) generating Enterobacteriaceae strains have now arisen in India, both in hospitals and within the community. The carbapenem class of antibiotics being one of the last-resort antibiotics to treat bacterial infection in humans, carbapenem resistance is a major concern in the healthcare sector. Several studies have reported that the carbapenem (meropenem) resistance rate among the isolated gram-negative bacteria (A. baumannii, P. aerugenosa, Klebsiella sp.) are 73%>30%<59% (Gandra et al., 2020) (Figure 3.2). Isolated Acinetobacter species from hospitalized patients in a tertiary care hospital in Delhi revealed resistance to imipenem/meropenem in 57-80% of cases, and tigecycline resistance in 70% of cases (WHO, 2016). In addition to this, metallo-beta-lactamase-1 (NDM-1), or bla_{NDM-1} , has been the prevailing gene encoding for carbapenem resistance in Enterobacteriaceae in New Delhi while bla_{KPC} is not frequently detected.

Between 2000 and 2015, the use of antibiotics, especially third-generation antibiotic cephalosporins, has increased significantly while the ingestion of penicillin remains constant, and the use of fluoroquinolones has been shown to be less effective



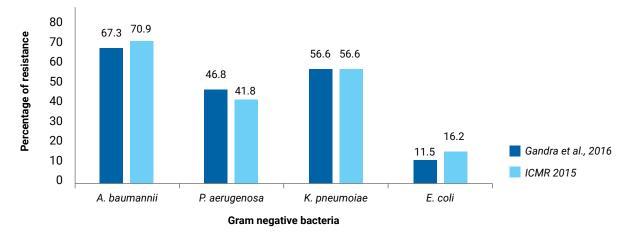


Figure 3.2: Carbapenem resistance among the isolated gram-negative bacteria from blood culture sample (Source:DBT report, 2017).

(DBT report, 2017). Among the typhoidal organisms, *S. typhi* is the most studied organism followed by *S. paratyphi*, with 15-18% of ciprofloxacin susceptibility. Studies have found that, *Aeromonas spp*, the most commonly isolated pathogen in diarrheal disease, shows resistance to the carbapenem class of antibiotics, especially imipenem (ICMR, 2017). Various studies have also revealed that *E. coli* was the most frequent isolate from urine and blood samples, sterile body fluids, superficial tissue infection, and deep tissue infection. The study reports of Gandra et al. (2016) and ICMR (2015) explain the high level of resistance to broad-spectrum antibiotics in some gram-negative bacteria (**Table 3.2** and **Table 3.3**).

3.3.2 Antimicrobial resistance in livestock/food animals:

In livestock/food animals, the practice of non-therapeutic use of antibiotics, either for prophylaxis or metaphylaxis, and as growth promoters is commonplace. Antibiotic resistant bacteria can be transmitted between humans and animals through contaminated food, water, and the environment. A study by Bhattacharya et al. (2016) reported 3.2% and 2.4% vancomycin resistance among *S. aureus* isolates from cow milk and goat milk. Antibiotics that are used to treat human diseases are frequently used in animals, prompting concerns about a fall in their efficacy for treating humans. In the poultry industry,

Table 3.2: Percentage of resistance of various antibiotics in 4 gram-negative bacteria isolated from blood culture (ICMR, 2015; Gandra et al., 2016; DBT report, 2017)

Gram-negative bacteria	Percentage of Ciprofloxacin resistance		Percentage of Ceftriaxone/Ceftazidime resistance		Percentage of Meropenem/ Imipenem resistance		Percentage of Piperacillin- Tazobactum resistance		Percentage of Colistin resistance	
	2014	2015	2014	2015	2014	2015	2014	2015	2014	2015
A. baumannii	84	NA	93	83.1	67.3	70.9	NA	NA	4.1	NA
E. coli	85.1	76.4	83.3	79	11.5	16.2	37.3	34	3.1	0.2
K. pneumoniae	72.9	NA	79.9	86.9	56.6	56.6	62.7	64.6	3.2	0.5
P. aeruginosa	55	54.5	67.9	44.9	46.8	41.8	61.8	26.9	0	0.6

Table 3.3: Antimicrobial resistance of different isolates from blood and CSF samples (ICMR, 2015)

	Percentage of Antibiotic resistance										
Bacteria	Penicillin	Macrolides	Fluoroquinolones	Cephalosporins	Carbapenems	Aminglycosides	Beta-lactum/ Beta lactamase inhibitor	Tetyracyclin	Glycylcyclines	Oxazolidinone	Polymyxins
Escherichia coli	✓		76.4	79,75.9	16.4,16.2	18.5	34		1		0.2
Klebsiella pneumoniae/ oxytoca				86.9,85.1	49,56.6	60.7	64.6		1.5		0.5
Enterobacter aerogenes/ cloacae			50.7	84,73.4	42.5,47.4	48.7	54.9		2.9		0
Acinetobacter baumannii			✓	83.1,82.9	70.9,70.1	73.8	✓		✓		✓
Pseudomonas aeruginosa			54.5	37, 44.9	32.2,41.8	70.4,42,28.8	26.9				0.6
Salmonella typhi/paratyphi	6.3		27.9	0.6				✓			
Streptococcus pneumoniae	✓	✓									
Staphylococcus aureus	42.6									0.2	
Enterococcus faecium/ faecalis	76.6					71.8					

antibiotics are used mostly as growth promoters as part of pre-mixed feed. Sahu & Saxena (2014) found that there is a significant difference in the presence of antibiotic resistant bacteria in boiler farms and layer farms. Around 87% of ESBL producing strains were found in boiler farms but only 42% in layer farms. Shrivastav et al. (2016) Kar et al. (2015) found 33.5% ESBL producing *E. coli* in boiler farms and 9.4% in layer farms in the poultry sector. Although the total number of antibiotics used in fisheries is likely to be far lower than that used in terrestrial, intensive animal production, the key issue is that the aquaculture sector uses more antibiotics that are clinically significant for the treatment of humans.

3.3.3 Antimicrobial resistance in the environment:

The environment plays a vital role in the transmission of antimicrobial resistance through the interlinkages between the components of ecosystems such as soil, water and human and animals. India has the highest rates of resistance to antimicrobial agents for both humans and food animals. The indiscriminate use of antimicrobials and poor wastewater treatment in India are major contributors to AMR. Environmental components like soil and water have also been shown to contain resistant organisms or genes. The 3 components – human, animals, and environment have been combined to develop the 'One Health' approach to healthcare in India. Here inadequately

treated wastewater containing antibiotic residues from the pharmaceuticals, healthcare sector, aquaculture, and agricultural, are the major sources of contamination of water bodies. Several studies have highlighted the percentages of antibiotic resistance in isolated bacteria/genes present in river water (**Table 3.4** and **Table 3.5**).

Studies have also reported that potable water sources apart from the rivers also contain bacteria with high levels of resistance to broad-spectrum antibiotics. In the Ayodhya-Faizabad area, a study that tested water from drinking and recreational sources like river, ponds, kund or holy ponds, hand pumps, tube well, dug well, etc. was conducted. The study found that approximately 17% of *E. coli* and 13% of *Klebsiella* showed resistance to third-generation cephalosporin (Kumar et al., 2013). Poor sanitation also plays a vital role in the transmission of ARB to the environment.

3.4 National and state-level initiatives to address AMR in India

The Global Action Plan on Antimicrobial Resistance (GAP-AMR) and the United Nations' resolution on AMR make the threat of AMR to public health a top priority. In 2015, the WHA endorsed the GAP-AMR, recognizing the urgency of the situation and the threat presented by AMR to healthcare. As a result, several countries have developed their own NAPs to

Report	Study area	Year of study	Isolated bacteria	Percentage of resistance to the particular antibiotic
Skariyachan et al., 2015	Cauvery river	2011-2012	E. coli	Ampicillin: 100 Cefotaxime:100 Ciprofloxacin:75 Imipenem:15
Akiba et al., 2015	Rivers from 5 states	2012-2014	Gram-negative bacteria	Extended spectrum Cephalosporins: 37.9
Azam et al., 2016	Yamuna river	2013-2014	E. coli	Ampicillin: 100 Cefotaxime:75 Ciprofloxacin:58 Imipenem:8

Table 3.5: Study report on the presence of antibiotic resistant genes in various rivers in India

Report	Study area	Year of study	Isolated genes
Ahammad et al., 2014	Ganga, Yamuna	2012	bla _{NDM-1} , bla _{OXA-48}
Devarajan et al., 2016	Cauvery	2012-2013	bla _{TEM} , bla _{CTX-M} , bla _{NDM-1}
Marathe et al., 2017	Mutha	-	bla _{NDM-1} , bla _{OXA-48} , mcr ₋₁

contain AMR (Rangjalkar & Chandy, 2019).

3.4.1 Key initiatives taken before and after the adoption of NAP-AMR in India

 In September 2011, India's health minister, together with the health ministers of all WHO southeast Asia Region member-states, adopted the "Jaipur Declaration on Antimicrobial Resistance" (mainly focused on prevention and control of antimicrobial resistance and improvement of public health)

- Enrolment in the WHO Global Antimicrobial Resistance Surveillance System (GLASS) and strengthening the AMR surveillance network for important infections
- With the help of the Food and Agriculture Organization (FAO), the Indian Network for Fisheries and Animal Antimicrobial Resistance was developed
- In February 2016, the Government of India and the WHO jointly convened an international conference on AMR, titled "Combating"

Table 3.6: Specific strategic priorities in India's NAP-AMR

Priority	Specific Objectives
Strategy 1	To improve and understand AMR through effective communication, education and training programs
Strategy 2	To strengthen laboratories and establish standards for AMR surveillance in humans, animals, food, and the environment
Strategy 3	To reduce the incidence of infection through effective infection, prevention, and control
Strategy 4	To optimize the use of antimicrobial agents in all sectors
Strategy 5	To promote funds for AMR-related activities, research, and technologies
Strategy 6	To strengthen India's leadership in AMR through international, national, and sub-national AMR collaborations

Antimicrobial Resistance: A Public Health Challenge and Priority," and the "Medicines with the Red Line" media campaign was launched

- The Central Pollution Control Board has prepared draft criteria for antibiotic residues in pharmaceutical industrial wastewater and common effluent treatment plants
- A meeting, titled "National Consultation to Operationalize Action Plan for AMR Containment", was jointly organized by the Ministry of Health and Family Welfare, the National Center for Disease Control (NCDC), the WHO Country Office for India, the state health ministries, and other relevant stakeholders, on the 24th and 25th of August, 2017, in New Delhi to begin the implementation phase of the NAP

3.4.2 Initiatives to address AMR at the state level

India approved its NAP-AMR on 19th April, 2017, at the Inter-Ministerial Consultation on Antimicrobial Resistance. The framework of the State Action Plan (SAP) on AMR is based on the 'One Health' approach across stated strategic targets, and is in line with the NAP-AMR. Based on their respective needs and priorities, and in alignment with NAP-AMR, states

such as Delhi, Madhya Pradesh, and Kerala have been identified within the SAP. The following are the strategic priorities:

- Awareness and comprehension communications and training
- Knowledge and evidence laboratories and surveillance
- Infection prevention and control human health, animal/food, and community
- · Usage optimization and restriction of antibiotics
- Antimicrobial stewardship in humans and animals
- Research and innovations Collaborations

3.5 Challenges to combating AMR in India and other developing countries

AMR is widely acknowledged as a major public health concern across the countries. The importance of the environment in the transmission of many bacterial infections has long been recognized. It is frequently linked to inadequate sewage infrastructure, fecal contamination of water, and organic fertilizers (Larson et al., 2018). The global challenges to

containing AMR are as follows:

- AMR is not sufficiently addressed in national health agenda
- High burden of antimicrobial resistant infections throughout the world
- Lack of education and awareness among the communities
- Inadequate implementation and programmatic support to AMR containment measures
- · Irrational use of antibiotics in healthcare settings
- Absence of nation-wide lab-based surveillance systems for tackling AMR
- Lack of awareness on the application of antibiotics in the farming and agriculture sector
- Contaminated water and poor sanitation practices are linked to the transmission of diseases, such as cholera, diarrhea, dysentery, etc., leading to AMR. Thus, there is a need to improve WASH (water, sanitation, hygiene) services in developing countries. In large cities, waste management and proper WASH can be difficult, and metropolitan areas have been linked to numerous outbreaks of infectious diseases, notably those transmitted through the fecal-oral route.
- High population density in developing countries also raises the risk of contracting infectious diseases that are transmitted through the air.



Environment Management

4 | Environment management to mitigate AMR

4.1 Background

Indiscriminate and irrational use of antimicrobials is one of the key causes behind AMR in India and other countries of the world. Antibiotics are used sometimes irrationally for surgical prophylaxis, therapeutic and non-therapeutic uses in humans, animals, in fisheries and in plant horticulture and studies have reported profound environmental fallouts as a consequence of such misuse. The use of animal manure in soil and inadequate treatment of effluents from healthcare facilities, pharmaceutical industry, farms and discarded medications from household also contribute to the problem of environmental contamination by antimicrobialresistant pathogens and create hazardous levels of antibiotic residues from the environmental point of view (Sahoo et al., 2012; Samanta et al., 2014; Sivagami et al., 2020).

4.2 Conceptual Framework for Environmental Management

Antibiotics pass out into the environment via many routes, like from healthcare establishments, animal waste, from veterinary farms, household waste and disposal of unused expired drugs. All of these add to the growing reservoir of antimicrobial resistance determinants in the environment. A report in 2018 by the Centre for Science and Environment demonstrated the existence of pan drug resistant E. coli isolates from different parts of India (Taneja & Sharma, 2019). In 2018, researchers from IIT also found high levels of carbapenem-resistant bacteria and bla_{NDM-1} genes (New Delhi metallo-beta-lactamase) in wastewater effluent from hospitals, sewage treatment plants, drains and five locations along the Yamuna River in Delhi. In 2018, a multi-institutional study found a pan drug-resistant E. coli isolate from a heavily polluted stretch of river Yamuna in Delhi, which was resistant to 20 antibiotics. Trends, relationships and case attribution of antibiotic resistance between environmental sources and children is discussed in a recent article (Mitchell et al., 2021). Uninhibited presence of antimicrobials of different classes and generations in huge quantities, contributes to selection of multidrug-resistant microbes which then become the prevalent species in the environment. Table 4.1 encompasses the conceptual framework for environmental management in India. (Bardhan et al., 2020). In addition, inappropriate management of biomedical waste is an important source of environmental spread of drug-resistant microbes besides being a high risk for acquiring infections for patients and healthcare workers alike (Kumar et al., 2014). The available sewage discharge or effluent treatment plants are not attuned to contain the resistant strains of bacteria and other pathogens. These high levels of antibiotic residues or genes from biomedical wastes lead to deposition directly into the surface water thereby polluting the environment. Leachable materials from septic systems and landfills are also discharged into various zones based on the soil and allied conditions. Therefore, these materials are enabled to permeate the groundwater or spread sideways into streams or other surface water in the environment. Subsequently, it is conveyed or transmitted to other levels leading to spread of environmentally detrimental resistant genes of pathogenic microorganisms (Sahoo et al., 2012).

The environmental fallouts of some of these interventions have not been given enough attention by experts and policymakers across domains. Even among the researchers' community, the environmental dimension has not been taken up, reflecting in the low number of articles across different abstracting databases. Researchers have traditionally focused heavily on some of the isolated problems without assessing their scope and possible remedies.

4.3 Findings of the scoping review

Scoping review and retrieval of relevant articles were based on extensive search of the available literature databases to address the scope of the problem and to include studies highlighting the mitigation strategies. From the initial search 521 articles were appeared which was subsequently screened through

Intervention areas		Responsible antibiotic use in food animals					
Policy/ Law/ Regulations	Supply of Antibiotics	Prod	uction				Consumers
	Not studied		ice need intibiotics	Vete	rinarians	Farms and Farmers	Not studied
Implementation	Surveillance of antibiotic use, Residues and Resistance						
tools and	Antibiotic use in	Antib	Antibiotic resistance Antibiotic residues in			Environmental	
Infrastructure	food, animals	in an	imals and f	ood	food fron	n animals	surveillance and
& Advocacy/		from	animals				resistance
Awareness and							
education/Training							
Record keeping	Environmental Management to Contain AMR						
databases &	Registration licer	sing	Biosecurit	y/San	itation	Waste	Research
Review Monitoring/	(Environmental		and hygiene/GMP		management		
Feedback	impact assessme	nt)					

Table 4.1: Conceptual framework for environmental management (adopted from Khurana, 2019)

different criteria and finally 45 full length articles of the domain were yielded.

The study by Nair et al., (2019) was performed among healthcare professionals in Paschim Bardhaman district of West Bengal, India. The study participants endorsed behavioral and social factors to be major determinants of AMR development. Moreover, the study participants felt that information was lacking about the rational use of antimicrobials. Das (2017) studied the emerging aspects of environmental management in India and the study findings indicated that the environmental dimension needed urgent attention from all stakeholders. Lübbert et al. (2017) studied environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India that was associated with dissemination of extended-spectrum betalactamase and carbapenemase producing pathogens in the environment. Most of the articles studied in the given domain were recent ones but transmission dynamics or mitigation strategies were not reported there. Around 48% of the included original studies were taken from the wastewater environment, while around 27% were taken from groundwater and the remaining 25% were taken from sewage sources from across the country. The literature search also revealed some of the practices and their gaps in different sectors with respect to environmental management strategies in containment of resistance pathogens in environment:

4.3.1 Role of practices in agriculture and livestock

In the agriculture setup antimicrobials are used mostly as insecticide or fungicides and as implements of biosecurity to pest infestation

affecting crops. The poultry farm scenario shows the case of litter and manure that is mostly found spread on fields; sometimes used directly even in aquaculture farms. Limited biosecurity measures are observed in this sector. Variations across different farm types are observed throughout. Notably, a study by Centre for Science and Environment (CSE) indicated high levels of multidrug resistant (MDR) bacteria in the poultry farm environment (Walia et al., 2019). It was also indicated that incidences of such MDR organisms are being transferred from farms to agricultural fields through E. coli and finally through aquaculture farms they are subsequently discharged into canals or agricultural fields. These wastes are sometimes reused in aquaculture ponds and are then subsequently let out in large pisciculture lakes (Bhushan et al., 2017; Sebastian et al., 2021).

The criteria for location of animal feed mills, newer and innovative approaches to biosecurity, sanitation and cleanliness are of great importance for curtailing the agents that spread the AMR bacteria. Manure storage and management of hatchery waste management is also deemed quite important to contain AMR. Waste water discharge including methods for treatment and disposal of effluent feed and pest management are of notable consequence to developing environmental AMR.

Environment regulators and policymakers should have a greater leadership role in developing AMR-centric environmental regulations for farms. Pollution-causing potential of the poultry farm sector should be re-prioritized. Less risky litter or manure management approaches such as biogas

generation must be preferred over land application. Other options of waste to energy conversion can also be explored. In-house biogas generation plants for Big or integrated poultry farms should be adopted. The use of common biogas generation plants for small poultry farmers should be explored. It is also important that application of untreated litter must be prohibited through laws, awareness and surveillance. Proper composting measures for treatment of litter or manure should be encouraged only under a very high level of supervision. Guidelines related to approval of composting sites, validation of treated manure and timing of application of litter or manure should be made (Jadeja & Worrich, 2022).

4.3.2 Role of practices in household

Pharmaceuticals including antimicrobials which are unused or expired at the household levels are often disposed improperly into drains along with regular household wastes. This is a significant cause behind the development of environmental AMR in India. Globally manufacturing companies ensure pharmaceutical take back from household level but no such provision was found through the report in India. Handling of expired drugs at the household level needs immediate attention from all stakeholders as it directly affects the rising trends and scenario of AMR in the environment.

4.3.3 Role of practices in Health care facilities

Healthcare facilities are the reservoir of the infectious pathogens which are being continuously spread by hospital personnel, hospitalized patients and visiting persons etc. This transmission of disease-causing microorganisms often results in Hospital-acquired infection (HAI) and the issue of AMR. In addition, irrationally prescribing of antibiotic at the healthcare systems also leads to the development of AMR among the patients.

4.3.4 Role of practices in pharmaceutical manufacturing industries

Improper discharge of sewage of pharmaceutical industry wastes is reported from this scoping review and also from consulting stakeholders. So, there is an urgent need for surveillance of this issue at the earliest. Solid wastes are given to scrap dealers who dump or burn it at any open area and potentially

hazardous effluents are injected into bore wells dug in ground at night. Effluent treatment plants (ETPs) also release toxic discharges during various times of the year. As reported smaller scale pharmaceutical manufacturing units drain their treated water waste directly into their sewage. Sewer lines of some industries are also reportedly not connected to Common effluent treatment plant (CETP) and open directly into the nearby river. Pipes and outlets from plants are channeled underground to open into low lying areas causing environmental accumulation of resistant pathogens (Damodhar & Reddy, 2013).

Wastes from household and healthcare facilities constitute one of the contributors of antibiotic resistance in the environment. Pharmaceutical waste like antibiotics and other antifungals including all items contaminated with these drugs along with glass or plastic ampoules, vials etc. Treatment and disposal option of expired 'antimicrobials and other allied items contaminated with antimicrobials drugs are to be returned back to the manufacturer or supplier for incineration at temperature >1200°C or to common bio-medical waste treatment facility or hazardous waste treatment, storage and disposal facility for incineration at >1200°C or encapsulation or plasma pyrolysis at >1200°C. All other discarded medicines are to be either sent back to manufacturer or disposed by incineration. The environmental fallouts of such incineration have evoked mixed responses from different stakeholders all over the world. Figure 4.1 presents a management algorithm for antimicrobial resistance and surveillance in the environment.

4.4 Major gaps existing in the domain of environmental management of AMR

- Poultry, hatchery and aquaculture transmission dynamics mostly left unaddressed.
- 2. No framework for freshwater aquaculture pertaining to domestic usage sectors.
- 3. Agricultural lands are being converted for aquaculture purposes and this can lead to an accumulation of antimicrobial residues from agricultural fields to reach the fishes and subsequently move in the trophic levels through bio magnification in environment.

