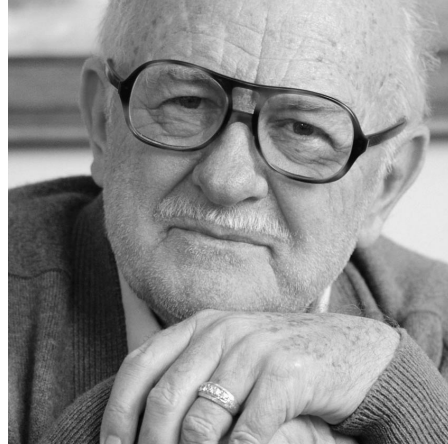
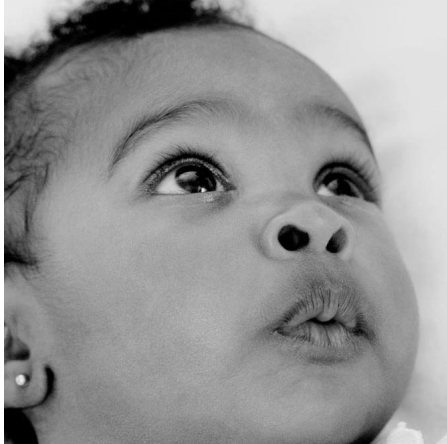


When Wonder Drugs Don't Work



HOW ANTIBIOTIC RESISTANCE
THREATENS CHILDREN, SENIORS,
AND THE MEDICALLY VULNERABLE

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ENVIRONMENTAL DEFENSE

finding the ways that work

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ENVIRONMENTAL DEFENSE

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Executive summary

For more than half a century, antibiotic drugs have ensured that potentially life-threatening bacterial infections are treatable. Today, however, more and more bacterial infections fail to respond to antibiotic treatment. A federal task force recently warned that antibiotic resistance is “a growing menace to all people” and concluded that if nothing is done, treatments for common infections will become “increasingly limited and expensive—and, in some cases, nonexistent.” Antibiotic resistance poses a threat to everyone, but several groups are especially vulnerable: children, seniors, and persons with certain medical conditions. This report focuses on the threat of antibiotic resistance to these groups.

Even careful use of antibiotics can result in the emergence of antibiotic-resistant bacteria. Widespread and inappropriate use greatly accelerates this process. The more bacteria are exposed to antibiotics, the more resistant they become. Because bacteria reproduce rapidly, these antibiotic-resistant bacteria can spread efficiently. Unlike higher organisms, bacteria can transfer DNA to other bacteria that are not their offspring, and even to members of completely unrelated bacterial species. In effect, bacteria can teach one another how to outwit antibiotics.

Antibiotic resistance carries a significant economic toll as well. The congressional Office of Technology Assessment calculated that resistance by just six types of bacteria increased hospital treatment costs by \$1.3 billion as of 1995. Few new drugs are now in the pipeline, and any new antibiotics will be considerably more expensive than existing ones; indeed, by some estimates, the research and development costs for a new drug top \$800 million.

Although the misuse of antibiotics in human medicine has been well publicized, less attention has been paid to the serious overuse of antibiotics in agriculture. One estimate is that 80 percent of all antibiotics sold in the United States is used in livestock production, with the lion’s share—roughly 70 percent of the total—fed to healthy farm animals to promote growth and prevent diseases that would otherwise result from the unsanitary conditions found in overcrowded agricultural facilities. Those antibiotics include many that are identical or closely related to drugs used in treating humans.

Because of the growing health crisis of antibiotic resistance, which could render these “wonder drugs” useless in treating infections, the American Medical Association now opposes the routine feeding of antibiotics to healthy farm animals. The American College of Preventive Medicine, the American Public Health Association, and the World Health Organization have taken similar positions. A National Academy of Sciences report estimates that eliminating such uses in poultry, cow, and swine production would cost U.S. consumers only about \$5 to \$10 per person annually.

Children are one group that would be particularly affected if antibiotic resistance continues to worsen. The availability of effective antibiotics has helped decrease infant mortality in the United States from about 20 percent in the late 19th century to under 1 percent in 1998. Despite this triumph, children continue to develop many non-fatal bacterial infections that require treatment with antibiotics. Children are more vulnerable than adults to bacterial illness, and this is reflected in their higher disease rates. Infants under the age of one, for example, are 10 times more likely than adults to contract a *Salmonella* infection.

The risk of bacterial infection is higher for infants and children, and treatment options are more limited, for several reasons. First, their immune systems are not fully developed and they have not yet acquired the full range of antibodies required to ward off infection. Second, children tend to be exposed to more pathogens through day-to-day activities such as childcare. Finally, many therapeutic medications have not been approved for use in children, in part because metabolic differences between children and adults can make use of certain drugs impractical or unsafe for children. For example, because tetracycline binds to immature calcium structures, it permanently disfigures enamel in teeth. Similarly, animal studies have shown that fluoroquinolones, a powerful class of drugs used to treat serious infections, can damage immature cartilage in bones and joints. As antibiotic resistance further depletes the number of effective drugs available, infants and children will have even fewer treatment options.

Senior citizens—people aged 65 and older—represent another group that is particularly at risk from antibiotic resistance. The fastest growing demographic group in the United States, seniors as a whole are more prosperous, more active, and healthier than ever before. Ironically, these factors allow many seniors to engage in activities such as travel and volunteer work that can increase their exposure to infectious agents. At the same time, seniors who enjoy less-robust health are likely to be hospitalized, or to reside in long-term care facilities. In these settings, they are especially at risk of encountering infection-causing bacteria in general, and antibiotic-resistant bacteria specifically. Residents of long-term care facilities are very dependent on antibiotics; indeed, approximately 40 percent of all prescription drugs dispensed in nursing homes are antibiotics.

Among seniors in the United States, death rates from heart disease and stroke have fallen in recent years. But deaths from infections continue to rise—and now account for nearly a third of deaths among people 65 and older. As people age, they develop debilitating conditions that reduce their ability to fight infection. An array of physiological changes, some of which impair immune-system function, further increase their susceptibility to infection. In addition, seniors are more sensitive to side effects of medications, further limiting antibiotic options. Unfortunately, as Americans age, so do our antibiotics. As noted above, new antibiotics will be considerably more expensive than existing ones. For a senior on a fixed income, developing a drug-resistant infection that can only be treated with a newer, more-expensive antibiotic can pose a serious financial hardship.

People with weakened immune systems, such as cancer patients undergoing chemotherapy or radiation treatment, transplant patients, and HIV/AIDS patients, make up a third group addressed in this report. Because their immune systems are less vigorous than those of healthy adults, these people are more vulnerable to infections and therefore more heavily dependent on effective antibiotics. Antibiotics have revolutionized cancer treatment by enabling the use of more aggressive therapies. This has led to dramatically higher survival rates. One of every two men and one of three women in the United States is expected to develop cancer during their lifetimes. Also discussed in this section are people with diabetes, a category that now includes 16 million Americans. Although diabetics are not necessarily more prone to infection than are members of the general population, the infections they do acquire tend to be more serious and harder to treat. For all

of these medically vulnerable groups—and for society as a whole—the loss of effective antibiotics would have immense ramifications.

The Centers for Disease Control and Prevention has observed that “decreasing inappropriate antibiotic use is the best way to control resistance.” Achieving this goal will require leadership by business, government, and individuals.

This report lays out a clear agenda for ending the inappropriate use of antibiotics in agriculture. Key steps include the following:

1. Congress or the U.S. Food and Drug Administration (FDA) must phase out the routine feeding of medically important antibiotics to healthy livestock and poultry and other inappropriate use of vital antibiotics in agriculture;
2. Producers and marketers of meat and poultry should voluntarily agree to stop selling or buying meat produced with routine feeding of antibiotics to healthy animals, and pharmaceutical companies should stop producing antibiotics for such use in animals; and
3. Congress or FDA should require the submission of accurate data on the quantities of antibiotics produced for use in human medicine and animal agriculture. These data must then be made available to the public.

In addition, every American can—and should—act on his or her own. We should urge policymakers and companies to take the above steps. We should listen to our doctors to make sure that we take antibiotics only when appropriate and not for viral infections such as colds or the flu, and we should take the entire course. When we shop or go to a restaurant, we should select meat that has been produced without the inappropriate use of antibiotics.

Unless we act now, we face a future of untreatable bacterial infections. Children, seniors, and those with weaker immune systems will be the first to pay the price with their health—or even their lives.

Antibiotic resistance: what it is and why it matters

A federal task force recently noted that antibiotic resistance is “a growing menace to all people” and cautioned that if current trends continue, treatments for common infections “will become increasingly limited and expensive—and, in some cases, nonexistent.”

Introduction

For the past sixty years, antibiotic drugs have turned bacterial infections into treatable conditions rather than the life-threatening scourges they once were. Today, however, the effectiveness of many antibiotics is waning dramatically, as more and more types of bacteria become resistant to them. According to a federal task force, antibiotic resistance is “a growing menace to all people,” and if current trends continue, treatments for common infections “will become increasingly limited and expensive—and, in some cases, nonexistent.”¹

While antibiotic resistance poses a threat to everyone, some groups will be especially hard hit if resistance continues to worsen. At greatest risk are children, seniors, and those with medical conditions that impair their ability to fight disease or make them especially susceptible to bacterial infections. This report focuses on the particular danger of antibiotic resistance to these at-risk groups. Chapter 1 presents an overview of the antibiotic resistance problem. Chapters 2, 3 and 4 respectively explore the particular vulnerabilities of children, seniors, and those with certain medical conditions. Finally, Chapter 5 describes how antibiotics are used—and overused—and sets forth brief recommendations for action.

The growing problem of antibiotic resistance

No single statistic can illustrate the overall problem of resistance, but disturbing trends abound for numerous “drug/bug” combinations. Resistance is generally expressed as the susceptibility of a particular type of bacteria (“bug”) to one or more antibiotics; bacteria can develop resistance to one type of drug while remaining susceptible to others, just as a particular drug may lose its effectiveness against certain bacteria while remaining effective against others.

