

February 10, 2017

To the Judges:

On a muggy day in June, a farmhand in China's Pearl River Delta hosed down the cement floor of a piggery where hogs sniffed and snorted. The dirty water from the pens flowed into a metal pipe, which emptied directly into a pond. As the yellowish-brown water splashed from the pipe, tilapia flapped and jumped, hungry for an afternoon feeding.

Chinese agriculture for thousands of years has thrived on this kind of recycling—the same nutrients that fattened the pigs also fed the fish. But the introduction of antibiotics into animal feed in recent years has transformed thousands of farms across Asia into training grounds for bacteria. They prime microbes to overcome some of the planet's most important medicines, converting simple infections into killers.

While the public health threat of dosing cattle and pigs with antibiotics is well known, Bloomberg reporters across the globe documented how that risk has spread to entirely new segments of agriculture. Reporters in Asia and the U.S. spent months uncovering the lack of transparency, accountability and integrity that are undermining food safety and allowing the spread of drug-resistant microbes across international borders. Their stories lifted the lid on the unexplored, sometimes fraudulent, and increasingly important methods food suppliers employ that expose unwitting consumers to the planet's most dangerous superbugs.

A Bloomberg team in India went where no reporters had ventured: inside the coops of the country's main commercial chicken-raising district. They showed how antibiotics vital to human health are routinely given to chickens in the world's fastest-growing poultry market. They were the first journalists to step onto farms contracted to India's biggest chicken companies and document the rampant, unregulated use of antibiotics, with drugs banned for animal use in other countries bought freely at rural veterinary shops.

A second team of reporters divulged how the abuse of antibiotics has reached into aquaculture, the fastest-growing segment of the world food economy. Using thousands of pages of government records and reporting from China, Malaysia and the U.S., they revealed how illegal transshipping, lax regulations and a lack of accountability have enabled antibiotic-laden shrimp from China to be laundered through Malaysia and then sent to thousands of restaurants and grocery stores in the U.S.

In China—the world's biggest user of antibiotics—consumers, scientists and the government are pushing for measures to curb dependence on bacteria-fighting drugs, especially in food production. Bloomberg reported how one piggery there is relying on impeccable hygiene and disease control to raise antibiotic-free hogs. Tackling antimicrobial resistance from the demand side isn't enough, though. The world needs new, effective treatments to replace the ones that no longer work. Bloomberg also took readers inside the labs trying to come up with novel ways to kill bacteria. It's a risky, \$1 billion endeavor, fraught with scientific, economic and regulatory hurdles that have meant that no new class of antibiotic has been discovered in 30 years.

Publication of the series prompted Suguna Foods Pvt., India's largest broiler company and KFC's local operator, to amend a public stance it had maintained for at least five years that it doesn't use antibiotics to produce its meat. Several of the stories were circulated by the Food and Agricultural Organization's chief veterinarian and flagged by the chairman of Public Health England to the U.K.'s top medical officer. "If this doesn't convince people to get serious about the agricultural side of the problem, I don't know what will," one researcher said.

For their bracing look at the rapid growth in the agricultural use of antibiotics and the innovative ways companies are attempting to profit from—or thwart—its spread, I'm proud to nominate it for the Gerald Loeb Award for explanatory reporting.

Sincerely,



John Micklethwait
Editor-in-Chief

Gerald Loeb Award
For Explanatory Reporting
Bloomberg News

“Superbug Spreaders”

Natalie Obiko Pearson, Sharang Limaye, Jason Gale, Lydia Mulvany,
Monte Reel and Stephanie Baker

1. “Antibiotic Apocalypse Fear Stoked by India’s Drugged Chickens,” by Natalie Obiko Pearson and Sharang Limaye, March 29, 2016
<https://www.bloomberg.com/news/features/2016-03-29/antibiotic-apocalypse-fear-stoked-by-india-s-drugged-chickens>
2. “Baby’s Death Shows Global Threat From Wonder Drugs Demise,” by Natalie Obiko Pearson and Adi Narayan, March 29, 2016
<https://www.bloomberg.com/news/articles/2016-03-29/baby-s-death-shows-global-threat-from-wonder-drug-s-demise>
3. “How Antibiotic-Tainted Seafood From China Ends Up on Your Table,” by Jason Gale, Lydia Mulvany and Monte Reel, December 15, 2016
<https://www.bloomberg.com/news/features/2016-12-15/how-antibiotic-tainted-seafood-from-china-ends-up-on-your-table>
4. “China’s Five-Star Pig Pens Are Latest Weapons in the Superbug War,” September 19, 2016 <https://www.bloomberg.com/news/features/2016-09-19/china-s-five-star-pig-pens-are-latest-weapon-in-the-superbug-war>
5. “Why Superbugs Are Beating Big Pharma,” by Stephanie Baker, September 21, 2016
<https://www.bloomberg.com/news/articles/2016-09-21/inside-the-10-year-1-billion-battle-for-the-next-critical-antibiotic>

Antibiotic Apocalypse Fear Stoked by India's Drugged Chickens

Feeding chickens antibiotics may speed diseases costing \$100 trillion

By Natalie Obiko Pearson and Sharang Limaye

Wearing only silver toe rings on her bare feet, Manisha Bal Reddy pads through her flock of 4,800 cackling chickens in a coop in south India to retrieve a blue and white bottle on the husk-covered floor. It contains a mix of three antibiotics, including the last one currently available to treat the most perilous bloodstream infections in people.

The drug cocktail is to be added to the birds' drinking water, according to notes scrawled in a candy-pink logbook. Daily entries direct Manisha and her husband, G. Bal Reddy, to use five antibiotics over six weeks. The instructions are written and signed by a supervisor from SR Group, the broiler company that supplied the couple with chicks, feed and medicines, and bought the birds back when they were ready for slaughter.



Photograph by Dhiraj Singh

All of the antibiotics listed in the logbook are legal for veterinary use in India, but two are banned or not approved for use in poultry in the U.S., Canada, the European Union and Australia, where authorities have sought to prolong their efficacy in people. Worldwide, animals consume more antibiotics than humans, an amount researchers estimate will jump 67 percent in the 20 years through 2030 as India, China, Brazil and other developing countries expand livestock production to meet unprecedented demand for animal protein.

While antibiotics are helping to sustain intensive food production, doctors worry their uncontrolled use on farms is turning animals into reservoirs of hard-to-kill bacteria that can spread rapidly and globally. G. Bal Reddy said it seems he's fighting a losing battle. "We have to use more medicines these days," he said. "Diseases have become harder to beat in the last two to three years."

About 100 miles from the poultry farm in Telangana state, medical college microbiologists studying a bacterium spreading mostly in hospitals reported in June that 6.7 percent of specimens were resistant to all antibiotics. While the Indian government doesn't keep data on deaths due to antibiotic-resistant infections, one study by researcher Ramanan Laxminarayan and colleagues estimated that more than 58,000 newborns died nationwide in 2013 from bacterial infections capable of evading most antibiotics.

"The world is on the brink of losing its miracle cures," World Health Organization Director-General Margaret Chan said in an email. Once antibiotics stop working, hip replacements, organ transplants, cancer chemotherapy and care of preterm infants will be far more difficult or even too dangerous to undertake.

Failure to act on drug-resistant infections will lead to 10 million extra deaths a year and cost the global economy \$100 trillion by 2050, according to a February 2016 report on antimicrobial resistance commissioned by U.K. Prime Minister David Cameron. Jim O'Neill, the British economist who coined the acronym BRIC for Brazil, Russia, India and China, is chair of the independent review.

"We need to act now—governments, industry and all 7 billion individuals—to eliminate this otherwise inevitability," said O'Neill, a former chairman of Goldman Sachs Asset Management, who is now Commercial Secretary to the Treasury, in an e-mail.

Drug-defying germs, which can spread internationally in infected travelers in hours, threaten to reverse a century of progress in human and animal health, and are a risk to global food security, the Food and Agriculture Organization said on Feb. 10.

"How can we reduce rural poverty when the drugs given to ill farm workers and their



Farmers in Ranga Reddy say they are advised to feed antibiotics to day-old chicks.

families no longer have effect?” FAO Deputy Director-General Maria Helena Semedo told European ministers of health and agriculture at a conference on antimicrobial resistance in Amsterdam. “How can we eliminate hunger or improve sustainability when we cannot cure sick animals?”

Rich countries began using antibiotics once the incidence of infectious diseases had plummeted following public-health improvements. In India, antibiotics are often used as a substitute for sanitation and hygiene, said researcher Laxminarayan, who is director of the Center for Disease Dynamics, Economics & Policy. Consequently, the nation shoulders among the highest rates of antibiotic resistance in the world.

A panel advising the Indian government in 2011 called for restrictions on antibiotic use in both people and animals following the discovery of a superbug-spawning gene in a patient from New Delhi that spread to dozens of countries within a few years. Five years later, there still are no regulations governing the use of antibiotics in livestock and a lack of enforcement of existing rules means medicines are often bought without a prescription.

“India does not have significant regulatory control over either the manufacture or

sale of antibiotic agents,” said Brian Evans, a deputy director general of the World Organisation for Animal Health, the Paris-based policy-setting group representing 180 countries. “Potentially, up to 50 percent of our member-countries do not have appropriate legislation at this time.”

The Bal Reddys’ farm is an example of what that laxity allows. The logbook, labeled “farmer’s flock record,” shows they were instructed to begin a series of antibiotic regimens on Oct. 25, the day after the couple took delivery of the newly hatched chicks. A solution combining enrofloxacin, ciprofloxacin and colistin was started on Nov. 19 and continued for six days. The bottle’s label says it’s an “animal feed supplement” that should be mixed in drinking water for the “prevention of respiratory infections.”

On Dec. 1, the Bal Reddys were instructed to use two more antibiotics to help sanitize their shed after the chickens were collected for slaughter. An additional antibiotic, gentamicin, was delivered on Nov. 16, though there is no record of it being used.

SR Group, the broiler company that supplied the drugs, only uses antibiotics when it’s “imperative” and employs as many as 20 veterinarians, said S. Ravinder Reddy, the company’s technical director. “Nobody uses antibiotics unnecessarily because we are professionals,” he said in a March 4 telephone interview. “We are not illiterate farmers. We know what we are doing.”

SR Group doesn’t allow the use of medicines that are also used in people on its flocks because of the threat to human health, Reddy said. “Whatever medicines that are used in chicken are not used in humans,” he said. Reddy didn’t respond to questions about observations that some farmers were instructed to use colistin and ciprofloxacin—antibiotics deemed “critically important” by the WHO.

Visits to 13 other farms in the Ranga Reddy district—some of which supply to, and are supervised by other broiler companies—revealed widespread use of antibiotics in feed and water, and by injection to thwart current and potential disease outbreaks.

The use of antibiotics at low or sub-therapeutic strengths is known to speed growth in food-animals—an outcome acknowledged by organizations including the American Veterinary Medical Association and the Animal Health Institute, which say the drugs help eliminate bugs so that the animals’ gut can absorb nutrients more efficiently with less feed.

Information about the antibiotics used, and their duration and method of delivery was gathered from interviews with farmers, product labels observed on the farms, delivery receipts and the handwritten instructions by field staff in flock management logbooks that carried the logos of some of India’s biggest chicken companies.



