

India, antimicrobial resistance factory

More than 90% of our antibiotics are manufactured in Chinese or Indian factories, whose some of the effluents end up in the environment, promoting outbreaks of antimicrobial resistance that can spread worldwide as a result of international trade.

Investigation in Hyderabad, India, a major production hub

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At first there is the smell, acrid and irritating, which immediately gives nausea. Then there is the landscape, a huge metal forest, made of high smoking chimneys, pipes, reservoirs, and sheds. There is finally a trickle of yellowish and viscous water, with bubbles dying on the surface. Like a purulent secretion coming from this forest of factories - and we can guess that its flow can increase tenfold because of the marks left on the banks and the waste hanging in the branches. This flow oozes freely across the fields, amidst some skeletal cows, grazing just in front of the village of Gaddapotharam. Before beginning its descent from the plateau, crossing a succession of villages, irrigating several lakes, including that of Gandigudem, where some 200 000 fish were found dead in October 2017. For more than ten years, Swedish, Indian and German researchers, as well as NGOs, such as the Dutch Changing Markets Foundation, have been documenting this persistent contamination. Each of these studies reveals the presence of significant quantities of hazardous products (arsenic, nickel, hexavalent chromium, etc.), surpassing all national and international standards. But there is even more insidious: in the middle of this toxic soup are astronomical antibiotic concentrations, several thousand times higher than what is usually found in hospital or urban effluents. And, as a corollary of this massive pressure, resistant microbes emerge. Aside from human and veterinary consumption of antibiotics, there is a third source of antibiotic resistance which is barely mentioned: that related to the manufacture of these products in Asian factories, which pay little attention to environmental contamination. In other words, those who are responsible for manufacturing our defense tools against bacterial infections actually accelerate their obsolescence...

Anecdotal? Certainly not, as more than 90% of the ingredients of our antibiotics are now manufactured in Chinese and Indian factories. Only four plants still manufacture these primary ingredients in France. Hyderabad, the capital of the Indian state of Telangana, is one of the major production hub in the world. They are all there: Mylan, with his green factories, Aurobindo, who opted for blue, Hetero Drugs, in red. There are also MSN, Neuland, Merck, and through intermediaries and subsidiaries, Sandoz, Sanofi, Pfizer... Some 150 pharmaceutical companies have settled in the suburbs of Hyderabad. *"In the 80s, it was mostly small Indian pharmaceutical plants, for the domestic market. Then in the 90s, because of the environmental standards that hardened in Europe, the manufacturers began to flow. They benefit from cheap labor, very low taxes, very light environmental regulations and thousands of lakes and rivers to dump their waste"* says Gudavarthy Vijay, professor of economics at the University of Hyderabad. Today, the so-called "thousand-lakes city" has

become one of the most polluted areas in the country, according to the Ministry of the Environment.

“Nothing is growing here anymore” says Anil Dayakar, one of the most active environmental activists on the issue, founder of the NGO Gamana. Around Gaddapotharam, one can still see traces of an ancient irrigation system and a rice field, abandoned ten years ago. In the same way, cattle do not produce any more milk and reproduce badly. As for the water from the wells, no one is risking drinking it: tanker trucks bring it. The concentrations of antibiotics measured in these rivers, lakes or wells reach milligrams per liter (up to 30 milligrams per liter), which is 100,000 to 1 million times higher than can be measured in European wastewater. Even patients on treatment do not show such blood levels! Daily discharges of ciprofloxacin correspond to the equivalent of what is consumed in Sweden (ie 9 million inhabitants) in five days, wrote in 2007 Joakim Larsson, a specialist of antibiotic resistance, and his team at the University of Gothenburg, Sweden.

