

DRUG RESISTANCE THROUGH THE BACK DOOR:

HOW THE PHARMACEUTICAL INDUSTRY IS FUELLING THE RISE OF
SUPERBUGS THROUGH POLLUTION IN ITS SUPPLY CHAINS





Polluted pond at Bollaram industrial area, Hyderabad, India
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EXECUTIVE SUMMARY

Healthcare professionals everywhere are fighting a round-the-clock battle to contain rising antimicrobial resistance rates. In Europe alone, around 25,000 people die every year as the result of contracting an infection which proves resistant to treatment. By 2050, that figure is expected to rise to 390,000, with the total death toll worldwide reaching 10 million.¹

Antimicrobial resistance (AMR), and particularly the diminishing effectiveness of antibiotics to treat bacterial infections, strikes at the foundations of modern medical practice.² Beyond the essential role antibiotics play in treating life-threatening conditions such as sepsis, countless medical procedures including hip replacements, caesarean sections and chemotherapy are reliant on their use. Nevertheless, many experts are now warning that we could be facing a future without antibiotics. This is a chilling prospect: without them, common illnesses, minor surgery and routine operations could become high risk procedures.³

In the UK, where antibiotic consumption is on the rise⁴ and drug resistance rates are also increasing, considerable human and financial resources are being channelled into tackling AMR including through improved hygiene in clinical settings and better prescribing practices. Concern about drug resistance has reached the highest levels of government: in 2014 Prime Minister David Cameron commissioned a Review on Antimicrobial Resistance led by a renowned international economist, Lord Jim O'Neill, to establish the scale of the human and economic threat. Its conclusions were sobering, with Lord O'Neill, warning of the end of modern medicine as we know it.⁵

Antibiotic resistance is a complex phenomenon with multiple interlinked causes. There is agreement across the board that the rampant misuse of anti-infectives in human medicine and farming is the major driver of AMR worldwide. In many countries, action is being taken to address these twin factors with varying degrees of success.

In recent years, scientific researchers have identified an additional cause of AMR: environmental pollution from the production of antibiotics. Factories in China and India, which produce the lion's share of the world's antibiotics supply, have been found to be dumping manufacturing waste into their surroundings, resulting in the contamination of rivers and lakes and fuelling the proliferation of drug-resistant bugs.

In its December 2015 report "Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste" the Review on Antimicrobial Resistance identified pollution in the pharmaceutical supply chain as a causal factor in the spread of AMR and called on the industry to take measures to tackle it, also noting that "Major buyers of generic antibiotics could factor appropriate management of environmental considerations, including the amount of APIs and antibiotics that the company or their suppliers generate as waste, into their procurement decisions".⁶

This briefing, which contains information from detailed reports and on-the-ground investigations into pharmaceutical pollution carried out in 2015 and 2016, shines a spotlight on the conditions in which some of the most commonly prescribed drugs in the UK are manufactured. It shows how dirty production and the dumping of inadequately treated antibiotic waste in China and India, where most of our drugs are produced, is fuelling the AMR crisis through the back door. Highlighting the astonishing lack of transparency in the pharmaceutical supply chain, it calls on the National Health Service (NHS) and other big purchasers to use their buying power to help bring about a sea change in drug manufacturing practices by blacklisting products manufactured by pharmaceutical companies at the heart of the antibiotics pollution scandal.

1. ANTIMICROBIAL RESISTANCE

It is less than a century since Sir Alexander Fleming, the man who discovered penicillin, issued his warning that bacteria could become resistant to antibiotics as a result of misuse. And yet experts are now saying that we stand on the cusp of an "antibiotic apocalypse" where treatment for even common infections becomes ineffective.

How did we end up here and what can we do about it?

A. The scale of the threat

Antimicrobial resistance arises when the microorganisms which cause infection survive exposure to a medicine that would normally kill them or stop their growth. Of particular concern in the case of antibiotics,⁷ AMR is a global problem and one of the biggest threats facing humanity this century. The Review on Antimicrobial Resistance, which issued its final recommendations in May 2016, estimated that by 2050, the number of annual deaths from drug resistance would reach 10 million worldwide from the current level of 700,000. Tasked among other things with examining the potential micro- and macroeconomic impacts of failure to adequately contain the spread of antimicrobial resistance globally, it found that the economic fallout would amount to a truly staggering cumulative loss of \$100 trillion to the world economy by 2050.

Microorganisms' ability to hitch a ride on a human host or traded goods means that resistance can travel quickly around the world. For example, travellers who visit a country with high prevalence of antimicrobial resistance may return home colonised or infected by multidrug-resistant bacteria which can then be transmitted to others.⁸ Resistance is therefore our collective problem, wherever it first occurs.

The European Centre for Disease Prevention and Control (ECDC) describes antibiotic resistance as a serious threat to public health in Europe, leading to increased healthcare costs, prolonged hospital stays, treatment failures, and sometimes death. It reports a significant increase in the percentage of *Klebsiella pneumoniae* (*K. pneumoniae*) resistant to fluoroquinolones, third-generation cephalosporins and aminoglycosides, as well as combined resistance to all three antibiotic groups, in the European Union. Resistance to third-generation cephalosporins and combined resistance to fluoroquinolones, third-generation

cephalosporins and aminoglycosides in *Escherichia coli* (*E. coli*) has also increased significantly.⁹ In a particularly worrying trend, cases of 'pan-resistant' infections caused by bacteria totally or almost totally resistant to antibiotics are also emerging in the EU.