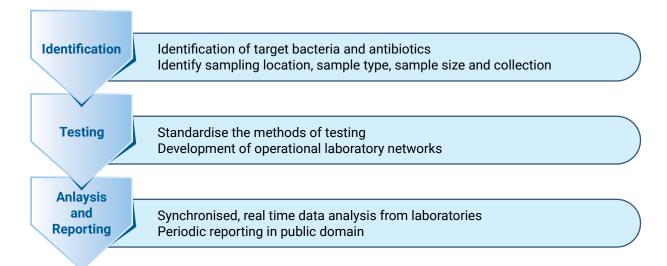


Figure 4.1: Management algorithm for antimicrobial resistance and surveillance in the environment (Adopted from Centre for Science and Environment, 2019)



5 Antimicrobial contamination of environment by human health sector

5.1 Background

This chapter covers environmental pollution caused by the use of antimicrobial agents in the human health sector, and in household sewage as well as their implications for the development of AMR in India. The scope and its environmental impact of antibiotic abuse has not been adequately addressed in research in India. It can be clearly depicted from the discussion in the current chapter that environmental balance and environmental impact assessment in the context of AMR has been left largely unaddressed in the country. There are reported instances of a number of the drug resistant microbes being found in the effluents from treatment plants that have been found to be phenotypically resistant to a carbapenem drug, imipenem (Nagarajan et al., 2012; Rudraswamy et al., 2012; Singh et al., 2012; Dubey et al., 2013; Kishore et al., 2014; Manar et al., 2014; Phukan et al., 2014; Aslesh et al., 2015; Jindal et al., 2015; Reddy et al., 2015; Azam et al., 2016; Berendes et al., 2019; Raj et al., 2019; Yadav, 2019; Aggarwal et al., 2020; 2020; Menon et al., 2021; Rohilla et al., 2021; Singh et al., 2021).

The spread of antibiotic resistance in the environment through resistant organisms further emphasizes the underlying hypothesis that resistance amplification seems to occur in sewage through some kind of gene transfer, possibly horizontal gene transfer (Aggarwal et al., 2020). In a similar survey of effluents collected from several geographically-dispersed wastewater plants in the USA, about 20.2% of the isolates were imipenem-resistant. The impact of AMR on the environment has also not been adequately reflected in existing research (Akiba et al., 2016; Bhowmik et al, 2021; Veeraraghavan et al., 2019; Bengtsson-Palme et al, 2014; Chakraborty et al., 2013; Chatterjee et al., 2019; Tseng et al., 2020; Chakraborty et al., 2021; Siddiqui et al., 2020; Kapoor et al., 2021).

The genesis of Antimicrobial-resistant bacteria (ARBs), that are detected in wastewater can be linked to antimicrobial resistance which serves as a source of infections and morbidity among individuals at

different levels. The fact that hospital effluent almost always mixes with wastewater from the community makes it difficult to determine the original source of specific antibiotic resistance genes (ARGs). This is particularly challenging in certain locations and leads to indeterminable and unaccounted-for detrimental effects where there is a comparatively high prevalence of antimicrobial resistant bacteria in the wider human or animal population, or in the natural environment. (Behera et al., 2012; Sahoo et al., 2014; Roy et al., 2015; Fernandes et al., 2015; Tiwari et al., 2018).

It is difficult to clearly define the root source of antimicrobial-resistant bacteria detected in a given wastewater influent system in the environment, and there is a significant knowledge gap in understanding which mitigation measures will be most effective. Similarly, levels of antimicrobials detected in wastewater environments do not always correlate with antimicrobial use in a healthcare facility. This is partly because degradation of antimicrobials in the environment and survival of bacteria in the environment depend on several factors. For example, antimicrobial half-lives range widely from minutes to tens of days, and survival rates of resistant bacteria are also geographically-dependent in the environmental milieu, and are highly variable. The relationship of antimicrobials and antimicrobial-resistant microbes in wastewater environments also depends on location because there are different environmental temperatures and different resistant colonization rates across the globe, which are variable in regard to their effects and impacts on the environment (Kotwani et al., 2011; Sudershan et al., 2012; Dash et al., 2013; Aarti et al., 2016; Falkenberg et al., 2018; Meenatchi et al., 2020; Chellapandi, 2021; Said et al., 2021; Karunanidhi et al., 2021; Srivastava et al., 2021).

5.2 Findings from scoping review

The fallouts of antimicrobial resistance on the environment has also not been addressed in existing research.

Figure 5.1 depicts the different categories of

wastes from healthcare and households. The new BMW management rules have notified to efficiently manage the biomedical waste in the country but the environmental dimensions of AMR are absent there. These rules have been modified to include the word "handling", and bring more clarity in the modes of their application. In addition, strict rules have been made to ensure that there is no pilferage of recyclables, secondary handling, and inadvertent scattering or spillage by animals during transport from the HCFs to the common treatment facility (Sivalingam et al., 2019; Kumar et al., 2013; Taneja et al., 2019; Banerjee et al., 2018; Dixit et al., 2019; Global Antibiotic Resistance Partnership, 2011; Viswanathan et al., 2011; Singhal et al., 2017).

Major findings from scoping review of available literature on environmental contamination through the use of antibiotics by humans:

Nair et al. (2019) have addressed the antibiotic use, resistance, development, and environmental factors through a qualitative study conducted among healthcare professionals in Paschim Bardhaman district of West Bengal, India. The study has discussed the environmental paradigm. Ganguly et al. (2011) have recommended that antibiotic use be rationalized to limit antibiotic resistance in India, but have made few references to its environmental aspects. Jindal et al. (2014) have detailed the challenges posed by AMR to public health but have failed to include its environmental dimensions. Philips et al. (2017) have

reviewed the emerging environmental contaminants in Indian environmental matrices. Kakkar et al. (2017) have explored the etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital, Aligarh, India, and its environmental determinants. Hanna et al. (2018) have studied the seasonal variations in water quality, antibiotic residues, resistant bacteria, and antibiotic resistance genes of *Escherichia coli* isolates from water and sediments of the Kshipra River in central India, and its environmental impacts. A study by Gandhra et al. (2019) was the first to report the emergence of the plasmid-borne $bla_{oxa-181}$ gene in *Ochrobactrum intermedium*.

5.3 Gaps identified from the scoping review

- There is a lack of research with regards to the AMR in the wastes generated from the healthcare facilities and household.
- There is a lack of research linking the antibiotic residues in BMWs, development of AMR and subsequent transmission via pathways in the environment.
- There is limited awareness about the environmental contamination caused by the use of antibiotics by humans

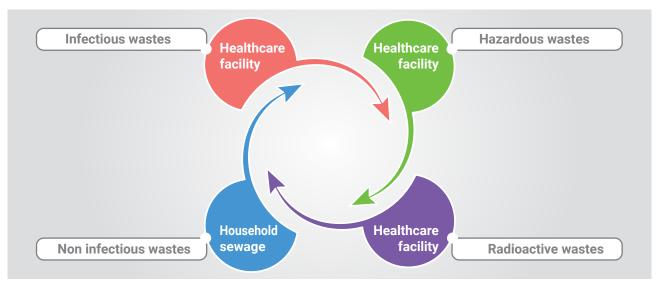
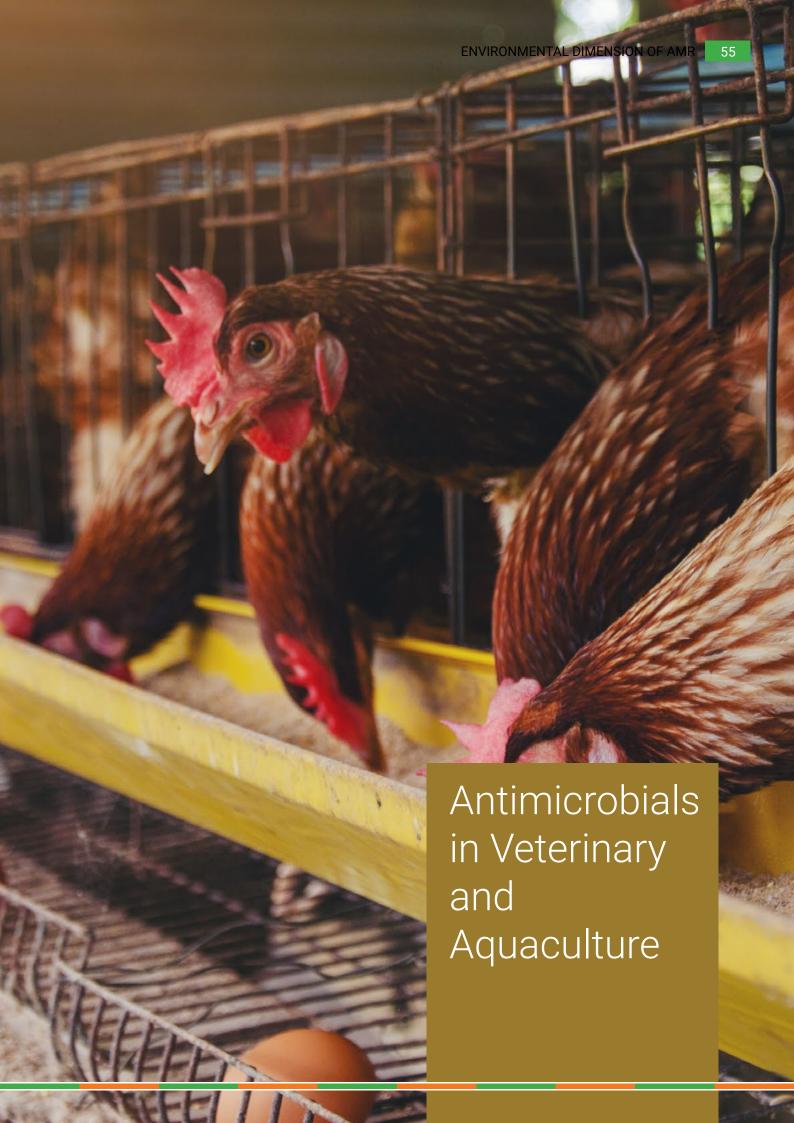


Figure 5.1: Categorization of environmental degradation caused by different kinds of wastes from healthcare and households



6 Antimicrobial contamination of environment by veterinary and aquaculture sectors

6.1 Antibiotic use and AMR in veterinary sectors in India

The indiscriminate use of antibiotics in the veterinary sector in India is a major source of spread of antimicrobial resistance (AMR) in the environment. The need to meet the increasing demand for food animals, driven by population growth, puts farmers under pressure to produce more with the limited resources and infrastructure available to them. In addition to the treatment of various infectious diseases, antibiotics are widely used with the feed of poultry and that of other animal farming to promote their growth. However, farmers' failure to observe the drug withdrawal period results in the consumption of contaminated food animals, ultimately leading to AMR (Mutua et al., 2020).

6.1.1 Antimicrobial resistance in poultry in India

Numerous studies have reported numerous incidences of AMR originating from the poultry sector in India. The spatial distribution of the number of studies from the poultry sector in India is shown in **Figure 6.1**.

Most of the studies on AMR have used bacterial samples originating from poultry birds (meat, eggs, cloacal swab, and fecal sample). Only a few studies have reported AMR in the drinking water of poultry farms. In a study by Kumar et al. (2012), 4 species (total 88) of *Salmonella* were taken from disease outbreaks in broilers from different regions of Haryana. The antibiotic susceptibility test of the isolates against different antibiotics showed various resistivity patterns (**Figure 6.2**).

Rajagopal and Mini (2013) reported the presence of antibiotic-resistant Salmonella sp. derived from the different organs of chickens in Kerala, and concluded that the isolates were 100% resistant to erythromycin. Shing et al. (2013) reported the presence of AMR in *Salmonella typhimurium* in the egg, feed, drinking water, cloacal swab, and faeces of fowls in Bareilly, Uttar Pradesh. The isolates were found to be 100% resistant to clindamycin, oxacillin, penicillin, and vancomycin. In a study conducted in Tamil Nadu, Balasubramaniam et al. (2014) reported that 88% of the *E. coli* isolated from cloacal swabs of flocks of 5 different layer farms were resistant to tetracycline. A total of 20 *Campylobacter*



Figure 6.1: Spatial distribution of the number of studies on AMR from the poultry sector in India

Antimicrobial Resistance of Salmonella sp. (Kumar et al., 2012)

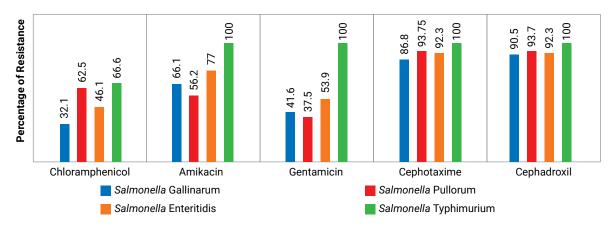


Figure 6.2: Antibiotic resistance pattern of Salmonella serovars derived from broiler farms from different regions of Haryana (Kumar et al., 2012).

jejuni were isolated from poultry origin in Kolkata by Kabir et al. (2015), and 100% of the isolates were resistant to tetracycline, nalidixic acid, ciprofloxacin, levofloxacin, ofloxacin, and sulfamethoxazole-trimethoprim. Bhushan et al. (2017) studied 47 poultry samples from four Indian states viz. Uttar Pradesh, Rajasthan, Haryana, and Punjab, and derived 187 isolates of three bacteria viz. *E. coli, K. pneumoniae* and *S. lentus*. Antibiotic resistance of the three strains to tetracyclines, amoxyclav, nitrofurantoin, levofloxacin,

ciprofloxacin, chloramphenicol, cefuroxime, cefotaxime, ceftriaxone, amikacin, gentamicin, co-trimoxazole, and meropenem was observed. There are many other similar studies on the antimicrobial resistance pattern of various bacterial strains isolated from poultry chickens and slaughterhouse environment (Hussain et al., 2017; Khan et al., 2018; Saharan et al., 2019a; Zehra et al., 2019; Tewari et al., 2019; Suman Kumar et al., 2021). Some other quantitative studies on the incidences of AMR in poultry have been presented in **Figure 6.3**.

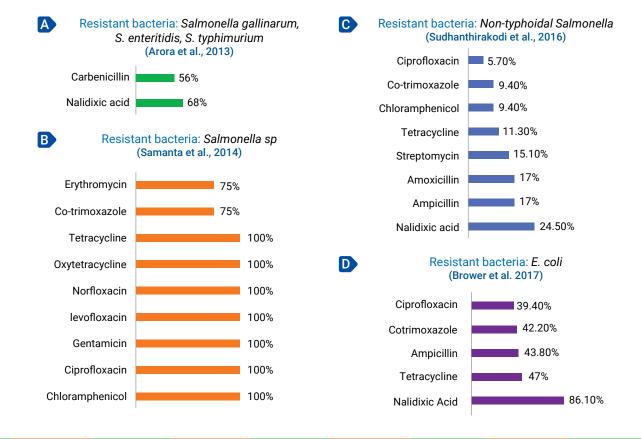




Figure 6.3: Study of AMR in poultry by different authors from various states in India — (a) Haryana (b) West Bengal (c) West Bengal (d) Punjab (e) Maharashtra (f) Maharashtra (g) Karnataka (h) Uttarakhand and Uttar Pradesh (i) Mizoram (j) Tamil Nadu.

6.1.2 Antimicrobial resistance scenario in dairy and pig farming in India

The distribution of the number of studies on AMR from dairy sector in the country is shown in **Figure 6.4**. Most of the studies on AMR bacteria in the dairy sector have focused on mastitis. The majority of these studies have reported the presence of resistant bacterial strains in clinical or subclinical mastitis bovine milk. Only a very

few studies isolated the bacterial samples from slaughterhouse carcasses, cutting knives, table surfaces, water samples, and hand rinses of butchers and animal handlers. Thaker et al. (2012) demonstrated the resistance pattern of *E. coli* in the cow milk sample and found 100% resistance to ampicillin, followed by streptomycin (57.89%) and oxytetracycline (47.37%). The emergence of antimicrobial resistance among bovine mastitis pathogens is due to the presence of different

resistant genes in the bacterial strains. A study from West Bengal, conducted by Bandyopadhyay et (2015),described intra-mammary infection of methicillin-resistant Staphylococcus epidermidis, methicillin-resistant Staphylococcus aureus, and ESBL-producing Escherichia in 2 Holstein Friesian crossbred cows with subclinical mastitis. In the Staphylococcus strains, different genes, like mecA (resistant to amikacin, tetracycline, and glycopeptides), sul1(resistant to sulfonamides), qnrS (resistant to quinolone), ESBL producers (resistant to third- and fourthgeneration cephalosporins), exhibited a varied range of AMR. Another study from Karnataka, by Preethirani et al. (2015), investigated the pattern of coagulase-negative resistance staphylococci (CoNS), Streptococci, Escherichia coli, and Staphylococcus aureus isolated from subclinical mastitis cow milk. The isolates exhibited resistance to many antibiotics (Figure 6.5). E. coli exhibited 100% resistance to amikacin, amoxycillin/sulbactam, ampicillin, cefotaxime, cefoxitin, ceftriaxone/sulbactam, methicillin, penicillin-G, and streptomycin. Koovapra et al. (2016) isolated extended-spectrum β-lactamase (ESBL) producing Klebsiella pneumoniae from milk samples of healthy cows with subclinical (n=159) and clinical (n=52) mastitis from West Bengal, Jharkhand, and Mizoram. In drug sensitivity assay, the isolates exhibited 100% resistance to ceftriaxone, ceftazidime, cefotaxime, aztreonam, cefpodoxime, ceftizoxime, and cefixime, 78% to gentamicin, 74% to tetracycline, 70% to sulpha/

trimethoprim combination, 61% to cefepime, and 51% to ciprofloxacin and piperacillin. Samples vancomycin-resistant S. aureus (VRSA) of isolated from raw milk samples in West Bengal by Bhattacharyya et al. (2016) demonstrated resistance to various antibiotics. Prevalence of Staphylococcus aureus in cows with subclinical mastitis and antimicrobial resistance was detected in Maharashtra by Gandhale et al. (2017). S. aureus isolated from mastitis milk, udder swabs, and floor swabs showed resistance to penicillin (91.76%), (71.76%),and kanamycin oxacillin (63.53%).Evaluation of clinical mastitis in bovines from the Jammu region by Bhat et al. (2017) revealed the presence of antibiotic-resistant Staphylococci and E. coli. The isolates were found to be 100% resistant to penicillin, followed by 29.41% resistance to both ceftriaxone and oxytetracycline. Gowda et al. (2017) collected samples of beef carcasses, knives, cutting table surfaces, and water from 4 cattle slaughterhouses in Kerala to determine the occurrence and antibiotic susceptibility of Listeria sp. and Staphylococcus aureus. The isolates were found to be resistant to penicillin (38.0%), ceftriaxone (31.9%), ampicillin (29.0%), amoxicillin (28.8%), tetracycline (24.4%), and chloramphenicol (23.9%). Sharma et al. (2017) reported the prevalence of Listeria monocytogenes in raw cow milk samples from Rajasthan. The isolates exhibited 100% resistance to penicillin G, piperacillin, oxacillin, and ceftriaxone, 80% resistance to ampicillin, amoxicillin-clavulanic acid, and nalidixic acid, and 60% resistance to ceftazidime. Verma et al.

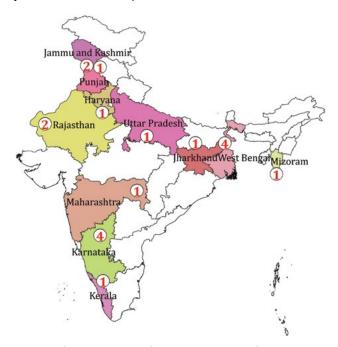
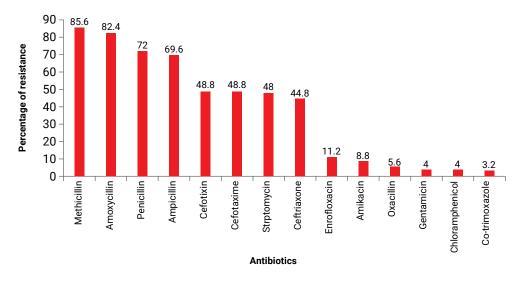
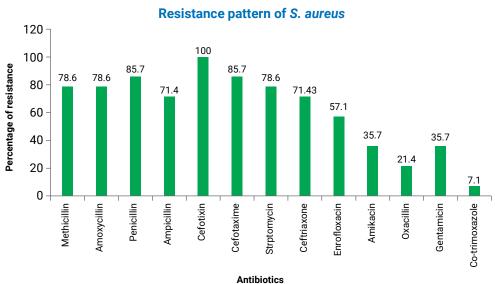


Figure 6.4: Distribution of the number of studies on AMR from the dairy sector in India

Resistance pattern of coagulase-negative Staphylococci (CoNS)





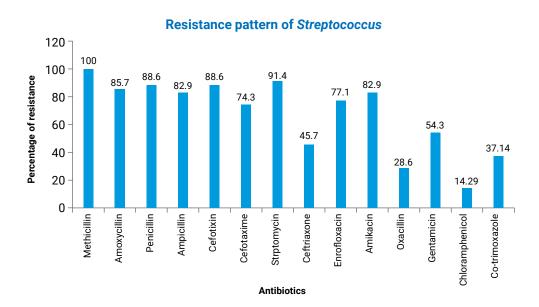


Figure 6.5: AMR pattern of coagulase-negative *Staphylococci* (CoNS), *Streptococci*, and *Staphylococcus* aureus isolated from subclinical mastitis cow milk.

(2018) assessed the status of bovine mastitis in and around the Meerut region of Uttar Pradesh. They analysed raw milk samples, and the major pathogens found were Staphylococcus Streptococcus sp., Proteus sp., and Candida sp. The isolates were found to have resistance against amoxyclav, and ampicillin. Ralte et al. (2019) studied the AMR pattern of various bacterial species obtained from a wide range of animals (cattle, buffalo, sheep, goat, and poultry). The isolated bacteria were Pasteurella sp., E. coli, Klebsiella sp., Salmonella sp., Pseudomonas sp., Staphylococcus sp., Streptococcus sp., Corynebacterium sp., and Bacillus sp. The resistance patterns of the bacterial strains against different antibiotics have been shown in Figure 6.6. Staphylococcus aureus is considered a major etiological agent of clinical and sub-clinical bovine mastitis. In a study by Annamanedi et al. (2021), 20.5% of the S. aureus isolates exhibited oxacillin resistance and 14.46% exhibited methicillin resistance. Lalzampuia et al. (2013) and Samanta et al. (2015) reported the presence of ESBL-producing E. coli isolates from faecal samples of healthy pigs in Mizoram and West Bengal, respectively.

