# 1 Antibiotics: What Are They?

## WHY IS THERE STILL SOME CONFUSION?

Nowadays, nearly everyone has heard of antibiotics. In fact, most people even have had firsthand experience using them at some point in their life. Whether they were prescribed antibiotics to treat strep throat as a child, or they used an antibiotic cream to manage their teenage acne, or they simply applied an antibiotic ointment to a skin abrasion—the use of antibiotics to treat and prevent infection has become a ubiquitous part of our everyday lives.

However, despite their widespread use, there remains significant confusion regarding several aspects of how antibiotics work and when they should be used. Many patients still ask their doctors: "Why can't I have antibiotics to cure my cold?" or "Why don't antibiotics work against infections like flu or COVID?" And while more informed individuals will know that antibiotics are drugs that specifically target bacteria by inhibiting their growth or outright killing them, these people are then puzzled when doctors sometimes prescribe antibiotics for patients hospitalized with viral infections. What they may not realize is that those doctors are doing so not to directly treat the virus but to prevent secondary infections of bacterial pathogens in individuals with viral-weakened immune systems. Unfortunately, many patients in this situation do not understand why they are taking antibiotics, thinking either that the doctor is just humoring them or, worse, that the antibiotics will actually kill the virus. When these individuals

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subsequently go on social media and spread their incomplete understanding, they sadly end up just eroding the general trust in the medical community.

Further confusion arises when discussing antibiotic resistance. After all, what exactly is antibiotic resistance? Most people correctly recognize that antibiotic resistance means that antibiotics are becoming less effective. However, to many, it is not obvious that antibiotic resistance refers to the bacteria becoming resistant to the drugs rather than individual people becoming resistant to treatment. After all, there are some people who have developed allergies against certain families of antibiotics (e.g., penicillins or macrolides). So in a sense, the misunderstanding is not completely unfounded, as some people's bodies do reject or "resist" these antibiotics. Ultimately, the real challenge is that the two different understandings of the issue have very different implications for what policies, if any, limiting antibiotic usage need to be implemented. If the bacteria are developing resistance, then it makes sense to have antibiotic stewardship policies that limit antibiotic use. However, if resistance occurs only in certain individuals, limiting the use of an antibiotic in one patient will not change the efficacy of that antibiotic when treating someone else.

Perhaps the most problematic source of confusion stems from the dissonance between what people hear from media and what they tangibly experience. Starting in the mid-1990s, stories about antibiotic-resistant bacteria suddenly started appearing everywhere. True to sensationalist form, or perhaps because of a lack of understanding of the problem, the press portrayed what was really a slowly developing, insidious trend to be a galloping crisis. Alarming headlines cautioned against the "Looming antibiotic crisis" and feared the "Return to the pre-antibiotic era on the horizon" and "Superbugs on the march." Writers of such stories conveyed the impression that doom was imminent. Yet 30 years later, antibiotics are still a routine part of our lives. Outside of medical and research circles, one could even be fooled into not knowing there was a problem. A big part of this perception stems from the fact that although many health organizations around the world have declared antimicrobial resistance and the emergence of pan-resistant bacteria ("superbugs") to be an urgent *global* public health threat, thus far antibiotic resistance has disproportionately impacted low- and middle-income countries. However, citizens of the developed world are now realizing that they are no longer safe in their ivory tower, as more recent news headlines make clear: "The superbug that doctors have been dreading just reached the U.S." (*Washington Post*, 2016); "Woman killed by a superbug resistant to every available antibiotic" (*Scientific American*, 2017); "Killer superbugs are coming for you" (*Los Angeles Times*, 2019); and "Drug-resistant infections in hospitals soared during the pandemic" (*New York Times*, 2022). Indeed, American organizations, such as the Centers for Disease Control and Prevention (CDC), the National Institutes of Health, and the American Society for Microbiology, have all joined the World Health Organization (WHO) in undertaking major initiatives to

combat antibiotic resistance, including making significant investments in research funding, advocating for policy changes, and creating community outreach and educational programs.

