India-UK partnership
on tackling antimicrobial resistance
in the environment from antimicrobial manufacturing waste

Briefing paper

July 2023

Manufacturing antibiotics: antibiotic resistance and aquatic ecotoxicity in the environment

Antimicrobial Resistance (AMR) is a global health and development threat. As part of the global efforts to contain antimicrobial resistant infections of humans and animals, there has been a call for research to inform the development of strategies to limit environmental contamination by antimicrobial waste from pharmaceutical manufacturing (see *India-UK Tackling AMR in the Environment from Antimicrobial Manufacturing Waste* research call*)*. This briefing paper outlines current evidence and knowledge gaps on the issue, with a focus on India where the role of antimicrobial manufacturing pollution is particularly pertinent.

Abbreviations

AMR	Antimicrobial Resistance
AMRIA	AMR Industry Alliance
APIs	Active Pharmaceutical Ingredients
ARB	Antibiotic-Resistant Bacteria
ARG	Antibiotic Resistance Genes
CAMF	Common Antibiotic Manufacturing Framework
DBT	Department of Biotechnology
EC10	Effect Concentration
ERA	Environmental Risk Assessment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FDF	Finished Dosage Forms
GAP-AMR	Global Action Plan on Antimicrobial Resistance
IDMA	Indian Drug Manufacturers Association
MIC	Minimum Inhibitory Concentration
MSC	Minimum Selective Concentration
NAP	National Action Plan
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-Operation and Development
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentrations
r-PNECs	Resistance Predicted No-Effect Concentrations
RQ	Risk Quotient
UI	Uncertainty Intervals
UKRI	United Kingdom Research and Innovation
UN	United Nations
UV	Ultraviolet
WHO	World Health Organization
ZLD	Zero-Liquid-Discharge

About AMR

Antimicrobial Resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi. It is a naturally occurring mechanism that causes these microorganisms to develop resistance to antimicrobial drugs, including antibiotics, antiparasitics, antivirals and antifungals used to prevent and treat infections in humans, animals and plants. Resistance, whether intrinsic or acquired, jeopardises our ability to treat infections and perform life-saving procedures such as surgery and chemotherapy, increasing the risk of spreading disease, serious illness and death (1).

Resistant infections occurred in the early days of antibiotic use, but the discovery of new antibiotics allowed simply switching treatment once resistance against a specific antibiotic was developed (2). However, several strains of bacteria have become resistant to many antibiotics (1) and with very few new antibiotics developed in recent years, we are running out of treatment options fast (3).

The World Health Organisation (WHO) and other leading global health experts warn that we are entering a "post-antibiotic era" (1) with an estimated 4.95 million (95% UI 3.62-6.57) deaths associated with AMR infections worldwide (1.27 million (95% UI 0.911-1.71) directly attributable to AMR) in 2019 according to Murray et al. (2022) (4). The UK Independent Review on AMR predicts this number to reach 10 million annually by 2050 if resistance is not addressed, with a cost of up to $100 trillion (5,6). Although several critics question the certainty of these estimates (7), the actual death toll and the cost of AMR may even be higher than predicted.

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Without urgent action, the already significant health and financial costs associated with the increasing rates of AMR can only rise sharply. Containing and controlling the spread of AMR requires national and international cross-sectoral coordination mechanisms that include human and animal health, the environment, development, industry and trade (8–10).

Global risk

Pharmaceuticals in the environment have been a cause for concern for more than 20 years (11). Antibiotics for example, are used in quantities similar to those of pesticides and other organic micropollutants, but they are not required to undergo the same level of testing for their environmental effects (12). Pharmaceuticals find their way into natural waters through their incomplete degradation during municipal wastewater treatment (13), the direct disposal of human waste (14) or their disposal via household waste (15), as well as discharges from hospitals (16), aquaculture and agricultural settings (17,18). However, recent studies have shown that some wastewater effluents from antibiotic manufacturing units contain a substantial amount of antibiotics, leading to the contamination of rivers and lakes (19–25). In some cases, levels in manufacturing effluents are even higher than the maximal therapeutic human plasma levels (26). These effluents may also be a source of Antibiotic-Resistant Bacteria (ARB) or Antibiotic Resistance Genes (ARG), according to a growing number of published

studies where high levels have been observed in various environments downstream from manufacturing hotspots (19,27).