This trend is mirrored in the UK. A November 2015 report from Public Health England (PHE) shows that overall antibiotic resistant infections increased through 2014. Rates of bloodstream infections caused by *E. coli* and *K. pneumoniae* increased by 15.6% and 20.8% respectively, from 2010 to 2014.¹⁰

These developments are all the more concerning in light of the lack of new antibiotic compounds in the research and development pipeline.¹¹ It has been 30 years since a new class of antibiotics was last introduced and only 3 of the 41 antibiotics in development have the potential to act against the majority of the most resistant bacteria.¹²

B. How does antibiotic resistance occur?

While antibiotic resistance is to some extent a naturally occurring phenomenon, the increasing use of antibiotics since the second half of the 20th century, when they were first mass marketed, has created strong selection pressure for resistant bacteria.

The overconsumption and misuse of antibiotics in human medicine and farming are major drivers of resistance. In 2015, the first 'State of the World's Antibiotics' report by the Washington-based Center for Disease Dynamics, Economics and Policy (CDDEP) recorded a 30 per cent increase in total human antibiotic consumption between 2000 and 2010, from approximately 50 billion to 70 billion standard units.¹³ Under current scenarios, this figure is set to rise over the coming decades as population levels increase and people in emerging countries become better off. Another problem is misuse, for instance when antibiotics are prescribed for viral infections, or when patients do not complete a course of treatment.

Antibiotic use in animal rearing is also high, and expected to increase rapidly in the coming years.¹⁴ Current consumption rates are projected to rise by two-thirds by 2030.¹⁵ In China alone, which already consumes a vast share of the world's antibiotics, consumption is expected to double by 2030.¹⁶ Most of these antibiotics are not even prescribed to treat sick animals, but are administered to promote growth and prophylactically to prevent sickness in animals bred in the cramped and unhealthy conditions typical of industrial farming.

In May 2016, the UK Government announced far-reaching measures to address AMR. Under the package, doctors have been instructed to halve inappropriate antibiotics prescriptions by 2020, equating to a reduction of 1.7m prescriptions annually by 2020. The second target is a commitment to halve the number of drug-resistant bloodstream infections acquired by patients in hospital by

the same year, reducing the need for antibiotics. Finally, it has pledged to cut the use of antibiotics in farm animals and farmed fish and control or ban those drugs that are important in human health.¹⁷

These important initiatives are helping put us on the right track when it comes to confronting the AMR threat. However, the current failure to address the spread of drug-resistant bacteria as a result of pollution from the pharmaceutical manufacturing process is a major oversight with potentially fatal consequences. Not to tackle this aspect risks undermining the vital efforts thousands of healthcare professionals are making to contain the AMR threat in the UK, Europe and around the world.

C. Pharmaceutical pollution: an ignored cause of AMR

The substantial quantities of antibiotics released from polluting factories, which frequently combine with runoff from farms and human waste in water bodies and sewage treatment plants, provide a perfect breeding ground for drug-resistant bacteria. Bacteria in these environments

are able to share or exchange genetic material, something which can also occur between different bacterial species.¹⁸ Experts view the promotion of antibiotic resistant bacteria as "by far the greatest human health risk" posed by the presence of pharmaceutical residues in the environment and note that, in addition to fostering the spread of resistant pathogens, antibiotic residues can also turn harmless environmental bacteria into carriers of resistance.¹⁹

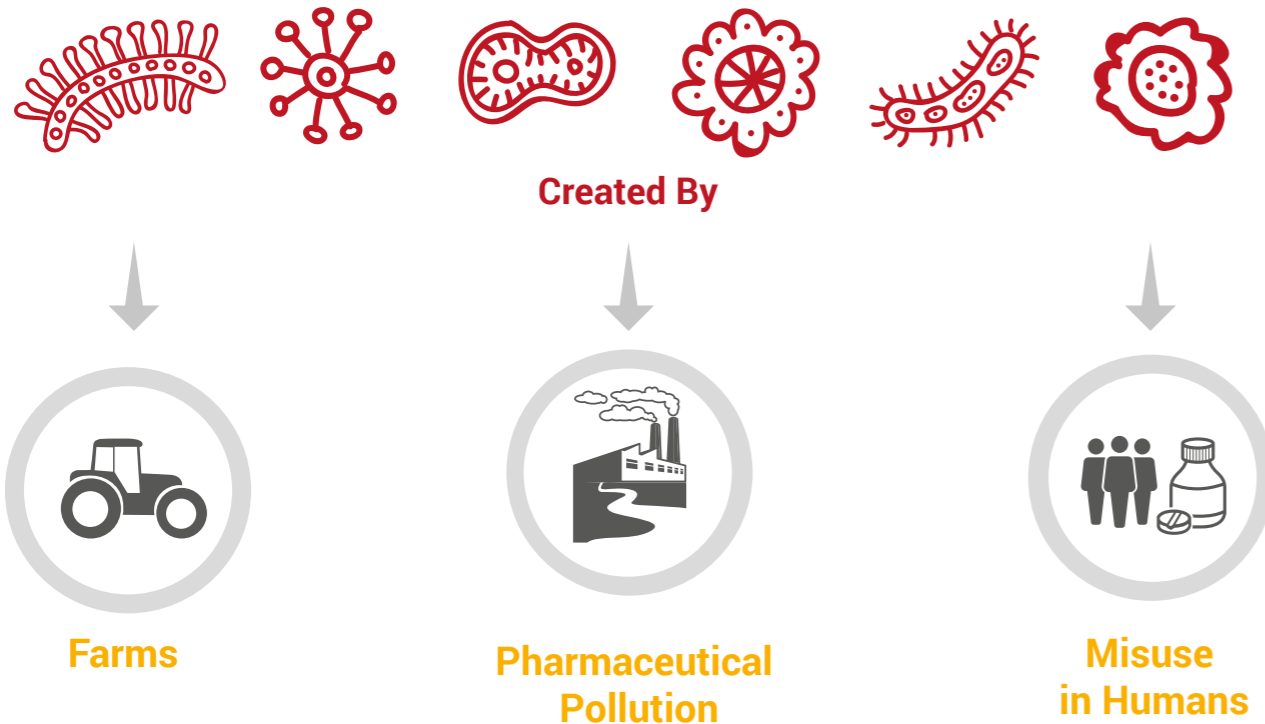
A 2013 study examining pharmaceutical pollution in highly populated Asian countries including China, India, Bangladesh and Pakistan described the "serious threats to the environment" posed by the relocation of pharmaceutical production to low-cost manufacturing countries. The paper showed that most of the examined manufacturing sites did not comply with environmental regulation and simply discharged wastewater into the domestic sewage network without any treatment, thereby exposing humans and animals to drug-resistant microbes via aerosols, endophytes²⁰, water and crops.²¹

