MENACE OF
ANTIBIOTIC POLLUTION
IN INDIAN RIVERS

Report by Toxics Link
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About Toxics Link

Toxics Link is an Indian environmental research and advocacy organization set up in 1996, engaged in disseminating information to help strengthen the campaign against toxics pollution, provide cleaner alternatives and bring together groups and people affected by this problem. Toxics Link’s Mission Statement - “Working together for environmental justice and freedom from toxics. We have taken upon ourselves to collect and share both information about the sources and the dangers of poisons in our environment and bodies, and information about clean and sustainable alternatives for India and the rest of the world.” Toxics Link has unique expertise in areas of hazardous, medical, and municipal wastes, international waste trade, and the emerging issues of pesticides, Persistent Organic Pollutants (POPs), hazardous heavy metal contamination etc., from the environment and public health point of view. We have successfully implemented various best practices and have brought in policy changes in the aforementioned areas apart from creating awareness among several stakeholder groups.

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# Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
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<tr>
<td>ARB</td>
<td>Antibiotic-resistant bacteria</td>
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<td>ARG</td>
<td>Antibiotic-resistant gene</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>SDG</td>
<td>Sustainable Development Goal</td>
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<td>WWTP</td>
<td>Wastewater treatment plant</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Cooperation and Development</td>
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<tr>
<td>ETP</td>
<td>Effluent treatment plant</td>
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<td>CETP</td>
<td>Common effluent treatment plant</td>
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<tr>
<td>NGT</td>
<td>National Green Tribunal</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>SAICM</td>
<td>Strategic Approach to International Chemicals Management</td>
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<td>MoHFW</td>
<td>Ministry of Health and Family Welfare</td>
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<tr>
<td>NCDC</td>
<td>National Centre for Disease Control</td>
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<tr>
<td>MoEF&amp;CC</td>
<td>Ministry of Environment, Forest and Climate Change</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid Chromatography-Mass Spectrometry</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of Quantification</td>
</tr>
<tr>
<td>PNEC</td>
<td>Predicted No-Effect Concentration</td>
</tr>
<tr>
<td>BQL</td>
<td>Below Quantification Limit</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>CPCB</td>
<td>Central Pollution Control Board</td>
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Antibiotics are important life-saving medicines and play a key role in the well being of human health. However, the unsustainable manufacturing processes coupled with indiscriminate use have given rise to antibiotic pollution in various environmental matrices. This has led to the emergence of growing global threat of Anti-Microbial Resistance (AMR). Widespread antibiotic pollution violates people’s right to a healthy environment, including their access to clean water. It further threatens their fundamental right to life through long-term exposure to antibiotic residues that are released into the environment. Therefore, the international bodies, including WHO and UNEP have recognised this threat of antibiotic pollution and call for collective efforts to minimize the risks associated with AMR.

Incidentally, India being one of the major users and producers of antibiotics in the world has resulted in the rising threat of AMR. In 2016, Mr. Narendra Modi, Honorable Prime Minister of India reiterated that “The discovery of antibiotics had dramatically revolutionized the treatment of communicable diseases in the 20th century, but their indiscriminate use is now leading the world into a situation where life-saving formulations are progressively losing their efficacy. India recognizes anti-microbial resistance as one of the major global threats to public health. We are committed to prevent, contain and combat anti-microbial resistance.” Following this, the Indian Ministry of Health and Family Welfare published the National Action Plan for containing AMR in April 2017. The Department of Biotechnology, Ministry of Science and Technology, Government of India, has also focused on antibiotics and AMR in its vision document “National Biotechnology Development Strategy [2020-25].” In early 2020, the Union Ministry of Environment, Forest and Climate Change (MoEF&CC) also put out the draft standards for antibiotic residues in the treated effluents from the pharmaceutical industry.

Toxics Link also had conducted an indicative study in 2019-2020, to assess the possible impacts of the effluents being released from the pharmaceutical units in Baddi-Nalagarh industrial zone, Himachal Pradesh, India. The samples collected from the effluent revealed high Ciprofloxacin (antibiotic) concentration. That study raised a larger issue of the magnitude of antibiotic pollution in Indian rivers. In recent years, there has been an increasing concern about the risk of antibiotic residues in the aquatic environment globally. However, data regarding the contamination and distribution of antibiotics in Indian rivers is limited. In this context, Toxics Link came up with the present research study to highlight the presence of antibiotics in some of the Indian rivers. The report aims to trigger more large-scale nationwide studies on the occurrence of antibiotics in the aquatic environment including their contribution to rising AMR in the country. This report can also serve as a basis for better understanding of antibiotic pollution situation in India and highlights the need to establish sustainable practices at every stage of the supply chain.
Between 2000 and 2015, global antibiotic consumption in humans increased by 65%.

Between 2017 and 2030, global antibiotic consumption in animals is expected to increase by 11.5%.
Antibiotics are a class of pharmaceuticals compounds that represent one of the major discoveries of the last century that changed the treatment of a wide range of infections in a significant way.¹ They have been extensively used for human and veterinary applications and their benefits have also been recognized in agriculture, aquaculture, beekeeping and livestock as growth promoters. Global antibiotic consumption in humans increased by 65% between 2000 and 2015, whereas consumption in animals is expected to increase by 11.5% between 2017 and 2030.²

Thus, the use of antibiotics has grown multiple folds in the last few years. However, poor management of antibiotics at all the phases of antibiotic lifecycle from design and production through use to disposal has led to antibiotic residues being increasingly found in terrestrial, freshwater, and marine environment. This has led to an exposure of bacterial communities and ecosystems to a large number of antibiotic residues, also resulting in an emerging public health concern of Antimicrobial Resistance (AMR).
1.1 RELEASE OF ANTIBIOTICS INTO THE ENVIRONMENT

There are multiple sources of antibiotic release into the environment. Effluents from antibiotic manufacturing, hospitals and municipalities, waste from large-scale animal farms and its use in aquaculture are the major sources of antibiotic pollution in the environment. Antibiotics used in animal and human therapy also reach the environment through urine and excreta. About 40–90% (depending on the class of drugs) of the administered antibiotic dose is excreted in the feces and urine as parent compound. Large amounts of antibiotics used in animal farming can lead to the contamination of agro-ecosystems through the application of contaminated manure on agricultural lands as fertilizer and the irrigation of crops with wastewater, leading to direct contamination of the environment with antibiotic residues. With no standardisation or mandatory testing of the end product, the largely locally-produced manure and compost products that are used on a large-scale as fertilizers may contain antibiotic residues. In addition, the improper disposal of unused medicinal products can lead to the discharge of antibiotic residues into the sewage systems.

