ENVIRONMENTAL POLLUTION AND HOW IT CAN TRIGGER ANTIMICROBIAL RESISTANCE

*Tim Rutten

The risk of antimicrobial resistance (AMR) has existed ever since antibiotics were discovered, and Alexander Fleming himself had warned, "The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism." We have, however, been guilty of not giving his prophecy the weightage it was due, and if we do not act today it could very well be that we willbring this antibiotic apocalypse on to ourselves.

What is this dreaded AMR?

Like all creatures, bacteria and other microbes, naturally mutate and evolve to increase their chances of survival. Prolonged exposure to, often sub-lethal levels of, antibiotics, however, acts as a catalyst to the equation, and hastens the process. So, over a period of time, these mutations result in bacterial strains that are resistant to the antibiotics to which they have been exposed. These resistant bacteria, or superbugs, no longer respond to treatments that involve those antibiotics, and can cause infections that are increasingly hard to cure.

When we consider the numerous applications of antibiotics, the enormity of how devastating AMR can be, becomes clearer. Antibiotics are not only used to treat common infections, most of the developments in medical procedures are heavily dependent on antibiotics, including minor and major surgeries, organ transplants, treatment of burns, longevity management in patients with immune-deficient conditions such as HIV, cancer, and other serious ailments.

Indeed, antibiotics are the foundation upon which most medical advancements have been built, and that foundation is now at great risk of collapsing. In 2014, around 700,000 people across the world succumbed antibiotic resistant infections and complications. Keeping in mind the state of reporting in underdeveloped countries, the actual figures are in all likelihood much higher. By 2050, estimates show that nearly 10 million people will have lost their lives to AMR! Of these, nearly 47.3% are expected to be in Asia, with Europe and North America far behind with 3.9% and 3.17% respectively.

The Cyclical Nature of AMR

In the past decades, people have often taken Fleming's words literally and limited their focus on AMR control to "treatment", without giving active thought to other contributors to the AMR burden.

Of course, it cannot be dismissedthat uncontrolled use or misuse of antibiotics in humans and animals has been a major contributor to the spur in antimicrobial resistance. It should however not be seen as the only cause. In reality, humans, along with animals and the environment, operate in an open system, and the interlinkages between them cannot be overlooked. The antibiotics humans or animals consume make it back into the soil and water through excretion, and can result in development of AMR in the environment. In addition, inappropriate waste practices at antibiotics production facilities are another source of antibiotics ending up in the environment. Resistant bacteria and/or even antibiotics reach our bodies through the water we use, and, supported by the growing use of antibiotics in livestock, through the food we consume. This natural cycle isn't operating in isolation either, and is further aggravated by human intervention and activities.

For a more holistic picture, it is important to start at the beginning of the antibiotic cycle. The point of manufacturing of the antibiotics is the first link. The pharmaceutical industry has for decades been striving to make medicines that are affordable and accessible to all. In the process, to maximize profitability while keeping costs low, sometimes corners are cut and little attention is paid to aspects that are not considered intrinsic to the manufacturing process, such as waste treatment. The cost-benefit analysis of extracting the remnant antibiotic residue from the effluent has traditionally not included cost to environment and society. The fact that environmental regulations across the world have not paid much attention to antibiotics as a pollutant and do not stipulate any maximum residue limits for antibiotics being discharged by pharmaceutical manufacturers has not helped.

India, along with China, manufactures 80-90% of antibiotics, which not only makes these countries indispensable to the world's healthcare system but also puts them at grave risk of AMR, when pharmaceutical waste containing antibiotics is not duly treated. The pharmaceutical industry in these countries has flourished due to their attractiveness as cost-effective manufacturing destinations, which puts constant pressure on these governments and industries to further reduce costs.

The situation around India's pharmaceutical hubs is critical. The Patancheru-Bollaram pharmaceutical cluster in Hyderabad houses over a hundred pharmaceutical units, and has been categorised as a 'critically polluted' area by the Ministry of Environment. However, Hyderabad accounts for about 20 per cent of India's pharmaceutical exports, which has given rise to apprehensions on restricting these units from polluting their surroundings.