The antibiotic resistance crisis truly is no longer some vague looming threat. We are experiencing it now. The only reason we have been able to keep our heads above water is the collective effort over the last couple decades by academic researchers, industry scientists, and health care workers to mitigate its effects. But unfortunately, we stand now on the brink of losing our ongoing battle against antibiotic resistance. Our ability to discover new antibiotics to replace those lost due to the rapid spread of antimicrobial resistance is simply not keeping up. For example, the rates of resistance to ciprofloxacin, a drug commonly used to treat urinary tract infections, are as high as 93% for *Escherichia coli* and 79% for *Klebsiella pneumoniae* in many parts of the world. *K. pneumoniae* is a major cause of life-threatening hospital-acquired pneumonia and sepsis (bloodstream) infections in newborns and intensive-care unit patients, and it is already resistant to many commonly used antibiotics. Until recently, carbapenem antibiotics were the last-resort antibiotic for treatment of infections by this multidrug-resistant bacterium, but now in some countries even carbapenem antibiotics no longer work in over 50% of patients. Likewise, the WHO reports an estimated half million new cases of infection per year with antibiotic-resistant *Mycobacterium tuberculosis*, of which the vast majority are resistant to the two best anti-tuberculosis drugs. These examples are just the tip of the iceberg. We will revisit these multidrug-resistant pathogens and others in later chapters.

Unsurprisingly, multidrug-resistant infections are extremely deadly. Less than 60% of multidrug-resistant tuberculosis infections are successfully cured. Similarly, patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections are 64% more likely to die compared to those infected with antibiotic-sensitive bacteria. Patients who are immunocompromised are particularly vulnerable since antibiotic treatment is the only hope of controlling the infections they might acquire. Accordingly, young children and newborns are especially susceptible to antibiotic-resistant bacteria because they do not have fully developed immune systems needed to fight off such infections.

In the constantly changing landscape of scientific and technological advancements, it can be hard to keep up with an ever-evolving understanding of the biological threats impinging on our well-being and the strategies currently available for us to combat them. Misunderstandings due to seemingly conflicting information can be amplified by unfiltered social media to the point that even researchers and medical professionals sometimes get things mixed up. Our goal in writing this book is to help demystify the current understanding of antibiotics and how they work and to resolve some of the confusion surrounding antibiotic resistance.

To this end, let us begin with some foundational information about microbes and a few relevant definitions about antibiotics. In the following chapters, we will try to paint a picture of what life was like before the advent of antibiotics to highlight the impact their introduction had. We will then provide an overview of how antibiotics work, how bacteria have gained resistance, and our current efforts toward combatting this resistance.

## WE LIVE IN A MICROBIAL WORLD

Throughout most of Earth's history, life has predominantly been microbial in form. Bacteria were the first life forms to emerge on Earth. They ruled the planet for over 3 billion years before insects, plants, and animals began to appear (Fig. 1.1). During that period, they colonized every part of the world, from the deepest oceans to the highest mountains. They can be found under ice in the Arctic and Antarctic regions. They can be found in boiling hot springs, in nuclear wastes, and as far underground in the land masses as humans have been able to dig. They have even been found in clouds and inside rocks. They survived the volcanic era of Earth's early days, as well as periodic fluctuations in temperatures ranging from ice ages to modern global warming conditions.

Animal- and human-associated microbes comprise an insignificant fraction of the global microbial population. There are roughly 7.5 billion people on Earth, so with an average of about $4 \times 10^{13}$ associated microbes (mostly bacteria) per adult human, there are roughly $3 \times 10^{23}$ human-associated microbes. By comparison, estimates place the total number of microbes on Earth at roughly $5 \times 10^{30}$—that is about 10 million for every 1 microbe in a person. On top of that, most of the microbes associated with humans are either neutral or benign to people. We live normally with these microbes in and on our bodies without any adverse effects or infections. Taking everything into consideration, only a minuscule portion of microbes actually cause infections; that is to say, only a tiny number of bacteria are pathogens.

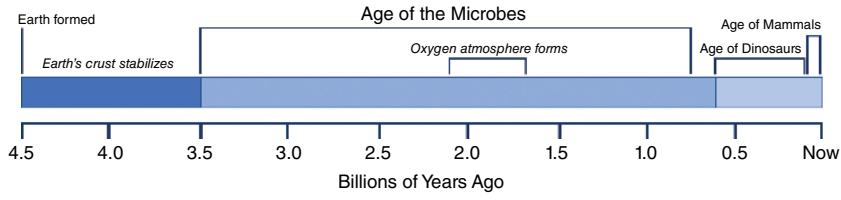


**FIGURE 1.1** *The history of life on Earth is dominated by microbial life.*

Our bodies' defenses are remarkably effective in preventing the microbes that we encounter from causing disease. But, alas, nothing is 100% effective. In addition to some microbes having developed ways to circumvent our defenses, breaches in these defenses, such as open wounds, surgery, or cancer chemotherapy, can leave the body temporarily vulnerable to invasion. One of the greatest advances in human health during the past century was the discovery that our natural immune defenses could be augmented with externally applied chemical defenses in the form of antiseptics, disinfectants, and antibiotics.