50 km away, in Edulabad, the same story is being repeated. Yet no pharmaceutical factory is installed here: this is the river that brings pollution from the industrial plants. Especially since 2009, after an 18 km long pipeline was built to transport some of the effluent to the main domestic wastewater treatment plant located on the Musi, a river that then irrigates the fields of Edulabad and of a hundred other municipalities. Here too, very high concentrations of antibiotics (more than 2 mg/L) were measured. A proof that this treatment plant is unable to treat this source of pollution. *“This false solution only moves the problem elsewhere”* says Shankar Batte, the Sarpanch of Edulabad. Above all, by mixing antibiotic effluents with waters fully loaded with organic matter (including pathogenic bacteria such as E. coli), it creates the ideal conditions for the emergence of superbugs (see Box 1). In 2016 and 2017, scientists discovered in the effluents of this plant bacterial colonies resistant to the three main families of antibiotics: fluoroquinolones, but also cephalosporins and carbapenems, considered as antibiotics of last resort.

“First the rivers, then the wells and the villages, then the plants and the cattle. And now the superbugs”, says Narasimha Reddy, doctor of political science, committed against this pollution since the 1990s. The specter of the emergence of pathogens resistant to all of our antibiotics now hovers over the city. However it is difficult or impossible to directly link the rejections of antibiotic manufacturers to the growing phenomena of antimicrobial resistance. *“It will always be very difficult to prove that the emergence of a multidrug-resistant pathogen is directly linked to industrial pollution. It would probably rather be a series of pieces of evidence that together would point coherently in one direction”*, explains Joakim Larsson, a scientist who has studied the issue of antibiotic releases by industry for quite a long time, including in Hyderabad. One thing is certain, *“when a doctor prescribes antibiotics, it’s a balanced decision between saving a patient and promoting antibiotic resistance. But when industries release antibiotics into the environment, there is clearly no benefit to be gained. If any, it would be saving on expenses for the manufacturers”*, says the Swedish researcher.

“It’s easy for companies to point out the individual use of antibiotics. We use so much of it today that it has become much easier for them to challenge their own involvement in the

problem of antimicrobial resistance", says Narasimha Reddy. A study paid by an association of Indian pharmaceutical companies has shown, for example, that strains of resistant bacteria can be found everywhere in the Hyderabad environment, *"even in a lake located 50 km upstream of the industrial clusters"*, notes its author, Professor Siddavattam Dayananda. Conclusion of the article: there is therefore no evidence that the presence of these superbugs is linked to the effluents of the factories... But the study do not mention the many cases of illegal discharge well known from local and even the police. In the main square of the village of Edulabad, Parim Chakravarthi comes to fill his can with 20 liters of drinking water. He says: *"Two months ago, one morning very early, we surprised a tanker truck that was about to dump its tank full of chemical effluents into the lake."* The driver ran away. *"We got the truck back"*, says Srinivas Reddy, the chief police officer at the local police station. *Two years ago we had exactly the same story at night. The case is now in the hands of the TSPCP"*.

The TSPCB, or Telangana State Pollution Control Board, is the body responsible for the prevention and control of air and water pollution. According to Chief Engineer Shri P. Vishwanatham, these illegal dumpings are extremely rare, *"once or twice a year"*. This neither matches the data of the various NGOs, nor what can be read in the local press. The unbearable smell? *"When you're next to a biscuit factory you also smell biscuit. There, it is the smell of drugs"*. The water pollution? *"An old story"*, says the engineer: *"all large plants are now equipped with ZLD (zero liquid discharge) they do not let out any pollution. The others bring their effluents to the waste treatment plant"*. Indeed, the companies claim to be equipped with this equipment supposed to treat and recycle all the liquid effluents inside the factories. Only solid waste (8000 tons per year for a company like Aurobindo) is deposited in a dedicated site. However, no industry has accepted to be transparent and to show us how this innovative system works. According to Aurobindo, the complete equipment requires an investment of nearly 9 million euros and an annual operating cost of 4.4 million euros. It is said here that companies are reluctant to use this system continuously, precisely because of this significant additional cost. An accusation impossible to verify given the opacity of these factories. Aurobindo, owner of Arrow which has a strong presence on the market of the antibiotherapy in France, hasn't hesitated to threaten us to sue us in case we'd claim that its factories take part in the local pollution.