For four important drug/bug combinations, resistance increased by between 40 and 49 percent in just five years (1994–1999).² Even more disturbing is the growing prevalence of “superbugs,” bacteria that are multi-drug resistant. As of 1998, strains of at least three bacterial species capable of causing life-threatening illnesses were resistant to *all* available antibiotics.³

Other troubling statistics on antibiotic resistance include the following:

- Nearly all strains of *Staphylococcus aureus* in the United States are resistant to penicillin,⁴ and many are resistant even to the newer methicillin-related drugs.⁵ Since 1997, some strains of *S. aureus* have been reported to be less susceptible to vancomycin, the last uniformly effective treatment.⁶ (*S. aureus* causes a variety of serious ailments, including pneumonia, surgical wound infections, and bloodstream infections.⁷)
- Today, one of approximately every six cases of *Campylobacter* infections (17.6 percent), the most common bacterial cause of foodborne infection in the United States, is resistant to fluoroquinolones, the drugs of choice for adults with severe food poisoning. As recently as ten years ago, such resistance was negligible.⁸

- No comprehensive tally of the human impacts of antibiotic resistance is available, but they are clearly substantial. One study concluded that methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria claimed more than 1,400 lives in New York City alone in 1995.⁹
- In addition to its impact on human health, antibiotic resistance has a significant economic impact as well. As of 1995, for example, resistance by just six pathogens was calculated to increase in-hospital treatment costs by \$1.3 billion.¹⁰

The possibility that new antibiotics will come to our rescue offers only limited hope, particularly for the near to medium term. Although drug companies may eventually develop and market new classes of antibiotics, most of the few promising new drugs now in the pipeline are variants of existing antibiotics, which means that bacteria may quickly become resistant to them. In the past thirty-five years, only one new type of antibiotic, linezolid, has been brought to market in the United States¹¹ (and resistance to linezolid is appearing with startling speed).¹²

Moreover, new antibiotics are likely to be expensive, at least in part because of the cost of developing new drugs. One recent study concluded that the average cost of developing a new prescription drug reached \$802 million in the 1990s,¹³ though that estimate has been challenged as overstated.¹⁴ Nonetheless, it is clear that drug-development costs are significant, and that new antibiotics tend to be significantly more expensive than older ones. For example, a single course of antibiotics to treat a urinary-tract infection would cost approximately \$20 if the bacteria were susceptible to an older drug, but nearly \$100—a five-fold differential—if a newer drug were required because of resistance.¹⁵

Already, higher drug costs discourage some patients from taking drugs as prescribed. In late 2001, a nationwide survey that found that 20 percent of adults questioned had not filled at least one of their prescriptions during the year due to restrictive costs.¹⁶ Steep drug costs may present a particular problem for individuals who are neither wealthy enough to have ample disposable income, nor poor enough to qualify for Medicaid. This category includes many senior citizens, families with young children, and people with major health problems—precisely the individuals most likely to need antibiotics.

In sum, the rate at which antibiotic resistance is worsening far exceeds the rate at which new drugs are being discovered and brought to market, and new drugs are increasingly difficult for many people to afford. Therefore, preserving the effectiveness of existing antibiotics is critical to protecting public health.

One study concluded that a single strain of resistant bacteria claimed more than 1,400 lives in New York City alone in 1995.

A note on terminology

Strictly speaking, the term “antibiotic” means a naturally occurring chemical (i.e., one not manufactured by humans) that kills or inhibits the growth of bacteria. Often, however, the term is used more broadly, to include synthetic chemicals that also kill or inhibit the growth of bacteria. The term is also generally used to include compounds that affect other microorganisms such as fungi and parasites (technically known as “antimicrobials”). The term antibiotic by definition excludes compounds that affect viruses.

BACTERIA, ANTIBIOTICS, AND ANTIBIOTIC RESISTANCE—THE BASICS¹⁷

Bacteria are everywhere. They are found by the millions on our skin, in our digestive tract, throughout the environment (in air, water, and soil), and on the things we touch every day. Most are harmless, and many are helpful because they compete with disease-causing bacteria, known as *pathogens*.

It is pathogenic bacteria that get most of the attention. They cause a remarkable variety of ailments, ranging from pneumonia, ear infections, meningitis, urinary tract infections, and food poisoning, to skin, bone, and bloodstream infections. Many types of bacteria are able to cause a range of different illnesses depending on what part of the body they invade. For example, *Streptococcus pneumoniae* causes not only pneumonia, as its name suggests, but also ear infections and meningitis. Conversely, some infections can be caused by several different bacteria and other microorganisms. Pneumonia, for instance, is a lung infection that can be caused by not only *Streptococcus pneumoniae* but also *Staphylococcus aureus*, *Legionella*, *Hemophilus influenzae*, and many other microorganisms.¹⁸ This is one reason that it is difficult to combat infectious diseases: different organisms can produce similar symptoms but must be treated with different antibiotics.

Most bacterial diseases are short-term, but researchers continue to discover that bacteria cause or contribute to certain chronic conditions as well. For example, many ulcers are caused by bacteria and can be treated with antibiotics.¹⁹ Researchers are currently examining the role bacteria may play in other chronic conditions such as some types of arthritis,²⁰ and even heart disease.²¹

To fight bacteria, antibiotics target specific parts of their structure or machinery. While over 100 antibiotics are now available in the U.S. for use in treating human illness, most of the clinically important antibiotics fall into about a dozen classes of fairly similar compounds.²² Often, if a strain of bacteria develops resistance to one member of the class, it develops at least partial resistance to some or all other members of that class as well. Typically, antibiotics affect not only the “target” bacteria—those causing the illness that the antibiotic is intended to treat or prevent—but also a wide array of bacteria that are just innocent bystanders.²³ Some antibiotics, known as broad-spectrum drugs, kill a particularly wide array of bacteria, while narrow-spectrum drugs are more targeted in their action.

Bacteria become resistant to antibiotics when they change, or mutate, in ways that reduce or erase the antibiotics’ effect on them (it is the bacteria, not people, that become resistant to antibiotics).²⁴ Put another way, resistance is the ability of bacteria to survive and even multiply despite the presence of an antibiotic at levels that could previously kill the bacteria or inhibit their growth.²⁵

When bacteria are first exposed to an antibiotic, those most susceptible to it die quickly, but the bacteria that survive will pass on their ability to resist to succeeding generations. As noted above, bacteria are remarkably numerous; they are also astonishingly prolific. Indeed, in some species, a single bacterium can produce a *billion* offspring in a single day under optimal conditions. Thus, even if initially no bacteria are able to survive the onslaught of an antibiotic, the random mutation of the bacteria’s DNA will produce a wide variety of genetic changes, some of which—sooner or later—will almost inevitably confer resistance. This may happen in one of several ways:

When bacteria are first exposed to an antibiotic, those most susceptible to it die quickly, but the bacteria that survive will pass on their ability to resist to succeeding generations.

- The bacteria's outer membranes may change in such a way that it no longer allows the antibiotic to enter the cell.
- The bacteria may develop biochemical pumps that remove the antibiotic from the bacteria before it can reach its target within the bacterial cell.
- The bacteria's receptors may change so that the antibiotic can no longer engage them.
- The bacteria may create enzymes that deactivate the antibiotic.²⁶

The problem of resistance is exacerbated by the fact that, unlike higher organisms, bacteria can transfer their DNA to other bacteria that are not their offspring—even to members of entirely unrelated species. Most frequently, such transfer occurs via a *plasmid*, a small circle of DNA that is not part of the bacteria's regular DNA (which is found in its chromosomes). In effect, bacteria can teach one another how to outwit antibiotics. Plasmid transfer is by no means rare. In fact, as one leading expert noted, “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.”²⁷ This phenomenon can occur in the environment and has been documented in the human intestine.²⁸

The problem is not just resistant germs; it is all resistance genes, in any type of bacteria.

Thus, even if the bacteria that first become resistant do not cause disease, they can transfer their resistance genes to other types of bacteria that do. In short, the problem of antibiotic resistance is not just confined to resistant *germs*, but rather encompasses *all* resistance *genes*, in any type of bacteria. Moreover, many plasmids carry several resistance genes, leading to “superbugs” that are able to withstand simultaneously three, four, or even more entire classes of antibiotics. These superbugs pose some of the toughest challenges to disease treatment today.

Given that resistance to antibiotics is already so widespread, an important question is whether antibiotic resistance is reversible. That is, once resistant bacteria have become prevalent, will they become less so if the use of antibiotics is reduced? Fortunately, the answer seems to be yes, at least in some instances. For example, a campaign in Finland to lower the resistance to erythromycin in certain kinds of infections by reducing its use almost halved the incidence of resistance in those bacteria to that drug.²⁹

Similarly, researchers in Denmark compared the levels of resistant bacteria in chickens just before and shortly after antibiotic use in chickens was sharply restricted in that country. The researchers found that the fraction of bacteria in chickens resistant to one drug (avoparcin) plummeted from nearly 73 percent to just over five percent in a five-year period. Resistance to another drug (virginiamycin) dropped from more than 66 percent in 1997 to less than 35 percent in 2000.³⁰

Although even the most careful use of antibiotics can eventually produce antibiotic-resistant bacteria, the widespread, indiscriminate, or inappropriate use of an antibiotic hastens the day when it loses its ability to treat disease. Put more colloquially, the more you use them, the faster you lose them. Thus, as further discussed in Chapter 5, a key strategy in combating antibiotic resistance is using antibiotics as sparingly as possible—and only where truly needed.

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At special risk: children

Jimmy was about eight years old when his parents rushed him to the clinic with a fever of 104°F, severe cough, painful breathing, and body-racking chills. They were terrified. Their child looked gravely ill. The doctor quickly made a diagnosis—bacterial pneumonia—and gave Jimmy a shot of penicillin.

