

Antibiotic residues in the environment of South East Asia

Cecilia Stålsby Lundborg and **Ashok Tamhankar** discuss how antibiotic residues in the environment contribute to antibiotic resistance in South East Asia and propose actions to mitigate the problem

The global action plan on antimicrobial resistance¹ emphasises the One Health approach—seeing humans, animals, the food chain, the environment, and the interconnectedness between them as one entity. With growing economic development in South East Asia, the production and use of antibiotics—and therefore also their residues in the environment—are expected to increase.

Antibiotic residues in the environment lead to resistant bacteria through selective pressure. Theoretically, a chance interaction between a single molecule of an antibiotic and a bacterium can trigger natural selection for resistance, or a mutation favouring resistance. Subsequently, a vertical gene transfer (from one generation to another) or a horizontal gene transfer (transfer of resistance genes from one bacterium to another through a plasmid) may occur (fig 1). Identification of a complete identical sequence of antibiotic resistance genes from soil bacteria and clinical pathogens has demonstrated the potential for horizontal gene transfer between environmental antibiotic resistant bacteria and pathogenic bacteria.^{2,3} Humans may be exposed to antibiotic residues or directly to antibiotic resistant bacteria, including pathogens, through food or environment, and potentially be infected. Reduced

effectiveness of antibiotics may result in prolonged or poorly controlled infections.

In this paper, we identify pathways that contribute to antibiotic residues in the environment and propose priority actions for South East Asian countries to monitor and limit this.

Sources of antibiotic residues in the environment

India and Bangladesh are major contributors to global pharmaceutical production.⁴ Antibiotics are also widely used in South East Asia for therapeutic and non-therapeutic purposes in humans, animals, aquaculture, and agriculture—including use for growth promotion. These activities produce antibiotic residues that contaminate the environment (fig 2). Antibiotics like fluoroquinolones and sulphonamides are chemically stable. Their residues are frequently detected in the environment, and resistance to them is commonly reported.^{2,3} Beta-lactam antibiotics produce degradable residues that are often not detected but still contribute to resistance.^{2,3}

Pharmaceutical plants release large amounts of antibiotics into the environment. Antibiotic residues in the effluent (~1500 m³ of wastewater a day) of one cluster of Indian pharmaceutical factories comprising 90 bulk drug manufacturers showed ciprofloxacin

concentrations of 28 000 µg/L and 31 000 µg/L on two consecutive days.⁵ Multiplying these concentrations by the amount of water released each day shows that several kilograms of antibiotics are released daily into the environment, and tons are released every year.⁵ Antibiotic concentrations measured in lakes close to the cluster showed ciprofloxacin concentration up to 6500 µg/L.⁶ There are several such clusters in India and Bangladesh.⁴ Smaller production units also contribute to residues.

From human consumption, conservative estimates suggest that nearly half of consumed antibiotics are released, in active form, through excretion.² Studies from South East Asia^{7,8} report residues of several antibiotics in hospital wastewater. However, it should be noted that the majority of antibiotics are used in the community, and this also contributes to environmental residues.

The use of antibiotics in animals contributes equally to residues. Studies from Bangladesh, India, Indonesia, and Thailand have reported antibiotic residues in aquaculture products and aquaculture water. Chloramphenicol was found in fish from Bangladesh,⁹ and in shrimps from India¹⁰ and Indonesia.¹¹ In Thailand, erythromycin and tetracyclines were detected in aquaculture water with oxytetracycline concentrations up to 180 ng/L.¹² In integrated aquaculture farms

KEY MESSAGES

- Antibiotic manufacture, as well as its use, contributes to antibiotic residues in the environment, which leads to development of resistant bacteria
- In South East Asia, wastewater containing antibiotics is often directly released into the environment without sufficient treatment
- Research must focus on developing efficient, affordable, small scale treatment plants to eliminate antibiotic residues and resistant bacteria at the point of origin, and tools to monitor their levels in the environment

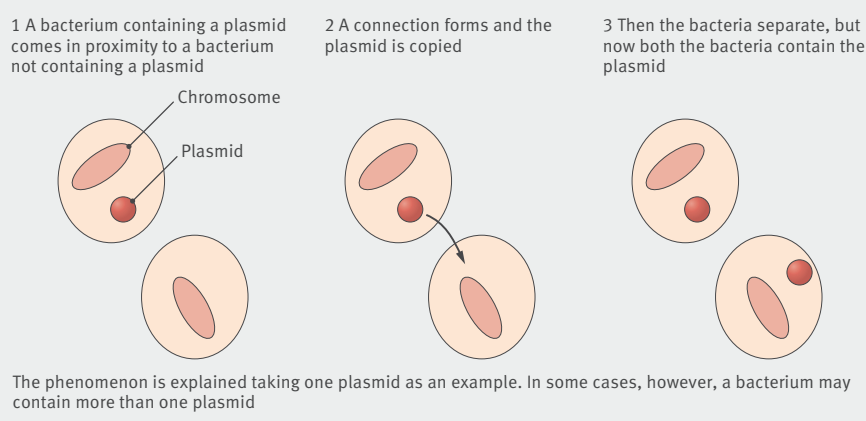


Fig 1 | How a plasmid, which might contain antibiotic resistance genes, gets copied from one bacterium to another

