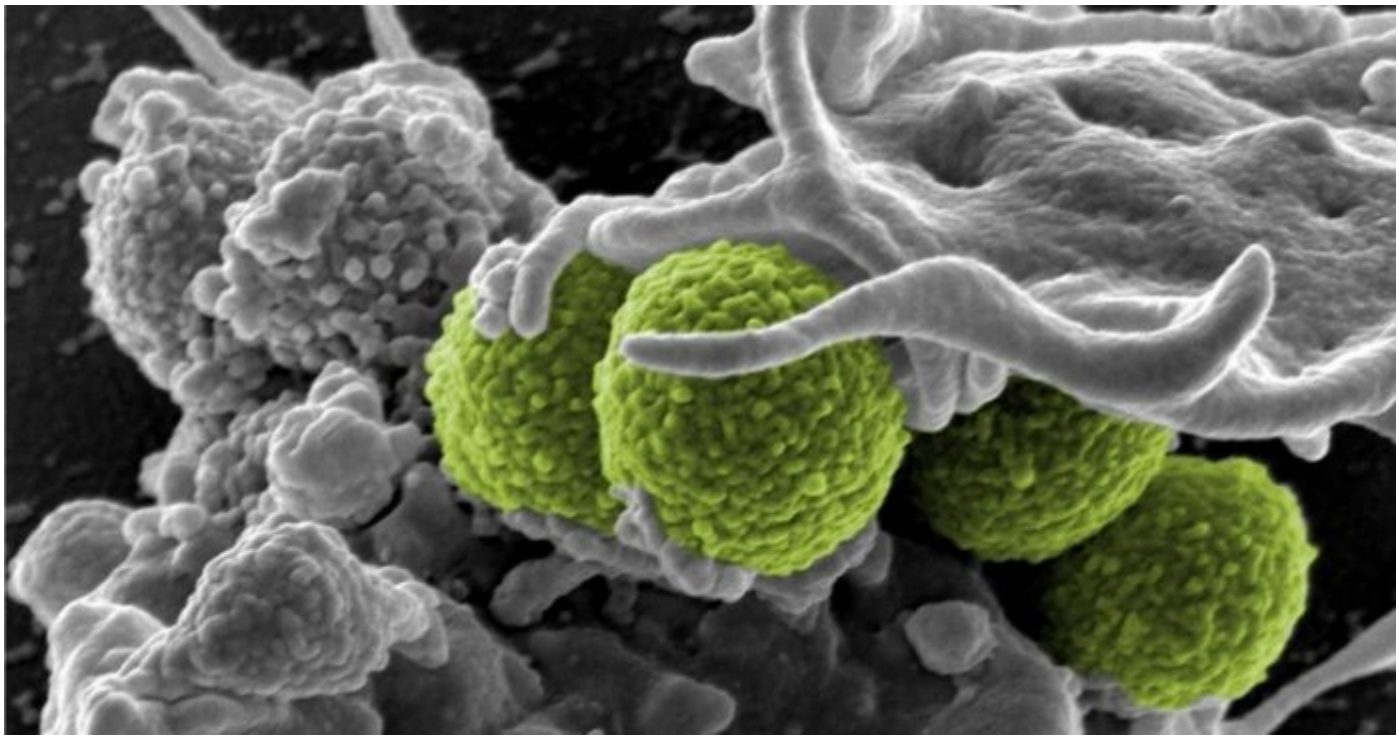
Big Pharma's pollution is creating deadly superbugs while the world looks the other way

Environmental standards do not feature in international regulations governing drug production.

By Madlen Davies - May 8, 2017 | News Investigation



SOURCEThe Bureau for Investigative Journalism

Industrial pollution from Indian pharmaceutical companies making medicines for nearly all the world's major drug companies is fuelling the creation of deadly superbugs, suggests new research. Global health authorities have no regulations in place to stop this happening.

A major study published today in the prestigious scientific journal *Infection* found "excessively high" levels of antibiotic and antifungal drug residue in water sources in and around a major drug production hub in the Indian city of Hyderabad, as well as high levels of bacteria and fungi resistant to those drugs. Scientists told the Bureau the quantities found meant the drug residues must have originated from pharmaceutical factories.