1.2 ENVIRONMENTAL RISKS OF ANTIBIOTICS

Antibiotic residues in the environment can have negative effects on biota and on human health by consumption of contaminated food and water and by contribution to the development and/or dissemination of AMR in different compartments of the environment. When the antibiotics are present in microbial system, it may lead to genetic or mutational changes in normally sensitive bacteria, allowing the bacteria to survive and further proliferate as antibiotic resistant bacteria (ARB) that carry antibiotic resistant genes (ARGs). Besides the risk of AMR, antibiotic residues can also be absorbed by plants, which in turn, can interfere with the plant physiological processes and cause potential ecotoxicological effects. Moreover, antibiotic residues can alter the human microbiome and cause health disturbances, such as allergic reactions, chronic toxic effects and disruption of the digestive system.
Water pollution is a broad environmental concern associated with the discharge of a large number of chemical compounds and pathogens from a range of human activities. While drug pollution in water has only recently permeated the public consciousness, it has been on the radar of scientific community for decades. The major routes of entry of antibiotic residues into water are shown in Fig 1. Many studies have reported the occurrence of antibiotics in surface and groundwater in the concentration range of ng/L to µg/L. Since rivers and lakes are widely used as resources for drinking water, irrigation and for recreational purposes, the entry of antibiotic and the resulting growth of ARGs in those systems make their management more complicated. Thus, the occurrence of these contaminants in water resources, especially surface water may pose health concerns and a water management challenge in many regions. Areas suffering from drinking water scarcity and poor wastewater management are particularly sensitive to such emerging contaminants. Antibiotic pollution may have noteworthy consequences on the aquatic environment but some of these effects are yet to be fully understood. As this report
documents the holistic picture of antibiotic pollution in Indian rivers, the impacts of antibiotic pollution in the aquatic environment are described below.

Figure 1. Routes of antibiotic residues into water
2.1 DISRUPTION OF MICROBIAL COMMUNITIES

Antibiotic pollution can affect the overall microbial community composition by favouring growth of certain bacteria over others. Antibiotic pollution in aquatic environments was found to reduce overall microbial diversity, including microbes responsible for carbon cycling and primary productivity. Antibiotics can also affect the distribution of microbial communities, leading to an abundance of parasites and pathogens in both soil and water environments; e.g., antibiotic presence in the aquatic environment led to an increased abundance of toxic Cyanobacteria species, causing eutrophication in freshwater environments and posing health risks to humans. Antibiotics also tend to cause reduced growth in algae and aquatic plants. Water insects accumulate antibiotics, passing drug residues up the food web and even to animals on land.

2.2 TOXICITY IN HIGHER ORGANISMS

Low concentrations of common antibiotics such as streptomycin and erythromycin have been shown to impact the survival and behaviour of micro invertebrates such as Daphnia magna and Artemia in laboratory conditions. Antibiotic pollution has also been observed to have negative effects on vertebrates; e.g., antibiotics were shown to induce adverse effects in zebrafish and catfish. Antibiotics were also found to be toxic to amphibians. Antibiotic pollution has also shown to impact higher organisms by disrupting the microbial populations associated with animal hosts. Even low concentrations of antibiotics in aquaculture can reduce microbial diversity in the fish gut and increase mortality.

ANTIBIOTICS IN DRINKING WATER

In 2012, World Health Organization (WHO) report confirmed the presence of pharmaceuticals in drinking water. This was attributed to the contamination by municipal wastewaters and industrial effluent discharges. Antibiotic residues are not completely removed or degraded in wastewater or drinking water treatment plants. Therefore, these compounds may be present in trace quantities in drinking water. However, the presence of these compounds even in minute quantity is a considerable concern owing to the cocktail effect.

For Example: If a glass of drinking water has one antibiotic, Ciprofloxacin (0.1 µg/L), it might not pose a serious health impact, but in a typical situation, this is not the case. A glass of water may have a few, let us assume 3 to 4 antibiotics (Ciprofloxacin, Sulfamethoxazole, Norfloxacin, Ofloxacin) each at 0.1 µg/L concentration or even more. Along with that, it may also have other chemical contaminants such as Bisphenol A (BPA), phthalates, etc. It is speculated that these compounds, could act synergistically to cause more severe health issues.

In a 2018 study conducted by the United States Geological Survey (USGS), pharmaceutical residues including antibiotics were found in a significant number of groundwater sources around the US that are used for drinking water.
2.3. ANTIMICROBIAL RESISTANCE: AN EMERGING PUBLIC HEALTH CONCERN

Antibiotics or antimicrobials are medicines commonly used to treat bacterial or microbial infections. However, when microbes are exposed to these medicines over time in smaller doses, they tend to become resistant to that particular medicine. As they become resistant, they spread the resistance to other microbes, thus creating colonies of resistant microbes. Though, AMR is a naturally occurring phenomenon, the increasing use and presence of antimicrobials has led to selective creation of anti-resistant microbes in the environment. Once the resistant microbes infect humans or animals, the infections become harder to treat as the same medicines do not work on them. This makes common infections harder to treat, accelerating the risk of disease spread, severe illness, and death.

The success of modernized medicine such as major surgeries, chemotherapy, etc., would also be not possible due to lack of effective antibiotics. It is like going back to the time when antibiotics did not exist. It is alarming that there is a rapid global spread of multi- and pan-resistant bacteria (also known as “superbugs”) that can cause infections which are difficult to treat with existing antibiotics.  

AMR is identified as one of the biggest health threats of the present time. With ever-increasing cases of AMR, it is a global issue of concern, and WHO has also declared it as one of the top 10 global public health threats.

At least an estimated 700,000 people die each year due to drug-resistant diseases.

If no action is taken, drug-resistant diseases could cause 10 million deaths each year by 2050.

A study suggests that in Hyderabad, exposure to an environmental source of antimicrobial drugs is placing pregnant women from low-income backgrounds at a higher risk for community acquired-antimicrobial resistance. Contamination of water sources with antimicrobial drugs has
Contamination of water sources with antimicrobial drugs has had grave consequences in India, where an estimated 58,000 newborns die from multidrug-resistant infections every year.\textsuperscript{25} India has been reporting multidrug-resistant tuberculosis (MDR-TB) cases since 2007. As per the National Drug Resistance Survey, more than a quarter of all TB patients in India have drug resistance to one of the anti-TB drugs.\textsuperscript{26} Carbapenems are considered last-resort antibiotics, often used to treat infections that are resistant to all other known agents. Compared to other regions globally, India has the highest incidence of carbapenem-resistant \textit{K. pneumoniae}.\textsuperscript{27}

\textbf{AMR: A GLOBAL CONCERN}

The issue with AMR is not local; it is global. It is facilitated by increasing travel and international trade, leading to the spread of resistant bacteria from one part of the world to another. COVID-19 is a huge example of this. The world observed how the original viral strain and the mutant ones developed in the country affected global pollution at large. Similarly, AMR cannot be seen as just an issue of major manufacturing countries like India and China but a concern for the entire world population. Prof Ramanan Laxminarayan, Director of the Center for Disease Dynamics, Economics & Policy (CDDEP), explained how multidrug-resistant bacteria can travel worldwide in a very short time.\textsuperscript{93} A Swiss study demonstrated that 75\% of 38 tourists traveling to India returned home with antibiotic-resistant bacteria in their guts. In addition, 11\% of tourists had bacteria resistant to the last-resort antibiotic colistin. Thus, there is an immediate need for developing strategies and regulations to tackle the issue both locally and globally.