While the top pharmaceutical companies in the world are based in the US and Europe, they increasingly rely on global supply chains, with China and India playing key roles in manufacturing. Pharmaceutical manufacturing includes both the production of Active Pharmaceutical Ingredients (APIs) and formulated drugs, in which China is usually considered the major producer of the former, whereas India plays a more important role in the production of formulations (28). Pharmaceutical formulation focuses on processing APIs into products suitable for administration to patients. The word *formulation* is often used in a way that includes Finished Dosage Forms (FDF) (i.e., tablet, liquid, capsule, cream, ointment, or injectable product) (29). China is the largest exporter of antibiotic APIs in the world, accounting for 71% of global inter-regions exports (across all antibiotics) in 2020 (30). The biggest share of antibiotic exports from India in recent years has been in the category of formulated medicines, but there has also been a growing interest in API production potential (28,31).

Policies to mitigate AMR risk across the world

In 1998, the World Health Assembly adopted the first resolution on AMR urging Member States to take action to combat it (32). Since then, there have been a series of World Health Assembly resolutions on AMR opening the way for the Sixty-eighth World Health Assembly in May 2015, which adopted a **Global Action Plan on Antimicrobial Resistance** (GAP-AMR) with five strategic goals (33) :

1. Improve awareness and understanding of AMR through effective communication, education, and training;
2. Strengthen the knowledge and evidence base through surveillance and research;
3. Reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures;
4. Optimise the use of antimicrobial medicines in both human and animal health and;
5. Develop the economic case for sustainable investment that takes into account the cost of AMR.

The GAP-AMR provided guidelines for countries to have National Action Plans (NAP) on AMR in place by 2017 (34). Later in 2016, the UN General Assembly agreed to a political declaration on AMR, which accepted the GAP-AMR as a blueprint; recognized and underlined the severity of the AMR threat to health and society in general; and committed to work at national, regional, and global levels to develop and implement multisectoral NAPs in accordance with the 'One Health' approach (35). By 2021, 73 of 194 member states had self-reported NAP formulation and 113 of 194 member states had signed the 'Call to Action' on AMR (36).

India developed its NAP on AMR in alignment with the WHO's Global Action Plan in 2017. It aimed to combat AMR effectively in India while also contributing to global efforts to combat AMR (37). Beyond the Global Action Plan's strategic priorities (awareness and understanding, knowledge and evidence/surveillance, infection prevention and control, optimised use, investments in research and innovation), the Indian NAP specifically recommended strengthening India's leadership on AMR, including monitoring antibiotic residue and bacterial load, the need for bacteria removal at treatment plants, and environmental risk assessments.

During the same year, the European Commission passed the new EU One Health Action Plan against AMR. The plan assists the EU and its member states in providing innovative, effective, and long-term AMR responses. It established a framework for a broader effort to reduce the emergence of AMR while also increasing the availability of new and effective antimicrobials in and outside the EU. The main goals were to make the EU a

best-practice region, increase research, development, and innovation, and shape the global agenda. Antibiotic manufacturing was mentioned as one source of antibiotics entering the environment, and knowledge gaps were highlighted, but no specific guidance on how to address these issues was provided. To address the release of antibiotics into the environment, the European Parliament Resolution on the action plan called for environmental risk assessments and green procurement (38).

The United Nations (UN) Inter Agency Coordination Group on AMR published policy guidelines for the implementation of global and national AMR strategies in 2019. The recommendations addressed, among other things, pharmaceutical wastewater and solid waste management, and they called for funding, multi-stakeholder partnerships, and private sector participation (39).

The UK Government's five-year NAP to combat AMR (2019-24) was one of the few NAPs that considered manufacturing, placing a strong emphasis on the environment. The plan stated the government's desire to work with other countries to ensure "responsible antimicrobial procurement from manufacturers with transparent world class environmental stewardship in their supply chains", as well as "collaborate with industry to promote the development of a global environmental stewardship certification system that can distinguish responsible antimicrobial manufacturers" (10).

The Organisation for Economic Co-operation and Development (OECD), has also suggested environmental criteria for public procurement and good manufacturing practice as mitigation options, as well as discharge limits and disclosure of discharges from supply chains (40). This followed an earlier consultation on "Points to consider for manufacturers and inspectors in the prevention of antimicrobial resistance" initiated by the WHO in an attempt to address fundamental regulation through Good Manufacturing Practice (41).

Emissions from antimicrobials manufacturing and AMR

Manufacturing plants can pollute the environment via wastewater discharges, vaporisation or inappropriate solid waste disposal (Figure 1). Antimicrobials are typically produced in batch processes leading to the presence of a wide variety of products in wastewaters which are generated in different operations, wherein copious quantities of water are used for washing of solid cake, or extraction, or washing of equipment (42). These activities increase the number of antimicrobials entering the environment, with their concentrations in effluents and the volume of effluent discharged determining their quantities. Manufacturing of APIs poses the highest risk of antibiotic residue discharge, due to the high production volumes resulting in potentially high API residue concentrations in wastewater effluents, and the fact that API production is often in liquid form, with a heightened risk of migration to the environment (30). Formulation plants use processes such as milling, mixing, grinding, compression, packaging and many types of fillers, binders, flavoring agents, preservatives, and antioxidants. Although much less impactful than API plants, formulation plants also generate significant amounts of waste, which may contain active antibiotics and other environmental pollutants (43–45).