The presence of drug residues in the natural environment allows the microbes living there to build up resistance to the ingredients in the medicines that are supposed to kill them, turning them into what we call superbugs. The resistant microbes travel easily and have multiplied in huge numbers all over the world, creating a grave public health emergency that is already thought to kill hundreds of thousands of people a year.

When antimicrobial drugs stop working common infections can become fatal, and scientists and

public health leaders say the worsening problem of antibiotic resistance (also known as AMR) could reverse half a century of medical progress if the world does not act fast. Yet while policies are being put into place to counter the overuse and misuse of drugs which has propelled the crisis, international regulators are allowing dirty drug production methods to continue unchecked.

Global authorities like the Food and Drug Administration and the European Medicines Agency strictly regulate drug supply chains in terms of drug safety – but environmental standards do not feature in their rulebook. Drug producers must adhere to Good Manufacturing Practices (GMP) guidelines – but those guidelines do not cover pollution.

Even the World Health Organisation (WHO) – a global public health body which has repeatedly called for concerted international action to tackle the dangerous threat of antibiotic resistance – buys antibiotics from companies whose drug ingredients are made in Hyderabad without carrying out environmental checks.

The international bodies say the governments of the countries where the drugs are made are the ones responsible for stopping pollution – but domestic legislation is having little impact on the ground, say the study's authors. The lack of international regulation must be addressed, they argue, highlighting the grave public health threat faced by antibiotic resistance as well as the rampant global spread of superbugs from India, which has become an epicentre of the crisis.

"Unprecedented antimicrobial drug contamination"

A group of scientists based at the University of Leipzig worked with German journalists to take an in-depth look at pharmaceutical pollution in Hyderabad, where 50% of India's drug exports are produced. A fifth of the world's generic drugs are produced in India, with factories based in Hyderabad supplying Big Pharma and public health authorities like World Health Organisation with millions of tons of antibiotics and antifungals each year.

The researchers tested 28 water samples in and around the Patancheru-Bollaram Industrial zone on the outskirts of the city, where more than than 30 drug manufacturing companies supplying nearly all the world's major drug companies are based. Thousands of tons of pharmaceutical waste are produced by the factories each day, the paper says.

Almost all the samples contained bacteria and fungi resistant to multiple drugs (known as MDR pathogens, the technical name for superbugs). Researchers then tested 16 of the samples for drug residues and found 13 of them were contaminated with antibiotics and antifungals. Previous studies have shown how exposure to antibiotics and antifungals in the environment causes bacteria and fungi to develop immunity to those drugs.

Environmental pollution and poor management of wastewater in Hyderabad is causing "unprecedented antimicrobial drug contamination" of surrounding water sources, conclude the researchers – contamination which appears to be driving the creation and spread of dangerous superbugs which have spread across the world. Combined with the mass misuse of antibiotics and poor sanitation, superbugs are already having severe consequences in India – an estimated 56,000 newborn babies die from resistant infections there each year.

"We need to take environmental contamination from bulk manufacturing facilities seriously and put an immediate end to the practice"

German broadcaster NDR, which contributed to the study, identified 19 companies operating inside the area tested as suppliers of antibiotics to the European market. Of those 19, the Bureau has identified at least four companies which supply the UK and five which supply the U.S.

The companies in question strongly deny that their factories pollute the environment, and the sheer number of factories operating in Hyderabad means it is impossible to identify exactly which companies are responsible for the contamination found in the samples tested.

What is clear is one of the world's biggest drug production hubs is producing dangerous levels of pharmaceutical pollution, and the international bodies tasked with ensuring drug safety are doing little to address it.

Health regulators have to take action, said Professor Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics & Policy and a leading voice on antibiotic resistance. "We need to take environmental contamination from bulk manufacturing facilities seriously and put an immediate end to the practice," he said. "This should be a part of GMP without question and pharmaceutical companies throughout the world should be subject to an audit to ensure that they are compliant with what the industry has promised to do."

The epicentre of a global crisis

The densely populated and increasingly prosperous city of Hyderabad in southern India was once an international trading centre for diamonds and pearls. Today, it is a major international hub for the pharmaceutical and biotech industries, producing millions of tons of medicines, chemicals and pesticides each year.