Studies by Centre for Science and Environment, a leading civil society, and Nordea, a global financial services research group, have shown unsustainably high levels of antibiotics in water bodies around pharmaceutical hubs (in some cases even greater than the concentration of antibiotics in the blood stream of a patient on antibiotics!) such as Hyderabad, and on-ground surveys have shown that the number of AMR cases in the surrounding areas have been uncharacteristically high. A study conducted at Kazipally Lake, near Patancheru, Hyderabad, revealed that the microbes in the lake harboured a wide range of resistance genes, almost 7000 times more than those found in lakes in Sweden.

The next link in the chain is use of antibiotics in humans and therapeutic use in animals, where the antibiotics consumed make their way into the environment through excretion. This burden has been substantially increased due to non-therapeutic use of antibiotics in animals (use as growth promoters rather than for curing disease). This reckless use also causes antibiotics in food, especially in poultry, meats, milk and other food products of animal origin, and repeating the rather predictable cycle of

consumption and excretion.

The final link is disposal of medicines and hospital waste. Expired antibiotics often have reduced efficacy and are inadequate to kill bacteria. Hospital waste, including patient waste, too, contains antibiotic residue that requires proper treatment before disposal. If inappropriately disposed of, however, they provide bacteria a perfect environment to mutate into resistant strains, and so proper disposal of these medicines and hospital wastes is essential to close the antibiotic loop.

To combat AMR, a holistic plan is required which addresses each one of these links.

Environment as a Conduit for Pharmaceutical Pollution

Environment, especially water, not just acts as a medium in which resistant bacteria can thrive, but also acts as a conduit for them to spread. For instance, when samples were collected from the river Yamuna, a major river in the Northern India, at different points of its flow, all samples showed significant presence of antibiotic residue. The Musi River and Kazipally Lake in Hyderabad, which have been treated as a receptacle for pharmaceutical waste by the nearby industries, have gained notoriety as a hotspot for drug resistance. A study conducted at Kazipally lake by Dr. Johan Bengtsson-Palme, Dr. Joakim Larsson and team, brought to light an added risk - not only were the resistant bacteria capable of reproducing and spreading geographically, but theycontained plasmids, which could, and did under lab conditions, hop from a resistant to normal bacterium of another class. This snowball effect can potentially wipe out the effectiveness of presently available antibiotics and take healthcare back by several decades, if not centuries.

However, the critical danger we have put the environment in has only recently started coming to light. AMR is not the only disaster waiting to strike, and the degree of environmental damage from pharmaceutical pollution is often invisible until catastrophe strikes. In October 2017, 2.3 lakh fish turned up dead in the Kazipally Lake, poisoned by the chemicals being pumped into the environment. In England's rivers, dumping of contraceptive pills and discharge from their factories has been causing widespread feminisation of fish, with male fish being found with eggs in their testicles. Sexual abnormalities like these could severely impact their breeding, leading to not only a steep decline in their population, or even extinction, but also have broader consequences for the ecosystem.

Evolving Global Policies on AMR

The WHO has identified Antimicrobial Resistance (AMR) as one of the most critical challenges in infectious diseases today. Globally, the subject has been discussed at the multi-country platforms, garnering not just the commitment of Governments, but also from the pharmaceutical and healthcare industry.

The Review on Antimicrobial Resistance (AMR), was commissioned in July 2014 by the Former UK Prime Minister, David Cameron, who asked economist Jim O'Neill to analyse the global problem of rising drug resistance and to propose concrete actions to tackle it internationally.

Subsequently, the May 2015 World Health Assembly adopted a Global Action Plan on AMR, underscoring the need for an effective "one health" approach involving coordination among numerous international sectors and actors, including human and veterinary medicine, agriculture, finance, environment, and well- informed consumers. This Action Plan has since been translated into national action plans (NAP) by many countries, including India. AMR has also received prominent attention at global forums, such as World Economic Forum, UN General Assembly, and G20, all highlighting the seriousness of the issue.

The WHO's Global Antimicrobial Surveillance System (GLASS) has been implemented to ensure uniform and complete reporting across nations in order to create a bank of updated data that portrays a realistic picture of the scale of the problem.

