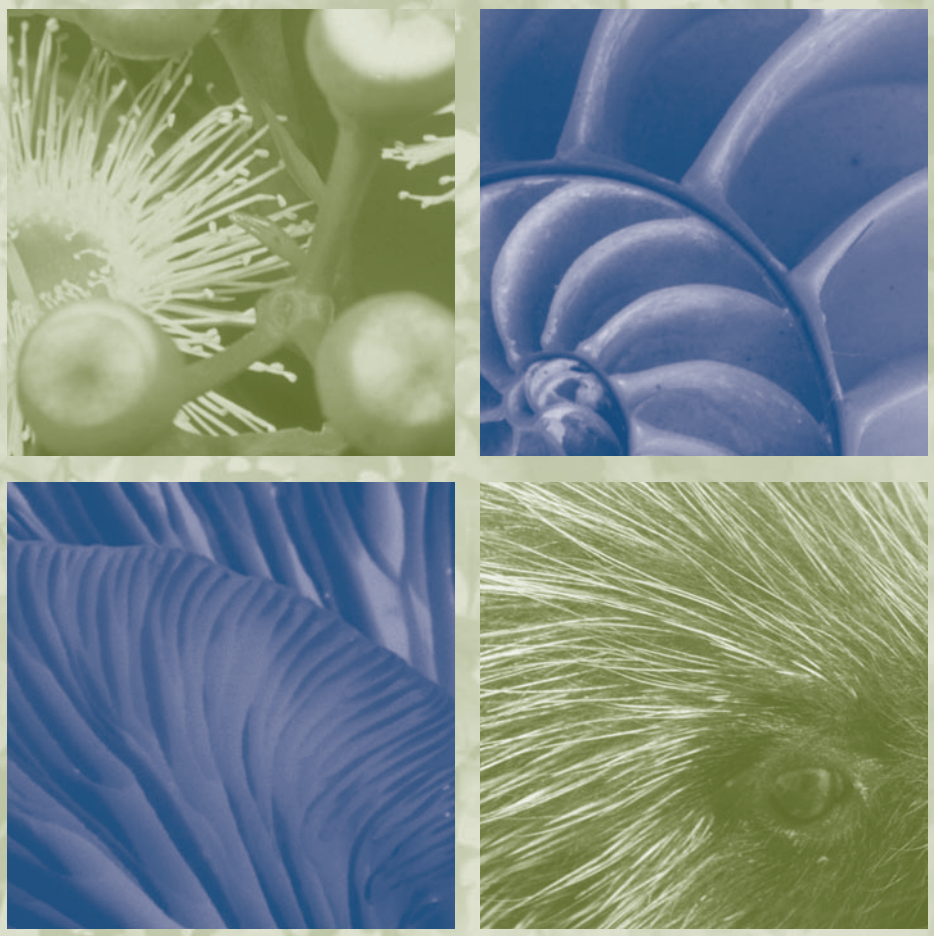
Evolutionary Science and Society:

Educating a New Generation



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Chapter 13

Evolution in Action:
Understanding Antibiotic Resistance

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Introduction

In the late 1990s, a two-year-old boy underwent a bone marrow transplant. Shortly after the transplant, he developed a bacterial infection in one of his surgical incisions. Doctors treated him with vancomycin, a powerful antibiotic effective against a broad range of bacterial infections. But this time, vancomycin did not work. After three days of antibiotic treatment, he was still sick and had a high fever. Doctors took a blood sample and found that the boy was infected with a strain of vancomycin-resistant *Enterococcus faecalis* (VRE). Fortunately, the bacteria proved to be sensitive to a different antibiotic, and two weeks later the child was fully recovered (Gray, Darbyshire, Beath, Kelly, & Mann, 2000).

Back in 1988, the antibiotic vancomycin had been the ultimate "silver bullet," virtually 100 percent effective against many species of bacteria. A decade later, more than a quarter of the patients in the intensive care wards of U.S. hospitals were carrying bacterial strains resistant to vancomycin. Worse yet, some of the strains could not be treated with any other drug!

What happened? How did a broadly effective drug stop working in a two-year-old boy, and in a large fraction of hospital patients in the United States and elsewhere in the world? And how can we keep our current generation of silver bullet antibiotics from suffering a similar fate?