Around 170 companies making bulk drugs like antibiotics operate in and around Hyderabad, the majority clustered in sprawling industrial estates along the banks of the Musi river. Companies in Europe and the U.S., as well as health authorities like WHO and the UK's NHS are reliant on drugs being produced in these factories.

The area has long been criticised for its pollution, which has continued unabated despite decades of campaigning by Indian NGOs, say the report authors. In 2009 the Patancheru-Bollaram zone was classified as "critically polluted" in India's national pollution index and construction in the area was banned. But the government relaxed the rules in 2014 and building was allowed to begin again.

56,000

Newborn Indian babies estimated to die from drug-resistant infections each year

70-90%

Of all travellers to India return with drug-resistant bacteria in their gut

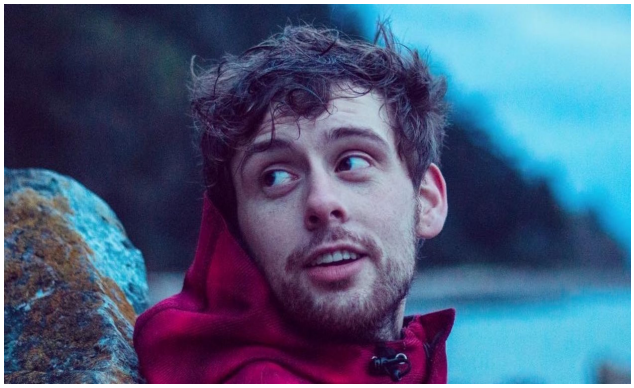
Last year India's Supreme Court ordered the country's pharmaceutical companies to operate a zero liquid waste policy, but "massive violations" have reportedly occurred, says the *Infection* report.

As India's drug production industry has grown, so has the prevalence of superbugs – a national crisis intensified by the widespread overuse and misuse of antibiotics, which are easily bought over the counter, and poor sanitation Alongside the creation of individual superbugs, genes and enzymes have developed which can pass between multiple types of bacteria, making them resistant to drugs.

India has become the epicentre of the global drug resistance crisis, with 56,000 newborn Indian babies estimated to die each year from drug-resistant blood infections, and 70 to 90% of people who travel to India returning home with multi-drug-resistant bacteria in their gut, according to the study.

The bacteria can remain in the gut without causing problems, but if they travel from there into a patient's bloodstream or urinary tract they can cause serious infections. They can also pass on resistance to other bacteria in the gut – so if a patient gets food poisoning the bacteria that caused it could acquire the resistance and become hard to treat.

An AMR nightmare: David Ricci's story



David Ricci was just 19 when his life changed dramatically. He was hit by a train while walking through the slums of the Indian city of Kolkata where he was helping care for orphaned children. He was left screaming in agonising pain on the pavement until he blacked out. Later, at a local hospital, a surgeon took a bundle of knives wrapped in a dirty cloth and amputated his leg without any anaesthetic – a traumatic event that was just the beginning of his ordeal.

Back in Seattle his wound became infected. Doctors pumped him with antibiotics with little effect until eventually they were forced to perform further surgery to cut out parts of his infected stump. Finally, he was told he had caught two superbugs, which the doctors struggled to treat. He was lucky the bugs were confined to the wound, doctors said. If they had got into his blood he would have died.

The bugs were immune to standard antibiotics so doctors had to to turn to stronger drugs used sparingly in modern medicine because they have nasty side effects. David was drip-fed colistin, a toxic antibiotic reserved for emergencies, but had to be taken off it after a week because his organs began to shut down. He was then given tigecycline, a new antibiotic developed for resistant infections. He had to inject the drug for six months, the dose bumped up whenever the infection returned. It made him feel so nauseous he could barely watch television or make a cup of coffee; he had to spend his days lying around in pain, hoping this course would finally kill the bacteria. "It felt like I was being treated for cancer", he said. "I would wake up thinking 'Please take me off it, please make this stop.'"