- \textbf{Antimicrobial Resistance: An Emerging Public Health Challenge (A factsheet by Toxics Link)}
  https://toxicslink.org/Publication/factsheet-no-61-on-antimicrobial-resistance-an-emerging-public-he
ANTIBIOTIC POLLUTION IN WATER AND SUSTAINABLE DEVELOPMENT GOALS

Antibiotic pollution has direct implications in the economic, environmental and social spheres, which are considered the three main pillars of sustainable development. Antibiotic pollution in the aquatic environment affects the following sustainable development goals (SDGs):

**SDG 3: Good health and well being**
The improper use of medicines may harm environmental health, especially the aquatic environment with the potential to cause public health issues. The irrational use of antibiotics has already proved to contribute to bacterial resistance.

**SDG 6: Clean Water and Sanitation**
Pharmaceutical compounds, including antibiotics, are not entirely removed from wastewater treatment plants (WWTPs). Moreover, many people still lack proper sanitation and the sewage goes straight into the environment without any treatment and with a pool of contaminants, including drugs. Therefore, pharmaceuticals reach soils, surface water, groundwater, sediments and even drinking water.

**SDG 12: Responsible Consumption and Production**
The pharmaceutical sector is expanding continuously to supply medicines to the increasing population. However, as the pharmaceutical waste and wastewater are not properly treated before being released into the environment and with improper disposal of unused and expired medicines, human consumption will have a more significant impact on the environment in the coming years. Furthermore, veterinary pharmaceuticals used in agriculture and aquaculture can enter water bodies directly or via surface runoff.

**SDG 14: Life Below Water**
Pharmaceutical compounds are designed to cause specific biological effects even at low doses and, therefore, have the potential to cause huge damage to organisms in the environment. The ecotoxicological effects of pharmaceuticals have already been described for many aquatic species. Pharmaceuticals have the potential to cause major ecological imbalances.
3.1 GLOBAL REPORTS

Extremely high pharmaceutical concentrations (in the order of mg/L), have been detected in industrial effluents and recipient streams in China, India, Israel, Korea and the USA. China is one of the world’s largest producers and consumers of antibiotics that are widely used for disease treatment in humans and livestock. A large number of studies have been carried to understand the presence of antibiotics in the aquatic environment of China. More than 90 antibiotics belonging to five major classes were monitored in water samples from China during 2005–2016, showing a concentration range of 0.1 to 1000 ng/L. In addition to major rivers, antibiotics were also detected in residential tap waters from different provinces of China. Besides China, antibiotics such as sulfamethoxazole, ciprofloxacin, trimethoprim, and erythromycin have been reported in high concentrations in the African rivers. Researchers have also most frequently reported multi-drug resistant E. coli strains in the African rivers; for example, in the Durban area of South Africa, aquatic systems were reported to contain species showing multi-resistance to common antibiotics such as penicillin, erythromycin, cephalosporin, and nalidixic acid. Detection rates of several pharmaceuticals were found to be higher in Asian and African rivers than European and North American rivers. According to the latest OECD (Organization for Economic Co-operation and Development) report (2017), Italy and France are among the highest consumers of antibiotics in Europe. About 5 to 22 pharmaceutical compounds were detected in surface waters.
water samples from receiving bodies in the Po Valley, Italy, with the concentrations of some compounds greater than 100 ng/L. In the US, 93 pharmaceuticals, including 27 antibiotics have been reported to be present and contaminate the surface water. Studies on antibiotics in surface waters conducted globally are summarised in Annexure I.

3.2 ANTIBIOTIC POLLUTION IN INDIA

The pharmaceutical sector in India has seen a tremendous growth in the last few decades with a steady rise in population and thanks to its reputation as a low-cost manufacturing destination for multinational drug companies. Currently, India ranks third by volume, accounting for 10% of the global pharmaceutical production. Indian medicines are exported worldwide, thereby India is known as the ‘Pharmacy of the World’. However, the lack of strict regulatory and legal actions has accelerated antibiotic pollution in India, damaging the land, water, food, and health. Although the Environment (Protection) Rules have been in force since 1986, India has been unable to control pollution in its pharmaceutical hubs like Patancheru-Bollaram Industrial Estate in Telangana, Baddi Industrial Area in Himachal Pradesh, and SIPCOT Industrial Estate in Cuddalore, Tamil Nadu. Recent National Green Tribunal (NGT) order regarding discharge of drug industry effluent into the rivers Sirsa and Satluj in Himachal Pradesh clearly highlights the fact that the effluent treatment plant (ETP) or common effluent treatment plant (CETP) in industrial areas are not specialized to neutralize pharmaceutical residues.

Not only in the areas close to the pharmaceutical manufacturing industries, antibiotics have also been detected in Indian water bodies in other regions. The highest concentration of antibiotics in Asia was reported in the Isakavagu-Nakkavagu streams of India, which eventually leads to Godavari River. The reported concentration in that study was highest for ciprofloxacin (2.5 × 10⁶ ng/L) followed by ofloxacin (1 × 10⁴ ng/L) and norfloxacin (4.7 × 10³ ng/L). Antibiotics such as fluoroquinolones were detected in major Indian rivers such as Kaveri, Yamuna and Ganga which also act as drinking water sources. There has been a concern among governmental and nongovernmental water regulators, water suppliers, and the public regarding the potential risks to human health from exposure to the antibiotic residues via drinking water.

![India Map]

It is also estimated that antibiotic use in food animals (poultry, pigs and cattle) is projected to grow by 312% making India the fourth-largest consumer of antibiotics in food animals by 2030.
drinking water. There are a very few studies reporting antibiotic contamination in water bodies in India despite it being one of the largest drug producers and consumers in the world. Excessive and inappropriate usage for human and animal consumption and unregulated/incorrect disposal practices are the major contributors to a high presence of antibiotics in the Indian environment. Several factors drive inappropriate antibiotic use in India such as self-medication, access to antibiotics without prescription, use of pharmacies and informal healthcare providers as sources of healthcare, and lack of knowledge about when to use antibiotics.\textsuperscript{41} It is also estimated that antibiotic use in food animals (poultry, pigs and cattle) is projected to grow by 312\%, making India the fourth-largest consumer of antibiotics in food animals by 2030. Apart from industrial and domestic sources, improper discard of such animal waste and carcasses, runoff following the application of agricultural manure and sludge and aquaculture industry are considered important antibiotic contributors to the aquatic environment in other countries but there is not enough data regarding these in Indian context.\textsuperscript{42} Although antimicrobial residues have been reported from aquaculture shrimps of India, the exact extent is yet not known.\textsuperscript{43}

Thus, it clearly highlights that the antibiotic pollution is rampant across India and not just in the industrialized regions.
The international community is working towards the reduction of irrational use of antibiotics in humans and animals; however, the initiatives to reduce the potential health and environmental impact of emissions from pharmaceutical manufacturing appear fragmented. In addition, there is a lack of recognized standards and protocols that could guide a consensus among the manufacturers and regulators of what sustainable manufacturing of antibiotics should look like and how it can be achieved.

4.1 GLOBAL INITIATIVES

The sheer magnitude of antibiotic pollution and AMR makes managing its social and economic fallout a global problem. To address this multi-sectoral issue, it is often framed within “The One Health model”, which links the human, animal, and environment health domains. In order to tackle the antibiotic pollution and resistance crisis, different policies have been undertaken at a global scale.