Population Diversity and the Evolution of Antibiotic Resistance

To answer these questions, we need to understand how antibiotic-resistant bacteria arise, and how resistant strains spread through human populations. First, what do we mean when we say that a patient has an antibiotic-resistant infection?

In this section, we review the process of natural selection and explain how human use of antibiotics works to increase the frequency of resistant cells within bacterial populations, and, ultimately, the frequency of resistant infections in human populations.

Normal Flora and Bacterial Infection

As normal humans, we carry populations of bacteria on our skin and in our mouths and digestive tracts. These bacterial populations are called the bacterial flora. Some of these bacteria are commensal, meaning that they usually live on our skin or inside us without causing harm. Our skin and tear ducts are covered with *Staphylococcus epidermidis,* for instance.

Some of our bacteria are mutualists, meaning that they provide benefit to us, and we provide benefit to them. For instance, the *Bifidobacterium bifidum* bacteria in our intestines help to exclude other bacteria that could cause diarrhea. We reciprocate by eating, thus providing them an ample supply of carbohydrates. Indeed, when we are healthy, our guts are thought to be home to some 10^{14} bacterial cells, including *B. bifidum, Escherichia coli,* and *Bacteroides fragilis.* The body of a normal adult human is estimated to be made of 10^{13} to 10^{15} cells, so the bacterial cells in our bodies may actually outnumber our own cells (Berg, 1996)!

Most of our resident bacteria are harmless, so these large bacterial populations normally do not cause problems. But things can be very different when otherwise commensalistic or mutualistic bacterial cells find their way into parts of the body where they don't belong. *Streptococcus pneumoniae,* for instance, is a common resident of healthy people's noses. But it can also cause pneumonia if it finds its way into our lungs. Even worse, entry of *S. pneumoniae* into the normally bacteria-free cerebrospinal fluid that surrounds the spine is a common cause of bacterial meningitis, which is fatal in some 15 percent of cases (Centers for Disease Control and Prevention [CDC], 1997).

Bacterial infections can also be caused by pathogens, species that generally do not live in our bodies when we are healthy. Strep throat, for

instance, is caused by *Streptococcus pyogenes,* a relative of *S. pneumoniae. S. pyogenes* does not live in our throats when we are healthy, but can be transmitted to us by those who are already infected.

Fortunately, antibiotic treatment is often effective against both infections caused by friendly bacteria that have found their way into typically germ-free parts of the human body and infections caused by pathogenic bacteria that have invaded our throats and digestive systems. Before the 1941 introduction of penicillin—the first antibiotic prepared for clinical use—there was no easy way to treat ear infections and bacterial pneumonia. Infections with *S. pyogenes* often progressed to scarlet fever, a serious illness characterized by a skin rash and, in some patients, permanent damage to the heart and kidneys. Antibiotics changed this by vastly improving the odds of recovery from bacterial infection. Indeed, by some estimates, penicillin was responsible for saving the lives of thousands of World War II soldiers whose wound infections otherwise would have killed them.

Today there are approximately 100 different antibiotics in active clinical use. How, then, is it possible that many hospital patients continue to develop infections that cannot be treated with any drug?

Mutation

The answer lies in the biology of bacterial populations and in the process of bacterial evolution. Just like human students at a school, the bacteria in each of the populations that we carry are very similar in their morphology, physiology, and genetics. But there are some important differences between bacterial populations and human populations.

Human populations—such as the population of students at a school—typically form by assembly. Genetic similarities among the students exist because, despite the fact that most of the students have different parents, grandparents, and great-grandparents, all humans are descended from an ancient common ancestor.

By contrast, the bacterial populations that reside in our bodies are typically formed by immediate descent. One or a small number of cells invades a host, then divides to form two cells, each of which divides to form two more cells, each of which divides to form two more cells, and so forth. Through this exponential growth process, each founding cell eventually gives rise to a large population of closely related bacteria. Thus, the genetic similarities among the individual bacterial mutualists in our bodies exist because all members of that population descended from the cell—or small group of cells—that founded the population.

But descent from a single founding cell does not guarantee that all of the cells within a bacterial population are genetically identical to one another. Every time a bacterial cell divides to form two daughter cells, its genome must be copied. Since DNA replication is not ideally precise, cell division sometimes results in mutations, random changes to the DNA sequences of the descendant cells. Mutations are like typos. They arise entirely by chance, and entirely without regard to their impact on the fitness of the document in which they occur—be it a genome or a term paper.