Antibiotic APIs are produced by chemical synthesis, fermentation or fermentation followed by one or more synthetic steps (semi-synthetic antibiotics) (46). Depending on the type of antibiotic being manufactured, the industrial technology used and the size of the manufacturing plant, the volume and composition of industrial effluent may differ (43).

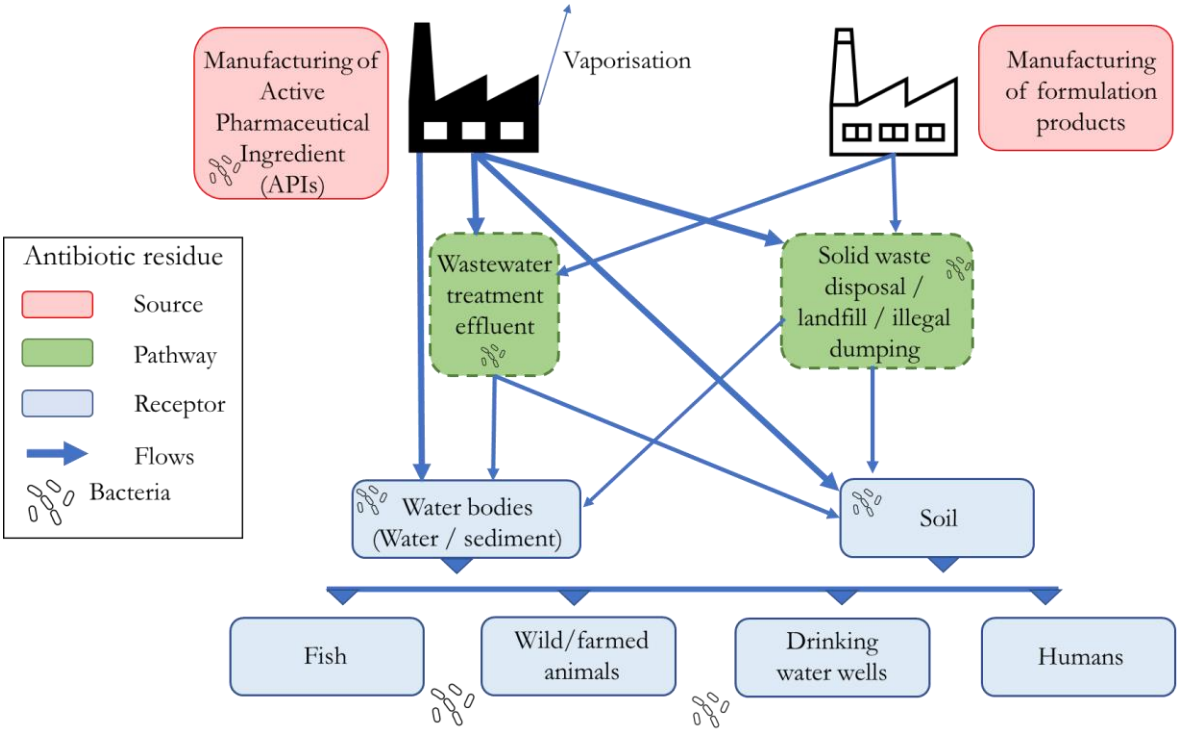

Figure 1. Pathways for antibiotic residues and resistance genes to the environment from manufacturing sources

Chemical synthesis involves various intermediate stages and chemical reactions performed sequentially (44) with the APIs typically isolated by using different separation processes, and then purified, dried, and milled before being sent to formulation plants (42). Wastewaters from chemical synthesis operations arise mainly from equipment cleaning, and they contain a variety of organic and inorganic constituents including spent solvents, catalysts, reactants and small amounts of intermediate or product, in addition to the usual manufacturing streams such as pump seal waters, waste scrubbers wastewaters, boiler blow down and floor washing (44). The ratio of consumption of process water to total water for a typical chemical synthesis plant is around 0.5 of around 80 m^3 per day total water use (44).

The fermentation process involves three main steps: seed inoculum and preparation, fermentation, and product recovery (42) with higher volumes of wastewaters created after each batch, consisting of; fermentation broth, mycelia, and the nutrients which are added for the cell cultivation (45). They also contain metal salts, nitrates, and phosphates and have organic load and total solids at similar levels to those from chemical syntheses (42). Wastewater is also produced from other plant operations although it is the volume of process wastewaters that are significantly higher in plants producing APIs through fermentation (47). The ratio of consumption of process water to total water for a typical fermentation synthesis plant is around 0.8 of around 4,180 m^3 of total water use per day (44).