4.1.1 WORLD HEALTH ORGANIZATION

In considering human pharmaceuticals, the WHO actively addresses pharmaceuticals and the environment through programming on access to quality medicines, “greening” healthcare, AMR as well as drinking-water quality and
safety. In 2005, WHO Drinking-water Quality Committee proposed that a working group of experts be assembled to undertake a rapid review of the state of the science of pharmaceuticals in drinking-water and develop guidance and recommendations in the form of a report and fact sheet. WHO has also developed a Global Action Plan on AMR to provide a framework for developing national action plans to prevent and manage AMR. The focus of the plan is on improved understanding of AMR, strengthening disease surveillance systems, optimizing the use of antimicrobials, preventing and controlling infection and ensuring sustainable investment in countering AMR. However, in the Global Action Plan and hence, many National Action Plans, there is little or no mention of limiting effluents from antibiotic manufacturing as a component in the fight against AMR.

4.1.2 EUROPEAN UNION

The European Commission is striving to tackle environmental pollution by pharmaceuticals as a means of curbing AMR. The European Union (EU) has banned the use of antibiotics for growth promotion since 2006. In 2019, the EU Commission adopted the Strategic Approach to Pharmaceuticals in the Environment with focus on actions to address the environmental implications of all phases of the lifecycle of pharmaceuticals, from design and production through use to disposal. The approach takes account of international environmental commitments (such as SDG 6 on water and sanitation, and the EU One Health Action Plan against AMR) and circular economy considerations. Although, not legally binding, it may set the future direction of policy as and when related EU directives and legislation are updated.

The European Commission has admitted that “pollution of waters and soils with pharmaceuticals is an emerging environmental issue and also a critical concern for public health”, but there are no standards regulating discharges of antibiotics from different sources.

Some EU member States; which are also part of Organisation of Economic Cooperation and Development (OECD) have initiated national programmes and strategies to reduce the risks posed by pharmaceutical micropollutants at low concentrations; which are summarised below:
Germany has developed a multi-stakeholder dialogue to facilitate action on “The Trace Substance Strategy”. A key output of the dialogue was Recommendations for reducing micropollutants in water developed by German Environment Agency (UBA) which provides specific recommendations to reduce human and veterinary pharmaceuticals in the environment. UBA proposed a combination of measures consisting of measures at the source, in use and for wastewater treatment serving the objective of comprehensive water protection.

In 2016, the second French National Plan known as The National Plan against Micropollutants 2016-2021 was launched. Some of the key actions in the plan specifically target pharmaceutical residues in water; such as sharing of data for better understanding of hazards and exposure regarding human and veterinarian pharmaceutical residues in waters, identification of pharmaceutical metabolites and assessing analytical capacities in order to establish an early monitoring system.

Sweden approved Greater environmental considerations in international and EU pharmaceutical legislation by 2020 (now extended to 2030). Four specific measures are considered to reduce the environmental impact of pharmaceuticals: increase access to information on the impact of medicinal products, establish appropriate and better environmental testing, revise the environmental risk assessment (ERA) guidelines, undertaking risk mitigation measures for human pharmaceuticals, and establish mandatory minimum requirements for good pharmaceutical manufacturing practices.

The UK Water Industry Research programme, with the support and collaboration of government and environmental regulators, initiated a multi-million-pound Chemical Investigation Programme (CIP) 2010–2020 to understand the challenges in meeting existing Environmental Quality Standards detailed in the Water Framework Directive, as well as emerging concerns such as pharmaceuticals.

The objectives of the CIP are:

i) understanding the true extent of discharges from WWTPs of both currently regulated chemicals and those of emerging concern;

ii) exploring mitigation options, such as new technologies; and

iii) appraising options including their economic and environmental costs.

In the Netherlands, a holistic approach is being used to address the issue of pharmaceutical residues from both human and veterinary use in water. The programme started in 2016 and considers the entire cycle and supports various stakeholders in their voluntary efforts to reduce pharmaceutical pollution in water. The two main drivers behind the programme were improved water quality and protection of drinking water.
4.1.3 INDUSTRY INITIATIVES

The AMR Industry Alliance is one of the largest private sector coalitions set up to provide sustainable solutions to curb AMR.

**Over 100 companies**

and associations signed the Industry Declaration on AMR at the World Economic Forum in Davos in 2016, followed by the adoption of a Roadmap, outlining a common set of principles for global action that focuses on investing in R&D to meet public health needs, reducing the development of AMR and reducing the environmental impact of manufacturing. In 2018 (later revised in 2021), these companies took a further step by publishing the first list of discharge targets based on Predicted No-Effect Concentrations (PNEC) for most common antibiotics used globally to guide environmental risk assessments for the manufacture of antibiotics. This is an important step towards mitigating antibiotic pollution as members of this initiative are working towards achieving these target values.51

The Strategic Approach to International Chemicals Management (SAICM) is a global policy framework adopted in 2006 to minimize and reduce the impact of chemicals on the environment and human health. In 2015, SAICM addressed Environmentally Persistent Pharmaceutical Pollutants (EPPPs) as an emerging issue due to the rising concentration of pharmaceutical compounds and their impacts on environment and health.52

**In 2018, India notified the Food Safety and Standards (contaminants, toxins, and residues) Amendment Regulations, relating to the tolerance limits of 43 antibiotics and other veterinary drugs in food products such as meat, poultry, fish, milk, etc.**

4.2 INDIAN INITIATIVES

The Ministry of Health and Family Welfare (MoHFW) released the National Policy for containment of Antimicrobial resistance in 2011.53 This policy encourages the development of regulations for antibiotic use in food animals, appropriate food labeling, and banning nontherapeutic uses of antibiotics in animals. It aims to regulate the sale and usage of antimicrobials, especially antibiotics, and monitor AMR. India has launched a “Red Line Campaign on Antibiotics” to further restrict over-the-counter availability and inappropriate consumption of antimicrobials.

Further, based on the Global Action Plan, the Ministry published the National Action Plan for containing AMR in April
2017, with MoHFW as the nodal ministry and the National Centre for Disease Control (NCDC) as the key surveillance body. Along with the National Action Plan, state-level action plans have also started to roll out with Kerala being the first state to notify its State Action Plan on AMR followed by Madhya Pradesh in 2019 and Delhi in 2020.

Further in 2018, India notified the Food Safety and Standards (contaminants, toxins, and residues) Amendment Regulations, relating to the tolerance limits of 43 antibiotics and other veterinary drugs in food products such as meat, poultry, fish, milk, etc. In 2019, the country took much-needed action and banned the use of colistin, a last-resort antibiotic in fish and livestock industries.

