Superbugs in the Anthropocene

A Profit-Driven Plague

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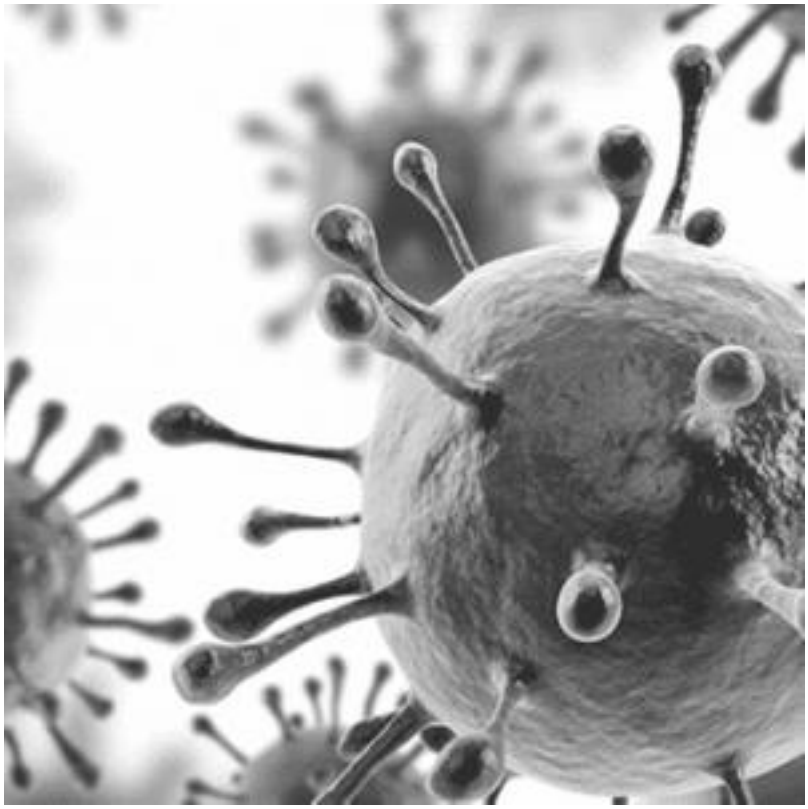
(Jun 01, 2019)

Review of the Month

Topics: Ecology , Health , Inequality

Places: Global



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He would like to thank John Bellamy Foster, Fred Magdoff, Michael Friedman, Lis Angus, and two anonymous scientific reviewers for their assistance with this article.

While I was writing this article, the press reported:

- A maternity hospital in Romania shut down because thirty-nine newborns were infected by a drug-resistant superbug. Eleven staff members were found to be carriers.
- In Gaza, the wounds of thousands of Palestinians shot by Israeli soldiers are infected with antibiotic-resistant bacteria, and the blockade prevents necessary medical supplies from reaching them.
- In Pakistan in the past two years, over five thousand people have contracted a strain of typhoid fever that is resistant to all recommended antibiotics.
- In an Indian hospital, a new strain of the common bacteria *Klebsiella pneumoniae*, described as both multidrug resistant and hypervirulent, killed more than half of the patients who contracted it.
- Tests found that 56 percent of *Staphylococcus* bacteria in two Afghan hospitals are resistant to multiple antibiotics.

Scarcely a day passes without more news of people contracting infections or infectious diseases that cannot be cured by the strongest medicines available. Antimicrobial Resistance (AMR) is a global health crisis driven by a pharmaceutical and health care system that puts profit before people. In addition to devastating climate change, the Anthropocene may be defined by epidemics that medicine cannot cure.

"A Ticking Time Bomb"

In 1876, Frederick Engels wrote: "Let us not, however, flatter ourselves overmuch on account of our human victories over nature. For each such victory, nature takes its revenge on us. Each victory, it is true, in the first place brings about the results we expected, but in the second and third places it has quite different, unforeseen effects which only too often cancel the first."[1]

Sarah Otto may never have read Engels, but the director of the Biodiversity Research Centre at the University of British Columbia echoed him in 2018: "With the evolution of antibiotic resistance, humans may impose selection, but we will often not retain the upper hand."[2]

Keywords

Microbe and microorganism are umbrella terms for microscopic organisms, including bacteria, viruses, archaea, and some fungi.

Bacteria are single-celled organisms that do not have a structured nucleus. Pathogens are bacteria that can cause disease. Viruses are very small parasites that can only grow or reproduce by infecting a living cell.

Antimicrobial and antibiotic are often used interchangeably, but properly speaking antimicrobial includes all chemicals that attack microbes, while antibiotic refers specifically to medicines that only attack bacteria.

A widely used test, developed by bacteriologist Hans Gram, divides bacteria into two broad classes, Gram-negative and Gram-positive. The former are naturally more resistant to antibiotics because their cell walls are less permeable.

Engels would certainly have considered the discovery of antibiotics as one of the greatest of "human victories over nature." Diseases that had shortened human lives for millennia were defeated. Wounds and infections that had almost always been fatal were cured in hours. The ultimate triumph of medicine—the end of all disease—seemed about to arrive.

But now the World Health Organization (WHO) says we face "a problem so serious that it threatens the achievements of modern medicine."[3] England's Chief Medical Officer, Professor Sally Davies, calls it "a ticking time bomb not only for the UK but also for the world…arguably as important as climate change."[4]

Nature's revenge—the unforeseen result that cancels the first—is upon us. Miracle drugs are losing their magic.

An End to Modern Medicine?

Like most scientific breakthroughs in the twentieth century, antibiotic drugs were developed for war. Alexander Fleming discovered penicillin in 1928, when an unknown fungus killed bacteria in a dish in his lab, but it remained a scientific curiosity until the early 1940s, when Howard Florey and Ernst Chain at Oxford University showed its practical medicinal value and the U.S. government decided that a drug that could save injured soldiers might help win the war. Several pharmaceutical companies were well paid to develop techniques for mass production and penicillin was introduced for battlefield use late in 1942. For the United States and its allies, the Second World War was the first major conflict in which infections did not cause the majority of amputations and fatalities.[5]

After the war, when penicillin became generally available, it was hailed as the miraculous beginning of a new era in human health. In 1948, bacteriologist Mary Barber wrote that penicillin was already "regarded by many in the nature of a charm, the mere sight of which was sufficient to make all bacteria tremble."[6] If some bacteria did not succumb to penicillin, they fell to newer antibiotics, and more magic bullets were on the way. Many experts predicted the imminent conquest of disease.

But nature always bats last.

Resistance to penicillin, which appeared on a limited scale in the 1940s, became a worldwide problem in the 1950s. Newer antibiotics quickly lost their power as well.

Tetracycline arrived in 1948, and resistance was nibbling at its effectiveness before the 1950s ended. Erythromycin was discovered in 1952, and erythromycin resistance arrived in 1955. Methicillin, a lab-synthesized relative of penicillin, was developed in 1960 specifically to counter penicillin resistance, yet within a year, staph bacteria developed defenses against it as well, earning the bug the name MRSA, methicillin-resistant *Staphylococcus aureus*. After MRSA, there were the ESBLs, extended-spectrum beta-lactamases, which defeated not only penicillin and its relatives but also a large family of antibiotics called cephalosporins. And after cephalosporins were undermined, new antibiotics were achieved and lost in turn.[7]

Bacteria are the oldest and most numerous organisms on Earth. No one knows how many there are, but a good estimate is five times 10^{30}—more than the number of stars in the universe. In addition to about thirty trillion human cells, your body contains some thirty-nine trillion bacteria, most of which provide metabolic services that you literally could not live without. A few—about one hundred species—can cause serious illnesses if they get into your blood. Antibiotics kill bacteria or stop them from reproducing and, if they work properly, they attack the disease-causing pathogens without damaging too many of the bacteria you actually need.