Photographer: Dhiraj Singh/Bloomberg

Butchers prepare chicken meat at Crawford market in Mumbai. Chicken consumption in India is now 14 times higher than in 1985.

Records shown by the farmers indicated that at least nine antibiotics were in use, five of which are critical for treating everything from pneumonia to lethal bloodstream infections in humans. Among them were products made by Bayer AG, Zoetis Inc. and Cadila Healthcare Ltd.'s Zydus animal health unit, which are prohibited for use in poultry in Canada, the U.S., the European Union and Australia.

Most of the farmers didn't know what an antibiotic was, describing it as just one of the vitamins, medicines and disinfectants they use to keep the birds healthy. On visits to three veterinary shops in the district, sales staff were willing to sell antibiotics without a prescription, which would violate a drug law. At least one of them violated another part of the law by not recording the purchaser's name and address.

None of the farms visited had treatment systems for managing effluent from their chicken coops, with the liquid waste typically running freely into gardens growing vegetables that were consumed by their families, with surplus sold to the public.

Enrofloxacin made by Bayer and Zoetis, and a similar drug levofloxacin, manufactured by Zydus, were contained in bottles shown by six farmers, who said the contents were added to water and given to chicks as young as 1 day old to stave off disease.



Photographer: Dhiraj Singh/Bloomberg

Dead chicks on a farm in Ranga Reddy, where farmers report bacterial diseases are becoming harder to defeat.

Both drugs are in the same antibiotic class and allowed for veterinary use in India. Still, enrofloxacin should only be used to treat ill animals and under the supervision of a veterinarian and not to prevent disease or promote growth, Bayer and Zoetis said. A Zydus spokeswoman acknowledged questions sent by e-mail, but didn't respond to follow-up e-mails seeking a response.

“Enforcement by local authorities of regulation requiring a veterinary prescription for these products will help protect the health of people and animals,” Zoetis said in an e-mailed response to questions.

The Indian government's National Policy for Containment of Antimicrobial Resistance, a 55-page document released in 2011, called for a ban on the non-therapeutic use of antibiotics and over-the-counter sales, and recommended rules for livestock use. The proposed drug restrictions incited protest and the policy was shelved soon after.

In 2013, India's Health Ministry added 24 antibiotics to a list of drugs whose sale requires pharmacists to retain details of the prescription in a register for three years. The measures, though, were primarily aimed at human medicine and cover only two of the nine antibiotics found on the Ranga Reddy poultry farms. There are no directives governing the usage of the other seven drugs.

Regulations made by the central government depend on under-resourced state officials

to implement and enforce, said N.K. Ganguly, a former director general of the Indian Council of Medical Research, who was one of 13 members of a task force that prepared the 2011 policy document. Still, he said he's confident India is on the right track.

"All of these you will see will start to take effect in another half a decade," Ganguly said. "It takes time with the vastness of the country."

As it is now, the government doesn't collect data nationally on the volume of antibiotics used in either animals or humans or prohibit their use as growth promoters in livestock. It banned the use of certain antibiotics only in aquaculture in 2011, and says it only monitors drug residues in chicken meat destined for export.

The agriculture ministry issued guidelines to state authorities in December 2014, advising that antibiotics shouldn't be allowed in feed, and should be tracked from manufacturer to users. The one-and-a-half-page circular didn't specify whether the suggestions were mandatory or how they would be enforced.

Agriculture Minister Radha Mohan Singh didn't respond to written and verbal interview requests. S.K. Dutta, assistant commissioner, and Sagar Mehra, director of the ministry's department of animal husbandry, dairying and fisheries, declined to say if a policy was being drafted or answer questions when contacted by phone.

"India is definitely the country of most importance when it comes to the need for surveillance," says Thomas Van Boeckel, a post-doctoral research fellow at the Swiss Federal Institute for Technology in Zurich, who was part of the team that conducted the first attempt to quantify global antibiotic consumption in animals.

India consumes the largest volume of antibiotics in the world, but the consumption per person, at 10.7 units, is about half the 22 units per person consumed in the U.S., according to the Center for Disease Dynamics, Economics & Policy in Washington.

Use of antibiotics in animals in India is projected to more than double by 2030, driven by a surge in chicken production, Van Boeckel and colleagues showed in a study in November 2014. In a country with twice as many meat-eaters as vegetarians, chicken consumption is now 14 times higher than in 1985.

The solution isn't to ban bactericidal drugs on farms, said Vincent Doumeizel, a vice president at Lloyd's Register Quality Assurance in London, where he focuses on food safety and sustainability. "It's absolutely impossible at the moment," he said. "Banning them would just collapse the current production system overnight."

"That leads us to the next question: are animals a good way to get protein?" Doumeizel

said. “That’s a big concern because we won’t be able to feed 9 billion people with animal protein.”

In the U.S., the Food and Drug Administration asked drug manufacturers in December 2013 to voluntarily stop selling antibiotics for growth promotion, but the regulator still allows them to be used to prevent infections.

“That’s a massive, massive loophole,” said Lance Price, a genomic epidemiologist at George Washington University, who testified to U.S. Congress in April 2013 on antibiotic resistance. “And if we don’t get good laws on the books, then how do we ask China or India to cut back?”

Seshagiri Rao, who is authorized to dispense prescribed veterinary medicines from a shop in Hayathnagar, in Ranga Reddy district, suspects something’s not right. Farmers are raising too many chickens, too fast, he said, having almost reduced by half the time it takes for chicks to reach slaughter-weight during the past two decades.

“The medicines we used seven or eight years ago don’t work anymore,” he said, adding that farmers have begun asking for new, more powerful remedies. “But what happens when those stop working? There’s nothing left.”

—With assistance from Ganesh Nagarajan and Pratik Parija.

Baby's Death Shows Global Threat From Wonder Drug's Demise

By Natalie Obiko Pearson and Adi Narayan

The antibiotic colistin was the last resort for saving babies at the King Edward Memorial Hospital in Pune, India. That defense was breached last year.

In early 2015, a pediatrician at the hospital for the first time encountered two cases in which newborns had bloodstream infections caused by bacteria resistant to the critically important medicine. One of the babies died; the other survived.

“That is a warning to us that maybe we’re already losing this drug,” said Umesh Vaidya, who runs the hospital’s 50-bed neonatal intensive care unit. “If we lose colistin, we have nothing. It’s an extreme, extreme worry for us.”

The more than half-century-old drug, spurned by doctors for decades because it damages the kidneys, came back into vogue in recent years after less toxic broad-spectrum antibiotics began to fail. Colistin has since saved thousands of patients -- a track record some researchers say is threatened by its indiscriminate use on farm animals, which may be passing on drug-resistant germs to unwary consumers.

Scientists in China reported in November a colistin resistance gene called *mcr-1* that can spread among and across different species of common bacteria, heralding a wave of untreatable ailments -- from urinary tract infections to pneumonia.

Selective Pressure

The use of colistin on farms may be to blame for the drug’s demise, said Jianzhong Shen, a professor of veterinary medicine at Beijing’s China Agricultural University. “The selective pressure imposed by increasingly heavy use of colistin in agriculture in China could have led to the acquisition of *mcr-1* by *E. coli*,” he said.

Since November, the resistance gene has been reported in at least 20 more countries and prompted calls to curb the drug’s use in animals. In India, where colistin is used by some farmers to promote growth and prevent disease in poultry flocks, hospital laboratories are finding colistin resistance in as many as 10-to-15 percent of specimens tested,

said Abdul Ghafur, an infectious diseases physician at the Apollo Hospital in Chennai.

India Also?

“If we look for mcr-1, we will definitely find it in India,” said Ghafur, who convened the first meeting of Indian medical societies in 2012 that led to a national plan to tackle antibiotic resistance. “If it’s in China, it should be in India also.”

Investigations are already underway. At New Delhi’s All India Institute of Medical Sciences, Vinod Paul and colleagues have tracked about 90,000 newborns to gauge the burden of drug-resistant infections and to identify their genetic causes, including mcr-1. The findings are being reviewed for publication, possibly by mid May, said Paul, who heads the hospital’s pediatrics department.

Consultant microbiologist Camilla Rodrigues hasn’t found the gene in about 100 specimens of colistin-resistant bacteria collected at Mumbai’s P.D. Hinduja Hospital since 2011, she said. “We’ve just been lucky so far,” said Rodrigues, who chairs the private hospital’s infection-control committee. “Once it shows up, it will be the beginning of the end. We are very worried about it.”

Pediatrician Vaidya said his neonatal patients with colistin-resistant infections had been transferred from other hospitals, where they had received multiple antibiotic treatments. Doctors, too, are often quick to prescribe colistin, especially if a sick child starts to deteriorate, he said.

‘Whims and Fancies’

“It plays to their anxieties,” Vaidya said. “Unfortunately, there is no tight regulation on prescribing. Every clinician will prescribe it according to his whims and fancies.”

Sales of colistin for human use in India have more than doubled since 2013 to 1.2



EnCiprox, which lists ciprofloxacin, enrofloxacin and colistin as ingredients, in a broiler house in Ranga Reddy. *Photographer: Dhiraj Singh/Bloomberg*

billion rupees (\$18 million) in the year ended February, according to data from AIOCD Pharmasofttech AWACS Pvt., a pharmaceutical market research company based in Chennai.

Pigs and Poultry

About 11,942 tons of colistin, worth \$187.2 million, was used worldwide last year -- mostly on swine and poultry farms, Beijing-based QYResearch Medical Research Center estimated. Of the 10-largest producers of colistin, one is Indian, one is Danish, and eight are Chinese, it said in a report in August.

In southeastern India's main poultry-producing district of Ranga Reddy, farmers reported using colistin on three of 14 farms visited, while three veterinary supply stores named combinations of colistin, ciprofloxacin and another antibiotic among their best-selling drugs. The antibiotics are permitted to be used on farms in India under veterinary supervision, and broiler companies said they are used only as a last resort.

Those colistin mixtures are especially hazardous because bacteria exposed to ciprofloxacin aren't able to readily repair their drug-damaged DNA, prompting them to scavenge for genetic material from other bacteria -- which could include colistin-resistant bugs, said Timothy Walsh, a professor of medical microbiology at Cardiff University in Wales.

'Defies All Imagination'

"The combination of colistin and ciprofloxacin is just stupidity on a scale that defies all imagination," said Walsh, who along with Shen, co-wrote the paper in *Lancet Infectious Diseases* that first described the *mcr-1* gene.

Cameo Health Care (India) Pvt., based in Thane, Maharashtra state, sells "CiproCame," a combination of colistin, ciprofloxacin and neomycin, and Bangalore-based Entrix Nutrition sells "EnCiprox" in 5-liter containers, a cocktail of colistin, ciprofloxacin and enrofloxacin. Both CiproCame and EnCiprox are labeled as "feed supplements" to be administered preventatively in poultry through their drinking water. Representatives at both companies didn't respond to e-mailed questions.