On 23 January 2020, the Ministry of Environment, Forest and Climate Change (MoEF&CC) proposed standards for antibiotic residues in the treated effluents of the pharmaceutical industries. The proposed draft, titled the Environment (Protection) Amendment Rules, 2019, provides stringent limits for 121 antibiotics. It is also applicable to treated effluents from CETPs with membership of bulk drug and formulation units. However, the proposed standards are still in the draft stage and if notified, India will become the first country in the world to have legally enforceable discharge limits for antibiotics in waste from the pharmaceutical industry. These proposed new standards are much more stringent than those suggested by the AMR Industry Alliance, with several of them even ten times lower. However, the Indian Drug Manufacturers Association (IDMA), representing leading pharmaceutical companies in India, have opposed the proposed regulations. Specifically, it has argued that the strict limits on pollution should instead be targets instead of enforceable standards, and that large numbers of factories should be exempted from the rules.

Although India is a major meat producer and the usage of antibiotics is high in poultry farms, there are no policies to control the use of these growth-promoting antibiotics. These compounds not only threaten animal health but also contribute to the rising concerns of AMR.

Despite some regulations in place, there is a lack of implementation, and hence India is unable to tackle the concerns with antibiotics in the required manner. Although India launched a Redline campaign back in 2016, over-the-counter availability, over-prescription, and self-medication remain significant contributors to antibiotic pollution in the country.
In 2019-2020, Toxics Link had initiated an indicative study to assess possible impacts of the effluents being released from the pharmaceutical units in Baddi-Nalagarh industrial zone, Himachal Pradesh. Toxics Link carried out the physical assessment of this pharmaceutical hub and also collected water samples from some of the locations to get an indication of the presence of antibiotics in water. The analysis of the samples collected from the effluent outlet in that zone revealed the presence of Ciprofloxacin at 296.1 µg/L. That study raised a larger issue of the magnitude of antibiotic pollution in Indian rivers. In recent years, there has been increasing concern about the risk of antibiotic residues in the aquatic environment globally. However, data regarding the contamination and distribution of antibiotics in Indian river water is limited. Therefore, Toxics Link came up with the present study on the presence of antibiotics in some of the Indian rivers to highlight the extent of antibiotic pollution in surface waters of India.
The monitoring of these compounds in aquatic environment is necessary to understand the extent of the presence of antibiotics in Indian water bodies and their environmental impacts, including their contribution to rising AMR in the country.

The report aims to trigger more large-scale nationwide studies on the occurrence of antibiotics in the aquatic environment and their ecological impacts. This report can also serve as a basis for better understanding of antibiotic pollution situation in India and highlights the need to establish and implement strong environmental standards at every stage of the supply chain. In light of the growing global threat antibiotic pollution represents, it is argued that the government must strictly monitor and regulate the pollution arising out of pharmaceutical sector as well as there must be swift actions and effective management of its environmental impacts by the pharmaceutical industry.

5.1 OBJECTIVES OF THE STUDY

This study was conducted with the following objectives:

01 To determine the presence of three antibiotics in selected Indian rivers in order to develop a better understanding of antibiotic pollution in the aquatic environment of India

02 To highlight the possible sources of antibiotic contamination in the selected rivers

03 To understand the impacts of antibiotics in water, with a focus on AMR rivers

04 To recommend required regulatory mechanism for mitigation of antibiotic pollution in water

5.2. METHODOLOGY

5.2.1 SAMPLING

- Twelve water samples were collected from 11 rivers located in 11 different regions of India in 1 L amber coloured glass bottles with the help of partner NGOs. However, antibiotics were detected in only four rivers and these rivers are shown in Fig 2 below. The sampling points along each river are also shown in Annexure II
- The collected samples were then transferred to Toxics Link office and stored in a refrigerator at -4 °C. All the samples were sent to Shriram Institute of Industrial Research, New Delhi for analysis without any pretreatment
- The water samples were analysed for three antibiotics (ofloxacin, norfloxacin and sulfamethoxazole)

5.2.2 SAMPLE PREPARATION PROCEDURE

- Prior to sample preparation, Oasis HLB cartridge was preconditioned by adding 5 mL methanol and 5 mL acidified water (pH = 2–3)
- 50 mL of sample was taken and its pH was adjusted to 2–3 with 1 M HCl. The sample was then filtered using 0.45 µm Millipore filter to remove the impurities present
- The water sample was passed through the pre-conditioned cartridge at a flow rate of 5–8 mL/min using a vacuum extraction manifold
• Next, 5 mL of ultra-pure water was used to wash the cartridge, which was subsequently air-dried for 5 min.
• The analyte was eluted into a glass test tube with 5 mL methanol.
• The eluted extracts were completely dried under a gentle flow of nitrogen, and the volume was reconstituted to 2 mL using a mix of water/methanol (1:1).
• The extracts were filtered through 0.45 μm filters, transferred to auto sampler vials, and were analyzed using Liquid Chromatography-Mass spectrometry/Mass spectrometry (LC-MS/MS).

**Figure 2. Sampling locations**

**5.2.3 ANALYTICAL METHOD**

*For Ofloxacin, Norfloxacin, and Sulfamethoxazole*

Mobile Phase: A- Water with 0.1 % Formic acid  
B- Methanol with 0.1 % Formic acid

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>A (%)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>18</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>
5.3 RESULTS AND DISCUSSION

5.3.1 ANTIBIOTICS IN RIVERS

- Out of twelve river water (surface water) samples, at least one antibiotic was detected in 4 samples as shown in Table 1 and Fig 3: Yamuna River (ITO, Delhi), Gomti River (Lucknow), Zuari River (Goa) and Cooum River (Chennai)
- Out of those four samples,

| 1 | Ofloxacin (0.54 to 0.71 µg/L) was detected in three samples from Yamuna River (New Delhi), Gomti River (Lucknow) and Cooum River (Chennai) |
| 2 | Norfloxacin (0.93 µg/L) was detected in the remaining one sample from Zuari River (Goa). |
| 3 | Sulfamethoxazole (0.2 µg/L) was also detected in Yamuna River (New Delhi) in addition to Ofloxacin |

- When the effluents from pharmaceutical industries are discharged into the surface waters, they are diluted and the concentrations of the compounds are reduced. That means, if we assume that the effluent concentration of an antibiotic as X, the surface water concentration of that antibiotic should be much lower than X due to dilution. However, the surface water concentrations of the antibiotics analyzed in the present study (Ofloxacin, Norfloxacin and Sulfamethoxazole) are still 2–5 times higher than the draft notification limits proposed by MoEF&CC for the respective compounds. Assuming there are no other antibiotic sources, it implies the pharmaceutical effluents discharged into the selected rivers have concentrations much higher than the detected concentrations and the draft notification limits.

Ofloxacin (0.71 µg/L) and Norfloxacin (0.93 µg/L) in water samples from Yamuna River and Zuari River, respectively were even higher than the less stringent PNEC guideline values given by AMR Industry Alliance.
The MoEF&CC draft limit for Ciprofloxacin is 0.02 µg/L. However, the present analytical method used by the lab has the limit of quantification (LOQ) for all the compounds as 0.2 µg/L. Therefore, the analytical method needs to be modified such that the LOQ of the compound is close to the draft limit and the concentrations below 0.2 µg/L could also be accurately quantified.