David had picked up various bugs in India that contained a gene known as NDM-1, named after New Delhi where it was first discovered in 2008. NDM-1 gives bacteria ability to produce enzymes which break down carbapenems, a group of powerful antibiotics which are used to treat infections that have become resistant to other drugs. Bacteria that are able to resist carbapenems have been called the "nightmare" bacteria by the U.S. Center for Disease Control and Prevention because half of all people who contract a bloodstream infection from them die.

"The whole experience has made me feel lucky to be alive"

NDM-1 has spread across the world since it was discovered. At least 175 people in the U.S. have been treated for an NDM-1 infection since 2009, although there are likely to have been many more cases as hospitals are not required to report it. While many cases come from abroad, infections in patients who have not left the U.S. are now being reported.

NDM-1 is also starting to appear in the UK. There have been 1,129 reports of the bacteria in England since 2003, and this is thought to be a conservative figure.

David eventually recovered, but antibiotic resistance has changed the course of his life. he works with campaigning organisations and talks to members of congress about the issue, and wants to work in medicine in the future.

"I feel like I have a purpose", he said. "The whole experience has made me feel lucky to be alive."

Antimicrobials found at levels thousands of times higher than the safe limit

Many previous studies have highlighted pharmaceutical pollution in India and China – which together produce most of the world's antibiotics – and shown how such pollution fuels the proliferation of superbugs worldwide. The

authors of the new *Infection* study set out to provide a detailed picture of the levels and types of pollution in Hyderabad and its links to drug resistance.

Researchers took water samples from rivers, lakes, groundwater, drinking water and surface water from rural and urban areas in and around the industrial estate, as well as pools near factories and water sources contaminated by sewage treatment plants. Four were taken from taps, one from a borehole, and the remaining 23 were classed as environmental samples.

The samples were tested for bacteria resistant to multiple drugs (known as MDR pathogens, the technical name for superbugs). The researchers then tested 16 of the samples for the antibiotics and antifungals used to treat infections.

"To our knowledge, this is the highest concentration of any drug ever measured in the environment"

All samples apart from one taken from tap water at a four star hotel were found to contain drug-resistant bacteria. All 23 environmental samples contained carbapenemase-producing bacteria – a group of bugs dubbed the "nightmare bacteria" because they are virtually untreatable and kill 40-50% of people whose blood gets infected with them.

Of the 16 samples then tested for drug residue, 13 were found to be contaminated with antibiotics and antifungals, some in disturbingly high levels. The researchers compared the levels of residue to limits recommended by leading microbiologists; once levels exceed those limits it is likely that superbugs will develop.

A sample taken from one sewer contained concentrations of the antifungal drug fluconazole – a drug used in ointments for fungal infections such as thrush and athlete's foot or given intravenously for more serious infections – at levels 950,000 times higher than the recommended safe limit. The researchers repeatedly analysed this finding to make sure it was correct. "To our knowledge, this is the highest concentration of any drug ever measured in the environment," wrote the authors.

A member of the inspection team looks at a pond connected to a sewer in the industrial zone. Image credirt: Christian Baars (NDR)

"Excessively high" concentrations of antibiotic and antifungal residue were found in the natural environment. Image credit: Christian Baars (NDR)

Samples from sewers in the industrial area were also found to contain "extremely high concentrations" of nine different antibiotics. Levels of moxifloxacin – used to treat lung, skin and sinus infections as well as tuberculosis – were up to 5,500 times higher than the recommended limit, while another common antibiotic ciprofloxacin was found at levels up to 700 times above that recommended. Concentrations of the antibiotics clarithromycin

and ampicillin were found at levels more than 100 times higher than the safe limit.

The amounts of antimicrobials found in the new tests were "eye-wateringly high", said Dr Mark Holmes, a microbiologist at the University of Cambridge. "The quantities involved mean the amount in the water is almost the same as a therapeutic dose," he said, calling on the Indian authorities to investigate immediately by testing each factory's effluent. "That's not just getting rid of a few tablets down the toilet."

16

Water samples tested for drug residue

13

Found to be contaminated

Pharmaceutical pollution is not the only way in which antibiotics get into the Indian environment – excrement from people and animals and waste from hospitals and farms also contain residues of the drugs. But some of the levels detected in the recent testing mean the residues can only have come from bulk manufacturing, according to scientists.