A few hours later, the doctor checked back on Jimmy and found his parents much relieved. Jimmy had improved rapidly, just as the doctor had predicted. And at a follow-up exam two days later, Jimmy was nearly recovered—no more fever, chills, or chest pain. His breathing was easy, and his cough was loosening up. He was going to be just fine. The year was 1978.¹

In the sixty years since antibiotics first came into use, these “wonder drugs” have saved the lives of countless children and reduced the severity of illness for many more. In particular, along with vaccines and improved sanitation, antibiotics have contributed importantly to the decrease in overall infant mortality in the United States, from about 20 percent in the late nineteenth century,² to less than 1 percent in 1998.³

Nonetheless, infections, many caused by bacteria, are not uncommon in American newborns. Indeed, it is estimated that as many as 10 percent of infants will acquire an infection within one month of birth.⁴ And despite the availability of antibiotics, infections still kill babies today. For American children in the first year of life, infections from all causes are the fourth most common cause of death, after birth defects, complications surrounding childbirth, and Sudden Infant Death Syndrome (SIDS).⁵ For children one to five years of age, septicemia (bacterial infection in the bloodstream) is the seventh leading cause of death.⁶ Fortunately, as children age, infection becomes a less common cause of death.

At all ages, however, the rate of nonfatal illness from bacterial infection is much higher than the rate of death and has not changed as dramatically over the same time span. Each year, healthy young children suffer between three and eight viral upper respiratory infections,⁷ which all too often become complicated by secondary bacterial infections of the middle ear.⁸ Bacteria are also responsible for some of the roughly 30 million episodes of diarrheal illness experienced annually by children under five (an average of one to two episodes per child per year), resulting in millions of visits to the doctor, hundreds of thousands of hospitalizations, and 300 to 400 deaths.⁹ Sore throats caused by Group A streptococci, so-called strep throats, become epidemic in school-age children during the cold months and require treatment with antibiotics to reduce the risk of rheumatic fever (which can cause permanent heart damage). Children may also contract serious bacterial infections of the central nervous system, bloodstream, lungs, urinary tract, and bones—infections that can cause death or permanent disability if not treated with antibiotics.

Children’s vulnerability to bacterial infections

Infants and young children are at increased risk for adverse outcomes from bacterial infections for three reasons. First, their immune systems are not yet fully functional; second, they are exposed to numerous pathogens because of their behavior patterns;

Antibiotics are major contributors to the decrease in overall infant mortality in the United States from as much as 20 percent in the late 19th century, to less than 1 percent in 1998.

and third, some antibiotics that have been approved for use in adults are not appropriate for use in children. Each of these factors is discussed below.

IMMATURE IMMUNE SYSTEMS

Newborns have few defenses against bacterial infections. Although they are born with some antibodies acquired from their mothers—so-called passive immunity—these antibodies are primarily effective against certain types of bacteria. Many other types of bacteria, however, cannot be controlled by antibodies alone.¹⁰

In addition to their limited production of antibodies, newborns possess only 20 to 30 percent of the quantity of stored bacteria-fighting white blood cells that adults do, making them highly susceptible to septicemia (a bacterial infection in the bloodstream that causes high fever). Moreover, compared with adults, newborns can create only about half as much *complement*, an important substance that helps white blood cells kill certain kinds of bacteria.¹¹ As a result, babies less than three months of age who have high fevers are usually treated with antibiotics. One or two in ten of such infants have bacterial infections and need the help of antibiotics to prevent death and disability.¹²

Premature infants—those born before 37 weeks of gestation—are especially vulnerable. They are three to ten times more likely to become infected than are full-term newborns.¹³ And because they have less well-developed immune systems than full-term babies do, they are less able to combat infections once acquired. Noninfectious complications of prematurity (such as respiratory distress caused by underdeveloped lungs) add physiological stress to their systems, require prolonged hospitalization, and increase the likelihood of infectious complications. Finally, the more premature the infants are, the less passive immunity they receive from their mothers, since the antibodies are not transferred through the placenta until late in the last trimester of pregnancy. As a result, premature babies are even more dependent on the efficacy of antibiotics for their survival.

Even among full-term newborns, the limited immunity that they acquire from their mothers starts to wear off before their own systems are fully functional. Babies' antibody¹⁴ levels fall steadily until they are four or five months of age, and by one year, only one of the four major forms of antibodies has reached an adult production level.¹⁵

Children continue to be at relatively high risk from infections from age three months to three years. Because some of their antibody-production systems still are not fully functional, children in this age group are more prone to bacterial blood infections than are older children.¹⁶ These bloodstream infections, in turn, can sometimes lead to infections of the central nervous system (meningitis), bones (osteomyelitis), or lungs (pneumonia). Successful treatment with antibiotics before the bacteria have a chance to localize thus can both save lives and prevent permanent disability.

As children grow into school age and beyond, their ability to resist infection improves. By the time they are ten or twelve, they are no longer more vulnerable than adults for physiological reasons although, as discussed below, they still have not acquired the full range of antibodies required to ward off infection.

GREATER EXPOSURE TO BACTERIA

Young children typically have high exposure to bacteria. Infants and toddlers explore and learn about the world by touching and mouthing items in their envi-

ronment. This normal healthy behavior also helps to train their immune systems by exposing them to bacteria, which, as noted in Chapter 1, are both ubiquitous and mostly harmless. Occasionally, pathogenic bacteria will enter a child's environment and these normal behaviors can result in an infection.¹⁷ While contaminated objects play a minor role in spreading bacteria in most settings, this mode of exposure may be of greater importance in group settings such as childcare where children share toys and other objects and where diapers are changed in a common area. An estimated 13 million children under six attend regular out-of-home childcare in the United States, as do 60 percent of children between six and thirteen.¹⁸ Infants and young children who attend childcare centers are predisposed to higher numbers of infections, primarily lung and bronchial infections or intestinal infections, and are at increased risk of getting antibiotic-resistant bacteria in their systems.¹⁹ For example, children attending childcare are more than twice as likely to have diarrhea than are children cared for at home.²⁰

Older children and young adults also have a somewhat greater-than-average risk of infection. Even after they are physiologically able to produce antibodies of the same type and quantity that adults do, younger people usually have not yet been exposed to some types of bacteria. Because the body makes antibodies to a particular type of bacteria only once it actually encounters it, younger people tend to have fewer antibodies than do mature adults, and therefore a lesser ability to ward off infection. As a result, for example, even young adults who come in close contact with a new group of people in a college dormitory²¹ or an army barracks are more likely to contract meningitis.

Although older children and young adults occasionally develop serious bacterial infections, the availability of effective antibiotics has made death from infection in this age group an unusual event today. But if bacteria continue to become increasingly resistant to antibiotics, this may soon change.

Many antibiotics approved for adults have not been approved for use in children, thus limiting the range of treatment options.

LIMITED THERAPEUTIC OPTIONS

Conducting pharmacological and clinical research on children is not easy, so most antibiotics and other drugs are first approved by the Food and Drug Administration (FDA) for use in adults. According to the American Academy of Pediatrics, 80 percent of available therapeutic medications have not been approved for use in children.²² While many antibiotics eventually enter pediatric use, it can take years for enough experience to be generated to provide confidence that use of new drugs in children is safe.

There are also physiological reasons for limiting the use of some drugs in children. Because they have immature metabolic pathways, children respond to drugs differently than adults do, and differently at various stages of childhood.²³ In some cases, these metabolic differences may make the use of certain drugs impractical or unsafe for children, even though they are safe for adults. Tetracycline is a good example of an antibiotic that is safe for adults but not children. Because tetracycline binds to immature calcium structures, it permanently disfigures the enamel in teeth. Therefore, tetracyclines are contraindicated for children under nine.²⁴ A newer example is fluoroquinolones, which in animal studies have been found to damage immature cartilage in still-growing bones and joints. For this reason, fluoroquinolones are not approved for use in anyone under eighteen.²⁵

In short, fewer antibiotics are available for treating children than for treating adults. Consequently, as bacteria's growing resistance to antibiotics further depletes the number of effective drugs available to physicians for use in children, infected infants and children will be especially hard hit.

Children's greater vulnerability: examples from foodborne illness

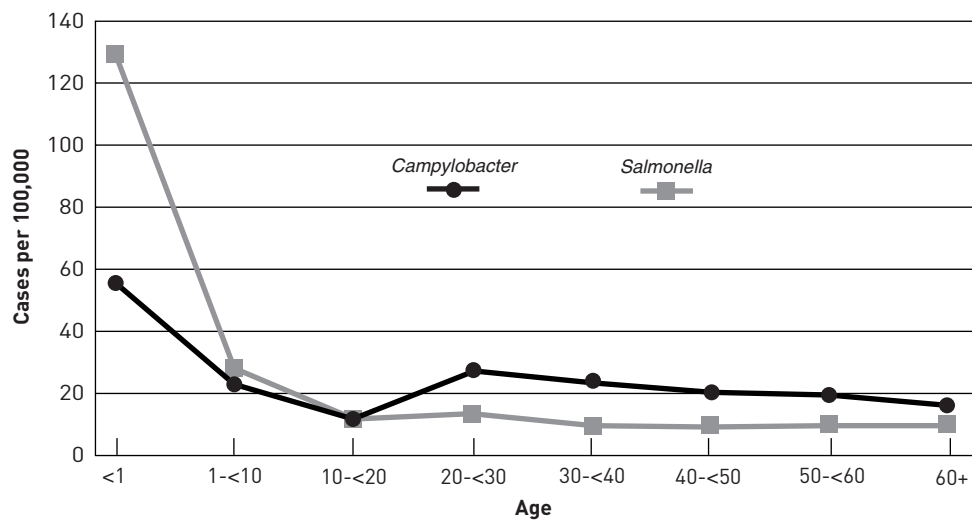
Children's greater vulnerability to bacterial illness is reflected in their higher rates of disease, including those caused by foodborne bacteria (see Figure 1). Two of the most important of these pathogens are *Campylobacter* and *Salmonella*.