In the case of Erythromycin, for example, 708 m^3 of water is needed per tonne produced, while for penicillin this ranges from 107 to 326 m^3 per tonne. Cephalosporin C requires 113 m^3 of process water per tonne produced through fermentation compared to 12 - 188 m^3 for metronidazole and 76 m^3 for ornidazole per tonne produced synthetically (47) Along with antibiotic residues, effluents from API manufacturing plants may contain considerable amounts of ARB and ARGs both from process wastewaters and from the washing of fermentation tanks and equipment (48,49).

It is estimated that approximately half of the pharmaceutical wastewaters produced worldwide are discarded without specific treatment (42), while in the conventional treatments often employed by API plants, many antibiotics are only partially eliminated (50,51). Moreover, these processes offer an environment suited for the evolution and subsequent spread of AMR through horizontal gene transfer (52). Effluents from formulation plants do not undergo on-site treatment, so are either diverted to municipal wastewater treatment plants or discharged into the environment without any treatment.

The Indian government expects manufacturing plants to use zero liquid discharge (ZLD) for effluents; a closed-loop system, that involves primary, secondary, and tertiary treatment with a final evaporation step to minimize the final volume of effluent generated (53). Although ZLD has the potential to minimize antibiotic discharges to the environment, it has not been operationalized by most API plants, as it requires lots of energy and is expensive to implement. Moreover, there are no regulations to enforce or monitor compliance in place (53).

Advanced treatment technologies for removing antibiotics from effluents are not widely available nor used. The same is the case with disinfection methods that could reduce the risk of AMR from effluents, mainly due to high cost, regulatory compliance, technical challenges, resource constraints and lack of awareness. Manufacturers who invest in these technologies may face competitive pressures, potentially leading to a disadvantage in the market (30). Available technologies that could reduce the levels of antibiotic residues and eliminate resistant microbial agents and their resistance genes in effluents include:

- **Electrochemical oxidation** (uses an electrical current to oxidize contaminants such as antibiotics in water; produces reactive chemical species such as hydroxyl radicals, which can damage microorganisms' cell walls and membranes).
- **Membrane filtration** (use of membranes to remove antibiotics and microorganisms) (54).
- **Ozonation** as an alternative to chlorine (use of ozone gas to disinfect effluent) (55).
- **Ultraviolet (UV)** (use of ultraviolet light to target microorganisms).
- **Heat treatment** (process of using heat to target microorganisms).

Antibiotics persist in the environment with a half-life of a few hours to a hundred days. They can enter water supplies as well as food chains and thus can be consumed through contaminated drinking water, meat, milk and other types of food. Antibiotic residues in drinking water can persist for months, and many are not completely removed by conventional drinking water treatment technologies (56). There are also reports of adverse and lethal effects on fish, amphibians and reptiles. In addition to direct consumption risks, antibiotic pollutants in water bodies and soil reduce overall microbial diversity and bacterial enzyme activities. These disruptions can lead to reduced soil fertility and an increased abundance of pathogens. Antibiotics can also increase the frequency of toxic cyanobacteria blooms, posing health risks to humans (57). But more concerning is that their occurrence in natural waters promotes resistance in the environment, which can be shared between bacterial species, turning once harmless bacteria into dangerous carriers of AMR (58). As a result, both water and soil systems can serve as reservoirs and carriers of resistance.

AMR can easily be transmitted to wild animals living in polluted environments. For example, gulls, waterfowl, mallards, corvids, and rodents from polluted areas can excrete a greater variety and quantity of resistant bacteria than those from unpolluted areas. These animals can indirectly infect humans through contaminated drinking or recreational water, as well as contaminated agricultural soil (59).

Aside from the risks of antibiotic residues in the natural environment, some studies have raised concerns about occupational exposure in manufacturing settings, potentially contributing to the development of AMR. For instance, Verma (60) demonstrated that pharmaceutical workers involved in manufacturing antibiotic drugs are

occupationally exposed to different antimicrobial_chemicals and that this causes their multidrug resistance profiles to be higher compared to general people. This demonstrates the importance of addressing occupational safety measures and implementing appropriate protocols to minimise the risk of antimicrobial exposure to workers.

The need for international standards

There are currently no universally agreed statutory standards to limit discharges of antibiotics from manufacturing plants. The development of such standards requires considerable research effort and is often limited by the lack of robust and reliable data.