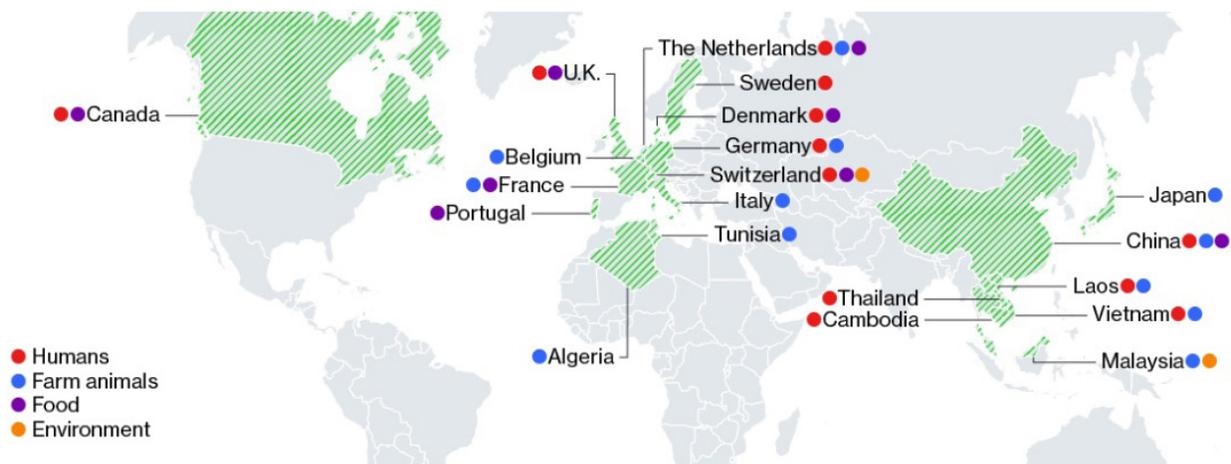
Microbial Mating

Shen, Walsh and colleagues showed that *mcr-1* is carried on mobile loops of DNA called plasmids that can be spread through a form of microbial mating. The gene's discovery was made during routine surveillance of drug-resistant germs in food animals and meat products in southern China. When researchers widened their search to hospitals, they found it in 16 of 1,322 specimens from inpatients suffering infections.

“What people don’t realize is it’s all linked -- it’s a single pool of bacteria between animals and humans,” said Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics & Policy in New Delhi and one of 15 experts appointed to a task force advising President Barack Obama on antibiotic resistance.

Since the Lancet paper was published, *mcr-1* has been found by researchers in Algeria, Belgium, Cambodia, Canada, Denmark, France, Germany, Italy, Japan, Laos, Malaysia, Netherlands, Portugal, Thailand, Tunisia, South Africa, Sweden, Switzerland, the U.K. and Vietnam.

Spread of the MCR-1 Gene



Source: Robert Skov, Dominique Monnet, *Eurosurveillance*, March 3, 2016

Spread of the MCR-1 gene through humans, farm animals, food and environment

The European Medicines Agency called for data on colistin ahead of a review of the drug’s use in animals requested by the European Commission. The London-based agency recommends that colistin’s veterinary use be limited to the treatment of infected animals and those in contact with them, not at low doses to prevent illnesses -- as it’s used in some countries, including India.

“Antibiotics are like a dam that protects us from this flood of potential pathogens,” said Lance Price, a genomic epidemiologist at George Washington University, who testified to U.S. Congress in April 2013 on antibiotic resistance. The “dam” was first built with Alexander Fleming discovering penicillin, and each new antibiotic stacked the dam higher. But as resistance spreads, that dam is cracking, Price said.

“Water is coming and big chunks are starting to fall out now,” he said. “We’ve lost the battle in some respects with what’s happened with colistin.”



Photographer: Forbes Conrad for Bloomberg Businessweek

A worker feeds fish at a farm in Datianlang in China's Guangdong province. The feed is laced with antibiotics.

How Antibiotic-Tainted Seafood From China Ends Up on Your Table

**You might want to pass on
the shrimp cocktail.**

By Jason Gale, Lydia Mulvany, and Monte Reel

From the air, the Pearl River Delta in southern China's Guangdong province resembles a mass of human cells under a microscope. Hundreds of thousands of tiny rectangular blocks, all of them shades of green, are clustered between cities and waterways. Livestock pens are scattered among the thousands of seafood farms that form the heart of the country's aquaculture industry, the largest in the world.

Beside one of those fish farms near Zhaoqing, on a muggy day in June, a farmhand wearing a broad-brimmed straw hat hoses down the cement floor of a piggery where white and roan hogs sniff and snort. The dirty water from the pens flows into a metal pipe, which empties directly into a pond shared by dozens of geese. As the yellowish-brown water splashes from the pipe, tilapia flap and jump, hungry for an afternoon feeding.

Chinese agriculture has thrived for thousands of years on this kind of recycling—the nutrients that fatten the pigs and geese also feed the fish. But the introduction of antibiotics into animal feed has transformed ecological efficiency into a threat to global public health.

At another farm, in Jiangmen, a farmer scatters a scoop of grain to rouse her slumbering swine, penned on the edge of a pond with 20,000 Mandarin fish. The feed contains three kinds of antibiotics, including colistin, which in humans is considered an antibiotic of last resort. Colistin is banned for swine use in the U.S., but until November, when the Chinese government finally clamped down, it was used extensively in animal feed in China. Vials and containers for nine other antibiotics lie around the 20-sow piggery—on shelves, in shopping bags, and atop trash piles. Seven of those drugs have been deemed critically important for human medicine by the World Health Organization.

The overuse of antibiotics has transformed what had been a hypothetical menace into a clear and present one: superbugs, bacteria that are highly resistant to antibiotics. By British government estimates, about 700,000 people die each year from antibiotic-resistant infections worldwide. If trends continue, that number is expected to soar to 10 million a year globally by 2050—more people than currently die from cancer.

In November 2015 scientists reported the discovery of a colistin-resistant gene in China that can turn a dozen or more types of bacteria into superbugs. Since then the gene has been found in patients, food, and environmental samples in more than 20 countries, including at least four patients in the U.S. Food, it now appears, can be a crucial vector. "People eating their shrimp cocktails and paella may be getting more than they bargained for," says Dr. Martin Blaser, a professor of microbiology and an infectious diseases physician at New York University Langone Medical Center who chairs President Barack Obama's advisory panel for combating antibiotic-resistant bacteria. "The penetration of antibiotics through the food chain is a big problem."



Photographer: Forbes Conrad for Bloomberg Businessweek

Medicine packaging at a pig farm in Guangdong.

Research has found that as much as 90 percent of the antibiotics administered to pigs pass undegraded through their urine and feces. This has a direct impact on farmed seafood. The waste from the pigpens at the Jiangmen farm flowing into the ponds, for example, exposes the fish to almost the same doses of medicine the livestock get—and that's in addition to the antibiotics added to the water to prevent and treat aquatic disease outbreaks. The fish pond drains into a canal connected to the West River, which eventually empties into the Pearl River estuary, on which sit Guangzhou, Shenzhen, Hong Kong, and Macau. The estuary receives 193 metric tons (213 tons) of antibiotics a year, Chinese scientists estimated in 2013.

The \$90 billion aquaculture trade accounts for almost half of all seafood harvested or caught, according to the United Nations. China supplies almost 60 percent of the global total and is the biggest exporter. U.S. food regulators have known about the country's antibiotic problem for more than a decade. The Food and Drug Administration intensified its monitoring of imported farm-raised seafood from China in the fall of 2006 and found a quarter of the samples tested contained residues of unapproved drugs and unsafe food additives. The following June an import alert was applied to all farm-raised shrimp and several other kinds of seafood from China, allowing the agency to detain the products at port until each shipment is proved, through laboratory analysis, to be untainted.

But antibiotic-contaminated seafood keeps turning up at U.S. ports, as well as in restaurants and grocery stores. That's because the distribution networks that move the seafood around the world are often as murky as the waters in which the fish are raised. Federal agencies trying to protect public health face multiple adversaries: microbes rapidly evolving to defeat antibiotics and shadowy seafood companies that quickly adapt to health regulations to circumvent them, moving dirty seafood around the world in much the same way criminal organizations launder dirty money.

The Chinese government is well aware that the use of antibiotics has gotten out of hand. In 2011 it initiated a campaign to reduce antibiotic use in humans, and since then the sale of antibiotics in Shanghai has fallen 31 percent. As last month's ban on colistin suggests, there's a new seriousness about antibiotic use in agricultural production as well. Nevertheless, China's rates of drug resistance remain among the highest in the world. Surveys across the country have found 42 percent to 83 percent of healthy people carry in their bowels bacteria that produce extended-spectrum beta-lactamases, or ESBLs, which create reservoirs of potential pathogens that can destroy penicillin and most of its variants. The aquaculture products sold in Shanghai teem with bacteria that can't be killed by common antibiotics. In almost a third of random seafood samples collected in Shanghai from 2006 to 2011, researchers found salmonella, a major cause of gastroenteritis in people. A closer examination of the germs showed that 43 percent of the samples harbored multidrug-resistant strains of bacteria.

Over the past year, scientists have tracked the spread of colistin-resistant bacteria throughout Asia, Europe, and the Western Hemisphere. In May the first report of an American infected with a colistin-resistant superbug was announced. More U.S. cases were reported in June and July. By August researchers were announcing that American patients had been infected with a strain of bacteria that had developed resistance to colistin and carbapenems, another type of antibiotic often used to treat patients in hospitals with multidrug-resistant infections.

Initially, the resistant bacteria from breeding grounds such as China were believed to spread mostly by international travel. Michael Mulvey, head of antimicrobial resistance at the National Microbiology Laboratory in Winnipeg, Manitoba, was among the first to realize that seafood could also be a vector. In 2015, Mulvey's lab secured funding for a study that enabled him and his colleagues to run a test for carbapenem-resistant bacteria on 1,328 samples of seafood collected from Canadian retail outlets from 2011 to 2015. Eight, or 0.6 percent, tested positive; all came from Southeast Asia. The findings meant that some of the planet's most difficult-to-treat bacteria could be lingering in people's refrigerators or on their kitchen countertops. "We are trying to make the case right now that it's there, it's in our seafood," Mulvey says.

Since the early 1990s, the average amount of shrimp Americans eat annually has



Photographer: Forbes Conrad for Bloomberg Businessweek

A worker on the Datianlang farm sets out to feed the fish.