This confirmed earlier studies, including a 2007 investigation by a team of Swedish scientists, who

Apparent effluent pollution on the Musi River in Hyderabad, a major pharmaceutical manufacturing hub. Copyright: Nordea Asset Management 2016



How antibiotic resistance spreads



Routine, non-therapeutic use of antibiotics in intensive livestock farming as a substitute to healthier living conditions and to make animals grow faster.

Release of antibiotics into the environment through mis-management in factories.

Overprescription and inappropriate use such as prescription for non-bacterial illnesses, failure to complete a course of treatment, etc.

How is AMR spreading around the world?

Drug-resistant bacteria are able to travel far and wide. They can be passed on in meat, spread via contaminated manure or water used to grow food crops, travel through the air, or flourish in the bodies of people who have been contaminated. We have moved beyond the stage where resistant bacteria were rare and mostly contained to hospital environments. Today, everyone is at risk.

The resistant bacteria, carrying the genetic code New Delhi Metallo-beta-lactamase-1 (NDM-1) that was first identified in India has already been found in more than 70 countries around the world. With globalisation and modern means of travel, any local health problem can soon become a disaster of global proportions.



investigated water pollution in Hyderabad, the centre of India's bulk drug manufacturing industry,²² in areas surrounding pharmaceutical production units. They reported extremely high emissions from factories in Patancheru, an industrial zone situated on the outskirts of the city. In some cases, the pharmaceutical concentrations in the water samples they took were higher than those found in the blood of patients taking medicine. The concentration of ciprofloxacin, a broad-spectrum antibiotic, was approximately one million times greater than the levels that are regularly found in treated municipal sewage effluent²³ and toxic to a range of organisms. The estimated total release of ciprofloxacin for 1 day was 44 kg, which is equivalent to Sweden's entire consumption over 5 days, or, to take a different measure, sufficient to treat everyone in a city of 44,000 inhabitants. Follow-up studies showed that the pharmaceutical pollution had contaminated river sediment²⁴, soils²⁵, and surface, ground and drinking water²⁶ to unprecedented levels.

A follow-up study in 2014 on Kazipally Lake, which is located in the vicinity of Patancheru, and is also affected by the direct dumping of waste from pharmaceutical

production established that it harboured a wide range of resistance genes (81 identified gene types) against "essentially every major class of antibiotics", as well as genes responsible for mobilisation of genetic material. Resistance genes were estimated to be 7,000 times more abundant than in a Swedish lake included for comparison, where only eight resistance genes were found.²⁷

Antibiotic pollution has also been reported at multiple sites in China, where drug resistance is also a real and growing threat. One recent study reported the presence of the New Delhi Metallo-Beta-Lactamase (NDM-1) antibiotic resistance gene at waste water treatment plants in Northern China.²⁸ The scientists concluded that there were four to five resistant bacteria leaving the treatment plant for any one bacterium that entered.²⁹ The NDM-1 gene makes bacteria carrying it resistant to most antibiotics except polymyxins, a group of highly potent drugs whose toxic side effects mean that they are reserved for treatment of only the most serious infections. Since the discovery of the gene in 2008, NDM-1 has been identified in more than 70 countries around the world, demonstrating how quickly resistance is transmitted.³⁰

Close-up of an effluent treatment plant at Gaddapotharam, a village on the outskirts of Hyderabad
Copyright: Nordea Asset Management 2016



The NHS spends roughly £11 billion a year on medicines

NHS

LloydsPharmacy

China is the top manufacturer of penicillin industrial salts, a vital building block in the production of many antibiotics and produces 80-90 percent of antibiotic active pharmaceutical ingredients (APIs).

According to the British Government, around 25% of UK medicines are made in India.

Aurobindo supplies antibiotics to NorthStar Rx, a US-based generic drug company which is a subsidiary of McKesson. Following its acquisition of Celesio in 2014, McKesson is now a leading player in Europe, and owns the Lloyds Pharmacy chain, which is the second biggest pharmacy chain in the UK

Many Chinese APIs are processed in India before arriving in the UK and other export markets as finished products. Manufacturer information on packaging and patient information leaflets is usually incomplete.

