

# Bad Medicine

*How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs*



Sum  
Of  
+ Us



# Glossary

## ACKNOWLEDGMENTS

This is a SumOfUs report based on research by Changing Markets and Profundo.

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SumOfUs: [www.sumofus.org](http://www.sumofus.org)

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### Antibiotics

Antibiotics are chemicals which kill or prevent the growth of bacteria. Naturally-occurring antibiotics have been used to treat bacterial infection for centuries. Since the mid-1940s, they have been mass-produced in factories, and are now among the most commonly prescribed drugs in the world. Some antibiotics kill a wide range of organisms (broad spectrum) while others are only effective against a few species (narrow spectrum). In livestock production, antibiotics are commonly used to make animals grow faster and to prevent healthy animals kept in unhealthy conditions from becoming sick.

### Antimicrobial Resistance (AMR)

Antimicrobial resistance refers to the phenomenon whereby microorganisms develop the ability to continue proliferating in the presence of an antibacterial, antiviral, antiparasitic, or anti fungal substance to which they were formerly sensitive. In this report, the term is mainly used to refer to bacterial resistance to antibiotics. AMR specific to antibacterial substances is fuelled by the excessive and inappropriate use of antibiotics in human beings and animals, as well as the dumping of antibiotic-laden waste by pharmaceutical manufacturers into the natural environment. It is a global public health problem which is expected to worsen considerably in the coming decades, leading to millions of deaths worldwide.

### Superbug

The term 'superbug' is commonly used to describe a strain of bacteria which has become resistant to antibiotics. Staphylococcus aureus (MRSA) is one example of a superbug which has become resistant to a variety of antibiotics.

### Active pharmaceutical ingredient (API)

The US Food and Drug Administration defines active pharmaceutical ingredients as any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in the production of a drug, becomes an active ingredient of the drug product. APIs are often manufactured separately from the finished dose products which are marketed to end-consumers.

### Generic drugs

According to the World Health Organization, a generic drug is a pharmaceutical product, usually intended to be interchangeable with an innovator product, that is manufactured without a licence from the innovator company and marketed after the expiry date of the patent or other exclusive rights.



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## The New York Times

### 'Superbugs' Kill India's Babies and Pose an Overseas Threat

By GARDNER HARRIS DEC. 3, 2014



A mother nursing her newborn at a hospital in Haryana, where almost every baby born in hospitals in recent years has been injected with antibiotics. Kuni Takahashi for The New York Times



Health

### Superbugs to kill 'more than cancer' by 2050

Fergus Walsh  
Medical correspondent

11 December 2014 | Health | 565



Drug resistant E.coli bacteria are already a significant problem in Europe

## HUFFPOST HEALTHY LIVING

### Worldwide Use Of Antibiotics In Livestock Is Fueling Risk Of Drug-Resistant Super Bugs

Reuters

Posted: 03/22/2015 8:01 pm EDT | Updated: 05/23/2015 5:59 am EDT



## THE TIMES OF INDIA

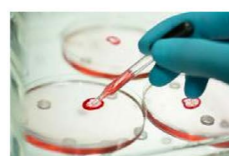
RELATED KEYWORDS: World-Health-Organization | WHO | Pneumonia | K-Pneumoniae | Carbapenem-Antibiotics | Antibiotic-Resistance | Antibiotic

### WHO declares antibiotic-resistant bacteria 'a major global threat'

Kounteya Sinha TSN | Apr 30, 2014, 07:31PM IST

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LONDON: The most comprehensive picture of antibiotic resistance, with data from 114 countries has revealed that resistance to the last-resort treatment for life-threatening infections caused by common intestinal bacteria *Klebsiella pneumoniae* — carbapenem antibiotics — has spread to all regions of the world.



Data has revealed that resistance to last-resort antibiotics for life-threatening infections caused by common intestinal bacteria has spread worldwide.

*K pneumoniae* is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, infections in new borns and intensive-care unit patients.

In some countries, because of resistance, carbapenem antibiotics would not work in more than half of people treated for *K pneumoniae* infections.

## BloombergBusiness

BloombergBusiness News Markets Insights Video

### China's Antibiotic Resistance Rate as High as 80%, Xinhua Says



## Executive Summary

The effective treatment of infections and diseases, which has been taken for granted for decades, is under threat. The emergence of virulent strains of drug-resistant bacteria, commonly known as superbugs, is prompting scientists and medical practitioners around the world to warn of a return to the pre-antibiotic era and a looming public health disaster.

Antimicrobial resistance (AMR) has been singled out as one of the main risks to mankind by the World Health Organization (WHO) and governments everywhere. The Chairman of a major UK Government-backed review into AMR estimates that by 2050, drug-resistant infections could kill 10 million people per year globally, and the UK's Chief Medical Officer has spoken of a "catastrophic threat." AMR is also extremely costly, with studies showing that the world could lose up to US\$100 trillion worth of economic output between now and mid-century if it is not addressed, lowering projected GDP by 2 to 3.5 percent.

The global spread of AMR means that serious and highly contagious illnesses such as gonorrhoea and pneumonia, may soon become incurable. As the number of untreatable cases rises worldwide, doctors and medical staff are increasingly falling back on antibiotics of last resort.

There are several factors fuelling the AMR crisis. An inexpensive and seemingly endless supply of antibiotics, coupled with perverse financial incentives encouraging their prescription, are leading to inappropriate use and overconsumption in humans and animals reared for food. The lack of investment by industry in new drug discovery is further exacerbating the situation.

One frequently overlooked cause of AMR, and the focus of this report, is environmental pollution from the production of the raw materials used to make antibiotics at the very beginning of the supply chain.

Most of the world's antibiotic drugs are manufactured in China and India. 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. The trade in antibiotic drugs between China and India is now worth billions of dollars, with large pharmaceutical companies in the United States and Europe among their biggest clients. In 2014, China was rocked by a series of investigations exposing pollution from antibiotics factories.

The pharmaceutical industry has long maintained that antibiotic manufacturing does not play a significant role in fuelling drug resistance, arguing that the final product is so valuable that it would not be economically rational to discharge vast quantities of it as waste. However, the Chinese revelations as well as several scientific studies have clearly demonstrated that this is not the case.

Hot on the heels of the recent pollution scandals, this report documents links between some of the global pharmaceutical industry's biggest household names and dirty antibiotics factories in China. On-the-ground investigations and desk research have uncovered a complex and murky web of commercial relationships between Chinese suppliers, Indian middlemen, and trusted global brands. While information on where pharmaceutical companies source their antibiotics may be provided confidentially to national authorities, it is classified as commercially sensitive, making it impossible to fill the supply chain gaps highlighted in our research.

Despite the shocking lack of transparency in the global pharmaceutical supply chain, our investigation has revealed that Pfizer is among the well-known brand names which has sourced antibiotics for human and animal use from NCPC, a company that stands accused of discharging pharmaceutical effluent into the environment and numerous other serious manufacturing deficiencies. There also appear to be direct links between one of the world's largest generic drug manufacturers, McKesson, which owns several European brands, and Indian company Aurobindo, which sources from at least four polluting Chinese factories. The world's largest generics manufacturer, Israeli company Teva, likewise has links with at least three of the Chinese companies identified in this report, all of which have been in the Chinese media spotlight for various offences including improper waste management and the release of noxious chemicals.

The report reveals that the largest pharmaceutical corporations are complicit in fuelling one of the most serious public health crises facing society today. It is essential for pharmaceutical companies to lift the veil on their supply chains and stop buying antibiotic APIs from polluting Chinese factories. In an age when AMR is threatening to destroy the health system as we know it, there is simply no excuse for turning a blind eye.

Policy-makers should demand more transparency and expand existing production standards and the Good Manufacturing Practices (GMP) framework to incorporate and enforce environmental protection criteria. This is a critical, yet still missing, part of the puzzle in the global strategy to combat AMR.



## Introduction

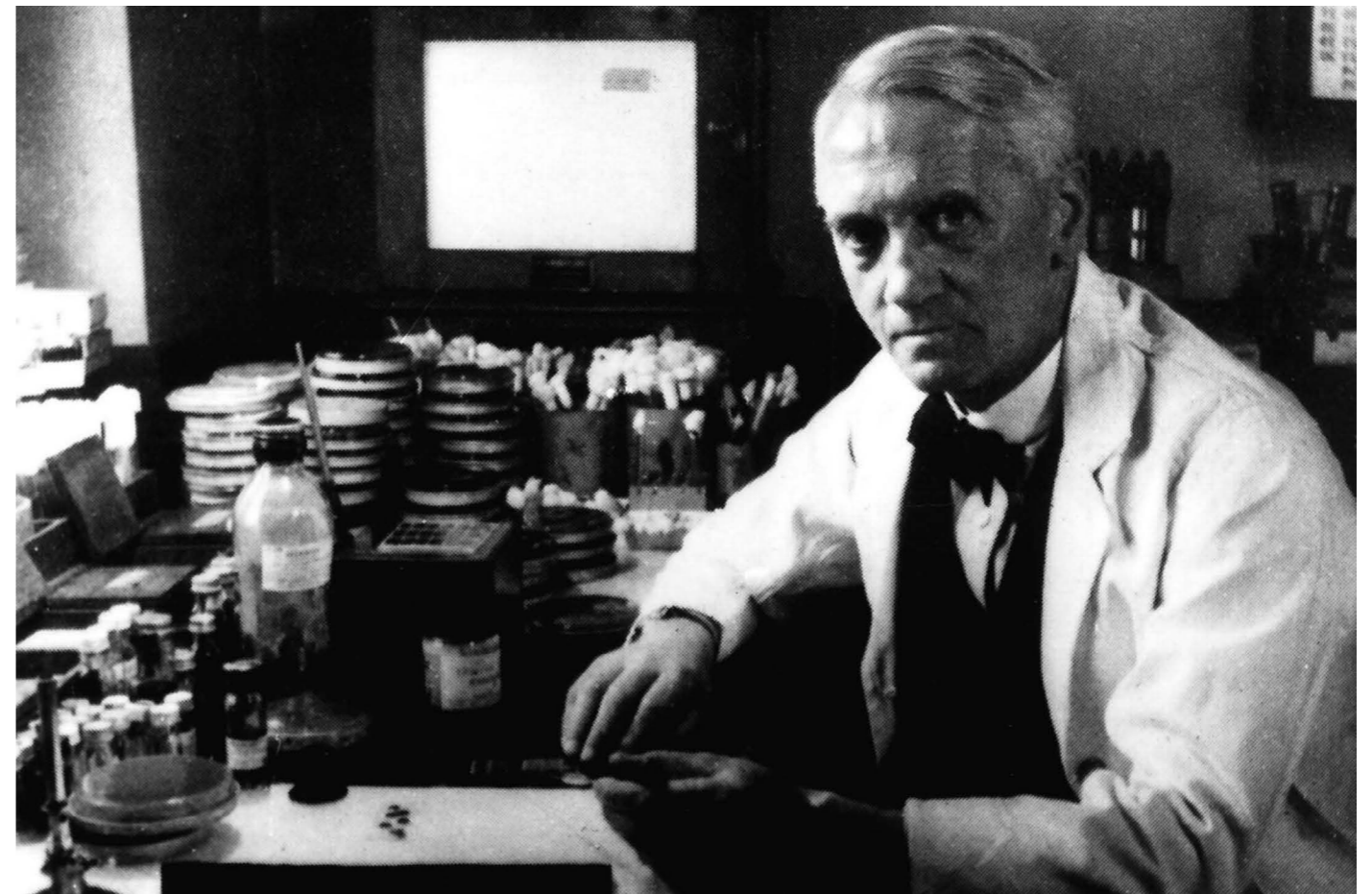
***This chapter describes what antibiotics are, how they were discovered by Alexander Fleming in the early 20th century and how their subsequent mass production revolutionised medicine. The global antibacterial drugs market was valued at US\$43.55 billion in 2012 and is expected to grow to reach an estimated value of US\$45.09 billion by 2019, dominated by generic drugs producers. Following the 'golden age' of antibiotics in the mid-20th century, very few new categories of antibiotics have been discovered, with most of the big pharmaceutical companies pulling out of research and development (R&D) owing to a lack of profitability.***

### **What are antibiotics?**

Antibiotics are drugs which kill or prevent the growth of bacteria, enabling the host's immune system to fight the infection. They occur naturally in soil bacteria and fungi and have been mass produced using chemical synthesis since the mid-20th century. Their use has prevented countless millions of deaths.