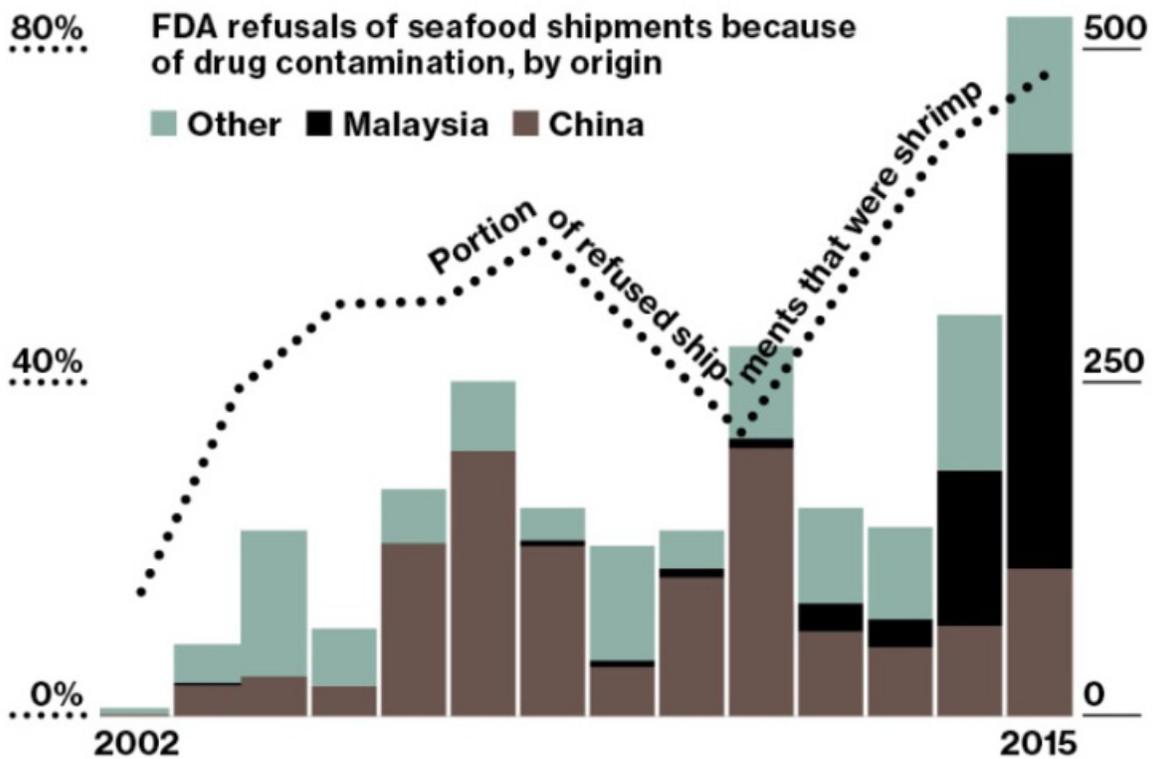
doubled, turning what was once a specialty dish into the country's single most popular seafood. As recently as the 1980s, most of the shrimp consumed in the U.S. was raised domestically, primarily off the Gulf Coast. From 1990 to 2006, shrimp import volumes doubled. They've since leveled out at roughly 1.3 billion pounds annually, and today about 90 percent of the shrimp eaten in America comes from abroad. China's share of imports touched an 11-year high in 2003 at 16 percent of the market. (It's now 5.6 percent.) In 2004, the U.S. Department of Commerce announced a 112 percent tariff on Chinese shrimp, effective 2005—a response to complaints of domestic producers that insisted Chinese suppliers were selling seafood below market prices. In 2007 came the import alert.

Malaysia jumped in to pick up the slack. In 2004 imports of Malaysian shrimp rose tenfold, according to U.S. government figures. They remained elevated for a decade, peaking at about 5 percent of the market in 2008 and 2011.

There's reason to doubt that all that Malaysian shrimp is Malaysian. Ronnie Tan, vice president of Blue Archipelago, Malaysia's largest seafood producer, says that depending on the year either three or four shrimp producers—including his own company—operate in the country. Malaysia produced about 32,000 tons of shrimp in 2015, he says; about 18,000 tons were consumed domestically, and about 12,000 tons went to Singapore.

DEADLIEST CATCH

In 2011, 75 percent of drug-contaminated shrimp shipments entering the U.S. originated in China, vs. 6 percent from Malaysia. By 2015, Malaysia accounted for 77 percent.



DATA: U.S. FOOD AND DRUG ADMINISTRATION; GRAPHIC BY BLOOMBERG BUSINESSWEEK

That would leave little legitimate Malaysian shrimp to go to the rest of the world. Yet according to U.S. Department of Agriculture figures, imports from Malaysia during the past decade have exceeded 20,000 tons a year on average.

It's a mystery that may be explained, at least partially, by examining the business practices of Jun Yang, a Chinese-born entrepreneur based in Texas. Homeland Security Investigations, a part of U.S. Immigrations and Customs Enforcement, first knew him as a honey broker. The agency arrested him in 2012 (then unarrested him so that he could cooperate with the investigation, then arrested him again) and charged him with making false claims about the honey he was selling. It was harvested in China but was passed through Malaysia, where it acquired Malaysian certificates of origin. This illegal transshipping, as the maneuver is called, allowed him to avoid paying almost \$38 million in antidumping duties. The investigators untangled a network of shell companies that seemed designed solely to deceive U.S. regulators. In November 2013, Yang was convicted and sentenced to three years in federal prison.



Photographer: Forbes Conrad for Bloomberg Businessweek

Antibiotic medicines at a veterinary pharmacy in Jiangmen.

The investigators also determined that Yang's main business wasn't honey—it was seafood. His company brokered shrimp for a Houston company called American Fisheries. At the time of Yang's first arrest, some of the shipments were still in cold-storage facilities. The feds required him, as part of his cooperation, to send samples to a laboratory for analysis. Five shipments tested positive for nitrofurans, a class of antibiotics banned in the U.S. Those tainted shrimp were eventually destroyed. All the tainted shipments had been labeled as products of Malaysia.

Despite Yang's cooperation with the government in the shrimp investigation, his information wasn't used to make a case. But American Fisheries itself may have provided a way to track the apparent transshipping scheme. In May 2013, American Fisheries sued Yang, saying it had received only \$6.1 million of the \$12.1 million Yang owed it for 74 shipments of shrimp, weighing as much as 28,000 kilograms (62,000 pounds) each, from June 2011 to January 2012. That case, still pending in Texas, as well as Yang's countersuit against American Fisheries, has uncovered a trove of documents that detail how a Shanghai-based company hatched a plan to get its Chinese-farmed shrimp into America.

In 2005, about nine months after the U.S. antidumping tariffs on Chinese shrimp went into effect, a group of seafood executives gathered in a Shanghai conference room. Many knew one another from when they'd all worked for Shanghai Fisheries, a large company

overseen by the government. The executives agreed to create a venture that would focus primarily on exporting shrimp to the U.S., despite the new tariff. They would finance and control the company from China, but it would be incorporated in Texas. That was the beginning of American Fisheries.

Some of the same executives also controlled a Shanghai Fisheries subsidiary called Guangzhou Lingshan, a seafood packing plant in the Pearl River Delta, and the plant was buying shrimp. By 2006 the company had purchased 3,000 tons of it from farmers around the town of Da'ao, according to local newspaper reports.

Guangzhou Lingshan built a lab inside the complex to test the quality of its shrimp, and the facility was considered one of the best in the region. Even so, former executives with the company say shrimp tainted with antibiotic traces made it into the company's stock. "You know what China was like," says Lv Wei, who worked for Guangzhou Lingshan in the trade department for nine years before leaving in 2013. Almost two-thirds of the shrimp that went through the packing facility ended up with American Fisheries, she says. "They all went through Malaysia." Shanghai Fisheries declined to comment on Guangzhou Lingshan.

No paperwork connected to those 2011 and 2012 shipments of Malaysian-labeled shrimp indicated they might have originated in China. The certificates of origin were



Photographer: Forbes Conrad for Bloomberg Businessweek

Aquaculture farms in Datianlang.

signed by officials at the Penang Malay Chamber of Commerce. On a day in August, a man named Mohd Noordin Ismail sits at a desk in the reception room of the chamber's offices in the seaside district of George Town. Bespectacled and wearing chunky gold rings on his fingers, Mohd Noordin has a foot-high stack of documents teetering in front of him. He says he's worked at the chamber of commerce for 40 years, and his duties include signing certificates of origin for products produced in Malaysia and then exported. The certification process, as he describes it, is built on trust. He's presented with documents provided by exporters, and he rubber-stamps the certificates under the assumption that the documents are genuine and correct. He doesn't verify their authenticity.

"We cannot trace if the shrimp is coming from Thailand or from China or from other countries," Mohd Noordin says. "We cannot trace."

The documents that bear his signature indicate the shrimp sent to American Fisheries was farmed at two Malaysian aquaculture facilities, Chai Kee Aquatic and Aiman Aquatic. But none of the addresses listed on those forms correspond to an aquaculture facility or to a place where shrimp could have been raised. On two separate import documents, the same address is listed as the harvesting site for both Chai Kee and Aiman Aquatic. That address corresponds to a long block of gated residential compounds. No ponds are visible on any of the properties. A woman who answers the door at one of the houses says her son was in the seafood business, but she says no aquaculture facilities could be found on her property or elsewhere in the neighborhood. Another address listed on the documents for Chai Kee doesn't appear on Google Maps, and neither the local police nor officials at the post office can locate the street named on the forms.

Mohd Noordin says it's possible the certificates of origin and his signature could have been forgeries and that the forms never passed his desk. Malaysia's shrimp industry is relatively small, but he says he'd never heard of either Chai Kee or Aiman. Since 2008, when the European Union temporarily banned imports from the country after several shipments tested positive for antibiotic residues and heavy metal content, only a few companies legitimately export shrimp to America, according to Mohd Noordin and others in the industry. Tan of Blue Archipelago says that while he has no direct evidence of transshipping activities, it's commonly speculated by seafood producers in Malaysia that Chinese producers use Malaysian companies—both legitimate producers and shell companies that exist only on paper—to sneak their shrimp into the U.S.

The American Fisheries court documents suggest the company and its various distributors carefully monitored the status of the shrimp shipments it brought into the U.S. and communicated via e-mail and telephone. Once the shrimp was on a ship bound for America, ownership of the shipment was transferred to a U.S.-registered company called YZ Marine. On paper, the company doesn't seem connected to American Fisheries and

its executives in Shanghai. But the court documents show that Feng Shao, president of American Fisheries, had access to YZ Marine's bank account and wrote a number of checks on it.

Lawyers for American Fisheries didn't respond to interview requests for this story, but in court documents related to the Yang suit they've denied the company illegally trans-shipped goods via Malaysia. They've acknowledged, however, that the company was fully financed and staffed via China and that its employees worked in Texas on three-month rotations because they lacked long-term U.S. work visas. Court records also show that when one shipment of Malaysian-labeled shrimp arrived in the U.S. at a lighter weight than anticipated, a member of the American Fisheries staff checked with Guangzhou Lingshan—the facility in the Pearl River Delta—to ask if there had been a packing mistake.

The groups lobbying hardest for intensified scrutiny of imported shrimp and fish are, unsurprisingly, the American producers of seafood. The Southern Shrimp Alliance, a trade organization of U.S. shrimp producers, says the U.S. market is awash in fraudulently labeled and unsafe seafood. “What we have learned is that there are well-developed channels for getting massive amounts of food and other consumer goods into this market while evading U.S. laws,” says John Williams, the organization's executive director.

Critics of increased inspection say it would cause gridlock at U.S. ports. “Think of all the trucks going by on an interstate, and you have a cop pulling people over for speeding,” says Peter Quinter, a customs and international trade lawyer in Miami. “You can't pull everyone over. ... Hiring more FDA officers is not the answer; it's like shutting down the highway.”

Arguments of that nature didn't stop the U.S. catfish industry from successfully pushing for more oversight on imports, a move that could provide a model for shrimp companies. For years the catfish industry argued that the FDA's testing protocol, which analyzes only 1 percent to 2 percent of incoming seafood, didn't adequately protect consumers. With the help of allies in Congress, catfish farmers got the USDA to take over import inspections from the FDA. The USDA's Food Safety and Inspection Service, which will inspect all catfish imports by September 2017, began conducting preliminary, noncomprehensive inspections this spring, and proponents are thrilled by a slew of recent enforcement actions.

