How antibiotic resistance is driven by pharmaceutical pollution

Factories in India making cheap antibiotics for the world are dumping their waste, with grim consequences for people living nearby – and global health too

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Batte Shankar is the head of Edulabad, one village affected by polluted water
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THE Medak district, to the north-west of Hyderabad in southern India, was once a pristine landscape. People came to bathe in the cool, refreshing lakes and streams. These days the air is foul. With every breath, chemicals irritate your lungs and, after a while, you feel nauseous. The colour of the water doesn't help: it ranges from bright orange to deep brown, and is often covered in a thick layer of white foam.

The reason for this blight is not well hidden. Behind high walls and barbed wire fences, factories churn out cheap drugs for the global market. Tall chimneys belch black smoke and tankers trundle along dirt tracks under cover of darkness to dump toxic chemical waste. “It’s like a slow poison,” says Batte Shankar, the head of one village we visited. “When you Europeans are taking these antibiotics to heal, it is good for you. But we are suffering.”

However, when we came to the region to investigate the environmental situation and its consequences for the health of the people who live there, we were also aware of something even more insidious.

The foetid lakes and streams contain extraordinarily high concentrations of antibiotics, creating reservoirs of the drug-resistant pathogens that kill hundreds of thousands of people every year. Some suspect these places might even be incubating new superbugs that could rapidly spread around the world.

Now the challenge is to figure out whether people in this part of India are being harmed by antibiotic pollution, and the extent to which global health is in the firing line. It is also part of a last-ditch attempt to convince the authorities in India and elsewhere to take the problem seriously before it is too late.

Drug factories near Hyderabad in India are polluting the water
Alice Bomboy

When the first tranche of antibiotics were introduced to the world in the 1950s, they were a revelation. Almost overnight, people stopped dying of common bacterial infections. But then the bacteria fought back. When you treat an infection, microbes carrying genes that make them immune to such drugs survive. If bacteria repeatedly encounter the same antibiotic, natural selection ensures that those microbes with resistance come to dominate the population – and the drugs stop working.

That is how we ended up where we are today, with antibiotic resistance rising to dangerously high levels across the world and our ability to treat common infectious diseases under serious threat. In Europe, drug-resistant infections are responsible for the deaths of 33,000 people every year, according to a recent study published in *The Lancet*. Worldwide, the annual death toll attributed to antibiotic resistance is estimated to be as high as 700,000 – and it is expected to get a lot higher. A 2016 report suggested that, by 2050, 10 million people will die each year as a result of the problem.

The crisis is typically attributed to the excessive use of antibiotics. Over the past decade or so, environmental contamination has also come under the spotlight. When we take antibiotics, we excrete somewhere between 30 and 90 per cent of the active compound and it is flushed down the toilet. Antibiotics used on farm animals also end up in rivers, lakes and groundwater.

A treatment plant in Hyderabad, India

Alice Bomboy

However, the one source that has largely been overlooked is the waste produced by the pharmaceutical factories that make the drugs in the first place. Many of those factories are in China and India, where cheap labour is abundant and environmental regulations tend to be scarce. The Medak district is a good example. It has become India's main pharmaceutical hub. More than 150 drug manufacturers have factories in the area, many of which produce antibiotics. Almost inevitably, the industry has taken its toll on the surroundings.

Gaddapotharam Lake once irrigated rice paddies
Alice Bomboy

When we toured the area last October with Anil Dayakar, an activist from an Indian environmental campaign group called Gamana, we saw it first hand. Gaddapotharam Lake, for example, was once used to irrigate rice paddies. It is now so contaminated that farmers have abandoned the area. We also visited Isnapur Lake, right in front of a cluster of pharmaceutical plants, where the smell is so foul that, within minutes, you feel physically sick. Here, Dayakar pointed out tracks left in the muddy banks by the tankers that come at night to dump industrial waste rather than taking it to the local treatment plant.

Effluent has led farmers to abandon the area around Gaddapotharam Lake
Alice Bomboy

Everywhere you look, you see pollution from the pharmaceutical factories. It wasn't until Joakim Larsson began to investigate further, however, that Dayakar and his colleagues really came to understand the full extent of the problem.

An environmental pharmacologist from the University of Gothenburg in Sweden, Larsson has spent most of his career exploring the impact of pharmaceutical consumption. "Basically, it's about how the environment is being contaminated through pee and poo," he says. In 2007, he also turned his attention to pollution from manufacturing, which brought him to Hyderabad. He wanted to see just how much of the antibiotic compounds being produced end up in the local lakes and streams.

What he found was astonishing. In effluent at the local industrial waste-water treatment plant, the concentration of a common antibiotic called ciprofloxacin was 1000 times higher than is required to kill the bacteria it targets – and a million times higher than the levels typically found in sewage outflows elsewhere in the world. "There was enough ciprofloxacin in the effluent leaving the plant each day to treat everyone in a city of 45,000 people," says Larsson.

The concentrations were so high, in fact, that Larsson had the samples independently analysed because he was worried that no one would believe the results. When the confirmation came, the upshot was clear. "After this study, we knew antibiotics were not

only contaminating the environment through excrement," says Larsson. They were also being released in large amounts as a result of pharmaceutical production.

Two years later, Larsson and his colleagues took samples from the stream running down from the same waste-water treatment plant, two nearby lakes that weren't thought to be contaminated and wells in six surrounding villages. Again, he found exceptionally high concentrations of drugs in several of the wells and in both lakes.

When we visited the Telangana State Pollution Control Board, which is responsible for preventing water pollution in the Medak area, it admitted that illegal dumping occurs. But it denied this was out of control. And it told us it isn't obliged to look for antibiotics in the environment. "This is not required by the national standards and we don't have the facility for that," says Sadiq Ali, who leads the board's laboratory in Hyderabad.