There are several different categories of antibiotics, classified according to the pathogen(s) they target. Some antibiotics such as Penicillin G are 'narrow spectrum', which means that they are only effective against a limited range of bacteria. 'Broad spectrum' antibiotics such as Tetracycline are effective against a wide range of organisms.<sup>1</sup> Antibiotics are used to treat humans as well as animals. In some countries, they are also used to treat bacterial diseases in plants and to protect crops.<sup>2</sup> Many common medical procedures, including hip replacements and organ transplants would become far more dangerous, and potentially deadly without them.<sup>3</sup>

The excessive use of antibiotic drugs as well as antibiotic pollution in the environment places selective pressure on bacteria to develop defences against these very substances,<sup>4</sup> leading to antimicrobial resistance, a phenomenon which is explored in detail in the following section. Obscure-sounding pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacteriaceae (CRE) have now entered common parlance, and the possibility



*Sir Alexander Fleming, the "father" of antibiotics, at work in his laboratory*



Introduction

of contracting one of these 'superbugs' strikes fear into the hearts of hospital patients around the world.

The consequences of a resurgence of incurable infectious disease as a result of the declining effectiveness of antibiotics would be serious and far-reaching, threatening global trade, travel and international security.<sup>5</sup> Governments and global institutions warn that the worst is yet to come.

**History**

In the pre-antibiotic era, the balance of power between humans and bacteria was firmly in favour of the bugs. Severe bacterial diseases such as the Black Death and cholera took millions of lives.<sup>6</sup> With no effective treatments, blood poisoning contracted from a simple cut or a scratch could be fatal and mortality rates for common diseases such as pneumonia, gonorrhoea, syphilis and rheumatic fever were high. Doctors were largely powerless; the few resources they did have to combat infection, such as antiseptics, were of little help.<sup>7</sup>

In the absence of more sophisticated forms of treatment, people relied on traditional remedies, including natural antibiotics from moulds, soil and plants to treat bacterial infections. In Ancient Egypt, Greece and China for example, mouldy bread was pressed against wounds to prevent infections, the curative effect coming from antibiotics produced by the mould.<sup>8</sup> Similarly, a substance that was identified in the 1970s as a potent anti-malarial drug, qinghaosu (artemisinin), was used by Chinese herbalists for thousands of years as a remedy for many illnesses.<sup>9</sup>

During the 19<sup>th</sup> century physicians gained a greater understanding of the role of microorganisms in disease, and began developing new medicines. One of the founding fathers of modern immunology was the German Paul Ehrlich. His quest for a 'magic bullet' that could selectively kill microorganisms without attacking the human host resulted in the discovery of several substances including a type of antibiotic, later named Salvarsan, which cured syphilis.<sup>10</sup> The real breakthrough occurred largely as a result of serendipity. During World War I, the British chemist Alexander Fleming had served as a doctor at a military hospital in France, where he had witnessed large numbers of soldiers dying from infected wounds and observed that the antiseptics the doctors used to combat infection did more harm than good.<sup>11</sup>

In September 1928, by then a professor of bacteriology at the University of London, Fleming returned to his laboratory after a family holiday and started to clean up petri dishes containing colonies of the bacteria *Staphylococcus*.<sup>12</sup> Noticing

some mould on one of the dishes, he observed that it had produced a liquid that had prevented bacterial growth around it. On further examination, he discovered the liquid was able to kill a wide range of harmful bacteria.<sup>13</sup>

**"When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer. But I suppose that was exactly what I did!"**

*Alexander Fleming later said about that day.*<sup>14</sup>

The antibiotic was named penicillin. However, it proved difficult to produce on a large scale. Not until more than a decade later, during World War II, was it manufactured commercially by a U.S. pharmaceutical company. The impact was immediate and penicillin was soon named "the miracle drug". While supplies were still limited, priority was given to the U.S. military, where it was used to treat infected wounds or for surgical procedures. However, following a dramatic rise in production in the mid-1940s, all restrictions were removed and penicillin was made widely available to the general public.<sup>15</sup> At one point nearly every major American pharmaceutical company produced antibiotics at plants dotted across the country. Since then, production has migrated from the West to factories in China and India.<sup>16</sup>

The decades following the Second World War are now seen as the golden era of antibiotics. The 1950s, 1960s and 1970s saw the discovery of a wide variety of antimicrobial drugs, which have since saved millions of lives all over the world, contributing to the control of infectious diseases which were the leading causes of human mortality in the "pre-antibiotic" era.<sup>17</sup> By contrast, only two completely new classes of antibiotics have been introduced since the 1980s.<sup>18</sup>

Today all but a few pharmaceutical companies have pulled out of R&D of new antibiotics. In a 2004 survey of publicly disclosed drug discoveries by the world's 15 largest pharmaceutical manufacturers, only 1.6 percent were antibacterial agents<sup>19</sup>. According to the industry, the main reason for this yawning research gap is the lack of profit potential. They argue that the development of new antibiotics is an expensive and complex process as the easy discoveries have already been made

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and there are far higher returns on drugs to treat chronic conditions such as diabetes or high blood pressure.<sup>20</sup> Because of the crucial role antibiotics play in protecting us from disease, there are growing calls for a new approach to the economics of antibiotic discovery. This would represent a departure from existing profit models, under which sales volumes and price determine the return on investment for a drug, and remodel existing economic incentives so as to encourage new R&D efforts and a more rational approach to their use.<sup>21</sup>

**Today's market**

The global antibacterial drugs market was valued at US\$43.55 billion in 2012 and is expected to grow to reach an estimated value of US\$45.09 billion by 2019.<sup>22</sup> Given the lack of new antibiotic drug discovery, the market is dominated by generics manufacturers, with India holding the largest share of global generic drug manufacturing.<sup>23</sup>

With respect to the key revenue generating drugs (branded and generic), U.S. pharma giant Pfizer accounted for the largest market share in 2012, followed by Merck (U.S.) and United Kingdom-based GlaxoSmithKline.<sup>24</sup>

While there is still higher per capita consumption of antibiotics in wealthy countries, consumption rates are rising rapidly in emerging economies and account for most of the recent market expansion<sup>25</sup> as well as the lion's share of projected growth over the coming decades.<sup>26</sup> In terms of overall volume, India was the largest consumer of antibiotics in 2010 with 10.7 units per person. China was the second largest with 7.5 units per person, and the USA was the third largest with 22.0 units per person.<sup>27</sup> However, this picture could change significantly when consumption in animal rearing is added to the equation.

The world is in the grip of a paradox. Growing antimicrobial resistance highlights the urgency of acting swiftly to bring global use of antibiotics in human and animal populations under control. However, current projections show that consumption is set to soar in the decades ahead. According to recent estimates, global consumption of antimicrobials is set to rise by 67 percent between 2010-2030. In the BRICS countries (Brazil, Russia, India, China, and South Africa), the estimated increase in antimicrobial consumption is 99 percent, which represents up to seven times projected population growth.<sup>28</sup> The use of antibiotics in animals is responsible for a large share of that increase.



The discovery of antibiotics revolutionised medicine © Iqbal Osman

# Antibiotic Resistance

## The looming public health disaster

02

**Antimicrobial resistance (AMR) is one of the main public health threats to humanity. Superbugs - bacteria that have developed resistance to antibiotics - already claim 700,000 lives a year. According to the UK Government-funded Review on AMR, 300 million premature deaths are expected over the next 35 years due to AMR.<sup>29</sup> AMR would also make medical procedures such as organ transplants, surgery and chemotherapy impossible. It would usher in a post-antibiotic era, where minor injuries could be lethal and where once curable diseases are once again untreatable. Several countries now consider AMR as a threat to national security and are calling for a global approach. However, this global approach has so far ignored one of the key causes of AMR, namely the manufacturing of antibiotic substances and its resulting environmental impact. Antibiotics production mostly takes place in China and India where poor environmental regulation results in the discharge of antibiotic waste into local rivers and groundwater, harming local inhabitants and spreading AMR. This chapter will describe the looming health disaster AMR represents, the main reasons behind the overuse and misuse of antibiotics, and what can be done to fix the broken model.**

The discovery of antibiotics in the 20th century fundamentally transformed human and veterinary medicine, saving millions of lives around the world. But this milestone in medical history came with a warning from the father of antibiotics himself, Alexander Fleming, that bacteria could become resistant to penicillin through exposure to non-lethal quantities of the drug, a danger he outlined when accepting the Nobel prize in 1945.<sup>30</sup> Sadly, humanity has been reckless and history is proving Alexander Fleming right. Since the first antibiotics hit the market in the mid-1940s there has been a race between scientific researchers to develop new antibiotics on the one hand, and resistant bacteria, evolving rapidly in response to selective pressure on the other. During the first decades of the antibiotic era, science was ahead of the game. Since then, the widespread use and misuse of antibiotics combined with the failure to develop new ones has changed all that. Resistant bacteria are now a worldwide threat to public health.<sup>31</sup> In some parts of the world, antibacterial resistance has reached “alarming levels” and is spreading in health care environments as well as within the broader community.<sup>32</sup>

### What is AMR?

**Antimicrobial resistance (AMR) is defined by the WHO as the resistance of a microorganism to an antimicrobial drug which was originally effective for treatment of infections caused by it. AMR threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. In this report, AMR is used to refer to bacterial resistance to antibiotics.<sup>33</sup>**

### The three main causes of AMR:

- **Inappropriate use in humans, such as over-prescription, prescription for non-bacterial illnesses, failure to complete a course of treatment, etc.;**
- **Routine, non-therapeutic use of antibiotics in intensive livestock farming as a substitute for healthier living conditions;**
- **Release of antibiotics into the environment through mismanagement in factories, improper disposal of medicine, or human and animal excretion.**

#### 1. Overuse in humans

Overuse in humans can result from doctors over-prescribing antibiotics or prescribing them inappropriately (e.g. for a common cold or a sore throat) or from patients not completing a course of treatment. Prescribing practices vary significantly between countries: in some parts of the world it is possible to buy antibiotics without a prescription; in others antibiotics sales make up a share of hospitals' and doctors' income. Good antibiotic stewardship is therefore of crucial importance in combatting AMR.<sup>35</sup> Preventing infection through better hygiene and other measures is also key to limiting the spread of bacteria and the use of antibiotics. Governments and foundations are currently putting significant resources into developing new types of antibiotics and diagnostic tests which would help differentiate between bacterial and viral infections.<sup>36</sup>

# How does AMR develop?

The development of resistance is a normal evolutionary process for all species, including microorganisms such as bacteria, viruses, parasites and fungi. It is an example of natural selection, where the bacteria that are resistant have more chances to survive, reproduce and pass on their genes, while weaker bacteria are killed off. The more the bacteria are exposed to antibiotics in the environment, animals or humans, the higher the chances are that antibiotic-resistant bacteria will multiply and thrive