## HOW DO ANTIBIOTICS DIFFER FROM ANTISEPTICS AND DISINFECTANTS?

There are many different chemical compounds that we use to kill or inhibit the growth of microbes, including bacteria, fungi, protozoa (parasites), and viruses. We refer to these compounds with broad killing or inhibiting activity as *antimicrobials*. These chemical agents can be obtained from natural sources (e.g., alcohols, natural acids like vinegar, or toxic metabolites) or they can be artificially produced (e.g., chlorine, iodine, bleach, detergents, and synthetic drugs). Antimicrobials that target only a subset of microbes have more precise names. For example, antimicrobials primarily targeting fungi are called *antifungals*; those that target parasites are *antiparasitics*; those that target viruses are *antivirals*; and those that target bacteria are called *antibacterials*. Although *antibiotic* was originally another word for antimicrobial, for a long time most antibiotics produced commercially or used in medicine specifically targeted only bacteria. Therefore, colloquially, the term *antibiotic* has come to be used interchangeably with *antibacterial*. Accordingly, in this book, we will use the term *antibiotic* to refer to antimicrobials that target bacteria.

So, how do antibiotics differ from disinfectants and antiseptics? Antimicrobial agents that fall into the category of *disinfectants* or *sanitizers* are very harsh chemicals that can only be used externally on inanimate objects or surfaces. These agents prevent infection by reducing the number of microbes that have access to vulnerable areas like cuts or surgical wounds. For example, household bleach, strong acids like hydrogen chloride, and alkylating agents like ethylene oxide are too harsh for human use and therefore are limited to use on nonbiological objects or surfaces. *Antiseptic* or *germicide* is the term used to describe antimicrobial compounds that are less harsh and can be applied to body surfaces. For example, antiseptic hand sanitizers used in hospitals and doctors' offices can be applied to skin. Additional antiseptics are triclosan (an ingredient once commonly used in antibacterial toothpaste, cosmetics, chopping boards, toys, and soaps), dilute hydrogen peroxide solutions, and mercury derivatives such as mercurochrome.

Some compounds, such as iodine and quaternary ammonium compounds (cationic detergents), fall into both categories, depending on the concentrations used and length of exposure.

Antiseptics and disinfectants are generally nonspecific in their killing power and tend to attack multiple targets in microbes. For example, iodine, chlorine, and hydrogen peroxide are strong oxidants that can inactivate many microbial proteins and damage microbial DNA. Similarly, antiseptics that target microbial cell membranes, such as quaternary ammonium compounds, insert themselves into cell membranes, causing cells to leak out vital ions and other small molecules. Unfortunately, these compounds do not act only against microbes—they can damage human cells, too. Therefore, when they are used on humans, their use is limited to topical application in areas where the outer layer of skin consists of dead cells that are unaffected by their toxic activities.

What distinguishes antibiotics from antiseptics and disinfectants is that antibiotics act in ways that are specific for bacteria, and not as general toxins that harm both the bacteria and the human body. The revolutionary feature of antibiotics is that they are designed to be devastating for bacteria but have few if any adverse effects on the human body. Because antibiotics are antimicrobials that are safe to ingest or inject into the body, antibiotics became extremely important for curing and preventing infections. Consequently, they have been touted as the "miracle drugs" of modern medicine. Surgeries and many other invasive medical procedures would not be possible without antibiotics. We will further discuss the vital role of antibiotics in modern medicine in chapter 2.

## HOW DO ANTIBIOTICS DIFFER FROM VACCINES?

When we are exposed to bacteria, and especially if those bacteria invade our body, our immune system will attack the bacteria and try to remove them. However, for most disease-causing bacteria, a naïve immune system can take a week or more before sufficient antibodies can be made to mount an adequate immune response. Unfortunately, by that time the invading bacteria will have already caused considerable tissue damage or even death. Using antibiotics can kill the pathogenic bacteria or at least inhibit their growth and replication long enough for the immune system to recognize the invaders and deal with them. The decisive advantage of using an antibiotic is the clearance of the pathogens from the body and a more rapid recovery from the symptoms they caused during the infection, reducing the necessary recovery time from a couple of weeks to a few days.

Vaccination is a related strategy for preventing infectious diseases. It also relies on the immune system for pathogen clearance, but instead of stalling the pathogen until a proper immune response can be mounted, it aims to accelerate the immune

response itself. Vaccines work by exposing the immune system to specific structures found on infectious microbes to prime the immune cells to attack those microbes when they are detected in the future. As soon as the priming structures are recognized in the body, the immune cells are stimulated to produce antibodies that facilitate the elimination of the pathogen. This priming enables the full immune response to be mounted within hours rather than days.