CAMPYLOBACTER

Campylobacter is the leading bacterial cause of foodborne illness in the United States, accounting for more than 2 million cases each year.²⁶ Until their first birthday, infants are twice as likely to suffer from a *Campylobacter* infection as are older individuals (54 versus 22 cases per 100,000 people).²⁷ In newborns, when such infections spread to the bloodstream, more than 30 percent of infected infants die.²⁸ Furthermore, almost 20 percent of all reported cases of *Campylobacter* infections occur in children under ten years of age,²⁹ even though they represent only 14 percent of the population.³⁰

Children with *Campylobacter* infections can be treated with erythromycin and related drugs; luckily, *Campylobacter*'s resistance to these drugs is still low in the United States. But if—or more accurately when—*Campylobacter* develops resistance to these drugs, it will be difficult to find alternatives suitable for use in children. Although fluoroquinolones are available for use in adults with *Campylobacter*, these drugs are not approved for use in children. Even if fluoroquinolones become acceptable pediatric alternatives, *Campylobacter* resistance to these valu-

FIGURE 1
Incidence of CAMPYLOBACTER and SALMONELLA infections by age group



FoodNet sites, 1998 (USDA Report to Congress, 1998, www.fsis.usda.gov/OPHS/rpcong09/rpcong98.htm)

able drugs has grown significantly in the last decade, jumping from insignificant levels to 18 percent.³¹

SALMONELLA

Each year, *Salmonella* causes 1.4 million people to become sick; 95 percent of these cases are due to contaminated food.³² More than one-third of all cases occur in children under age ten,³³ even though they constitute only 14 percent of the population.³⁴ Infants under one year are ten times more likely than the general population to become infected with *Salmonella* (129 versus 12 cases per 100,000 people).³⁵ Such infections are also more likely to spread to the bloodstream, particularly in infants under 3 months of age and children with underlying illnesses.³⁶

The physiology of infants and young children is what makes them particularly prone to *Salmonella* and other foodborne infections. The body's best defense against these organisms is the stomach, because its high acidity can destroy bacteria before they reach the intestine and cause infection. Children are at greater risk, in part because their stomachs produce less acid and food stays in the stomach for a shorter period, making it easier for bacteria to reach the intestine while still alive. As a result, infants and toddlers can become infected by foods with lower levels of bacterial contamination than those needed to cause infection in older individuals. In addition, when children become infected, their bodies are less able to confine the infection, thus leading to more serious illness. Unfortunately, *Salmonella* and other bacterial pathogens are becoming increasingly resistant to existing antibiotics, so fewer and fewer treatments will be available to treat children with such infections.

More than one-third of all *Salmonella* infections occur in children under ten, even though they constitute only 14 percent of the population.

¹ This narrative offers a general illustration rather than describing a particular individual's actual experience.

² R.E. Behrman, "Overview of Pediatrics," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), p. 1.

³ S.L. Murphy, "Deaths: Final Data for 1998," in Centers for Disease Control and Prevention, National Center for Health Statistics, *National Vital Statistics Reports* 48 (2000): 2, www.cdc.gov/nchs/data/nvsr/nvsr48/nvs48_11.pdf. Summarized as Centers for Disease Control, National Center for Health Statistics, "Deaths/Mortality," www.cdc.gov/nchs/fastats/infmort.htm.

⁴ S.P. Gotoff, "Infections of the Neonatal Infant," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), p. 538.

⁵ Murphy, "Deaths: Final Data for 1998," pp. 1-108, www.cdc.gov/nchs/data/nvsr/nvsr48/nvs48_11.pdf. Summarized as Centers for Disease Control, National Center for Health Statistics, "Deaths/Mortality," www.cdc.gov/nchs/fastats/infmort.htm.

⁶ Ibid.

⁷ N.E. Herendeen and P.G. Szilagyi, "Infections of the Upper Respiratory Tract," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), p. 1261.

⁸ Bacterial middle ear infections are the leading diagnosis requiring antibiotic treatment in children and adults. In the United States in 1990, 24.5 million visits to the doctor's office were for middle-ear infections. See S.M. Schappert. "Office Visits for Otitis Media: United States, 1975-90." *Advance data from Vital and Health Statistics, No. 214*. Hyattsville, MD: National Center for Health Statistics (1992), www.cdc.gov/nchs/data/ad/ad214.pdf.

⁹ L.K. Pickering and J.D. Snyder, "Gastroenteritis," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), p. 765.

¹⁰ Gotoff, "Infections of the Neonatal Infant," p. 539.

- ¹¹ Ibid., p. 539.
- ¹² K.R. Powell, "Fever without a Focus," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), pp. 742, 743.
- ¹³ Gotoff, "Infections of the Neonatal Infant," p. 541.
- ¹⁴ Although the word *antibody* sounds similar to *antibiotic*, the two are very different. Antibodies are cells naturally produced by the body's own immune system to fight disease, and antibiotics are chemicals that are administered to sick individuals to assist the body's immune system in fighting off infection.
- ¹⁵ R.H. Buckley, "Evaluation of the Immune System—the Child with Suspected Immunodeficiency," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), p. 595.
- ¹⁶ Powell, "Fever without a Focus," p. 743.
- ¹⁷ This is not an argument for using antibacterial soaps and cleaners. In fact, some studies suggest that the use of these products may even be detrimental and encourage the proliferation of bacteria that are resistant to antibacterial agents. See E. Susman, "Too Clean for Comfort," *Environmental Health Perspectives* 109 (2001): A18; See Alliance for Prudent Use of Antibiotics, "Overuse of the antimicrobial triclosan in antibacterial soaps may promote triclosan-resistance," www.healthsci.tufts.edu/apua/News/Antibacterials.html.
- ¹⁸ L.K. Pickering and D.J. Laborde, "Childcare and Communicable Diseases," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), p. 1092.
- ¹⁹ 1997 Red Book: Report of the Committee on Infectious Diseases. American Academy of Pediatrics. Ed.: L.K. Pickering. "Red Book: Report of the Committee on Infectious Diseases 24th Edition," American Academy of Pediatrics publishers. Oak Grove Village, Illinois.
- ²⁰ S. J. Holmes, A.L. Morrow, and L.K. Pickering, "Child-Care Practices: Effects of Social Change on the Epidemiology of Infectious Disease and Antibiotic Resistance," *Epidemiologic Reviews* 18 (1996): 10–28.
- ²¹ M.G. Bruce et al., "Risk Factors for Meningococcal Disease in College Students," *Journal of the American Medical Association* 286 (2001): 688–93.
- ²² Committee on Drugs, American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations," *Pediatrics* 95 (1995): 286–94, www.aap.org/policy/00655.html.
- ²³ P. S. Guzelian, C.J. Henry, and S.S. Olin, "Similarities and Differences between Children and Adults: Implications for Risk Assessment" (Washington, D.C.: ILSI Press, 1992), part 2, pp. 97–138.
- ²⁴ 2000 Red Book: Report of the Committee on Infectious Diseases. American Academy of Pediatrics. Ed.: L.K. Pickering. "Red Book: Report of the Committee on Infectious Diseases 25th Edition," American Academy of Pediatrics publishers. Oak Grove Village, Illinois.
- ²⁵ M.L. Buck, "Ciprofloxacin Use in Children: A Review of Recent Findings," *Pediatric Pharmacotherapy* 4 (1998), hsc.virginia.edu/cmc/pedpharm/v4n12.htm.
- ²⁶ P.S. Mead et al., "Food-Related Illness and Death in the United States," *Emerging Infectious Diseases* 5 (1999): 607–25, www.cdc.gov/ncidod/EID/vol5no5/pdf/mead.pdf.
- ²⁷ USDA Report to Congress, "FoodNet: An Active Surveillance System for Bacterial Foodborne Diseases in the United States" (1998), www.fsis.usda.gov/OPHS/rpcong09/rpcong98.htm.
- ²⁸ G.P. Heresi, J.R. Murphy and T.G. Cleary, "Campylobacter," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), pp. 855–57.
- ²⁹ USDA, Food Safety and Inspection Service, "The Establishment and Implementation of an Active Surveillance System for Bacterial Foodborne Diseases in the United States," 1997, www.fsis.usda.gov/OPHS/fsisrep1.htm.
- ³⁰ U.S. Census. "Resident Population Estimates of the United States by Age and Sex: April 1, 1990 to July 1, 1999, with Short-Term Projection to November 1, 2000," Population Estimates Program, Population Division, U.S. Census Bureau, www.census.gov/population/estimates/nation/intfile2-1.txt.
- ³¹ K.E. Smith et al., "Quinolone-Resistant *Campylobacter jejuni* Infections in Minnesota, 1992–1998," *New England Journal of Medicine* 340 (1999): 1525–32 (1992 data were for quinolones, a precursor class of antibiotics to fluoroquinolones; quinolone resistance usually indicates resistance or reduced

- susceptibility to fluoroquinolones); Centers for Disease Control. 1999. "Annual Report: National Antimicrobial Resistance Monitoring System: Enteric Bacteria," www.cdc.gov/narms/annual/1999/pdf/NARMS_final_report_1999_full.PDF .
- ³² Mead et al., "Food-Related Illness and Death in the United States," p. 614.
- ³³ USDA Food Safety and Inspection Service, "Establishment and Implementation," p. 6.
- ³⁴ U.S. Census, "Resident Population Estimates of the United States by Age and Sex: April 1, 1990 to July 1, 1999, with Short-Term Projection to November 1, 2000."
- ³⁵ USDA Report to Congress, "FoodNet: An Active Surveillance System for Bacterial Foodborne Diseases in the United States" (1998).
- ³⁶ T.B. Cleary, "Salmonella," in *Nelson Textbook of Pediatrics*, 16th ed., ed. R.E. Behrman, R.M. Kliegman, and H.B. Jenson (Philadelphia: Saunders, 2000), pp. 842–48.