Mutations can affect any of an organism's genetically encoded traits; the biological consequences of these mutations for the cells that carry them can range from inconsequential to catastrophic. For example, a mutation could change a cell's metabolic pathways, its ability to tolerate extreme temperatures, or the proteins that it secretes. Some mutations change the bacterial proteins that are often the targets of antibiotic treatment.

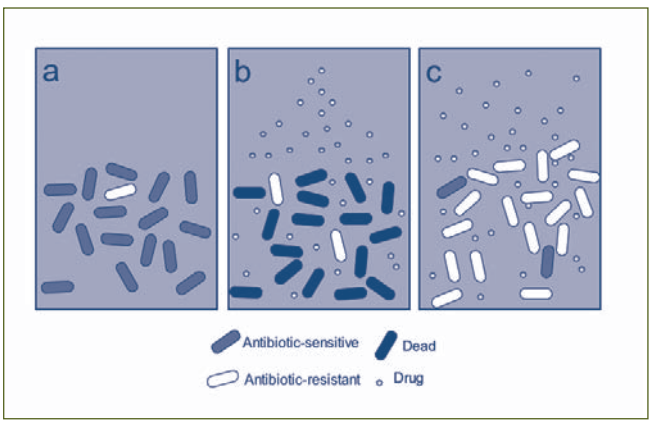

Figure 1. The evolution of resistance in the presence of antibiotics.
(a) Moderate mutation rates and large population sizes ensure the frequent production of mutant bacteria. In the absence of antibiotics, resistance typically imposes a fitness cost, and mutants do not increase in frequency. (b) Antibiotics create an environment in which resistant bacteria can divide faster than sensitive bacteria. (c) Resistant bacteria eventually come to dominate the population, and the infection can no longer be treated with the original antibiotic.

In a sense, mutations are not all that common. Biologists often talk about mutation rates—the frequencies of mutation per DNA site or per genome. Mutation rates often are around 2 x 10-3 events per genome per replication—that is, there is a 0.002 chance that a given genome replication event results

in a cell carrying a mutation. Those odds seem rather low, and it's not obvious why resistant mutations should arise so often.

But the mutation rate itself tells only half the story. As we mentioned above, bacterial populations are typically very large. A single gram of fecal matter contains between 10^{10} and 10^{11} bacterial cells! With populations so large, even seemingly small mutation rates are large enough to guarantee an ample supply of resistance mutations.

Selection

Some mutations are universally deleterious: they reduce a cell's ability to survive and reproduce, regardless of the environment in which they arise. For example, a mutation that interfered with a bacterium's ability to synthesize DNA would be catastrophic. A cell with such a mutation would be unable to replicate its genome and would be unable to pass its genome on to a daughter cell. A cell with such a mutation would not be able to reproduce in any environment!

But the effects of many mutations are contingent on the environment in which they occur. In a population of bacteria living in a 98.6° degree Fahrenheit human body, a cell bearing a mutation that increased cold tolerance would have no competitive advantage over cells that did not bear that mutation. Indeed, if the mutation increased cold tolerance at the expense of heat tolerance, it would be disadvantageous in a warm environment. Its bearer would reproduce more slowly than would cells without the mutation, and thus would be eliminated by natural selection.

By contrast, if the exact same mutant arose in a population of bacteria growing in a carton of leftovers at the back of your refrigerator, its fate would be quite different. By enabling a cell to reproduce at a higher rate, the cold-tolerance mutation would increase in frequency, and would eventually come to dominate the population. In the leftovers, the cold-tolerance mutation would increase in frequency; in the human body, that very same mutation would be removed from the population by natural selection.

Now consider a random mutation that changes a bacterial protein required for a certain antibiotic to enter cells of its target bacterial species. The antibiotic would not be able to enter a mutant cell and interfere with protein synthesis. Like a cold-tolerance mutation in a warm environment, an antibiotic-resistance mutation would confer no selective advantage to a cell in a host not using antibiotics. Indeed, if the drug-resistance mutation encoded a protein useless for anything other than antibiotic resistance, it might sap energy from other essential processes, thereby impairing its bearer's capacity to survive and reproduce. Thus, in a patient not taking antibiotics, random mutations conferring antibiotic resistance would fail to increase in frequency.