Polluting Indian companies producing antibiotics for the European and US markets:

Polluting Chinese factories exporting antibiotic APIs to India and with established links to US market:

Most of the world's pharmaceuticals are made by contract manufacturers in China and India, with outsourcing by major pharmaceutical companies headquartered in Europe and the United States accounting for a significant share of this production

Where do our antibiotics come from?



2. WHERE ARE OUR DRUGS MADE?

Most of the world's drugs are made by contract manufacturers in China and India, with outsourcing by major pharmaceutical companies headquartered in Europe and the United States accounting for a significant share of this production.

According to the Government approximately 25% of UK medicines are made in India.³¹ India's pharmaceutical exports to the UK from April 2015 to February 2016 stood at \$512 million (£384 million³²).

Given the lack of new antibiotic drug discovery, the anti-infectives market is dominated by generics manufacturers, with India holding the largest share of global generic drug manufacturing.³⁴ With respect to the key revenue generating drugs (branded and generic), US pharma giant Pfizer accounted for the largest share of the anti-infectives market in 2012, followed by Merck (US) and the UK's GlaxoSmithKline.³⁵

China is now the top manufacturer of penicillin industrial salts, a vital building block in the production of many antibiotics and produces 80-90 percent of antibiotic active pharmaceutical ingredients (APIs). India, which has the world's third largest pharmaceutical industry, represents a smaller yet still sizeable share of global antibiotic API manufacturing. Indian companies have also positioned themselves as leaders in the production of finished dose antibiotic products using APIs mainly imported from China.

In recent years, there have been numerous high-profile pollution scandals at pharmaceutical factories in both China and India. Antibiotics factories crop up frequently in NGO and media reports, suggesting that the high antibiotics concentrations discovered in Hyderabad are not a one-off but rather part of a wider pattern of pharmaceutical pollution in the countries which supply our medicines.

Antibiotics Supply Chain – Complexity and lack of transparency facilitate irresponsible practices within the pharmaceutical industry

The pharmaceutical supply chain is both complex and opaque. What is more, attempts by foreign inspection authorities such as the United States Food and Drug Administration (FDA) to increase oversight of Chinese pharmaceutical manufacturers in reaction to ongoing safety concerns have been unsuccessful owing to the Chinese government's failure to provide visas for additional inspectors to enter the country.³⁶

A spate of scandals has led to regulatory improvements, as demonstrated by the introduction of Good Manufacturing Practice (GMP) which pharmaceutical producers must adhere to in order to export their products to the EU³⁷ and US markets.³⁸ A yawning transparency gap nonetheless remains. In addition to this, GMP principles do not include any environmental criteria. This is a major omission given that good environmental stewardship and health are intrinsically linked, strikingly so in the case of the global AMR health crisis.

Many Chinese APIs are processed in India before making it on to export markets as finished products. This makes the task of identifying the factory in which the raw materials were manufactured extremely challenging. What is more, manufacturer information on medicine packets and patient information leaflets is usually incomplete and does not specify the origin of the APIs. And while EU importers of APIs do have to report on their origin, the EudraGMDP database³⁹ on manufacturing sites, importers, and distributors of APIs is also incomplete.⁴⁰

Environmental and Health NGOs have voiced concern about the impact of pollution in the pharmaceutical supply chain and urged the industry to provide more transparency and accountability on the consumption and origin of antibiotics. In December 2015, the European Public Health Alliance (EPHA) and Healthcare Without Harm (HCWH) organised a joint event at the European Parliament in Brussels on "Pharma Pollution: An Ignored Cause of Antimicrobial Resistance" which drew attention to the need to control antibiotics during production, use and disposal in order to protect the environment and human health.⁴¹

3. CASE STUDIES

A. CHINA

In June 2015, an investigation published by the online campaigning organisation SumOfUs lifted the lid on a series of serious pollution incidents at antibiotics manufacturing sites in China. The report "*Bad Medicine: How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs*"⁴² showed how major pharmaceutical companies including Pfizer, Teva and McKesson had sourced antibiotics from some of these sites. This section provides a snapshot of the report's key findings and identifies some of the companies at the heart of the scandal.⁴³



Company: NCPC – North China Pharmaceutical Group
Location: Shijiazhuang, Hebei Province
Reportedly supplying: Aurobindo, Balkanpharma Razgrad (Actavis)⁴⁴, GSK, Lupin, Pfizer, Sanofi.

NCPC is a State-owned company and claims to be the largest manufacturer of antibiotics including penicillin, amoxicillin, streptomycin and cefradine in China. The company has repeatedly been in the firing line for discharging pharmaceutical effluent into the surrounding environment. In June 2012, the Sina news agency reported that it had dumped untreated antibiotic waste in the Hutuo river, which runs through the city of Shijiazhuang in Hebei Province.

In 2010, an on-site inspection by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) found that one of the company's antibiotics production units did

not comply with Good Manufacturing Practices (GMP) and had committed a series of major manufacturing violations. This view was echoed by the French Health Products Safety Agency (ANSM - *Agence nationale de sécurité du médicament et des produits de santé*) when it visited the site in 2013, with many of the deficiencies noted by the British inspection in 2010 remaining unresolved. The French authorities returned in November 2014 to inspect one of NCPC's other sites in Shijiazhuang, NCPC Semisyntech. This time the criticism reserved for NCPC was even more severe, pointing to manipulation and falsification of documents and recommending a product recall. ANSM subsequently issued an EU Statement of Non-Compliance resulting in the withdrawal of two of the factory's benzylpenicillin products from the EU market.