Environmental AMR is one of the most serious global concerns that needs more attention for its regulation. A study by Parkunan et al. (2019) on the knowledge, attitude, and practices among veterinarians in Haryana revealed that though the clinicians were aware of the fundamental clinical aspects of antibiotic resistance (AR) i.e., mode of transmission of resistance, response during treatment failure, and safe disposal of hospital waste, they lacked knowledge of 2 major ways to restrict AMR transmission i.e., 'antibiotic stewardship' and 'interruption of AMR transmission by means of cross-kingdom pathogen', thus indicating lack of awareness among clinicians to improve their knowledge regarding AMR. In a recent study, Vijay et al. (2021) conducted a crosssectional survey about Knowledge, Attitude and Practices (KAP) among veterinarians regarding antibiotic use and the emergence of AMR in dairy herds in 25 states of India. Out of a total of 466 respondents, 69.5% exhibited average knowledge, 93.2% exhibited a neutral attitude, and 51.3% had moderate practice scores with respect to judicious antibiotic usage. 90.6% of the respondents reported their 'own experience' as the criteria for antibiotic selection during the treatment. The use

of WHO-listed highest priority Critically Important Antimicrobials for Human Medicine was also reported by them, especially quinolones (76.8%) and third-generation cephalosporins (47.8%). The study results demonstrated the average KAP score among veterinarians, a lack of awareness among farmers, a tendency to use of antibiotics indiscriminately, and a lack of antibiotic stewardship in the veterinary sector in India.

6.1.3 The overlap between OIE-listed antimicrobials for veterinary use and WHO-listed Critically Important Antimicrobials for Human Medicines and their implications for environmental AMR

47 Critically Important Antimicrobials that have been categorized as Critically Important for Human Medicine by WHO continue to be included in the OIE list of antibiotics for veterinary uses (Table 6.1). These antibiotics have been also categorized either as Veterinary Critically Important Antimicrobials (VCIA) or Veterinary Highly Important Antimicrobials (VHIA) by OIE. While only a few of these antibiotics are used to treat one or two specific animal species, the rest can be freely applied to the treatment of various animal species. Alarming reports of the prevalence of AMR bacteria in the veterinary sectors throughout the country is accompanied by evidence that many of these bacteria can sustain in the animal reservoir and contaminate the environment through various modes. These resistant bacterial strains in the environment can be transmitted to humans through the food chain and cause serious human health hazards. The antibiotics that are being used continuously for the treatment of both animal and human diseases will no longer remain effective for humans after a certain period due to the presence of common antibiotic-resistant bacterial genes.

6.1.4 Critically Important Antimicrobials used in the poultry and dairy sectors in India and their implications for the environment

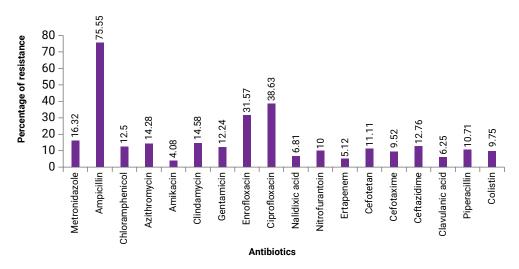
Most of the poultry and other veterinary diseases result from poor farm management, especially manure management, which allows the farm environment to harbour harmful pathogens that cause veterinary diseases. A foul odour develops in the farm due to the generation of ammonia, volatile organic compounds, and hydrogen sulphide. This odour attracts flies that can transmit disease-causing bacteria to humans, causing cholera, typhoid, etc. (Maheshwari, 2013). If these bacterial strains are resistant to certain antibiotics,

Table 6.1: List of antibiotics present in both the OIE and WHO lists.

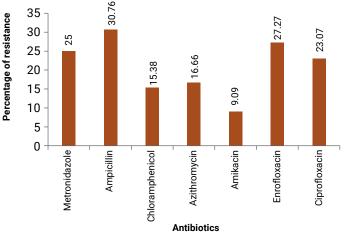
List of antimicrobials	Species	OIE status of antimicrobials	Antimicrobial family	WHO status
Amikacin	EQU			
Apramycin	AVI, BOV, LEP, OVI, SUI			
Dihydrostreptomycin	AVI, BOV, CAP, EQU, LEP, OVI, SUI			
Framycetin	BOV, CAP, OVI			
Gentamicin	AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI			
Kanamycin	AVI, BOV, EQU, PIS, SUI		Aminoglycosides	
Neomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, SUI			
Paromomycin	AVI, BOV, CAP, OVI, LEP, SUI			
Streptomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	(VCIA)		
Tobramycin	EQU			
Amoxicillin	AVI, BOV, CAP, EQU, OVI, PIS, SUI			
Ampicillin	AVI, BOV, CAP, EQU, OVI, PIS, SUI		Penicillins (aminopenicillins)	
Hetacillin	BOV		(arimoperiiciiiiis)	
Ticarcillin	EQU		Penicillins (antipseudomonal)	
Amoxicillin + clavulanic Acid	AVI, BOV, CAP, EQU, OVI, SUI		Aminopenicillins	
Ampicillin + sulbactam	AVI, BOV, SUI		with betalactamase inhibitors	
Rifampicin	EQU		Ancomyoine	
Rifaximin	BOV, CAP, EQU, LEP, OVI, SUI	(VHIA)	Ansamycins	
Fosfomycin	AVI, BOV, PIS, SUI	(**************************************	Phosphonic acid derivatives	
Cefoperazone	BOV, CAP, OVI			
fquinome BOV, CAP, EQU, LEP, OVI, SUI		()(0)()	O a m h a l a a m a min a	Critically
Ceftiofur	AVI, BOV, CAP, EQU, LEP, OVI, SUI	(VCIA)	Cephalosporins	Critically Important Antimicrobials
Ceftriaxone	AVI, BOV, OVI, SUI			
Erythromycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI			for Human Medicine
Gamithromycin	BOV			Medicine
Josamycin	AVI, PIS, SUI			
Kitasamycin	AVI, SUI, PIS			
Oleandomycin	BOV			
Spiramycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI		Macrolides and ketolides	
Tildipirosin	BOV, SUI		Retolides	
Tilmicosin	AVI, BOV, CAP, LEP, OVI, SUI	(VCIA)		
Tulathromycin	BOV, SUI			
Tylosin	API, AVI, BOV, CAP, LEP, OVI, SUI			
Tylvalosin	AVI, SUI			
Ciprofloxacin	AVI, BOV, SUI			
Danofloxacin	AVI, BOV, CAP, LEP, OVI, SUI			
Difloxacin	AVI, BOV, LEP, SUI			
Enrofloxacin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI			
Flumequine	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	(VHIA)]	
Marbofloxacin AVI, BOV, EQU, LEP, SUI		(VCIA)	Quinolones and fluoroquinolones	
Nalidixic acid	BOV		- Haoroquinolones	
Norfloxacin	AVI, BOV, CAP, LEP, OVI, SUI]	
Ofloxacin	AVI, SUI			
Orbifloxacin	BOV, SUI]		
Oxolinic acid	AVI, BOV, LEP, PIS, SUI, OVI]	
Polymyxin E (colistin)	AVI, BOV, CAP, EQU, LEP, OVI, SUI	(VHIA)	Deliment	
Polymyxin B	BOV, CAP, EQU, LEP, OVI, AVI		Polymyxins	

AVI: Avian; EQU: Equine; API: Bee; BOV: Bovine; CAP: Caprine; CAM: Camel; LEP: Rabbit; OVI: Ovine; PIS: Fish; SUI: Swine. VCIA: Veterinary Critically Important Antimicrobials; VHIA: Veterinary Highly Important Antimicrobials [Source: OIE List of Antimicrobial Agents of Veterinary Importance, 2019; Khurana et al. (2021).]

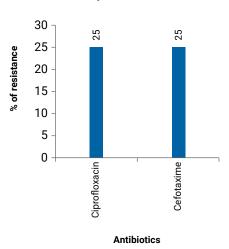
Resistance pattern of E. coli



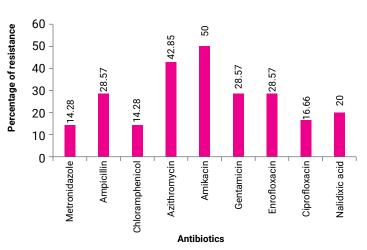




Resistance pattern of Citrobacter sp.



Resistance pattern of Pasteurella sp.



Resistance pattern of Salmonella sp.

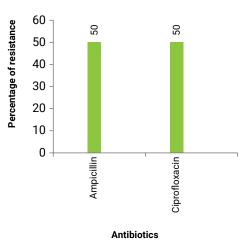
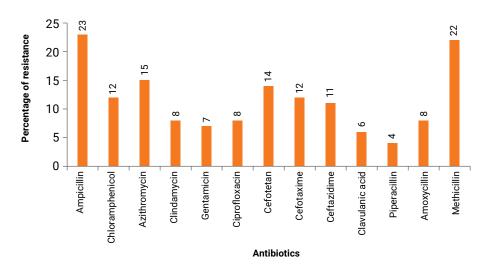
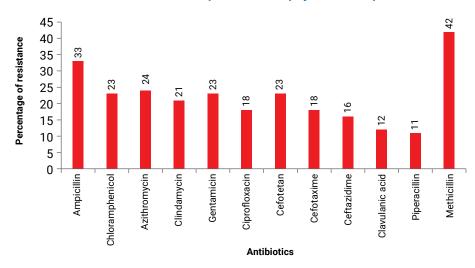


Figure 6.6: AMR patterns of nine bacterial strains obtained from a variety of animals (cattle, buffalo, sheep, goat, and poultry) in Punjab (Ralte et al., 2019). (Cont'd...)

Resistance pattern of Streptococcus sp.

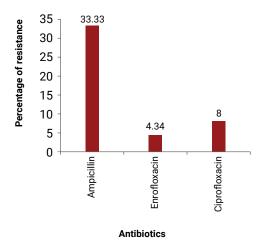


Resistance pattern of Staphylococcus sp.



Resistance pattern of Corynebacterium sp.

Resistance pattern of Pseudomonas sp.



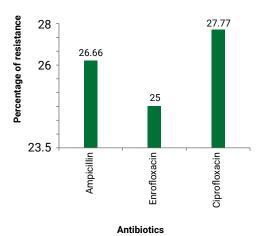


Figure 6.6: AMR patterns of nine bacterial strains obtained from a variety of animals (cattle, buffalo, sheep, goat, and poultry) in Punjab (Ralte et al., 2019).

administered antibiotics for the treatment of human diseases will fail. Moreover, the antibiotic-resistant bacteria present in the soil of the farm environment contaminate nearby water bodies through runoff, thereby not only creating human health issues but also infecting animals in adjacent farms.

The Centre for Science and Environment, Delhi, has prepared the lists (**Table 6.2** and **Table 6.3**) of antibiotics used in the Indian poultry and dairy sectors through extensive research and parallel expert consultation. The lists also report the practice of using many Critically Important Antimicrobials for the treatment and control of various animal diseases.

6.1.5 Major gaps in the context of the environment, identified from the scoping review

The gaps in the context of the environment, identified from the scoping review are as follows:

 Though there are many reports on antibiotic resistance patterns of the bacterial strains from the veterinary sectors, the impacts of antibioticresistant bacteria and genes on the environment and on human health are the least studied and reported.

- There is a lack of proper Knowledge, Attitude, and Practices (KAP) among veterinarians, regarding antibiotic use and the emergence of environmental AMR in the dairy and poultry sectors.
- There is a dearth of literature/studies/data on antibiotic pollution in the environment emanating from veterinary hospitals.

6.1.6 Research for developing alternatives to antibiotics for food-producing animals in India

There is some literature on the research and development of alternatives to antibiotics for food-producing animals in the country. Though the studies conducted so far have focused only on the poultry sector, their prevalence indicates a positive approach, at the country level, to replace antibiotic growth promoters (AGP). The key findings of the studies have been presented in **Table 6.4**.

6.1.7 Key informant interview (KII)

For developing the abstraction matrix of KII in the veterinary sector was conducted at the two tiers — Tier-I (two veterinarians) and Tier-II (one extension officer). The abstraction matrix has been shown in **Figure 6.7**.

Table 6.2: Critically important antimicrobials used in the poultry sector in India for the treatment and control of diseases

Antibiotics	Antimicrobial family	Disease				
Amikacin		Infectious coryza, pullorum disease, fowl typhoid, colibacillosis, salmonellosis				
Gentamicin	Aminaglyagaidas	Pullorum disease, fowl typhoid, salmonellosis				
Neomycin	Aminoglycosides	Pullorum disease, colibacillosis, necrotic enteritis; fungal disease: aspergillosis, mycotoxicosis				
Streptomycin		Fowl cholera				
Amoxicillin	Penicillin	Necrotic enteritis; viral disease: Ranikhet disease				
Ampicillin	Penicillin	Necrotic enteritis				
Ciprofloxacin		Pullorum disease, fowl typhoid, colibacillosis, salmonellosis				
Enrofloxacin	Quinolones and fluoroquinolones	Fowl cholera, infectious coryza, pullorum disease, fowl typhoid, colibacillosis, necrotic enteritis, salmonellosis, chronic respiratory disease viral diseases: Ranikhet disease, infectious bronchitis, avian influenza, Marek's disease, infectious bursal disease				
Norfloxacin		Colibacillosis				
Erythromycin		Infectious coryza				
Tylosin	Macrolides and ketolides	Chronic respiratory disease; fungal disease: mycotoxicosis				
Tylvalosin		Chronic respiratory disease				
Azithromycin	Macrolides and ketolides	Fowl cholera				
Levofloxacin	Quinolones and fluoroquinolones	Fowl cholera, Infectious coryza, pullorum disease, fowl typhoid, colibacillosis, necrotic enteritis, salmonellosis; viral disease: Ranikhet disease				

Source: Khurana et al. (2021)

6.2 Antibiotics and AMR in aquaculture

6.2.1 Antibiotics used in the aquaculture sector in India

Per capita fish consumption in India is continuously increasing, driven by the growing population of the country, and cannot be met only through capture fisheries. The aquaculture sector started flourishing to support the huge demand for commercial fish that is a major source of animal protein in the regular diet for many Indians. Brackish water shrimps constitute a major portion of aquaculture products. Large-scale industrial production of brackish water

Table 6.3: Critically Important Antimicrobials used in the dairy sector in India for the treatment and control of diseases

Antimicrobials	Antimicrobial family	Disease		
Amikacin		Mastitis, brucellosis		
Gentamicin	Aminoglycosides	Mastitis, diarrhoea; viral disease: foot and mouth disease		
Streptomycin		Mastitis, black quarter, brucellosis, tuberculosis; viral disease: foot and mouth disease		
Cefotaxime		Mastitis, haemorrhagic septicaemia		
Ceftazidime	Third-, fourth- and fifth-generation	Mastitis		
Ceftizoxime		Mastitis		
Levofloxacin	Quinolones and fluoroquinolones	Mastitis		
Moxifloxacin	Quillolottes and fluoroquillolottes	Mastitis		
Amoxicillin		Mastitis; viral disease: foot and mouth disease		
Ampicillin	Penicillins	Mastitis, black quarter, brucellosis; viral disease: foot and mouth disease, infectious bovine rhinotracheitis		
Ciprofloxacin		Anthrax, diarrhoea; viral disease: foot and mouth disease		
Enrofloxacin	Quinolones and fluoroquinolones	Mastitis, haemorrhagic septicaemia, diarrhoea; viral disease: foot and mouth disease, infectious bovine rhinotracheitis		
Norfloxacin		Diarrhoea		
Ofloxacin		Diarrhoea		
Cefoperazone		Mastitis		
Ceftiofur	Third founds and fifth manager	Mastitis, haemorrhagic septicaemia, anthrax		
Ceftriaxone	Third-, fourth- and fifth-generation cephalosporins	Mastitis, haemorrhagic septicaemia; viral disease: foot and mouth disease		
Cefquinome		Mastitis		
Rifampicin	Ansamycins	Brucellosis, tuberculosis		
Ethambutol	Drugs used solely to treat	Tuberculosis		
Isoniazid	tuberculosis or other mycobacterial diseases	Tuberculosis		

Table 6.4: Various studies that reported some alternatives to the use of antibiotics as growth promoters

Author	Research Institute	Key findings	
Debnath et al., 2014	(i) College of Veterinary Science and Animal Husbandry, R.K. Nagar, Tripura (ii) R& D team, Ayurvet Ltd., Baddi, Himachal Pradeshh	Assessed the efficacy of the herbal growth promoter product developed by M/s Ayurvet Ltd. Baddi, India, in comparison with antibiotic growth promoters. The product is comprised of the oils of various herbs viz. Allium sativum (Garlic), Zingiber officinale (Ginger), Trigonella foenum graecum (Methi), Eruca sativa (Arugula). 120-day old chicks were assessed. It was reported that the chicks fed with herbal growth promoter at the rate of 500g/tonne basal feed showed much better growth and feed conversion ratio than the control group and others fed with antibiotic growth promoter (Vetclin 112).	
Patel et al., 2016	Sardarkrushinagar Dantiwada Agricultural University, Banaskantha, Gujarat	Studied the efficacy of <i>Emblica officinalis</i> (Amla) fruit powder as a growth promoter in commercial broiler chickens. It was reported that the average body weight of the chickens fed with <i>E. officinalis</i> powder along with basal diet was significantly higher at the end of 6th week. The use of this fruit powder as a growth promoter was also reported to be cost-effective.	
Jayaraman et al., 2017	(i) Kemin Industries South Asia Private Limited, India (ii) West Bengal University of Animal and Fishery Sciences	Compared the growth-promoting efficacy of <i>Bacillus subtilis</i> PB6 in broiler chickens with that of antibiotic growth promoters.	

shrimp has become possible due to the adoption of new technologies, improved feed formulations, and production of specific pathogen-free (SPF) postlarvae. This intensification of farming practices to achieve higher productivity targets often results in disease outbreaks. Thus, in order to mitigate the risk of disease outbreaks, antibiotics are used in aquaculture farms, mainly as chemotherapeutic agents. The list of antibiotics that are reportedly used in the aquaculture sector in India and their status as per the WHO list of Critically Important Antimicrobials for Human Medicine have been shown in Table 6.5.

6.2.2 Incidence of AMR in the aquaculture sector in India

Many studies on the prevalence of AMR bacteria in aquaculture have been conducted by Indian researchers, but many of these studies only discussed the global scenario of AMR in aquaculture, and could not, therefore, be considered for this chapter. The few studies that included primary observations on AMR bacteria and their resistant pattern in both the freshwater and brackish water aquaculture in the country have been considered. The bacterial species that have been mostly reported to develop AMR in aquaculture are E. coli, Vibrio cholerae, V. parahaemolyticus, V. vulnificus, Klebsiella pneumoniae, Salmonella spp., Aeromonas hydrophila, A. caviae, A. enteropelogenes, A. punctata,

- Lack of knowledge of farmers on withdrawal period of antibiotic
- Lacking knowledge in farmers regarding the use of antibiotics on food animals
- Farmers tend to apply antibiotics without maintaining the prescribed doses frequency
- Framers lack knowledge about disposal of dead animals
- Lacking awareness on disposal of farm waste
- Less attention is given by farmers on controlling flies on farms
- Applying antibiotics on food animals for taking preventive measures
- Using antibiotics to prevent secondary bacterial infection occurred during the outbreak of viral diseases
- Farmers are compelled to administer antibiotics for restricting diseases caused by rodents
- Farmers visit uncertified practitioners for treatment of diseased farm animals
- Higher cost of probiotics and prebiotics pushes farmers to use antibiotics on the animal as a growth promoter
- Guidelines are not available to veterinary doctors for proper choice of treating animal disease
- Lack of testing facilities for the antibiotic residue of both domestic and exportable animal foods
- Absence of Government infrastructure to make health care of farm animals accessible to the farmers
- Lacking infrastructural provision of government to develop knowledge on the environmental AMR
- Absence of system for treating waste generated from animal farms and veterinary hospitals

THEMES

Lack of awareness on AMR among farmers

Factors influencing the application of antibiotics in animal farm

Present

Scenario

of

Antimicrobial

Resistance

(AMR)

in

Veterinary

Sector

in India

Absence of current Governance to dealt with AMR

Ways to improve the quality of food animals

- Veterinary doctors should be aided to prescribe antibiotics rationally
- Developing a composite disease surveillance protocol with special attention to AMR
- Need for surveillance of the antibiotic usage in the veterinary sector
- Educating farmers on the optimum utilization of antibiotics in farm management
- Making a change in behaviour amongst stakeholders from antibiotic prescription to usage

Immediate alternatives

- Restriction of OTC sale of antibiotics
- Promotion of composting of farm waste by following CPCB guideline
- Vaccination of animals to prevent disease attack
- Use of low-cost natural ingredients as immunity boosters

infrastructural support in

Figure 6.7: Abstraction matrix of KIIs from veterinary sector

A. aquarorium, Pseudomonas spp., Edwardsiella tarda, Enterococcus faecalis, Staphylococci aureus, S. haemolyticus, S. epidermidis, S. saprophytics, S. intermedius, S. kloosii. Most of the studies reported the AMR bacteria and their resistance pattern the fish or shrimp samples. Only few samples reported AMR in the environmental samples such as water, soil and sediment samples of aquaculture farms. In a study from Kolkata, Abraham (2011) detected AMR bacteria in the fresh water fishes. Two studies from Kerala reported the resistance pattern of different isolates of Vibrio sp. aquaculture products (Sudha et al., 2014; Sony et al., 2021). Some other similar studies from Maharashtra, Tamil Nadu, Rajasthan and Assam also reported the detection of AMR bacteria isolated from fish or shrimp samples (Marathe et al. 2016; Arumugam et al., 2017; Saharan et al., 2019b; Sivaraman et al., 2020; Ramesh and Souissi, 2021). The studies reporting the prevalence of AMR in the environmental samples of aquaculture sector in India, and their key findings have been presented in Table 6.6.

6.2.3 Major gap identified from the scoping review:

 Very few studies have reported antimicrobial resistance in the water and sediment samples taken from aquaculture farms along with the fish/shrimp samples. However, more studies on the impact of ARBs from the aquaculture sector on the environment and on humans are required.

6.2.4 Alternatives to the use of antibiotics in aquaculture farming

The use of antibiotics in the aquaculture sector in India being a significant threat to human health and the environment, there is a need to develop alternative therapies to prevent and control bacterial pathogens. Some potential alternatives are currently being used to develop better management practices as well as sustainable aquaculture. Some of the alternative compounds reported by Patil et al. (2016) and Aich et al. (2018) have been discussed in **Table 6.7**.