Typically, the environmental risk associated with the presence of antibiotics in receiving waters is determined by the Predicted Environmental Concentration (PEC), and the Predicted No-Effect Concentration (PNEC). This information is often used as a comprehensive reference by industry and regulatory bodies when developing standards. For example, in Europe, Environmental Risk Assessment (ERA) aims to establish safe concentrations for the protection of wildlife populations, ecosystem structure and function; including the calculation of PNECs for aquatic organisms (52). It is required for the approval of all new medicines if the PEC exceeds 10 ng/L. PEC is based on modelling using data from known environmental factors such as the ability of the compound to be degraded (persistence), the ability to penetrate biological membranes and accumulate within the flora and fauna (bioavailability), and the ability for organisms in the environment to metabolise and detoxify the pharmaceutical (fate), minimizing any adverse effects resulting from its presence in the environment (61).

If the PEC is found to be higher than the PNEC, further research on environmental risk and better pharmaceutical management practices are required. This process aims to protect ecological receptors in the receiving environment using traditional environmental endpoints. There are reported environmental PNEC values (PNEC-ENV) derived from toxicity endpoint data with an assessment factor applied, consistent with the policy guidance (62,63). For example, because cyanobacteria are considered most sensitive to antibiotics (52,64), data sets are normally considered complete if cyanobacteria data are available following the OECD 2011 guideline, or equivalent (65). If cyanobacteria data are not available, the lowest chronic No Observed Effect Concentration (NOEC) or 10% Effect Concentration (EC10) are used when chronic data for 3 trophic levels are available. Provided that there is good evidence for lack of mammalian toxicity, an assessment factor of 10 is applied to the lowest chronic NOEC or EC10 of cyanobacterial, green algal, and daphnid tests even in the absence of fish data (66).

However, the risk of AMR selection is not currently included in environmental risk assessments. Several studies have estimated both ecological and AMR risks in aquatic environments (67,68). Indeed, environmental AMR risk assessment is an emerging field of study, with several options proposed for deriving PNECs that could be protective against the selection of AMR. Tell et al. (69) summarised approaches to estimate PNECs from the literature (64,70,71) and discussions at key scientific meetings (72). These techniques are listed below:

1) The Minimum Inhibitory Concentration (MIC) approach. The MIC is the lowest antibiotic concentration that inhibits 100% of the visible growth of a given strain of bacteria after 24 hours of incubation (69). The MICs are measured in clinically relevant bacteria and documented in the European Committee on Antimicrobial Susceptibility Testing database (73). Although resistance can emerge at concentrations below the MIC, these data can still be extrapolated to a PNEC for resistance (74). Bengtsson-Palme and Larsson (2016) derived

PNECs for resistance per antibiotic, by extrapolating MIC values from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database and applying a safety factor of 10 to account for AMR selection risk (70). While these MIC-derived PNECs for resistance selection have been widely used in research (75–77) and in industrial initiatives (78) there is still a need to perform experimental studies to validate or adjust them (79), particularly in relation to environmental heterogeneity.

2) *The Minimum Selective Concentration (MSC) approach*. The MSC is the minimal concentration of chemical required to provide a selective advantage to a microorganism carrying the resistance gene relative to the same bacterium that is sensitive to the chemical, i.e., not containing the resistance gene (58). The MSC "is a theoretical threshold that can be carefully determined in the laboratory" for each microbe and antibiotic combination (58) and it can be over 200-fold lower than the MIC of the susceptible strain (78). To date, however, there are insufficient MSC data to estimate PNECs for the vast majority of antibiotics, and there is no standardized and validated method for determining an MSC (75–77). In addition, MSCs differ when isogenic strains are cultured in single species competition experiments, compared to within a bacterial community (80). Furthermore, it is debatable whether a PNEC should be derived from MSCs as this can be greatly impacted by the number of test concentrations included in the model and the intervals between these test concentrations (81).

3) Microbial communities cannot transmit resistance without the dissemination of ARGs, so it has been suggested that ARGs themselves are a type of pollution (82). Thus, assessments of ARGs in the environment could provide information into the likelihood of gene transfer and the development of resistance in other members of a microbial community. Quantifying the environmental and human health risks associated with the relative abundance of certain ARGs in a given environmental sample or discharge requires additional research before they can be utilised to define environmental protection objectives (72). In addition, more studies are needed to establish the dominant routes for the transfer of ARGs between environmental and pathogenic bacteria, so that they can induce resistant infectious disease in humans.

Industry initiatives

In 2016, more than one hundred businesses and trade associations signed the Davos Declaration on AMR at the World Economic Forum, laying the groundwork for the AMR Industry Alliance (AMRIA) and calling for a sustainable and predictable market (83). At the UN High Level Meeting on AMR in September 2017, a smaller group of companies signed the Industry Roadmap for Progress on Combating Antimicrobial Resistance, which among other things highlighted the reduction of environmental impact from the production of antibiotics and established a common set of principles for global action (43).