The history of antibiotics is often described as a biochemical arms race—bacteria develop immunity to existing drugs, scientists develop new drugs, bacteria evolve again, and so on. That cycle continued for a few decades until science fell behind. Over one hundred different antibiotics were developed and introduced in the 1950s and 1960s, but the last major additions to the arsenal were made in the 1980s. Development slowed markedly in the 1990s and fell off a cliff after 2000. The few antibiotics introduced in this century are basically variations on past themes. Most drugmakers have pulled out of the race entirely, eliminating antibiotic research and development in favor of more lucrative drugs.[8]

Meanwhile, antibiotic resistance continues to spread. The promise of a world without disease has been replaced by warnings of evermore virulent pathogens, created by the very drugs that were supposed to save us. Drug-resistant infections are now the third leading cause of death in the United States, killing an estimated 162 thousand people a year.[9] The toll is far higher in Africa, Asia, and Latin America.

The Case of MRSA

The ability of bacteria to overcome antibiotics has been well demonstrated by a member of the *Staphylococcus* family. First identified in 1889, *Staphylococcus* cells live, by the millions, in the nostrils and on the skin of about 30 percent of the population. Normally they are harmless, but if they get into your blood or gut, they can cause illnesses ranging from minor skin infections to life-threatening heart disease.

Of the dozen or so varieties, *Staphylococcus aureus* is particularly virulent—it can cause pneumonia, heart failure, toxic shock syndrome, bacteremia, sepsis, and other serious diseases. It is also particularly good at defending itself.

Until the 1940s, most *S. aureus* infections were fatal. Penicillin was effective against it until the mid–1950s, when hospitals reported resistance, and research showed that the bacteria had learned to produce *penicillinase*, an enzyme that disables the antibiotic. By the late 1960s, penicillin no longer worked on about 80 percent of all identified *S. aureus* infections.

Methicillin, introduced in 1960, was specifically designed to fight *S. aureus*, but, within a year, hospitals in Britain found a more deadly strain of *S. aureus* that methicillin could not stop. Methicillin-resistant *S. aureus* (MRSA) spread through hospitals across Europe in the 1960s, reaching North America by the end of the decade.

By the 1990s, it was in almost every country and had developed resistance to many antibiotics, becoming one of the most widespread and deadly superbugs. Initially found only in hospitals, MRSA infections are now more often contracted in the community. The Infectious Diseases Society says that MRSA kills more people in the United States each year than emphysema, HIV/AIDS, Parkinson's disease, and homicide combined.

An expert panel appointed by the British government has warned that, if present trends continue, by 2050 the global death rate due to antibiotic resistance will be ten million a year.[10] That is a death every three seconds, more than the combined total from cancer and diabetes.

The potential death toll from incurable infection is frightening, but the threat goes beyond that. As Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, writes, if antibiotics do not work, then many medical procedures that rely on them will no longer be safe.

Without effective and nontoxic antibiotics to control infection, any surgery becomes inherently dangerous, so all but the most critical, lifesaving procedures would be complex risk-benefit decisions. You'd have a hard time doing open-heart surgery, organ transplants, or joint replacements, and there would be no more *in vitro* fertilization. Caesarian delivery would be far more risky. Cancer chemotherapy would take a giant step backward, as would neonatal and regular intensive care. For that matter, no one would go to a hospital unless they absolutely had to because of all the germs on the floors and other surfaces and floating around in the air. Rheumatic fever would have lifelong consequences. TB [tuberculosis] sanitaria could be back in business. You could just about do a postapocalyptic sci-fi movie on the subject.[11]

Margaret Chan, former director of WHO, summarizes: "A post-antibiotic era means, in effect, an end to modern medicine as we know it."[12]

How close is that future? Until recently, the most dangerous category of bacteria was *Multi*drug Resistant. Recently, WHO added *Extensively* Drug Resistant. Now, some researchers unofficially describe certain bacteria as *Totally* Drug Resistant.[13] No wonder WHO calls a postantibiotic era "a real possibility for the 21st century."[14] This article focuses on resistance to antibiotics, but similar problems are developing with antifungal and antiviral medicines.

"The Risk Is Not Evenly Distributed"

In 2010, Carlos Franco-Paredes and Jose Ignacio Santos-Preciado wrote: "While it is recognized that the burden of antimicrobial resistance represents a significant threat to the health-care costs and clinical outcomes of infectious diseases in resource-rich countries, the impact on resource-poor countries has been shown to be devastating."[15] It is a law of life under capitalism that social problems in the global North are crises in the global South; that social crises in the North are catastrophes in the South. This is increasingly true in the Anthropocene, when the impacts of higher temperatures, violent storms, and rising sea levels are particularly severe in the poorest countries and disproportionately harm poor people everywhere.

AMR proves the law again. As the authors of a WHO report on infectious disease say, "biologically, we are all at risk—but the risk is not evenly distributed."[16] When researchers predicted that by 2050 ten million people a year will die from untreatable infections, their calculation included more than eight million deaths in Asia and Africa.

Diseases that antibiotics have largely controlled in the North, including tuberculosis and cholera, are not only epidemic in the South, but they have also mutated into much harder-to-treat forms. Worldwide, 1.6 million die each year from tuberculosis, making it the leading cause of death from infectious disease. There are 10 million new cases each year and 450 thousand of those are drug resistant. Thirty countries account for more than 85 percent of all cases of tuberculosis, and all but two (Russian Federation and Brazil) are in Africa or South/Southeast Asia.

In the rich countries of the Organisation for Economic Co-operation and Development (OECD), 17 percent of bacterial infections are resistant to some antibiotics now. That is bad news, but most antibiotics still work most of the time and alternatives are usually available. If you live in the global North and have strep throat or an infected injury, an antibiotic can probably cure it. But, as the OECD's 2018 report *Stemming the Superbug Tide* remarks, the odds are much worse if you live in a poorer country.

In low and middle-income countries, resistance is already high and AMR is projected to grow more rapidly than in OECD countries. For example, in Indonesia, Brazil and the Russian Federation, between 40% and 60% of infections are already resistant, compared to an average of 17% in OECD countries. In the same countries, growth of AMR rates is forecast to be 4 to 7 times faster than growth in OECD countries between now and 2030. Such high resistance rates in health care systems, which are already weakened by constrained budgets, will create the conditions for an enormous death toll that will be mainly borne by new-borns, very young children and the elderly population.[17]

Carlos F. Amábile-Cuevas, the internationally recognized authority on antibiotic resistance who heads Mexico's Fundación Lusara, explains why the crisis is so much more severe in the South:

Infectious diseases are much more common here, as poor sanitary and work-safety conditions, starvation and malnutrition, lack of medical services (and an excess of "alternative medicine" options), and larger exposure to environmental agents that increase the likelihood of infection (e.g., weather changes, arthropod vectors) affect much more and a much larger fraction of the population than in developed countries. Conditions are only likely to get worse as the divide between rich and poor countries widens, as it

does between rich and poor people within poor countries, and also as climate change, war, and migration introduce entirely new variables to systems that were in an equilibrium of sorts for many years.[18]

Two factors came together to create the AMR crisis: the spectacular ability of bacteria to adapt to threats, and a pharmaceutical industry whose primary concern is maximizing sales and profits.