Table 1. Antibiotics in selected Indian rivers

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Location</th>
<th>Antibiotics</th>
<th>Concentrations (µg/L) (LOQ is given in brackets besides concentration values)</th>
<th>MoEF&amp;CC draft notification limits (µg/L)</th>
<th>Lowest PNEC value (AMR Industry Alliance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yamuna River, Delhi</td>
<td>Ciprofloxacin, Ofloxacin, Norfloxacin, Sulfamethoxazole</td>
<td>BQL (0.2), 0.71 (0.2), BQL (0.2), 0.2 (0.2)</td>
<td>0.02, 0.2</td>
<td>0.06, 0.5</td>
</tr>
<tr>
<td>2</td>
<td>Gomti river, Lucknow</td>
<td>Ciprofloxacin, Ofloxacin, Norfloxacin, Sulfamethoxazole</td>
<td>BQL (0.2), 0.54 (0.2), BQL (0.2), BQL (0.2)</td>
<td>0.02, 0.2</td>
<td>0.06, 0.5</td>
</tr>
<tr>
<td>3</td>
<td>Zuari river, Goa</td>
<td>Ciprofloxacin, Ofloxacin, Norfloxacin, Sulfamethoxazole</td>
<td>BQL (0.2), BQL (0.2), 0.93 (0.2), BQL (0.2)</td>
<td>0.02, 0.2</td>
<td>0.06, 0.5</td>
</tr>
<tr>
<td>4</td>
<td>Cooum river, Chennai</td>
<td>Ciprofloxacin, Ofloxacin, Norfloxacin, Sulfamethoxazole</td>
<td>BQL (0.2), 0.54 (0.2), BQL (0.2), BQL (0.2)</td>
<td>0.02, 0.2</td>
<td>0.06, 0.5</td>
</tr>
</tbody>
</table>

*BQL: Below Quantification Limits
**PNEC: Predicted No-Effect Concentration

Figure 3. Antibiotic residues in selected Indian rivers
5.3.2 COMPARISON WITH PREVIOUS INDIAN STUDIES

A comparison of antibiotic concentrations in the present study observed with previous Indian studies are provided in Annexure III. The concentrations of Ofloxacin (0.54 to 0.71 µg/L) and Norfloxacin (0.93 µg/L) in the present study were lower than the corresponding concentrations, i.e. (0.2 to 10 µg/L) and (0 to 4.7 µg/L) in Isakavagu and Nakkavagu Rivers, Hyderabad. Sulfamethoxazole (0.2 µg/L) concentration in Yamuna River was comparable to the mean concentrations in Vrishabhavathi river (0.35 µg/L) near Bengaluru and Kaveri River (0.14 µg/L) in Karnataka but higher than the concentrations observed in the Ganges (0 to 0.03 µg/L) and Swarna (0 to 0.001 µg/L) and Nethravati rivers (0 to 0.017 µg/L) in southwestern India.

In addition to antibiotics, two non-steroidal anti-inflammatory drugs residues (NSAIDs)-Diclofenac and Ibuprofen were also found in Cooum River, Chennai in the present study. The concentration of these compounds are 0.46 and 0.34 µg/L respectively. Ibuprofen and diclofenac are highly prescribed drugs worldwide and their presence in aquatic system may pose a potential risk to aquatic organisms. Although the concentrations of NSAIDs in surface waters are low, the high biological activity of these molecules may confer them a potential toxicity towards non-target aquatic organisms therefore efforts may be required to minimize the risks of these pharmaceutical compounds.

5.3.3 POSSIBLE SOURCES OF CONTAMINATION IN EACH RIVER

- Zuari River

Goa has a large established pharmaceutical industry with estimated yearly revenues of more than Rs. 7500 crores and growing at a healthy annual rate of about 15%. It is estimated that the pharmaceutical industry in Goa contributes around 10–12% to Indian pharmaceutical output and about 70% of their produce is exported to the most developed countries in the world; while 30% is consumed in the domestic market. Verna is a small village which falls between Panjim, Margao and Vasco. Verna Industrial Estate is one of the major industrial hubs in Goa housing around 500 industries units, including many pharmaceutical companies. Zuari River, which is a tidal river and the largest river of Goa, flows very close to the industrial estate before joining the Arabian Sea. Verna Industrial Estate is located at a distance of about 2 km from the river, on a plateau and the possibility of industrial discharge from these industries to Zuari River cannot be
neglected. This river also has many sewage outfalls which might contribute to antibiotics in the river. Among the polluted river stretches in Goa, Zuari River falls under priority V, as identified by the Central Pollution Control Board (CPCB). Thus, the major sources of antibiotics in Zuari River may be the direct discharge of domestic sewage into the river and the discharge from the industrial area.

Figure 4. Norfloxacin Concentration in Zuari river vs Draft regulation

- **Gomti River**

Gomti River is an important source of water supply to the cities of Lucknow, Jaunpur, and several towns and villages before it joins the Ganga near Varanasi, Uttar Pradesh. Gomti river faces multiple challenges in Lucknow from sewage pollution to groundwater extraction, thus making Gomti the most polluted river in Uttar Pradesh. Monitoring by the state authorities shows that the water is unfit for even bathing and this has been in common knowledge since 2010. The CPCB has declared the Lucknow-Jaunpur stretch of the river among the most polluted river stretches in the country. The major sources contributing to Gomti pollution are sewage and industrial effluents. Many pharmaceutical industries are located close to the course of Gomti River in Lucknow and may contribute to pharma-laden wastewater.

Figure 5. Ofloxacin concentration in Gomti river vs Draft regulation
• **Cooum River**

Cooum River is highly polluted and toxic and flows through several areas of Chennai city. Owing to intensive use of surface water upstream for agriculture, indiscriminate pumping of groundwater leading to reduced base flow in the river, discharge of untreated sewage and industrial effluents and encroachment along the banks, the river, especially the downstream, has been highly polluted. The Cooum river is supposed to be 80% more polluted than the treated sewage. Many pharmaceuticals and personal care products (PPCPs) including sulfamethoxazole have been previously detected in Cooum River. According to a news article published in 2020, there are many hospitals situated around this river, which dispose medical wastes into Cooum. Thus, medical waste can also be a major source of antibiotics into this river in addition to sewage and industrial effluents.

Figure 6. **Ofloxacin concentration in Cooum river vs Draft regulation**

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• **Yamuna River**

Only 2% of Yamuna River length flows through Delhi between Wazirabad and Okhla yet the city contributes to about 71% of its total wastewater load. Delhi also has the highest number of working sewage treatment plants with the highest sewage treatment capacity in India. Antibiotics; namely, ciprofloxacin and ampicillin were previously detected in water from site close to the present sampling point in Yamuna River. In addition, six other pharmaceutically active compounds (aspirin, ibuprofen, paracetamol, caffeine, carbamazepine and codeine) were also previously detected in water from that site. In 2020, a study by Lamda et al. detected the presence of critical drug resistant pathogens listed by WHO in ‘urgent need of new antibiotics’ in Yamuna river water samples.
This is a serious health concern and would further increase the disease burden in India. Thus, the major source of antibiotics to the river may be the sewage discharged into the river.