6.2.5 Key informant interview (KII)

Based on the gaps identified from the scoping review, key informants' interviews (KII) were conducted at 2 tiers — Tier-I and Tier-II. Tier-I includes aquaculture

Antibiotics	WHO status of Critically Important Antimicrobials for Human Medicine
Amoxicillin	Critically Important
Ampicillin	Critically Important
Amikacin	Critically Important
Azithromycin	Critically mportant
Cephalexin	Highly Important
Chloramphenicol	Highly Important
Ciprofloxacin	Critically Important
Dicloxacillin	Highly Important
Enrofloxacin	Critically Important
Erythromycin	Critically Important
Flumequine	Critically Important
Furazolidone	Important
Gentamicin	Critically Important
Kanamycin	Critically Important
Nalidixic Acid	Critically Important
Nitrofurantoin	Important
Norfloxacin	Critically Important
Oxytetracycline	Highly Important
Penicillin	Critically Important
Rifampicin	Critically Important
Streptomycin	Critically Important
Sulfonamides	Highly Important
Tetracycline	Highly Important
Trimethoprim	Highly Important
Vancomycin	Critically Important

Table 6.5: List of antibiotics used in the aquaculture sector in India, and their WHO status

(Source: Abraham, 2011; Swapna et al., 2012; Joseph et al., 2013; Silvester et al., 2015; Chandra Bhushan et al., 2016; Rahiman et al., 2016; Stalin and Srinivasan, 2016; Arumugam et al., 2017; Singh et al., 2018; Saharan et al., 2019b; Rathore et al., 2020; Narayanan et al., 2020; Sivaraman et al., 2020; Rajan et al., 2021; Ramesh and Souissi, 2021; Sony et al., 2021)

Table 6.6: Incidence of AMR in the aquaculture sector in India

Author & Year	Place of study	Bacterial strain	Bacterial sample collected from	Study findings and resistance pattern
Joseph et al., 2013	Kerala	Aeromonas hydrophila, A. enteropelogenes, A. caviae, A. punctata, and A. aquarorium	Aquaculture products, sediment and water samples from aquafarm	Ampicillin (46.66%), nalidixic acid (20%), tetracycline (6.66%), cotrimoxazole (6.66%) and rifampicin (6.66%).
Silvester et al., 2015	Cochin, Kerala	V. parahaemolyticus	Sediment and water samples of Cochin estuary and water samples from adjoining aquaculture farms	Resistant to Amoxycillin (100%). A high percentage of resistance to ampicillin, sulphamethoxazole, and erythromycin was also observed.
Rahiman et al., 2016	Kerala		Samples from the natural environment included water, sediment, eggs, larvae, postlarvae (PL), and gut samples of M. rosenbergii, and samples from the culture environment included water, sediment, eggs, feed pellets, and gut samples	Bacteria from water samples of natural and culture environments were frequently resistant to ampicillin, erythromycin, and penicillin, while more than 50% of the strains from sediment were resistant to erythromycin, nalidixic acid, and penicillin.
Stalin and Srinivasan, 2016	Tamil Nadu	Vibrio harveyi	Water suspended sediment samples of black tiger shrimp ponds	V. harveyi was resistant to ciprofloxacin, penicillin, and rifampicin,
Singh et al., 2018	Punjab	Vibrio isolates	Soil, water and fish samples from aquafarms	Showed resistance to ampicillin and erythromycin.
Narayanan et al., 2020	Kerala	V. parahaemolyticus	Water, sediment and shrimp samples from aquafarm Cefotaxime (74%), cefoxitin (48 cefepine (44.4%), and ceftazidi (29.6%).	
Rajan et al., 2021	Kerala	Methicillin resistant Staphylococci	Aquaculture farm environment Multi-drug resistance (72.3%), erythromycin (78.7%), norfloxacin and trimethoprim-sulfamethoxace (53.2%), and gentamicin. (34%).	

Table 6.7: A list of potential alternative compounds to antibiotic use in aquaculture

Compound	Description
Probiotics	Innocuous live micro-organisms to avoid bacterial infection. Probiotics that are currently widely used in aquaculture: Lactobacillus spp., Streptococcus spp, Pseudomonas spp., Enterococcus spp., Nitrosomonas spp., Aeromonas spp., Saccharomyces spp., etc.
Prebiotics	Indigestible components present in the diet that are metabolized by specific microorganisms prove to be helpful for the growth of the host. Prebiotics Most commonly used in aquaculture are: fructooligosaccharide (FOS), transgalactooligosaccharide (TOS), inulin, glucooligosaccharide, xylooligosaccharide, isomaltooligosaccharide, soybeanoligosaccharide, polydextrose, and lactosucrose.
Essential oils	A natural volatile liquid extract from plants, that generally has antibacterial, antifungal, insecticidal properties. Most studied essential oils are thymol from thyme and oregano, cinnamaldehyde from cinnamon, and eugenol from the clove.
Phage therapy	Bacteriophages are known as viruses that can infect, multiply and kill susceptible bacteria. Phages have been studied for their therapeutic properties for controlling infectious bacteria.

farmers who are aware of antibiotic use in aquaculture practices, and Tier-II includes Government officers/scientists with knowledge in the relevant domain. The abstraction matrices of both Tier-I and Tier-II of the KIIs have been presented in **Figure 6.8**.

6.3 Possible environmental transmission pathways of AMR bacteria from the veterinary, and aquaculture sectors to humans

Collating all the information from the various literatures and key informant interviews, the possible environmental transmission pathways of ARBs and ARGs from the veterinary, and aquaculture sectors

to humans and vice versa have been shown in **Figure 6.9**

- AMR bacteria from the 3 sectors can be directly transmitted to humans through the consumption of various contaminated food items.
- Poor litter and manure management in veterinary farms can result in direct transmission of ARB to humans through vectors such as flies, which can cause serious health hazards such as cholera, diarrhoea, etc. In addition, the handling of infected animals can result in direct transmission of ARBs to humans.

- The use of litter and manures in agriculture can contaminate the environment (soil and water) with ARBs that can be transmitted to humans. Moreover, ARBs present in crops and vegetables can also be transmitted to humans through food.
- Apart from various other modes of transmission, slaughterhouse wastes can be a potential source of ARBs. Often slaughterhouse wastes containing antibiotic residues and ARBs are used as food for carnivorous fish like Clarias gariepinus in many places in the country. These
- wastes are also used in the lakes and ponds having herbivorous fish, where they enhance the organic matter content, resulting in more phytoplankton production. The consumption of contaminated fish results in the transmission of ARBs to humans through the food chain.
- Again, these ARBs from human reservoirs can be transmitted to the environment through sewage.

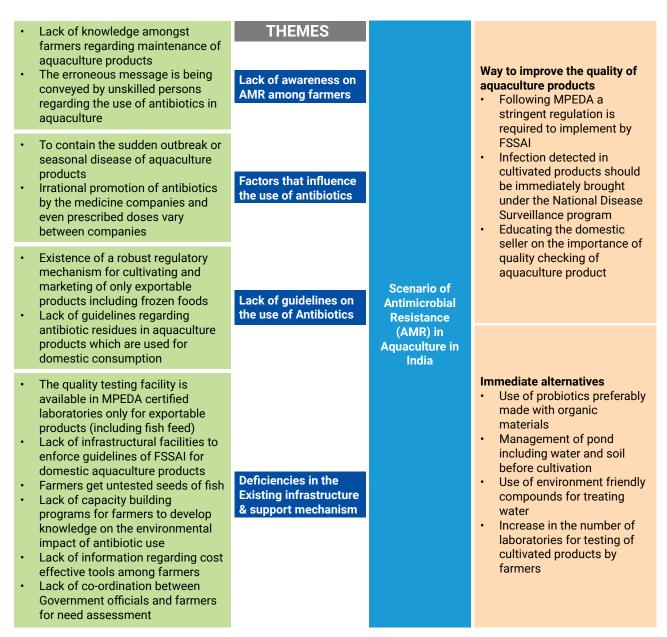


Figure 6.8: Abstraction matrix of KIIs in the aquaculture sector

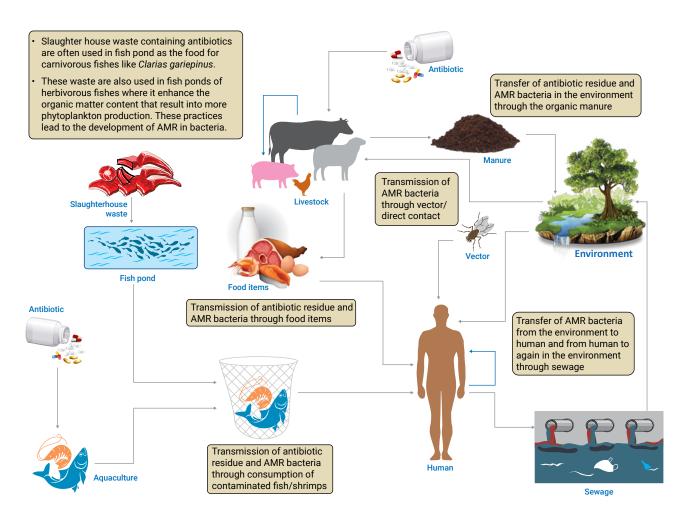


Figure 6.9: Possible environmental transmission pathways of ARBs from the veterinary and aquaculture sectors to humans and vice versa



7 | Antimicrobial contamination of environment by other sectors

7.1 The pharmaceutical industry as a potential source of antibiotic pollution

7.1.1 Overview of antimicrobial discharge related pollution in India

According to the Indian Economic Survey of 2021, the size of the domestic pharmaceutical market is estimated at USD 42 billion. India's pharmaceutical industry supplies over 40% of generics in the USA, and 25% of all medicines in the UK (https://www.ibef.org/ industry/pharmaceutical-india#:~:text=India's%20 domestic%20pharmaceutical%20market%20 is,bio%2Dindustry%2C%20and%20bioinformatics). It is estimated that predominantly available antimicrobials in the international market is manufactured by China and India (WHO, 2015). However, the wastewater effluents from the antibiotic manufacturing units often discharge untreated solid and liquid waste into the environment, leading to the contamination of rivers and lakes by antibiotic residues. The environmental consequences of pharmaceutical manufacturing remain unaddressed, and contribute to widespread reports and concerns about antibiotic pollution. As a result, a number of global procurers of antibiotics have begun to adopt green manufacturing practices. The Nordic countries, for example, have started to include 'sustainable manufacturing' in their selection criteria. Recently in India a collaborative platform known as 'Responsible Antibiotic Manufacturing Platform (RAMP)' has been launched by joint venture of Stockholm International Water Institute (SIWI) and Shawview Consulting with an aim to tackle AMR through reduced emission of antibiotics from the manufacturer.

In 2020, India became the first country to

draft guidelines to monitor antibiotic residues in the environment (Govt. order no. CG-DL-E-27012020-215690 Reg. no. D.L- 33004/99). But these guidelines are yet to be implemented, and there is much debate about the proposed concentration levels to be measured. While there is a growing body of studies by scientists, the industry and the government, on the antimicrobial pollution and its broad environmental consequence, very few studies on the impacts of antibiotic pollution on human and animal health exist.

7.1.2 Major findings from the scoping review of literature on the incidence of AMR in pharmaceutical effluents in India

Recent studies by researchers and scientists have documented high concentrations of antibiotic residues in different rivers across the country (Taneja & Sharma, 2019). The state wise spatial distribution of studies is shown in **Figure 7.1**. The findings have indicated that significantly high amounts of antibiotics (beyond residual limits proposed in Govt. order no. CG-DL-E-27012020-215690 Reg. no. D.L-33004/99) could be detected in the urban waters. The risk quotient (RQ) of urban waters was higher than reported for other Indian rivers. The study also highlighted those metals such as cobalt and manganese appear to induce antibiotic resistant bacteria (ARB) in the environment and is interlinked with resistance development.

The seriousness of this problem has prompted the Green Tribunal to lay down a Green Tribunal pollution order with respect to the pollution of River Musi by the bulk drug and formulation industry and other sources. A monitoring committee report is

https://www.ibef.org/industry/pharmaceutical-india.aspx

¹ **Withdrawal periods** simply denotes the period between the first application of a specific antibiotic in an animal and the fall in its residues in the animal, below the Maximum Residue level (MRL), so that foodstuffs may be produced from those animals. Withdrawal periods should never exceed 28 days for livestock and 500 degree-days for marine products. In the case marine products, the period must be calculated. For example, if the fish is cultured at 20°C, the withdrawal period is 25 days (500/20 =25), i.e., the estimation of withdrawal periods is regulated by environmental conditions.

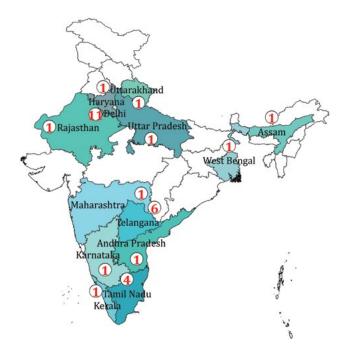


Figure 7.1: Spatial distribution of the number of studies on environmental contamination of resistant bacteria through pharmaceutical effluents

noteworthy in this regard for highlighting remedial action plan on river Musi as received by National Green Tribunal and CPCB (OA No 426 of 2018). Similar case studies have been conducted by other organizations, such as the study of the Sirsa river in Solan by the Veterans Forum for Transparency, and the study of Thane Belapur common effluent treatment plant (CETP), conducted by IIT Mumbai.

Aziz et al. (2018) explored the effluents being discharged into the waters of river Yamuna, Delhi, and their impact on the environment in India. Williams et al. (2019) studied the environmental

effects of wastewaters in Udaipur, which contributed to the water sources around the urban areas in the environment containing up to 1900 ng/L of certain antimicrobials. Bajpai et al. (2019) found nitrates, silica, and selected antimicrobials, including 2 strains of isolated multi-first-line drug resistant microbes in 66.7% of the groundwater samples tested from the various parts of the country. Sakeena et al. (2018) studied the attitudes of healthcare professionals and pharmacists towards pharmaceutical pollution.

Hatha et al. (2020) estimated the virulence-enhancing mechanism of *E. coli*, pathogenic Vibrio sp. and

Table 7.1: Major findings from the scoping review of available literature on the incidence of AMR

Author	Study area	Description and key findings
Dixit et al., 2013	New Delhi, India	Antimicrobial resistance and emergence of New Delhi metallo Beta lactamase. 15% of the sewage samples were found to have resistant bacterial growth. Environmental impact assessment in this context was studied to some extent.
Bengtsson Palme et al., 2014	Hyderabad, India	About 13% of the samples tested were found to be resistant to fluoroquinolones and caused environmental degradation in Hyderabad. The environmental aspect was also addressed.
Skariyachan et al., 2015	Karnataka, India	Elucidated the profiling of fecal coliform. About 44.7% of the coliform bacteria studied were found to have one or more sites of resistance in their genetic constitution, but environmental impact assessment was not carried out.
Taharni et al., 2015	Coimbatore	Studied and evaluated 113 antibiotic-resistant bacteria from pharmaceutical industrial effluents and wastewaters in Coimbatore.
Lubbert et al., 2017	Hyderabad, India	The lack of surveillance and management of wastewater in the environment leading to environmental contamination and development of resistant organisms was reported.

aeromonads due to environmental contamination and cross resistance. A study conducted by Alsan et al. (2018) on the theme of poverty and communityacquired antimicrobial resistance with extended spectrum beta lactamase-producing organisms in Hyderabad, India, found that 7.4% of the samples from urban slum environments had ESBL residues. Another interesting study from West Bengal, conducted by Barbhuiya et al. (2021) found that the maximum concentration of antimicrobials ciprofloxacin and ofloxacin in the wastewater samples of West Bengal were 17.8 µg/L and 3.4 µg/L, respectively, leading to the accumulation of antimicrobial residues in the environment. The minimum inhibitory concentration (MIC) of the bacteria was found to be 25 and 40 μg /L, respectively. The study also demonstrated that human factor-influenced aquatic environment fallouts had residue concentrations up to 35 µg/ ml of Multi drug resistant (MDR), Extensively drug resistant (XDR), and Pan drug resistant (PDR) strains,

with impacts on the biotic and abiotic environments. Figure 7.2 highlights the antimicrobial levels detected in the environmental samples of the bulk drug manufacturing units, sewage treatment plant and Musi River in Hyderabad (Lübbert et al., 2017) and Figure 7.3 depicts the resistance of bacterial strains to some extended spectrum beta lactam antibiotics obtained from industrial waste effluents (Shukla et al., 2021).

7.1.3 Major gaps identified from this scoping review:

- There is a lack of research to link wastewater and groundwater pollution mapping in the environment to pharmaceutical industrial discharge. Although some studies on antibiotic pollution have been conducted, they are restricted to certain cities like Hyderabad, Pune, Delhi, Guwahati, etc.
- The effluent waste discharges from a number

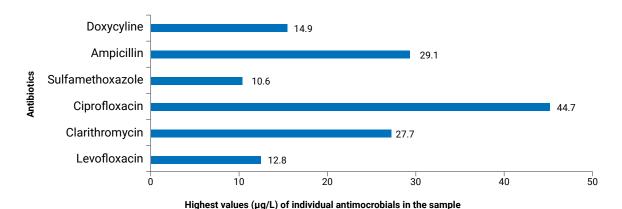


Figure 7.2: Detection of active pharmaceutical ingredients in water samples of the bulk drug manufacturing units, sewage treatment plants and Musi River in Hyderabad.

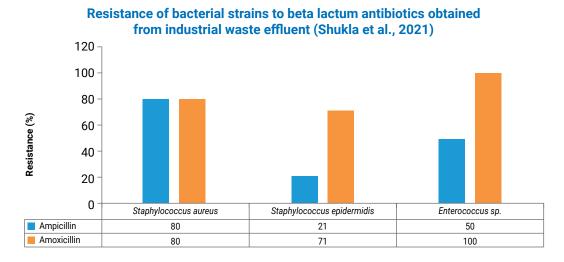


Figure 7.3: Resistance of bacterial strains to some beta lactam antibiotics obtained from industrial waste effluents

of pharmaceutical companies that are involved in manufacturing antibiotics (both API and formulation) is not available in the public domain

- There is no existing research on the extent of environmental impact of the waste produced by the pharmaceutical industry
- There are no universally accepted methods for monitoring antibiotic residues in the environment. The challenge becomes more acute in CETPs, where it is difficult to isolate antibiotics from other waste materials.
- The cost of conducting laboratory tests to measure water samples for the detection of antibiotics is very high, and these tests are difficult to undertake.

7.1.4 Key informant interview (KII)

Interviews were conducted with stakeholders from the pharmaceutical sector for developing the abstraction matrix of KII. The interviews were conducted with stakeholders from 2 tiers — Tier-I (1 medical store owner) and Tier-II (2 scientists and 1 environment officer from a pharma company). The abstraction matrix is presented in **Figure 7.4**.

7.2 Biomedical waste as a potential source of antibiotic pollution in the environment

7.2.1 Background

Biomedical waste (BMW) is any waste produced

following the example of European countries

during the diagnosis, treatment or immunization of human/animal, research activities, in the production or testing of biological elements, and in health camps. BMWs are first characterized, then quantified, segregated, stored, transported, and treated. The basic principle of good BMW practice is based on the concept of reduce, recycle and reuse. The best BMW management (BMWM) methods aim at avoiding generation of waste or recovering as much waste as possible, rather than disposing all of it (Datta et al., 2018; Joshi et al., 2015; Saha et al., 2019; Joshi et al., 2018).

Though only about 10%–25% of BMW is hazardous, it presents physical, chemical, and/or microbiological risk to the general population, healthcare workers, and the environment (Datta et al., 2018). Many Indian studies have found evidence of carbapenemresistant Enterobacteriaceae and New Delhi Metallo-β lactamase-1 (NDM-1), high numbers of colistin-resistant and carbapenem-hydrolyzing Proteobacteria in hospital-generated wastewater. A study conducted in several districts of West Bengal, with water samples from hospital-associated areas (HAA), including untreated hospital wastewater from out-falls to community drains and natural water bodies within hospital premises belonging to 11 government-run hospitals, reported the presence of a high proportion of isolates that were nonsusceptible to the widely-used antibiotics cefotaxime and piperacillin/tazobactam (Bardhan et al., 2020).

THEMES CPCB and SPCBs have strong vigilance, maintenance of database in the server and surprise inspection of plants To prevent groundwater contamination effluent discharged of pharmaceutical industries is being treated following Existing infrastructure to Environmental (Protection) Act, 1986 and MoEF&CC inhibit the spread of AMR quidelines pathogens Outsourcing of solid waste by third party agency Guidelines prescribe for managing expired drugs in medical store, which is checked by regional drug inspectors at a certain interval Need of inclusion Zero liquid discharge in upcoming guideline Felt need of upgradation of Need of provision also in guideline for pretesting of level of present guideline AMR bacteria in discharged water before recycling Industries or plants tend also to reach the level of zero liquid discharge Need of capacity building among pharmacy students and personnel to develop knowledge for containing spread of Scope of improvement in AMR in environment existing infrastructure by Felt need of strengthening QC unit in pharma industries capacity building of personnel

Source: KII of Tier -2 (3) of Pharma Industries

Scopes to curtail

spread of AMR in India through

Pharmaceutical

Industries

Figure 7.4: Abstraction matrix of KIIs in the pharmaceutical sector

Some of the major findings from other India-based studies have been discussed below.

There are several studies on the environmental AMR through bio-medical waste all over the country (Figure 7.5). Diwan et al. (2010) found evidence of antibiotics entering the aquatic environment through hospital effluent and landfills. The disposal of hospital waste is very hazardous, and increases resistant bacteria in the recipient sewers through mechanisms like introduction and selection (Omoni et al., 2015). Being an important part of biomedical wastes, antimicrobials are transmitted into the environment through sewage effluents and landfills, and can cause AMR. A study conducted in a tuberculosis hospital in North India reported that Carbapenem resistant organisms (namely the carbapenamases) are in a high-circulation burden within the human gut, revealing that hospitals are providing an environment for resistance origination and amplification. The magnitude of this problem can be inferred from the results of this study, where a large number of the organisms (62.3%) collected from an effluent treatment plant (ETP) were found to be phenotypically resistant to a carbapenem drug (imipenem), with resistant organisms being found in substantial numbers in both the incoming (48.8%) and outgoing (51.2%) wastewater streams. Moreover, the spread of resistance from around half of the incoming stream organisms (53.8%) to around three-quarters of the outgoing stream organisms (73.3%) further emphasizes the point that resistance amplification does occur in sewage through some kind of gene transfer, possibly horizontal gene transfer (P<0.05). In a similar survey of effluents from several geographically-dispersed wastewater plants in the USA, 20.2% of the isolates were imipenem resistant (Aggarwal, et al., 2020).