"Unprecedented in the History of Evolution"

The famous maxim of geneticist Theodosius Dobzhansky—*nothing in biology makes sense except in the light of evolution*—is absolutely true of antibiotics and antibiotic resistance.[19] Despite the reluctance of medical journals and the popular press to use the *e* word, AMR is evolution in overdrive.[20]

Bacteria lack the complex internal structures that characterize the cells of fungi, plants, and animals, but that does not mean that these single-celled organisms are simple. Rather than growing physically bigger and more structured, bacteria have evolved as masters of biochemistry. They have survived for billions of years by inventing an extraordinary range of metabolic processes that detect, consume, block, transform, and produce chemicals of all kinds. They constantly modify and manipulate the world around them and they evolve quickly when faced with new challenges. What has been called "the high evolutionary potential of bacteria" and their "enormous potential for adaptation" has enabled them to colonize every imaginable ecological niche—high in the atmosphere, on the ocean floor, deep in the earth's crust.[21] Some species thrive in the hottest geysers while others live in arctic ice or stomach acid or oil wells or radioactive waste. Some even live by eating antibiotics.

According to orthodox evolutionary theory, new traits can appear when an organism's DNA is incorrectly copied during reproduction. If the mutant offspring are better able to survive and reproduce, natural selection will preserve the trait and eventually those with the new DNA will outnumber those without it. Bacterial populations number in the trillions and each cell can divide in as little as twenty minutes, so bacteria can change and adapt to new circumstances far more rapidly than plants, animals, and other multicellular organisms.[22] (In the 10 days a fruit fly takes to reproduce, 720 new generations of *E. coli* are born in your gut.)

That is how some antibiotic resistance emerges, but it does not explain the improbably rapid evolution of bacteria that are resistant to multiple drugs, *including antibiotics they have never been exposed to*. This is a result of a *different* adaptive process that biologists discovered in the 1950s and 1960s. Bacteria do not only inherit DNA from their parents, but they can also acquire it directly from other bacteria in what is called horizontal (or lateral) gene transfer (HGT).

In addition to inventing new resistance genes, bacteria can acquire existing ones, in ready-made batches, from other cells.

Over hundreds of millions of years, every type of bacteria, not just the few species that can harm humans, has fought the biochemical poisons it encountered in its environments, and natural selection favored the winners. Those that failed disappeared; those that succeeded incorporated new genes in their genomes as "the scars of the natural history of bacteria and the diversity of toxic molecules that they have encountered, including antibiotics."[23]

Many of those genes are found in *plasmids*, free-floating loops of DNA that are part of each cell's genome but separate from its chromosome. Each plasmid carries between three and three hundred different genes, and each bacterium may host many different plasmids.[24] The most common form of HGT involves plasmids moving from one bacterium to another, even between species, carrying new traits to the recipient cell. Such exchanges occur more frequently when the population is under attack by antibiotics, increasing each cell's chance of acquiring resistance genes. Since each plasmid can contain several different resistance genes, a bacterium that acquires resistance to the currently threatening antibiotic may also, as a side effect, acquire resistance to others.[25]

The ease and frequency with which bacteria exchange DNA leads some scientists to question whether the concept of *species* is appropriate for microbes. As Stuart B. Levy, director of the Center for Genetic Adaptation and Drug Resistance at Tufts University, comments, "the exchange of genes is so pervasive that the entire bacterial world can be thought of as one huge multicellular organism in which the cells interchange their genes with ease."[26] Whether or not that is correct, it is certain that HGT has played a major role in the rapid spread of antibiotic resistance around the world.

Since the 1940s, antibiotics have forced radical changes in the tempo and direction of bacterial evolution. As well as favoring variants that are resistant to the specific antibiotics in use, natural selection also favors variants that respond to antibiotic stress by mutating or exchanging genes faster than others and by reproducing more often.[27] "Bacteria have become so efficient in building and sharing resistance that they no longer need months or years to adapt. Four days after streptomycin therapy begins, for a kidney infection for instance, streptomycin-resistant bacteria outnumber the susceptible bacteria in the patient's urine samples."[28]

Antibiotics are the most powerful evolutionary force that bacteria have ever encountered and bacteria have mounted powerful defenses, producing the kinds of unexpected effects that Engels described. Antibiotic pressure on natural selection has shifted the composition of bacterial populations, killing off or marginalizing susceptible strains and enabling resistant strains to outnumber them. Levy, who has spent most of his career studying the subject, says that "antibiotic resistance exemplifies *par excellence* Darwinism." In his view, "the mounting increase in the use of antibiotics, not only in people, but also in animals and in agriculture, has delivered a selection unprecedented in the history of evolution."[29]

As a result, every new antibiotic has been *and will be* countered by the evolution of resistance. Noted biochemist Gerard Wright is blunt: "Resistance-proof antibiotics are a fiction."[30]

Antibiotics are either products of living organisms or creations of humans in the lab. Regardless of their origins, they are all subject to natural selection.… Bacteria have acquired the ability to respond to toxins such as antibiotics over millions to billions of years. The impact on our use of these compounds to improve health is therefore hardly surprising.[31]

Given the ability of bacteria to replicate quickly, the ease of horizontal gene transfer, the selective pressure from antibiotic use and the fact that antibiotics predate the dinosaurs (and even the Cambrian explosion) the inevitability of resistance becomes obvious.[32]

Pills, Promotion, and Profits

Antimicrobials are unique among medicines in that the more widely they are used, the less effective they become. Prudent use of antibiotics could have limited the activation and spread of resistance genes, but exactly the opposite occurred. If pharmaceutical companies had deliberately set out to encourage antibiotic resistance, they would have made every effort to ensure that the drugs were disseminated as fast and irrationally as possible—which is exactly what happened.

Fleming did not patent penicillin—he honorably rejected the very idea of claiming ownership of a natural substance. So, after the war, when material shortages ended and the manufacturing processes were widely known, new companies jumped into the penicillin business, driving prices down. A single dose cost the U.S. military twenty dollars in 1943; by 1951 the cost was twenty-five cents; and two years later it was less than one cent.[33] The president of Pfizer told New York stock-market analysts: "If you want to lose your shirt in a hurry, start making penicillin and streptomycin."[34]

The major drug companies adopted a multipronged response to falling prices and commodification. For unpatented drugs, they sought high-volume sales, promoting penicillin for every conceivable use and for some uses that seem inconceivable. The marketers went wild, particularly in the United States where prescriptions were not required until 1951. "Penicillin was not only dispensed to patients in hospitals; manufacturers tossed it into ointments, throat lozenges, gum, toothpaste, inhalable powders, even lipstick."[35]

At the same time, corporate researchers searched the world for new natural bacteria killers. Lederle Laboratories, a subsidiary of chemical giant American Cyanamid, had the first success, introducing Aureomycin in 1948. That was quickly followed by Terramycin from Pfizer in 1949 and over one hundred more from various companies in the next decade. Most were first found, in tiny amounts, in soil, home to the highest concentrations of bacteria.

The goal of these research and development efforts was not *better* drugs, but *different* drugs that could be patented and sold at higher prices than generic penicillin. New antibiotics were launched with minimal testing, whether or not there was a medical need for them. In 1957, an article in the *Journal of the American Medical Association* complained of "dozens of unimportant modifications designed to compete with drugs that are already available."[36]

Sales and prices were also boosted by creating patentable combinations of existing drugs.

As of November, 1956, there were on the market twenty-nine preparations containing two antibiotics, twenty containing three, eight containing four, and four preparations that contained five antibiotics apiece.… There is no good reason for the use of any of these sixty-one mixtures.[37]

Several companies offered supposed cold remedies that combined antibiotics with antihistamines and decongestants. Colds are caused by viruses, not bacteria, so antibiotics are powerless against them, but by the early 1960s U.S. doctors were writing four million prescriptions a year for such combinations. One of these—an antibiotic and antihistamine concoction offered by Lederle Laboratories under the name Achrocidin—was said to account for 5 percent of all antibiotic sales in the United States.[38]

The antibiotics in such products were not just medically worthless, but they also promoted the evolution of resistant bacteria in the bodies of consumers, increasing the danger posed by future infections.