Company: CSPC Pharmaceutical Group/Inner Mongolia Changsheng Pharmaceuticals - Shiyao Zhongrun plant
Location: Hohhot, Inner Mongolia
Reportedly supplying: Pharmagen (customers: GSK, Bristol-Myers Squibb, Wyeth and Novartis), Teva.

CSPC Pharmaceutical is one of China's largest drug companies. Until June 2013, it operated one of the biggest antibiotics production plants in the world, Shiyao Zhongrun at a huge industrial park in Inner Mongolia. It also operates a large plant in Shijiazhuang, Hebei Province in the same city as many of NCPC's subsidiaries.⁴⁵

In June 2014, China's state news channel, CCTV, broadcast a report from Tuo City, Inner Mongolia revealing that factories at the Tuoketuo Pharmaceutical Industrial Park, including the Shiyao Zhongrun plant had been pumping tonnes of toxic and antibiotic-rich effluent into the fields

NCPC INTERNATIONAL

NCPC is the first and sole Pfizer's supplier of sterile API for human in China, the OEM partner on "Augmentin" for GSK, and "Claforan" for Aventis, therefore the quality assurance system can reach the top level in the world.

Extract from an NCPC marketing presentation obtained from the company in 2015



Effluent pipe from Shiyao Zhongrun Pharmaceutical Plant
 Copyright: Shao Wenjie

and waterways surrounding the factory, as well as the nearby Yellow River. By that point, the plant had already been in trouble with the provincial authorities for years. A report by the international NGO IPEN and China's Green Beagle Institute⁴⁶ described how in 2011, the Inner Mongolia provincial government fined the company CNY514,600 (€62,737) for illegally discharging waste water into municipal sewers. A worker at the company told the report's authors that Shiyao Zhongrun had violated waste dumping laws on at least three other occasions in 2005, 2006 and 2009. It was also reported that total waste water emissions from the 25 manufacturing facilities at the Tuoketuo complex amounted to one million tonnes annually, flowing to Wushija Town, which lies 20km downstream of the industrial park.⁴⁷

In June 2013, CSPC Pharmaceutical Group sold CSPC Zhongrun Pharmaceutical (Inner Mongolia) to Inner Mongolia Changsheng Pharmaceuticals.



Company: Sinopharm WeiQida
Location: Datong, Shanxi Province
Reportedly supplying: Alkem Laboratories, Aurobindo, Bayer, GSK, Johnson & Johnson, Pfizer, Roche, Sanofi, Teva.

In May 2014 a CCTV report investigated pollution emanating from the Yudong sewage treatment plant to the south of Datong city. The plant treats sewage from more than ten pharmaceutical factories, among them factories belonging to Sinopharm WeiQiDa. The investigation showed that the treatment plant was discharging clean water in daytime and sewage during the night into the Yuhe River.

There is a direct connection between Indian generic drug manufacturer Aurobindo Pharma and Sinopharm WeiQida through Aurobindo's 10% stake in Sinopharm, which is designed to provide it with an uninterrupted supply of raw materials at competitive prices.⁴⁸



Company: Shandong Lukang Pharmaceuticals
Location: Jining, Shandong Province
Reportedly supplying: Numerous Indian companies including DPB Antibiotics (customers: Pfizer, Aurobindo, Cipla and Lupin), United Biotech, Unimex Pvt, Shree Pharma, as well as Rochem in the United States.

In December 2014, another CCTV investigation revealed that Jining, Shandong Province-based manufacturer Shandong Lukang Pharmaceutical had discharged polluted water containing over 50,000 nanograms of antibiotics per litre, about 10,000 times higher than the concentrations present in clean water. Witnesses told journalists that the company's response to the additional cost of treating the wastewater from the plant was simply to dump it in the factory's surroundings, from where it

would end up in the Beijing-Hangzhou Canal.



Company: Harbin Pharmaceutical Group
Location: Harbin, Heilongjiang Province
Reportedly supplying: Aurobindo, Demo Pharmaceutical (Greece).

Harbin Pharmaceutical Group owns a manufacturing facility located in the centre of Harbin, a city of 10 million inhabitants. In June 2011, the manufacturer was involved in a pollution scandal after it released wastewater and noxious gases into its surroundings. The company also dumped a large amount of residue in the Songhua River. Wu Zhijun, one of the company's top officials, apologised to his fellow citizens on national television and the company was ordered to move the factory to the city's outskirts.

Harbin Pharmaceuticals states on its website that its products are sold in more than fifty countries. One of the antibiotic APIs it manufactures is cefepime, a fourth generation cephalosporin antibiotic. On the products page for cefepime Harbin notes the main markets: North America, Central/South America, Western Europe, Eastern Europe, Australasia, Asia, Middle East, Africa.



Company: Tonglian Group
Location: Hulun Buir, Inner Mongolia
Reportedly supplying: Not known

Tonglian Group operates a factory in Hulun Buir Inner Mongolia which produces penicillin industrial salts. In February 2014, the company came under fire from the Ministry of Environmental Protection for pumping waste water into a tributary of the Hailar River. media reports described "malodorous emissions" and large-scale extraction of groundwater, leading to a drop in groundwater levels. The company, which had also expanded production without obtaining a permit, came in for heavy criticism from the authorities and was fined.



Company: TUL – United Laboratories
Location: Bayannur, Inner Mongolia
Reportedly supplying: Teva, numerous Indian companies including Cadila Healthcare and Alkem Laboratories.