Antimicrobial resistant bacteria detected in wastewater can correlate to the antimicrobial resistant bacteria (ARB) causing infections within the facility, but that is not always the case. The fact that hospital effluent almost always mixes with wastewater from the community making it difficult to determine the original source of specific ARGs or resistant bacteria that are received at community wastewater treatment plants (WWTPs). This is particularly challenging in locations where there is a comparatively high prevalence of ARB in the wider human or animal population, or the natural environment.

Clearly defining the root source of antimicrobial-resistant bacteria detected in a given wastewater influent is difficult, and is a knowledge gap in understanding which mitigation measures will be most effective. Similarly, levels of antimicrobials detected in wastewater is not always related with antimicrobial use in the healthcare facility. This is partly because degradation of antimicrobials and survival of bacteria in the environment depends

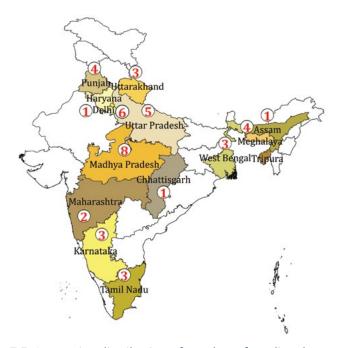


Figure 7.5: State wise distribution of number of studies that reported environmental AMR from bio-medical waste

on several factors. For example, antimicrobial halflives range widely from minutes to tens of days, and survival rates of resistant bacteria are also geographically-dependent and highly variable. The relationship of both antimicrobials and antimicrobialresistant microbes in wastewater also depends on location because there are different environmental temperatures and resistant colonization rates across the globe.

In 2016, the amended BMW rules have created the scope for inclusion of various health camps, such as vaccination camps, blood donation camps, and surgical camps, in the segregation, packaging, transport, and storage of BMW waste. In addition, the healthcare facility (HCF) has to do pre-treatment of various laboratory wastes and blood bags, to decrease chances of infections being transmitted to healthcare workers (HCWs) handling waste at treatment stage, according to guidelines of the WHO and other agencies.

As per the updated rules, plastic bags, gloves, and blood bags have to be phased out within two years to eliminate emissions of dioxins and furans during their burning into the environment. The rules also call for a bar code system for all bags/containers used for BMW treatment and disposal. This step will help in tracking and identifying bags during inspection for quality control and quality assurance. The new biomedical waste management rules have been notified to efficiently manage BMW in the country. In addition, strict rules have been made to ensure no pilferage of recyclables, secondary handling, and inadvertent scattering or spillage by animals during transport from the HCFs to the common BMW treatment facility (CBMWTF). There are presently 198 CBMWTFs in operation in India, 28 of which are under construction. There is a great need for rapid development of many more CBMWTFs to fulfill the need for the treatment and disposal of all BMW generated in India.

However, wastewater-based epidemiological (WBE) surveillance and newer technologies for the treatment of BMW can reduce the development of environmental AMR through BMW. According to the WHO, the global life expectancy is increasing year after year. However, deaths due to infectious disease are increasing. A study conducted by the WHO in 2006 reveals that more than 50,000 people die every day from infectious diseases. One of the major causes for the increase in infectious diseases is improper waste management.

7.2.2 Environmental management system

The environmental management system (EMS) is a broad framework aimed at providing effective direction to an institution in response to changing external and internal factors. The most commonly used technique for the disposal of BMW in India is incineration. It is a controlled combustion process where waste is completely oxidized and harmful microorganisms present in it are destroyed/denatured under high temperature. Datta et al. (2018) reported that countries like Denmark also use waste-to-energy incineration extensively, in localized combined heat and power facilities supporting district heating schemes. The environmental framework or a customized version of it may be adopted to minimize biomedical waste in India.

7.2.3 Incidences of AMR in the bio-medical wastes (BMW) in India

Several authors have studied the AMR bacteria in the bio-medical waste in India have been shown in the **Table 7.2**

Aggarwal et al. (2020) reported the prevalence of carbapenem-resistant organisms in various countries. Hanna et al. (2020) found resistant strains and patterns in the river waters associated with a healthcare facility. **Figure 7.6** illustrates the findings from a study by Bardhan et al. (2020), showing the prevalence of Proteobacteria in waterbodies in West Bengal. Similarly, **Figure 7.7** illustrates the findings from studies reporting resistant strains from BMW facilities.

7.2.4 Major gaps identified from the scoping review

- There is a lack of research linking the antibiotic residues in BMW and their development and subsequent transmission to the environment
- Wastewater-based epidemiological (WBE) surveillance and other newer technologies for treatment of BMWM can reduce the development of environmental AMR through BMW.

7.2.5 Key informant interview (KII)

For developing the abstraction matrix of KII for the biomedical sector, interviews were conducted at 2 tiers — Tier-I (1 respondent from a third-party waste management agency) and Tier-II (2 hospital management personnel and 1 officer from state pollution control board). **Figure 7.8** shows the abstraction matrix.

7.3 Antibiotic-resistant bacteria and genes in water or the environment

7.3.1 An overview of AMR bacteria/genes in water or the aquatic environment:

Antimicrobial resistant bacteria (ARB), antimicrobial resistant genes (ARG), and antibiotics are the 3 major contaminant components responsible for antibiotic resistance in environment, besides the conventional contaminants like PAH, pesticides, and heavy metals. The main source of the abovementioned components is untreated effluents from hospitals, domestic sewage, and the industrial sector (pharmaceuticals). Apart from wastewater, other liquid and solid wastes can also introduce a cause for the release of ARB in the environment. It has already been reported that the majority of antibiotics used are not completely absorbed in human and animal bodies. This helps to increase exposure of microbial communities inside our body and contributes to the

pool of resistant genes among human pathogen (Rutgersson et al., 2014). Various studies have reported Escherichia coli which forms a part of the bacterial commensal flora of the human and animal gut. Furthermore, various factors, such as physicochemical environments, and temporal and seasonal variations are responsible for the transmission of antimicrobial residues from the aquatic environment to the soil or sediment (Diwan et al., 2018). According to some studies, most of the bacteria detected showed resistance to commonly used antibiotics such as ampicillin, amoxicillin, cefixime, tetracycline, polymyxin, ofloxacin, gentamycin, carbapenems and, most importantly, the β -lactam group of antibiotics. It has been predicted that the antibiotic consumption in low-and-middle-income countries (LMICs) will be increase up to 200% by 2030. In the aquatic environment, microorganisms are exposed to multiple drug residues, and their

Table 7.2: Major findings from scoping review of available literature on AMR development from BMW in India

Author	Study area and findings/description
Diwan et al., 2010	Emergence of antibiotic-resistant bacteria in the waters and environment associated with a hospital in Ujjain, India.
Kapoor et al., 2014	Knowledge and awareness regarding BMWM in dental teaching institutes in India
Upadhyay et al., 2015	TEM-mediated extended-spectrum cephalosporin resistance in clinical and environmental isolates of gram-negative bacilli in northeast India.
Sarotra et al., 2016	Healthcare professional training in BMWM at a tertiary care hospital in India.
Aggarwal et al., 2021	Found metallo-beta-lactamase enzyme gene bla_{NDM-1} associated with the Int-1 gene in gram-negative bacteria from the effluent treatment plant of a hospital in Delhi, India.
Bardhan et al., 2020	Depicted prevalence of colistin-resistant, carbapenem-hydrolyzing Proteobacteria in waterbodies in the vicinity of a hospital in West Bengal, India.
Singh et al., 2020	Showed that a structured training on all aspects of BMW can have statistically significant improvement in healthcare workers (HCWs).
Kapoor et al., 2021	Evaluated low-cost phage-based microbial source tracking tools for elucidating human fecal contamination pathways in Kolkata, India. Environmental impact was studied.



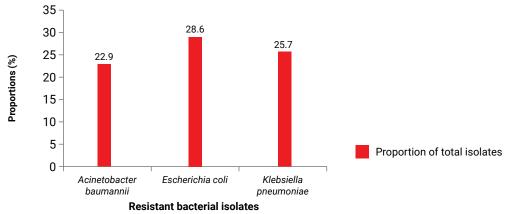


Figure 7.6: Prevalence of Proteobacteria in waterbodies in West Bengal (Bardhan et al., 2020)

Studies reported resistant bacterial strains from Biomedical Waste (n=43) 12 -10 No. of Studies reported resistant bacteria 8 6 4 2 2 0 Escherichia Staphylococcus Klebsiella Acinetobacter Pseudomonas Clostridium Enterobacter difficile coli aureus pneumoniae baimannii aeruginosa cloacae

Figure 7.7: A representation of studies reporting resistant strains from BMW facilities

Resistant Bacteria from dumping site

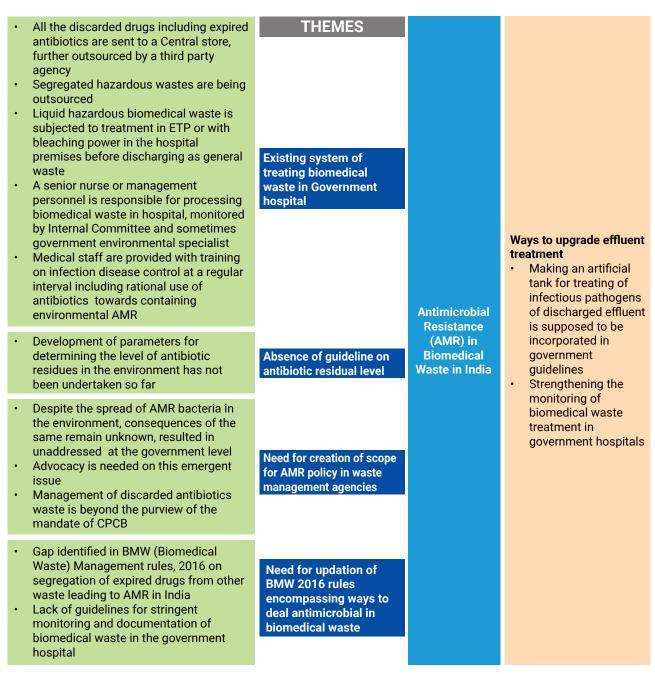


Figure 7.8: Abstraction matrix of KIIs from the biomedical sector

frequent exposure to these residues may lead to mutations and development of new strains. These multidrug resistant (MDR) bacterial inhabitants pose a significant risk of community transmission. Some strains of bacteria have also been found to exhibit resistance to metallic ions in addition to antibiotics (Azam et al., 2016). In a study conducted by Mitchell et al. (2021), the temporal association of AMR among children aged between 1 and 3 years, animals, and water sources, like drinking water sources, household water, and wastewater sources from the same community area of rural India was delineated. After analyzing the stool samples of both humans and animals, and water samples, the authors found a significant relationship between human antibiotic resistance and household drinking water, compared to other sources.

Antibiotic resistant genes (ARGs) are the core group of the structural elements of a resistant bacterium. Usage of antibiotics may accelerate the growth of ARGs in resistant bacteria. Around a hundred varieties of ARGs have been found to decode a broad range of antibiotics which have been found in pathogenic microbes, present not only in hospital and animal husbandry wastewaters but also in sewage, WWTPs, surface water, groundwater, and drinking water.

7.3.2 Sources of antibiotics and the contamination of the aquatic environment

The major sources of environmentally-relevant antibiotics are WWTP influents and effluents, secondarily terrestrial runoffs, and effluents from landfills and farms, including atmospheric deposition. In case of the aquatic environment, ciprofloxacin and fluroquinolones antibiotics are most commonly used, and appear to pose a great risk for aquatic biota and humans. In India, most sections of the pharmaceutical industry discharge a large quantities of effluent containing high levels of broad-spectrum antibiotic, whose residue may develop antibiotic resistant pathogens.

According to Mutiyar & Mittal et al. (2014), ciprofloxacin, and fluoroquinolone groups of antibiotics may cause high risk assessment in waterbodies. It was found that the presence of antibiotic residue in waterbodies may cause high value result in hazardous quotient (HQ) values that are high. The concentrations of HQ present in industrial effluents are higher than other water matrices. When industrial effluents flow into waterbodies, antibiotic residue contained in the effluents may create environmental risk using HQ approach. Studies have

also reported that groundwater also contains high levels of antibiotic residue.

Some studies that tested wastewater samples from different sources like tertiary care hospitals, effluent treatment plant (ETP), and sewage treatment plant (STP), have indicated that E. coli, S. aureus, and P. aeruginosa found in the samples were resistant extended-spectrum β-lactamase fluoroquinolone, extended-spectrum-cephalosporin (ESC), and carbapenem. Apart from this, some isolated strains also showed 100% resistance to lead, zinc and some applied antibiotics. Maximum incidences of metal-antibiotic double resistance exist in Lead + all antibiotic (100%), whereas, copper + penicillin, and nickel + ampicillin showed 95% resistance. In addition, blaNDM gene was also detected, and showed carbapenem resistance (Diwan et al., 2012; Chauhan et al., 2015; Akiba et al., 2016). According to Lubert et al., (2017), insufficient wastewater management by bulk drug manufacturing facilities leads to unprecedented contamination of water resources with antibiotic residue. This study reports that, in a total of 23 environmental samples, 100% of the isolates were ESBL positive, whereas >95% of the isolates showed carbapenem resistance. According to Kumar et al. (2013) and Poonia et al. (2014), isolated E. coli and Klebsiella sp. from water sources showed 17% and 50% and 13% and 72% resistance respectively to the third-generation antibiotic cephalosporin. Marathe et al. (2017) have concluded that the ARGs in river sediment was 30 times higher within the city than the upstream sampling sites. Last-resort antibiotic colistin resistant gene mcr⁻¹ was also detected from the upstream site. There is a strong correlation between the abundance of Acinetobacter and OXA-58 carbapenemase gene (more than 23rd fold higher) and tigecycline resistance gene tet(X) (>206-fold) in the samples.

7.3.3 Representative studies on the presence of antibiotic resistance bacteria in the soil/sediment in India

Natural soil is a diverse pool of bacterial species. The use of untreated wastewater in irrigating soil is the primary reason for the presence of ARGs in soil/sediment. In several studies, an analysis of results was performed as a co-selector of antibiotics resistance, revealing the moderate-to-high concentration of metals like copper, mercury, cadmium, and zinc in the soil, compared to the water environment, soil/sediment is the main reservoir of heavy metal &

antibiotic resistant bacteria (Nguyen et al., 2019). *P. aeruginosa* & *E. faecium* were the most considerable bacteria present in the sediment. Several reports explain that in soil contaminated with heavy metals (most commonly cadmium), there is a significant relation between MDR and metal tolerance.

A study by Bhattacharya et al. (2019), which was mainly focused on the distribution of ARG/ARB in relation to heavy metals / PAH concentration in mangrove sediments, collected sediment samples from the Sundarban estuarine system, that experience huge anthropogenic influence. 18 MDR bacterial strains were isolated from the mangrove estuary. A study by Malik et al. (2011) revealed the resistance mechanism of Pseudomonas spp. against metal and antibiotics in agricultural soil. The authors had collected water samples from different sources like the Yamuna River, wastewater, groundwater, that are used for irrigation purposes. Around 87.5% of isolates were found to be resistant to sulphadiazine, whereas 79.1% were resistant to both ampicillin and erythromycin. It was also found that soil irrigated with groundwater contains fewer metals and antibiotic resistant pathogen, whereas soil irrigated with wastewater and surface water has a high concentration of metals and antibiotic resistant pathogens.

According to a study by Diwan et al. (2018), seasonal variation also plays a vital role in the accumulation of ARBs & ARGs in the sediment. Isolated *E. coli* from sediment showed significant meropenem resistance in the autumn season. The study also revealed that the physico-chemical characteristics of soil may also be responsible for the accumulation of antibiotic residues in the soil. As a result, sulfonamides showed a high value of sorption with respect to the pH concentration of soil.

7.3.4 Major gaps identified from the scoping review:

- WWTPs and STPs generate effluents and sludge. Solid and liquid waste from livestock farms contain significant levels of ARBs and ARGs, and antibiotic residue are released into water bodies without being treated. Such improper waste management and disposal poses a serious threat to human health as well as the environment
- Poor sanitation practices are one of the main causes of environmental AMR
- · At industrial sites, effluents are not monitored

- regularly, to avoid formation of antimicrobial resistant organisms
- There is a lack of knowledge or awareness among the farmers regarding the use of wastewater for irrigation and pisciculture

7.4 Plant agriculture / plant agro-farming

7.4.1 Overview on the usage of antibiotics in the agricultural sector

The purpose of using antibiotics in plant agriculture, over the last few decades, is to control various bacterial diseases. Antibiotics are mixed along with synthetic chemicals to form antibacterial, antifungal compounds. Together, these are commonly known as pesticides, insecticides, fungicides, and herbicides. Globally, plant agriculture most frequently uses antibiotics like streptomycin, oxytetracycline, tetracycline, aminoglycosides, β-lactam, macrolides, and sulphonamides, which may pose a significant risk to the environment. Out of all the above-mentioned antibiotics, streptomycin is the most widely used, followed by oxytetracycline to control fire blight disease in plants in the USA (Taylor et al., 2020). In the Indian subcontinent, farmers use antimicrobials because there are very few formulations of insecticides that can address disease-causing pathogens like rice blast or some other plant disease. In recent times, some good antimicrobials have shown their efficacy against plant diseases like rice blast, and rot disease in potatoes. But the use of these antimicrobial formulations in comparison with market-based pesticides is quite low. Aside from this, the use of organic manure (poultry litter, manure from livestock, etc.) in plant agriculture is another major source of ARB in the agricultural environment (soil, water, and crop), that gets transmitted to humans through the food web. Apart from this, residues and metabolites of antibiotics also contaminate our surrounding environment.

7.4.2 Possible transmission pathways of antimicrobial agents, ARB and ARG from the agroecosystem to the environment:

The agricultural system is critically responsible for transmission of antibiotic resistance mechanism into the environment through different pathways. Depending on seasonal variations, antibiotic dosage is applied to crops. Direct or indirect application of antimicrobials to plant agriculture can create environmental pollution by contaminating agricultural

soil, groundwater, and surface water while it's the residues affect human health (Figure 7.9).

According to the Central Insecticide Board and Registration Committee, Department of Agriculture, Cooperation and Farmers Welfare, under the Ministry of Agriculture and Farmers Welfare (2021), prescribed guideline on the major use of antibiotics added with chemicals formulation to form fungicides and insecticides. Insecticides are used as foliar spray to control diseases like fire blight, citrus canker, bacterial leaf spot, bacterial leaf blight, soft rot and so on (Table 7.3). Similarly, Table 7.4 describes some chemical properties of formulations containing antibiotics and pesticides, thus emphasizing environmental risks.

7.4.3 Scoping review on the use of antimicrobials in plant agriculture

Kalia and Gosal (2011) have conducted a study on the uses of antibiotics along with pesticides in the production of cotton (45% of total pesticides), rice (23% of total pesticides), fruits and vegetables (approximately 8% of total pesticides), cereals, oil, seeds, and pulses (6 -7% of the total pesticides). Indian states such as Haryana, Uttar Pradesh, and Punjab have the highest rates of pesticide consumption in the agriculture sector. A study conducted by Subhas et al. (2017) focused mainly on the state-wise consumption of pesticides per hectare in India. The report of the expert committee of the

Central Insecticide Laboratory (CIL) and the State Pesticide Testing Laboratory (SPTL) has mentioned that a total of 28 antibacterial/antifungal chemical compounds (pesticides) have been banned for manufacturing, import, and use, while 13 pesticides are also restricted, and 8 have been withdrawn. Such a study shows the antibiotic resistance genes at various levels of the ecosystem, due to application of antibiotic-rich manure and spraying of antibiotic onto the crops (Mann et al., 2021).

7.4.4 Gaps identified from the scoping review

There is a lack of awareness among farmers regarding safe application practices of pesticides, their effect on a particular crop, and their environmental impact. It is economically viable for the farmer to administer antimicrobials depending on the incidence of plant diseases and the extent of crop damage. There is no sustainable methodology to remove the existing residues of harmful antibacterial/antifungal agents or pesticides from the soil or agricultural products, and to protect against environmental pollution.

7.4.5 Key informant interview (KII)

For developing the abstraction matrix of KII in the plant agriculture sector, interviews were conducted at the Tier-II (one scientist and one govt. official of agriculture dept.) level only. **Figure 7.10** illustrates the abstraction matrix).

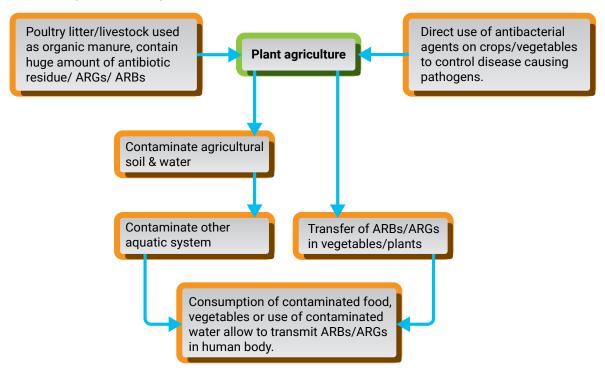


Figure 7.9: The transmission pathway of ARBs/ARGs from plant agriculture to humans or the environment

Table 7.3: Most commonly used antibiotic formulations and pesticides in different crops/vegetables

Antibiotics in combination with chemicals	Applied area	Method of application	
	Fire blight disease of apple	Duly advisable to spray during blossom time	
	Citrus canker of citrus	Sprayed over the foliage and young fruits	
Streptomycin Sulphate 90%+Tetracyclin	Soft rot, bacterial brown wilt, and ring disease of potato	Applied over the seed before planting	
Hydrochloride 10%	Bacterial leaf spot in tomato	Sprayed over the seedlings	
	Bacterial leaf blight in paddy	Applied during seed treatment and seedling treatment.	

(Source: Central Insecticide Board & Registration Committee, Department of Agriculture, Cooperation & Farmers Welfare under the Ministry of Agriculture & Farmers Welfare, 2021)

Table 7.4: Some chemical properties of antibiotics along with pesticides emphasizing environmental risk

Property	Environmental Risk
Mobility	Through leaching, run-off potentiality & volatile properties these compounds are enter into the environment.
Partitioning	Through bioaccumulation & run off from sediment, soil they enter into the environment.
Persistence	Due to biodegradation the antibiotic residue remains persist into the environment.

