UK-India AMR Programme: India Stakeholders Workshop Summary

(IIT-Bombay 4th & 5th December 2023)

The UK-India research programme '*Tackling AMR in the Environment from Anti-Microbial Manufacturing Waste*' held a two-day in-person workshop at the Indian Institute of Technology Bombay (IIT-B) with invited participation from stakeholders of various backgrounds with interests in AMR in India. The aim of the workshop was to facilitate engagement and discussion between stakeholders and researchers of the programme. Stakeholders were encouraged to share their reflections on the programme activities and findings and communicate their perspectives on AMR policy and practice in India. This helped to raise awareness of ongoing projects and initiatives and explore the challenges and opportunities to moving forwards in addressing the issue of AMR in the environment.

The event was streamed live online to enable wider participation and offer those stakeholders who could not attend in person the opportunity to share their views. The UK-India programme is organising an online Global Stakeholders Forum Workshop in March 2024 and participation is encouraged.

Stakeholders Workshop Day 1 *(4th Dec)*

The event began with an overview of the AMR-India research programme and the activities of the Programme Coordination Team (https://indiaukamrenvironment.org/) led by Prof. Fiona Henriquez. This detailed the aim of the programme:
to better understand the extent of environmental antimicrobial pollution from antimicrobial manufacturing waste and its impact on human and animal health, and develop and validate globally relevant standardisation methods and tools for detection
and introduced the five collaborative projects funded by NERC (National Environment Research Council, UIK) and DBT (Department of Biotechnology, India) under the programme (AMRFlows, AMR-WATCH, AMSPARE, ResPharm, and SELECTAR).

It was highlighted that the programme intends to host an online Global Stakeholders Forum Workshop in March 2024 to share findings and facilitate wider discussion on addressing AMR from the global pharmaceutical community.

Prof. John Connolly then presented a summary of the previous stakeholder meeting held online in September. He highlighted the key themes that emerged: Feasibility (of monitoring antibiotic contamination in the environment); Evidence; Transparency; and Collaboration and Communication.

Each of the five projects then provided a 15-minute summary to orientate the stakeholders and encourage discussion for the roundtable events, followed by questions and discussion.

Stakeholder Roundtable 1: Government and Civil Society *(facilitated by Prof. Helen Lambert)*

Guest Speakers

Shri Dinabandhu Gouda *(Director, IPC-I, Central Pollution Control Board (CPCB), Delhi)*

- Recently released a report on AMR & Pharmaceutical Manufacturing
- India exports more pharmaceuticals than it imports

- But “pollution” does not currently include antibiotic considerations
- Capacities for enforcement are lacking

Dr Geetanjali Kapoor *(One Health Trust (OHT))*

- The OHT has a global reach, with a team located in India and the US
- They focus on various areas of research and stakeholder engagement
- They were involved in the Mapping AMR & AMU Partnership (MAAP) project which analysed data across 14 African Union Member States to provide insight into levels of resistance and antimicrobial consumption

Shrimati Swati Srivastava *(Deputy Drugs Controller (India), Central Drugs Standard Control Organisation (CSCDO), New Delhi)*

- Have implemented a ban on 80 fixed dose combinations of antimicrobials and in 2019 introduced a ban on colistin for agricultural use
- The main role of CDSCO in relation to AMR in the environment is regulatory inspections and a mandate to check effluent waste (via PCBs) and hospital effluent
- GMP Schedule M rules will be amended regarding recall or expired drugs & records
- Manufacturers (including smaller companies) must work to the GMP standards; there is also said to be an Indian version
- A stakeholder meeting is being planned and the government is taking such issues seriously
- But enforcement is challenging, particularly for chemist shop prescribing

Stakeholder Roundtable 2: Industry *(facilitated by Prof. John Connolly)*

Dr Siddharth Prakash *(Responsible Antibiotics Manufacturing Platform (RAMP))*

- There are examples of manufacturing standards in Nordic countries which we can look towards to incentivise companies
- We must also consider the costs of action as this will likely fall on local suppliers and exporters, but changes can be made that are not costly and these should be explored (GSK given as an example case)
- RAMP is calling for a multistakeholder platform to raise awareness, build capacities, and training opportunities; the platform should include representation from areas such as academia, operations, and policy research and advocacy