Altogether, general cleanliness achieved by using disinfectants and antiseptics and bolstering of the immune system through vaccination are usually sufficient to form an effective bulwark against infectious disease. However, when these preventative measures fail and infection takes hold, because antibiotics are both safe to use in the body and effective during an ongoing infection, we rely upon antibiotics to be the true last line of defense against pathogens.

## WHY DON'T MOST ANTIBIOTICS WORK AGAINST FUNGI AND PARASITES?

As mentioned earlier, most antibiotics are antibacterial compounds that have no efficacy against viruses. With a few exceptions, antibacterial compounds are likewise ineffective against fungi and protozoa. As we will see later in chapter 4, bacterial cells are in many ways biologically distinct from animal and human cells. Although many of the molecular components, i.e., proteins, nucleic acids, sugars, lipids, and other metabolites, are functionally equivalent between bacterial cells and human or animal cells, several essential proteins and large molecular structures are sufficiently different that they can be used as targets for antibiotics. Indeed, nearly all antibiotics exploit these differences by targeting the unique features in bacteria, and so they have little to no effect on the functionally equivalent components in nonbacterial cells. In so doing, they can inhibit bacterial growth without causing toxicity toward humans or animals.

Unfortunately, the cellular components of microbes like fungi and protozoa are more like those found in animals and humans than those in bacteria. As such, most antibacterials do not work against them. This similarity to animals and humans is also one of the main reasons we have so few effective antifungals or antiparasitic drugs, and why the drugs we do have tend to cause some degree of toxicity in animals and humans. Additionally, because fungi and protozoa are so similar, the differences that can be exploited frequently are only species- or genus-specific. This narrow spectrum of action means that a drug effective for treating one type of fungal or protozoal disease is often ineffective against other fungi or protozoa. By contrast, because bacteria are sufficiently distinct from humans and animals, the drugs targeting them can be broadly acting against a wide range of bacteria.

## WHY DON'T ANTIBIOTICS WORK AGAINST VIRUSES?

In the case of viruses, scientists face a daunting challenge identifying essential viral components to target with antivirals that are not also essential to their human or animal hosts. Viruses, unlike bacteria, fungi, and protozoa, are not free-living microbes. Rather, they are the ultimate freeloaders, relying almost entirely on the cellular machinery of host cells to replicate. Viruses bind to the surface of a mammalian cell and proceed to invade it. During the early stages of this process, the virus sheds its surface covering, called a capsid, to release the DNA or RNA comprising its genetic material into the host cell. This genetic material then highjacks the cell's biosynthetic machinery to reproduce. In most cases, the viral genome and a few virus-associated proteins (the nucleoprotein core) are transported to the nucleus, where the viral genome is copied many times over, and proteins comprising the viral capsid are made at high levels. The newly replicated viral genomes and capsid proteins are then assembled into viral particles and exit the cell, either by bursting out of the cell or by budding out inside vesicles comprising the host cell membrane.

Viral proteins brought in with the viral genome may take part in the viral proliferation process, but most of the action is carried out by enzymes and cell components of the mammalian cell. Therefore, there are very few steps in the viral life cycle that can be targeted by antiviral compounds without also harming the mammalian host cell. These virus-specific targets are, with a few exceptions, limited to the viral surface proteins that mediate attachment to the mammalian cell, the viral proteins that participate in the copying of the viral genome, and those involved in the viral uncoating and budding-out processes. Obviously, these targets are not the same as bacterial cell targets, and so naturally, antibiotics are not effective against viruses.

## POINTS TO PONDER

At the end of each chapter, we will include a short "Points to Ponder" section that is intended to highlight some interesting and important questions, issues, or considerations for which there are no easy responses or solutions. They are meant to serve as talking points to spur further discourse regarding the importance of antibiotics, how concerned we should be about antibiotic resistance, and what we should do about the growing rate of antibiotic resistance. With that in mind, what do you think about individuals who reject the notion that antibiotics are essential? These people argue that antibiotics are just weakening the human population by allowing individuals with weaker immune systems to survive and remain in the gene pool. Is this a scientifically sound argument? If so, what societal cost are we willing to accept to pay for such a natural selection-honed immune system?

Keeping with the theme of balancing individual costs and societal benefits is the issue of antibiotic stewardship. As we will discuss later in this book, any time you use an antibiotic there is a small chance that antibiotic resistance can emerge. How important to you personally is preserving the efficacy of our current antibiotics? Are you willing behave in ways that help preserve the efficacy of the antibiotics we currently have—or to put it another way, how much inconvenience are you willing to tolerate personally so that antibiotics will still be available for future generations?