01

**Lots of bacteria  
...few are  
resistant**

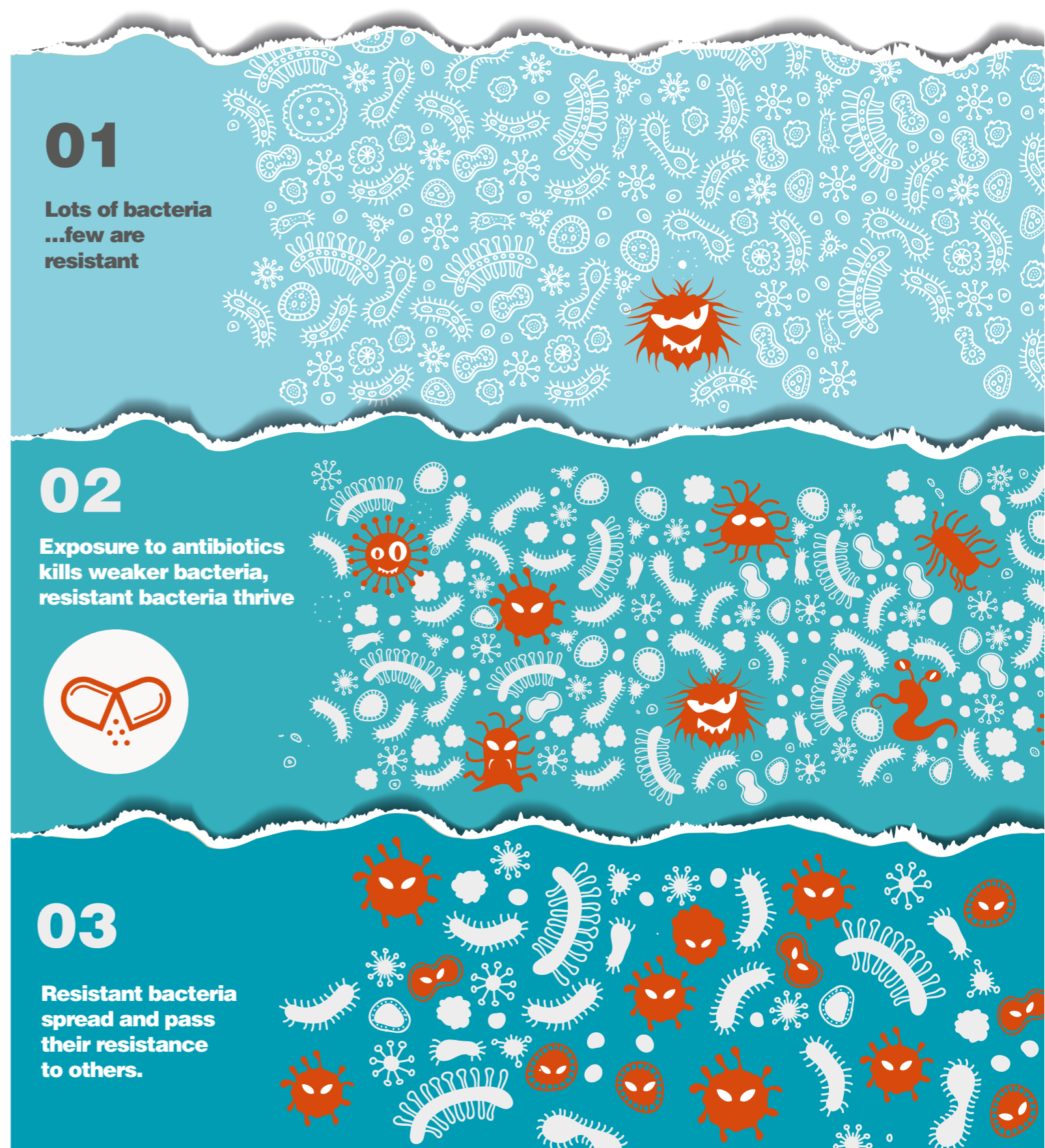
02

**Exposure to antibiotics  
kills weaker bacteria,  
resistant bacteria thrive**



03

**Resistant bacteria  
spread and pass  
their resistance  
to others.**



**2. Non-therapeutic use in animals**

Another cause of AMR is the routine feeding of antibiotics to animals in industrial livestock production to help them endure crowded, dirty, and stressful conditions and grow faster. According to the WHO, more antibiotics are given to healthy animals than are used to treat diseases among human patients.<sup>37</sup> The extensive use of antibiotics in animal breeding stems from the 1940s and 1950s when the industry discovered that antibiotics could serve as growth stimulants and for disease control, which made it possible to rear large flocks of chickens or herds of cows in confinement.<sup>38</sup> This latter use is referred to as the 'prophylactic' use of antibiotics. In the United States, it represents 80 percent of all sales of antibiotics.<sup>39</sup> In China, more than 50 percent of the antibiotics sold are used in the animal husbandry and feed industry.<sup>40</sup> While Europe has restricted the use of antibiotics as growth promoters, their use in animals is still flourishing. In Germany alone, animals are given three times more antibiotics than total human consumption.<sup>41</sup> The prophylactic use of antibiotics in animal breeding is

livestock rearing. In light of the huge threat to human health and animal welfare posed by AMR, numerous organisations have launched major campaigns aimed at putting a stop to the non-therapeutic use of antibiotics in animals and calling for the restriction of some types of antibiotics exclusively for human use. The EU is considering banning the prophylactic use of antibiotics<sup>45</sup> and some countries such as Denmark<sup>46</sup> and Sweden have already begun to drastically reduce their consumption.



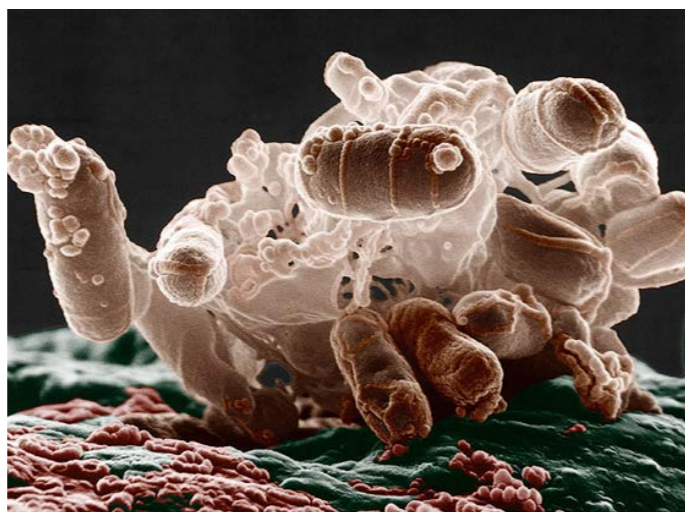
Microscope image of neisseria gonorrhoeae, bacteria responsible for the common sexually transmitted infection gonorrhoea. © National Institute of Allergy and Infectious Diseases (NIAID)

**Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe. Stopping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria.**

U.S. Centre for Disease and Control Prevention, 2013, <http://www.cdc.gov/drugresistance/threat-report-2013/>

problematic because the regular administration of low doses of drugs wipes out weaker bacteria and leaves the field open for stronger strains.<sup>42</sup> When the manure is sold on as fertiliser or washed downstream into rivers and groundwater, the resistant genes are spread to the wider bacterial community. In 2012, Chinese researchers studying the manure from pig farms in China found 149 unique resistance genes.<sup>43</sup> In the U.S. in 2013, the Food and Drug Administration (FDA) found that 65 percent of chicken breasts and 44 percent of ground beef carried bacteria resistant to tetracycline, and 11 percent of pork chops carried bacteria resistant to five classes of drugs.<sup>44</sup>

The rising global demand for cheap meat is expected to further increase the already extensive use of antibiotics in



A cluster of E.coli bacteria under the microscope. Some strains of this bacteria can cause diarrhoea, urinary tract infections, respiratory illness and pneumonia. © Microbe World

**3. Pharmaceutical pollution**

Finally, another major cause of AMR is the release of antibiotics into the environment either as a result of bad manufacturing practices or through human and animal excretion and careless disposal at the end of life (for example people flushing drugs down the toilet). This aspect of AMR is not part of most of the global or national strategies that are being developed to contain the spread of resistance. The manufacturing of antibiotic APIs is particularly problematic owing to the substantial quantities and concentrations of antibiotics released, providing an ideal breeding ground for drug resistant bacteria. Bacteria in these environments are able to share or exchange sections of genetic material with other bacteria - this can even occur between different bacterial species.<sup>47</sup>

**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. 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 France, Japan, Oman and the United States.<sup>48</sup> With globalisation and modern means of travel, any local health problem can soon become a disaster of global proportions.

**The human and economic cost of AMR**

Infections caused by superbugs already claim 700,000 lives

annually around the world. Every year, 2 million Americans are infected with bacteria that are resistant to antibiotics resulting in 23,000 deaths.<sup>49</sup> In China and the EU, 80,000 and 25,000 people respectively die annually from hospital-acquired antibiotic-resistant infections.<sup>50</sup>

In India a growing number of babies carrying antibiotic-resistant bacteria are born each year. More than 58,000 Indian babies died in 2013 as a result of AMR and doctors are increasingly worried that drug-resistant infections could present a serious setback to progress in reducing Indian infant mortality rates. Newborns are particularly vulnerable to AMR because their immune systems are fragile, leaving little time for doctors to find a drug that works. However every section of the population is at risk.<sup>51</sup>

In 2050, an estimated 10 million people will die every year if the current situation continues unchecked.<sup>52</sup> Most of the deaths will occur in highly populated areas in Asia and Africa, but Europe and the U.S. are also facing a more than 14-fold increase in mortality related to drug-resistant infections.

Because antibiotics play such a critical role in surgical interventions and in treating diseases ranging from cancer to diabetes, AMR could lead to the loss of many modern and life-improving medical treatments, above and beyond the antibiotics themselves.<sup>53</sup>

As we have seen, tackling infections caused by resistant bacteria requires the use of antibiotics with harmful side effects. Longer recovery times, more complex treatment,

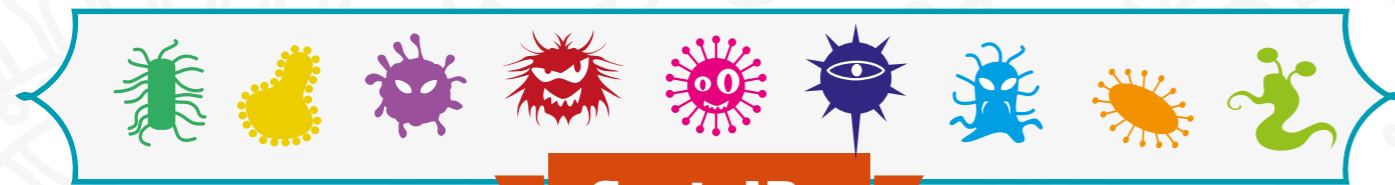
**Table 1. Estimated deaths per year caused by AMR in 2050**

REGION	ESTIMATED DEATHS PER YEAR 2050
Asia	4,730,000
Africa	4,150,000
Latin America	392,000
Europe	390,000
North America	317,000
Oceania	22,000

Source: Review on Antimicrobial Resistance, December 2014, Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations



# How antibiotic resistance spreads



**Created By**



## Farms

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



## Pharmaceutical Pollution

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



## Overuse in Humans

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 France, Japan, Oman and the United States. With globalisation and modern means of travel, any local health problem can soon become a disaster of global proportions.



**Sum  
Of  
Us**



## Antibiotic Resistance

and more frequent hospitalisations entail higher health care costs, imposing a greater economic burden on families and societies.<sup>54</sup>

It is difficult to measure the full economic effects of AMR. However, studies that have estimated how increased resistance to antibiotics would affect the health and mortality rate of the labour force indicate that it has already led to a drop in a Gross Domestic Product (GDP) of up to 1.6 percent.<sup>55</sup> Other studies have shown that the world could lose up to US\$100 trillion worth of economic output between now and mid-century if it is not addressed, lowering projected GDP by 2 to 3.5 percent.<sup>56</sup> The economic effects of antimicrobial resistance are unevenly distributed, with the lowest income countries paying the highest price. In the report "The global economic impact of anti-microbial resistance", the consulting group KPMG identified the economic burden associated with four potential AMR scenarios:

- Scenario A - an absolute increase in current rates of resistance by 40 percent;
- Scenario B - 100 percent resistance rate applied across all countries;
- Scenario C - Doubling of current infection rates for the three bacteria, HIV and Tuberculosis, and an absolute rise in current rates of resistance by 40 percent;
- Scenario D - Doubling of current infection rates for the three bacteria, HIV and Tuberculosis, and 100 percent resistance rate in all countries.<sup>57</sup>

Because of the complexity involved in estimating the full

impact of AMR, the analysis was restricted to a selection of three bacteria and three diseases: Staphylococcus aureus (best known in its methicillin resistant form – MRSA), Escherichia coli (widely known as E. coli), and Klebsiella pneumoniae, HIV, Tuberculosis and Malaria.

In the table below 'best case' corresponds to Scenario A and 'worst case' to Scenario D. All scenarios show that there will be a significant reduction in GDP as a result of AMR: between 1 and 6 percent, with up to 20 percent in the worst case for Africa, where the majority of deaths are predicted to take place.