In 2018, members of AMRIA developed their Common Antibiotic Manufacturing Framework (CAMF). The framework provides a methodology and a minimum set of requirements for conducting a site risk evaluation in pharmaceutical supply chains. It establishes minimum requirements for environmental compliance between companies in terms of antibiotic water / solid waste management and industry audits (84).

During the same year, the members of AMRIA developed a unified approach to establishing discharge targets for antibiotic manufacturing, referred to as PNECs for use in environmental risk assessments of antibiotics (78). It involved standards to protect the environment (64,85) and separate standards to mitigate the risk of resistance promotion (70).

In 2022, AMRIA published a progress report, where they stated that 85% of the members involved in manufacturing antibiotics have been assessing their sites against CAMF (86). The majority (76%) of antibiotic manufacturing sites owned by Alliance members and assessed against the CAMF, fully met all framework

requirements, and almost all (98%) met requirements either fully or partially (87), most products manufactured at Alliance members' sites (88%) have been assessed against their targets, and most of the assessed products (87%) met these targets (87). However, not all of global production falls under AMRIA.

Later in 2022, AMRIA published an antibiotic manufacturing standard with updated key requirements based on the extensive implementation experience of AMRIA members, the introduction of antibiotic PNECs and the inclusion of feedback from stakeholders. This antibiotic manufacturing standard specified requirements to reduce the development of AMR and the risk of aquatic (surface water) ecotoxicity in the environment resulting from antibiotic manufacturing operations. It covers the process of commercial manufacturing of antibiotic APIs and formulations. A site might manufacture multiple antibiotic APIs and/or final dosage forms containing antibiotics, and each process is to follow the requirements of the antibiotic manufacturing standard (59).

This antibiotic manufacturing standard also includes:

- The management of antibiotic process wastewaters discharged during manufacturing to meet PNECs.
- Methods to minimize the amount and concentration of antibiotics lost to wastewater.
- Handling, treatment and disposal of other antibiotic waste to minimize or eliminate the release of antibiotics into the environment.
- Processes and systems to demonstrate conformity to this antibiotic manufacturing standard.

Although AMRIA's effort has shown some promising results, their framework and guidance, targets and standards, compliance and audit remain non-binding and non-statutory.

Country focus: India

Globally, India is one of the worst affected countries by AMR (88). For many life-threatening infections, such as tuberculosis, more than half of bacterial isolates have been found to be resistant to first-line therapies (4,89). The emergence of newer multi-drug resistant organisms poses additional diagnostic and therapeutic challenges in the country, who is still striving to combat illnesses such as tuberculosis, malaria and cholera. The pathogens of which are becoming more and more drug resistant (87).

The role of manufacturing

Several studies conducted by Indian and international experts have found high concentrations of antibiotics in local water bodies surrounding manufacturing clusters (26,90,91). These antibiotic manufacturing zones were shown to be hot spots for antibiotic pollution in the environment, particularly in contaminated air, water and soil surrounding pharmaceutical facilities in Hyderabad. For instance, extreme cases of ciprofloxacin discharge levels of 44 kg per day, sufficient to treat a city of 44,000 ill people, and resulting in concentrations 1,000 times higher than what is toxic to bacteria have been reported (22). People living in the vicinity of pharmaceutical manufacturing sites, who are often poor and reliant on subsistence farming, are those whose health could be most affected by effluents and waste being deposited in their rivers, lakes, groundwater and fields.

India's Central Pollution Control Board (92) categorizes API manufacturing as one of the most polluting industries in the country but explicitly excludes formulation manufacturers from this categorization. Indeed, in March 2018, it prepared draft standards for residual antibiotics in industrial effluents, with the government establishing an expert working group to evaluate the draft guidelines and receive inputs from the industry. In January 2020, a draft bill introducing limits on concentrations of 121 antibiotics in effluents that can be

discharged into rivers and the surrounding environment, was published (93). The proposed thresholds not only were stricter than the PNEC limits used by the AMRIA Manufacturing Framework (by an average factor of 2.55 for the 121 APIs that were common between the two), but also were to be measured directly in industrial effluents rather than the receiving aquatic environment, hence before dilution (94).

However, in the final notification of the "Environment (Protection) Second Amendment Rules, 2021" published in August 2021, all antimicrobial limits in pharmaceutical effluent had been removed, and the rules simply stated that all effluents are to be classified as hazardous waste (95). Moreover, in the initial draft there were statements on what defines ZLD specifying that; "ZLD system in Bulk Drug and formulation industry is considered when treated effluent meeting the limits prescribed for compulsory parameters shall be used in Process or Utilities (boiler/ Cooling tower etc.)" and that "the reuse of treated effluent in gardening/ horticulture shall not be considered as ZLD in Bulk Drug and formulation industries", however, both of these statements were removed from the final document, which in turn might lead to inappropriate disposal practices due to the lack of harmonised understanding of the term among manufacturers.