The fate of this same drug-resistance mutation would be very different in a patient using antibiotics. In this case, the cell bearing the mutation would be able to reproduce in the presence of the antibiotic. In contrast, the wild-type drug-sensitive cells would either fail to reproduce or die in the presence of the drug. Ironically, drugs designed specifically to kill bacteria that cause infection end up selecting for bacteria that both cause infection and do not respond to antibiotic treatment.

Frequency Change: Consequences of Mutation and Selection for Bacterial Populations

Once a growth-enhancing mutation arises in a bacterial population, it quickly rises to high frequency. It is said to become fixed in the population when its frequency becomes effectively one. Since many bacterial cells divide as often as once per hour, it often doesn't take long for resistance mutations to achieve high frequencies.

Consider, for example, a drug-resistance mutant able to divide twice as quickly as wild-type cells in the presence of an antibiotic. If this mutation first arose when the wild-type population was composed of 10,000 cells, its initial frequency in the population would be 1/10,000. Over the next 24 hours, the sensitive lineage would go through 24 generations, resulting in 1.7×10^{11} sensitive cells. But over that same 24-hour period, the resistant lineage would go through 48 generations, resulting in 2.8×10^{14} resistant cells. In a single day, then, natural selection could drive a mutant with a twofold growth rate advantage from a frequency of 0.01 percent to a frequency of 99.9 percent!

A patient carrying a population of disease-causing bacteria in which 99.9 percent of the cells were resistant would not get better in response to antibiotic treatment and would be diagnosed with a resistant infection.

From Resistant Mutations to Resistant Infections

But how does the emergence of a drug-resistant mutant in just one or a few patients lead to resistant infections in many other individuals? The answer lies in the patterns of human antibiotic use. Antibiotic use by humans can be divided into two broad categories: antibiotic use for human health purposes, and antibiotic use in raising livestock. We describe these in turn and discuss their significance for the evolution of antibiotic resistance.

Antibiotic Resistance in Hospitals

Antibiotics are used widely for human health, both as drugs prescribed to outpatients and within hospitals. Antibiotics are used at the highest frequencies in hospitals, and this is where many resistant strains of bacteria first arise. Let us look at this process in further detail.

In hospitals, antibiotics are widely used both to treat preexisting bacterial infections and to prevent surgical incisions from becoming infected. Antibiotics rid patients of their normal, friendly bacterial populations, protecting most from surgery-associated infections. However, due to random mutation, a subset of these people are, by chance, carrying drug-resistant bacterial cells when they first enter the hospital.

Antibiotic treatment eliminates most or all of the sensitive bacterial cells from these patients. Freed from competition with these sensitive strains, drug-resistant cells can rise to high frequency.

For an individual patient, emergence of antibiotic resistance is bad news. If her surgical wounds become colonized by the resistant strain, clearing the infection can be very difficult. A fair number of hospitalized patients die as a result of resistant infections (Hsu & Chu, 2004).

But a patient with a resistant strain is also bad news for the other patients. Through no fault of her own, a hospitalized patient may not keep resistant strains to herself. Medical staff often visit multiple patients without washing their hands, clothing, and equipment (Stone, Teare, & Cookson, 2001). As a result, health care workers often serve as vectors, carrying resistant strains from infected patients to patients whose normal, drug-sensitive flora have been killed by antibiotic treatment. Resistant strains encounter no competitors in these flora-free patients and easily establish new, resistant infections.

Transmission of resistant strains among hospitalized patients accounts for a large fraction of new resistant infections. Patients who might otherwise have recovered from surgery with very few complications sometimes acquire resistant infections that significantly prolong their hospital stays. Moreover, hospital patients carrying resistant bacteria sometimes transmit those resistant strains to family members. As a result, resistant strains that evolved in the hospital sometimes escape into the community.

The Emergence of Antibiotic Resistance in Agriculture

Some of the drug-resistant strains that threaten public health arise first in livestock and are only secondarily transmitted into the general human population. Farmers often use antibiotics to increase the growth rate of animals raised to produce dairy, egg, and meat products for human consumption. Indeed, it is estimated that each year some 24.6 million pounds of antibiotics are used in healthy animals in the United States (Union of Concerned Scientists, 2001). An additional 2 million pounds are used to treat sick livestock. Just as with humans in the hospital, antibiotic use leads to increases in the frequency of resistant strains within a single farm animal—and this ultimately results in an increase in the frequency of resistant infections in the livestock population at large.