At special risk: senior citizens

As Mary sat down to breakfast on the morning of her seventy-fifth birthday, her “appetizer” was an array of pills. One of them was an antibiotic newly prescribed by her doctor to treat a lingering case of bacterial pneumonia—two earlier prescriptions hadn’t worked. It seemed that half of her friends at the senior center also had to try several antibiotics before their doctors could find an effective one. Meanwhile, she and her friends stayed sick. Mary dutifully swallowed the new antibiotic, hoping it would rid her of the wracking cough that sometimes felt as though it would crack her ribs—which would probably mean having to leave the home that her young grandchildren loved to visit.

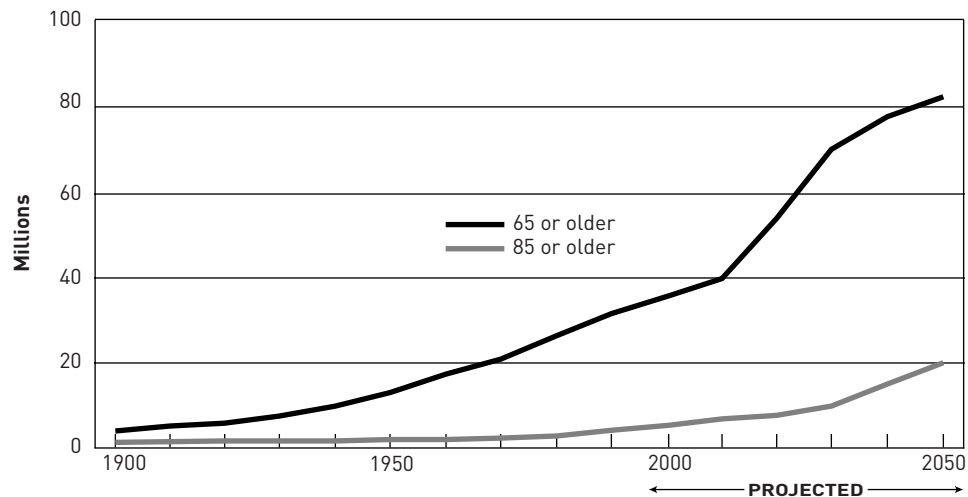
“Go, antibiotic!” she whispered, washing the blue tablet down with a swallow of orange juice. “Zap that bug!”¹

By 2030, seniors are expected to comprise 20 percent of the U.S. population.

Seniors—people aged sixty-five years or older—are the fastest-growing demographic group in the United States. Already comprising 13 percent of the population, the proportion of seniors is expected to rise to 20 percent by 2030, a total of 70 million (see Figure 2).²

This demographic shift will have several effects on the nation’s overall health status. First, chronic illness, disability, and bacterial and other infections are more common among seniors than those under sixty-five. Though senior citizens comprise less than 13 percent of the total population, they account for about half of all days spent in the hospital and for 36 percent of all patients admitted to hospitals. Their hospital stays are also disproportionately long, making up 49 percent of all days spent in the hospital, and the average hospital stay is 6.8 days for seniors, versus 5.5

FIGURE 2
Total number of persons age 65 or older, by age group, 1900 to 2050



Federal Interagency Forum on Aging-Related Statistics. (Older Americans 2000: Key Indicators of Well-Being, www.agingstats.gov/chartbook2000/population.html.)

Note: Data for the years 2000 to 2050 are middle-series projections of the population. Reference population: These data refer to the resident population. Source: U.S. Census Bureau, Decennial Census Data and population Projections.

days for people under age sixty-five. Finally, older people have more contacts with doctors, an average of 11.7 contacts per year, compared with 4.9 for younger people.³

Unfortunately, as the population is aging, so also are our antibiotics. This is particularly bad news for seniors, who are highly vulnerable to bacterial infections in general. As one researcher put it, “Geriatric patients . . . may be compared to ‘sentinel chickens’—the first to be affected by new or emerging infections in hospitals and other health-care environments.”⁴ Despite the progress in recent years in lowering seniors’ death rates from some ailments (for example, heart disease and stroke), the number of deaths from infections has increased.⁵ Infections are now responsible for 30 percent of the deaths in senior citizens.⁶ Infections also frequently result in nonfatal illnesses; indeed, they are the most common cause of hospitalization for older adults.⁷

Seniors’ vulnerability to bacterial infections

Several factors make seniors more vulnerable than younger adults to serious complications and even death from many bacterial infections. These include age-related decreases in the effectiveness of the immune system, higher exposures to infectious bacteria resulting from lifestyle factors, and reduced ability to tolerate the side effects of antibiotics (or other treatments) because of drug interactions or underlying conditions. In addition, seniors tend to have higher rates of certain illnesses that also lead to increased vulnerability to infection. Each of these points is described more fully below.

“Geriatric patients . . . may be compared to ‘sentinel chickens’—the first to be affected by new or emerging infections.”

LESS EFFECTIVE IMMUNE SYSTEM

With age, the immune system changes.⁸ Even the immune system of a healthy older person is generally somewhat less robust than that of a younger adult, as a result of several physiological changes in the systems that the body uses to fend off infectious disease.

These systems can be divided into two broad categories: nonspecific defense mechanisms, and specific immune responses.⁹ Nonspecific defense mechanisms are physical processes for keeping harmful items out of the body or for clearing them rapidly once they enter (for example, cough and gag reflexes, intact skin and mucus membranes, the acidity of stomach secretions, and the efficient clearance of urine and feces). By contrast, specific immune responses involve biochemical processes such as recognition of foreign antigens (microorganisms, parasites, proteins) and subsequent production of specific immune cells, antibodies, and inflammatory chemicals. With age, both systems become less effective.

Non-specific host defenses. Many seniors have a reduced “cough reflex” that increases the likelihood of aspiration (unwanted inhalation) of bacteria from the mouth, nose, and throat deep into the lungs, which in turn increases the risk of developing pneumonia.¹⁰ This problem may be compounded by a weakened gag reflex that limits the ability to expel aspirated material. A weakened cough reflex can result from a variety of factors, including injury to the ribs (which may in turn have occurred because of osteoporosis), excessive drowsiness as a side effect of medication, or stroke.

Similarly, many seniors have less-acidic gastric secretions, predisposing them to infections caused by foodborne and waterborne pathogens. For example, these

patients are particularly prone to *Salmonella* infections because more bacteria are able to reach the intestine after surviving passage through a less-acidic stomach; once in the intestine, they can cause infection.¹¹ Likewise, a loss of gastric acidity, resulting from the use of antacids and certain antihistamines, predisposes patients to infections from food or water.¹²

In addition, regular and complete evacuation of the bladder and colon are important defense mechanisms against infection from intestinal bacteria. Both of these functions can become less effective with age because of medical conditions such as diabetes or stroke, or as a side effect of medications that impair bladder and bowel function, predisposing seniors to both diarrheal and urinary tract infections. Other factors associated with urinary tract infections in seniors are incontinence of stool and urine, and the presence of indwelling urinary catheters.¹³ Men are especially at risk for urinary retention and infection due to enlargement of the prostate gland, which is more common in older men.

Moreover, with age, the skin loses its elasticity and regenerative properties, so that it ruptures more easily and takes longer to heal. For example, seniors who are confined to bed or a wheelchair can develop bedsores or pressure ulcers. Like all breaches in the skin's integrity, such sores provide portals of entry for bacteria.

In short, an array of physiological changes can damage senior citizens' non-specific defense mechanisms, resulting in increased susceptibility to infection.

The diets of almost 80 percent of the senior citizens are rated as either poor or needing improvement.

Specific immune response. Although the human immune system is very good at protecting itself against microbial invaders, several of its components become less efficient in older people. An example is alterations in different types of white blood cells. One kind of white blood cell, known as T-cell lymphocytes, plays a critical role in responding to microbial invasions. The T-cell lymphocytes respond both by turning on B-cell lymphocytes (which make specific antibodies to infectious agents) and by producing inflammatory chemicals (which help destroy the foreign material). With age, however, the body's production of T-cells capable of responding to new infectious challenges declines, as does the B-cells' ability to produce specific antibodies.¹⁴ As a result, seniors are less capable of mounting a vigorous immune response to bacteria to which they have not been previously exposed, or to newly encountered bacteria (including mutated versions of previously encountered bacteria). By the same token, vaccines against bacterial diseases may not work well for the older population, since vaccines work by "priming" the body's own immune system to fight a particular microbe.

Effects of chronic conditions

As people age, they are more likely to develop debilitating conditions that reduce their ability to fight infection. First among these conditions is malnutrition, an inadequate quantity and/or quality of calories and nutrients. The diets of approximately one-third of senior citizens are deficient in vitamins and trace minerals,¹⁵ and almost 80 percent are rated as either poor or needing improvement.¹⁶ Inadequate nutrition can have a variety of causes. Prominent among them is loss of appetite, which in turn can result from age-related alterations in taste and smell, from depression or dementia, or as a side effect of many prescription drugs. Malnutrition can also be caused by disorders that impair the body's ability to absorb

nutrients from the digestive tract, or it can result from disabilities that make shopping and food preparation difficult.¹⁷ All aspects of the nonspecific and specific immune responses can be adversely affected by malnutrition.

Chronic conditions such as cancer, diabetes, and heart disease also become more prevalent with age and are in turn associated with higher rates of illness and death from infections.¹⁸ For example, two-thirds of all cancers¹⁹ and half of all new cases²⁰ occur in people age sixty-five and older.