Surprisingly, the same is true in Europe. Rules there cover some polluting substances emitted in the air or water, but not active pharmaceutical ingredients, says Kia Salin, an environmental strategist at the Swedish Medical Products Agency.

"The water contained such a high concentration of antibiotics, researchers feared no one would believe their results"

The lack of regulation is largely down to lobbying. Several of the most prominent pharmaceutical companies have openly and repeatedly said that, while they recognise the need to address pollution from manufacturing, they prefer a "voluntary" approach. Even so, this sorry state of affairs persists in part because the link between antibiotic pollution and the rise of drug-resistant pathogens is still hard to assess.

The doctors we met in Hyderabad estimate that between 30 and 40 per cent of the patients visiting their hospitals carry multidrug-resistant microbes. Unfortunately, it isn't easy to demonstrate a direct connection between pollution and individual infections. "It is true that we don't know to what extent the presence of antibiotics in the environment leads to health problems through the development of antimicrobial resistance," says Larsson.

Superbug soup

What is beyond doubt, however, is that the environment surrounding these factories harbours plenty of the genetic material that makes infectious bacteria resistant. In 2011, Larsson and his colleagues published a study showing that resistance genes made up a worryingly high percentage of the DNA samples taken from three sites downstream of a waste-water plant in the Patancheru industrial area, another cluster of pharmaceutical factories.

What Larsson really wanted to find out was whether people living near the factories carried more resistant bacteria than people elsewhere. The plan was to analyse faecal samples from people living in and around Patancheru, and from those further away, to investigate the extent to which they carried bacteria with resistance to ciprofloxacin. But the researchers were too late. “The resistance was already everywhere, not only in Patancheru, but all around Hyderabad,” says Larsson. “It spreads so quickly that it’s difficult to show when and where resistance appears in the first place.”

Some of the people who work near the drug factories around Hyderabad complain of constant skin problems
Alice Bomboy

Ultimately, it may be impossible to track down the source of resistance affecting individuals. Over the past few years, however, several studies published by Larsson and others have strongly indicated that antibiotic contamination promotes the propagation of resistance genes and accelerates their spread among bacteria. In 2015, for instance, Larsson and his colleagues investigated Kazipally and Asanikunta lakes in the same part of India. They are known to be heavily polluted with a group of antibiotics known as fluoroquinolones, which includes ciprofloxacin. The researchers sampled sediments from both lakes and measured the proportions of resistant bacteria they hosted. The results were alarming: 50 per cent of the bacteria there were resistant to ciprofloxacin compared with just 2 per cent in Swedish lakes and unpolluted Indian lakes.

The implications aren't hard to fathom. When bacteria reside in highly concentrated antibiotic soups like those around Patancheru, any without resistance will quickly die off. Only those with resistance genes will survive and multiply. "The antibiotics in the industrial waste [around Patancheru] are selecting for resistance," says Larsson. "That is beyond reasonable doubt."

And even if the resistance genes aren't present in human pathogens to begin with, they can easily end up in them. In Kazipally Lake, the researchers also identified 11 different kinds of self-replicating rings of DNA, known as plasmids, that were carrying resistance genes. Plasmids are known to play a key role in the spread of antibiotic resistance because they facilitate horizontal gene transfer. This is when genetic material from one microbe ends up in another organism without the need for traditional "vertical" transmission of DNA from parent to offspring. So resistance genes don't have to be inherited to spread.

"Do people living close to the antibiotic factories carry more resistant superbugs than others?"

Due to the strong selection pressure they create, high concentrations of antibiotics in the environment could also give rise to new resistance genes that may render yet more antibiotics useless. In the various samples from lakes and streams around Hyderabad, Larsson and his colleagues found many previously unidentified resistance plasmids.

It is possible, then, that the area is harbouring the next New Delhi metalloenzyme (NDM-1), a novel resistance gene that makes microbes immune to a class of antibiotics called carbapenems. It was discovered in a man in Sweden in 2008 after a trip to India, before rapidly spreading around the world. Earlier this year, it showed up in the Arctic.

Legislative inaction

For those living close to the pharmaceutical factories around Hyderabad, the situation is excruciating. In July 2018, community activists from the region sent a letter to the European Commission. "[We] urge you to take action and address the grave environmental and human health crisis currently unfolding in India linked to the production of pharmaceuticals for global markets," they wrote.

Action is long overdue. In 2016, 13 drugs companies signed a declaration for collective action on antibiotic resistance, committing to review their manufacturing and supply chains to control pollution. But that is just a "road map". It isn't legally binding, and international authorities have been slow to force the industry's hand on the issue. In March this year, the European Commission unveiled its Strategic Approach to Pharmaceuticals in the Environment. According to the non-profit European Public Health Alliance, however, the initiative "shies away from considering new legislative measures".

If antibiotic pollution continues unabated in developing nations such as India, it will be a huge problem and not only in such places. The case of NDM-1 shows how widely new forms of resistance can spread. And one recent study revealed that 90 per cent of tourists visiting India went home carrying multidrug-resistant bacteria they didn't have before the trip.

But Hyderabad's hinterlands aren't going to stop churning out antibiotics any time soon. In March 2018, local officials announced the construction of Pharma City, a new pharmaceutical park at Mucherla, south of the city, that will host between 900 and 1000 companies. Indeed, local authorities promote this latest venture with the slogan, "minimum inspection, maximum facilitation".

So it seems that despite the best efforts of Larsson and others, for the time being at least, the region will continue to pay a high price for the cheap antibiotics its factories produce.