Figure 7. Ofloxacin and Sulfamethoxazole concentrations in Yamuna river vs Draft regulation

5.4 INFERENCES FROM THE STUDY

The present study has detected substantial concentrations of three antibiotics (Ofloxacin, Norfloxacin, Sulfamethoxazole) in the selected rivers of India (The ecotoxicological impacts of these antibiotics are discussed in Annexure IV). Though the sample size is limited and not all the antibiotics analysed are detected in every river water sample collected, the findings are alarming and highlight the potential possibility of widespread antibiotic pollution in the country. Most importantly, the locations where antibiotic residues are detected, are not necessarily in close proximity to major pharmaceutical industries. Therefore, the major source of antibiotic residues into these rivers may be mostly sewage (both treated as well as untreated) from point and non-point sources, especially into rivers located in populated Indian metro cities of Chennai (Cooum) and Delhi (Yamuna).

The study indicates that antibiotic residues are ubiquitous and can present an imminent threat to the water resources in India. However, Indian studies in this area of concern are limited. Moreover, there is no major policy discussion taking place on the possible impacts of antibiotic pollution on the ecosystem and its possible impacts on the human health as well as animal life. In addition to rivers and lakes, most of our rural population is dependent on groundwater sources (wells, etc.) for their drinking water needs. Hence, the widespread presence of these compounds in water sources raises questions on their consumption safety. Therefore, even the indicative presence of these compounds in our drinking water should be considered as a serious health concern.

Although India has a program to curb AMR, the action plans and policies fail to specifically aim in curbing antibiotic and ARG pollution of natural environments. The national plans across the globe including India have missed framing policies in preventing the environmental release of antibiotics by drug manufacturing facilities. Given the magnitude of localized antibiotic pollution, the policies focusing on monitoring and regulating antibiotics in effluents from manufacturing facilities gain significance. Although India has proposed antibiotic discharge standards, the draft is yet to be notified. It should also be noted that successful pollution mitigation policies depend mainly on efficient monitoring and reliable data generation and Indian regulatory agencies often fare poorly on both these counts.
The inexistence of specific regulations could be explained by a lack of consensus on safe environmental concentrations of antibiotic residues in terms of development of resistance and a lack of clear and robust scientific evidence on antibiotic pollution. Unfortunately, at this moment, there is also no standard experimental protocol for environmental analysis of antibiotics and their degradation products. Lastly, currently no policies are in place to address the problems of antibiotic and ARG pollution of WWTPs. As current WWTP design does not specifically consider the removal of antibiotics and ARGs, policies need to be aimed at upgrading WWTP technologies.\textsuperscript{69,70}

5.5 LIMITATIONS OF THE STUDY

The present study gives an indication of the potential dangers of antibiotic pollution in rivers. The study has certain limitations which needs to be highlighted.

| 01 | Sample size (number of water samples) is very limited considering the length and breadth of the country |
| 02 | Only a few target antibiotics could be analysed |
| 03 | Limitations in analytical accuracy and sensitivity to measure low antibiotic concentrations |
| 04 | In the river water there are multiple sources of pollution, hence it is difficult to ascertain the exact source of antibiotic discharge to the river considering there is no upstream regulation of antibiotics in India |
| 05 | Antibiotic concentrations may be affected by river flow conditions, type and time of sampling, river depth and distance from the point of wastewater discharge |
| 06 | Measured concentrations highlight the growing antibiotic pollution in the country; however, it is difficult to infer the impact of measured concentrations on human health and environment |
| 07 | The research data on antibiotic pollution in Indian rivers and its impact on human health and environment is very limited therefore it is a bit difficult to draw a decisive conclusion to the study |
Despite the environmental and public health risks, there is minimal surveillance of antibiotic residues in Indian waters. A detailed information on the antibiotic residues in the aquatic environment will help to achieve a reliable basis of environmental risk assessment and take proactive steps to tackle antibiotic contamination. To stem the propagation of antibiotic pollution, India will need to track all the potential contamination sources and hotspots. In a recent significant development, the Hon’ble National Green Tribunal in the case of “Veterans Forum for Transparency in Public Life v/s State of Himachal Pradesh & Ors” took cognizance of antibiotic pollution from the Baddi industrial area in Himachal Pradesh and ordered for suitable actions to curb pharmaceutical pollution.

In the context of developments and the research findings, following recommendations are being proposed to minimize the risks associated with it.

**Policymakers**

- Development and implementation of a strict policy to avoid over-the-counter or online sale of drugs without any prescription
- Notification and implementation of stringent national policies on antibiotic laden wastewater from the industries
- Ensure implementation of the existing national and state action plans on AMR
- Preparation of some user-friendly guidelines to be
followed by healthcare facilities and general consumers on how to dispose of expired or unused medicines properly
• Spreading awareness amongst the people not to dispose of their unused or expired medicines by throwing them with general waste or disposing them down the drain
• Limiting the use and types of antibiotics in animal production and aquaculture. Further, undertaking planned and coordinated phase-out of antibiotics used for growth promotion in these sectors
• Design policies for management of manure containing antibiotics
• More research studies should be initiated on antibiotic pollution in river as well as surface water
• Identify the hotspots of antibiotic pollution in the country

**Industries**

• Technological interventions in WWTPs to obtain maximum removal efficiencies of antibiotics
• Abide by the existing norms of effluent discharge
• Not discharging untreated effluent in the nearby water bodies.
• Monitoring and upgrading their treatment plants regularly to ensure no antibiotics are released into the environment

**Healthcare facilities**

• Create take-back programmes and install booths within their facilities where the patients can return their unused medicines
• Maintain an arrangement with the manufacturers in taking back the unused or expired medicine and disposing them in an appropriate manner
• Not disposing pharmaceutical waste with municipal waste and creating a setup for separately handling this type of waste
• Incorporating a strict policy to avoid the over-the-counter or online sale of drugs without any prescription
• Prescribe and dispense antibiotics only when they are needed, according to current guidelines
• Report antibiotic-resistant infections to surveillance teams
• Biomedical waste management and Handling rules, 2016 puts discarded medicines and cytotoxic drugs as category 1, which is needed to be disposed of by Incineration and Landfills. Therefore, on-source segregation and strict implementation are required by the healthcare facilities to manage pharmaceutical waste
• Ensure treatment of wastewater from healthcare facilities before release

**Consumers**

• Use antibiotics only when prescribed by a certified health professional
• Never demand antibiotics if your health worker says you do not need them
• Never share or use leftover antibiotics
• Do not discard leftover medicines in your general waste bin or down the drain
• Ask your doctor or your pharmacy to take back your expired and leftover medicines
REFERENCES


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Annexure I: Global studies on occurrence of antibiotics in the aquatic environment