At the TSPCB, they say they randomly control manufacturers every six months. The agency also carries out regular samplings in the effluents downstream the factories. According to their data, only 10% of factories do not meet the national criteria. *"In this case, we send a notification to the concerned manufacturer"*, says Mohammad Sadiq Ali, who heads the TSPCB laboratory. *Then we give them time to fix the problem. But if a second sample is bad, we can ask to close the plant"*. Of the 150 pharmaceutical companies, two are temporarily closed for pollution each year, says Shri P. Vishwanatham.

But what is presented to us as an excellent control process hides a considerable flaw: *"We are not looking for antibiotics and other pharmaceutical residues. We do not have the laboratory for that and it's not written into our national recommendations"*. A shocking gap, which is actually not specific to India. Nowhere in the world are the emissions of

pharmaceutical products rejected by manufacturers regulated by official standards. *“In Europe, if you have a permit to manufacture pharmaceuticals, the Industrial Emissions Directive will tell you to respect limits regarding several polluting substances emitted in the air or water. Among them are a number of volatile compounds, metals, etc. But there are no mention of active pharmaceutical ingredients (the raw materials used to manufacture drugs, ed.)”* says Kia Salin of the Swedish Medicines Agency. Measures restricting the marketing of medicines concern only the quality and traceability of products. Recommendations also exist to limit the environmental impact of their use by patients, but never focus on the manufacturing process. A major legislative gap that many associations, MEPs and EU member states have been fighting for almost ten years (see Box 2). Unsuccessfully for the moment.

Another major weakness in controlling this pollution is the problem of corruption, which plagues Indian politics and its institutions. Visakhapatnam, located 600 km east of Hyderabad, has become a new hub of pharmaceutical production, allowing dilution of effluents directly into the Bay of Bengal. In July 2018, one of the environmental engineers of the local PCB was accused by the anti-corruption Bureau of personal enrichment by issuing authorizations and inappropriate certificates to industrials. *“You can wake up a man who sleeps but not a man who pretends to sleep”*, said Anil Dayakar, for whom all actors close their eyes to this insidious pollution.

In Hyderabad, the various hospitals consulted estimate that 30 and 40% of the patients carry multidrug-resistance. *“Wherever you have antibiotics, resistant bacteria can emerge. Outside the hospital and inside”*, says Ratna Rao, who heads the microbiology lab at Apollo City Hospital, one of the largest private clinics in the city. Antibiotic resistance is a collective task. Especially today with all those people who travel from one place to another. According to the different studies, between 70 and 90% of people returning from India carry multidrug-resistant bacteria, whereas they didn't before they left. *“For most of these people, this will go unnoticed and the bacteria will disappear after a month. The problem arises if, for one reason or another, the person becomes infected with these bacteria (urinary tract infection for example) or if he transmits them to other people who are suffering from an immune deficiency or who have wounds”*, explains Etienne Ruppé, bacteriologist at the Bichat-Claude Bernard Hospital in Paris, who has conducted several studies among French travelers.

In 2008, multidrug-resistant bacteria were found in Sweden in a diabetic patient who had been hospitalized a few months earlier in India. The researchers had then identified a new resistance gene, encoding an enzyme called "New Delhi metallo-beta-lactamase 1" (NDM-1, which had not pleased the Indian authorities). This enzyme is able to inhibit most of our antibiotics, even those of last resort. A study in 2010 revealed that this new resistance mechanism was already widely distributed in India, Pakistan, but also in the United Kingdom. *“We first pointed out the important medical tourism between the United Kingdom and India, before discovering, in 2011, that these multi-resistant bacteria could also be acquired ... by drinking tap water from New Delhi!”*, says Etienne Ruppé, whose book *Les antibiotiques, c'est la panique* has just been published by Editions Quæ.

It is estimated that around 700,000 people die each year worldwide from antibiotic-resistant infections, 25,000 of which are in Europe, and probably three times as much in India alone. If these miracle drugs stop working, no country will be more affected than India given the burden of infectious diseases in this region. And we shouldn't rely on new molecules: there is not much in the pipelines of pharmaceutical companies.