TUL is one of the biggest antibiotics producers in China and has at least six production bases, including United Laboratories in Inner Mongolia and a plant in Chengdu, Sichuan Province. TUL's factory in Inner Mongolia has repeatedly been criticised in the media and by the local authorities for improper waste management, including the dumping of waste water into Lake Wuliangshuai. In 2008, the factory was ordered to suspend operations and install proper waste treatment after reports that the factory had secretly buried its waste in a 50-hectare pit. Effluent was also being discharged through irrigation ditches linking to the Yellow River. According to media reports in May 2014,



Screenshots from a CCTV report broadcast on Chinese television in December 2014, which revealed that Shandong Province-based manufacturer Lukang Pharmaceuticals was illegally dumping and transporting waste water by truck. Samples taken from the effluent showed high concentrations of antibiotics, with levels of one antibiotic almost 10,000 times higher than clean water samples.

United Laboratories' production line was shut down and others suspended operations for several months.

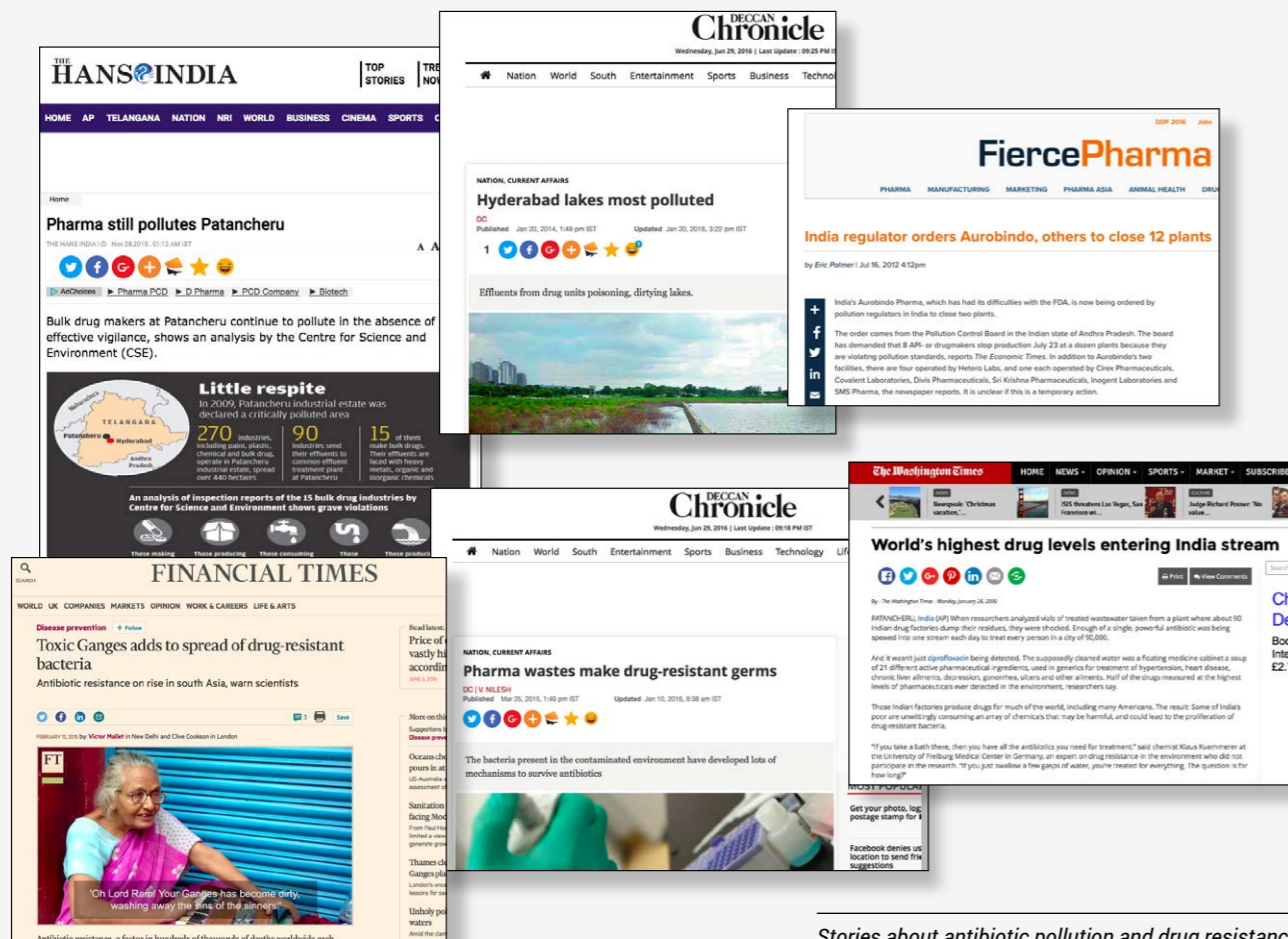
B. INDIA

There is much concern about the environmental and human impacts of antibiotic pollution in India, where many of the raw materials supplied by Chinese factories are processed into finished drugs. India has a large pharmaceutical industry, with manufacturing hubs located around the country in states including Andhra Pradesh, Telangana, Maharashtra, Gujarat, Tamil Nadu and West Bengal.

As described previously, antibiotic pollution has contaminated many water bodies in Hyderabad, one of the poles of India's bulk drug manufacturing industry. Pharmaceutical pollution has plagued Hyderabad for many decades and shows no sign of abating. In November 2015, the Indian NGO Centre for Science and Environment (CSE) published an analysis showing that 15 of the drug manufacturers operating in the Patancheru-Bollaram cluster on the outskirts of Hyderabad were committing a wide range of environmental violations.⁴⁹ In March 2016, a major Scandinavian bank, Nordea Asset Management, issued a report examining the "Impacts of Pharmaceutical Pollution on Communities and Environment in India"⁵⁰ in Hyderabad and Visakhapatnam, another pharmaceutical manufacturing hub located in Andhra Pradesh. The report shed light on the behaviour of some of the companies operating there, and investigated links with foreign export markets. Some of the key findings are highlighted below.