Mr. Manjit Singh *(Sustainability Edge Consulting (formerly with Centrient Pharma))*

- Investment is a significant challenge – treatment of wastewater has a cost and the burden will fall mainly on local suppliers and exporters - but it is important to have assessments against PNECs and technologies are available.
- Many practice-based changes may be made to reduce API emissions without large investment. Disincentivising AB manufacture must be avoided as they are essential drugs.
- Lack of knowledge is the biggest challenge, which is slowly building up; more companies need to include AMR within their overall sustainability missions and this should be incorporated into business strategy
- Sustainability is increasingly important and some multinational corporations are exiting India due to poor environmental standards.
- The effort must be collective and include players beyond industry

Stakeholder presentation

Steve Brooks *(AMR Industry Alliance)*

- AMRIA was established in 2017 and will be present at the UNGA meeting in 2024
- It is a large private sector coalition of 100+ companies, representing 30% of human health antibiotics supply chain
- AMRIA focuses on 4 areas: access, appropriate use, manufacturing, and research and science.
- AMRIA has been working in partnership with the British Standards Institute (BSI) for over 3.5 years, in 2022 publishing a set of standards for antibiotic manufacturing that members must comply with and in 2023 launching a certification scheme as a mechanism to provide independent assessment and assurance that companies are meeting standards
- Companies can demonstrate compliance with industry PNECs that AMRIA has established through methods such as mass balance or sampling and analysis, but must justify their approach to obtain certification
- There will be ongoing evaluations for 3 years then a re-issue of certification is required
- All information is in the public domain
- Recognition that there is more to be done (e.g., wider reach, inclusion of animal AB manufacturing as well as human) but represents a significant step forward; there remains no conclusive evidence on how to calculate human health risk.

Stakeholders Workshop Day 2 *(5th Dec)*

Introduced with summary from the previous day and welcome to stakeholders

Stakeholder Roundtable 3: Health sector *(facilitated by Dr Sheetal Kale)*

Guest Speakers

Rajesh Bhatia *(Department of Communicable Diseases, WHO (South-East-Asia))*

- A central, major player for AMR andenvironment is required
- We must also look beyond industry, there is little known around efficient processing across sources in India
- There is a lack of environmental focus in the GAP and NAPs
- India has focus and NAP 2.0 is in progress, but the NAP has essentially been aspirational thus far
- The inadequate evidence base claims can be refuted to some extent, there is a vast amount of publications in this area but a need to streamline and synthesise available data
- Behaviour change is the most significant task
- The public health sector should advocate and address environmental dimensions
- Essential elements of environmental surveillance of AMR need to be proposed, together with protocols for surveillance of resistant pathogens in effluents, sewage and municipal waste

Dr Jaya Ranjalkar *(ReAct, Asia Pacific)*

- ReAct started in 2005 and has 5 offices globally, undertaking advocacy, networking and supporting NAP implementation; safe disposal at community level is covered within its programme although hospital and pharma waste is
- Environment is often considered last despite being a One Health component
- There is a need for capacity building on environmental pollution including management of hospital, pharma and farm effluent. We need models and clear indicators for the pharmaceutical industry, farms, and hospitals
- There need to be incentives for industry such as funding to support adoption of standards and ensure access to antibiotics is not affected

Dr Anil Kumar *(Senior Medical Officer, Baddi)* was unable to attend due to urgent work.

Stakeholder Presentations

KK Sharma *(Consortium for Common Cause/Veterans Forum (VF) for Transparency in Public Life)*

- The VF has followed the process of the draft notification (2020) published by the Ministry of Environment, Forestry and Climate Change (MoEFCC) on the regulation of pharmaceutical effluent at each stage of revision and submission, advocating for its implementation but the finalised version did not include PNECs.
- Pharmaceutical companies direct their waste through Common Effluent Treatment Plants (CEPTs) after primary treatment at own plants (EFTs) but these systems are not equipped to remove APIs
- The VF is working to change things for manufacturing waste management and have been gathering data on antibiotic concentrations from pharmaceutical manufacturing in Baddi. There are 118 recorded pharma manufacturing clusters in India but this may be an underestimate. There are 10,000 manufacturing units of which around 100 are large ones. A pan-India survey is planned and wider map of pharmaceutical clusters is envisioned with information detailing where units are located, how the effluent is surveyed, how far away the CETPs are etc.
- The VF is currently mounting a case in the Supreme Court on which they are awaiting decision
- The VF are concerned about pollution and their focus is on legal routes, they are committed to the inclusion of PNECs and intend to continue to share their findings