Another push for high-volume sales was a process Lederle branded as *Acronizing*—reducing meat spoilage by soaking it in an antibiotic bath before shipping. Sales were over twenty million dollars in 1956 and by 1958 half of the slaughterhouses in the United States had licensed it. Lederle claimed that cooking would destroy the drugs, but apparently did no research on how handling raw meat drenched in Aureomycin might affect slaughterhouse workers or homemakers—let alone on how such uses accelerated the evolution of resistance.[39]

But the biggest innovation was marketing and advertising on an unprecedented scale. The drug industry "discovered that the techniques that had been used so successfully in the advertising of soaps and tooth pastes and of cigarettes, automobiles, and whiskey could be used as successfully to advertise drugs to doctors."[40]

Lederle led the way, shipping ten railcars of Aureomycin samples to physicians, followed by a direct mail campaign that delivered over a hundred promotional letters to every doctor in the United States. In total, it spent some two million dollars to convince prescribers that its product was "the most versatile antibiotic yet discovered, with a wider range of activity than any other known remedy."[41]

Pfizer quickly joined in and took the lead. After spending four million dollars to develop Terramycin, it spent twice that amount—the equivalent of eighty million dollars today—on a two-year blitz campaign targeting doctors. Competitors followed suit, spending millions on sales visits, mailings, and advertising in journals, deluging doctors with promotional materials, samples, gifts, and barely concealed bribes such as free trips to so-called seminars in vacation resorts. In 1960, Henry Welch, director of the U.S. Federal Drug Administration's antibiotics division and an outspoken supporter of the industry, was forced to resign when it was revealed that he had received over 260 thousand dollars in payments from the companies he was supposed to regulate.

Truth in advertising was not a concern. One Pfizer advertisement, for example, displayed the business cards of doctors with different specialties, implying that they agreed with the headlined claim that "more and more physicians find Sigmamycin the antibiotic therapy of choice." As *Saturday Review*'s science editor reported in a widely cited exposé, the cards were fake: none of the doctors existed.[42]

But many real doctors did accept the drug companies' miracle drug narrative and began prescribing antibiotics even when there was no evidence that they could help—a practice that continues today. A 2016 study found that despite educational campaigns urging prudent use, 30 percent of antibiotic prescriptions in the United States are inappropriate—most of these are for viral infections such as colds, which do not respond to antibiotics.[43]

In addition to pushing doctors to overprescribe antibiotics, pharmaceutical companies produced a steady stream of propaganda designed to create consumer demand. In addition to advertisements, subsidized or ghost-written articles hailing the benefits of antibiotics appeared frequently in mass-circulation magazines. Soon, writes historian Elizabeth Watkins, "Americans had been conditioned to expect good things from science, and they also came to expect pills from their physicians."[44]

The marketing campaigns worked beyond the dreams of avarice. U.S. antibiotic production rose from 240 thousand pounds in 1948 to over 3 million pounds in 1956.[45] Pfizer alone increased its annual sales from 39 million dollars to 254 million between 1947 and 1959.[46] Most importantly for investors, those sales were immensely profitable: by the mid–1950s, pharmaceutical companies were the most profitable corporations in the United States and superprofits continue to this day. As Michael Friedman reports:

The pharmaceutical sector is the world's most profitable, alongside banking. The ten largest pharmaceutical corporations made a combined profit of $90 billion in 2013, for a net profit of 19 percent. In 2009, global antibiotic sales were worth $42 billion, equivalent to 5 percent of the pharmaceutical market. This figure rose to $43.55 billion in 2012, and is expected to grow to $45.09 billion by 2019.[47]

The pharmaceutical giants maintain these figures by spending up to twice as much on sales and marketing as on research and development.[48]

Drug Hucksters Go South

Despite pious declarations that it puts people first, Big Pharma is, as a former editor of the *New England Journal of Medicine* writes, "primarily a marketing machine to sell drugs of dubious benefit."[49] Its ethical standards are low, even by normal corporate standards. A report by the NGO Public Citizen shows that from 1991 through 2015, U.S. pharmaceutical companies paid 35.7

billion dollars to settle 373 federal and state charges, mainly related to drug-pricing fraud and unlawful promotion of drugs. Many, including giants Pfizer, Merck, GlaxoSmithKline, Novartis, and Bristol-Myers Squibb, paid large fines for multiple offenses. Public Citizen concludes that the companies view such payments as a cost of doing business. "These illegal but profitable activities will continue to be part of companies' business model."[50]

If drug companies are so willing to break U.S. laws, it should not be surprising that they and their affiliates have long taken maximum advantage of weak or nonexistent regulation in the global South. As a result, long-standing health problems caused by poverty have been exacerbated by the massive overuse and misuse of antibiotics that has been actively promoted by the pharmaceutical industry at every level.

In books and papers published between 1973 and 1992, Milton Silverman, Mia Lydecker, and Philip R. Lee of the University of California, San Francisco systematically documented abuses of medical and business ethics by drug companies in search of third world sales. They showed, for example, that supposedly educational materials produced by drug companies differed substantially from North to South and between countries in the South.

In contrast to the promotional material provided to physicians in the United States and Great Britain, material presented to physicians in Third World countries was found to be marked by gross exaggeration of product effectiveness and minimized or completely omitted potential hazards.…

The identical products marketed by the same company may be promoted in some countries only for the control of typhoid fever and other serious diseases, while in other countries they are recommended for the treatment of such scarcely life-threatening conditions as tonsillitis, laryngitis, bronchitis and bacterial skin infections.

A common practice is handing out samples that doctors can resell. "The physician not only prescribes the drug (for a fee) but also sells the drug (for a profit) to the patient. Under such conditions overprescribing is almost inevitable."[51]

In 1992, Silverman, Lydecker, and Lee showed that the practices that originated with multinationals—high-pressure sales to doctors by direct-sales agents, misrepresentation about products, bribery, and so on—had been widely adopted by domestic manufacturers in the South. In 2018, researchers in Bangladesh found such practices were still common.

Overstatement and misinformation about antibiotics are very common in Bangladesh, which significantly influences doctors' prescribing behaviors. Currently pharmaceutical companies are the only organizations in Bangladesh providing medicine information to health professionals, and in some cases, the information provided is not consistent with recommendations from public health bodies. A large number of physicians are reported to accept economic incentives from the pharmaceutical companies.… As a result, the physicians receiving economic incentives feel obliged to prescribe company's branded medicines including antimicrobials irrespective of quality consideration.[52]

As WHO says, "promotional activities of the drug manufacturers have created a demand greater than the actual needs."[53] An Oxfam study found that as a direct result of intensive promotion by both multinationals and local manufacturers, overprescribing and misuse of antibiotics is rife throughout the global South.

All the key first-line antibiotics are used irrationally throughout the Third World. The pattern seems to be, when in doubt, prescribe an antibiotic. A pharmacist in Bangladesh will recommend a penicillin injection for a baby with nappy rash. Hospital doctors in North Yemen will give penicillin injections to a breast-feeding mother with sore nipples. In Bangladesh a young boy knocked down by a motorised rickshaw is prescribed tetracycline (and half a dozen other drugs) for a mild concussion. Even in remote areas of the Amazon, poorly trained health workers have been distributing tetracycline capsules with apparent total disregard for the problems of drug resistance.[54]

A recent CNN report on antibiotic resistance in Afghanistan found both inappropriate prescribing by doctors and widespread use of antibiotics without medical advice.