(Source: Ramakrishnan et al., 2019)

- Enactment of Insecticide Act prohibited importing, selling and manufacturing of unregistered insecticides including antibiotic
- Central Insecticide Board and Registration Committee published periodically a list of fungicides formulation including antibiotics and its time of application
- Framers are guided by government personnel or input dealer on the use of antibiotic formulation highlighted in government guideline
- Having the desire to make more profit or to avoid crop loss due to bacterial diseases, farmers use an overdose of antibiotic
- Farmers are not aware about the economic threshold level of crop failure
- Preponderance of some bacterial diseases amongst some vegetable
- Seasonal attack of bacteria on crops, especially in rainy season
- Availability of fungicides in a form of formulation with antibiotics is likely to increase unnecessary application of antibiotic on crops
- Lack of resources in agriculture extension department to render service more number of framers
- Lacking bacterial disease surveilling mechanism
- Lacking capacity building program on farmers regarding the development of knowledge and use of antibiotics at an optimum level

THEMES

Existing support system to guide farmers in application of antibiotic formulation on crops

Lack of awareness among farmers on use of antibiotic

Factors influences over use of antibiotics on crops

Lack of existing infrastructural & support mechanism

Scope of upgrading existing infrastructural support

- Development of remote sensing and GIS based surveillance mechanism
- Government guideline is needed on bacterial disease control
- Surveillance is needed for diagnosis and management of bacterial disease

Present

Scenario of

Antimicrobial

Resistance

(AMR) in Plant

Agriculture in

India

 Testing of a specific antibiotic formulation on different crops in combination with a range of fungicides, insecticides and fertilizers in various agro-climatic zones

Best practices

- Changing cropping cycle in subsequent years or delaying in the cultivation of a series of crops to reduce the load of a particular pathogen
- Wide application of traditional practice to prevent pest attack
- Extensive use of disease resistant cultivators

Figure 7.10: Abstraction matrix of KIIs from plant agriculture



8 | Policy intervention on AMR in India and its effectiveness

In a developing country like India, the indiscriminate and excessive use of antimicrobials causes environmental antimicrobial resistance (AMR) (Tangcharoensathien et al., 2018). Moreover, the scarcity of good sanitation infrastructure in low-andmiddle-income countries (LMICs) also increase the burden of contagious bacteria in the environment, resulting in a serious condition (Burgmann et al., 2018). As a result, there is a mounting need for the implementation of robust surveillance systems to monitor the prudent use of antibiotics or to substitute the same to lessen the consequences of AMRin India. In line with the different international organizations working on AMR, the Government of India has also taken initiatives to adopt different strategies, encompassing laws, regulations, policies and guidelines, for the sake of preserving human health, animal health, and the environment.

8.1 Guidelines related to public health/human health

Figure 8.1 lists the different programmes and guidelines proposed by the Ministry of Health and Family Welfare (MoH&FW), Government of India, at different points in time to reduce multidrug resistance (MDR) and subsequent morbidity in human beings due to the transmission of AMR bacteria. These initiatives accompanied the implementation of the 'National Programme on AMR Containment' during the 12th five-year plan (2012-2017), developed by the National Centre for Disease Control. To set up a laboratory-based surveillance of AMR, a network has been developed to phase in laboratories, and now includes the laboratories of 30 state medical colleges in 24 states and Union Territories. It also emphasized on monitoring antibiotic use, strengthening infection control, encouraging antibiotic stewardship activities in different healthcare settings, and awarenessgeneration among healthcare providers and the community regarding the rational use of antibiotics (NCDC, 2012). The Antimicrobial Stewardship Programme (AMSP) Guideline, implemented in 2018, (Balaji et al., 2018) aims for a good clinical outcome with less adverse effects of antibiotics. It adopted some strategic measures such as-rationalization of the antibiotic administration at an optimum level, development of standard guidelines for treatment and implementation of antibiotic policies, auditing and streamlining prescription (mentioned the generic name of antibiotics), and improvement of the same through education and administrative actions. The Treatment Guidelines for Antimicrobial Use in Common Syndromes (ICMR), 2019, highlighted the need for the rational application of antibiotics according to the National List of Essential Medicines (NLEM) and developing framework for treating several infectious diseases. It suggested some steps for the prudent utilization of antibiotics - making a clinical diagnosis, limiting explicit antibiotic therapy, having proper knowledge of infection, selecting appropriate antibiotics, not using antibiotics in viral infections, using of antibiotics optimally, and of pharmaco kinetics-pharmaco dynamics (PK-PD) parameters. In the same vein, the National Guidelines for Infection Prevention and Control in Healthcare Facilities was published in 2020 by the National Centre for Disease Control, Directorate General of Health Services, the Ministry of Health and Family Welfare (MoH&FW), which emphasized the need for strengthening of healthcare facilities (HCFs) in India to restrict the spread of AMR pathogens in HCFs in the private and the public sectors. Some essentials of effective execution of infection prevention and control (IPC) guidelines

Guidelines

- National Programme on AMR Containment (NCDC)
- Antimicrobial Stewardship Program (AMSP) Guideline, 2018 (ICMR)
- Treatment guideline for Antimicrobial Use in Common Syndromes (ICMR), 2019
- National Guidelines for Infection Prevention and Control in Healthcare Facilities, 2020 (NCDC)

Figure 8.1: Guidelines on the rational use of antibiotics on human beings in India

include the setting up of the best practices and standards for operating procedures, hiring of trained human resources, ensuring adequate availability of Personal Protective Equipment (PPE), establishing a linkage with the antimicrobial stewardship program (AMSP), and other patient safety programs in the healthcare facility, surveillance system, laboratory support, and environmental protection.

Gaps in the Guidelines

- The AMSP is in the emerging phase as the nationwide utilization of its components have not yet been fully undertaken. There is also an urgent need forusing information technology for monitoring and surveillance, to meet the goal set in India's Nation Action Plan on AMR, 2017 (Sahni et al., 2020)
- Since the Treatment guidelines for Antimicrobial Use in Common Syndromes and the National Guidelines for Infection Prevention and Control in Healthcare Facilities are very recent initiatives, their effectiveness forhuman health as well as their environmental impact are yet to be assessed

8.2 Laws, regulations, policies, action plans and guidelines related to animal health

Some European countries, the USA, and some developed countries in Asia have enforced laws to benchmark antibiotic consumption as a growth promoter, for the sake of human and animal health, as their advanced hygiene practices and modern production systems would be able to sustain productivity. On the other hand, the banning of growth-promoting antibiotics would derail the economic viability of low-income countries (Laxminarayan et al., 2015). According to the report of the Centre for Disease Dynamics & Policy (CDDEP) (2016), the amendments to the Drug and Cosmetics Rules (Figure 8.2) were only enforced by the MoH&FW to restrict the use of antibiotics in food animals. The Gazette of India published G.S.R 28 (E), a guideline

that emphasized labelling withdrawal periods1 on medicine being used for treating animals, in 2012. Moreover, the Drug and Cosmetics Rules enlisted 536 antibiotics under Schedule H (the second amendment, 2006) and made prescription mandatory for the purchase and consumption of antibiotics, which was also applicable for Schedule H1 drugs2 (the fourth amendment, 2013). Another amendment in 2015 firmly prescribed that the advertisement of the drugs enlisted under different Schedule (H, H1, or X) was punishable unless endorsed by the Government. With regard to exportable animal products, the Drugs and Cosmetics Rules, in its 1995 amendment, strictlyprohibited the use of antibiotics such as nitrofurans, chloramphenicol, neomycin, dapsone, sulfamethoxazole, dimetridazole, metronidazole, ronidazole, ipronidazole, and other nitroimidazoles, sulfonamide, fluoroguinolones and glycopeptides in fresh, frozen, and processed fish, hatcheries, and the cultivation of shrimp or other fish, and products of fisheries without the approval of certified veterinary practitioners or specialists in fishery [(S.O. 722 (E) and 1227 (E), respectively, of the Gazette of India)]. It mustalso be mentioned that the amendment of the law in 1997 [S.O. 1037 (E)] limited the residue level of antibiotics like tetracycline, oxytetracycline, trimethoprim, and oxolinic acid in eggs and egg products. Likewise, the Coastal Aquaculture Authority (CAA) Act, 2005, prohibited or banned the application of antibiotics and pharmacologically active substances in shrimp cultivation. Even larval and farm feed, feed additives, chemical substances and drugs, probiotics, fertilizers, immune-stimulants, etc. can be enlisted only when verified as antibiotics free. The enlisted antibiotics as well as pharmacologically active elements banned for shrimp cultivation mentioned in the CAA have been listed below (Table 8.1), and needs to be regulated for farming of other aquaculture products (Guidelines annexed to CAA rules, 2005). The Export Inspection Council (EIC, 2011 and 2019) also executed a residue monitoring plan for conducting surveillance of antibiotics residues in animal food,

¹ **Withdrawal periods** simply denotes the period between the first application of a specific antibiotic in an animal and the fall in its residues in the animal below the Maximum Residue level (MRL), so that the foodstuffs may be produced from those animals. Withdrawal periods should never exceed 28 days for livestock and 500 degree-days for marine products. In the case marine products, the period must be calculated. For example, if the fish is cultured at 20oC, the withdrawal period is 25 days (500/20 =25), i.e., the estimation of withdrawal periods is regulated by environmental conditions.

² **Schedule H1** drugs: alprazolam, buprenorphine, baloflxacin, capreomycin, cefdinir, cefepime, cefditoren, cefetamet, cefoperazone, cefexime, cefotaxime, cefpodoxime, cefpirome, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, chlordiazepoxide, clofazimine, codeine, cycloserine, diazepam, diphenoxylate, doripenem, ertapenem, etambutol hcl, ethinamide, feropenem, gemiflxacin, imipenem, isoniazid, levoflxacin, meropenem, midazolam, moxiflxacin, nitrazepam, pentazocine, pruliflxacin, pyrazinamide, ribabutin, rafampicin, sodium paraminosalicylate.

especially milk and honey, with these measures having come into force in the years 2011-12 and 2019-20, respectively. The surveillance system was assigned for taking some corrective actions if the level of non-compliance by the exporter was found to be surpassing the limited level of antimicrobials. **Table 8.2** contains the list of antimicrobial residues in milk and honey, delineated by the EIC.

The Marine Products Export Development Authority (MPEDA) under Ministry of Commerce and Industry, Government of India, has made it compulsory of testing pre-harvest products before exporting to EU

countries. MPEDA has founded 12 ELISA screening laboratories for testing/screening of aquaculture pre-harvested produce (shrimp) for the presence of residues of banned antibiotics like Chloramphenicol & Nitrofuran Metabolites (AOZ. AMOZ, AHD & SEM). To furtherstrengthen the surveillance mechanism, the National Residue Action Plan, 2019, through which sampling schedule and sampling strategies are drawn every year for monitoring the residues of substances such as Antibacterial / Veterinary Medicinal Products and environmental contaminants, has been undertaken by the MPEDA. Samples collected

Table 8.1: List of Antibiotics and pharmacologically active substances banned by the CAA

Sl. No.	Names of the antibiotics and pharmacologically active substances
1	Chloramphenicol
2	Nitrofurans including: Furaltadone, Furazolidone, Furylfuramide, Nifuratel, Nifuroxime, Nifurprazine, Nitrofurantoin, Nitrofurazone
3	Neomycin
4	Nalidixic acid
5	Sulphamethoxazole
6	Aristolochia spp and preparations thereof
7	Chloroform
8	Chlorpromazine
9	Colchicine
10	Dapsone
11	Dimetridazole
12	Metronidazole
13	Ronidazole
14	Ipronidazole
15	Other nitroimidazoles
16	Clenbuterol
17	Diethylstilbestrol (DES)
18	Sulfonamide drugs (except approved Sulfadimethoxine, Sulfabromomethazine and Sulfaethoxypyridazine)
19	Fluroquinolones
20	Glycopeptides

Table 8.2: List of antimicrobials residue restricted in milk and honey by the Export Inspection Council

Milk (2011-12)	Honey (2019-20)
Sulfonamides, tetracyclines, nitrofurantoin, aminoglycosides, anthelminthic, nitroimidazole, anthelmintic, beta-lactam, doxycycline, enrofloxacin, chloramphenicol, erythromycin, spiramycin, thiamphenicol, tilmicosin, trimethoprim, tylosin	Sulfonamides, tetracyclines, beta- lactam, macrolides, imidazole, dihydrostreptomycin, ciprofloxacin

from hatcheries, feed mills, aquaculture farms and processing plants of coastal areas are tested for the presence of any residue/contaminant.

Figure 8.2 lists some policies introduced by the different ministries and bodies at thestate and national levels in India. In 2011, the MoH&FW introduced the National Policy for Containment of Antimicrobial Resistance to promote the development of suitable protocols for using antibiotics in food animals, inhibit the usage of non-therapeutic antibiotics in animals, food labelling through the formation of an inter-sectoral committee, and also regulated the saleof antibiotics, especially Schedule H1 antibioticsmentioned in the Drugs and Cosmetics Rules, without the consent of registered practitioners (Srivastava, 2011). It also proposed to confine the access to antibiotic strips with colour-coding and higher generation antibiotics like Carbapenems, Daptomycin, Tigecycline to tertiary hospitals. 'The Chennai Declaration (2012) - A Roadmap to Tackle the Challenge of Antimicrobial Resistance Clinical Infectious Disease Society', was an annual conference organized by the Clinical Infectious Diseases Society, which outlined the withdrawal period to minimize the existence of antibiotic residues in milk and meat and the measures needed to evaluate, regulate and monitor the usage of antibiotics and their residues in animal food (Ghafur et al., 2013). The conference also highlighted the need for banning of over-thecounter (OTC) sale of antibiotics. In 2019, apivotal program, namely the National Animal Diseases Control Programme (NADCP) was implemented to focus on controlling Foot & Mouth Disease and Brucellosis among cattle (cattle, buffalo, sheep, goat and pig) through vaccination (Kumar et al., 2021).

Some recommendations were issued by different

governmental bodies in India were also highlighted in the CDDEP report (2016). Three nodal bodies, namely the National Centre for Disease Control, the Central Drugs Standard Control Organizations and the Directorate General of Health Services, under the MoH&FW have recommended putting an end to widespread consumption of antibiotics in animals for non-therapeutic processes. The Bureau of Indian Standards (BIS) proposed discontinuation of antibiotic administration as a growth promoter in poultry feed. Moreover, the Central Drugs Standard Control Organization (CDSCO) emphasized the phasing out of antibiotic application in feed animals, andthestrict application of the Drug and Cosmetic Rules. The guidelines of the Department of Animal Husbandry, Dairying, and Fisheries, under the Ministry of Agriculture & Farmers Welfare, has been indifferent in this regard, suggesting the use of antibiotics only on food animals when prescribed by veterinarians, and discouraging the application of Critically Important Antibiotics for Human Use on animals. It has alsobeen advised that farmers beeducatedso that they may improve farm management practices by incorporating biosecurity. Moreover, the attitudeof different departmental personnel and the stakeholders towards how the prudent use of antibiotics in animals can promote the health of humans, animalsand the environment also varies. The MoH&FW has suggested that the manufacturing, selling and distribution of "Colistin and its formulations for food-producing animals, poultry, aquafarming, and animal feed supplements" be restricted [S.O. 2607 (E)]. The Food Safety and Standards Authority of India (FSSAI) has also recommended a revised list of antibiotics, with restricted usage to reduce environmental AMR though the list of antibiotics

Laws and Regulations

- Amendments to the Drug and Cosmetics Rules in 2006, 2010, 2013 and 2015 regarding consumable animal products (MoH&FW)
- Amendments to the Drug and Cosmetics Rules in 2002 and 2003 (MoH&FW)
- Coastal Aquaculture Authority (CAA) Act 2005 (Ministry of Commerce and Industry)
 - Residue Monitoring Plan by the Export Inspection Council (EIC), 2011 and 2019
- Marine Products Export Development Authority (MPEDA), (Ministry of Commerce and Industry)

Policies and Action Plans

- National Policy for Containment of Antimicrobial Resistance, 2011
- Chennai Declaration (2012) A Roadmap to Tackle the Challange of Antimicrobial Resistance (Clinical Infectious Diseases Society)
- National Animal Disease Control Programme, 2019 (NADCP) (Department of Animal Husbandry & Dairying)

Figure 8.2: Legislations and policies to contain AMR in livestock and animals' products in India

does not includechloramphenicol, doxycycline, nitrofurans and furazolidone. The Central Pollution Control Board (CPCB) has published guidelines on the disposal mechanism of manure and litter of poultry and dairy farmto minimize the effect on the environment, in 2021.

For managing wastesfromdairy farm, the CPCB recommended that untreated waste should not be released to the outer part of the premises, cow dung should be collected at regular interval, and be utilized in vermicomposting, making biogas, dung wood, etc., premises and surroundings should be sanitized and disinfected, following the Biomedical Waste Management Rules, 2016, for the disposal of domestic hazardous wastes, the floor be cleaned, and wastewater be treated, following the prescribed standards of the concerned State Pollution Control Board or Pollution Control Committee (SPCBs/ PCCs). Similarly, the waste from poultry farms must be managed by removing the excreta every alternate day to maintain the dryness of bedding materials, and further utilizing it in composting. The manure should be kept segregated from run-off water and protected from emitting odor. Burial pit,composting or incineration should be used to dispose of dead birds. The CPCB also recommended the dry cleaning of the floor with disinfectant, and the use ofhot water and pressure pump. Covering the farm with nets and provisioning of traps, insecticides, fly-repellents, etc., have also been recommended, to control flies, and trapping glue boards, tracking powder and rodent-proof doors and windows to control rodents. The use of antibiotics in poultry feed should be regulated as per the prescribed guidelines of the Department of Animal Husbandry, Dairying and Fisheries and the MoH&FW and the Drug Controller General of India.

Gap in the laws, regulations, policies, action plans and guidelines

- The enforcement of the CAA, 2005, has not been able to diminish the indiscriminate use of antibiotics (Bhushan et al., 2016)
- The effectiveness of the policies mentioned in Figure 8.2 have not yet been assessed in available literature
- Despite the formulation of all these guidelines, the phasing out of antibiotic application for nontherapeutic practice and the inhibition of the usage of essential antimicrobials for humans

- on animals have not been comprehensively addressed in these advisories
- A lack of interdepartmental co-ordination between the BIS and the FSSAI regarding the recommended list of antibiotics has tended to mislead stakeholders on the application of antibiotics on food animals
- As the administration of antimicrobials is inevitable to sustain the food security and economic viability in a country like India,it is an immediate necessity to assess whether the guidelines are being followed by various stakeholders

8.3 Laws and guidelines related to plant agriculture

To reduce AMR bacteria in the environment, the Government of India is also concerned with the overuse of antibiotic formulation as pesticides in crop production though very few initiatives (Figure 8.3) have been taken so far. The Insecticide Act, 1968, has come into force to prohibit the import, manufacturing and saleof insecticides including some antibiotics like streptomycin and tetracycline, by mandating theregistration of insecticides and the licensing of the concerned persons. Noncompliances might be subjected to suspension of license. The Department of Agriculture, Cooperation and Farmers Welfare, under the aegis of the Ministry of Agriculture and Farmers Welfare, has the mandate to publish plant-specific formulation of pesticides, and changes to the same as and when required. Somerecently published guidelines have prescribed the formulation of fungicides and their combined use, including antibiotic formulation, for specific plants.

Gaps in the laws, regulations and guidelines

Despite the enactment of the law to restrict the manufacture and saleof insecticides, and the publication of guidelines on the use of fungicides, resistant bacteria are still reported in plants. This points to the need to explore the effectiveness of the implementation of the guidelines.

8.4 Laws, regulations and guidelines related to environmental AMR risk reduction

Figure 8.4 list some laws, regulations and guidelines in India, that aim tocurtail the spread of antimicrobial resistant bacteria in the environment. The Ministry of Environment and Forest and Climate Change (MoEF&CC), the Government of India, enforced

Laws and Regulations

The Insecticide Act, 1968

Guidelines

 'Major usage of pesticides (2021)' by the Central Insecticide Board & Registration Committee, the Department of Agriculture, Cooperation & Farmers Welfare, Ministry of Agriculture & Farmers Welfare

Figure 8.3: Legislation, regulations and guidelines to reduce antibiotic use in plant agriculture

Laws and Regulations

- The Environment (Protection) Act, 1986
- · Biomedical Waste (BMW) Management Rules, 2016 (MoEF&CC)

Guidelines

- Antibiotic Residues in the treated effluent of Bulk Drug and Formulation Industry and CETP (MoEF&CC)
- Swachh Bharat Mission, 2014(Ministry of Drinking Water and Sanitation)

Figure 8.4: Legislations, regulation and guidelines for the management of environmental pollutants to curb AMR in India

the Environmental (Protection) Act, 1986 and the Biomedical Waste (BMW) Management Rules, 2016 for the sake of controlling environmental pollution with AMR. In the Environmental (Protection) Act, any kinds of harmful components irrespective of their state (solid, liquid and gaseous), including hazardous chemicals were incorporated as environmental pollutants but there was no such scope to deal with antimicrobial waste. Later on, with the enforcement of the Biomedical Waste Management Rules, the treatment of waste included generation, collection, storage, transportation, treating, disposal, and

handling of all forms of BMW from healthcare facilities, animal houses, veterinary institutions, blood banks, laboratories, ayush, etc.

Apart from the above mentioned laws and regulations, the Ministry of Environment and Forest and Climate Change Guidelines issued in 2020 has set some parameters to monitor the effluents and sludge discharged from pharmaceutical manufacturing plants, with the residual levels of antimicrobials listed in the G.S.R. 44(E) (Antibiotic Residues in the treated effluent of Bulk Drug and formulation industry and

Highlights

MoH&FW implemented the **National Health Policy, 2017**, which recommended restricting overuse of antibiotic medication, prohibiting antibiotics use as a growth promoter in livestock, and auditing of prescription to monitor the antibiotic administration in healthcare facilities and the community.