Unfortunately, the antibiotic-resistant lineages that become common in livestock do not remain confined to livestock. They find their way into hospitals and the community by two main routes.

First, infected farmworkers can transmit resistant lineages to hospitalized patients, should they themselves ever enter the hospital. Alternatively, just as healthy physicians can transmit resistant strains among patients, healthy farmworkers can transport resistant lineages home to their families and other contacts.

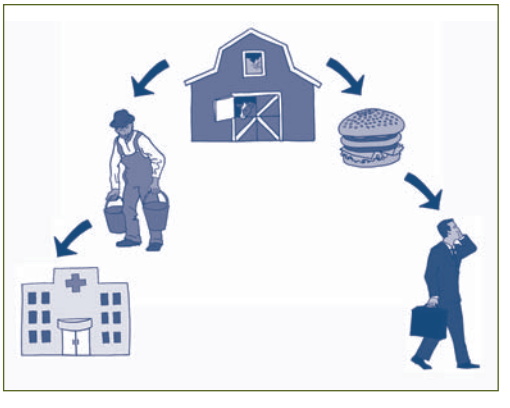

Figure 2. How resistant bacteria travel from livestock to humans. (Illustration: Matina Donaldson)

Animal products marketed for human consumption provide another mode of transmission of resistant lineages. In one Irish study, some 70 percent of chilled, dead chickens available for sale at a local grocery store were found to harbor *Salmonella* species resistant to at least one antibiotic. Data from the local human community suggest that many of these strains find their way from colonized food products into human consumers: resistant *Salmonella* lineages were found in 84 percent of fecal isolates from humans in the neighborhood where the chickens were purchased (Wilson, 2004).

While bacteria on food products are often eliminated by the high temperatures involved in cooking, inadequate hand washing (Hillers, Medeiros, Kendal, Chen, & DiMascola, 2003) and consumption of raw products can enable transmission of these resistant strains from livestock to humans, paving the way for cases of drug-resistant food poisoning. Even fruits and vegetables can become covered with drug-resistant bacteria, perhaps through the fertilization of fields with manure from antibiotic-treated livestock. In one study, 34 percent of *Enterococcus* isolates from produce raised in the southeastern United States were antibiotic resistant (Johnston & Jaykus, 2004).

How Mutations Produce Resistance to Antibiotics

As noted above, antibiotic resistance can emerge by natural selection only when some individuals in the population harbor genes that encode resistance and increase their bearers' fitness in the presence of antibiotics. Here we discuss two typical sources of resistance genes: point mutation and lateral gene transfer.

Origin of Resistant Alleles by Point Mutation

In some cases, it takes only one or a very few point mutations to produce antibiotic resistance. Macrolide resistance provides a striking example. Macrolide antibiotics are commonly used to treat bacterial infections of the skin and respiratory tract, including the chronic *Pseudomonas aeruginosa* infections typical in cystic fibrosis patients, whose impaired lungs make them unable to clear the bacteria. Many people who grew up in the United States have used erythromycin, a macrolide that is commonly prescribed to treat ear infections in children.

Macrolides work by binding to the 23S of bacterial ribosomal RNA. Ribosomal RNA is used to makes proteins; binding of the antibiotic interferes with this process and prevents the bacterium from producing functional proteins. Since proteins are required for everything from metabolism to DNA replication, interfering with protein synthesis is a reliable way to kill a bacterium.

Unfortunately for humans—though quite fortunately for bacteria—macrolide resistance can arise by mutation of a single nucleotide in the gene that encodes the 23S ribosomal RNA. That's bad news, given the high rate at which mutations arise in bacterial populations. What's more, there are at least nine different nucleotide sites that confer nearly identical degrees of resistance to these drugs. This large number of targets increases the probability that mutation will result in a resistant mutant.

Acquisition of Resistance Genes by Lateral Gene Transfer

From the bacterial perspective, point mutation is a convenient source of resistance alleles, particularly those that function by modifying drug-binding sites. However, point mutations are not always the most efficient route to resistance. For protection against some drugs, bacteria use more-complex resistance mechanisms. They deploy molecular efflux pumps to actively remove antibiotics from the cytoplasm. They modify cell wall structure to prevent antibiotics from entering the cell. They use alternative metabolic pathways to work around the pathways that antibiotics disrupt. Some bacteria even secrete enzymes that actively destroy antibiotics! These are broad scale changes involving complex mechanisms and are not likely to arise from one or a few point mutations. What is the source of this kind of resistance?