Fueling the superbug problem in Afghanistan is the unregulated sale of antibiotics in human medicine and agriculture. Drugs are advertised on television and available to buy over the counter from pharmacies without a prescription or diagnosis from a doctor.

"They give them out like sweets," said Dr. Doris Burtscher, a medical anthropologist at Médecins Sans Frontières. Burtscher compiled a report in 2015 about attitudes to antibiotics at a public hospital in Kabul and found that the drugs were taken for such issues as bruised knees, nosebleeds and body pain, as well as by women after menstruating.[55]

In most of the global South, even in countries where prescriptions are supposedly required, street vendors and pharmacies with untrained staff are a primary source of medicine. Drugs, especially antibiotics, are sold routinely for every ailment. As Infectious Diseases Advisor Rupa Kanapathipillai of Médecins Sans Frontières (MSF—Doctors Without Borders) says, this can have deadly results.

Particularly in a lot of the countries where MSF works, patients can purchase broad-spectrum antibiotics in markets and pharmacies without prescriptions. They then become unnecessarily exposed to different types of antibacterial agents—so to different types of antibiotics. Bacteria become exposed to these types of antibiotics, and are more likely to develop resistance to them.[56]

Burtscher told CNN that overuse in Afghanistan reflects a "strong cultural trend toward taking antibiotics." If so, the "cultural trend" was created and reinforced by an industry that has deliberately promoted miracle drugs as the solution to all health problems. As Silverman, Lydecker, and Lee write, heavy promotion by manufacturers and doctors has ensured that "much of the public has become convinced that there must be a pill for every ill."[57]

Oxfam's Dianna Melrose agrees: "Since both manufacturers and prescribers give too much encouragement to the indiscriminate use of antibiotics, it is hardly surprising that ordinary people have come to see antibiotics as panaceas."[58]

Per capita consumption of antibiotics is still highest in the United States, but Southern countries are gaining fast: between 2000 and 2015, antibiotic consumption rose 103 percent in India, 79 percent in China, and 65 percent in Pakistan. If current trends continue, global consumption will increase 200 percent by 2030 and most of that growth will be in the South.[59]

Since up to 80 percent of every antibiotic dose is excreted unchanged, most antibiotics enter the environment. If appropriate sewage treatment is available, some antibiotics may be eliminated, but even advanced treatment systems do not remove resistant bacteria. Where sewage treatment is inadequate, or, as in most of the global South, where there is no sewage treatment at all, the antibiotics and resistant germs that humans excrete end up in rivers, lakes, oceans, and groundwater.

This is a particularly critical issue with effluent from hospitals, which typically contains high concentrations of antibiotics and bacteria. For example, a study of wastewater treatment in hospitals in Vietnam found that, even after treatment, "significant concentrations of antibiotics were still present in the hospital effluents which, when released to the environment, could promote the selection of antibiotic resistant bacteria."[60]

Big Pharma and Big Farms

Antibiotic waste from human use is a serious environmental problem, but it pales beside the impact of feeding antibiotics to animals who consume and excrete far more than humans. Globally, the great majority of all antibiotic production is fed to livestock—and since even the world's most advanced hospitals produce resistant bacteria, no one should be surprised that barns crammed with animals are producing far more.

Without antibiotics, what Tony Weis calls the *meatfication* of the Western diet—"a *quadrupling* of world meat production in a mere half-century"—would not have been possible.[61] When large numbers of genetically similar animals are confined in the close, unhygienic conditions that have characterized industrial livestock production, rapid spread of disease is all but inevitable. So when confined animal feeding operations (CAFOs) became widespread in the United States after the Second World War, pharmaceutical marketers saw a golden opportunity. They began selling antibiotics in bulk to the then-new factory farms, claiming that low doses in feed would prevent disease and somehow cause animals to grow bigger and faster—despite the absence of scientific evidence that so-called growth promotion additives (GPAs) actually promoted growth.

Countries that have banned the use of antibiotics for growth promotion have seen no significant decline in production, lending credence to the view held by some that GPAs were no more than "a brilliant means for drug companies to sell otherwise worthless, leftover mash…a huge exercise in American hucksterism." An epidemiologist with the Centers for Disease Control comments: "If there was evidence they worked, the pharmaceutical industry would have provided that. They would have been falling all over themselves to show the evidence it worked."[62]

The authors of a UK government report on AMR suggest, in fact, "that antibiotics are more effective growth promoters when used for animals kept in cramped, dirty, unregulated conditions than for animals living in cleaner, more open, more controlled environments. Under suboptimal conditions, the growth promoters are for all practical purposes a substitute for good infection prevention and control."[63] In short, as Ellen Silbergeld of the John Hopkins School of Public Health says, antibiotics are used "to

compensate for what is accepted practice in poultry and swine houses, which I prefer to analogize to badly run and overcrowded hospitals."[64]

Unfortunately and inevitably, the antibiotics used in agriculture, and the resistant bacteria they produce, do not only affect the animals.

In 1976, Levy demonstrated the problem on a small scale by dividing three hundred three-month-old chicks into two groups: half received tetracycline in their feed; half did not. The control group did not change, but tetracycline-resistant bacteria appeared almost immediately in the feces of the others. After twelve weeks, those chicks were also excreting bacteria that were resistant to streptomycin, sulfonamides, ampicillin, and carbenicillin, *none of which they had been exposed to*. Five months after tetracycline was first used on the farm, "family members living about 500 feet from the chicken barn were also found to harbor high numbers of resistant fecal bacteria including multiply resistant bacteria; none of these individuals was taking an antibiotic."[65]

If a few chicks could develop and spread resistant genes that quickly, how much worse is the situation in and around industrial farms that raise tens of thousands of animals? Science journalist Maryn McKenna tells us:

Researchers have found resistant bacteria in the soil around chicken farms, in groundwater under hog farms, and in dust borne away from an intensive farm by the wind. The trucks that bear chickens from farm to slaughter, stacked up in towers of wire cages, stream a plume of resistant bacteria behind them that can contaminate cars on the same road. Scientists have found resistant bacteria being carried away by flies from chicken farms in Delaware and Maryland and hog farms in Kansas and North Carolina.…

All of those accidental exportations cause the environment outside farms to be loaded not just with resistant bacteria but with genes that confer resistance.[66]

Workers on factory farms and in slaughterhouses become unwitting carriers, spreading resistant bacteria and genes into the community. A 2018 report on the pork industry, published by the Natural Resources Defense Council, summarizes some recent studies:

A study of more than 1,300 Iowans determined that people working on pig farms were six times more likely to be carriers of multidrug-resistant *S. aureus* [MRSA] than were Iowans not exposed to pigs. In particular, pig workers and their children are more highly colonized with methicillin-resistant S. aureus than the general public. A separate study examined workers from 22 industrialized pig operations and found that 45.5 percent were carriers of MRSA. Of all the Staphylococcus bacteria carried by these workers, 82 percent were found to be resistant to tetracycline, the antibiotic most widely used in pig production. A third study, somewhat earlier and more limited, looked at 20 workers from two pig operations in Iowa and Illinois and found 45 percent of them were colonized with MRSA bacteria.

Slaughterhouse workers face elevated risks as well. One recent study found 21.6 percent of them were carrying *S. aureus* bacteria; the *S. aureus* isolated were resistant to more than 2.5 times the number of antibiotic classes than were *S. aureus* from the slaughterhouse workers' neighbors. Nearly 22 percent of these workers specifically carried MRSA.[67]

CAFOs in the United States produce over forty times more solid waste (mostly feces) than all publicly owned wastewater treatment plants combined. Almost all of it enters the environment without treatment.[68]

The manure produced by industrial hog operations (IHOs) accumulates in immense cesspools—euphemistically called lagoons—before being sprayed or spread on the land, contaminating soil, sediment, and groundwater. In North Carolina, a state that has more than two thousand giant hog farms and four thousand pig-shit lagoons, researchers found that "people living near IHO liquid waste application sites have elevated rates of infection with methicillin resistant *Staphylococcus aureus*," and that African Americans, Latinos, and indigenous people are disproportionately affected.[69]

Silbergeld and her colleagues call factory farms "agricultural incubators" for resistant bacteria.