In April the FDA issued an import alert that said its district offices could detain and test all imports of shrimp and prawns from Peninsular Malaysia, a region that includes Penang. Malaysia's Ministry of Health responded by announcing that it would tighten controls at processing plants and assume the authority to issue certificates of origin

from chambers of commerce. The U.S. in the past year has started at least two investigations involving Chinese shrimp producers suspected of shipping their seafood through Malaysia, according to a U.S. Immigration and Customs Enforcement official who is familiar with the investigations. Both probes are ongoing.

The FDA alert has virtually halted Malaysian shrimp imports. But that doesn't mean tainted Chinese shrimp aren't making it into the U.S. Industry and trade experts say many companies transship Chinese shrimp by following the American Fisheries model, each of them creating disposable import companies that can simply fold, or reincorporate under another name, at the first sign of regulatory scrutiny. Over the years, when Malaysian shrimp exporters were added to the FDA's "red list"—meaning their shipments would have to be stopped at U.S. ports—the companies didn't try to clear their names, as companies from other countries did, says Nathan Rickard, an attorney specializing in international trade whose clients include the Southern Shrimp Alliance. They just incorporated new entities with new names to do the same work.

It appears now that dirty shrimp is being routed through different countries. One that might be taking Malaysia's place as an international transshipping hub is Ecuador, domestic shrimp producers say.

"The import alert was a huge step forward to prevent contaminated shrimp from getting to U.S. consumers, but we have also seen significant shifts in trade patterns indicating new routes and methods for getting bad shrimp into the U.S. market," says Williams, of the Southern Shrimp Alliance. "As long as there are distributors, retailers, and restaurants that, provided that the price is low, do not know and do not care where their shrimp is coming from, we expect to see shrimp-trade fraud."

A recent case illustrates the domestic producers' concerns. Ocean Rancho, a company based in Rancho Cucamonga, Calif., has imported Malaysian shrimp. The company was formed by a man named Kai Hua Tan, an employee of a shrimp-farming company in mainland China called Zhanjiang Newpro Foods. Tan also has links to Tasty Goody Chinese Fast Food, a chain of 11 restaurants in California. In November 2014 the U.S. Department of Commerce said it had obtained documents showing that Zhanjiang Newpro had evaded tariffs using a transshipping scheme. When the company refused to answer questions about its operations during a review, the department imposed antidumping penalties. Ocean Rancho declared bankruptcy and dissolved, citing about \$1.6 million in duties owed to U.S. Customs and Border Protection. (Tan didn't respond to voicemails left at his listed phone number, or to phone calls and e-mails to Tasty Goody.)

Around the same time, a new company, Mita Group, formed. It has the same address and phone number Ocean Rancho used on shipping documents. No one answering

the phone there would speak with a reporter. Last year, Mita Group imported at least 700,000 pounds of shrimp—from Ecuador.

—With Wenxin Fan and Pooi Koon Chong

China's Five-Star Pig Pens Are Latest Weapon in the Superbug War

By Bloomberg News

On Shen Jian-Ping's antibiotic-free pig farm outside of Shanghai, biosecurity is something of an obsession. Vehicles entering the property are disinfected with a chlorine tire bath and alcohol spray, animals drink sterilized water and the closest visitors will get to seeing a live hog is via a TV in the visitors' center.

The wiry 46-year-old has spent 4.7 million yuan (\$700,000) giving his swine roomier, better-ventilated digs and there are three full-time veterinarians to help keep the 465-sow herd healthy. "It's like the piglets are now living in a villa that's clean and comfortable," said Shen as he sipped green tea on the patio outside his office. "And it smells much better."



Photographer: Qilai Shen/Bloomberg

Piglets seen behind closed doors at Shen Jian-Ping's antibiotic-free pig farm.

Drug Binge

China consumes half the world's antibiotics, with the majority administered to animals



Antibiotics consumed (metric tons) in 2013

Source: Ying Guang-Guo et al in Environmental Science & Technology, May 2015

Bloomberg 

Shen is in the vanguard of a new approach to livestock management in a country that consumes half the planet's pork—and half its infection-fighting medicines. China's over-reliance on antibiotics in food production places the country at heightened risk of spawning superbugs, genetically-evolved bacterial strains resistant to current medicines that experts fear could trigger a global health crisis.

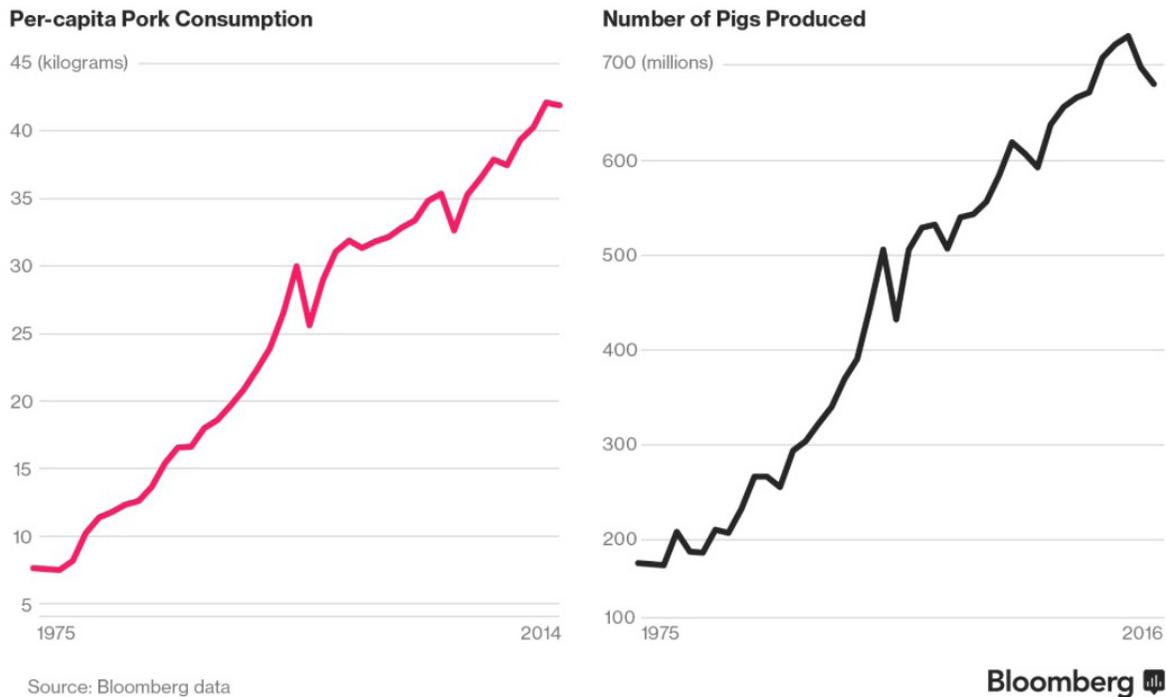
Antibiotics have been routinely fed to livestock to prevent disease and spur growth in dozens of industrialized countries for decades. However, in China pig feed typically contains multiple types of bacteria-killing drugs that are used in far greater volumes, said Ying Guang-Guo, professor of environmental chemistry and ecotoxicology with the Chinese Academy of Sciences in the southern city of Guangzhou.

Chinese pigs consume about 19,600 metric tons of antibiotics annually through their feed, scientists estimated in a 2013 study. The average growing pig in China excretes 175 milligrams of antibiotics per day in its urine and feces, according to Ying's research. He extrapolated that across the nation's entire pig population to estimate that 2,460 tons of drugs are released annually. Those chemicals may then leach into water wells and streams, or contaminate manure used to fertilize vegetable fields. Traces have even been found in Shanghai drinking water and school kids.

This epic outpouring of antibiotic residue in China is a golden opportunity for bacteria, and the genes that the microbes accumulate, to fine-tune their defenses and create new superbugs that can evade modern medicines. "It's gene pollution," said Zhu Yong-Guan, who runs the Institute of Urban Environment within the Chinese Academy of Sciences. "The danger is that these genes can be very mobile. They can be carried by bacteria and the bacteria can travel globally by air travelers, and through the movement of water or commodities."

Pig Run

Swine output has surged to feed pork-hungry China



Hog farmer Shen knows his pig feed. Before starting his piggery five years ago, Shen made and supplied fodder to swine farms near his home town of Tongxiang, 130 kilometers (80 miles) from Shanghai.

He worries most about excessive use of colistin. Developed for humans in the 1950s, doctors quickly stopped using it because it damages the kidneys. That didn't prevent its application in poultry and pig farms in Europe, China, Brazil and India.

Now, faced with patients with superbug infections, doctors consider the drug a treatment of last resort. Last November, scientists reported a colistin-resistance gene in China known as *mcr-1*, which can fortify a dozen or more types of bacteria and has been found in patients, food and environmental samples in at least 20 countries. Four patients have been infected with it in the U.S., the Centers for Disease Control and Prevention said this month.

About 11,942 tons of colistin, worth \$187.2 million, was used worldwide in 2014, according to Beijing-based QYResearch Medical Research Center. Of the 10-largest producers of colistin, one is Indian, one is Danish and eight are Chinese, it said in a report last year.

Pig farmers are largely unaware of the drug's importance or the need to restrict it, Shen said. "Most of them only wish to grow pigs faster," he said.



Photographer: Qilai Shen/Bloomberg

Adult pigs in a pig pen at Shen's farm.

That rankled with Shen, who traveled to Belgium and the Netherlands in 2011 to study how farmers there were raising hogs without antibiotics so he could try to replicate their methods back home.

His initial attempt failed. Sixty percent, or more than 1,000, of his swine died in the first winter. “We didn’t know how complicated it would be,” said Shen, who said he obtained a distance-learning degree in poultry production from China Agricultural University.