How the UK-India collaboration is responding to these needs

In 2016, a strategic partnership between the Department of Biotechnology (DBT), the Government of India, and the United Kingdom Research and Innovation (UKRI) commissioned a study to map the AMR research landscape in India. The study, conducted by the Centre for Disease Dynamics, Economics and Policy, indicated that AMR studies in India were limited in all areas, including humans, animals, the environment and others (96).

The following recommendations, relating to the environmental aspects of AMR, were made to:

- Investigate the extent of antibiotic pollution in the environment caused by pharmaceutical industrial waste (wastewater, solid waste, and air) in various parts of India.
- Develop standards and detection tools for antibiotic residues in pharmaceutical industrial effluents;
- Examine the acquisition of ARB during religious mass gatherings in rivers.
- Focus on waste management to reduce the contamination of rivers during religious mass gatherings.
- Create innovative technologies to remove ARB and ARGs from sewage treatment plants (STPs) and hospital wastewater.
- Examine behavioural aspects of human waste disposal and its contribution to the problem of antibiotic resistance.

The study triggered funding for additional research and as a result, the Natural Environment Research Council (NERC), on behalf of UKRI and the DBT funded the collaborative and cross-disciplinary research programme: **"India-UK: Tackling antimicrobial resistance in the environment from antimicrobial manufacturing waste"**(97). The participating projects were selected and funded to contribute to the risk assessment of human, animal, and environmental health and the development of international environmental standards for antimicrobials in effluent from manufacturing facilities and receiving environments.

This partnership between DBT and UKRI seeks to:

- Understand the extent of antimicrobial pollution from antimicrobial manufacturing waste (wastewater, solid waste and atmospheric emissions), its pathways through environmental systems, and its role in driving the emergence and circulation of AMR in the environment.

- Develop and validate globally relevant standardised methods and tools for the detection of active antimicrobials and resistant bacteria in effluents and receiving environments.
- Determine the impact on human and animal health from environmental exposure to high levels of antimicrobial pollution and resistant bacteria and genes.

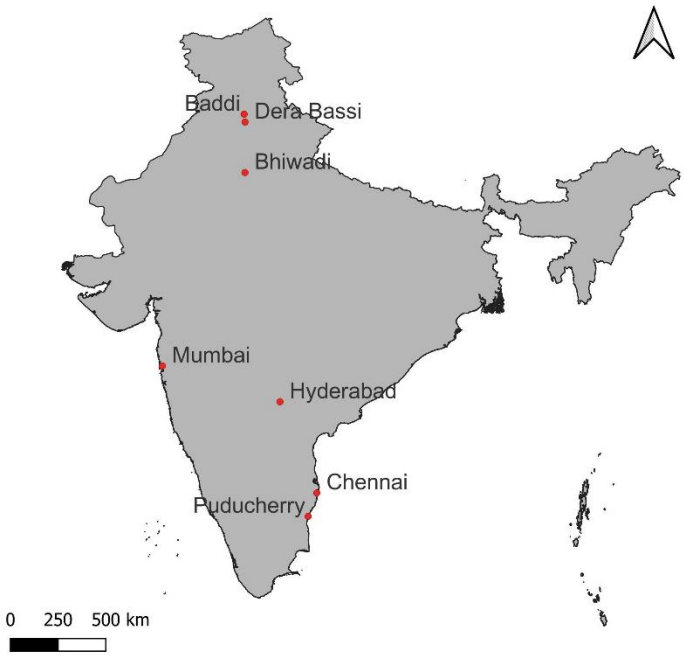

Figure 2. Sampling areas across India

The programme is comprised of five projects with teams spanning 11 institutions in the UK and 17 partner institutions in India (see Figure 3). Investigations are focused on: industrial areas and pharmaceutical factories located in seven important manufacturing settings (see Figure 2), the effluent treatment plants designed to process their effluents and the impact of pollution on the surrounding villages, water bodies, and agricultural soil. The projects are currently conducting extensive fieldwork, laboratory analysis, experiments, risk modelling, face-to-face meetings and other engagement activities with antimicrobial producers, pollution control agencies, health protection agencies and other stakeholders in the areas studied.