The use of antimicrobials as feed additives results in uncontrolled and subtherapeutic doses over the lifetime of animals raised in grossly unhygienic surroundings. This presents the worst possible scenario for resistance selection and infection control. Coupled with incomplete biosecurity and biocontainment, and mostly nonexistent waste treatment, these conditions lead to dissemination into human hosts and the environment, with amplification of reservoirs of resistance.[70]

Large volumes of antibiotics are also used to prevent infections in fish farms, orchards, and beehives. And possibly the most outrageous use of all: some golf courses even spray oxytetracycline to kill bacteria that cause turfgrass to wilt.

Until recently in the United States, anyone could walk into a feed store and buy tons of antibiotic-dosed grain or barrels of straight drugs if they preferred to mix their own. No prescription required, no questions asked. As much as 80 percent of annual U.S. production was given to chickens, pigs, cattle, and other livestock. In 2017, *after* the Food and Drug Administration banned the use of antibiotics for growth promotion, antibiotics for animals still constituted 64 percent of U.S. sales by weight. Over 90 percent of that was delivered in healthy animals' food and water for so-called disease prevention. The requirement of a veterinarian's prescription does not appear to be a major obstacle to antibiotic use. The fact that many physicians routinely overprescribe antibiotics for people suggests that agribusiness giants will not have any difficulty finding veterinarians who are willing to do the same for livestock, especially in states that allow animal doctors to prescribe *and sell* medicines. This, combined with the general reduction of environmental protections in the Trump era, means that animal antibiotic use in the United States may soon return to former levels.

Deliberate Ignorance

Scientists have learned an enormous amount about bacteria in the decades since antibiotics were introduced, so it might be argued that the overpromotion and overuse of antibiotics after the Second World War resulted from lack of knowledge of the dangers. As the prophet Isaiah said, the combination of greed and ignorance is particularly dangerous.[i]

Perhaps ignorance played a role, but if so, it was *deliberate* ignorance, like the so-called climate science skepticism so conveniently adopted by the executives of fossil fuel companies. The precise mechanisms may not have been discovered, but the resistance problem was well-known *before* the drug companies became big-time antibiotic pushers.

Sulfa drugs, anti-infective chemicals that were developed in Germany in the 1930s, had lost effectiveness against many bacteria by the beginning of the war. Howard Florey and Ernst Chain observed some resistance to penicillin in laboratory tests as early as 1940. In his 1945 Nobel Prize speech, Alexander Fleming warned that antibiotic use should be carefully managed, because "it is not difficult to make microbes resistant to penicillin."[ii] In 1948, Mary Barber, discoverer of the first resistant strain of *Staphylococcus aureus*, warned that "the present widespread and often indiscriminate use of penicillin, particularly as a preventive measure, is seriously menacing its future reputation."[iii]

In 1955, a partial literature survey identified 564 published scientific papers on antibiotic resistance.[iv] In the same year, in the *Proceedings of the Royal Society of Medicine*, prominent British surgeon Lindsay Batten cautioned that "we may come to the end of antibiotics. We may run clean out of effective ammunition and *then* how the bacteria and moulds will lord it."[v]Shortly after horizontal gene transfer was discovered, the *New England Journal of Medicine* warned: "Unless drastic measures are taken very soon, physicians may find themselves back in the preantibiotic Middle Ages in the treatment of infectious diseases."[vi]

The role of factory farming in spreading resistance was also known long ago. As early as 1953, physician Barnett Stross, speaking in the British House of Commons, argued that "if pigs are fed in this way, new types of bacteria may evolve and thrive which are resistant to the penicillin…[and] if there be migration of the bacteria to humans we may find ourselves in trouble."[vii] And shortly before her death in 1964, Rachel Carson, author of the environmental classic *Silent Spring*, wrote that "diseases sweep through these establishments, which indeed are kept going only by the continuous administration of antibiotics. Disease organisms then become resistant to the antibiotics."[viii]

Those warnings, and many others, were ignored. If human health had been Big Pharma's main concern, it would have changed course long ago. A rational approach would have been to avoid all unnecessary use of antibiotics, monitor essential uses carefully, and study how to minimize bacterial evolution. But human health has never been a priority for the pharmaceutical industry: drugs are a way to accumulate capital and human health is, at best, a side effect.

Notes

1. i. Isaiah 56:9–12 quoted in Silbergeld, *Chickenizing Farms and Food*, 129.
2. ii. Alexander Fleming, "Penicillin" (Nobel Lecture, December 11, 1945).
3. iii. Mary Barber quoted in Podolsky, "The Evolving Response to Antibiotic Resistance (1945–2018)."
4. iv. John E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine* (Oxford: Oxford University Press, 2007), 227.
5. v. "Joint Meeting No. 1: Section of General Practice with Section of Medicine," *Proceedings of the Royal Society of Medicine* 48, no. 355 (1954): 360.
6. vi. "Infectious Drug Resistance," *New England Journal of Medicine* 275, no. 5 (1966): 277.

7. vii. Barnett Stross quoted in Philip Lymbery and Isabel Oakeshott, *Farmageddon: The True Cost of Cheap Meat* (London: Bloomsbury, 2017), 136–37.
8. viii. Rachel Carson, foreword to *Animal Machines*, by Ruth Harrison (1964; repr., London: CABI, 2013), 32.

Industrial Pollution

If you are prescribed an antibiotic in Europe or North America, it is almost certain that the active pharmaceutical ingredients (APIs) were manufactured in China, then made into pills or capsules and packaged in India. In the past three decades, most drug-manufacturing operations in the North have been shut down and Big Pharma has outsourced production to the global South, where wages are low and regulation is weak. China now makes 80 to 90 percent of APIs and India is the largest producer of finished medicines, particularly private-label generics. Some manufacturing has also moved to Pakistan, Bangladesh, and Southeast Asia.

While some Southern operations are subsidiaries of Northern drug companies, or joint ventures, most production is done by locally owned companies that compete to produce drugs for multinationals. There are about five thousand pharmaceutical factories in China and over eight thousand in India, but most antibiotic production takes place in about two hundred facilities owned by a handful of large companies. India's Sun Pharma, for example, has over thirty thousand employees and forty factories.[71] The supply chains are complex and virtually impossible to trace: the Northern companies whose names go on the box or bottle and the Southern manufacturers who make the contents all treat their arrangements as trade secrets and publish as little information as possible.

In any industry, corporations whose business strategy is to be the lowest-cost provider of commodity products must do everything possible to cut costs. In pharmaceuticals, that includes offloading the cost of waste disposal onto the environment. Local regulators and inspectors look the other way, either because they are political appointees who do not want to challenge local businesses, or because they are corrupt, or (often) both.

Trade secrecy and political protection of polluters means that no comprehensive picture exists of pharmaceutical-industry pollution in the South, but a growing number of studies indicate that release of antibiotics and resistant bacteria into land and water is a major problem.