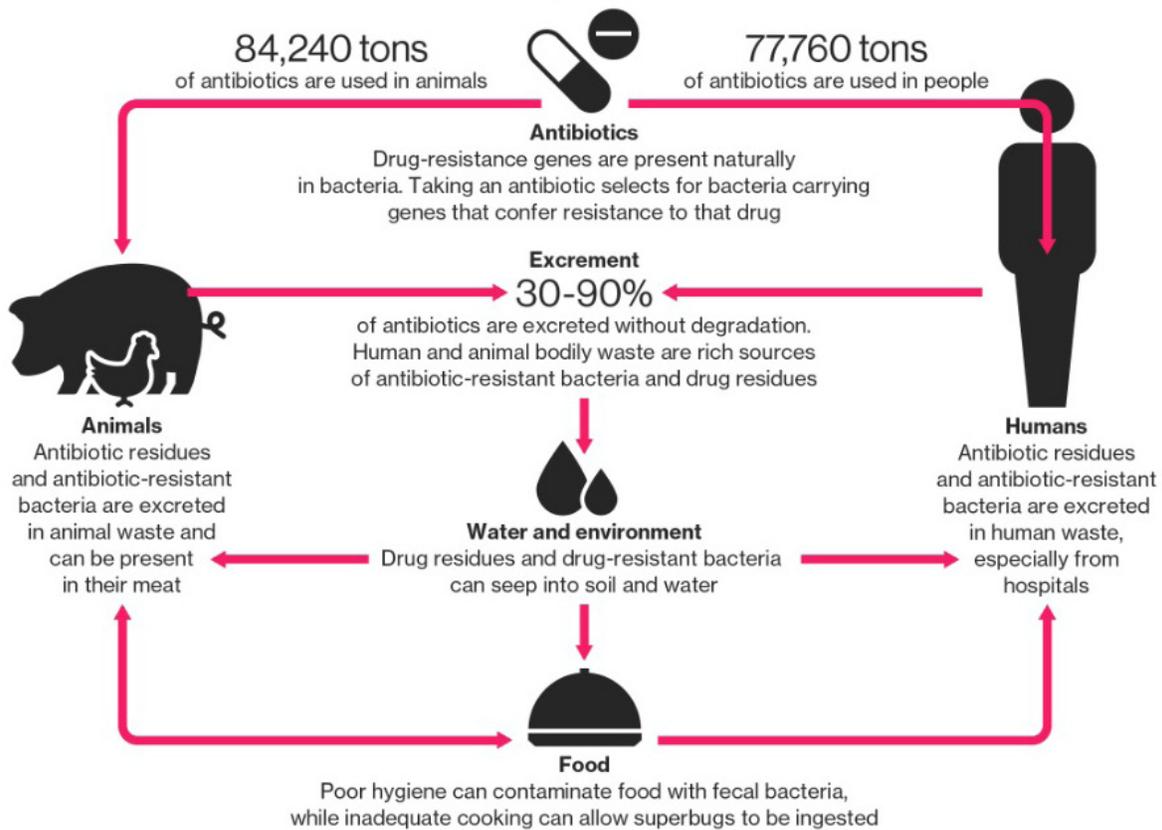
Marc Huon, a pig-management specialist in Belgium, was hired to redesign Shen’s pigsty. The first priority, Huon said, was to give each pig more space, better ventilation and to remove stress on the animals caused by temperature fluctuations. He also recommended a higher-protein diet based on a broader range of nutrients and the addition of supplements, including prebiotics to promote helpful intestinal bacteria in the pigs.

Water piped into the temperature-controlled barn has been filtered and purified with charcoal, and heated and irradiated to remove pathogens. “The water our pigs drink is better than the tap water in Shanghai—much better,” Shen said. These days, mortality is 5-to-6 percent—much less than the 15-to-16 percent average on neighboring piggeries, he said.

It takes Shen’s pigs about eight months to reach the 115-to-135 kilogram (250-300

Circulating Superbugs

How antibiotic use selects and amplifies drug-resistant bacteria in China



Source: Ajit K. Sarmah et al in *Chemosphere*, October 2006
Ying Guang-Guo et al in *Environmental Science & Technology*, May 2015

Bloomberg

pound) target weight for slaughter. That's four-to-five weeks longer than pigs fed antibiotics and other growth promoters, according to Huon. The Belgian's nutrition plan emphasizes meat quality over weight gain. "It's just a copy and paste of what we are doing here," Huon said over the telephone from Belgium.

The Netherlands and Belgium have been reducing the use of antimicrobial drugs on farms for years, following Denmark's lead in banning the non-therapeutic use of antibiotics in pigs in 1999.

The antibiotic-free status of Shen's meat is validated by an independent auditor. Shen said he's thought about going organic, but says it's too difficult to source fully organic fodder. As it is, antibiotics are used only to treat sick pigs, with the meat from those animals sold separately to local butchers. A QR code on the pack of every antibiotic-free product Shen sells enables shoppers to view real-time images of his piggery using their smartphones.

"I explained to Shen four years ago that this would be a good solution for him to



Photographer: Qilai Shen/Bloomberg

Two large water filtration tanks provide clean drinking water to the pigs at Shen's

distinguish himself from the others,” Huon said. “Today, the biggest problem is that farmers only think about money.”

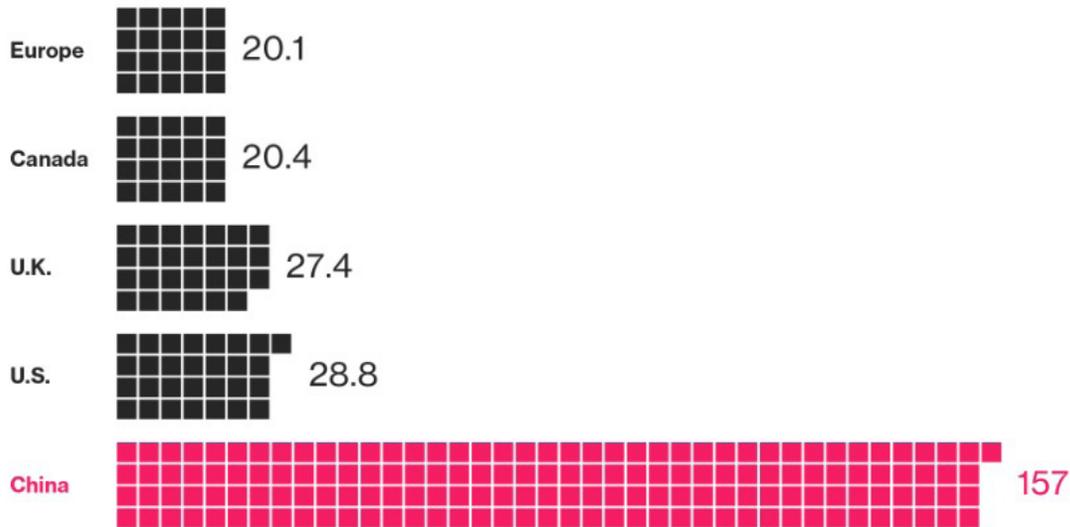
That said, there's a growing public awareness of food production safety, said Ying, the researcher in Guangzhou, who's published more than 100 papers on antibiotic emissions and environmental contamination in China. “Ordinary people are very worried nowadays because of the media reports,” he said. “There is big pressure to do something.”

Farmers, too, have reason to be alarmed. A study published this month based on rectal swabs from pigs in the eastern province of Shandong and farm workers raising them found that more than half of the swine carried a particular super-resistant *E. coli* known as ESBL that was also present in a fifth of the farm workers. Some of the germs were genetically identical, indicating pigs were the likely source.

When the rotting carcasses of more than 16,000 pigs—some of which were reportedly diseased—were found in early 2013 in the tributaries of the main river running through Shanghai, threatening the region's water supply, authorities acted quickly. Millions of small piggeries were closed in a nationwide rationalization program aimed at shifting pork production to larger, more efficient farms. It resulted in one of the largest culls in history—a reduction in hog numbers equivalent to the disappearance of the U.S., Canadian and Mexican pork industries from global supply in less than two years, according to Rabobank Groep.

Drug Overdose

China consumes almost six times more antibiotics per person than the UK



Average defined daily dose for 1,000 people

Source: Ying Guang-Guo et al in Environmental Science & Technology, May 2015

Bloomberg

Around Tongxiang, where Shen lives, there were about 3,000 piggeries, mostly raising fewer than 100 pigs, before the closures. He counts about 50 now.

Drug-resistant infections will lead to 1 million premature deaths annually in China alone by 2050 and crimp \$20 trillion from the country's potential output without preventive action, according to research on antimicrobial resistance prepared by a team led by Jim O'Neill, the British economist who coined the acronym BRIC for Brazil, Russia, India and China.

The World Bank on Monday said antimicrobial resistance would cause annual global gross domestic product to fall 1.1-to-3.8 percent by 2050, raise annual health-care costs by as much as \$1 trillion, and lead to a 2.6-to-7.5 percent a year decline in livestock production.

Leaders of the Group of 20, who met this month in Hangzhou, China, pledged to promote prudent use of antibiotics, and affirmed the need to fight resistance, including through supporting drug research. At the United Nations in New York on Wednesday, world leaders will discuss a global response, including tackling the irrational human- and veterinary-use of antibiotics and how to support efforts in developing countries.

“The problem is extensive and it may be speeding upwards quickly, but it's also clear



Photographer: Qilai Shen/Bloomberg

A retail store operated by Shen, selling antibiotic-free pork.

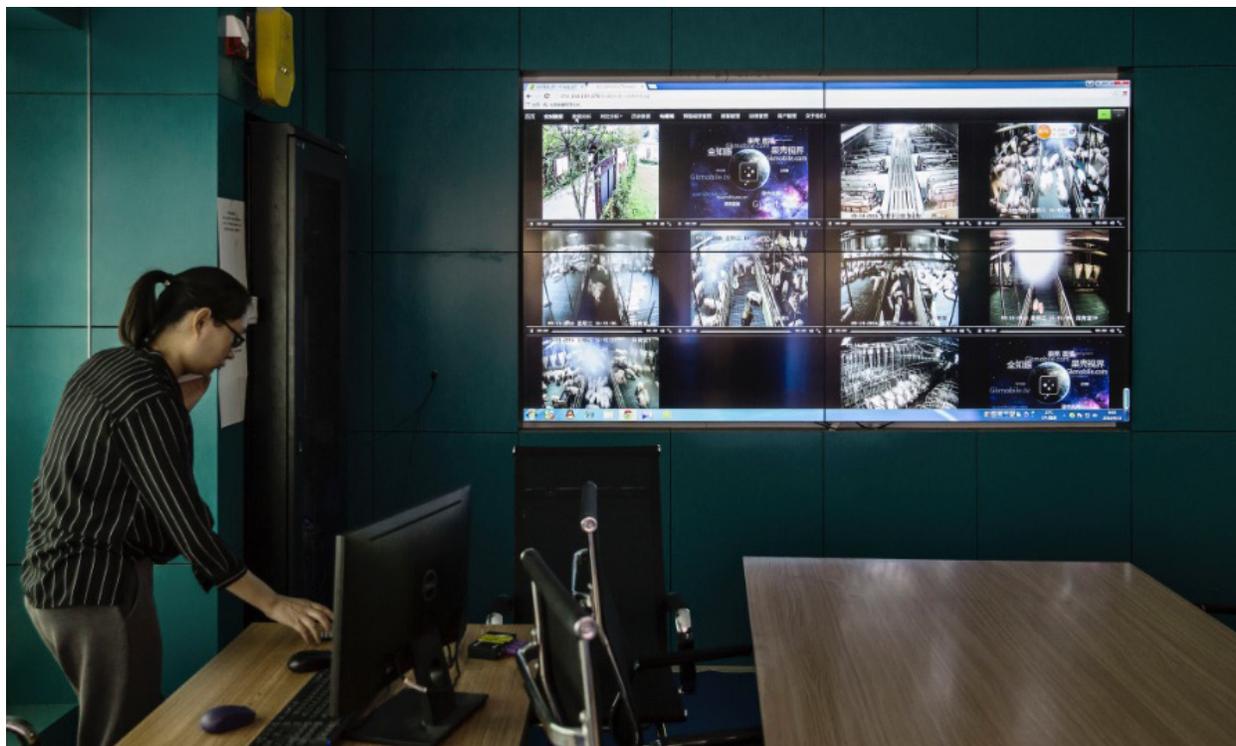
that we now have a level of attention that we have never had before,” said Keiji Fukuda, the World Health Organization’s special representative on antimicrobial resistance, in a telephone interview from Geneva. “We have to push that and use that as much as possible.”

In Shanghai and urban areas of surrounding Jiangsu and Zhejiang provinces, a study of urine samples from more than 1,000 primary school-age children found four out of five specimens harbored one or more antibiotics. Twenty-one different antibiotics were detected, including among children who hadn’t been treated with the medicines for several years.