Everywhere, we try to reduce human and animal antibiotics consumption, in the hope of curbing this phenomenon. But these efforts may be in vain as long as we continue to generate superbugs during the actual manufacturing process. *"We know how to produce these drugs with less ecological impact, says Alban Dhanani, in charge of antibiotics at the French National Agency for the Safety of Medicines (ANSM). The blocking element lies in the economic model that is not adapted to antibiotics"*. In fact, all experts say: producing antibiotics is not a profitable activity. *"The prices are so low, we must produce huge volumes to hope to get out"*, confirms Marie-Helene Dick, president of Panpharma, the leader of injectable antibiotics in France. The company buys all its raw material abroad, especially in China where *"since two winters, our suppliers have to close their factories because of pollution"*, explaining the situation of permanent tension or even shortages. Hence, there is an insoluble contradiction between the public health recommendations, which aim to limit the use of antibiotics, and this economic model that pushes towards mass consumption. A paradox that is not ready to unravel: the new slogan of Telangana State is *"minimum inspection, maximum facilitation"*. A gigantic project, called "Pharma City" is on track. It is expected to attract no less than 900 to 1,000 industry users. Hyderabad will continue to pay the high price of our cheap drugs...

Box 1: Handshake of resistance genes

Bacteria have a huge advantage on us: they can share DNA as we shake hands. By a phenomenon called horizontal gene transfer, DNA can travel from one bacteria to another. Instead of giving hands, bacteria use an appendage called pili, a kind of tube in which mobile DNA can run through. Originally torn from the genome of bacteria, these traveling DNA named plasmids may include antimicrobial resistance genes. These genes result from a thousand-year struggle between microorganisms, which naturally produce antimicrobial molecules to limit the proliferation of competing bugs. Bacteria must indeed constantly develop parades to survive, either by degrading these molecules or by rendering them inactive. The same mechanism can be promoted when the environment contains a large number of man-made antibiotics. The most resistant microbes take advantage of the situation and share their advantages with the neighboring bacteria. And if excrement discharge take place at the same place, it's the jackpot. Why ? Because in our excrement are bacteria potentially pathogenic for humans, who can then acquire new forms of resistance. This is exactly what is happening today in Hyderabad, with this mixture of effluents from the antibiotics factories and black waters of the city. Added to this is the Indian overpopulation and the hygiene conditions of the villages upstream: the recipe seems perfect to see the emergence of epidemics of superbugs ...

Box 2: European inaction pointed out

In 2017, 759 tons of antibiotics for human health were sold in France. Can consumers continue to turn a blind eye to environmental and health damage unfolding thousands of miles away from home by the manufacture of drugs used to treat them? This is basically the question asked by Indian activists and representatives of local communities last July, when they sent a letter to the European Commission, urging to act against "*the serious crisis related to the production of drugs*" currently underway in their country. Several associations, such as Changing Markets, Health Care Without Harm and the European Public Health Alliance, alongside countries like Sweden, are pushing for higher environmental standards - with no real progress to date. It was not until 2011 that a European Action Plan against antimicrobial resistance mentioned the problem of pollution by production sites. In 2013, a directive requires Member States to develop a strategic approach against water pollution by pharmaceutical substances within two years. But the discussions have only started this year... One of the intended measures plan to include environmental criteria in the GMP guidelines for Good Manufacturing Practice. "*This is a system already in place: European inspectors can travel to India to visit factories manufacturing medicines for the European market and make sure that they are safe for consumption. Such a procedure could be extended quite simply to environmental pollution*", says Kia Salin of the Swedish Medicines Agency. But this proposition has already been partially sabotaged under the pressure of pharmaceutical lobbies, who openly welcome European inaction. "*I have never seen the industry be so outspoken about their opposition to legislation. What makes it even worse is that this is the part of the industry that should lead the efforts to address AMR, the so-called AMR industry alliance!*", said Nusa Urbancic, Campaign Director for Changing Markets.