Perhaps the most disturbing example is in the city of Hyderabad in southeastern India, one of the largest centers of bulk drug production in the world. In 2007, researchers examined effluent from the wastewater-treatment plant that receives and processes waste from some ninety drug manufacturers in Patancheru, an industrial suburb. Samples of effluent from the plant—treated liquid that flows into a stream and then into several rivers—contained the highest levels of drugs any study had found in effluent anywhere. Notably, the antibiotic ciprofloxacin was found in concentrations one thousand times higher than the dosage recommended for patients with serious bacterial infections. The scientists calculated that manufacturers in the area must be discarding forty-five kilograms of ciprofloxacin a day, enough to treat forty-four thousand people.[72]

A follow-up study in 2009 found "unprecedented drug contamination of surface, ground, and drinking water" around Hyderabad and "very high concentrations" of ciprofloxacin and other antibiotics in two nearby lakes. In one of the lakes, the concentration of antibiotics was higher than is normally found in the blood of patients under treatment.[73] A lake that was once popular for swimming and fishing has been described as "a giant Petri dish for anti-microbial resistance."[74]

These studies were headed by Joakim Larsson of Sweden's Gothenburg University. As he writes, the antibiotic pollution in Hyderabad is not unique. Similar concentrations of oxytetracycline and penicillin have been found in treated effluent from Chinese factories, and high concentrations of APIs have been found in waste discharged from drug factories in South Korea, Taiwan, and Pakistan.[75]

A report published in 2016 by the liberal watchdog group SumOfUs remarked that

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.[76]

As the European Public Health Alliance argues,

antimicrobial resistance (AMR) and pharmaceutical pollution in the environment (PIE) are twin problems that are closely connected.…

Weak domestic regulations, insufficient inspection capacities and lax procurement rules allow multinational companies to bypass international standards and pollute unchecked. Antibiotic residues pose a growing problem: not only do they contaminate surface and ground waters, soil, and sediment—with consequences for aquatic life, crops and plants, and quality of drinking water—they also contribute to the proliferation of resistant bacteria, which are passed on to local people and animals via polluted water. International travel and trade carry resistant bacteria around the globe.[77]

A Perfect Storm in the Resistome

The major problem with antibiotic overuse and pollution is not immediate transmission of disease, although that is a concern, but the increasing volume of resistant genes and harmful bacteria in the environment. Resistance as such is only detected when someone is infected *and* antibiotic treatment fails, possibly far from where the bacteria first appeared. If you carry bacteria with resistant genes, you are not only in greater danger of contracting untreatable infections in the future, but you will also almost certainly pass resistant bacteria onto other people, since every time you breathe or touch anything, you leave some of your trillions of bacteria behind and pick up bacteria left by others. As more resistant bacteria enter the environment, there are evermore opportunities for their genes to spread.

The worldwide pool of resistance genes that bacteria may acquire is called the *antibiotic resistome*. Resistance originally evolved to deal with the small concentrations of toxins found in nature, so for most of history the resistome was limited in size and scope, and many of the genes were inactive most of the time. A team headed by William Gaze of the European Centre for Environment and Human Health explains how mass use of antibiotics has changed that.

Humans have created environments with unprecedented mixing opportunities between environmental bacteria and human pathogens in the presence of such selective agents through, for example, sewage and waste water treatment plants, chemical production factories, and the practice of spreading manure on farmland. These opportunities provide conditions that greatly facilitate gene mobilization.

The result is a perfect storm of opportunity for bacterial human pathogens that exploits millions of years of evolution, uncounted microbial generations, and modern human activity.

HGT hot spots—areas with high concentrations of bacteria, where gene transfer can easily occur—have probably existed since shortly after the first bacteria appeared. In the past eight decades, misuse and overuse of antibiotics has concentrated resistance genes in those hot spots, creating “a cocktail with high numbers of bacteria of human and animal origin that offer an unprecedented opportunity for genetic exchange between environmental bacteria and pathogens.”[78]

Hot spots, in soil and water as well as in hospitals, factories, sewage-treatment plants, and factory farms, provide excellent conditions for the spread of multidrug-resistant bacteria in local ecosystems and around the world.

The net result is an exploded mobile metagenome of shared genetic traits that is fluid and readily promulgated through microbial populations. The rapid movement of water, plants, animals, soil, and humans across the planet virtually ensures that such traits and associated organisms, once easily ecologically segregated, can move seamlessly through habitats across the globe. The result is that no regions are safe or can escape the introduction and movement of antimicrobial drug-resistant organisms and their genes. [79]

There are no national borders in the resistome, no barriers that prevent or even slow the global spread of resistance genes. Consider carpabenam and colistin, last-resort antibiotics that no bacteria could resist. Bacteria with a gene that provides resistance to carpabenam were first seen in India in 2008. By 2012, the gene was found over one thousand times in fifty-five countries. Bacteria with a gene that resists colistin appeared in China in 2015 and it spread to bacteria in more than thirty countries in less than a year.

As microbiologist Thomas O’Brien says, “use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else.”[80]

Not Just Pathogens

Most research and policy discussion on antibiotic resistance has focused on its direct effects on human health and health care. That is not surprising, since untreatable infections are already a global medical problem that is likely to get much worse.

Nevertheless, it is important to recognize that the millions of metric tons of antibiotics that have been added to the environment are not simply affecting the few types of bacteria that cause diseases in humans and other animals. Microbes that provide essential life-support services also have to cope with unprecedented amounts of toxins.

For example, the global carbon and nitrogen cycles are fundamental to the functioning of the biosphere and the maintenance of life of all kinds—and neither would be possible without the metabolic operations of specific types of bacteria. Those biogeochemical cycles evolved on Earth when antibiotics only existed in tiny amounts, and we have no idea what the long-term effects of high environmental concentrations might be.

As biologist Michael Gillings writes,

the antibiotic revolution may be having effects across the entire microbial biosphere.…

We need to address the antibiotic resistance problem from a broader evolutionary and ecological perspective. The ability of natural selection to shape species and communities is the same for microorganisms as it is for larger species, and the ecological theory of community assembly developed for multicellular organisms can be applied to the microbiome. The risk associated with the environmental spread of resistance genes with known adverse consequences for human welfare has had little attention, nor has the potential for pollution with antibiotics to widely affect the global microbiome.[81]

Planetary Boundaries

When Earth System scientists first concluded that a new epoch in planetary history had begun, they illustrated their findings with twenty-four graphs showing global-scale environmental changes since the Industrial Revolution. Every one of the graphs—water use, atmospheric carbon dioxide, biodiversity decline, great floods, and more—rose very slowly or not at all until about 1950, and then turned sharply upward. Those hockey-stick curves illustrate what is now called the Great Acceleration—"the most rapid transformation of the human relationship with the natural world in the history of humankind."[82]

Earth System scientists now view the Great Acceleration as a decisive turning point, a time of transition between the eleven-thousand-year-old Holocene epoch and the Anthropocene. There is a continuing discussion about whether and how to amend the formal Geological Time Scale, but there is no question that qualitative changes to the Earth System began in the mid–twentieth century and have accelerated since.

A graph of antibiotic production would closely resemble the Great Acceleration graphs—nonexistent before 1942, followed by a rapid and exponential rise from mid–century on. The similarity is no coincidence. The introduction of mass-produced drugs is part of the third technological revolution, described by Ernest Mandel as "an epoch of unprecedented fusion of science, technology, and production" that has transformed agriculture, manufacturing, transportation, telecommunications, materials, chemicals, and, of course, greenhouse gases.[83] The rise of antibiotic production and use is part of this revolution and the Great Acceleration.