Close-up of chemical pools in lakebed at Kazipally Lake, Hyderabad - Copyright: Nordea Asset Management 2016





Stories about antibiotic pollution and drug resistance in India frequently make headline news.



Company: Aurobindo
Location: Hyderabad & Visakhapatnam, owns operations and subsidiaries worldwide
Links: McKesson (owner of Lloyds Pharmacy chain); also supplies under its own name to markets around the world

Hyderabad-based Aurobindo is one of India's largest vertically integrated pharmaceutical companies. Four of the company's six "key" formulation plants in India manufacture antibiotics⁵¹ and it also appears to outsource some of its production to smaller contract manufacturers within India. It exports to over 150 countries worldwide and derives more than 86% of its revenues from international operations.⁵² Aurobindo's manufacturing units in Hyderabad and Visakhapatnam have repeatedly infringed environmental regulations. According to CSE, which examined inspection reports by the Telangana State Pollution Board, the company is consuming more water and generating more waste than permitted (one unit – Aurobindo Unit IX - generates over four times more hazardous waste than it should). What is more, this waste is not being treated appropriately.⁵³ The on-the-ground investigation carried out for Nordea Asset Management in early 2016 further observed waste water flowing from Aurobindo's Unit XII in Bachupally on the outskirts of Hyderabad as well as polluted water and chemical effluent adjacent to Aurobindo's Unit V near Isnapur Lake, Pashamylaram (also Hyderabad) and Unit XI in Pydibhimavaram Village, near Visakhapatnam.⁵⁴

Many of Aurobindo's Hyderabad factories send waste to the Patancheru Common Effluent Treatment Plant (CETP), where Swedish researchers found "exceptional" concentrations of fluoroquinolone antibiotics in 2007.⁵⁵

Aurobindo's customers include "premium multinational companies" and many of its facilities have been approved by regulatory agencies such as the US FDA, the UK Medicines and Healthcare Products Regulatory Authority (MHRA) and Health Canada. It also has multiple approvals under the EU GMP framework.⁵⁶

According to reports, it plans to make India its sourcing hub for the European generic drug business it acquired from Actavis Plc in 2014.⁵⁷ Since launching its European commercial operations in 2006 with the acquisition of Milpharm in the UK and Pharmacin in the Netherlands in 2007, and following the Actavis deal, Aurobindo has added operations in Member States including France, Italy, Spain, Portugal, Belgium, Romania, Malta and Germany to its portfolio.⁵⁸

Aurobindo's UK subsidiary, Milpharm Ltd., supplies the antibiotics ciprofloxacin and cephalexin to the UK market. Indian trade data shows that the company has held import licenses for several Chinese API manufacturers reported to be dumping antibiotic effluent into their surroundings in China, namely: Sinopharm Weiqida, Harbin Pharmaceutical Group, NCPG and CSPC.⁵⁹ As noted, Aurobindo holds a 10% strategic stake in Sinopharm Weiqida.⁶⁰



Company: Mylan Laboratories Ltd.
Location: Hyderabad, Visakhapatnam, Mumbai
Links: Sandoz (Novartis); also supplies under its own name to markets around the world

Mylan Laboratories Ltd is the Indian subsidiary of Mylan Inc, a global generic and specialty pharmaceuticals company registered in the Netherlands and with operational headquarters in Hatfield, Hertfordshire in the United Kingdom. All active ingredients are manufactured in India (4 facilities in Hyderabad; 4 in Visakhapatnam; and one in Mumbai). It makes ciprofloxacin and amoxicillin antibiotics and claims to supply one in 13 prescriptions in the US.

In 2013 Mylan issued recalls for 11,650 cartons of ciprofloxacin tablets because the drugs "were produced and distributed with active ingredients not manufactured according to Good Manufacturing Practices".

Mylan production units in Hyderabad are reported to be dumping large volumes of effluent in the environment.



Company: Dr Reddy's
Location: Hyderabad, owns operations and subsidiaries worldwide
Links: GSK; also supplies under its own name to markets around the world

Dr Reddy's is a major vertically integrated company. Like Aurobindo, it appears to act both as a contract manufacturer for foreign pharmaceutical companies and

also supplies medicines to export markets under its own brand name. Like Aurobindo, it is reported to be outsourcing some of its production to smaller companies in India. A 2012 study on drug pricing by India's Ministry of Corporate Affairs revealed that Dr Reddy's was benefiting from a 509 per cent mark up for Ciprolet, the company's version of the antibiotic ciprofloxacin, the same drug discovered in the water samples taken at Patancheru treatment plant by the team of Swedish researchers in 2007. Dr Reddy's sells ciprofloxacin to the UK and US markets.

Dr Reddy's manufacturing plants in Hyderabad produced high levels of hazardous waste, in one case more than three times the amount permitted, according to CSE.



Company: Hetero Drugs Ltd.
Location: Hyderabad
Links: Roche; export markets around the world

Hetero Drugs Ltd. manufactures a range of antibiotics including levofloxacin, linezolid and moxifloxacin. Hetero's subsidiary Hetero Malta Ltd has been issued with an import licence by the Maltese authorities, which suggests that it is exporting drugs from India to Malta for wider distribution on the European market.