When more complex mechanisms are in order, bacteria often gather and appropriate existing mechanisms, rather than reinvent the wheel. To this end, bacteria often swap genes with other bacteria of the same species, or even of different species. This cell-to-cell sharing of genetic information—a sort of prokaryotic Napster—allows bacteria of one species to take up resistance genes that have evolved in other species.

These *laterally transferred genes* are often transported on plasmids, self-contained, extrachromosomal circular DNA fragments that can be transmitted from one bacterial cell to another. Once these plasmids enter a bacterial cell, they are used to encode proteins such as efflux pumps, cell surface receptors, and drug-degrading enzymes—all of which can

protect a cell against antibiotics. One of the most common plasmid-transferred resistance mechanisms involves *Beta*-lactamase, an enzyme that bacteria can secrete into the environment in which they live. *Beta*-lactamase degrades penicillin, methicillin, and other antibiotics in the *Beta*-lactam family. Plasmids bearing the *Beta*-lactam gene are commonly found in methicillin-resistant *Staphyloccocus aureus* (MRSA) infections that typically occur in the skin and in the surgical wounds of hospitalized patients. Just as with point mutations, the fate of a plasmid-borne antibiotic-resistance gene is critically dependent on the environment in which it arises. Certainly, a bacterium carrying a drug-resistance plasmid enjoys a growth advantage in the presence of an antibiotic. But for many bacterial lineages, carrying plasmids is costly, meaning that plasmids themselves actually decrease the growth rate when the antibiotic is not present. So—just as for a cold-tolerance mutation in a warm environment—the fate of a bacterium carrying a novel drug-resistance plasmid depends heavily on whether or not drugs are present.

Other laterally transferred genes are passed among bacterial lineages without using a plasmid vector. Recipient cells integrate these genes into their own chromosomes and use them to encode drug efflux pumps and other proteins that protect against antibiotics. Once foreign DNA becomes integrated into a chromosome, it travels a trajectory similar to that of a point mutation: cells with the new, laterally transferred gene enjoy a growth advantage in the presence of antibiotic and quickly come to dominate the population.

The Ancient History of Antibiotic-Resistance Genes

These laterally transferred resistance genes had to get their start somewhere. What is the original source of the resistance genes that are sometimes transferred into disease-causing bacteria?

To answer this question, we have to understand the natural ecology of antibiotics. Humans initiated the pharmaceutical use of antibiotics only 70 years ago. But we were by no means the first to use these drugs: some bacterial and fungal species started making and using antibiotics long before humans appeared.

Like humans, bacteria and fungi benefit from excluding some bacterial species from their tissues and their habitats. Soil bacteria and fungi often live together in highly structured environments. Since these species typically are not mobile over large distances, the only nutrients available to them are the ones present in their immediate locale. Close quarters and immobility lead to scarce nutrients and stringent competition.

Some species have responded to this competition by evolving chemical warfare agents to exclude other species. The majority of antibiotics used by humans come from these microbial inventions. For instance, the tetracycline, streptomycin, neomycin, and chloramphenicol in clinical use today all originated in *Streptomyces,* a genus of soil bacterium that forms long, sporelike structures and produces the compounds responsible for the earthy smell of damp soil. On average, 50 percent of *Streptomyces* isolates produce antibiotics toxic to other species identified in the immediate area; some lineages produce several chemically dissimilar drugs. (Madigan, Martinko, & Parker, 2000).

Indeed, antibiotics first became known to humans in 1928, when British researcher Alexander Fleming found a fungus that prevented bacterial growth on a petri dish. Fleming famously summarized the ultimate evolutionary origins of antibiotics: "Nature makes penicillin," he wrote, "I just found it."

Not surprisingly, the evolution of antibiotics and the evolution of antibiotic-resistance genes went hand in hand. Bacteria producing antibiotics would enjoy no net benefit if their antibiotics killed both competitors *and* themselves. As a result, bacteria are typically resistant to the antibiotics they produce. *Streptomyces* bacteria, for instance, often carry several genes that enable them to resist the antibiotics that they themselves produce. To discover the ancient histories of many antibiotic-resistance genes, we need look no further than the microbes that invented antibiotics in the first place.