Dr R.K. Shandil *(Foundation for Neglected Disease Research (FNDR))*

- AMR is one of the “arms” of the FNDR, focused on detection and removal
- The FNDR advocates a One Health approach and also works on new diagnostics, drug discovery, and some tools and services.
- There is a gap regarding the removal of antimicrobials which FNDR intends to support through the development of a device for the depletion of antimicrobials in wastewater which also absorbs other contaminants such as heavy metals
- The device uses an absorption system and this has been piloted within a hospital ETP for 6 days, there are plans to upscale efforts and validate the device across multiple locations with the aim of supporting waste management beyond industry to include community, animal, and hospital settings

Key themes and discussion points

Project coordination

The audience had some questions regarding whether projects were mutually exclusive or contained overlaps. It was explained that all projects worked to contribute to the overarching general objective of increasing understanding towards AMR in the environment but applied different methods.

Integration emerged as important, methods need to be categorised and data must be shared among projects to understand challenges and identify avenues for progression. Project data should also be publicly available as highlighted by ResPharm. This could help to support wider awareness, encourage engagement, and provide opportunity for further idea generation.

Audience members were also interested in the concentrations associated with resistance used within projects. This was answered from one of the teams to be based on CLSI standards. When integrating project data, the approach taken, and methods used should be clearly outlined.

What constitutes “the environment”? And the need to view AMR in the environment holistically

After an overview introduction from a CPCB official, it was commented from the audience that the environment for humans is often more thought of towards patients admitted to hospital (focusing on addressing AMR through methods such as infection prevention control (IPC) and decontamination etc) but an interdisciplinary focus is needed as the environment is wider than this (e.g., animal, agriculture, industry, community).

The environment is a key link between sectors. Waste can enter the environment through various sources. If we want to address AMR in the environment effectively, we need to work collaboratively and include focus on waste management in other areas such as domestic sewage, healthcare facilities, and farms. It was highlighted that safe disposal of pharmaceuticals at community level is also a necessary focus. Clear indicators and models were called for these areas, including industry.

Prevention is important. High concentration hotspots such as those from industry can be treated at source, but this is likely to be significantly more difficult for CETPs. Attention to avenues such as consumption may help to reduce antibiotic residues.

Knowledge, awareness, and the availability of information

AMRFlows highlight sewage as a major contributor to AMR. Prescribing practices (e.g., inappropriate prescriptions, dosage inconsistencies) and community level awareness regarding antibiotic consumption and disposal require improvements as indicated by ResPharm findings. Education and guidance are essential (this should also include animal and agriculture sectors). However, engagement can be difficult (doctors in Puducherry

example given). It was asked whether students are taught about AMR as this is something the UK is said to be working on. A representative from REACT stated that an AMR module is being advocated for students and that competitions and seminars have been held to encourage student engagement and awareness. More sharing of data is encouraged within and between public and private healthcare institutions. It was noted that antibiogram data is not currently shared and there is a need to do this at least at state level and ensure access for both public and private sectors.

More information from industry is required. There should be a list of manufacturers, what they are producing at each site, what treatment technologies are being used (to enable quantification of removal), and API journey tracking along the supply chain. Audience members were also interested in understanding how licenses are given to manufacturers. A CSCDO stakeholder explained adherence to the GMP and international guidance is required and that manufacturers are subject to inspections. The CSCDO is keen on developing a unified portal on production which includes antibiotics.

Landscape complexity and the need for clearer leadership

It was noted by the audience that the UK has not brought in limits. Global standards are lacking regarding pharmaceutical manufacturing waste management. The AMR Industry Alliance (AMRIA) has set standards requiring compliance from its member companies and the WHO is also developing an independent set of standards. There was lack of consensus regarding the use of PNEC (Predicted No Effect Concentration) values for environmental assessment.

The department of communicable disease presentation emphasised that the landscape is very complex, with some initiatives working at cross-purposes. A “major central player” for AMR in the environment was called for. AMSPARE highlighted that leadership is required to bridge stakeholder interests and support collaboration. We need to be clear on existing initiatives and programmes etc to understand where they feed into each other and identify gaps.