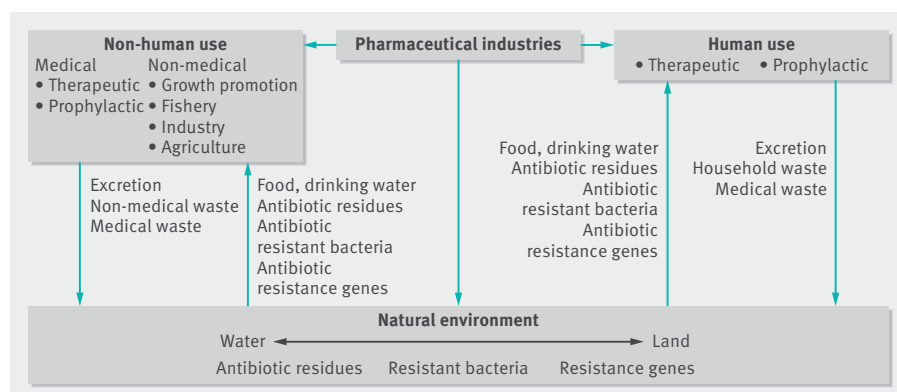


Fig 2 | Potential routes of creation of antibiotic residues in the environment and transmission to and from the environment of antibiotic residues, antibiotic resistant bacteria, and antibiotic resistance genes

excreta from chickens, that may have been given antibiotics, is used as feed. This can lead to the transfer of residues to fish used for human consumption.¹³

Risks with antibiotic residues in the environment

Wastewater from hospitals, livestock and poultry farms, aquaculture farms, and human dwellings is sometimes released, without any treatment, into the environment. Even if it goes to municipal sewage treatment plants, their antibiotic removal capacity is not adequate¹⁴ and this water may end up in drinking water sources like rivers and lakes. Many countries do not have routine monitoring of pharmaceuticals, including antibiotics, in drinking water because of the associated high costs.¹⁵

A study from Thailand reported levels of ciprofloxacin up to 200 ng/L in wastewater treatment plants and receiving waters.¹⁶ A study from five tropical Asian countries found predominance of sulfonamides in rivers and coastal waters, and it was estimated that about 12 tons of sulfamethoxazole per year was released into the sea.¹²

When untreated or inadequately treated wastewater containing antibiotics is released into water bodies, antibiotics and their metabolites can enter the food chain. Persistence, bioaccumulation, and toxicity may vary between different antibiotics, but all contribute to resistance and have adverse effects on living organisms. Laboratory experiments mimicking the concentration of pharmaceutical plant effluent in India with antibiotics at the lowest tested effluent concentration (0.2%) showed a 40% reduction in the growth of exposed tadpoles.¹⁷ A risk assessment in India using urban wastewater showed trimethoprim toxicity to bacteria, duckweed, algae, daphnia, rotifers, and fish in bioassays.¹⁸ Antibiotics have also been shown to accumulate in plant parts like leaves, stem, and roots.¹⁹

Present situation of wastewater remediation

Sewage or wastewater treatment plants help remove antibiotics from wastewater to varying degrees. However, antibiotics have been found in effluent from treatment plants even in high income countries, indicating that current technology does not completely eliminate antibiotics.^{2,3,15,20} The situation is worse in South East Asia as up to 80% of the wastewater is not treated at all and contaminates ground water, surface waters, soil, and even crops.¹⁴

In Thailand up to 3 µg/L of oxytetracycline and up to 1.6 µg/L of enrofloxacin were detected in conventional treatment plant effluent.²¹ Advanced treatments with chlorination and ultraviolet radiation can increase the removal efficiency by up to 50-90%.^{15,16} However, another study from Thailand showed residues for roxithromycin, sulfamethazine, and sulfamethoxazole even with advanced treatment.⁸ Effluent from a treatment plant serving drug manufacturers in India contained up to 31 000 µg/L of ciprofloxacin.⁵ Ampicillin up to 21 µg/L was detected in effluent from a treatment plant serving community wastewater in an Indian city.²²

Laboratory experiments show that very low antibiotic concentrations, similar to those in the environment, can select for and maintain resistance.²³ It is uncertain if antibiotics can be totally eliminated from wastewaters or maintained at levels below the risk for development of resistance. Therefore, predicted no effect environmental concentrations (PNEC) for resistance selection have been postulated for some antibiotics—for example, ciprofloxacin 64 pg/mL, azithromycin 250 pg/mL, meropenem 64 pg/mL, oxytetracycline 500 pg/mL, sulfamethoxazole 16 ng/mL, and colistin 2 ng/mL.²⁴ These concentrations serve as a guideline in setting up environmental monitoring programmes and for interventions to keep environmental antibiotic concentrations below a certain limit.

Recommendations to reduce antibiotic residues

The global action plan on antimicrobial resistance encourages interventions and policies to protect human health, and the environment as a whole, in the face of uncertain risks.²⁵ Solutions to reduce antibiotic residues in the environment are crucial to reduce development of resistance, and must be integrated within existing national programmes.