Vancomycin provides a compelling if troubling example. As mentioned in the introduction, vancomycin was, for several decades, the silver bullet antibiotic of last resort. In the 1980s and 1990s, however, vancomycin-resistant infections with *Enterococcus faecalis* became a frequent—and sometimes fatal—problem for hospitalized patients.

Vancomycin resistance in *E. faecalis* is conferred by a cluster of three genes that encode protein variants that vastly decrease the ability of vancomycin to bind to the cell surface of *E. faecalis*. As vancomycin

resistance became a significant health problem, researchers began to look for the source of these laterally transferred genes. The culprit donor turned out to *Amycolatopsis orientalis,* a nonpathogenic soil microbe that naturally produces vancomycin.

Inventing New Antibiotics

One way that we can deal with antibiotic resistance is to invent new drugs to which bacteria are not resistant. While this approach may be effective on the short term, bacteria catch up rapidly.

Time and again, we have invented and deployed new antibiotics to deal with the evolution of resistance to an existing antibiotic. Each time, bacteria have quickly evolved resistance to the new antibiotic—and we have been forced to develop yet another new drug. Figure 3 shows one such sequence of events. In the 1960s, physicians began using the antibiotic methicillin to treat bacteria that had evolved resistance to the widely used macrolide antibiotics. By the 1980s, methicillin-resistant bacteria were very common in hospitals. To deal with these methicillin-resistant strains, physicians started using a new antibiotic, vancomycin. But after a few years of using vancomycin to treat methicillin-resistant strains, bacteria evolved vancomycin resistance.

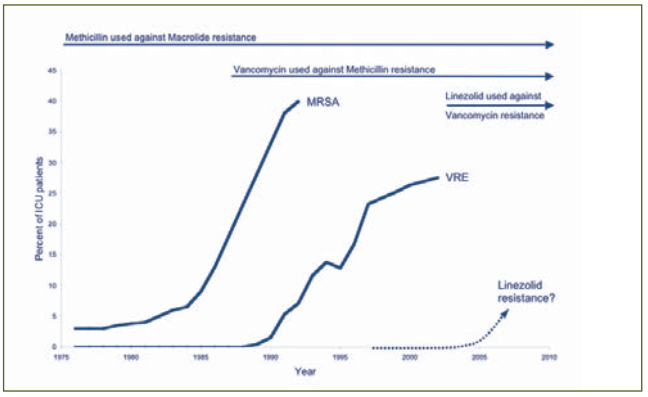

Figure 3. Antibiotic use and evolution of resistance in U.S. hospitals. Solid lines: percentage of hospital-acquired *Enterococci* strains resistant to vancomycin (VRE) and percentage of hospital-acquired *Staphylococcus* aureus strains resistant to methicillin (MRSA) in large hospitals. Dashed line: linezolid resistance is expected to increase in the near future. (VRE and MRSA data are from the National Nosocomial Infections Surveillance [NNIS] System; the curve for linezolid resistance is a projection.)

When it became clear that vancomycin was no longer the cure-all many had hoped for, researchers worked to develop a drug that could treat vancomycin-resistant infections. One such innovation was linezolid, the first of an entirely new class of antibiotics that inhibit protein synthesis. But linezolid may go the way of the macrolides, methicillin, and vancomycin before it. In 2002, a 41-year-old woman with leukemia took vancomycin to treat a *Klebsiella pneumoniae* infection. She soon developed sepsis, a very dangerous blood infection, and it became clear that the infection was vancomycin resistant. Physicians then resorted to linezolid—the new drug of last resort. The woman died before a bacterial culture confirmed what her doctors feared: she was infected with a strain that had evolved resistance to linezolid (Potoski, Mangino, & Goff, 2002). Based in part on this experience, many disease experts now expect that we will face a similar rise of linezolid resistance in the relatively near future.

Reducing Antibiotic Use

If inventing new antibiotics will not solve the problem indefinitely, what can we do? Are there other ways to decrease the incidence of resistant infections?

As mentioned above, many of the resistance genes that promote growth in the *presence* of antibiotics also reduce growth rates in the *absence* of antibiotics. For at least some forms of resistance, then, reducing antibiotic use would enable us to create an environment in which sensitive mutants divide faster than their resistant competitors.

But can we reduce antibiotic use without dire effects on human health? As a patient, it would certainly be hard to stomach the idea of not taking antibiotics to treat a persistent bacterial infection. And it would be unthinkable to withhold treatment from a hospital patient suffering from a potentially fatal infectious disease.