## The economic paradox

It is obvious that the model that is driving the misuse and overuse of antibiotics around the world is broken. There are two main factors fuelling this. The first is the low price of the most commonly used antibiotics, which incentivises consumption. The second factor relates to the perverse financial incentives which make some veterinarians and even hospitals in some countries dependent on the sale of drugs for their income: veterinarians are sometimes allowed to both prescribe and sell medication. In addition to this they may receive a volume discount from pharmaceutical companies, which in turn drives high volume purchases.<sup>58</sup> In many countries, antibiotics for human use are available without prescription or can be freely bought on the internet. At the heart of all of this is the cheap production of drugs, which takes place through a series of complex interactions between India, China and big Western companies.

**Table 2. Reduction in GDP caused by AMR.**

REGION	BEST CASE	WORST CASE
Europe	1,01%	4,51%
Africa	6,28%	20,0%
LATAM	1,13%	4,85%
ASIA	1,78%	6,27%
MENA	1,11%	4,17%
North America	0,73%	3,17%
World	1,66%	6,08%

Source: KPMG, December 2014, The global economic impact of anti-microbial resistance

## 02

### Antibiotic Resistance

Jeffrey Stein, who served as chief executive of antibiotic developer Trius Therapeutics (now Cubist Pharmaceuticals), has described the misuse of antibiotics as “the one therapeutic area where prescribing decisions are made based on price rather than efficacy”.<sup>59</sup> The low price strikes three ways by (1) providing a cheap alternative to food for animal farmers seeking an easy way to increase meat production, (2) making it possible for medical practitioners to satisfy demanding patients by inappropriately prescribing antibiotics for viral infections and (3) failing to incentivise pharmaceutical companies to develop new antibiotics because of low expected return on investment.

However, pharmaceutical companies have been anything but sparing in recent years when it comes to antibiotics sales. In 2010, German drug maker Bayer earned €166 million, an 11 percent increase over the previous year, on sales of the animal antibiotic Baytril. Annual sales of veterinary drugs in Germany had reached €730 million by 2012.<sup>60</sup>

***"Some veterinarians' profit margins are bigger than those of cocaine dealers [...]. When a veterinarian finds a sick chick among 20,000 other chicks, he treats the discovery as justification to preventively treat the entire flock with antibiotics."***<sup>61</sup>

*Der Spiegel report on factory use of antibiotics in Germany, 2012*

China produces most of the world's antibiotic APIs, keeping prices low to secure its competitive advantage, which in turn drives overconsumption. Compounding this, the price pressure, combined with weak regulation leads some factory owners to take production shortcuts, which negatively impacts the quality of the end products and discourages proper management of antibiotic effluent, which ends up in rivers and groundwater surrounding manufacturing sites.



## 03

### Production and pollution

***China has become the world's largest producer and exporter of APIs owing to its cheaper labour and capital costs, and lighter regulatory burden. Government-supported investment in penicillin fermenters resulted in an almost ten-fold increase in the number of pharmaceutical firms between 1980 and 1999, putting most of China's Western competitors out of business. China currently supplies up to 90 percent of all raw materials for antibiotics. These are mostly exported to India, where they are processed and sold on to markets around the world. Supply chains and ownership structures in the antibiotics industry are very opaque, and the Chinese take-over of the market has come with a series of scandals affecting public health and pollution. In 2014, Chinese national television exposed a series of pollution scandals linked to antibiotics manufacturing plants. Research in India by Swedish scientists has shown that antibiotic pollution from pharmaceutical production plants leads to the proliferation of resistant bacteria, fuelling global AMR. Resistant bacteria have also been discovered in waste water treatment plants in China and represent a major global threat, as they spread easily through international travel and trade.***

#### **How China became the world's biggest producer of APIs**

China is the world's largest producer and exporter of APIs.<sup>62</sup> Chinese drug production is a major source of supply for the global generic medicines sector with more than 95% of chemicals manufactured in the country used to produce non-branded drugs. Cheap generic production is supported by national drug price control policies. Despite the size of Chinese pharmaceutical exports (US\$67 billion annually), virtually none of this revenue is derived from truly innovative products.<sup>63</sup>

There are several reasons for China's dominance on the global API market, including cheaper labour and capital costs and a lighter regulatory and environmental burden. In the 1980s,

the Chinese government made a strategic decision to invest in penicillin fermenters, sparking fierce price competition and forcing most Western producers off the market.<sup>64</sup> Between 1980 and 1999, the number of pharmaceutical firms in China increased almost tenfold, from 680 to 6,357. By the 1990s, China had built a relatively robust pharmaceutical sector and later made some more serious attempts to regulate and weed out non-compliant manufacturers.<sup>65</sup> However, this process was beset by scandals and controversy.

In 2013, its reputation damaged by successive setbacks, the SFDA reorganised and changed its name to the China Food and Drug Administration, CFDA.<sup>71</sup> Although some efforts have been made to strengthen regulation of the pharmaceutical industry, China still has a long way to go. In its report to Congress in October 2014, the US-China Economic and

The story of Zheng Xiaoyu is a fitting illustration of the turbulent fortunes of the Chinese pharmaceutical industry. In 1998, Zheng became the first director of China's State Food and Drug Administration (SFDA).<sup>66</sup> One of Zheng's reforms was to enforce new production standards in the form of Good Manufacturing Practice (GMP) certification. The agency declared that companies which were not GMP-certified by July 2004 would lose their operating licence. By May 2005, nearly 4,000 pharmaceutical manufacturers, or 78 percent of firms, had been certified as GMP-compliant.<sup>67</sup> In parallel to this, the Chinese government launched an initiative to curb soaring drug prices. Faced with the prospect of reduced revenues and increased training and equipment costs, many companies flouted the new rules and resorted to bribing government officials, including Mr. Zheng himself. In 2007, after leading the agency for eight years and presiding over 150,000 drug approvals,<sup>68</sup> Zheng was found guilty of corruption and executed.<sup>69</sup> In the wake of the scandal, an industry analyst told The New York Times, "If the head of the drug agency is corrupt, you can imagine how corrupt the whole system is." This inference was borne out shortly after, when in 2008 counterfeit heparin, a widely used anticoagulant, produced in China caused around 80 deaths among dialysis patients in the United States. In 2012, the SFDA was forced to clamp down on two more scandals: toxin-tainted gel capsules and antibiotics produced using reprocessed cooking oil.<sup>70</sup>

Security Review Commission describes China's political structure as fragmented and authoritarian with built-in conflicts of interest which contribute to regulatory failure. The CFDA's lack of influence is compounded by lack of resources and administrative overload at the regional and provincial level combined with corruption and bribery at local level, where officials often turn a blind eye to the polluting habits of pharmaceutical manufacturers in light of their contribution to the economy and the tax revenue they generate.<sup>72</sup>

environment and for communities living close to the factories.

### The cost of cheap antibiotics

In 2007, the first in a series of papers by a Swedish researcher Joakim Larsson was published, showing very high emissions of pharmaceuticals from drug manufacturers in Patancheru, near Hyderabad, India. Tests on effluent from a treatment plant receiving wastewater from about 90 manufacturing plants showed that concentrations for some pharmaceuticals

In 2010 the Chinese government identified the pharmaceutical industry as being one of the nation's key sources of pollution and released a more stringent set of standards for the discharge of pharmaceutical pollutants into water. However, the industry has repeatedly breached the new government standards, citing high costs and low profit margins as an excuse.<sup>80</sup> Low-cost production is the key competitive advantage of the Chinese antibiotics manufacturing industry, but it is fuelling an unsustainable model of production and consumption which could result in an environmental disaster. A flood of recent reports in the Chinese media has shown that the presence of antibiotics in the environment in China has reached dizzying proportions: in 2014, Chinese researchers found antibiotic substances in offshore waters including the Yellow Sea and Bohai Sea.<sup>81</sup>

India imports over 80 percent of API ingredients from Chinese manufacturers which it mainly uses to produce antibiotics and painkillers.<sup>73</sup> The key reason for India's dependence on China is Chinese manufacturers' ability to supply the market at very low cost.<sup>74</sup> Imports of APIs and advanced intermediates to India have grown by close to 20 percent a year, rising from US\$800 million (€586 million) in 2004 to US\$3.4 billion (€2.8 billion) in 2014. Trade estimates show that China accounts for 58 percent of such imports by value and 80 percent by volume.<sup>75</sup> Some sources put the figure at above 90 percent.<sup>76</sup> India's drug industry is export-oriented, which means that a substantial portion of Chinese-origin ingredients processed in India may be exported to the United States or Europe in finished drug products.<sup>77</sup> Indian customs data show that the share of India's organic chemical imports originating in China and the share of India's drug exports destined for the United States have both risen in recent years.<sup>78</sup> This has led to the emergence of a three-tier chain in the global market for pharmaceutical APIs, which takes root in China, passes through India and ends up on markets around the world.<sup>79</sup>

China's rise to the top as a producer of APIs for antibiotics and other pharmaceuticals is a consequence of a worldwide quest for cheaper medicine. This comes at a huge cost - both for the

were greater than those found in the blood of patients undergoing treatment.<sup>82</sup> The researchers told Bloomberg that concentrations of antibiotics in the river sediment further downstream were so high that if "ciprofloxacin (a type of antibiotic [...]) had been more expensive, we could mine it from the ground."<sup>83</sup>

The dumping of antibiotic waste by manufacturing plants creates ideal conditions for the massive proliferation of multi-drug-resistant bacteria and the emergence of antibiotic resistance. Concentrations of antibiotics in effluent from manufacturing plants are much higher than those resulting from excretion.<sup>84</sup> Antibiotic pollution therefore accelerates the spread of resistance genes and their transfer from environmental microbes to other species and eventually to bacteria that are dangerous to humans.<sup>85</sup> In addition to this, antibiotic pollution can harm environmental bacteria and algae present in water and soil and alter species distribution, which is harmful for the ecosystem as a whole.<sup>86</sup>

The impact of antibiotic pollution on the creation of resistant bacteria was recently examined by researchers who took samples from an Indian waste water treatment plant receiving discharges from several drug manufacturers in Hyderabad.



Effluent from antibiotics manufacturing plants creates a fertile breeding ground for drug-resistant bacteria © Shao Wenjie

The study confirmed that it was the perfect breeding ground for the creation of resistant bacteria, with 86% of the strains found showing resistance to twenty or more antibiotics.<sup>87</sup> Strong concentrations of antibiotics in the waste water created an environment where only the strongest bacteria could survive. These bacteria became resistant to multiple antibiotics and also exchanged their genes with other bacteria present in the environment. The researchers concluded that the levels of multi-drug resistance exhibited in their study were (according to their best knowledge) the highest reported from any environmental sample.

Another study investigating waste water treatment plants in North China discovered the New Delhi Metallo-Beta-Lactamase (NDM1) strain of antibiotic-resistant bacteria<sup>88</sup> (see Section 2). NDM1 bacteria were not only escaping purification but also breeding and spreading their genes to other bacteria in water and soil. Scientists concluded that there were four to five super bugs coming out of the waste water plant for any one bug that came in.<sup>89</sup> This is particularly scary as there is currently no antibiotic capable of killing this specific strain of bacteria, which has already entered Europe in the body of a Swedish tourist and has also been discovered as far afield as France, Japan, Oman and the United States.<sup>90</sup> NDM1 has already spread its resistance genes to other common bacteria, such as E. coli, salmonella and K pneumonias and made them resistant to even the strongest available antibiotics.<sup>91</sup>

### China as a hotspot for emerging microbial threats

India is often identified in the media and academic studies as a hotbed of resistant bacteria, but China is also a major contributor to the global spread of untreatable infectious disease and a hotspot for the emergence of new microbial threats. The 2003 SARS epidemic first brought to the world's attention the threat posed by the emergence of new infectious diseases in China.