<table>
<thead>
<tr>
<th>Rivers</th>
<th>Country</th>
<th>Year</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Lui, Selangor, and Gombak rivers            | Malaysia              | 2018 | • Ciprofloxacin concentrations were 52.5–138, 225.2–300 and 143.8–258.5 ng/L in Lui, Gombak and Selangor rivers, respectively  
• Sulfamethoxazole concentrations were 19.3–75.5, 96.8–109.3 and 84.3–114.2 ng/L in Lui, Gombak and Selangor rivers, respectively | Praveena et al.⁷¹  |
| Yeongsan River                              | Republic of Korea     | 2019 | • Surface water samples were collected from seven mainstreams and 11 tributaries of the Yeongsan River  
• Sulfamethoxazole (113.2 ng/L) and Clarithromycin (42.7 ng/L) were found                                                                 | Na et al.⁷²        |
| Yellow River and Huai River                 | Hanan province, China | 2020 | • Concentration of 10 priority pharmaceuticals, including antibiotics ranged from ND to 3474 ng/L in the Yellow River and from 4.35 to 146 ng/L in the Huai River | Feng et al.⁷³      |
| Nairobi River Basin                         | Kenya                 | 2016 | • Maximum (median) concentrations in the river waters for sulfamethoxazole, trimethoprim and ciprofloxacin were 13,800 (1800), 2650 (327), and 509 (129) ng/L, respectively  
• Maximum concentrations in river waters were generally higher than those of the wastewater treatment plant effluents signifying that the rivers are substantially contaminated by domestic wastewater | Ngumba et al.⁷⁴   |
<table>
<thead>
<tr>
<th>Rivers</th>
<th>Country</th>
<th>Year</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Multiple rivers                | Ghana             | 2018 | • 12 antibiotics were analyzed and all water bodies studied were significantly contaminated with antibiotics  
• Sulfamethoxazole (2861 ng/L) recorded the highest concentration | Azanu et al. [73] |
| Nakivubo wetland area and Lake Victoria, | Kampala, Uganda    | 2020 | • 17 pharmaceutical compounds, including antibiotics summing up to a maximum of 5.7 µg/L were detected  
• Sulfamethoxazole was the predominant antibiotic | Dalahmeh et al. [76] |
| River Po                       | Italy             | 2012 | • Most abundant antibiotics in the largest Italian river, were ciprofloxacin, ofloxacin, lincomycin and vancomycin with mean concentrations from 5 to 10 ng/L | Zuccato et al. [77] |
| Sava River                     | Croatia           | 2020 | • Alarming levels of two common antibiotics: azithromycin and erythromycin  
• These antibiotics were causing bacteria in sediment to develop AMR | Simicevic [78] |
| Hudson River Estuary and New York Harbor | USA               | 2018 | • 16 highly prescribed pharmaceuticals, including 2 antibiotics (sulfamethoxazole and trimethoprim) were detected | Cantwell et al. [79] |
| Estuarine waters of Puget Sound | Washington, USA   | 2016 | • 16 antibiotic compounds were detected in three local estuaries within a large estuarine ecosystem | Meador et al. [80] |
Annexure II. **Sampling point along Gomti River, Lucknow**

- **Sampling point along Cooum River, Chennai**

- **Sampling point along Gomti River, Lucknow**
• Sampling point along Zuari River, Goa

• Sampling point along Yamuna River, Delhi
### Annexure III. Comparison of present concentrations with previous Indian studies

<table>
<thead>
<tr>
<th>Rivers</th>
<th>Compounds</th>
<th>Concentrations (µg/L)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamuna River, Delhi</td>
<td>Ofloxacin</td>
<td>0.71</td>
<td>Present Study</td>
</tr>
<tr>
<td>Gomti River, Lucknow</td>
<td></td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Cooum River, Chennai</td>
<td></td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Isakavagu and Nakkavagu Rivers, Hyderabad</td>
<td></td>
<td>0.2–10</td>
<td>(Fick et al. 2009)</td>
</tr>
<tr>
<td>Zuari River, Goa</td>
<td>Norfloxacin</td>
<td>0.93</td>
<td>Present Study</td>
</tr>
<tr>
<td>Isakavagu and Nakkavagu Rivers, Hyderabad</td>
<td></td>
<td>ND–4.7</td>
<td>(Fick et al. 2009)</td>
</tr>
<tr>
<td>Yamuna River, Delhi</td>
<td>Sulfamethoxazole</td>
<td>0.2</td>
<td>Present Study</td>
</tr>
<tr>
<td>Vrishabhavathi River, Bengaluru</td>
<td></td>
<td>0.35 (mean)</td>
<td>(Iyanee et al. 2013)</td>
</tr>
<tr>
<td>Kaveri River, Karnataka</td>
<td></td>
<td>0.14 (mean)</td>
<td></td>
</tr>
<tr>
<td>Ganges</td>
<td></td>
<td>ND–0.03</td>
<td>(Sharma et al. 2019)</td>
</tr>
<tr>
<td>Swarna</td>
<td></td>
<td>ND–0.001</td>
<td>(Joshua et al. 2020)</td>
</tr>
<tr>
<td>Nethravati</td>
<td></td>
<td>ND–0.017</td>
<td></td>
</tr>
</tbody>
</table>

### Annexure IV: Antibiotics detected in the study and their ecotoxicological effects

**Norfloxacin**

- Norfloxacin, second generation fluoroquinolone antibiotic, is predominantly used in the treatment of urinary tract infections such as cystitis and chronic prostatitis.
- It is recommended that norfloxacin is only considered as second line medicine, when first line empiric antibiotics such as trimethoprim have failed or resistance is confirmed.

**Ecotoxicology effects**

- Norfloxacin pollution was found to alter species composition and stability of plankton communities.
- High concentration of norfloxacin interferes with the denitrification process in groundwater, thereby leading to decreased nitrate removal rate and enhanced N2O emission.
- It has genotoxic potential and causes significant DNA damage in goldfish. It is also shown to have negative effects on the defence function and intestinal health of juvenile fish.
- In a recent study by Wang et al., Norfloxacin inhibited the dissipation of herbicides in sediment and microcosm. This indicated that co-contamination with norfloxacin could increase the persistence of herbicides in aquatic environment.
- Infections caused by bacteria (Escherichia coli) resistant to norfloxacin has been observed in hospitalized cirrhotic patients.
**Ofloxacin**

- Ofloxacin is a broad-spectrum fluoroquinolone antibiotic used to treat bacterial infections that cause bronchitis, pneumonia, chlamydia, gonorrhea, skin infections, urinary tract infections, and infections of the prostate
- It is also used as a second-line antituberculosis drug used to treat multidrug-resistant tuberculosis

**Ecotoxicology effects**

- Ofloxacin alters the bacterial structure and composition but also change their functional properties in constructed wetlands
- The ecotoxicity of ofloxacin to freshwater species Daphnia magna was found to increase with increasing concentrations
- It was found to inhibit nitrification of activated sludge microorganisms
- Enterococcal isolates from the intestinal tract of poultry were found to be resistant to it

**Sulfamethoxazole**

- Sulfamethoxazole is an oral sulfonamide antibiotic, given in combination with trimethoprim, used to treat a variety of infections of the urinary tract, respiratory system, and gastrointestinal tract
- Trimethoprim-sulfamethoxazole is generally used as first-line therapy for uncomplicated urinary tract infections in women

**Ecotoxicology effects**

- Sulfamethoxazole altered the composition of enriched nitrate-reducing microcosms and inhibited nitrate reduction capabilities in groundwater
- It inhibited the growth and Chlorophyll-a content of algal cells
- Sulfonamides such as sulfamethoxazole can alter bacterial structure and induce deformities in freshwater biofilms