Fortunately, there are plentiful opportunities to decrease the incidence of infectious disease without threatening the lives of individual patients. We can encourage medical staff and their patients to avoid using antibiotics for colds and other infections of viral origin; antibiotics are useless against viruses anyway. We can also encourage physicians to use narrow-spectrum antibiotics—drugs that affect only a few species of bacteria instead of many species—whenever possible. This limits the extent of natural selection for antibiotic resistance. Each of these strategies will help conserve antibiotic efficacy for infections for which there is no alternative treatment strategy.

Putting Resistance into Perspective

Antibiotic resistance is scary, and it poses a significant threat to human health. Nonetheless, it is

important to maintain perspective on the magnitude of this threat. Antibiotics help us treat many bacterial diseases and facilitate invasive surgeries by reducing the chance of infection. Still, they are not principally responsible for our contemporary freedom from the great plagues humankind faced in the 14th century, or from the burden of the infectious diseases that were rampant in American cities during the late 19th century.

Figure 4 illustrates the rate of infectious disease mortality—the number of individuals per 100,000 Americans who died of infectious diseases each year—from 1900 until 1996 (Armstrong, Conn, & Pinner, 1999). At the turn of the 20th century, nearly 800 per 10,0000 Americans died each year of infectious diseases. By 1996, despite the rise of AIDS, this mortality rate had dropped more than tenfold to roughly 60 infectious disease deaths per 100,000 people per year. This is a tremendous improvement—but notice that most of this change cannot be attributed to the deployment of antibiotics! By 1940, infectious disease mortality had already dropped to about 210 deaths per 100,000 people per year. Antibiotics did even not become available for clinical use until 1941!

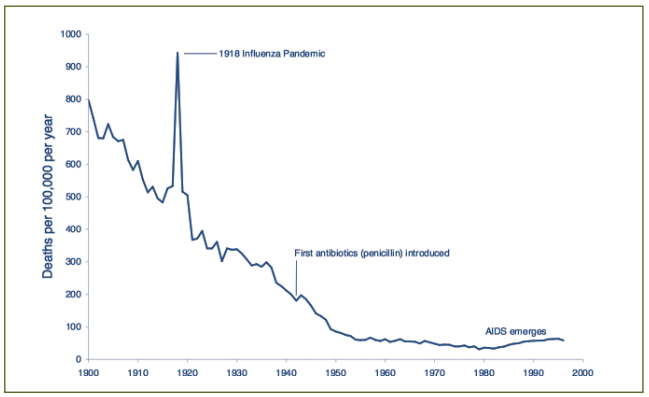

Figure 4. Infectious disease mortality in the United States across the 20th century. (Redrawn from Armstrong, Conn, & Pinner, 1999)

What accounts for the rapid and substantial decline in infectious disease mortality in the United States before 1941? Much of this decline resulted from innovations in disease prevention, rather than from the development of new drugs. Foremost among these preventative innovations was the germ theory of disease, first championed by Louis Pasteur and Robert Koch in the 1850s. Pasteur and Koch recognized that much of human disease was due to the transmission of infectious agents. Germ theory inspired a number of pivotal technologies in health care, such as surgeons' use of masks and obstetricians' hand washing before delivering babies. Improved sanitation, including indoor plumbing and running water, also helped decrease the transmission of infectious disease. Innovations in food handling and preparation—most notably refrigeration and pasteurization, both implemented widely in the United States during the first half of the 20th century—reduced foodborne disease transmission. Huge improvements in nutrition followed the discovery of the key role of certain minerals in the human diet, including iodine and vitamin D (CDC, 1999). Better nutrition produced a tremendous decline in the proportion of the American population that was chronically malnourished and therefore highly susceptible to infectious disease.

Thus, on the one hand, even if we do at some point lose the race against antibiotic-resistant bacteria, we should not expect to be plunged back into a dark age where plagues ravage entire countries and infectious disease mortality climbs upward of 30 percent per year during the worst of epidemics. On the other hand, antibiotics are crucial components of modern medicine, both because they help treat existing infections and because they enable us to perform surgeries without overwhelming risk of life-threatening infection. Without antibiotics, operations that today seem simple could again become significantly more complicated and considerably more dangerous. Such are the stakes we face in what is literally a battle against evolution.

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