China suffers from high and increasing rates of antibiotic resistance. One 2012 study reported an average rise in the antibiotic resistance rate in China of 22% over 6 years, compared with 6% growth recorded for the USA over a similar time period.<sup>92</sup> Soaring drug resistance in China is driven by the incorrect use of antibiotics

and strong financial incentives for drug prescription (profits from drug sales make up a large share of Chinese hospitals' income).<sup>93</sup> Excessive use of antibiotics in intensive livestock rearing<sup>94</sup> and their resulting release into the environment only serve to exacerbate the problem<sup>95</sup>: according to a 2013 study published in the U.S. Proceedings of the National Academy of Sciences (PNAS), researchers examining manure samples from large-scale, antibiotic-intensive Chinese pig farms found 149 different genes showing antibiotic resistance in manure and in the soil.<sup>96</sup>

Another study<sup>97</sup> examining pharmaceutical pollution in highly populated Asian countries concluded that this phenomenon poses global risks because of expanding international travel and trade links. The paper showed that most of the examined manufacturing sites do not comply with environmental regulation and discharge their highly contaminated waste water, thereby exposing humans and animals to drug-resistant microbes via aerosols, endophytes, water and crops. It is clear to see how problematic this is in an era of globalisation: In 2013, 26 million foreigners visited China (5.6 million from Europe, 2.1 million from the United States).<sup>98</sup> In addition to this, in 2014, 109 million trips abroad were made from China.<sup>99</sup> Foreign visitors to China and Chinese tourists travelling abroad are all potential carriers of multi-drug resistant microbes to the rest of the world.<sup>100</sup> China's exports of agricultural products have also increased,<sup>101</sup> providing another venue for

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the proliferation of resistant bacteria that can travel on meat and other food products.

#### Better alternatives are needed

A significant body of research clearly demonstrates that the unmonitored dumping of antibiotic-laden effluent in areas surrounding pharmaceutical production plants is endemic,<sup>102</sup> contributing to the creation and spread of resistant bacteria. This runs counter to industry claims that the discharge of APIs is unlikely owing to the high cost of raw materials.<sup>103</sup> However, not all API production results in such damaging impacts. Factories can be managed in a way that limits the quantities of antibiotics and other toxic chemicals that are released to the environment. Cleaning up the manufacturing process requires the

these principles, which are entirely voluntary, must “have systems in place to ensure the safe handling, movement, storage, recycling, reuse, or management of waste, air emissions and wastewater discharges.” However, the lack of transparency regarding the origin of APIs, makes it difficult to verify, whether these guidelines are respected. This means that many big U.S. and European companies can simply hide behind their opaque supply chains and turn a blind eye to environmental problems associated with drug manufacturing. The following section takes a closer look at some of China’s most notorious antibiotics factories, examining links to Indian drug processing companies and exploring how pharmaceutical raw ingredients made in highly dubious circumstances are ending up in pharmacies around the world.

**Companies at every level of the antibiotics supply chain must prioritise environmental management; in particular, the factories supplying intermediates or APIs must be required to prove that they are committed to clean production throughout the manufacturing process.**

installation of dedicated waste water treatment equipment which is maintained on a regular basis as well as the effective management of any effluent. In addition, factories should adopt production techniques which minimise the use of chemicals, which in turn reduces the amount of dangerous residues from API production.

Unfortunately, environmental regulation and its enforcement are currently left up to national regulators. Compliance with ‘Good Manufacturing Practices’ (GMP), a set of standards which are defined by the WHO and which are a mandatory requirement for accessing the EU and U.S. markets, do not include environmental criteria.

A number of big pharmaceutical companies have joined together in the Pharmaceutical Supply Chain Initiative (PSCI), which has established a set of industry Principles for Responsible Supply Chain Management, covering five areas including the environment.<sup>104</sup> Companies which sign up to



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**Our investigation has uncovered a serious lack of publicly available information, which remains a major stumbling block to acquiring the full picture. Nonetheless, it is clear that U.S. and European companies are sourcing pharmaceutical raw materials from some of China’s most highly polluting factories. The investigation was inspired by reports in the Chinese media that have exposed pollution from specific factories in China as a very serious problem severely affecting communities surrounding the factories and impacting water and soil quality. Measures taken to address the issue have either not been implemented or have focused on relocating factories, public apologies from company officials, or a transfer of ownership. The problem so far has been considered as a localised pollution problem with very few links made to the corporate clients of these polluting factories. Pfizer is among the well-known brand names that has sourced antibiotics for human and animal use from one of the Chinese sites. There are also links between three polluting Chinese companies and one of the world’s largest generic drug manufacturers, McKesson, which owns several European brands (Lloyds Pharmacy in the UK, Ireland, France and Sweden, Celesio in Germany and OCP in France and Portugal). The world’s largest generics manufacturer, Israeli company Teva, which has a presence in over 60 countries, also appears to be sourcing antibiotics from several polluting factories. Actors at every step in the supply chain have a responsibility to improve this highly unsatisfactory situation. Pharmaceutical companies must make a proactive effort to clean up their supply chains, and policy-makers must adopt measures that increase transparency and accountability in the industry.**



### CASE STUDY: PFIZER



U.S. multinational Pfizer Inc. is one of the world’s largest pharmaceutical companies, with operations in more than 175 countries and over 200 ‘supply partners’ globally.<sup>105</sup> Once a pioneer of the mass production of penicillin, it has now largely abandoned antibiotics manufacturing<sup>106</sup>, having decided that “enhancing [its] focus on infection prevention would represent a more prudent return on investment.”<sup>107</sup>

Pfizer first established operations in China in 1983<sup>108</sup> and now has investments equivalent to approximately US\$1 billion in the country.<sup>109</sup> Like other multinational drug companies, Pfizer is increasingly turning to partnerships and joint ventures with local partners in the research, marketing, and manufacturing of its products in order to grow its Chinese market share.<sup>110</sup>

Research and interviews carried out for this report indicate that Pfizer is sourcing antibiotics for human use from NCPC’s Semisyntech plant (formerly know as Hebei Huari Pharmaceutical). In 2011, it was reported that NCPC had become Pfizer’s sole supplier of sterile APIs for human use in China after being awarded the contract for production of its sterile fortified procaine penicillin potassium products.<sup>111</sup> Conversations with NCPC in early 2015 appear to confirm that it still has a supply agreement with Pfizer. In January 2015, the World Health Organization published an inspection report following an EU statement of non-compliance relating to the Semisyntech facility for serious deficiencies concerning documentation and data integrity<sup>112</sup> (see Section 4 for more details).

In addition to this, a veterinary product marketed by Pfizer Animal Health<sup>113</sup>, LINCOMIX 50- lincomycin hydrochloride granule, contains API manufactured by North China Pharmaceutical Group Hualuan Co. Following a deal completed in June 2013, Pfizer Animal Health has become Zoetis, a separate and fully independent company.<sup>114</sup> Sinopharm also claims to have a ‘strategic partnership’ with Pfizer.<sup>115</sup>

There are also established links between Pfizer and Indian manufacturer Aurobindo. In 2009, Pfizer extended a licensing agreement with Aurobindo, acquiring rights to 55 solid oral dose and five sterile injectables in 70 markets<sup>116</sup> and according to U.S. import data, Pfizer has imported Penicillin V Potassium tablets shipped by Aurobindo at least



once since the beginning of 2012.<sup>117</sup> In turn, there are clear links between Aurobindo and several of the Chinese API producers featured in this report. According to information from the Indian Central Drugs Standards Authority<sup>118</sup>, Aurobindo Pharma held import licenses for the following Chinese manufacturers:

- Sinopharm Weiqida<sup>119</sup>
- Harbin Pharmaceutical Group<sup>120</sup>
- NCPC<sup>121</sup>
- CSPC<sup>122</sup>

### Responsibility

Pfizer is well aware of the public health risk posed by overconsumption and inappropriate use of antibiotics. In China, it supports a Ministry of Health initiative to educate Chinese doctors about the dangers of misusing and overusing antibiotics.<sup>123</sup> It also acknowledges concerns about the safety of pharmaceutical products manufactured in Asia in the wake of public health scandals, with a company representative recently recognising that “It raises questions in people’s minds,” but pointing to the company’s policy on performing due diligence when selecting its suppliers.<sup>124</sup>

Pfizer is a member of the Pharmaceutical Supply Chain Initiative (PSCI) together with other major pharmaceutical companies. The PSCI’s first move was to establish the Pharmaceutical Industry Principles for Responsible Supply Chain Management, covering five areas including the environment.<sup>125</sup> The Principles, which PSCI members including Pfizer encourage their suppliers to commit to and support<sup>126</sup>, specify that: **“Suppliers shall operate in an environmentally responsible and efficient manner to minimize adverse impacts on the environment.”**

### Pharmaceutical Industry Principles for Responsible Supply Chain Management regarding the environment:

#### 1. Environmental Authorizations

Suppliers shall comply with all applicable environmental regulations. All required environmental permits, licenses, information registrations and restrictions shall be obtained and their operational and reporting requirements followed.

#### 2. Waste and Emissions

Suppliers shall have systems in place to ensure the safe handling, movement, storage, recycling, reuse, or management of waste, air emissions and wastewater discharges. Any waste, wastewater or emissions with the potential to adversely impact human or environmental health shall be appropriately managed, controlled and treated prior to release into the environment.

#### 3. Spills and Releases

Suppliers shall have systems in place to prevent and mitigate accidental spills and releases to the environment.

Pfizer’s own Policy on Pharmaceuticals in the Environment states that the *company* has an **“active program to assess and address the issues associated with pharmaceuticals in the environment (PIE)”** and states that it has **“teamed with a number of [its] manufacturing suppliers to evaluate their materials handling and production equipment cleaning processes”** with the aim of ensuring that the “manufacture, use and disposal of [its] medicines does not adversely affect human health or the environment.”<sup>127</sup>

### The Antibiotics Supply Chain

Modern-day pharmaceutical sourcing is characterised by complexity and a lack of transparency. It involves an increasing number of geographically dispersed individuals, producers and companies and diverse distribution channels.<sup>128</sup> Because of this, the pharmaceutical supply chain is more vulnerable to governance breakdown and corruption than other commodities.<sup>129</sup> Attempts by the U.S. FDA to increase its 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.<sup>130,131</sup>

A spate of scandals has led to minor 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 EU<sup>132</sup> and U.S. markets.<sup>133</sup> A yawning transparency gap nonetheless remains, and nowhere more so than in the antibiotics supply chain. Even more importantly, GMP principles do not include any environmental criteria. This is a surprising 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 they were manufactured extremely challenging. In the European Union, for example, importers of finished dose drugs are only required to provide publicly accessible information on the origin of the finished products, and not of the APIs which they contain.<sup>134</sup> While EU importers of APIs have to report on their origin, the EudraGMDP database<sup>135</sup> on manufacturing sites, importers, and distributors of APIs is still not complete as not all competent authorities in Europe have established systems for timely inclusion of registration data.<sup>136</sup>

In the United States, the FDA has been criticised in the past for not requiring manufacturers to provide sufficient public information on suppliers and manufacturing locations, with various different databases listing different types of information.<sup>137,138</sup>

The Drug Quality and Security Act (DQSA) was signed into U.S. law in November 2013 with the intention of more effectively protecting the U.S. pharmaceutical supply chain from potentially contaminated or counterfeit products. To this end, an electronic, interoperable traceability system will be rolled out over the coming years by drug manufacturers,

wholesale drug distributors, repackagers and dispensers, overriding various individual state policies.<sup>139</sup> However, these traceability requirements will only apply to prescription drugs in finished dosage forms for administration to a patient without further manufacturing, and therefore not to the APIs used in producing these drugs.<sup>140</sup>

Drug manufacturers themselves are complicit in this lack of transparency. Companies often consider their supply chains to be trade secrets with suppliers of fine chemicals and APIs to pharmaceutical companies often operating under nondisclosure agreements.<sup>141</sup> This makes the exact origin of a drug’s ingredients difficult or impossible to trace.

Nevertheless, as the following pages will show, careful research has made it possible to establish connections between highly polluting antibiotic manufacturing plants in China and large Indian drug companies, which in turn supply major pharmaceutical brands in Europe and the United States.

### The Investigation

On-the-ground investigations and desk research carried out for this report have identified clear links between dirty API factories in China, Indian middlemen, and trusted brand names in Europe and the US. In order to connect the dots between manufacturing sites and pharmacy shelves we have consulted customs data, import licenses<sup>142</sup>, databases and company financial and legal documents, as well as reports from regulatory bodies in several countries. The result is a number of supply chain puzzles; in some of them pieces are still missing or assumptions have to be made, in others the connection between the Chinese factory and the household name is clear.