A large challenge in preventing the growth of AMR via pharmaceutical pollution, however, is the lack of formal regulations for antibiotic content in pharmaceutical effluent anywhere across the world. Unfortunately, until recently there has been limited global push on this, maybe caused by the concentration of pharmaceutical manufacturing in India and China, far away and invisible to many other countries, while forgetting that resistant microbes know no borders.

In December 2017, the United Nations Environment Assembly of the United Nations Environment Programme (UNEP) specifically delved into the environmental burden of AMR, and urged member states to intensify efforts to manage chemical and pharmaceutical waste sustainably throughout the supply chain by 2020. They reiterated the need for a holistic, multi-sectoral approach to contain AMR, and put special emphasis on the need for further research and surveillance to understand and tackle the role of environmental pollution in the spread of AMR. The Assembly also encouraged member states to consider measures to reduce environmental contamination by antibiotic manufacturers to minimize their contribution to AMR.

There are, of course, several best practices in other countries that can be used as a benchmark. For instance, in 2012, Sweden became the first country in the world to introduce environmental criteria into national contracts with pharmaceutical suppliers. Since then, Swedish procurement guidelines have contained special contract terms relating to the minimisation of environmental impacts in the manufacturing of pharmaceutical products.

Developments in India

As one of the countries at greatest risk, India catapulted into action in 2016, when the Minister of Health convened a National Workshop on Development of a National Action Plan on Antimicrobial Resistance along with WHO Country Office for India. The Royal Embassy of Netherlands also convened a closed-door workshop with the support of Ministry of Health and Family Welfare in December 2016, to discuss the need for a "one-health approach" to AMR, and to further strengthen the Indo-Dutch cooperation on AMR.

In April 2017, the Ministry of Health and 10 other ministries came together to launch the National Action Plan on AMR, based on the 'one-health' approach of the Global Action Plan. The Indian National Plan highlights the need for tackling AMR across multiple sectors such as human health, animal husbandry, agriculture, industry and environment, and among others, sets a target of setting standards for antibiotic residue in industry effluent.

The recently released second-edition of Nordea-Changing Markets' report (January 2018) explored the impact of pollution from pharmaceutical production sites in Hyderabad. It was evident that despite promising statements of intent from industry players, irresponsible practices in supply chains are yet to be curbed. This reiterates the role of the Government in keeping the industry in check, and the first step for that is the establishment of standards that will form the basis of regulations.

India's Central Pollution Control Board is already working on drafting these standards, and if released soon, these could globally be the first enforced regulations for controlling antibiotic residue in pharmaceutical waste.

Responsibility of the Pharmaceutical Industry

As the pharmaceutical industry draws benefit from sale of antibiotics, it is

also their responsibilityto produce, sell and dispose antibiotics responsibly. Short-term gains achieved through cost-cutting and shirking on proper waste management are being made at the long-term, almost inevitable, risk of total failure of antibiotics which will result in a collapse of their businesses, but more importantly at a huge expense and suffering for society. It is essential for pharmaceutical companies today to use foresight while making their operational and business plans.

Even while the policy and regulatory system struggles to catch up with the needs of today, the industry must proactively and voluntarily improve their waste treatment processes and impose self-checks on their effluent discharge. This is as much for their own sake, as it is for the humanitarian cause of safeguarding public health.

Since the 1980s, the rate of new antibiotic discovery has fallen dramatically, with the few 'new' antibiotics discovered, being the result of older breakthroughs. Presently, the pipeline of new antibiotics is almost dry, with fewer than 50 products under development, and keeping in mind the long R&D period required, it is important for R&D on antibiotics to pick up pace now.Traditionally, funds for R&D have been used only for the development of new drugs, but that is no longer sufficient, and money must be invested in research for waste management process improvement as well, to ensure the antibiotics of today are preserved.

It was this realisation, perhaps, that led to the signing of the Industry Declaration on AMR in January 2016 at the World Economic Forum, followed closely by the Industry Roadmap on combatting AMR during the UN General Assembly in September 2016. To mobilize the Industry Roadmap, the AMR Industry Alliance was formed in May 2017, with representation from over 100 pharmaceutical, R&D, and healthcare companies, including DSM Sinochem Pharmaceuticals.