Professor Joakim Larsson, of the University of Gothenburg believes the levels of antimicrobials found could not be explained by anything else other than industrial discharges. "So it tells us that the problem is still there, it needs to be solved," he told German journalists who worked on the report.

The pharmaceutical industry in Hyderabad produces "enormous amounts" of waste each day, says the *Infection* report. Effluent is transported in trucks to one waste treatment plant, it says, where it is treated before being sent to a mega sewage plant. There, it is mixed with sewage and further treated then discharged into the nearby Musi river.

Adhering to the zero liquid waste policy ordered by the Supreme Court requires expensive technology, and some waste is still clandestinely sent to the waste treatment plant or dumped straight into the surrounding environment, according to the report.

Links to U.S. and UK markets

Virtually all of the world's major drug companies are supplied by production plants in Hyderabad. Various companies whose factories are located next to or near sites where the water samples were taken supply the U.S. and UK markets, though with such huge amounts of antibiotics present throughout the Indian environment it is impossible to concretely link specific factories to specific test results.

Using the Bulk Drug Manufacturing Industry's 2015 manual, which lists all Indian drug manufacturers, their locations and their products, journalists at NDR were able to identify 19 companies operating in the Patancheru-Bollaram area which produce the antimicrobial drugs found in the water samples. (There may be other unnamed manufacturers operating in the area or companies which do not advertise which antimicrobials they produce.)

The Bureau has linked a number of these companies to the U.S. and UK markets. MSN Pharmachem is one of the fastest growing drug manufacturers in India. It makes the raw ingredient of the antibiotic moxifloxacin on behalf of international drug companies Macleods and Sun Pharmaceuticals, which then turn it into a finished product supplied to the World Health Organisation.

Other major companies operating in the zone which supply the U.S. and UK markets include Aurobindo, a leading Indian producer which exports to more than 150 countries around the globe, and Mylan, a company which claims its products fill one out of every 13 prescriptions dispensed in America. Mylan also supplies the European Union market, and says it is the fourth biggest supplier of generic (non-branded) drugs in the UK.

"We are committed to a clean environment, health of all our employees, neighbors, partners and customers"

The companies strongly refute suggestions that their factories are responsible for pollution.

MSN Pharmachem said it conformed to the highest industry standards, applicable laws and regulations, and operated a zero discharge policy at its factories.

"Our sites are regularly monitored internally and inspected externally," said a spokesperson. "We are committed to a clean environment, health of all our employees, neighbors, partners and customers."

Aurobindo said it was impossible any pollution could have originated from its factories as it also operated a zero liquid waste policy – all waste is treated and recycled within the plants. It also said the topography and water flows of the relevant locations meant not even rainwater or drain water would be able to flow from its factories to the sample collection sites.

Mylan also said its factory could not have contributed to the residues identified by the researchers, as all its plants operated a zero liquid waste policy whereby all effluent is recycled and reused on site. It has its own wastewater treatment systems at all its Hyderabad plants, said a spokesperson, which use advanced technology to eliminate harmful waste. "These plants are operated 24 hours a day, seven days a week by qualified individuals," said the statement.

Macleods and Sun Pharmaceuticals did not respond to requests for comment.

A WHO spokesperson said the organisation did not buy the drug ingredients, just the final medicine, and had no contact with ingredient manufacturers. "Manufacturing sites are typically inspected for Good Manufacturing Practice (GMP) which focuses on ensuring consistent quality for the product in question from the perspective of human health risk," said a statement. "GMP does not address waste management and environmental management measures vis-à- vis emissions and pollution control – as here relevant domestic environmental and industrial regulations would apply."

Food poisoning turned into a near-death experience

Andrew, 57, and his wife Sally fell ill with upset stomachs soon after arriving in New Delhi to take up a new job.

While his wife quickly recovered, Andrew took weeks to get better. He had another bout of severe sickness and diarrhoea a few months later, and kept getting ill sporadically for the rest of the year.

"What we didn't know then was that he'd contracted a serious bacterial infection that was now living in his body," said Sally. "His personality changed. He became extremely anxious, he couldn't relax, felt ill and was distracted. I was so worried, our life was really deteriorating in every aspect."

His condition got worse over time, and Andrew was admitted into hospital where he was told he had a urinary tract infection.