As explained above, identifying links between API manufacturers in China at the beginning of the supply chain, and known brands at the end of the supply chain is impeded by the fact that little information on supplier-customer relationships is available in the public domain. Suppliers often operate under strict non-disclosure agreements and most of the trade goes through India, which is slow to publish information on import licences. For example, information on import licences issued in 2014 were not yet publicly available at the time of writing. It is astonishing that an industry of such crucial importance for human and animal health is not subject to greater transparency requirements.

Proving the existence of links to specific sites is further complicated by the fact that manufacturers of final dosage drugs may hold import licenses for APIs from relevant sites



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in China, but also manufacture APIs themselves. In addition to this, the companies often operate within large groups with many subsidiaries and production sites.<sup>143</sup>

### Antibiotics manufacturing in China: exposing bad practices

While pharmaceutical manufacturing in many parts of the world is subject to strict national regulations, lax regulatory enforcement, corruption, and corporate negligence have enabled China's antibiotics manufacturers to pollute in impunity for decades.

The unmonitored dumping of pharmaceutical effluent has contaminated land and waterways surrounding the factories with toxic chemicals and active antibiotic substances, making local communities' lives a misery and fuelling the global AMR crisis. The problem is not restricted to the plants' immediate environment: recent studies and investigations have found antibiotics in almost all of China's major rivers, including the Zhu River, the Hai River, the Yellow River, the Yangtze River, the Huangpu River and the Liao River.<sup>144</sup>

#### I. NCPC

NCPC is a State-owned company and claims to be the largest manufacturer of antibiotics including penicillin, amoxicillin, streptomycin and cefradine in China.<sup>145</sup>

NCPC has repeatedly been in the firing line for discharging pharmaceutical effluent into the surrounding environment. In June 2012, Sina reported that it had dumped untreated antibiotic waste in the Hutuo river, which runs through Shijiazhuang<sup>146</sup> and in 2013, the company was reported to local authorities for causing air pollution.<sup>147</sup> Effluent from factories in Shijiazhuang is commonly processed by small 'workshops' surrounding the plants, with large quantities simply being dumped as a consequence of inadequate waste management.<sup>148</sup>

In 2010, the regional regulatory authorities ordered the local authorities to strengthen the supervision of NCPC's waste treatment centre. That same month, October 2010, an on-site inspection by the British Medicines and Healthcare products Regulatory Agency found that one of the company's factories<sup>149</sup> did not comply with Good Manufacturing Practice (GMP)<sup>150</sup>:

**"This inspection identified three critical deficiencies and five major deficiencies against the EU Good Manufacturing Practices Guide Part II: Critical: Buildings and facilities were**

**inadequate. The process solvent used at final API stage was contaminated. The site was being contaminated with biomass from the Phenoxymethyl penicillin Potassium (PenicillinV) fermentation. Major: The handling of drums, hoses and pipe work introduced contamination to the process. Process validation was inadequate. There was no system to control out of specification batches that had been merged. The maintenance and management of cell banks was inadequate. Commitments from the last EDQM [European Directorate for the Quality of Medicines and Healthcare] inspection had not been adequately completed."**

In an inspection at the same site in September 2013, the French Health Products Safety Agency (ANSM - Agence nationale de sécurité du médicament et des produits de santé) was of the same view that the factory was not in compliance with the EU's GMP standards, with many of the deficiencies noted by the British inspection in 2010 remaining unresolved.<sup>151</sup> The French authorities returned in November 2014 to inspect one of NCPC's other sites in Shijiazhuang, NCPC Semisyntec.<sup>152</sup> This time the company's handling of another antibiotic API (benzylpenicillin) was considered not in compliance with EU GMP standard and the criticism reserved for NCPC was even more severe, pointing to manipulation and falsification of documents and recommending a product recall<sup>153</sup>. ANSM subsequently issued an EU Statement of Non-Compliance (SoNC)<sup>154</sup> resulting in the withdrawal of two of the factory's benzylpenicillin products from the EU market.<sup>155</sup>

In January 2015, the WHO published a statement as a follow up to the EU Statement of Non-Compliance for NCPC Semisyntec, noting that "the North China Pharmaceutical Group is a very large group, with over 25 subsidiary and affiliated companies manufacturing a wide range of APIs and intermediates, mainly in the Shijiazhuang area of China. Therefore, when performing risk assessments relating to products manufactured by North China Pharmaceutical Group, care must be taken to avoid confusing companies and sites."<sup>156</sup>

While the picture is complex, our research has identified links between NCPC and some of the major Indian drug companies which supply the U.S. and European market, as well as direct links between NCPC and Western markets.

Pfizer is one company which has sourced antibiotics for human use from NCPC. In 2011, it was reported that NCPC's Semisyntec plant (formerly known as Hebei Huari Pharmaceutical) had become Pfizer's supplier of sterile APIs for human use in China after being awarded the contract for production of its sterile fortified procaine penicillin potassium products.<sup>157</sup>

### French National Agency for Medicines and Health Products Safety

Report No: 14MPP092

## STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer<sup>1</sup>

### Part 1

Issued following an inspection in accordance with :

Several EU inspections have shown NCPC's failure to comply with GMP rules

Conversations with NCPC in early 2015 appeared to confirm that the company has supply agreements with a variety of big names in the pharmaceutical industry, with an NCPC representative stating that it remains the "first and sole

supplier" of Pfizer's sterile API for humans in China and is also a supply partner on Augmentin for GSK, and Claforan for Sanofi Aventis. In addition to this, various Indian drug manufacturers have held import licenses for antibiotic raw materials produced



### CASE STUDY: MCKESSON

## MCKESSON

Empowering Healthcare

*NorthStar Rx is a U.S.-based generic drug producer which operates as a subsidiary of McKesson. McKesson in turn is the largest player active in pharmaceutical sourcing and supply chain management in the U.S., with NorthStar and Sunmark as key brands.<sup>169</sup>*

*After acquiring a majority stake in Celesio (Germany) in 2014, McKesson also became one of the leading players in healthcare systems in Europe. In the UK, it is the second largest healthcare chain after Boots. Celesio's pharmacies operate under various names in different European markets, including Lloyds Pharmacy in Ireland and the UK, Lloyds Apotek in Sweden, Lloyds Pharma in Belgium, Lloyds Farmacia in Italy, and NMD and Vitus Apotek in Norway. On the French and Portuguese market it operates under the name OCP. It has significant market shares in wholesale operations in various European markets and leading retail market positions in several of them.<sup>170</sup>*

*In addition to the takeover of Celesio, McKesson took over Rite Aid's generic distribution business in 2014. Rite Aid is one of the leading retail pharmacy chains in the U.S. NorthStarRx, McKesson's private-label generic manufacturing business, was expected to [play a role for] both Rite Aid and Celesio. Once the changes have been implemented, McKesson-Celesio-Rite Aid will be the largest generics buyer in the world.<sup>171,172</sup>*

*NorthStar markets NorthStar Rx Amoxicillin Capsules, Amoxicillin and Clavulanate Potassium tablets and NorthStar Rx Amoxicillin and Clavulanate Potassium powder for suspension in the U.S., produced by Indian generics manufacturer Aurobindo Pharma.<sup>173</sup>*

*According to information from the Indian Central Drugs Standards Authority<sup>174</sup>, Aurobindo Pharma held import licenses for the following Chinese API manufacturers:*

- Sinopharm Weiqida<sup>175</sup>
- Harbin Pharmaceutical Group<sup>176</sup>
- NCPC<sup>177</sup>
- CSPC<sup>178</sup>



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by NCPC, among them generics producers Aurobindo Pharma and Lupin.<sup>160</sup>

In 2013, the Bulgarian pharmaceutical company Balkanpharma Razgrad A.D.<sup>161</sup>, which has since been acquired by Actavis, filed an API registration in the EU for the API Lincomycin,<sup>162</sup> naming a subsidiary of NCPC<sup>163</sup> as the manufacturer.<sup>164</sup> In addition to this, a veterinary product marketed in the United States by Pfizer Animal Health<sup>165</sup>, LINCOMIX 50- lincomycin hydrochloride granule, contains API manufactured by North China Pharmaceutical Group Hualuan Co.<sup>166</sup>

There is clear proof that other NCPC APIs are entering the U.S. market: in April 2015, NCPC sent chemical supplier Flavine North America a shipment of Penicillin G Potassium<sup>167</sup> and there is a possibility that they are being used in other products for sale on the U.S. market.<sup>168</sup>

## II. CSPC/INNER MONGOLIA CHANGSHENG PHARMACEUTICALS

CSPC Pharmaceutical is one of China's largest pharmaceutical companies. Until June 2013, it operated one of the largest antibiotic production plants in the world, Shiyao Zhongrun at a huge industrial park in Inner Mongolia. It also operates a major plant in Shijiazhuang, Hebei Province in the same city as many of NCPC's subsidiaries.<sup>179</sup>

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 and waterways surrounding the factory, as well as the nearby Yellow River.

By 2014, the Shiyao Zhongrun<sup>180</sup> plant had already been in trouble with the provincial authorities for years. A report by the international NGO IPEN and China's Green Beagle Institute<sup>181</sup> 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.<sup>182</sup>

In June 2013, CSPC Pharmaceutical Group signed an agreement to sell CSPC Zhongrun Pharmaceutical (Inner Mongolia)<sup>183</sup>.

The buyer was Inner Mongolia Changsheng Pharmaceuticals.<sup>184</sup>

Shiyao Zhongrun's successor, Inner Mongolia Changsheng Pharmaceuticals exports antibiotic APIs to various parts of the world, including the Pakistani pharmaceutical company Pharmagen.<sup>185</sup> According to its company website, Pharmagen delivers antibiotic APIs to a wide range of multinational companies including GlaxoSmithKline, Bristol-Myers Squibb, Wyeth and Novartis.<sup>186</sup>

Inner Mongolia Changsheng Pharmaceuticals also ships antibiotic APIs to a U.S.-subsidiary of generics giant Teva Pharmaceuticals<sup>187, 188</sup>, which appears to have a long-standing commercial relationship with the site, dating back to when it was owned by CSPC.<sup>189</sup>



Waste water from the Tuoketuo Pharmaceutical Industrial Park in Inner Mongolia has polluted local waterways and groundwater © Shao Wenjie



CSPC formerly operated a major antibiotics production plant at the Tuoketuo Pharmaceutical Industrial Park. The factory, which has been in trouble with the authorities for years, is now run by Inner Mongolia Changsheng Pharmaceuticals. © Shao Wenjie

04

The investigation



## CASE STUDY: TEVA PHARMACEUTICAL INDUSTRIES (ISRAEL)



Teva is the leading global generics manufacturer and ranks among the top ten pharmaceutical companies in the world and operates in 60 countries.<sup>190</sup> According to company literature, 1.5 million prescriptions for Teva pharmaceuticals are written each day in the United States and 2.7 million in the European Union. Teva Active Pharmaceutical Ingredients is the leading manufacturer of APIs in the world, manufacturing more than 300 of them.<sup>191</sup>

U.S. Customs data reveals that Teva Pharmaceuticals USA Inc recently has received shipments of Aminopenicillanic acid from:

### Sinopharm WeiQiDa Pharmaceutical (Datong site)

Nine shipments, each containing 12 tons of aminopenicillanic acid from the site directly to Teva during 2014. This could mean both Ampicillin and Amoxicillin, of which TEVA sells both under a generic name<sup>192</sup>

### CSPC/Changsheng Pharmaceutical (Inner Mongolia site)

In February and April 2015, Teva Pharmaceuticals USA received three shipments of 6-Aminopenicillanic Acid from Inner Mongolia Changsheng Pharmaceuticals<sup>193</sup>. Teva previously imported the same API from the factory when it was owned by CSPC under the name CSPC Zhongrun Inner Mongolia.<sup>194</sup>

### United Laboratories TUL (Inner Mongolia site)

In January 2014 Teva Pharmaceuticals received a shipment of 6-Amino Penicillanic Acid from The United Laboratories Inner Mongolia Co., Ltd<sup>195</sup>.

6-aminopenicillanic acid is used for making the amoxicillin in Teva's generic Amoxicillin and Clavulanate Potassium<sup>196</sup>.