The members of the AMR Industry Alliance have committed to reduce environmental impact from production of antibiotics, and will:

- Review their own manufacturing and supply chains to assess and control releases of antibiotics into the environment
- Establish a common framework for managing antibiotic discharge, building on existing work by Pharmaceutical Supply Chain Initiative (PSCI), etc. and start applying it across their own processes by 2018
- Develop a practical, transparent mechanism to demonstrate their adherence to the framework
- Work with technical experts to establish science-based targets for antibiotic discharge concentrations and good practice methods to reduce environmental impact by 2020.

DSM Sinochem Pharmaceuticals (DSP), for instance, uses the cleanest technology available to ensure lowest possible environmental impact throughout their supply chain. This includes operation of dedicated wastewater treatment plants 24/7/365, at every antibiotic manufacturing site.Besides process improvement, DSP also focuses on intense self-regulation, and we have developed in house technology to measure beta lactams in ourwaste with a detection limit of 50 parts per billion. We also constantly endeavour to improve on the tests to enhance its detection limits and applicability.

Globally, DSP supports WHO's Call to Action against AMR, and has long since been actively involved in advocacy efforts to create policy impetus around AMR. Our objective is to create awareness about AMR and urge policy makers and Governments to take concurrent, streamlined, multi-pronged action (One-health approach) to curb it. In an effort to create awareness and intent for change, we also engage with governments, industry peers, civil societies, influencers and experts, sharing best practices and urging them to develop, influence and implement regulations on the industry to discourage irresponsible discharge into the environment.

Towards our customers and business partners in the industry, in partnership with India's premier technology institute, IIT Delhi, we conduct educational STEM workshops to share technology developments, best practices that can be implemented in their own operations and overall awareness about AMR and the industry's role in containing it.

There is immense scope for the industry to contribute to the slowing down of AMR of which the main elements are captured in the commitments of the Industry Roadmap on combatting AMR:

1. **Reduce the environmental impact from the production of antibiotics**, including a review of the companies' manufacturing and supply chains, and work with stakeholders to establish a common framework for assessing and managing antibiotic discharge;
2. **Help ensure antibiotics are used only by patients who need them**, recognizing this requires concerted efforts from many stakeholders, through continued provider and patient education, an examination of the companies' promotional activities, sharing of surveillance data with public health bodies and healthcare professionals, and collaboration with stakeholders to reduce uncontrolled antibiotic purchase;
3. **Improve access to current and future antibiotics, vaccines, and diagnostics**, including working with stakeholders to strengthen global health systems and address access bottlenecks; establishing new business models that balance access needs, appropriate antibiotic use, expanded vaccine coverage and adequate return to companies; and working to reduce the prevalence of substandard /counterfeit antibiotics in high-risk markets; and
4. **Explore new opportunities for open collaborations between industry and the public sector** to address challenges in the research and development of new antibiotics, vaccines, and diagnostics, recognizing the value these bring to society.

We are in this together

Regulators,the industry, health care specialist, patients and all other stakeholders in society have a joint responsibility to ensure that antibiotics remain effective.The onus of containing AMR lies on each one of us, just like we will all be affected when antibiotics no longer work. All of us, as individuals, have a role to play in consuming antibiotics responsibly and in disposing off expired medicines we may find in our cabinets.

As the industry, our role is larger, because as providers, we should also be the stewards. We should be responsible for not just our manufacturing and environmental footprint, but help to ensure that antibiotics are used by only those who need them. The regulators' role is to ensure that all manufacturers, hospitals, etc. treat their waste adequately, as per fair, science-based parameters.

It is important to keep in mind that the antibiotics that cure us, if misused, can also kill us, and without antibiotics, the world could regress to what can only be called the 'dark pre-antibiotic age' of medicine. The millions of lives saved by antibiotics each year will be put in jeopardy, and illnesses as basic as diarrhoea, will become life-threatening again.

The failure of the healthcare system will also result in the toppling of the pharmaceutical industry, not just antibiotic manufacturers, but also manufacturers of other medications and medical devices where the procedure or treatment is dependent on antibiotics, such as surgeries, management of terminal illnesses, etc.

So, the loss will be on all of humanity to bear, and it is only fair that we share the responsibilityto fight all causes of AMR ■

**** Mr. Tim Rutten is Business Director-Asia Pacific & Africa at DSM Sinochem Pharmaceuticals***