Engaging Industry

Access to industry was commented to be difficult, with particular emphasis on getting smaller companies on board. The issue of awareness was suggested to be the biggest challenge and efforts need to be made to raise this wider. More companies should include AMR within their mission, potential to connect priorities and integrate AMR considerations into sustainability and climate change efforts should be explored. This must be collective and go beyond industry to include agriculture, healthcare, consumption etc.

Legislation is advocated to promote adherence to manufacturing discharge limits, but we also need to consider the feasibility of this. It was asked what good legislation would practically do in India if implemented tomorrow? Capacities remain an issue, and enforcement of such standards may also be difficult to monitor. The cost of action will likely fall on local suppliers and exporters, a careful balance is needed to ensure the supply chain is not affected – limited access to antibiotics remains a major killer.

The use of incentives may influence industry behaviour. Avenues such as the AMRIA certification scheme and improving public education and awareness on the issue of AMR in the environment may encourage greener manufacturing and purchasing decisions. However, it was noted that obtaining AMRIA certification is costly and separate certificates are required for each medicine. The AMRIA presenter acknowledged that companies may need training but that they should look at their position to work towards certification and not use cost as a barrier. It was also indicated that changes can be made that are not costly, and reference was made to GSK as an example. In another comment regarding general cost concerns, the PCB indicated that it sometimes gives grants to industries.

A member of the audience asked the AMRIA presenter if there was accreditation or some pathway for handling disposal, and whether guidance extends beyond industry to include e.g. farmers. The speaker responded that the intent is for certification standards to be applied to all, though not including subsequent use guidance as in prescriptions. The standards are a “living document” which will be updated with changing evidence. AMRIA commented that while their standards may not be the best way, it is good for traction and is a step forward. Industry should “control the controllable”.

Scientific considerations

It is not easy to delineate pharmaceutical manufacturing waste in the environment, establishing contribution is extremely difficult and confounded by other forms of waste, especially sewage. However, this acknowledgement does not mean that we should not act and take a preventative approach. Policy and science should change and improve over time.

Data and evidence remain an issue for promoting change. However, the presentation from the department of communicable disease provided figures of the volume of publications around the topic of AMR and the environment to show that there is a large evidence base that needs to be streamlined.

It was highlighted that in research the detection of antibiotics is also important to encouraging change, not only focusing on antibiotic resistant bacteria and antibiotic resistance gene detection. Although sub level concentrations can be more dangerous for resistance selection, this does not mean that hotspots such as those around industry are not significant – the potential for dilution is important. Risk should be thought about holistically.

Considerations were also encouraged by members of the audience towards exploring the impact of historical pressures. The possibility of obtaining historical records of industry production for comparisons was suggested. Climate impacts were also noted, with wet seasons potentially increasing dissemination of API and ARGs in water environments. Sampling depth emerged as a discussion point. Question of whether salinity of water samples has an effect was also mentioned.

There are also wider microbiome implications for AMR, as discussed by AMSPARE regarding the potential masking of the extent of this issue by acanthamoeba.

PNECs emerged as a consistent discussion point, not only in terms of where these should be applied in the environment (e.g., at release by industry, but this is less feasible for general CETPs), but also toward their general utility. PNECs are derived from controlled laboratory environments; more field studies are needed to inform PNECs (& MSCs) in

complex microbial environments. PNECs are also only applicable to aqueous waste and not solid (removal of solid waste is a challenge, the ZLD can become a problem of underground waste). There is also the challenge of addressing PNECs in practice because they are said to be often exceeded. We need to think about removal as well as detection.

Other suggestions for future initiatives

Concentration of antibiotics in sewage could be predicted through sales data – avoiding the need for sampling. With Hydromodels the flow of water and hence dilution of sewage through river environments could then be predicted. This is said to be possible but difficult, a lot of data is required, and it must be done cost effectively. The potential to train school children to test water in their environment for ammonia concentration was highlighted, this can indicate sewage pollution (which contributes to resistance).

RAMP envisions a multistakeholder platform for awareness raising, capacity building, and training covering several areas – academic (training, course completion certificate), operational (testing, treatment etc), policy research & advocacy (NAPs, guidelines etc).