## III. Sinopharm

Sinopharm (China National Pharmaceutical Group Corporation) is under the direct leadership of the Government's State-owned Assets Supervision and Administration Commission.<sup>197</sup> Its stock exchange listed subsidiary Sinopharm WeiQiDa<sup>198</sup> operates two factories in Datong, Shanxi Province: Sinopharm Group WeiQiDa Pharmaceutical Company Limited and Sinopharm Group Datong WeiQiDa Zhongkang Pharmaceutical Company Limited<sup>199</sup>. Sinopharm is the largest pharmaceutical distributor in China, holding approximately 13% of the market as of May 2013.<sup>200</sup>

Datong sits in the heart of Shanxi Province, China's coal belt, and was in the past labelled the most polluted city in China. An ancient city boasting plenty of historical attractions, it has spent the past few years on a major drive to increase tourism to the area.<sup>201</sup> Sinopharm has certainly not helped to improve the city's tarnished image.

Since 2009, Sinopharm WeiQiDa in Datong has received repeated criticism from the local environmental pollution board (EPB). In 2013, it came under fire for discharging 30,000 tonnes of black sludge, the majority of which was pharmaceutical wastewater, into the Sanggan River to the south of Datong.<sup>202</sup>

In May 2014 a CCTV report investigated the 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 the factories belonging to Sinopharm WeiQiDa.

The investigations showed that the treatment plant was discharging clean water in daytime and sewage during the night into the Yuhe River, a major river in Shanxi Province. In another crass cover-up attempt, the company was sending trucks filled with sludge from the plant to a nearby village, where it was tipped into a big hole next to agricultural land.<sup>203</sup>



# Bad Factories

The factories investigated for this report are operated by subsidiaries of some of China's largest pharmaceutical companies. They have all flouted provincial and local laws to dump tonnes of pharmaceutical waste into their surrounding environment, polluting groundwater and waterways, and impacting local communities.

## 01 North China Pharmaceutical Company - NCP (Shijiazhuang, Hebei Province)

NCP is located in Shijiazhuang, Hebei Province, a city of 10 million inhabitants. It has repeatedly been in the firing line for discharging pharmaceutical effluent into the surrounding environment. The company is reported to be dumping tonnes of antibiotic effluent in its surrounding environment.

## 02 CSPC Pharmaceutical Group (Shijiazhuang, Hebei Province)

CSPC operates a major antibiotics manufacturing plant in Shijiazhuang, Hebei Province. Local residents have complained about bad smells from the factory, and the plant is said to be exceeding waste water discharge limits. CSPC has committed to relocate this factory by 2016.

## 03 Inner Mongolia Changsheng Pharmaceutical Co. Ltd - formerly CSPC Pharmaceutical Group's Shiyao Zhongrun site (Hohhot, Inner Mongolia)

Until recently, CSPC operated one of the largest antibiotic production plants in the world, Shiyao Zhongrun, at a huge industrial park in Inner Mongolia. In 2013, the plant was sold to Inner Mongolia Changsheng Pharmaceuticals Ltd. In 2014, it was reported that factories at the Inner Mongolia industrial park, including the Changsheng facility, had pumped toxic and antibiotic-laden effluent into surrounding fields and waterways and the nearby Yellow River.

## 04 Sinopharm WeiQiDa (Datong, Shanxi Province)

Sinopharm WeiQiDa operates two factories in Datong, Shanxi Province, a city of 3 million inhabitants. In 2013, one of its plants discharged 30,000 tonnes of black sludge, most of which was pharmaceutical wastewater, into the Sanggan River to the south of Datong. A waste treatment plant used by several Sinopharm subsidiaries was also found to be discharging effluent into the Yuhe River.

## 05 Shandong Lukang (Jining, Shandong Province)

In 2014, it was revealed that waste water discharged by Shandong Lukang Pharmaceutical in Jining, a city of 8 million inhabitants, contained over 50,000 nanograms of antibiotics per litre, about 10,000 times higher than the concentrations present in clean water.

## 06 Harbin Pharmaceutical Group (Harbin, Heilongjiang Province)

Harbin Pharmaceutical Group's manufacturing facility is located in the centre of Harbin, Heilongjiang, a city of 10 million inhabitants. It has been accused of dumping polluted waste water and releasing noxious gases to the local environment on repeated occasions.

## 07 Tonglian Group (Hulun Buir, Inner Mongolia)

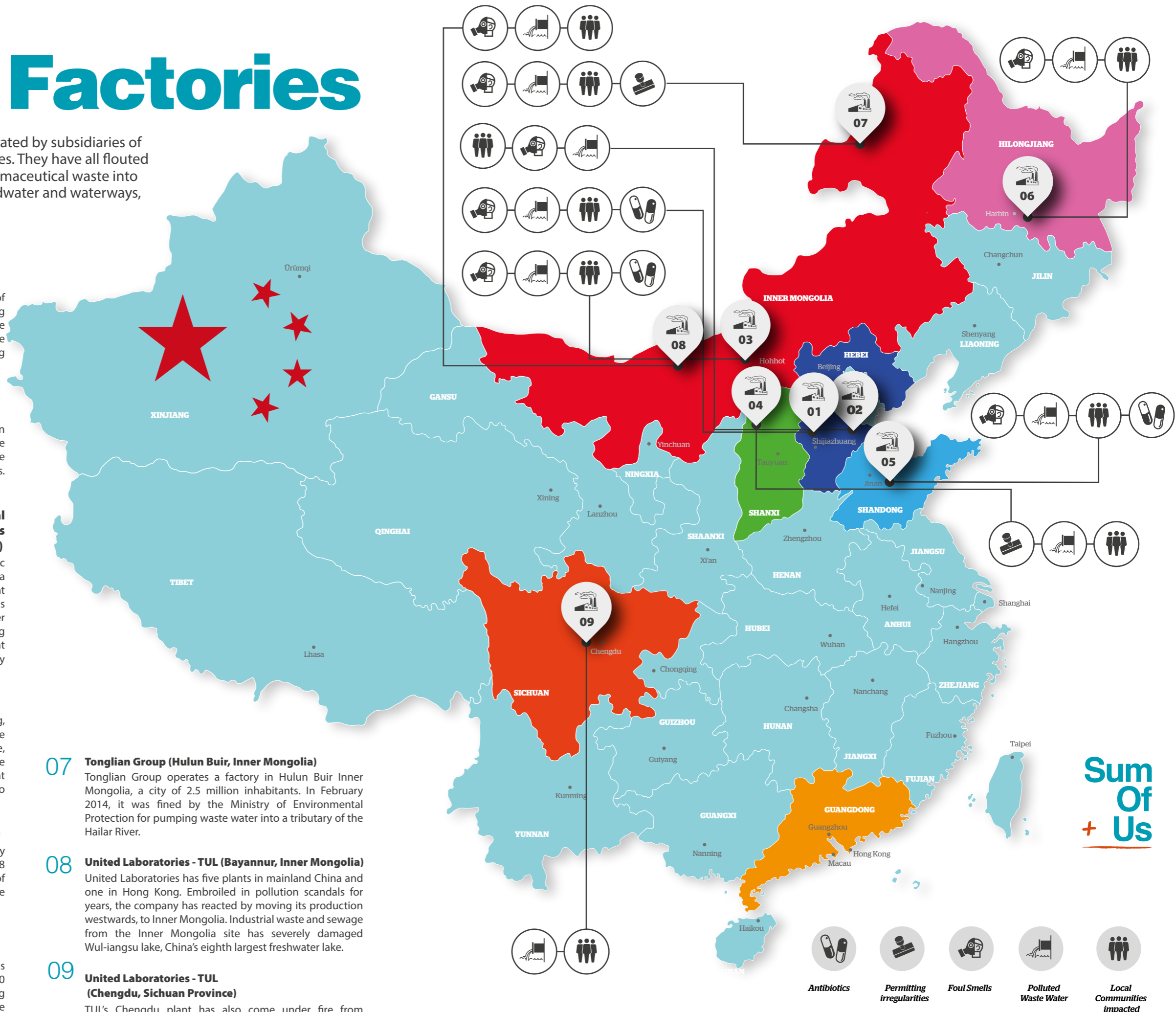
Tonglian Group operates a factory in Hulun Buir Inner Mongolia, a city of 2.5 million inhabitants. In February 2014, it was fined by the Ministry of Environmental Protection for pumping waste water into a tributary of the Hailar River.

## 08 United Laboratories - TUL (Bayannur, Inner Mongolia)

United Laboratories has five plants in mainland China and one in Hong Kong. Embroiled in pollution scandals for years, the company has reacted by moving its production westwards, to Inner Mongolia. Industrial waste and sewage from the Inner Mongolia site has severely damaged Wul-iangsu lake, China's eighth largest freshwater lake.

## 09 United Laboratories - TUL (Chengdu, Sichuan Province)

TUL's Chengdu plant has also come under fire from environmental authorities for serial pollution offences.



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Us

Antibiotics  
Permitting irregularities  
Foul Smells  
Polluted Waste Water  
Local Communities impacted



In 2010, Sinopharm was ordered by the local government to relocate its plant<sup>204</sup>, a short-term solution to a huge problem which will endure for as long as the company fails to clean up its act. To date, there is no evidence to suggest that Sinopharm has complied with the local government order.

According to its website, Sinopharm has 'strategic partnerships' with some of the world's leading pharmaceutical companies including Pfizer (United States), GlaxoSmithKline (UK), Johnson & Johnson (US), Sanofi (France), Bayer (Germany), and Roche (France).<sup>205</sup>

It has limited presence on foreign markets but intends to add to its existing business in pharmaceutical manufacturing, distribution and retail through the acquisition of firms in Europe.<sup>206</sup>

There is a direct connection between Indian generic drug manufacturer Aurobindo Pharma and Sinopharm Weiqida through Aurobindo's retention of a stake in its former

CASE STUDY:  
**AUROBINDO PHARMACEUTICAL**



Aurobindo Pharma Limited is a pharmaceutical manufacturer specialising in anti-infectives. The company is headquartered in Hitec City, Hyderabad, India. Aurobindo manufactures generic pharmaceuticals and active pharmaceutical ingredients. The company has a globally network of subsidiaries, and exports products.

In 2011 Aurobindo divested most of its ownership of its Chinese subsidiary Aurobindo (Datong) Bio Pharma (ADBPL) to Sinopharm, keeping a 19.5 percent stake in order to ensure the supply of raw materials at a competitive price.<sup>213</sup> It still holds a 10 percent share in the factory in Datong.<sup>214</sup>

In April 2014, Aurobindo acquired the commercial operations of Actavis in seven EU Member States: France, Italy, Spain, Portugal, Belgium, Germany and the Netherlands. This includes products, marketing authorisations and dossier license rights. The two companies also entered into a long-term strategic supply arrangement. Aurobindo Pharma thus acquired considerable market share in several European countries. Over the 24 months following the deal, it will replace half of Actavis products with Aurobindo's own low-cost high-margin products to bring down its overall costs. The company is likely to move the supply of some of the products from the Actavis facility to its own facility.<sup>215</sup>

**IV. Shandong Lukang**

In December 2014, Chinese antibiotics manufacturers were in the headlines once again, caught up in yet another pollution scandal. An in-depth investigation by State broadcaster CCTV had 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.<sup>216</sup>

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.<sup>217</sup> The report also alleged that Shandong Lukang, one of the largest antibiotics producers in China, usually received secret tip-offs from local environmental authorities ahead of inspections.

Shandong Lukang exports its products to approximately 40 countries around the world.<sup>218</sup>

of gonorrhoea. Rochem, which describes itself as a "bridge between China and the changing pharmaceutical market"<sup>219</sup>, represents Shandong Lukang and helped them pass a U.S. FDA inspection in April.<sup>220</sup>

Rochem is also Shandong Lukang Pharmaceutical Co. Ltd's Distributor and Regulatory Agent for Spectinomycin HCl and Spectinomycin Sulfate to the global markets.<sup>221</sup> In the U.S. spectinomycin is solely intended for veterinary use (its use for humans has been discontinued in the U.S. years ago<sup>222</sup>).