The Government of India (MoH&FW) endeavoured to introduce a strategic plan of action, namely the National Action Plan on Antimicrobial Resistance in 2017 to prevent and control AMR in a holistic manner following 'One Health' approach of the WHO that could also contribute to the global effort. It also encompassed the AMR burden in livestock, other food animals and premixed feed with a serious consideration for human health and the environment as available data did not adequately reflect the application of antibiotics in animal husbandry. The plan of action adopted several strategic priorities - '(i) improving awareness and understanding of AMR through effective; communication, education and training; (ii) strengthening knowledge and evidence through surveillance; (iii) reducing the incidence of infection through effective infection prevention and control; (iv) optimizing the use of antimicrobial agents in health, animals and food; (v) promoting investments for AMR activities, research and innovations; and (vi) strengthening India's leadership on AMR'. For the successful accomplishment of these priorities, it also developed guidelines of key actions and strategic interventions accordingly and proposed a monitoring and evaluation framework to reinforce the surveillance system of antibiotic administration in animal food and human beings and discharge of antibiotic wastes from farms, factories and veterinary and human health care settings. [This plan of action has witnessed several challenges in accomplishment due to misperception among the stakeholders regarding the use of antibiotics, poor diagnostic infrastructure, lack of direction for preventing environmental contamination occurred from pharma industries, hospital and agricultural waste, hindrance in imposing regulations (Ranjalkar&Chandy, 2019)], which needs to be addressed urgently.

CETP). As improper sanitation, hygiene and waste management are major causes of environmental contamination, leading to the incidence of diarrhea, cholera and other vector-borne diseases in the country, the Ministry of Drinking Water and Sanitation has paid more attention to cleanliness, resulting in the commencement of the Swachh Bharat Mission in 2014 (Guideline for Swachh Bharat Mission, 2017). The guideline focused on the availability of safe drinking water, reduction of open defecation and management of solid and liquid waste (Ministry of Drinking water and Sanitation, 2017).

Gap in the laws, regulations and guidelines

- The segregation and treatment of expired drugs or antibiotic waste are barely present in the mandate of the Biomedical Waste Management Rules, 2016, which resulted in inclining incidents of environmental AMR in India
- The enforcement of permissible levels of residue prescribed by the MoEF&CC Guidelines

- is presently underway, as a result of which its effectiveness cannot yet be assessed
- Zero discharge effluents are yet to be included in the good manufacturing practice of pharmaceutical industries (Mutiyar & Mittal, 2014)

8.5 Strategic Priorities of NAP-AMRvs the environmental AMR scenario in India

Though India has adopted several strategic plans on the National Action Plan on AMR in 2017 based on scoping review, interview of stakeholders and review of the policies it may be assumed that we have only moved few steps and have to cross several milestones to accomplish the goal. From the **Table 8.3** it could be easily understood where we stand at present to combat the environmental AMR.

8.6 Recommendations for environmental mainstreaming as per NAP-AMR strategies

Based on the present study and identified gaps in the different sectors, some major recommendations

Table 8.3: Strategic Priorities of NAP-AMR vs antibiotic use and environmental AMR scenario across different priority domains in India

Strategic	Priority Domains					
Priorities of NAP	Aquaculture	Livestock and Poultry	Plant agriculture	Pharmaceutical Industries	Biomedical waste	
Improve awareness and understanding of AMR through effective communication, education and training	Studies have reported lack of proper knowledge among farmers on maintenance of aquatic animals Consulting certified veterinarians for the treatment of diseased animals is not in practice among the farmers Lack of consciousness among them regarding antibiotic use in culturing aquatic animals Lack of liaison between government officials and farmers	Studies have reported a lack of proper knowledge on antibiotic selection for treatment of diseased animals Lack of awareness among the farmers regarding antibiotic use in livestock There is a tendency among the farmers to not consult certified veterinarians for the treatment of diseased animals	Farmers do not have any knowledge on AMR and the rational use of antibiotics in plant agriculture Lack of knowledge in determining the economic threshold value of the crop failure result in unwise administration of antibiotics	Lack of knowledge, attitude and practice on environmental AMR among different personnel of pharma sectors and other stakeholders	 Educating medical staff on environmental AMR as well as rational use of antibiotics is a prerequisite Strong advocacy is needed for biomedical waste management agencies Lack of multisectoral coordination 	
Strengthen knowledge and evidence through surveillance	Absence of a strong surveillance on antibiotic use and its residue level in consumable domestic products at the farm level Few farmers avail the services oftesting or screening centers Farmers procureuntested seeds of fish	Absence of a strong surveillance on antibiotic use as growth promoter at the farm level Absence of a strong surveillance or monitoring on the antibiotic residues in consumable food animals	Lack of surveillance on AMR bacteria and antibiotic residues in plant agriculture Absence of proper guidelines for the farmers to control bacterial attack on plants	Several innovative methodologies are emerging for measuring antibiotic residues These include mass balance, LC-MS and use of fiber optic sensors These methodologies need to be field tested to assess their viability for adoption	More strong surveillance is required at the place for monitoring biomedical waste segregation and disposal	

Strategic		Priority Domains			
Priorities of NAP	Aquaculture	Livestock and Poultry	Plant agriculture	Pharmaceutical Industries	Biomedical waste
Reduce the incidence of infection through effective infection prevention and control	Incidences of infection and AMR development in aquaculture are being reported from all around the country	Many incidences of infection and AMR development in livestock are being reported from all around the country	Reports on antibiotic use in plant agriculture are very scarce as it is mostly used with insecticide and fungicides Effective infection control mechanism needs to be developed	There are many AMR incidences in pharmaceutical industrial effluent There is a need for pretesting AMR pathogens in discharged effluents from pharma industries There is a need to conduct studies on the impact on humans and animals	Equipped ETP setup needs to be developed at all hospitals to reduce environmental AMR incidences from hospital effluents More care is required to reduce hospital-acquired infections Segregation of expired drugs from other wastes needs more attention in biomedical waste management
Optimize the use of antimicrobial agents in health, animals and food	Given the surveillance of MPEDA, antibiotic use in scientific aquaculture has been optimized in some parts of the country	The use of antibiotics is still not optimized in livestock farming and infection control	The usage of antimicrobials on crops needs to be optimized	Not applicable	Rational Use of Medicines (RUM) by ICMR is in action to optimize pharmacotherapy for promoting human health
Promote investments for AMR activities, research and innovations	Few studies on developing alternatives to antibiotic growth promoter in aquaculture can be found	Few studies on developing alternatives to antibiotic growth promoter in poultry can be found	Application of biosecurity and bacterial disease resistant cultivators have not been widely practiced Change in crop cycling is practiced in very few places	More research and testing of innovative technologies are required to optimize AMR incidences from pharmaceutical effluents Need to work at the factory and CETP levels	Best practices to reduce antibiotic use and treat its waste have not yet been documented More infrastructural facilities are required at the government hospitals to monitor AMR in them
Strengthen India's leadership on AMR	CAA has banned the use of 20 antibiotics and pharmacologically active substances in aquaculture. ICAR, in collaboration with FAO and USAID, has been running a programme called 'Indian Network of Fisheries & Animal Antimicrobial Resistance (INFAAR)'	As per CDDEP report (2015), though many countries have banned antibiotic growth promoters in the livestock sector, India has not yet banned it	Insecticide Act, 1968, restricted the importing, selling and manufacturing of unregistered insecticides including antibiotics Central Insecticide Board and Registration Committee prescribed a list of fungicides and their composition of use with antibiotic	Draft guidelines by MoEF&CC on permissible levels of antibiotic residue for pharma industries need to be enacted Effluents are treated at factory and CETP levels before discharging to prevent the contamination of groundwater and other aquatic ecosystems Develop industry and government capacity for responsible antibiotic manufacturing	Biomedical Waste (BMW) Management Rules, 2016, is now in action

have been listed (**Table 8.4**) against each strategic priority of the NAP-AMR. It may help in further

refinement of the NAP-AMR with more focus on the environmental dimension of AMR.

Table 8.4: Recommendations on the different strategic priorities of NAP-AMR for giving more focus on environmental dimension of AMR

Strategic Priorities of NAP	Recommendations
Improve awareness and understanding of AMR through effective communication, education and training	 Capacity building of State Pollution Control Boards in terms of number of resources and their skillsets to carry out AMR monitoring. Awareness generation amongst the affected communities, e.g., farmers, livestock farm owners/operators on benefits of non-antibiotic growth promoters, adverse impacts of AMR bacteria on livestock health, human health, good practices on disposal of dead animals.
Strengthen knowledge and evidence through surveillance	 Development of guidelines for field testing and monitoring of residual antibiotic in effluent streams – mass balance of antibiotic traces in effluent streams, LC-MS and fiber optic sensor technology. Enhanced and evidence-based surveillance of impacts of presence of residual antibiotics in flora, fauna and among humans.
Reduce the incidence of infection through effective infection prevention and control	 Inclusion of regulations on collection, segregation, handling and treatment of end-of-life antibiotics, residual antibiotics, ARBs, ARGs in environmental effluents in existing environmental rules (e.g., solid waste management and biomedical waste management rules).
Optimize the use of antimicrobial agents in health, animals and food	 Enforceable regulations to ban OTC sale of antibiotics (e.g., prohibitive penal clauses in the regulations). Promote alternatives to antibiotics in livestock and aquaculture.
Promote investments for AMR activities, research and innovations	 Promote enhanced private sector participation (e.g., the pharmaceutical majors, companies with large agriculture value chain etc) in AMR prevention – e.g., developing laboratory testing infrastructure. Introduce Government incentives (e.g., subsidies) on use of non-antibiotic growth promoters. Ensure development of environmental standards for residual levels of antibiotics in different environmental pathways e.g., at the inlet and outlets of CETPs, dischargeable limits at the factory outlets for pharmaceuticals, dead livestock, rural waterbodies in and around livestock farms etc. Ensure development of remediation guidelines for residual antibiotics in both soil and water.
Strengthen India's leadership on AMR	 Strengthen collaborative approaches amongst Department of Environment (State Pollution Control Boards), Department of Animal Husbandry, Dairying, & Fisheries Organizations, Department of Agriculture & Farmer Welfare and Public Health Promote judicious consumer practice as a part of Responsible Antibiotic Manufacturing Platform.

8.7 Alternative or improved practices to reduce environmental AMR

So far, the evidence has indicated that rigorous initiativeshave not yet replaced the administration of antibiotics in human beings and animals. Though existing literature suggest the prudent use of antibiotics (Ying et al., 2017), the consequences of AMRincidencehaveremained unaddressed. However, to promote good health in human beings and the environment, diverse but remarkable mechanisms to minimize the detrimental consequences of antibiotic resistance have been adopted to some extent in different corners of this world. Some shreds of evidence on the same are given below:

 Most of the European Nations (like Sweden, Denmark, the Netherlands, and Germany), the USA, Mexico, New Zealand, Canada, and South Korea have banned the use of antibiotics in animal feed for promoting their growth (Gelband et al., 2015)

- The UK has adopted prophylactic measures to optimize antimicrobial usage (Alayande et al., 2020)
- It was atemporary in practice in countries such as Belgium and Germany to use prescribed doses ofzinc oxide at the juvenile stage of pig farming (Backhans et al., 2015)
- In order to make agriculture sustainable, many countries are making efforts to adopt a new approach of Plant Growth Promoting Rhizobacteria (PGPR) (Gupta et al., 2015) though the wide application of this innovation is yet to be undertaken

With respect to the risk reduction of AMR in the environment, there is an urgent need to develop a

good treatment mechanism in India for managing effluents from the pharmaceutical industry and antibiotic waste discharged from healthcare facilities and communities. Responsible antibiotic manufacturing to reduce AMR requires interventions at the factory and CETP levels to develop and test appropriate monitoring and risk mitigation strategies. Public private partnerships such as the Responsible Antibiotic Manufacturing Platform (RAMP) provide opportunities to work with manufacturers, technology providers, regulators and global procurement agencies to develop integrated solutions to reduce AMR in the environment. Interestingly, some models have been set up by the developed countries, which might be cited to refurbish the existing mechanism of treatingthe effluent discharged in India, though scarcely any system on segregation and process of antibiotic waste from other solid-liquid waste has been exemplified.

- European countries such as Denmark and Germany have implemented WASH (Water, Sanitation and Hygiene) programs and safety plans like Ozonation, use of activated carbon, bio-filters and UV disinfection, and treated effluent discharge of pharmaceutical industries (Nanthakumar et al., 2019)
- On-site inspections and the assessment of manufacturers' dossiers under GMP environmental procedures are practiced in countries like Canada and the USA (FDA, 2018; Health Canada, 2018)
- Under the terms of the Swedish environment criteria, producers have to implement any necessary changes to minimize environmental impact within six months of signing a procurement contract (The Swedish Environmental Protection Agency, 2016)
- The Swedish procurement agreement calls for open dialogue between contractors and suppliers with regard to their control over chemical discharges. It also includes a clause for purchasers to inspect suppliers' facilities either in person or through a third party (The Swedish Environmental Protection Agency, 2016)
- South Asian countries like Thailand are conducting AMR surveillance in the environment, especially along river banks, following the 'One

Health' approach (Juisiri, 2021).

- EU countries like Denmark and Sweden, Australia, and the USA have conducted public health awareness campaigns on the use of antibiotics (Saam et al., 2016)
- Vietnam has executed the cold plasma technique to remove antibiotic residues in the environment (Nguyen et al., 2021)
- In Thailand, treatment of antibiotics in wastewater is practiced using advanced oxidation processes (AOP) (Kurt et al., 2017)
- The Netherlands hasimplemented on-site hospital wastewater systems for surveilling treated hospital effluent quality in order to preserve the environment (Paulus et al., 2019)
- The AMR Industry Alliance has developed the common antibiotic manufacturing framework that provides guidance at the factory level to promote sustainable antibiotic manufacturing practices as well as conduct mass balance calculations to assess levels of antibiotic residues. A majority of global and some Indian generic companies are members of the Alliance, and have begun to implement these guidelines across their factories
- The WHO is developing new guidelines on waste and wastewater management in pharmaceutical manufacturing, with an emphasis on antibiotic production

Despite the introduction and implementation of several laws, regulations, policies and guidelines by the Government of India, their implementation for optimizing consumption of antimicrobials and good management of waste has faced several challenges. There are lacunae in the enforcement of laws and regulations and the implementation of policies and guidelines, which might be considered to further the scope of strengthening existing infrastructure and revise existing guidelines. Further, India needs to adopt some practices that are operational in developed countries as suitable alternatives after analyzing socio-economic conditions and customizing the practices accordingly. This might result in significant in reduction of AMR bacteria in the environment.



9 | Major challenges in containing AMR transmission in the environment

Antimicrobial resistance (AMR) is a complex and multidisciplinary problem for any nation to tackle. The emergence of newer multidrug resistant (MDR) organisms poses newer diagnostic and therapeutic challenges while factors such as poverty, illiteracy, overcrowding, and malnutrition further compound the situation. This more often 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 the lack of proper diagnostic modalities for identifying the pathogen and its drug susceptibility. The environmental aspect of AMR

is also very important for addressing the problem of AMR in India as the environment is inextricably connected to human and animal life in all phases. In the environment the major sources of transmission are the water, soil and waste. AMR bacteria from various sources contaminate the surface water, ground water, soil. Various challenges such as programmatic challenges, technological challenges, institutional challenges and financial challenges ultimately affect these three environmental components. The major challenges identified from the present study and their link with the environmental components have been shown in **Table 9.1**.

Major challenges in containing AMR in the context of environment



Programmatic

- The existing policies on environment do not include aspects of AMR, similarly the health policies do not cover environmental pathways of AMR
- Inadequate regulations on OTC sale of antibiotics
- Inadequate capacity with the environmental regulators (in terms of resources and skill sets) to develop and implement guidelines around prevention of AMR in environmental streams
- Inadequate healthcare infrastructure compared to the magnitude of infections
- Lack of institutional guidelines for rational antibiotic use in healthcare settings.

Water Treatment & Sanitation

 Poor WASH system allows indiscriminate mixing of disposed end of life antibiotics in the effluent streams

Soil Testing and Treatment

- Inadequate soil testing guidelines for detection of residual antibiotics in soil
- No standards around soil remediation for residual antibiotics

Waste handling and Disposal

- Injudicious handling of antibiotics waste in terms of collection, segregation, treatment and disposal
- Poor management of collection, segregation, treatment and disposal of antibiotics in the solid waste/municipal waste



Technological

- Lack of laboratory-based strong surveillance on AMR.
- Methods of measuring traces of antibiotics in different environmental streams, guidelines on allowable thresholds, instrumentation needed for such measurements etc. are either not clearly laid out in any environmental standards or not field tested for validation and large-scale adoption.
- Lack of innovation on cost-effective alternatives to antibiotic growth promoters.
- Lack of technology for attaining Zero liquid discharge of effluents (ZLD) from antibiotic manufacturers.
- Inadequate technical standardization of laboratory cultures and biomarkers to assess the need of antibiotic administration.



Institutional

- Lack of research and development on monitoring systems and containment procedures of AMR in different environmental streams.
- Absence of collaboration amongst Departments of Environment (State Pollution Control Boards), Department of Animal Husbandry, Dairying, & Fisheries Organizations, Department of Agriculture & Farmer Welfare and Department of Public Health
- Inadequate awareness amongst farmers on use and benefits of non-antibiotic growth promoters and adverse impacts of AMR bacteria on human health.



Financial

 Absence of incentivization (e.g., subsidies) mechanism to take up costlier alternatives to antibiotic growth promoters leads to rampant use of antibiotics in livestock and aquaculture sectors

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Action Points

10 | Strengthening mitigation of AMR in the environment

Though resistance is a natural process, antimicrobial use in the human and animal sectors triggers the resistance of bacterial species, resulting in higher mortality, financial crisis in households and healthcare units. All these affect the pace of achieving the Sustainable Development Goals. It is clearly understood that the main reasons behind this petrifying situation is the lack of access to good quality antibiotics, irrational use of it and the lack of public awareness regarding antibiotic consumption. Some surveillance systems have already been adopted by the Government of India for restricting the irrational application of antibiotics on humans and food animals and reducing the load of AMR bacteria in the environment. However, these efforts must be supplemented by awareness-generation amongst stakeholders of different sectors and strengthening infrastructure with maximum utilization of existing resources in an integrated approach.

10.1 Enhancing the understanding and awareness of AMR in India, with an emphasis on the role of the environment

Some possible methods for awareness-generation about AMR among frontline stakeholders like policymakers, antimicrobial prescribers, and users have been listed below:

- Awareness surveys and Knowledge, Attitude and Practice (KAP) studies across different levels of the community are essential to obtain an overview of community perception of environmental AMR
- A community-based approach could be considered as an effective tool for prudent use of antibiotics and good hygiene practices, in which public ownership is essential for advocating for their own health
- The promotion of 'redline campaign' would be helpful in increasing public awareness on antibiotic resistance
- The behavioral and cultural practices of antimicrobial use in the community could be improved through role-play and distribution of

- different kinds of Information, Education and Communication (IEC) materials
- Social networks can play an important role in developing awareness on AMR in public health and the environment
- The media can play a vital role in public awareness campaigning on the emergence of environmental AMR
- Evaluation of awareness interventions is needed to assess the magnitude of knowledge developed among the target groups
- Strengthening antimicrobial stewardship activities could be undertaken to ensure appropriate practicing behavior among the medical practitioners
- Stakeholder analysis on the basis of communication competence of the stakes on the issue of environmental AMR should be prepared before planning an awareness program

10.2 Surveillance on AMR in the environment, humans, animals and foods

Surveillance for the implementation of policies and development of strategic interventions to prevent infectious diseases is indispensable. Estimation of the AMR burden for addressing its consequences and trajectory of developing resistance in human beings, animals is an urgent need in India. Hence, to track the occurrence of AMR, pattern of bacterial mutation in environment, measure the antimicrobial usage and the level of residue in food products, few surveillance systems have been developed in India as explained.

Food and Agriculture Organization (FAO), United States Agency for International Development (USAID) and Indian Council of Agricultural Research (ICAR) have jointly founded a network, namely the Indian Network of Fisheries and Animal Antimicrobial Resistance (INFAAR), in 2018 aiming at identifying AMR in various production systems. It has also conducted an investigation into the spread of resistance to hypothesize the sources of resistant bacteria

(Kumar et al., 2021).

- An information technology enabled system has been set up by the Department of Animal Husbandry and Dairying (DAHD), Ministry of Fisheries, Animal Husbandry and Dairying, Government of India namely Animal Disease Reporting System (NADRS) in 2014 for developing a rigorous reporting mechanism. The objective of the surveillance system is to monitor and collect data on diseases from different areas in India, so that precautionary and remedial action plans could be formulated immediately during disease emergencies (Kumar et al., 2021)
- remote sensing and GIS (Geographic Information System) based surveillance mechanism known as the National Animal Disease Referral Expert System (NADRES), developed by ICAR-NIVEDI (ICAR - National Institute of Veterinary Epidemiology and Disease Informatics) has been assigned for collecting information on animal diseases (like zoonotic diseases) along with associated risk factors from different districts over specific spans of time so that the trend of diseases in livestock could be predicted based on past data for preparing strategic intervention (Kumar et al., 2021)
- To estimate antibiotic resistant bacterial infection in healthcare facilities, ICMR initiated the Antimicrobial Resistance Surveillance and Research Network (AMRSN) in 2013. The AMRSN is a reliable data source providing information on bacterial resistance incidences and pattern, based on which epidemiological improvisation could be set up as a therapeutic strategy. This network focuses on six pathogenic groups Enterobacteriaceae causing sepsis, enteric fever pathogens, gram-negative non-fermenters, gram-positives: staphylococci and enterococci, diarrheagenic bacterial organisms, and fungal pathogens (ICMR, 2013)
- Since 2015, two major national network projects— 'National surveillance Programme for Aquatic Animal Diseases (NSPAAD)' and 'Consortia Research Project on Development of Vaccines and Diagnostics (CRP on V&D)' are being run by ICAR-Central Brackish Water Aquaculture. One of the major objectives of these networks is to monitor infections through regular survey, profiling and study of drugs/chemicals usage in aquaculture,

- covering freshwater, brackish and marine rearing systems (Vijayan, 2016)
- The Directorate of Marketing and Inspection under the Ministry of Agriculture and Farmer Welfare initiated efforts to endorse some producers of animal food like frozen raw meat and eggs by setting up the 'Agricultural Marketing Information Network (AGMARK)', and also measured the level of antibiotic residues in the same (CDDEP Report, 2016).

However, stringent surveillance mechanisms are effectively imposed for only exportable animal foods. Non-compliance is subjected to corrective action like cancellation of consignment of producer. On the other hand, imposing a rigorous monitoring on the use of antimicrobials on the production of domestic animal foods and their residues discharged to the environment is currently not economically viable option in our country. In a similar vein, the antibiotic or antimicrobial consumption in the healthcare setup or households, management of their wastes have not received enough attention in view of environmental antimicrobial pollution.