Authors of the study, published last year in the journal *Environmental Science & Technology*, blamed antibiotic contamination of food and the environment caused by the misuse of the drugs, which they said may be associated with inflammatory bowel disease, childhood asthma, obesity and tumors. “Therefore, the elimination of water pollutants is one of the hotspots of scientific research,” the study’s 13 authors wrote.

China’s government released a national action plan in August to tackle antimicrobial resistance. Among goals for the next five years is to phase out the use on farms of important antibiotics as growth promoters and to strengthen the oversight and control of their sale in veterinary medicine.

“Antimicrobial resistance is not only a problem that exists in our country, but also a



Photographer: Qilai Shen/Bloomberg

Video feeds monitor pig pens at Shen's farm.

major challenge facing the global public health field,” said Ma Xiaowei, deputy head of China’s National Health and Family Planning Commission. His comments were posted on the commission’s website in April from a meeting where 12 government departments discussed the action plan. Mitigating the risk “is a necessary requirement to protect the health rights of the people” and help China reach its goal of being a prosperous society while showing that it’s a responsible major power, he said.

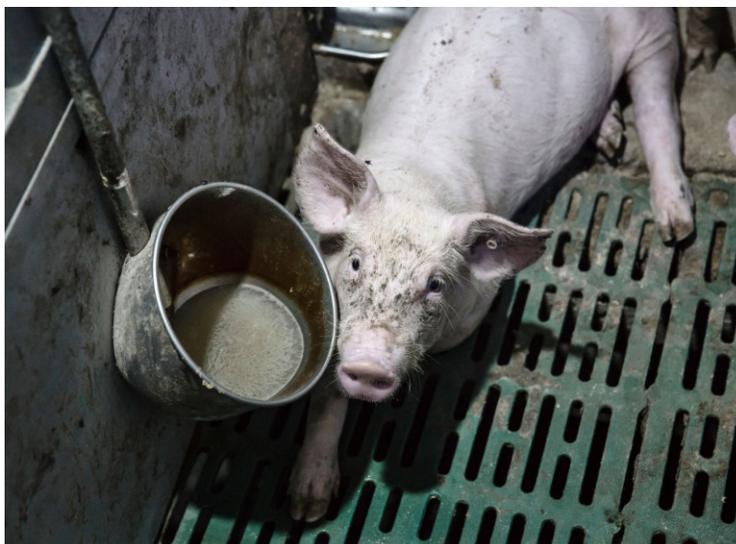
The health ministry in June released dietary guidelines that recommend citizens reduce meat consumption by half.

The prospect of a decline in meat consumption isn’t deterring Shen, who plans to increase his annual output by 50 percent to 15,000 head this year and 50,000 in three years. He is scouting for land around Beijing and in the southern province of Guangdong to establish other antibiotic-free piggeries. “Chinese people want safe and reliable food, but they can’t often find it,” he said.

Shen’s antibiotic-free pork is sold through retail outlets locally in Jiaxing City and via e-commerce sites, including Alibaba, under the “Tongxiang” label. Priced at about 70 yuan a kilogram (\$4.77/pound), it’s almost twice as expensive as regular pork, which sells for about 40 yuan/kg. Shen’s pig livers command 10 times the going rate.

“In the past, nobody would buy such expensive pork,” Shen said. “Now, kids are more likely to get sick and people are increasingly aware of the impact of antibiotics.”

Researcher Zhu believes that one promising approach in controlling the spread of antibiotic resistance genes involves removing them from animal excrement while preserving the manure's nutrient content so that it can be safely used as fertilizer. He has worked with Shen to filter bacteria and other unwanted residues from animal waste using membrane technology, then ultra-heat-treating the solids to produce bio-char, which Shen sells in bags from the visitor center on his farm.



Photographer: Qilai Shen/Bloomberg

A young piglet in a pen at Shen's farm.

“We are developing technologies for sustainable intensive animal farming,” Zhu said. If you sterilize the pig manure to remove the bacteria, you can reduce the risk dramatically.”

Farmer Shen, meanwhile, thinks it's crucial to educate kindergarten children about the effects of antibiotics in the food system. His farm hosts two or three tours a week and invites students to make dumplings from his pork and watch a demonstration of how differently his pig livers look after cooking compared with those from swine raised on antibiotics.

“We let them taste pork from us and from others,” he said. “The health of Chinese kids will see a big problem if nothing changes.”



Why Superbugs Are Beating Big Pharma

A look deep inside the race to save 10 million lives a year

By Stephanie Baker

In a cramped lab in rural Pennsylvania, surrounded by technicians in obligatory white lab coats and fume hoods leaking an occasional acrid smell, Neil Pearson holds up a plastic model of a chemical compound that resembles a spidery piece of Lego.

Pearson, a 54-year-old chemist and senior fellow at British pharmaceutical giant GlaxoSmithkline Plc, explains how he spent more than a decade tinkering with chemical compounds before engineering a molecule that may yield the industry's first truly new antibiotic in 30 years to fight the rise of superbugs that risk killing an extra 10 million people every year by 2050.

Adverse reactions, including possible eye and heart problems discovered in animals, forced Pearson to start over multiple times, with each re-jigging of the compound's atomic structure requiring a fresh round of tests to prove it was safe and effective. Pearson, wearing clear lab glasses, likens it to a game of snakes and ladders.

"I ain't got many ladders, but I have tons of snakes," he says in an accent that gives a hint of his childhood growing up in Dudley, an industrial town in the English Midlands. "I am stubborn. It's so hard. You get lots of knockbacks."

Outlier Lab

Pearson's slicked back salt-and-pepper hair is just one sign of his years in the lab doing what few pharmaceutical companies are doing these days: trying to come up with novel



Photographer:

Scientist Neil Pearson.

ways to kill bacteria that have become increasingly resistant to existing antibiotics. In 2007, he uprooted his family from England to work in Glaxo's research hub, set amid rolling farmland an hour outside Philadelphia.

Glaxo is now testing Pearson's drug, gepotidacin, on gonorrhea patients in the U.S. after trialing it on patients with severe skin infections. With lab studies suggesting it could fight plague, a potential bioterrorism agent, it's among only eight genuinely new classes of antibiotics in clinical development anywhere in the world.

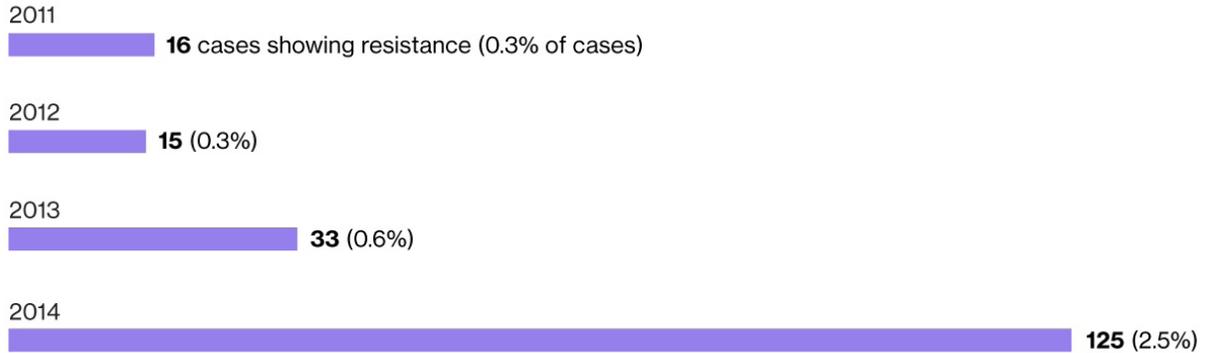
Not since Eli Lilly & Co. discovered daptomycin in 1984 has the pharmaceutical industry come up with a completely novel antibiotic, according to the Pew Charitable Trusts. sDuring that time, all but a few big pharma companies have shuttered their bacterial research units, shrinking the universe of expertise.

Just this month, AstraZeneca Plc became the latest big pharmaceutical company to pull out of antibacterial drug development when it sold its antibiotics business to Pfizer Inc. GlaxoSmithKline is one of the few big players that's kept at it, sinking about \$1 billion of its own money over the past decade into antibacterial research.

Alarming reports keep coming about bacteria that can evade modern medicine's trusted arsenal of antibiotics. This month, researchers at the University of Cambridge found that a quarter of all supermarket chicken sold in Britain harbors drug-resistant E. coli,

Superbug Resistance

The CDC reported that the number of U.S. cases of gonorrhea showing resistance to azithromycin, one of the main antibiotics used to treat the disease, had almost quadrupled from 2013 to 2014

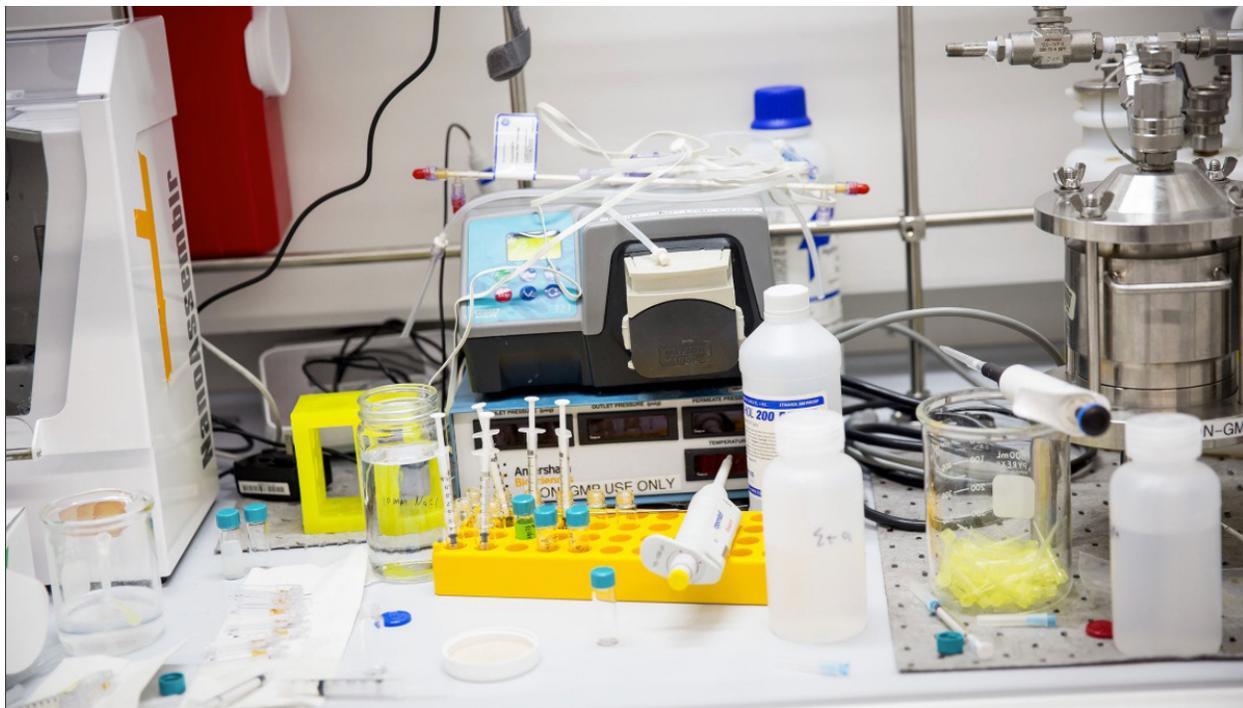


Source: CDC

Bloomberg

which can cause kidney failure and, in severe cases, death. Also this month, the Centers for Disease Control and Prevention reported a fourth U.S. case of a superbug carrying the so-called mcr-1 gene that makes bacteria resistant to the last-resort antibiotic colistin.