Veterinary products linked to Shandong Lukang on the U.S. market include:

- Speclinx 50- spectinomycin hydrochloride and lincomycin hydrochloride powder by Bimeda, Inc. Division of Cross Vetpharm Group Ltd. with API produced by Shandong Lukang Pharmaceutical Co.;<sup>223</sup>
- Lincomycin S 50- lincomycin hydrochloride and spectinomycin hydrochloride powder by Aspen Veterinary



A report broadcast on Chinese television in December 2014, revealed that Shandong Province-based manufacturer Lukang Pharmaceutical 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. Local residents complained of a strong smell from the nearby Beijing-Hangzhou Canal and 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 Canal. The report also alleged that Lukang, one of the largest antibiotics producers in China, usually received secret tip-offs from local environmental authorities ahead of inspections.

U.S. company Rochem International, an importer of Chinese pharmaceuticals to the U.S. market, has a cooperation agreement with Shandong Lukang, distributing "to the global markets" the precursor to an antibiotic used in the treatment

Resources with API manufactured by Shandong Lukang Pharmaceutical Co.<sup>224</sup>

Our research shows that Shandong Lukang also exports

antibiotic APIs to a variety of Indian companies, which in turn have clients in the U.S. and Europe.<sup>225</sup>

### V. Harbin Pharmaceutical Group

Harbin Pharmaceutical Group's manufacturing facility is located in the centre of Harbin, Heilongjiang, a heavily populated city of 10 million inhabitants. In June 2011, the manufacturer was involved in a pollution scandal after it released polluted wastewater and noxious gases to the surrounding area. The company had also dumped a large amount of residue in the Songhua river. By the time the scandal hit the headlines, the factory had been emitting foul wastes for years. Wu Zhijun, one of the company's top officials, apologised to his fellow citizens on national television. Following the scandal the company was ordered to move the factory to the city's outskirts.<sup>226</sup>

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<sup>227</sup>.

The Greek company Demo Pharmaceutical<sup>228</sup> has filed an API registration with the European Medicines Agency (EMA) for cefapime, listing Harbin Pharmaceutical Group as a manufacturer<sup>229</sup>. Demo Pharmaceutical's branded product Verapime contains the active ingredient cefapime<sup>230</sup>.

Aurobindo Pharma had an Indian import license for Penicillin G Potassium from Harbin, valid September 2011 to February 2013, a connection which implies a possible link to McKesson (see case study). Import licenses linked to Harbin and valid from 2013 until early 2016 have been issued for various other Indian pharmaceutical companies in recent years, including, for example, Abbott Healthcare, DSM Sinochem Pharmaceuticals India or Ranbaxy Laboratories.<sup>231</sup>

### VI. Tonglian Group

Tonglian Group operates a factory in Hulun Buir Inner Mongolia<sup>232</sup> 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.<sup>233</sup> The company, which had also expanded production without obtaining a permit, came in for heavy criticism from the authorities and was fined.<sup>234</sup> Our investigation could not ascertain the destination of APIs produced by Tonglian group.

### VII. United Laboratories - TUL

TUL is one of the biggest antibiotics producers in China. It is a Hong Kong-based company with at least six production bases, including United Laboratories in Inner Mongolia and a plant in Chengdu, Sichuan Province.<sup>235</sup> The company's main products are antibiotic APIs.<sup>236</sup>

United Laboratories have been criticised for a lack of environmental protection for the past 10 years. Over the years the company has moved its production westwards, towards Inner Mongolia, where the factory has repeatedly been criticised in the media and by the authorities for improper waste management, including odour pollution and waste water discharged into the lake Wuliangshuai. The authorities had asked the company to clean up the mess years earlier, but the pollution continued. In 2008, the Inner Mongolian 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. Wastewater was also discharged through irrigation ditches linking to the Yellow River<sup>237</sup>.

According to media reports in May 2014, United Lab's production line was shut down and others suspended operations for several months<sup>238</sup>.

Our research reveals a 2014 shipment of antibiotic APIs (aminopenicillin acid) from TUL to a U.S.-subsidiary of Israeli generics giant Teva Pharmaceuticals.<sup>239</sup>

Almost sixty Indian companies are in possession of an import license for TUL's antibiotic APIs.<sup>240</sup>

## Conclusions and recommendations for action

Our research has revealed that the pharmaceutical industry, with its complex web of interconnections and opaque supply chains is also playing a role in fuelling the international AMR crisis. China supplies the vast majority of antibiotic raw materials to the global market; it seems from extensive research that several multinational drug companies are sourcing antibiotics from Chinese factories which have been exposed in the media as dumping waste water and antibiotic APIs in the environment. Some of these factories have been fined or have promised to relocate, but there is little evidence that more serious measures are being taken to effectively address the problem.

**AMR is a global emergency which requires a comprehensive approach, obliging companies to take responsibility for their supply chains. The unmonitored dumping of API-rich effluent into rivers and waterways in China and India is demonstrably leading to the proliferation of resistant bacteria, which is not only damaging for local populations, but can also lead to the spread of these bacteria around the world through travel and trade. The message is clear: bad production practices in one location impact public health all over the world and therefore need to be addressed globally.**

#### For pharmaceutical companies:

1. Stop buying APIs from factories which manufacture in an environmentally irresponsible way until effective measures to clean up production processes are implemented and enforced. This should include measures to address any environmental damage and any compensation for the affected communities.
2. Embrace full transparency and promote the transfer and adoption of cleaner production technologies and pollution prevention policies across their supply chains. The pharmaceutical industry already has a set of voluntary principles on supply chain management, which include guidelines on environmental protection. Among other things, these guidelines say that "[s]uppliers shall have systems in place to ensure the safe handling, movement, storage, recycling, reuse, or management of waste, air emissions and wastewater discharges." These principles should become an industry standard and be duly enforced for all actors in the supply chain.

#### For EU legislators and governments:

1. The EU and U.S. should amend the rules under the GMP (Good Manufacturing Practice) framework for the production of pharmaceutical products by including environmental criteria. GMP rules are largely harmonised and cover all companies importing APIs and/or products into the EU or U.S. Amending these principles would therefore have a tangible impact on production. This process should define pollution prevention policies, in particular best available techniques and best environmental practices (BAT/BEP), and ensure the enforcement of good waste management.
2. The EU and U.S. should enforce greater transparency across the supply chain by asking pharmaceutical companies to disclose the origin of their drugs right back to the factory that produced the ingredients. This would not only be useful for encouraging good production practic-

es, but would also contribute to greater patient safety.

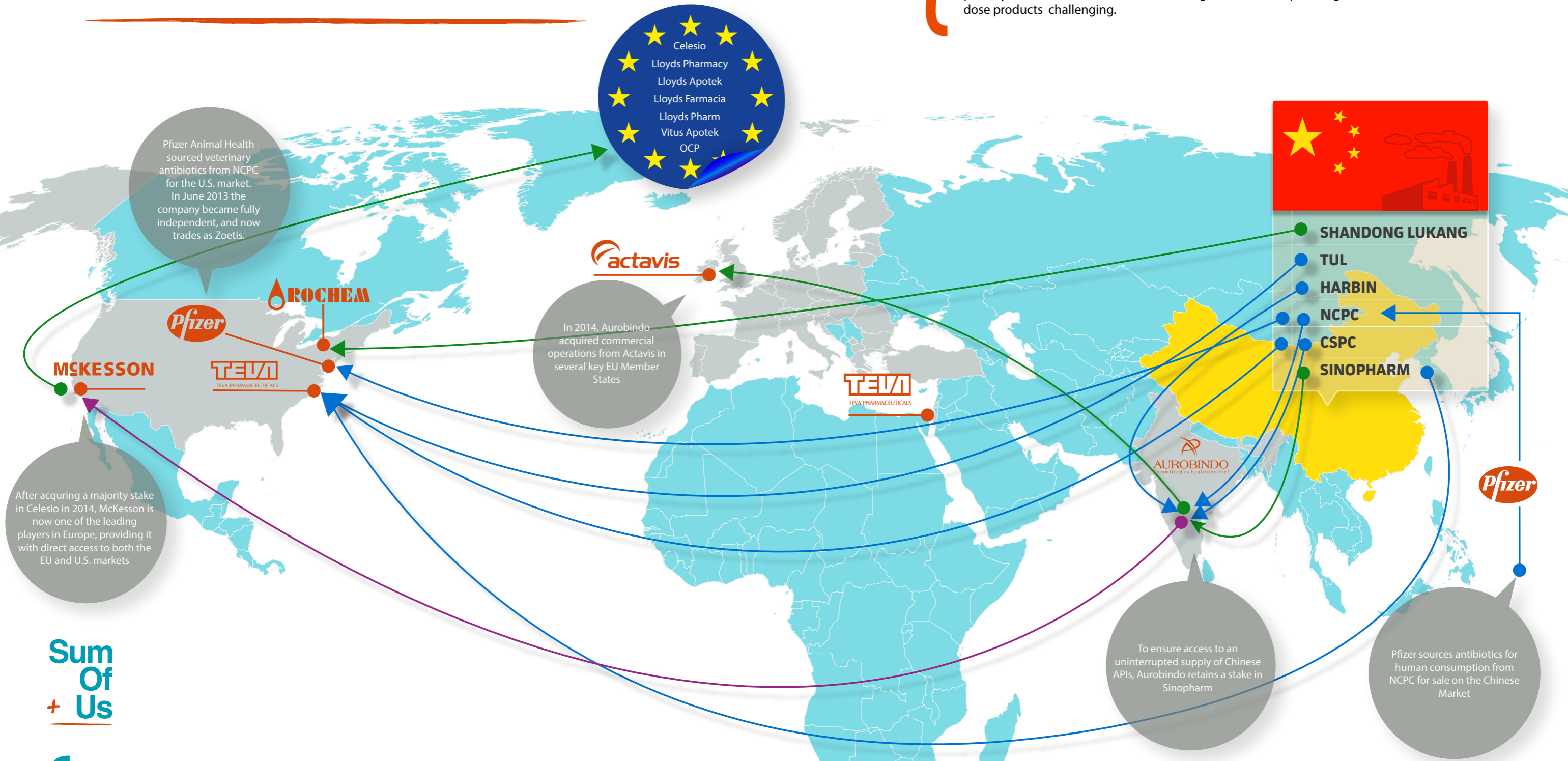
#### For international stakeholders:

1. Include pharmaceutical pollution, in particular antibiotic pollution and its contribution to AMR, as a global emerging issue under Strategic Approach to International Chemicals Management (SAICM), so as to foster international exchange on the best ways to tackle this growing problem. SAICM has as its overall objective the achievement of the sound management of chemicals throughout their life cycle so that, by 2020, chemicals are produced and used in ways that minimise significant adverse impacts on human health and the environment.
2. Include environmental criteria in the implementation of good manufacturing practices and make this part of the WHO global policy package to combat antimicrobial resistance. WHO has developed a draft global action plan for combatting AMR which was discussed by world governments in May. The WHO should include the impacts of pharmaceutical production on the development of resistant bacteria in its plan. In addition to this, WHO GMP guidelines should also be updated to include principles on environmental protection.

It is only by adopting a global and truly comprehensive approach to antibiotics manufacturing, with companies at every step of the way accepting responsibility for their actions, that the world will be able to prevent the dawning of a post-antibiotic era, where the contraction of a currently harmless infection once again becomes a potential death sentence. At present, this is neither part of the WHO's international strategy nor of action plans being developed at national level. It is time for the pharmaceutical industry to embrace transparency from the very beginning to the very end of the supply chain, and take on an active role in heading off a public health disaster of global proportions, a move that would once more make it part of the solution, rather than the problem.

# + Bad Factories & their Customers

**The lack of transparency**  
 Pharmaceutical supply chains lack transparency. In the EU, for example, importers must report the origin of APIs at their point of entry into the EU and prove that they have been manufactured in compliance with GMP. When importing finished dose products, they must also inform the authorities about where the product was manufactured when applying for its authorisation. However, none of this information is publicly available, which makes establishing links between polluting factories in China and the finished dose products challenging.



Sum Of Us +

## Good manufacturing practices ?

To be able to import to the EU or to the U.S. market, companies need to prove that the products they are importing were produced in line with Good Manufacturing Practices (GMP). GMP criteria are not prescriptive and provide pharmaceutical manufacturers with flexibility on how to meet the minimum requirements to ensure that their product does not pose a risk to consumers. National authorities also have a right to inspect factories to verify whether GMP are being properly implemented. There are currently no GMP criteria on safety in the workplace or environmental protection - these depend exclusively on national legislation and enforcement.



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