Some scientists now argue that antibiotics should be viewed as nonrenewable resources and antimicrobial resistance as a global environmental crisis. As a team headed by Peter Søgaard Jørgensen of the Royal Swedish Academy of Sciences recently wrote:

There are…strong parallels between how the burning of fossil fuels has altered our climate and how "pollution" with antibiotics has depleted the abundance of easily treatable microorganisms and diminished the many benefits human receive from microorganisms. Antibiotics resemble fossil fuels in their foundational role in industrial societies and the consequent need for concerted collective action.[84]

Jørgensen is a Principal Investigator in the Living with Resistance project, an international multidisciplinary effort to "address the socio-ecological dilemmas that constrain society's response to resistance evolution."[85] In a review article published recently in *Nature Sustainability*, they propose that antibiotic resistance be added to the "planetary boundaries" defining "a safe operating space for humanity" that were identified by the Stockholm Resilience Centre in 2009 and updated in 2015.[86]

The question, Jørgensen and colleagues maintain, is "whether we have already crossed the safe zones of the Anthropocene operating space for biocide susceptibility." They propose three zones of increasing risk for pathogens—safe, uncertain, and surpassed—based on how many antibiotics are no longer effective against them (zero to all) and the availability of alternatives (many to none).

The result of this sorting is not heartening—"the Anthropocene operating space for antibiotic susceptibility [has been] globally surpassed for Gram-negative bacteria and in the uncertain zone for Gram-positive bacteria." This does not mean that every infection caused by Gram-negative pathogen is incurable, but that current methods of treating such infections frequently fail. Overall, "we are entering a new phase in which levels of multiple resistance and pan-resistance put the sustainability of current practices at increasing risk."[87]

This initial approach to antibacterial planetary boundaries will undoubtedly be reviewed and modified over time, but it is an important step toward integrating microbiology into our understanding of the Anthropocene.

The Gunfighter Illusion

In 1959, when the biochemical arms race between antibiotics and bacteria was heating up, the noted microbiologist and environmentalist René Dubos warned against a strategy that was entirely dependent on magic bullets.

The belief that disease can be conquered through the use of drugs fails to take into account the difficulties arising from the ecological complexity of human problems. It is an attitude comparable to the naïve cowboy philosophy that permeates the wild West thriller. In the crime-ridden frontier town the hero, singlehanded, blasts out the desperadoes who were running rampant through the settlement. The story ends on a happy note because it appears that peace has been restored. But in reality the death of the villains does not solve the fundamental problem, for the rotten social conditions which had opened the town to the desperadoes will soon allow others to come in, unless something is done to correct the primary source of trouble.[88]

Sixty years later, Dubos's warning seems remarkably prescient. The cowboy hero is mortally wounded, the desperadoes are stronger than ever, and the rotten social conditions remain.

Those who hailed the first antibiotics as miracle drugs were not wrong. What those chemicals could have been was a way to work with nature, to use natural processes to overcome diseases that had plagued us for thousands of years. Used with appropriate humility and careful stewardship, in conjunction with a global drive to eradicate the conditions that cause infectious diseases, penicillin and its successors could have been boons to humanity for centuries. But that would have required a radically different economy and society.

Instead, the new drugs were promoted and sold as high-volume commodities whose primary function was to generate fast profits. Pharmaceutical giants and manufacturers, doctors and private hospitals, pharmacies and more—at every stage, the profit-economy has pushed antibiotics for short-term gain, without regard for long-term effects. The expression *to kill the goose that lays the golden egg* has rarely been more appropriate.

Capitalism always operates in the short term and its defenders always insist that new technology will solve any problems that might arise. For several decades, antibiotics seemed to confirm that superstition—for every drug that stopped working, new ones were discovered. But that did not last. The early discoveries were low-hanging fruit and searching the higher branches has been hard and largely unsuccessful.

Mainstream economists like to claim that the market solves all—if there is a need, customer demand will produce solutions. But today, when bacteria have found ways to resist every available antibiotic, most pharmaceutical companies have abandoned the search for others. Not because new antibiotics would not be profitable, but because they would not be profitable *enough*. Big Pharma makes double-digit profits from drugs it sells for thousands of dollars a dose to patients who must take them frequently for many years. Antibiotics just do not fit that business model.

And yet, despite Big Pharma's responsibility for creating the crisis, many mainstream proposals for addressing the AMR crisis involve bribing pharmaceutical makers to get back into the business. With the excuse of correcting a "market failure," supposed experts urge governments to guarantee still more profits for the companies that have already made billions by hustling antibiotics into oblivion. As Amábile-Cuevas argues, such plans only illustrate the pervasive and destructive impact of free-market theology.

From the clinical side, free-market notions have only allowed antibiotic abuse, especially of broad-spectrum antibiotics that are good for business as they can be used against many diseases; the abandonment of antibiotic R&D, as there are other more profitable avenues for pharmaceutical research; and the immoral notion of the need for "incentives," including higher prices, to [lure] *big-pharma* back to the antibiotic business.

From the agricultural arena, which is the main antibiotic abuser, the only reasons for antibiotic usage are of financial nature, most particularly the massive use of antibiotics for "growth promotion." Agricultural use of antibiotics, of *all* antibiotics—not only those

without direct clinical use, must cease immediately, worldwide. This would prevent the further selection of resistant organisms within food animals, which in turn get into our foodstuff; and the release of antibiotics and resistant organisms in the many forms of waste these activities generate, that end up one way or another in the environment.…

Antibiotics and antibiotic resistance in the environment mark one of the many convergences of public health and ecology; in the end, both deal with the wellbeing of living organisms. Free-market theologies have their focus and faith at precisely the other end of the scale. While it may be permissible for free-market to decide whether a brand of cell phones or cosmetics prevail or not, environmental and health regulations must be completely detached from it. This may sound unrealistic, but our very lives depend on understanding it, and acting accordingly.[89]

To tackle antimicrobial resistance, we must rescue public health from profit-making corporations, but getting the profiteers out of medicine is only part of the solution. Massive damage has already been done by pharmaceutical pollution and it cannot be easily reversed. Natural selection has spread antibiotic resistance worldwide, but, so far, as we know, there are no counter-selection mechanisms that would remove resistance genes if antibiotic pollution stopped. Even if such a countervailing force does exist, it will not eliminate AMR quickly.

This means that the use of antibiotics—including any new ones that may be discovered—must be stringently limited to essential cases and all waste must be contained and destroyed. Agricultural use of antibiotics, except to treat specific diseases in individual animals, must be stopped—period.

Expropriating Big Pharma must be accompanied by a global campaign to eliminate the "rotten social conditions" that lie behind antibiotic overuse and misuse. For example, diarrhea is a major killer in the global South, claiming 1.1 million lives a year. The UK Review on Antimicrobial Resistance found that in just four countries (India, Indonesia, Nigeria, and Brazil), "close to 500 million courses of antibiotics a year are each year used to treat diarrhoea." The commissioners concluded that "with universal access to improved water and sanitation…this would be reduced by some 60 percent."[90]

As this example shows, antibiotic resistance is not simply a medical or biological problem; it is a social and economic crisis. While we can and should fight for clean water, sanitation, and primary health care as basic human rights, experience shows that such changes will be resisted by a system that measures the value of human lives in dollars and judges every reform by its effect on corporate profit.

Addressing AMR effectively will require a level of global effort and redirection of resources comparable to the fight against climate change, biodiversity loss, and other ecological crises that define the Anthropocene. If pharmaceutical business as usual prevails, the new epoch will be a time when few if any antibiotics work and bacterial evolution will remake Earth's life-support systems in ways we cannot predict.

Postscript

While this article was in production, the U.S. Environmental Protection Agency proposed to allow growers to spray as much as 650 thousand pounds of streptomycin a year on citrus trees in Florida, to combat citrus greening disease. That is nearly fifty times as much as the antibiotics humans use each year, but the Environmental Protection Agency has not studied how the spraying will affect antibiotic resistance, and there is no evidence that it would be effective against citrus greening.

Notes

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