The hospital prescribed powerful intravenous antibiotics, which initially seemed to work, but a few weeks later he woke up with a fever. He was rushed back to hospital, where doctors said dangerously ill with sepsis – his organs were shutting down.

He recovered enough to return to the UK, where doctors at the London School of Hygiene & Tropical Medicine said his infection contained NDM-1. Tests showed it was resistant to all antibiotics save one, fosfomycin. Andrew and Sally got their affairs in order, fearing he would die if the infection returned.

Friends began to avoid him believing they might catch the bacteria. Now retired and under the care of specialists, he and his wife worry that NDM-1 is so widespread in India it is only a matter of time before it becomes more common in the UK.

"Unless companies are called for account for their distribution of waste, until the Indian government starts teaching hand hygiene in

hospitals and in catering facilities like hotels and restaurants, the possibility of this infection spreading worldwide is huge," said Sally. "It's a cliché to say 'I don't want people to go through what we went through' but it's true. It's changed our life."

Names have been changed to protect identities

No mention of pollution in global regulations

There are reams of regulations and stipulations that manufacturers have to adhere to in order to export their products to the U.S. and Europe – known as the Good Manufacturing Practices (GMP) framework. These focus on making sure drugs are safe, pure, and effective.

Stringent inspections by the FDA, WHO and European authorities check that these rules are being followed.

However these regulations do not address environmental concerns. Inspectors have no mandate to sanction a factory for polluting, failing to treat its waste or other environmental problems – this falls within the remit of local governments.

Within India, there are environmental regulations covering what ingredients factories are allowed to produce, how they use water and how they dispose of their waste. In Hyderabad, the Telangana State Pollution Board (TSPCB) inspects factories based on these.

However these inspection have been labelled toothless by local and international campaign groups. In November 2015, an analysis of TSPCB inspection reports by the Centre for Science and Environment in Delhi found that 15 bulk drug manufacturers within the Patancheru Bollaram industrial area were producing ingredients for which they did not have permission, using more water than the permitted limit, and dumping more effluents and hazardous waste than allowed.

"This glaring omission must be rectified by including legally binding environmental standards in GMP protocols"

Lots of promises have been made. More than 100 drug companies (including Mylan) signed a declaration at the World Economic Forum in Davos at the beginning of last year pledging to clean up production; commitments which were repeated in an industry roadmap released by 13 major manufacturers in the run-up to the first ever high-level United Nations meeting on antimicrobial resistance last September.

Last week the European Commission also published a roadmap acknowledging the release of antimicrobial ingredients into the environment during manufacture "may pose a risk." It promised it would explore how to address the challenge in 2018, but fell short of committing to actual policy.

The UK government promised to take action on pollution in NHS supply chains following a previous Bureau report last October, but could not comment on whether this had been followed up due to purdah rules prohibiting any policy announcements in the run-up to an election.

And WHO, along with sister UN agencies, signed a "Statement of Intent" last December aimed at "advancing environmental and socially

responsible procurement" of their health products. Just this week, WHO director-general Margaret Chan warned the world was moving towards a "post-antibiotic era" and called once again for concerted global action. She listed actions which were urgently needed, including cutting antibiotic prescriptions, developing new drugs, and coordinated government policies around the world. She did not mention pharmaceutical pollution.

The European Public Health Alliance, an umbrella group for more than 90 non-profit organisations, lambasted the failure of international regulators to do anything about the "rife" pollution which was a "clear cause" of AMR.

"This glaring omission must be rectified by including legally binding environmental standards in GMP protocols, particularly with regard to contamination with antimicrobial substances – as a condition for authorisation and import of drugs," said a spokesperson. "Voluntary agreements are not enough to stop a race to the bottom, where pharmaceutical companies exploit weak links in global supply chains, in places where there is little or no enforcement of vital environmental standards."

Tighter regulations on pollution must be introduced, said Dr Yohei Doi, Associate Professor of Medicine at the University of Pittsburgh School of Medicine, and it was up to international buyers of drugs such as the FDA to make this happen. "It's the buyers in the U.S. that pay for these things," he said. "As long as people buy these drugs, the companies will keep making them in this way."