GREATER EXPOSURE TO BACTERIA

Seniors are a diverse group. In the United States, this older population as a whole is more prosperous, more active, and healthier than ever before.²¹ Ironically, these very factors allow many seniors to engage in activities that can increase their exposure to infectious agents. Domestic and international travel may bring them in contact with exotic bacteria.²² So can leisure activities such as gardening (which involves exposure to bacteria in soil) and community volunteer work (particularly if it includes contact with young children, other seniors, or immigrants, or takes place in medical settings).²³ These active seniors may also come into more frequent contact with health-care related infectious agents on trips to see their physician or while visiting friends and family in hospital and long-term care facilities.

Seniors who reside in long-term care facilities are especially likely to be exposed to infection-causing bacteria.

Less healthy seniors—particularly those who reside in long-term care facilities—are even more likely to be exposed to infection-causing bacteria. While the number of individuals living in nursing homes has decreased significantly in recent years, they still constitute nearly 5 percent of people over age sixty-five.²⁴ Bacterial infections are relatively common among residents of long-term care facilities, with infections of the urinary tract, respiratory tract, and skin and soft tissues among the most common.²⁵ This relatively high rate of infection arises from several factors, including close living quarters and the patients' general debility.

Other factors also contribute to relatively high rates of infection in seniors compared to younger adults. For a variety of reasons, seniors are more likely to suffer from conditions that promote bacterial infection, such as pressure ulcers (bedsores) and/or incontinence. Pressure ulcers often occur in seniors who are confined to bed or a wheelchair because of a serious illness such as cancer, an osteoporosis-related injury after a fall, or cognitive impairment—all conditions more prevalent among seniors. Likewise, incontinence is both a side effect of some medications and a common result of serious cognitive impairment. Particularly in the latter event, patients may not alert a caretaker to the need for help cleaning themselves for prolonged time periods, thereby increasing the risk of skin or urinary tract infections. About one-third of individuals over age eighty-five suffer from cognitive impairment (from stroke, Alzheimer's disease, or other causes).²⁶

Finally, seniors are at particular risk of developing an infection if they require devices such as urinary catheters, IV tubes, and venous "ports" for dialysis or other surgically implanted tubes. These types of devices all involve a breach of the skin, sometimes for months or even years; local or systemic infections often result. In catheter-related infections, for example, the patient's skin is a likely source of bacteria such as *Staphylococcus epidermidis*, which may cause bloodstream infections. Catheter-related infections have been found to increase morbidity and mortality

by 10 to 20 percent, increase hospital stays by an average of seven days, and substantially raise medical costs.²⁷

The frequency of bacterial infection translates into an extensive use of antibiotics—approximately 40 percent of all prescription drugs used in nursing homes are antibiotics—and into recurring problems with antibiotic-resistant infections.²⁸ For example, 30 percent of the patients in some U.S. nursing homes are “colonized” with a particular strain of bacteria known as methicillin-resistant *Staphylococcus aureus* (MRSA)²⁹ (an individual is said to be *colonized* by a certain type of bacteria if they are present in or on his or her body but are not currently causing illness). MRSA causes serious skin infections, pneumonia, and other ailments, and only one or two drugs (such as vancomycin) are still highly effective against it. If (or more realistically when) MRSA develops resistance to vancomycin, large numbers of untreatable serious infections are likely to result. Other resistant pathogens increasingly found in long-term care facilities include vancomycin-resistant enterococcus (VRE), penicillin-resistant *Streptococcus pneumoniae*, and quinolone-resistant *Enterobacteriaceae*, among others.³⁰ These bacteria variously cause pneumonia, heart-valve infections, meningitis, and other serious illnesses.

LIMITED THERAPEUTIC OPTIONS

Because of age-related declines in certain organs, seniors are particularly susceptible to side effects from certain antibiotics.

Once bacterial infections strike seniors, antibiotic treatment may be complicated by a number of age-related changes in physiology. For reasons that are not well understood, seniors are generally more sensitive to the unpleasant side effects of all medications, including antibiotics, and thus may not be able to tolerate the full range of available antibiotics. Furthermore, the need to avoid adverse drug interactions may significantly limit antibiotic options for seniors who are taking other medications. Most seniors take one or more medications for treatment of chronic conditions like high blood pressure, heart disease, arthritis, and/or diabetes (indeed, the average nursing home resident is taking five to ten medications at any one time).³¹ Certain medications lower the blood levels of other drugs and make them less potent, or may even interfere with the drug’s action. Finally, antibiotics can dangerously increase blood levels of drugs like blood thinners and cause bleeding complications.³²

Seniors may also be more susceptible to serious side effects from certain antibiotics. Certain classes of antibiotics, for example, adversely affect kidney function or the ear; even though such impacts may be tolerable in younger persons, in an older individual they may aggravate age-related declines and lead to outright kidney failure or deafness. An aging patient may also not be able to absorb, metabolize, or eliminate antibiotics as effectively as a younger person can, making it more difficult to prescribe the optimal dose to treat an infection.³³ For example, if a dose of antibiotic is not adequately eliminated by the kidneys, it can accumulate in the body and cause severe side effects (it is often difficult to accurately assess kidney function in older patients).

Psychosocial reasons may also limit antibiotic options. A patient’s ability to complete a prescribed course of treatment may be impaired by a number of factors:

- The inability to follow directions because of problems with hearing, seeing, or understanding them.
- The inability to remember to take pills because of memory loss.

- The fear of interactions with other drugs.
- The erroneous attribution of side effects to the prescription.
- The difficulty of opening a childproof container.³⁴
- The inability to afford antibiotics, particularly for individuals who suffer from recurrent infections.³⁵

Finally, chronic diseases in older people are sometimes more difficult to diagnose, thereby delaying their treatment. These difficulties reflect the fact that seniors may not present the same kinds of symptoms as do younger people, in part because of their reduced immune function. For example, seniors are less likely to have a fever or certain kinds of localized symptoms. They are also more likely to have chronic conditions that mask the symptoms of a bacterial illness, as when nausea is attributed to cancer chemotherapy rather than a foodborne illness. In addition, many seniors whose mental capacity is diminished may have trouble describing their symptoms.³⁶

Seniors' greater vulnerability: examples from foodborne illness

Seniors are disproportionately likely to suffer from particularly severe cases of foodborne illness.

Senior citizens are one of the groups at highest risk of dying from foodborne pathogens. Although approximately 30 percent of foodborne infections are bacterial, they account for 60 percent of hospitalizations and almost 72 percent of the deaths from foodborne diseases of known cause.³⁷ Even though the majority of cases of bacterial foodborne illness occur in children under the age of ten, some pathogens are more predominant in seniors and near-seniors. For instance, persons age sixty and older account for 54 percent of the total foodborne cases of *Listeria* and 17 percent of the cases of *Vibrio*; both *Listeria* and *Vibrio* are bacterial pathogens with high fatality rates.³⁸

Even those foodborne infections that are no more prevalent in the older population than the general population can be more lethal for seniors. Ninety-five percent of *Salmonella* infections, which cause 1.4 million illnesses annually, are spread by contaminated food.³⁹ Although such infections are not more common in healthy seniors, debilitated seniors, such as those in nursing homes, are at increased risk. A survey of foodborne illnesses in nursing homes from 1975 through 1987 reported that 52 percent of all outbreaks and 81 percent of all outbreak-related deaths were due to *Salmonella*.⁴⁰ Data suggest that mortality rates are twenty-five times higher for seniors in nursing homes who contract a *Salmonella* infection, in comparison with the general population.⁴¹

Campylobacter, which is the leading cause of foodborne bacterial infection in the United States and accounts for almost 2 million cases of food-related illness annually,⁴² is not found more often in older patients and is rarely fatal, even among seniors. But *Campylobacter* infections can be complicated by temporary, but profound, muscle weakness and paralysis called Guillain-Barré syndrome. This complication arises in about 1 out of every 1,000 *Campylobacter* cases,⁴³ but 38 percent of the time it occurs in seniors, who also account for 66 percent of the deaths from this condition.⁴⁴ In addition, nursing home patients may have an increased mortality rate, in comparison with the general population, if infected with *Campylobacter*.⁴⁵

Likewise, although *Listeria* accounts for far less than one-tenth of 1 percent of all identified bacterial foodborne infections in the United States, it is responsible

for nearly 4 percent of the total number of hospitalizations for foodborne infections and 28 percent of the deaths.⁴⁶ Seniors bear more than half the burden of infection and are two to three times more likely to die from *Listeria* infections than are younger members of the general population.

Antibiotic resistance is a major problem with the principal foodborne bacterial pathogens. Although most cases of bacterial foodborne diarrhea are self-limiting, some are severe enough to require antibiotic treatment. Such treatment may be needed because of continuing symptoms and dehydration, which may be further complicated in older persons due to an age-related decrease in the thirst response, or because the bacteria have spread to the bloodstream and organs outside the intestine. The major foodborne bacterial pathogens have long been resistant to the original antibiotics of choice (which are inexpensive and have relatively benign side effects). For example, the multidrug-resistant *Salmonella* cultured from humans with diarrhea has been increasing since the early 1980s, accounting for 19 percent of cases in 1995 in the United States.⁴⁷ Strains of *Salmonella* now exist that are resistant to virtually all available drugs.⁴⁸

¹ This narrative offers a general illustration rather than describing a particular individual's actual experience.

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At special risk: the medically vulnerable

The infectious-disease physician looked at her appointment schedule and sighed. It was going to be a long afternoon at the hospital—a cancer patient, a transplant patient, three people with HIV, someone wrestling with complications from diabetes, and another patient battling a post-surgical infection.

All were patients she had recently diagnosed as having bacterial infections. The good news was that their infections should be treatable with antibiotics. The bad news was that the first antibiotics she had prescribed hadn't done the job for several of these patients. But with luck, the bacteria would respond to the next antibiotic.