The on-the-ground investigation featured in the Nordea report as well as information from CSE indicate that many of Hetero's manufacturing sites are flouting environmental regulations.



Polluted water flowing into Isnapur Lake, Pashamylaram, Hyderabad. Aurobindo's Unit V is located a few hundred metres from Isnapur Lake, just inside the Patancheru industrial area
 Copyright: Nordea Asset Management, 2016

4. WHAT CAN THE NHS AND OTHER MAJOR PURCHASERS OF ANTIBIOTICS DO?

This briefing has highlighted substantial shortcomings in drug manufacturing standards in India and China, and described rampant pollution at numerous production sites. While it is difficult to paint a precise picture of the pharmaceutical supply chain owing to significant transparency gaps, it is clear that responsibility for tackling pollution from the antibiotic manufacturing process lies squarely with the pharmaceutical industry. With drug companies failing to take this responsibility to heart, there is a clear role for the NHS and other major purchasers of antibiotics to use their significant buying power to make the industry clean up its act.

*In its December 2015 report "Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste" the Review on Antimicrobial Resistance called for the rapid development of minimum standards to reduce antimicrobial manufacturing waste released into the environment, stating that "This needs to be viewed as a straightforward issue of industrial pollution, and it is the responsibility of all actors in the supply chain to ensure that industrial waste is treated properly as a matter of good manufacturing practice."*⁶¹

Owing to the highly mobile nature of the AMR threat, the clear evidence of antibiotic pollution at sites in China and India raises worrying questions about the hidden human health impacts related to the production of the antibiotics which fill our shelves here in the UK.

Indeed, we argue that in light of the role antibiotics produced by polluting factories play in fuelling antimicrobial resistance, the NHS and other buyers must take immediate action to blacklist the most egregious polluters, beginning with the Indian company Aurobindo, which has not only purchased antibiotic APIs from dirty factories in China but also been implicated in numerous pollution scandals in India, and is taking an increasingly large stake in markets around Europe.

UK healthcare professionals grapple with AMR on a daily basis, and have dedicated their careers to preventing and curing sickness. There has been laudable progress in terms of reducing the volume of antibiotics supplied to patients within the NHS, as demonstrated by the 2.6 million drop in antibiotics prescriptions in 2015-16,⁶² and it would be morally indefensible for these efforts to be stymied by the actions of unscrupulous drug manufacturers and the global pharmaceutical giants who appear to be turning a blind eye to what is happening in their supply chain.

The NHS spends billions of pounds on procurement every year, with an annual medicines budget of roughly £11 billion.⁶³ In light of the AMR threat, it must use its vast purchasing power to effect meaningful change in an industry which has been under virtually no pressure to address this environmental and human health threat arising from its supply chain. To start with, the NHS must cease purchasing antibiotics manufactured in conditions which pose a danger human health, and put pressure on pharmaceutical companies to clean up their act, and help their suppliers do the same.

The NHS already has an established commitment to sustainability. Areas of focus to date include carbon emissions, food quality, and labour standards in countries where the NHS procures clinical supplies. On this last aspect, there is a defined a set of ethical procurement criteria in the shape of the Labour Standards Assurance System (LSAS), which was developed in response to a campaign by the British Medical Association (BMA). In 2011, the Department of Health (DH), Ethical Trading Initiative and BMA jointly published guidance to support the inclusion of ethical and labour standards in the health and social care sector's procurement. NHS Supply Chain has since put in place an implementation programme to ensure that these issues are embedded within high risk contracts, suppliers and supply chains.⁶⁴ Based on what we know about antibiotic manufacturing, this approach and the ethical procurement framework now need to be extended to address the AMR threat by including environmental safeguards. Other pharmaceutical buyers must also take a similar approach.

The recent discovery in China of a gene (mcr-1) which renders bacteria immune to all antibiotics, including those of "last resort", followed by the news shortly thereafter that the same gene had been found in 20 other countries including Denmark, Malaysia, Canada, South Africa, Japan, Thailand, Switzerland and United States⁶⁵ underlines the enormity of the challenge, and the impossibility of containing it if we fail to heed the warning signals. The stark reality is that we are simply not doing enough to tackle AMR. If we are to succeed in averting catastrophe, we must address each and every one of the three causes of AMR now, leaving no stone unturned

5 THINGS THE NHS AND OTHER MAJOR PURCHASERS OF MEDICINES CAN DO TO HELP STAMP OUT POLLUTION IN THE ANTIBIOTICS SUPPLY CHAIN



1. BLACKLIST pharmaceutical companies which are contributing to the spread of AMR through irresponsible manufacturing practices

- 2. Demand that the pharmaceutical industry CLEAN UP ITS SUPPLY CHAIN and INTRODUCE GREATER TRANSPARENCY** on the origin of antibiotic drugs
- 3. Review their ETHICAL PROCUREMENT POLICY** with a view to embedding environmental/AMR criteria in contractual requirements
- 4. Review all related procurement levers including SUPPLIER CODES OF CONDUCT** with a view to **MAINSTREAMING ENVIRONMENTAL/AMR CRITERIA** across all relevant policies
- 5. Promote legislation to incorporate ENVIRONMENTAL CRITERIA into GOOD MANUFACTURING PRACTICES (GMP)**

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DRUG RESISTANCE THROUGH THE BACK DOOR:
HOW THE PHARMACEUTICAL INDUSTRY IS FUELLING THE RISE OF
SUPERBUGS THROUGH POLLUTION IN ITS SUPPLY CHAINS



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