The infections have rattled scientists, coming less than a year after researchers first reported the gene in China, where the antibiotic is used frequently in farm animals. Adding to the worrying reports, the CDC reported that U.S. cases of gonorrhea showing



Photographer: Forbes Conrad for Bloomberg Businessweek

The new lab.

resistance to the recommended treatment regimen had quadrupled from 2013 to 2014. Fears of superbugs spreading have prompted the United Nations to convene a high-level meeting with heads of state in New York Wednesday to devise ways to combat antimicrobial resistance. The meeting comes two years after the World Health Organization warned that, without action, the planet was headed for a post-antibiotic era, in which common infections and minor injuries that have been treatable for decades could once again kill.

“High-tech medicine faces a very substantial threat,” potentially jeopardizing everything from intensive care units to major surgery, says David Livermore, a professor of medical microbiology at the University of East Anglia, north of London. “We face major resistance problems with gonorrhea and tuberculosis.”

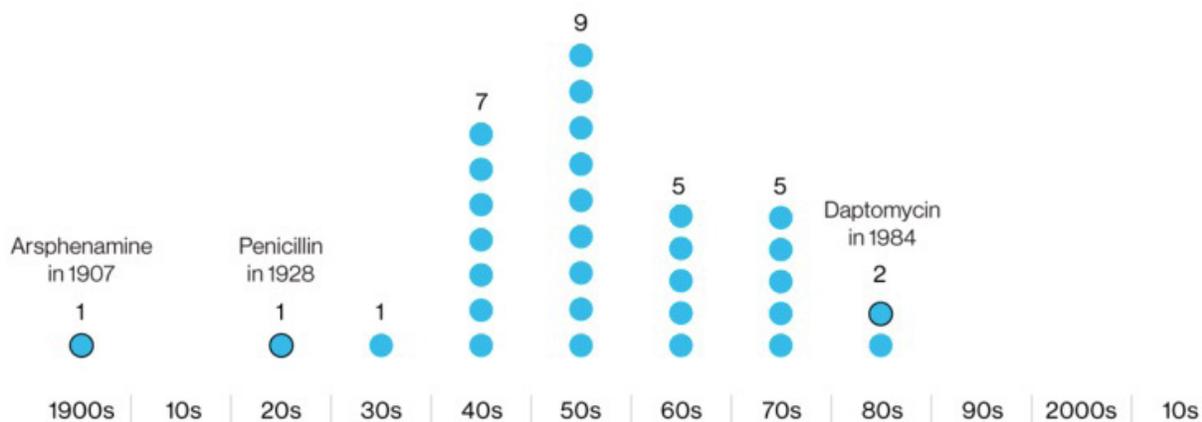
Despite the rise of superbugs, big pharma has largely exited antibiotic research because the payoff is so low. Even if Glaxo brings a new medication to the market, by definition it can't be a blockbuster drug. Overuse of antibiotics has encouraged resistance, which means new treatments must be used sparingly.

Last year, Glaxo sold 712 million pounds (\$930 million) of antibacterials, mostly its widely-prescribed penicillin-based Augmentin. These days, antibiotics are largely off patent and cheap. Unlike profitable cancer or heart medications that patients can take for years, antibiotics can save lives but are used for just weeks.

Investors have criticized Glaxo's departing chief executive officer Andrew Witty for overseeing what they perceive as a weak research and development pipeline just as the company's best-selling asthma drug Advair is bracing for generic competition in the U.S. Witty, 52, who received a knighthood in 2012, will step down in March, leaving

The Thirty-Year Void in Antibiotic Discoveries

Antibiotic class discoveries, by decade



Source: The Pew Charitable Trusts

antibiotics research bereft of one of its biggest champions. His successor will be Emma Walmsley, London-based Glaxo announced Tuesday.

Antibiotic Agitator

“He feels the industry should do something,” says Roy Anderson, 69, professor of infectious disease epidemiology at Imperial College, London and a board member at Glaxo.

Witty’s gamble is beginning to bear fruit. This week, the U.S. Food and Drug Administration gave gepotidacin special status that will speed up its review and extend market exclusivity if it is approved. In addition to gepotidacin, Glaxo has just started testing on people another experimental antibiotic called GSK3342830. It shows promise in fighting germs harboring the mcr-1 gene as well as the group of so-called gram-negative bacteria whose outer membranes make them better at evading drugs.

While it’s not in a new class of antibiotics and it’s early days, it may address the growing problem of infections picked up in hospitals that don’t respond to the current treatment war chest.

Few companies understand the scientific challenges of developing a new antibiotic better than Glaxo. More than a decade after Alexander Fleming discovered penicillin by accident in 1928 at his London lab, Oxford University scientists Howard Florey and



Photographer:

Scientist David Payne.

Ernst Chain turned it into a drug that could be mass produced. It was Glaxo that manufactured the majority of Britain's penicillin used during World War II, saving the lives of thousands of soldiers.

Penicillin changed the world. Infections that previously killed people were now treatable, paving the way for safer operations from organ transplants to hip replacements. Penicillin's discovery ushered in the golden age of antibiotic research from the 1940s to the 1970s. Many of the drugs in use today are derived from penicillin, which forms the backbone of an antibiotic family known as beta-lactams. They work by blocking the construction of bacterial cell walls.

There have been decades of modifications of that class of antibiotics as bacteria continue to mutate to confer resistance. Of the 37 antibiotics currently in clinical trials, about a quarter involve some form of beta-lactam inhibitors and fewer than 10 are genuinely new-class, according to the Pew Charitable Trusts.

'Playing Catch-Up'

"It doesn't feel like we have a sustainable solution for what bugs will throw at us over the next five to 10 years," said David Payne, the head of Glaxo's antibacterial research. "We're playing catch-up."

Payne, a 51-year-old Brit from South London with sandy-brown hair, ought to know.



Photographer:

Scientists work in the new lab.

Ever since earning his doctorate at the University of Edinburgh in 1990, he's watched an explosion of what's called extended-spectrum beta-lactamases, or ESBLs -- enzymes produced by bacteria to destroy penicillin and its variants. He identified a few on his own while doing his PhD, and then watched the number of ESBLs mushroom from a handful into the hundreds today.

Microbial Sex

ESBLs infiltrate bacterial communities on the back of plasmids. These mobile loops of DNA act like silicon chips, arming microbes with extra genetic tools to help them survive in hostile environments. Passed from bacteria to bacteria through a form of microbial sex, plasmids enable antibiotic-resistance genes to spread like wildfire.

The recent discovery of the gene causing resistance to colistin, the last-resort antibiotic, is significant because it's carried on a plasmid. In other words, it's bound to spread.

In 1995, while working for Smithkline Beecham Plc, which Glaxo bought in 2000, Payne thought the mapping of bacterial genomes would usher in a new age of antibiotic discovery. He set out on an ambitious research program identifying 70 different genes that bacteria needed in order to survive.

Payne's team then proceeded to screen those 70 targets against a million different chemical compounds to see if any of them would kill bacteria. The process took seven years and the results were disappointing. He found only five compounds that were worth



Photographer:

The new lab.

pursuing, but all of them eventually failed. Pfizer and AstraZeneca had also tried the same approach with similar disappointing outcomes, he says.

Not the Way

“We learned a lot,” Payne says. “We learned that wasn’t the way to spend a lot of time and money trying to find antibiotics.”

Since then, his team has pursued an exhaustive process of fiddling with chemical structures to find molecules that can disarm bacteria in new ways. Stephen Baker, head of chemistry at Glaxo’s antibacterial research unit, is another Brit transplanted to the middle of rural Pennsylvania trying to crack the antibiotic puzzle. Holding up a multi-colored 3-D printed model of an enzyme, he modestly compares his job to his son playing with Lego.

“I realized that’s what we do -- we’re Lego engineers, but with no instruction manual,” he says.

Finding a compound that can shut down bacteria is relatively easy, Baker says, but discovering one that won’t kill the patient in the process is much harder. Unlike say antihistamines, where the typical dose is in milligrams -- think of tiny hay fever pills -- antibiotics are usually prescribed by the grams, making them potentially more toxic.

Safety Hurdle

In 2007, after a decade of tinkering, Pearson finally zeroed in on gepotidacin, one of four molecules that showed potential after Glaxo screened a set of compounds from another, non-antibiotic program. Three of those compounds successfully disabled bacteria in the lab, but failed safety tests in animals.

Once Pearson was satisfied that gepotidacin was safe, he demonstrated that it worked differently to any antibiotic on the market in the way it inhibits gyrase, an enzyme that enables bacterial cells to replicate their DNA as they multiply.

“We believe there is a very good innate barrier to resistance in this medicine,” Witty told investors in New York in November, adding that results show gepotidacin is working against gonorrhea.

Despite all the time, effort and money Glaxo has spent, gepotidacin won’t knock out all superbugs. Though it’s active against staphylococcus bacteria, including the superbug MRSA, and has potential against multi-drug resistant E.coli found in many urinary tract infections, it’s not hitting the broad spectrum of so-called gram-negative pathogens that often cause difficult to treat infections.

No Penicillin

“Gepotidacin is nice to have in the arsenal, but it’s not the next penicillin,” says the University of East Anglia’s Livermore. “It’s arguable whether money gets you there or luck gets you there. Those who spent large amounts of money, including Glaxo, haven’t been massively successful.”

Payne agrees that the potential return on Glaxo’s investment isn’t commensurate with the work they did. “It’s taken a really long time and a lot of resource to get to this point,” he says.

It doesn’t square with big pharma’s traditional model of bringing blockbuster drugs to the market that recoup many times their research and development costs in profit.

Taxpayer Money

In Glaxo’s case, it also received help from American taxpayers. The Defense Threat Reduction Agency, part of the U.S. Defense Department, and the Biomedical Advanced Research and Development Authority, part of the Department of Health and Human Services, agreed to provide a total of \$240 million to fund the company’s antibiotics research in separate grants.

The cost of bringing an antibiotic candidate to market is about \$1 billion and takes an average of a decade, according to Anderson, the Imperial College professor and Glaxo board member. With the need to test drugs in hundreds of patients, sometimes with life-threatening infections, development costs can skyrocket, with no guarantee of success. In fact, only one in five antibiotics entering human testing will be approved by regulators, according to the Pew Charitable Trusts.

Time is running out for patients. Sepsis caused by drug-resistant bacteria is killing more than 56,000 newborns in India and almost 26,000 in Pakistan each year, researchers Ramanan Laxminarayan and Zulfiqar Bhutta wrote in the *Lancet Global Health* journal this month.

In May, Jim O’Neill, the former Goldman Sachs economist who led a two-year review into antimicrobial resistance for the British government, warned that superbugs will cost the global economy \$100 trillion by 2050 if nothing is done.

“It’s all our fault,” Anderson says. “We’re so obsessed with safety that we demand clinical trials that investigate every possible side effect of any chemical intrusion in our body. It’s understandable. But that comes with a cost.”

—*With assistance from Ketaki Gokhale.*