She shook her head and sighed again. In the dozen years she has been in practice, it had become far harder to find drugs that both killed the pathogens and could be tolerated by the patients. And the number of resistant strains of bacteria continued to climb each year. She paused to hope that she wouldn't find herself facing any untreatable infections that day, then marched off to see her next patient.¹

Several medical conditions predispose people to bacterial infections and/or make such infections harder to fight off. This chapter looks at a few of these groups of medically vulnerable individuals: cancer patients, organ transplant recipients, people with HIV/AIDS, and diabetics. The chapter concludes by briefly describing many other groups of people that also may find themselves temporarily susceptible to resistant infections, such as those who undergo surgery or treatment for burns.

For virtually all cancer patients, especially those undergoing chemotherapy, antibiotics play a key role in their treatment.

Cancer patients

The American Cancer Society estimates that one of every two American men and one of three American women will develop cancer during their lifetime.² Two-thirds of all cancers³ and half of all new cases⁴ occur in people age sixty-five and older. Because the U.S. population as a whole is growing older on average,⁵ the number of people with cancer is likely to climb as well.

After rising for several decades, cancer death rates began to fall in the late 1990s as survival rates finally began to improve.⁶ Even so, cancer remains the second leading cause of death in the United States (surpassed only by heart disease), accounting for over 500,000 deaths annually.⁷

The cause of death for many cancer patients is not the cancer per se but rather respiratory failure, liver or kidney failure, or—surprisingly—infection. For some cancers, like lymphoma and acute leukemia, infection accounts for more than half the fatalities.⁸ For virtually all cancer patients, especially those undergoing chemotherapy, antibiotics play a key role in their treatment. Indeed, antibiotics have revolutionized cancer treatment by enabling the use of more aggressive therapies that have led to higher survival rates. In particular, many more patients undergoing chemotherapy, bone-marrow transplants, and surgery would succumb to infection absent antibiotics. People with certain types of cancer are also particularly prone to infections from the cancer itself, and from exposure to pathogens in medical settings. These infections may be bacterial, viral, or fungal, with bacteria causing a significant proportion.

VULNERABILITY DUE TO CANCER

Depending on the type and location of a malignancy, cancer can directly increase the likelihood of acquiring an infection. Solid tumors—those that do not involve the blood and lymph system—may cause organ malfunction or obstruct the normal drainage of lymph, urine, or other fluids, thus creating conditions favoring infection. In cases of lymphoma and leukemia, cancer affects the immune system itself, thereby directly interfering with the patient’s ability to resist infection. With other cancers, severe wasting and malnutrition may also impair the immune system and render patients especially susceptible to infection.

VULNERABILITY DUE TO CANCER TREATMENT

Cancer is typically treated with surgery, radiation, chemotherapy, and/or bone marrow transplantation.⁹ Although each type of treatment can increase the risk of bacterial infection, chemotherapy and bone marrow transplantation are the most likely to do so.

Surgery is used for a number of reasons in cancer treatment: to excise tumors completely, to assess the spread of tumors, to remove or bypass obstructions caused by tumors so as to make patients more comfortable, and/or to reconstruct the anatomy after such operations. A large majority of cancer patients undergo at least one surgical procedure. Infections at the site of the surgery are a well-described risk of any operation and account for nearly 40 percent of all infections in surgical patients overall and about 15 percent of all hospital-acquired infections. Most surgery-related infections are bacterial, and increasingly these bacteria are multi-drug resistant “superbugs” against which antibiotics are less and less effective.¹⁰

Surgery can also alter anatomy in a way that makes cancer patients either more likely to acquire infections or less able to control or contain them. For example, after a tumor is removed, fluids may collect in the spaces left vacant by the tumor’s removal, creating potential breeding sites for bacteria. Similarly, if a cancer spreads to lymph nodes or the spleen—both of which are important in providing a strong immune response—these organs may be surgically removed, weakening the patient’s ability to fight infection.¹¹

Radiation therapy is used both to cure and to provide relief from symptoms in cancer patients, often in combination with other therapies. It functions by disrupting the division of rapidly proliferating cancer cells, thus killing them. Unfortunately, however, radiation is not selective and so destroys other rapidly dividing cells (such as those that line the mucus membranes and bone marrow cells) if they are in the radiation’s pathway.¹² For example, radiation treatment for head and neck cancers often results in ulcers in the mouth, breaching the mouth’s protective barrier and giving bacteria an easy entryway. Similarly, the irradiation of bones reduces a patient’s ability to fight disease because bone marrow cells produce infection-fighting white blood cells.

Chemotherapy is the administration of drugs to kill cancer cells and is the mainstay of treatment for cancers that have metastasized, that is, spread beyond the site where they originated. Chemotherapy also is used to reduce the symptoms of incurable cancers and as adjuvant (that is, supplemental) therapy after surgery or radiation. Like radiation, all but the newest chemotherapy drugs are nonspecific and target all rapidly dividing cells, including many that play a key role in the immune system.

Two common consequences of chemotherapy are important with respect to the risk of infection. First, chemotherapy usually kills most of the white blood cells called granulocytes that play a key role in fighting bacterial infection. Extreme depletion of granulocytes substantially increases the risk of infection,¹³ and the immediate administration of antibiotics is the only way to prevent death when granulocyte levels plummet and infection strikes.¹⁴ Second, mucositis—severe damage to and inflammation of the lining of the mouth, gastrointestinal, and respiratory tracts—also creates a large area through which disease-causing organisms may enter the body.¹⁵ Infection is common, and antibiotics are critical to preventing severe or fatal consequences.

Bone marrow transplants and blood stem cell transplants¹⁶ have become standard therapies when high doses of chemotherapy are needed. The procedure involves the removal and storage of marrow or stem cells before the patient receives high-dose chemotherapy to kill the cancer. But high doses of these drugs also can be lethal because of prolonged suppression of bone marrow function. They are possible only because the stored marrow or stem cells can be returned to the patient to restore bone marrow function after the chemotherapy drugs have been cleared out of the system.

During intensive chemotherapy and before the marrow has resumed normal function, infection is a major cause of mortality.¹⁷ When a patient's own bone marrow must be replaced with that from a donor, the situation becomes even more complicated. Such a patient's immune system must be suppressed for months or even years to prevent rejection of the donated marrow. Because bacterial infections are particularly likely to kill bone marrow transplant patients in the first month or two after the transplant, effective antibiotics are a mainstay of treatment and necessary for the patient's survival.

Following a bone-marrow transplant, effective antibiotics are necessary for the patient's survival.

VULNERABILITY DUE TO EXPOSURE

Cancer patients also are susceptible to infection because of their extensive exposure to disease-causing organisms during frequent visits to the doctor or clinic for treatment and checkups, and during repeated hospitalizations for treatment or because of complications. Unfortunately, pathogens acquired in hospitals and clinics are much more likely to be resistant to antibiotics, making such infections very difficult to treat. In addition, many cancer patients have permanent catheters, to allow access to blood veins for chemotherapy, blood tests, and transfusions; such catheters offer bacteria easy entry into the body.

Moreover, even bacteria that do not usually pose a threat to healthy people can cause disease in cancer patients because of these patients' less-effective immune systems. These bacteria are among the types that have become resistant to many kinds of antibiotics and consequently are more difficult to treat.¹⁸ In other words, for cancer patients (and others with impaired immune function), the reduced efficacy of antibiotics can make even these ordinarily harmless bacteria deadly.

Diabetics

Diabetes is an epidemic illness in the United States today. Approximately 16 million Americans have diabetes (though roughly a third are not aware of their condition), with 2,200 new cases diagnosed each day.¹⁹ Diabetes is now the seventh

Diabetes is now an epidemic illness in the United States, and diabetics are more likely to have severe bacterial infections.

leading cause of mortality in this country, causing nearly 200,000 deaths annually.²⁰ In adults, the prevalence of diabetes rose 33 percent between 1990 and 1998, with the largest increase among people in their thirties (76 percent).²¹ Because some types of diabetes are associated with obesity, a sedentary lifestyle, and old age, and given the current trend toward a heavier, less athletic, and older population, diabetes may well become even more prevalent in the future.

Diabetes can be treated but not cured. Complications from the disease include blindness, kidney failure, heart disease, stroke, and lower-extremity amputations. Diabetics' immune systems also are somewhat impaired. While diabetics are not necessarily more susceptible to infections than non-diabetics are, the types of infections they develop differ from those encountered by most other groups; common infections occur at different rates in diabetics; and finally, these infections are often more serious.²² For example, as many as 30,000 diabetics die each year from complications of flu and pneumonia, three times the mortality rate in people without the disease.²³ And when a diabetic contracts pneumonia, the illness is more likely to be caused by dangerous bacteria like *Staphylococcus aureus*. Even when a more common germ like *Streptococcus pneumoniae* causes pneumonia, in diabetics the infection is more likely to spread to the bloodstream and/or be fatal.²⁴ Other serious infections are also more common in diabetics, ranging from *Salmonella*, which can cause serious foodborne illness and complications, to *E. coli* and *Klebsiella*, which causes many ailments, including pneumonia and kidney infections.²⁵ These organisms are often multi-drug resistant (that is, resistant to three or more types of antibiotics), which makes treating serious infections all the more difficult.

Skin and soft-tissue infections are also particular problems for diabetics. Because diabetes often results in long-term complications affecting the nerves and circulatory system, diabetics' feet are susceptible to injury and the development of ulcers. The combination of skin-barrier breaches and compromised circulation make infection more likely, including severe infections that can spread to bones and muscle.²⁶ The same factors that cause infection also make treatment more difficult: poor circulation makes it hard for the ulcer to heal, and bacteria can cause infections lasting for long periods of time. Consequently, diabetic patients may require many weeks or months of broad-spectrum antibiotics, with high risk of developing antibiotic-resistant bacterial infection. Further, an uncontrollable infection can result in the amputation of the limb or death.