Increase awareness about antibiotic residues and optimise antibiotic use

The World Health Organization, South-East Asia Regional Office (WHO SEARO) has recently undertaken initiatives to map information on environmental antibiotic residues in the region and is planning activities to spread awareness. Education and training of all stakeholders—the public, health professionals, manufacturers, and policy makers—on the origin of residues and the associated risks is essential. This training must focus on the whole chain from production, prescribing, and use, to the importance of wastewater management and correct disposal of unused drugs.

Awareness of rational use of antibiotics in humans and animals is important. Infection prevention and control measures can also help reduce the overall use of antibiotics. Take-back programmes involving return of unused or excess drugs to pharmacies is recommended by WHO,¹⁵ though such initiatives have not yet been tried at scale in South East Asia.

Wastewater treatment plants to keep residues entering the environment to a minimum

The number of wastewater treatment plants in the region is inadequate.¹⁴ Considering resource limitations, decentralised, on site treatment plants equipped to neutralise antibiotics and resistant bacteria (OSTP-Zero ARB) must be considered.²⁶ These can provide an efficient, and low cost solution at the point of origin, such as pharmaceutical industries, hospitals, agriculture and aquaculture, and in the community.¹⁴ Public-private partnerships and industry incentives to establish such treatment plants may accelerate progress.

Septic tanks are beneficial as human waste is collected, but these might also serve as storehouses of antibiotics and breeding grounds for resistant bacteria. The contents must not be released untreated into the environment when the tanks are emptied.¹⁴ Small size OSTP-Zero ARB can be a solution for these as well.

Monitoring, research, and innovation

It is estimated that many tons of antibiotic residues are released into the environment in South East Asia every year. Yet there is

lack of documentation of antibiotic residues in wastewaters from hospital, industry, treatment plant effluents, aquaculture, and drinking water sources. Routine surveillance of environmental antibiotic concentrations and resistant bacteria can guide the development and implementation of contextually appropriate interventions.

Innovative, affordable, and easy to use methods for detecting antibiotic residues and resistant bacteria are needed. The tools that are currently available, such as high performance liquid chromatography coupled with tandem mass spectrometry, are expensive for routine monitoring. Qualitative information such as the presence of an antibiotic or antibiotic mixture above a certain limit of detection would also be adequate if methods for detecting precise concentrations are costly.

In addition, implementation research can help evaluate adoption of interventions such as take back programmes for the management of leftover antibiotics. Mathematical modelling based on antibiotic use can potentially be used to quantify residues and their influence on resistance. Qualitative studies among key stakeholders including the community, industries, and policy makers are essential to understand how they perceive the problem and to develop feasible solutions.

Innovations should target efficient and affordable technology to remove antibiotic residues and resistant bacteria, preferably at the point of origin. Technology to recover and, where possible, reuse antibiotics and pharmaceutical molecules is an area of research.

Photocatalysis—use of a substance to accelerate a process of a chemical reaction in the presence of light, such as solar or ultraviolet radiation or light emitting diode—holds promise for disinfection of bacteria and decontamination of antibiotics.²⁷

Need for regulation

WHO has called for policies to improve the management of pharmaceutical waste and minimise residues entering the environment.¹⁵ Specific regulations are, however, limited by a lack of consensus on safe environmental concentrations of antibiotic residues from the perspective of development of resistance.²⁴

Environmental risk assessments to study interactions of agents or hazards, humans and ecological resources are conducted for launching new medicines in Europe and the US, but not for medicines already on the market.²⁸ These requirements don't address resistance implications, but focus on ecological toxicity to various species.²⁸ Ecopharmacovigilance is a relatively new concept to track the environmental risks of

drugs and involves detection, assessment, and prevention of adverse effects to humans or other species. This is gaining interest in Europe and also in India as it exports medicines to many countries across the globe.^{28 29}

Sustainable development goal 12.4 states that by 2020 countries must “achieve the environmentally sound management of chemicals and all wastes throughout their life cycle, in accordance with agreed international frameworks, and significantly reduce their release to air, water, and soil in order to minimise their adverse impacts on human health and the environment.”³⁰ Pharmaceuticals must be addressed within this target. The sustainable development goals serve as a framework together with global¹ and national action plans for regulation on release of antibiotic residues.

Contributors and sources: Both authors are working together on projects on antibiotic residues and antibiotic resistance in the environment in India and Vietnam. CSL is professor and research group leader and has been principal investigator in several research projects on a wide range of aspects concerning antibiotics, in many of which AJT has been involved. CSL has been course leader for several international courses on antimicrobial resistance, to which AJT has contributed. CSL was scientific adviser to the Swedish Research Council on development research and also to ReAct—Action on Antibiotic Resistance. She has been working with Strama, Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance for 15 years. AJT, a former senior scientist with Bio-Medical group of BARC, India, is founder member and national coordinator of Indian Initiative for Management of Antibiotic Resistance. Both authors contributed equally to the article, which is based on a report submitted to the WHO SEARO by them. Both are guarantors.

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