Programme Participants

Figure 3: Maps of Indian (left) and UK (right) institutions involved in the UKRI-DBT AMR partnership

Interactive maps outlining institutions in the collaboration are available online (see below):

Indian Collaborators(98)**:**
https://map.proxi.co/#command-center?topic_id=63fe38b695e823de974920c5&topic_key=XerCNZmkrqK94svcGyE0wl9udUdYgT

UK Collaborators(99)**:**
https://map.proxi.co/#command-center?topic_id=63ff39ed6183c1c956984618&topic_key=LRIis4QttRTOgHsLsM3vkRUSjXU8Yu

For more information on the Programme Coordination Team please visit our website: https://indiaukamrenvironment.org/

Table 1: An overview of the projects involved in the India-UK AMR partnership

Name	Principal Investigator(s)	Participating Organisations	Overview
AMRflows- Antimicrobials and resistance from manufacturing flows to people: joined up experiments, mathematical modelling and risk analysis	Prof Shashidhar Thatikonda shashidhar@ce.iith.ac.in Dr Jan Kreft j.kreft@bham.ac.uk	University of Birmingham Indian Institute of Technology Hyderabad Indian Institute of Technology Madras Indian Institute of Technology Gandhinagar The James Hutton Institute University of Newcastle	**Aim:** To combine field measurements, lab work and mathematical modelling to enable risk analysis and evaluation of mitigation strategies, to produce evidence-based policy advice. AMRflows investigates antibiotic pollution in the river systems of Musi (Hyderabad) and Adyar (Chennai) to determine the survival and selection of resistance, the breadth of its exposure and whether this resistance is transmitted to other bacteria before it is lost. (100,101) For more information please visit: https://more.bham.ac.uk/amrflows/
AMRWATCH- Defining the AMR Burden of Antimicrobial Manufacturing Waste	Prof Nick Voulvoulis n.voulvoulis@imperial.ac.uk Prof Joseph Selvin josephselvinss@gmail.com	Aarupadai Veedu Medical College & Hospital (AVMC) Indian Institute of Technology (BHU) Indira Gandhi Medical College & Research Institute Varanasi (IGMCRI) Imperial College London Pondicherry University	**Aim:** To investigate the link between methods of antibiotic manufacturing and their contamination levels in manufacturing wastes and the environment. Focusing on Chennai and Puducherry, AMRWATCH is sampling for antibiotics and antimicrobial resistance in waters, sediments, animals, and humans, contrasting their findings with control upstream environments. (101,102) For more information please visit: https://www.imperial.ac.uk/amr-watch/
AMSPARE- Advanced Metagenomics, Sensors and Photocatalysis for Antimicrobial Resistance Elimination	Prof Fiona Henriquez fiona.henriquez@uws.ac.uk Prof Soumyo Mukherji mukherji@iitb.ac.in	Indian Institute of Technology Bombay University of the West of Scotland	**Aim:** To understand the impact of antibiotic pollution on environmental microbiology and design effective measures for monitoring and removal AMSPARE studies the lifecycle of pharmaceutical manufacturing wastewater in order to improve regulatory control in pharmaceutical waste management. (101,103) For more information please visit: https://www.uws.ac.uk/research/research-institutes-centres-groups/infection-and-microbiology-research-group/antimicrobial-resistance-amr-in-the-environment/

ResPharm – Resolving the fate and studying the impact of pharmaceutical wastes on the environment and local community of a pharmaceutical manufacturing hub -	Professor Elizabeth Wellington E.M.H.Wellington@warwick.ac.uk	Aligarh Muslim University (AMU) Banaras Hindu University (BHU) Bristol Medical School (University of Bristol) CSIR-National Environmental Engineering Research Institute (CSIR-NEERI) Earlham Institute IEH Consulting Ltd. Indian Institute of Technology Delhi Post Graduate Institute of Medical Education & Research (PGIMER) University of Warwick Quadram Institute	**Aim:** To attribute the impacts of AMR exposure to pharmaceutical manufacturing waste via direct and indirect exposure to resistant bacteria. Respharm is studying a pharmaceutical hub in Baddi to test in real-time how pollution impacts both the local community and the resistant status of bacteria around them. (101,104) For more information please visit: http://respharm.net/
SELECTAR - Selection for antimicrobial resistance by antimicrobial production waste	Professor A McNally A.McNally.1@bham.ac.uk Dr Laura Carter L.J.Carter@leeds.ac.uk	Aligarh Muslim University University of Birmingham CSIR-Central Drug Research Institute University of Leeds Indian Institute of Technology Delhi Jamia Millia Islamia University Panjab University	**Aim**: To determine the ability of antimicrobial production waste to select for antimicrobial resistance in clinically relevant bacteria. SELECTAR uses guided and unguided chemical analyses of production waste to quantify active antimicrobials and identify the chemical complexity of antimicrobial production waste. This will allow them to determine the effect such waste has on the microbial ecosystem, specifically; whether it kills all beneficial bacteria to only leave harmful resistant bacteria alive? (101,105) For more information please visit: https://environment.leeds.ac.uk/geography-research-river-basin-processes-management/dir-record/research-projects/1639/selectar-selection-for-antimicrobial-resistance-by-antimicrobial-production-waste

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