10.3 Strengthening the regulatory and policy framework for the environmental dimension on AMR, and its enforcement

In India, several regulations and policies for limiting the contamination of AMR bacteria in the environment from different point sources like healthcare facilities, households, industries and farms are in operation. But there is a dearth of studies reviewing these ongoing regulations and policies, except for the National Action Plan on AMR, 2017. Besides that, lack of data in the public domain, indicating lack of transparency, may be a major hindrance in the formulation of policies. Therefore, containing environmental AMR at the earliest is a pressing issue to promote human and environmental health. Population growth in India poses great difficulties for development and the best possible ways for maximizing utilization of existing resources to contain environmental AMR can be categorized under 4 heads - technological intervention, institution approach, programmatic approach and collaborative approach. Moreover, a strong network between several government nodal agencies working across different priority domains must be developed. This could help in generating data for the assessment of the environmental risk of AMR.

10.3.1. Recommendation for Plant agriculture sector

Technological Intervention

- Increasing application of biocontrol agents and bio-pesticides
- Widespread adoption of biosecurity widely
- Cultivating disease resistant cultivators extensively
- Modification in a series of crop cultivation or crop cycling in a few subsequent years

Institutional approach to prioritize the following research areas

- Experimentation on compatibility of specific antibiotics with various fungicides and insecticides, and efficacy on a range of crops, in different soil parameters and agro-climatic zones
- Conducting research on social implications of antibiotic usage and adoption of behavioral interventions
- Research on economically viable practices

Top to Bottom

Programmatic/ Policy approach

- Conducting capacity building programs for farmers on the use of fungicides and insecticides along with the extent of their use
- Pro-activeness of agricultural extension officers to stop malpractices in antibiotic formulation
- Provide subsidy or incentives to encourage farmers to use alternatives to antibiotics
- Recruitment of Microbiologist and Environmentalist in the Department of Agriculture and Farmer Welfare for monitoring AMR bacteria in agriculture samples
- Capacity building of existing resources such as trainers and extension officers in district-level agriculture departments

Coordination

Coordination among the Ministry of Agriculture & Farmer Welfare, Ministry of Environment, Forest & Climate Change and Ministry of Health and Family Welfare

Fai Sta Au

3ottom to Top

Collaboration among the Department of Agriculture & Farmer Welfare, Indian Council of Agricultural Research, State Pollution Control Board, and Food Safety & Standards Authority of India

Multi-disciplinary team including Microbiologist, Environmentalist, Scientist, Trainer, Extension Officers and Policy implementing officers

Farmers' associations

10.3.2 Recommendation for Aquaculture sector

Technological Intervention

- Increase availability of specific pathogen-free seed to avoid pathogen attack
- Develop cost-effective immune stimulants to prevent pathogen attack
- Develop cost-effective waste treatment setup of effluent discharge in all aquaculture farms including hatcheries

Institutional approach to prioritize the following research areas

- Research to develop culture practice to substitute antibiotics from aquaculture system
- More research on AMR in samples from the aquaculture farm environment
- Exploration of the social implications of antibiotic usage and adoption of behavioral intervention
- Assessment of needs for alternate practices along with their economic feasibility

Programmatic/ Policy approach

- Standardization of criteria for the companies producing medicines for aquaculture products
- Execution of strong surveillance by FSSAI to monitor antibiotic residues in the domestically consumed aquaculture products
- Conducting training for farmers on good water quality management, maintaining hygiene in the farm environment the rational application of antibiotics
- Provide subsidy or incentives to encourage the farmers to use alternatives to antibiotics
- Recognition of aquaculture waste as a potential pollutant by the MoEF&CC and undertaking it in its mandate
- Recruitment of Microbiologist and Environmentalist in the Department of Animal Husbandry, Dairying, & Fisheries, and Organizations for analyzing parameters of environmental samples
- Orientation of block-level fisheries officers to develop their awareness on environmental AMR from the aquaculture sector

Collaborative Approach

Coordination among the Ministry of Agriculture & Farmer Welfare, Ministry of Environment, Forests, and Climate Change, Ministry of Jal Shakti and Ministry of Health and Family Welfare

Collaboration among the Department of Agriculture & Farmer Welfare, Indian Council of Agricultural Research, Department of Water Resources, River Development & Ganga Rejuvenation, Central/State Pollution Control Board, Food Safety & Standards Authority of India, Bureau of Indian Standards, Marine Products Export Development Authority, Department of Animal Husbandry, Dairying, & Fisheries Organizations, Centre Drugs Standard Control, etc.

Multi-disciplinary team consisting of state and block-level fisheries officers, Microbiologist, Environmentalist, Scientists, Trainer

Farmers' associations





Top to Bottom

10.3.3 Recommendation for Veterinary sector

Technological Intervention

- Development of low-cost natural ingredients as growth promoters
- Discovery of new vaccines
- Adopting low-cost waste management practices in farms
- After aerobic composting of litters/manures those can be reused by farmers or many other people

Institutional approach to prioritize the following research areas

- There is a need for research to develop cost-effective alternatives to antibiotic growth promoters
- More research on AMR in the samples of the farm environment
- Study on behavioural intervention on stakeholders
- Examination of the social implications of antibiotic usage and on alternative practices

Programmatic/ Policy approach

- · Banning OTC sale of antibiotics
- Educating farmers about the withdrawal period and prescribed dose and frequency of antibiotics
- Appropriate diagnosis of disease and identification of causal factors
- Develop database and surveillance on antibiotic pollution from veterinary hospitals
- Adherence to CPCB guidelines for controlling flies and rodents, waste management, and WASH practices in farms, and disposal of dead animals
- Develop the capacity to stop farmers from unwise disposal of waste and dead animals
- Provisioning AMR in existing disease surveillance mechanisms for diseases in animals
- Formulation of a standard guideline for veterinarians to visit and treat animals at the doorstep of farmers
- Improvisation in government infrastructure for knowledge development of farmers on environmental AMR
- Recruitment of Microbiologists and Environmentalists in the concerned department for monitoring and reporting AMR status in the farm environment
- Provide subsidy or incentives to encourage farmers to use alternatives to antibiotic growth promoters
- Orientation of block-level veterinarians to develop awareness on AMR in the farm environment

Collaborative Approach

Bottom to Top

Coordination among the Ministry of Agriculture & Farmer Welfare, Ministry of Environment, Forest & Climate Change, and Ministry of Health and Family Welfare

Collaboration among the Department of Agriculture & Farmer Welfare, Indian Council of Agricultural Research, Central/State Pollution Control Board, Food Safety & Standards Authority of India, Bureau of Indian Standards, Department of Animal Husbandry, Dairying, & Fisheries Organizations, Centre Drugs Standard Control, Veterinary council, etc.

Multi-disciplinary team consisting of Microbiologist, Environmentalist, Veterinarians, Scientist, Trainer, Extension Officers and Policy implementing officer

Farmers' associations

10.3.4 Recommendation for Biomedical sector

Technological Intervention

- Functioning of ETPs at hospitals with periodic assessment and reporting of antimicrobial residue
- Recording and analyzing data on usage of antimicrobials and AMR cases in hospitals
- · Discovery of new vaccines
- Effective WASH intervention in overcrowded communities
- Segregation of rejected antibiotic waste from other solid or liquid waste in households

Institutional approach to prioritize the following research areas

Top to Bottom

- There is a need to examine all the facets of AMSP
- Research for measuring the magnitude of antibiotic pollution from the biomedical sector
- Research for strengthening monitoring tools for regulating AMR organisms and antibiotic residues

Programmatic/ Policy approach

- Formulation of proper guideline for segregation of antibiotics from the solid waste/municipal waste and proper disposal
- Rigorous behavioral intervention at household level for disposal of expired medicines
- Developing a surveillance mechanism for checking contamination of drinking water
- Framing of antibiotic stewardship plans for healthcare settings
- Investing on the advancement of diagnosis infrastructure for early identification of infection
- Following the existing guidelines in auditing of prescriptions in healthcare settings
- Evaluation of the effectiveness of the Infection Control committee in hospitals
- Maintenance of hygiene in hospital premises and surrounding areas
- Conducting KAP on pharmacist and healthcare providers
- Recruitment of Microbiologist and Environmentalist for monitoring magnitude of AMR in hospital environments
- Revision of existing policies and formulation of new ones with special emphasis on AMR containment

Collaborative Approach

Bottom to Top

Coordination among the Ministry of Environment, Forest & Climate Change, Ministry of Health and Family Welfare and Ministry of Drinking Water and Sanitation

Collaboration among Central/State Pollution Control Board, Indian Council of Medical Research, Public Health Engineering Department, Drug Control General of India. etc.

Multi-disciplinary team consisting of Microbiologist, Environmentalist, Hospital personnel, Drug Inspector, Scientist, Engineers and Policy implementing officer

Community Health Workers and Community leaders

Top to Bottom t, or,

10.3.5 Recommendation for Pharmaceutical Industries

Technological Intervention

- Development of measuring tools for the level of AMR bacteria in wastewaters
- Monitoring antibiotic residues including mass balance calculations, LC-MS and fiber optic sensor technology need to be field tested at the factory and CETP levels
- Good technology for manufacturing pharmaceutical products with a reduced amount of antibiotic residue, preferably zero level discharge into the environment should be developed
- The Effluent Treatment Plant (ETP) of pharmaceutical industries needs to incorporate the provision of measuring the level of AMR bacteria before recycling the water

Institutional approach to prioritize the following research areas

Measuring the magnitude of antibiotic pollution in pharmaceutical waste in different areas of India

Top to Bottom

Programmatic/ Policy approach

- Formulation of government guidelines for monitoring antibiotic residues in the environment and building the capacity of industry, and the need to develop robust, transparent and cost-effective monitoring infrastructure including lab testing, etc.at SPCBs
- Promotion of pharma companies transitioning towards sustainable antibiotic manufacturing practices
- Promotion of research on ethno-veterinary antibiotics to monitor their unique contributions to AMR.
- Central and state level support to the domestic industry, especially the small manufacturers that lack the resources to become environmentally sustainable.
- Innovative and cost-effective solutions need to be developed for widespread adoption. These include easy and inexpensive process in place of more capital-intensive solutions.
- The lessons learnt from the factory and CETP levels in reducing AMR through good antibiotic manufacturing practices can be leveraged to design the state AMR action plans

Collaborative Approach

Coordination among the Ministry of Environment, Forest & Climate Change, Ministry of Health and Family Welfare and Ministry of Drinking Water and Sanitation

Collaboration among Central/State Pollution Control Board, Indian Council of Medical Research, Pharmaceutical Export Promotion Council of India, Drug Control General of India, Public Health Engineering (PHE) Department, etc.

Multi-disciplinary team consisting of Microbiologist, Environmentalist, Drug Inspector, Scientist, Engineers of PHE and Policy implementing officer

Group of Representatives of pharma companies

10.4 The way forward

3ottom to Top

Though public health status is an important national indicator, the allocation of funds for executing national policies tomanage health-related schemes is sometimes difficult as healthcare comes under the purview of the state government. Therefore, coordination between the states and the Centre is essential for addressing the issue of AMR, necessitating the formation of specific committees with representation from the different governmental departments, practitioners, farmers' associations, and respective institutes for addressing the knowledge gaps from the ground level (practitioners and farmers) to the higher level (policymakers). In the same manner, policies formulated at the higher level

can percolate to the ground level. As the 'One health' approach requires the interlinking of human, animal, and environmental health, a steering committee governed by a national-level administrator, with representation from sector-specific committees to address their issues and develop appropriate policy intervention and governance, have to be established. However, the policies should focus on the following action points, categorised as 'short-term' and 'long-term'.

Collectively, these approaches can lead us in strengthening India's leadership in containing environmental AMR as well as achieving AMR stewardship (Figure 10.1).

The short-term action points include:



Institutional and regulatory strengthening for improved effluent treatment and handling in sectors



Inclusion of Residual
Antibiotic Management
in Environmental policies
and guidelines from the
perspective of both
manufacturing and use
of antibiotics



Provision of subsidies or incentives to farmers for encouraging them to adopt alternatives to antibiotic growth promoters



Enhanced participation
of pharmaceutical
companies towards
sustainable antibiotic
manufacturing practices

The long-term action points include:

Rational use of antibiotics both in humans and animals



Multisectoral engagement for tracking and collection of AMR data from human health, animal health and the environment, using the 'One Health' approach



Development of strong surveillance to monitor the antibiotic residues and transmission of AMR bacteria from healthcare facilities, pharmaceutical effluents, food animals, water etc.



Promotion of more research and technological innovation to optimize the use of antibiotics in certain sectors as well as to reduce the incidence of AMR



Making the engagement of microbiologists and environmental specialists in the sectors contributing to environmental AMR mandatory, for time-to-time monitoring and reporting of the resistance patterns of the different bacteria in the environmental samples



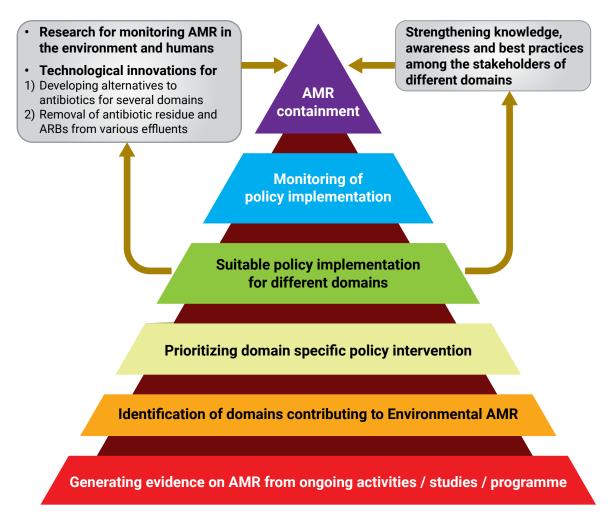


Figure 10.1: Suggested approaches towards containing the environmental AMR in India



Conclusion

11 | Limitations of the present study and Conclusion

11.1 Limitations of the study

There are a few limitations of the scoping review.

- The literatures were obtained from Google Scholar and PubMed where most of our desired literature is available. So, some studies that are not available on these domains may have been missed out.
- Due to present COVID scenario, the key informants from different states were interviewed either telephonically or virtually. Moreover, owing to the time constraints, the KIIs were conducted on a sectorial basis (e.g., pharmaceutical, biomedical, aquaculture, poultry and livestock sectors) rather than the ecosystem-wise (e.g., mountain region, industrial region, coastal region, forest, etc.) which was planned initially.

11.2 Conclusion

This robust report generated through deep diving into the dimensions of 'One health', envisages overall cognizance of the policy decision makers about the scope of emerging AMR in the human health, animal health, and its impact on the environment.

Key points and action plans as enumerated in the report are as follows:

- Effluents containing antibiotic residues from pharmaceuticals and healthcare facilities, expired drugs, excreta from households, manures and litters from livestock are responsible for the pollution of the environment (water and soil) with Antimicrobial Resistant Bacteria (ARB), Resistance Genes (RGs) (not resistant) and antimicrobial residues.
- Use of antibiotics in aquaculture and plant agriculture directly causes water and soil pollution resulting in the development of antibiotic resistance among bacteria found in the environment.

- Since environmental policies do not include components of AMR and health policies do not focus on environmental dimensions on the development of AMR, this important issue needs to be addressed on urgent basis for development of action plan and policy at the national level.
- Methods need to be adopted to measure traces of antibiotics in various environmental samples and guidelines should be developed on minimum allowable thresholds of Antibiotics.
- Instrumentation required for such exercise should be identified and systematically tested in the field for validation and large-scale implementation.
- Alternatives to antibiotics need to be identified as growth promoters which should be distributed through subsidized price & incentivization of the available alternatives.
- The sector-specific recommendations mentioned in this report would serve as the guidelines for conducting future research and innovations targeted towards development of indigenous cost-effective measures further bolstered by the knowledge obtained from best practices of other nations.
- A paradigm shift is warranted to modify the existing Acts & guidelines through development of suitable policy governance documents addressing the need of the six pillars of the National Action Plan on AMR protecting the environment and averting the public health threats of AMR.
- Finally, the present report is expected to provide directives towards adopting future strategies, focusing investment and identifying leadership for containment of AMR at the national level.



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ANNEXURE

Notable Research Institutes working on the Environmental aspects of AMR in India

SI.	Institute	Location	Research domain	
1.	IIT, Hyderabad	Hyderabad, Telangana	Biomedical waste, pharma effluents	
2.	Manipal Academy of Higher Education	Manipal, Karnataka	Biomedical waste, pharma effluents	
3.	Swami Rama Himalayan University	Dehradun, Uttarakhand	Pharma effluents, groundwater	
4.	Manipal University	Manipal, Karnataka	Pharma effluents. groundwater, biomedical waste	
5.	IIT, Delhi	New Delhi	Pharma effluents. groundwater, biomedical waste, riverine environment	
6.	Dr. NGP Arts and Science College	Coimbatore, Tamil Nadu	Pharma effluents. Groundwater	
7.	Jamia Milia Islamia, New Delhi	New Delhi	Pharma effluents.groundwater, riverine environment	
8.	IIT, Gandhinagar	Gandhinagar, Gujrat	Pharma effluents. groundwater, waste water effluent, influents and effluents from Sewage Treatment Plant	
9.	Department of Pharmacology, Vallabbhai Patel Chest Institute	New Delhi	Pharma effluents, biomedical waste	
10.	Cochin University of Science and Technology	Kochi, Kerala	Pharma effluents. Groundwater aquaculture environment, riverine sediment	
11.	Jagannath Gupta Institute of Engineering & Technology	Udaipur, Rajasthan	Pharma effluents, groundwater, aquatic environment, riverine sediment	
12.	The foundation for Medical Research	Pune, Maharashtra	Biomedical waste, pharma effluents	
13	Amity University	New Delhi, Uttar Pradesh	Pharma effluents. groundwater, aquatic environment, riverine sediment, effluent water and household sewage	
14	IIEST, Shibpur	West Bengal	Groundwater, aquatic environment	
15.	National Environmental Engineering Research Institute (CSIR-NEERI)	Nagpur, Maharashtra	Groundwater, aquatic environment	
16.	Alagappa University	Tamil Nadu	Aquaculture environment, river basin area	
17.	Guru Angad Dev Veterinary and Animal Sciences University	Punjab	Aquaculture environment	
18.	ICAR-Central Institute of Fisheries Technology	Kerala	Aquaculture environment	
19.	ICAR-Indian Veterinary Research Institute (ICAR-IVRI)	Uttar Pradesh	Slaughterhouse environment	
20.	Indian Council of Agricultural Research	New Delhi	Slaughterhouse environment	
21.	Central Avian Research Institute	Izatnagar, UP	Poultry environment	
22.	M. J. P. Rohilkhand University	Bareilly, UP	Poultry environment	
23.	Salim Ali Centre for Ornithology and Natural History	Coimbatore, Tamil Nadu	Poultry environment	
24.	College of Veterinary and Animal Sciences	Kerala, India	Slaughterhouse environment	
25.	National Institute of Tuberculosis and Respiratory Diseases	New Delhi	Biomedical waste, pharma effluents	
26.	National Institute of Biomedical Genomics	Kalyani, West Bengal	Pharma effluents, groundwater aquatic environment, rivering sediment	

27.	ICMR National Institute of Cholera and Enteric Diseases	Kolkata, West Bengal	Potable water
28.	Government Medical College Hospital	Chandigarh	Biomedical waste
29.	Post-Graduate Institute of Medical Education and Research	Chandigarh	Groundwater, biomedical waste
30.	R.D. Gardi Medical College	Ujjain, Madhya Pradesh	Pharma effluents. groundwater, biomedical waste, riverine environment
31.	Agartala Government Medical College	Agartala, Tripura	Biomedical waste
32.	Pt Ravishankar Shukla University	Raipur, Chhattisgarh	Biomedical waste
33.	AIIMS, Rishikesh	Rishikesh, Uttarakhand	Biomedical waste
34.	J.S.S University	Mysuru, Karnataka	Biomedical waste
35.	King George's Medical University	Lucknow, Uttar Pradesh	Biomedical waste
36.	Postgraduate Institute of Medical Sciences and Research	Bengaluru	Biomedical waste
37.	Yenepoya Medical College	Mangalore, Karnataka	Biomedical waste
38.	University of Delhi	New Delhi	Biomedical waste
39.	NEHU, Meghalaya	Shillong, Meghalaya	Biomedical waste
40.	Maulana Azad Medical College	New Delhi	Biomedical waste
41.	Indian Statistical Institute, North East Centre	Assam	Groundwater, biomedical waste
42.	Jawaharlal Nehru University	New Delhi	Biomedical waste, riverine water
43.	Kongu Engineering College,	Tamil Nadu.	Pharma effluents. groundwater, biomedical waste
44.	Aligarh Muslim University	Aligarh	Ground water, riverine environment, agricultural soil
45.	University of Madras	Chennai	Riverine environment, waste water from Sewage Treatment Plant
46.	University of Patna	Patna	Riverine environment, waste water from Sewage Treatment Plant
47.	University of Calcutta	Kolkata	Riverine sediment
48.	CSIR-National Chemical Laboratory (NCL)	Pune	Surface water
49.	NGM college	Tamil Nadu	River Basin area
50.	Academy of Scientific and Innovative Research	Ghaziabad	Surface water
51.	Jamal Mohamed College	Tamil Nadu	Riverine environment
52.	Pune University	Pune	Riverine environment
53.	Defence Research Laboratory	Assam	Riverine environment
54.	DRDO	New Delhi	Riverine environment
55.	Sri Krishnadevaraya University	Hyderabad	Plant agriculture
56.	Savitribai Phule Pune University	Pune	Riverine sediment
57.	Sikkim Manipal University	Sikkim	Springs, Surface water
58.	Banaras Hindu University	Varanasi	Riverine sediment
59.	National Centre for Cell Science	Pune	Sediment, river, soil
60.	Dayananda Sagar Institutions	Karnataka	Riverine environment
61.	Bharathidasan University	Tamil Nadu	Riverine sediment
62.	Gurucharan College	Assam	Agricultural soil
63.	Punjab Agricultural University	Ludhiana	Agricultural soil
64.	Deenbandhu Chhotu Ram University of Science and Technology	Haryana	Agricultural soil





ICMR-National Institute of Cholera and Enteric Diseases (ICMR-NICED) Indian Council of Medical Research

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