Transplant recipients

The transplantation of solid organs (organs other than bone marrow and corneas) is a major triumph of modern medicine. In 2000, almost 23,000 Americans received new organs and a new lease on life, more than an 80 percent increase from the number in 1988.²⁷

Most transplants are performed in patients suffering from kidney, liver, or heart failure, but the intestines, pancreas, and lungs have also been transplanted. Because of important advancements in transplantation procedures, the first-year survival rates of the transplanted organ now exceed 80 percent.²⁸

Higher survival rates, in large part, stem from progress in keeping the patient's body from rejecting newly transplanted tissue, in turn by suppressing the patient's own immune function.²⁹ To this end, medications that suppress immune functions

Following a transplant, medications that suppress immune functions are administered to patients for extended periods, making them extremely vulnerable to infection.

are administered to transplant patients for extended periods, or even on a life-long basis. Unfortunately, these drugs also limit the ability of the transplant patient's immune system to recognize and fight microbial invaders, thereby making these patients extremely vulnerable to infection. While transplantation can successfully treat some ailments (indeed, is sometimes the only treatment option), one drawback is the permanent increase in the patient's susceptibility to infection. Until new methods are developed to prevent organ rejection without suppressing the immune system, transplant patients will remain especially vulnerable to infectious disease.

Susceptibility to infection varies greatly among different types of transplant patients and over time. In general, though, solid-organ transplant recipients are roughly three times more likely to die from surgical-site infections or intra-abdominal infections, septicemia (bloodstream infections), or pneumonia than are healthy people undergoing surgery.³⁰ Without effective antibiotics, these statistics would be even grimmer.

The greatest risk for bacterial infection is during the first month following the transplant.³¹ Immediately after the procedure, transplant patients receive very high doses of immune-suppressive drugs to prevent an acute rejection of the transplanted tissue. During this month, they also must remain in the hospital, where they are exposed to the bacteria (often, drug-resistant ones) that also reside there. Like cancer patients who have undergone major surgery, transplant patients typically are given catheters and/or similar devices that serve as potential conduits for bacteria.

From one to six months after the transplant, bacterial infections become less prominent, and viral infections dominate. Certain kinds of transplants, however, leave patients at continued risk for bacterial infections. For example, kidney transplant patients have ongoing problems with urinary tract infections that require treatment with antibiotics. Even after roughly half a year, 5 to 10 percent of transplant patients develop recurrent or chronic rejection, for which they need prolonged, intense doses of immunosuppressive drugs. Indeed, these individuals require long-term antibiotic treatment and must be careful to minimize their exposure to bacteria.³² Absent effective antibiotics, this group would be at extreme risk of frequent and potentially fatal infections. In a recent review on infections in transplant patients, the authors concluded:

Infection and rejection, the two primary barriers to successful organ transplantation, are inextricably linked. . . . To increase the safety of organ transplantation further, we need improved diagnostic tests to detect infection early and to monitor immune function, as well as new therapies to overcome antimicrobial resistance.³³

HIV/AIDS patients

Approximately 900,000 persons in the United States are infected with Human Immunodeficiency Virus (HIV).³⁴ HIV infects the cells of the immune system and reduces both their number and their capacity to fight off infection. Because HIV is a viral rather than a bacterial disease, antibiotics cannot be used to treat it directly.³⁵ But antibiotics are nonetheless critical in treating HIV patients, because HIV's principal effect is disrupting the body's immune system. Ironically, many of the therapies available to treat HIV infections also kill the body's own infection-

fighting white blood cells. Unchecked, HIV progresses to Acquired Immuno-deficiency Syndrome (AIDS), a fatal disease characterized in its advanced stages by numerous bacterial, viral, and fungal infections, certain cancers, nutritional wasting, and/or deterioration of the central nervous system.

Although the prognosis for patients with HIV and AIDS has improved markedly owing to the availability of highly active anti-retroviral therapies (HAART),³⁶ patients are still at increased risk for infection. Although some HIV-related infections occur only in the disease's advanced stages, bacterial infections can occur at any time. Bacterial infections that are particular problems for these patients include those caused by *Streptococcus pneumoniae* and *Salmonella*, as well as tuberculosis.

Bacterial pneumonia is often the first sign of HIV disease.³⁷ Pneumonia caused by *S. pneumoniae* is much more common in HIV-infected patients than in the general population.³⁸ When *S. pneumoniae* is resistant to penicillin, HIV-positive patients have a mortality rate 7.8 times higher than if their disease was fully or even partially sensitive to penicillin.³⁹ By contrast, in individuals with normal immune systems, there is no demonstrable difference in mortality or morbidity from pneumonia caused by penicillin-resistant pneumococcal bacteria as long as appropriate antibiotics are employed.⁴⁰

HIV-infected patients are also more at risk of developing serious foodborne bacterial infections. In fact, in the 1980s, persistent infection with *Salmonella* was identified as one of the infections defining AIDS, because HIV-infected individuals were twenty times more likely to be infected with *Salmonella*; once infected, they were five times more likely to have it spread to their bloodstream.⁴¹ Unlike healthy persons who usually require no therapy for *Salmonella*, AIDS/HIV patients need to take antibiotics daily to prevent recurrent septicemia (a severe bacterial infection of the blood).

Since the development of improved HAART therapies in the 1990s, *Salmonella* has become less prominent in AIDS patients, but other foodborne and waterborne bacterial pathogens continue to plague this vulnerable population. Compared with the average person, infections by *Campylobacter* (the most prevalent bacterial foodborne pathogen in the United States) are 39 times more likely in AIDS patients;⁴² *Listeria* infections are more than 60 times more common in HIV-infected individuals, and 145 times more likely in people with full-blown AIDS.⁴³ Other bacterial infections, such as tuberculosis, continue to complicate HIV disease; indeed, worldwide, bacterial infections are a principal cause of death in HIV-infected people,⁴⁴ with antibiotic-resistant infections a particular threat.

Finally, it is important to remember that the HIV virus is highly adaptable. Researchers, clinicians, and patients all expect that the current lull in disease activity will rapidly end as the virus becomes resistant to the HAART drugs. When this happens, infectious complications of HIV disease will increase. This provides yet another reason for guarding the efficacy of antibiotics for the treatment of HIV and AIDS patients.

Other at-risk groups—and everyone else

Many other groups will also be affected if antibiotic resistance continues to worsen. For example, rheumatoid arthritis affects more than 2 million Americans.⁴⁵ Some of the medications, such as steroids, that these arthritis sufferers take to control

Antibiotics are critical in treating HIV patients, because HIV's chief effect is disrupting the body's immune system.

Some of the medications that certain arthritis sufferers take to control their disease also inhibit their immune system.

their disease also inhibit their immune system. Because the aging process also tends to weaken the vigor of the immune system,⁴⁶ older patients on such medications may be especially susceptible to bacterial infections—and concomitantly vulnerable if antibiotics lose their effectiveness.

Another example comes from the other end of the age spectrum: the children and growing number of young adults with cystic fibrosis. Although they are benefiting from new therapies, such as lung transplants, these patients are highly dependent on antibiotics for their survival.⁴⁷ Increases in antibiotic resistance without replacement medications or alternative therapies could reverse this outcome.

The preceding discussion focuses on groups with particular medical conditions, but it should be noted that even the healthiest individuals may need, for instance, surgery following an automobile or other kind of accident. Any surgery carries with it the risk of infection, and hospital-acquired infections are increasingly likely to involve antibiotic-resistant organisms.⁴⁸ And even the hale and hearty occasionally develop pneumonia, severe food poisoning, or other bacterial illnesses that need to be treated with antibiotics. Therefore, preserving the effectiveness of antibiotics is an important goal for everyone.

¹ This narrative offers a general illustration rather than describing a particular individual's actual experience.

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Current uses of antibiotics, and strategies to reduce their overuse

Overview

Antibiotics are used for several distinct purposes.¹ The best known are those described in Chapter 1, namely treating people for illnesses caused by bacteria. Similarly, when dogs, cats, and other companion animals have bacterial diseases, they may be treated with antibiotics. In the United States, these uses generally require a prescription by a physician or veterinarian.²

Less well known is the widespread use of antibiotics in agriculture,³ mostly in food animals (predominantly cattle, swine, and poultry).⁴ Such uses generally do not occur via prescription.⁵

Antibiotics are often used inappropriately in both human medicine and agriculture. Physicians sometimes prescribe antibiotics when they should not, for example, for patients who expect to receive a prescription when they visit the doctor's office—even if their illness is caused by a virus and thus is not treatable with antibiotics. Indeed, it has been estimated that between 20 and 50 percent of the outpatient prescriptions for antibiotics in the 1990s were unnecessary.⁶ In recent years, significant efforts have been made to educate physicians and patients alike about the importance of not using antibiotics unnecessarily.⁷

Some uses of antibiotics in agriculture are increasingly controversial. Because agricultural uses of antibiotics are not widely known, the next section provides additional details on this topic.

Antibiotics in animal agriculture⁸

Antibiotics are used in two ways in raising food animals: therapeutically, to treat bacterial disease in sick animals, and nontherapeutically, to promote slightly faster growth and prevent disease in healthy animals, particularly at intensive agricultural operations (also known as Confined Animal Feeding Operations, or CAFOs, sometimes called “factory farms”).⁹ A few therapeutic uses in animal agriculture require a veterinarian's prescription, but nontherapeutic uses never do. Nontherapeutic antibiotics are added to feed, usually by the feed producer, though sometimes by the farmer. Indeed, sacks or containers of antibiotics, often by the pound, are available for anyone to purchase in many farm-supply stores.

Nontherapeutic antibiotics are given to animals in relatively low doses in feed or water over an extended period. According to a leading expert, this practice constitutes “the perfect formula for selecting increasing numbers of resistant bacteria in the treated animals,”¹⁰ because it kills the susceptible bacteria while leaving the resistant strains to reproduce. Of particular concern is the nontherapeutic use of antibiotics that are identical to, or closely related to, antibiotics also used to treat human illnesses—for example, penicillin, tetracycline, and erythromycin.

In June 2001, the American Medical Association adopted a formal resolution opposing the nontherapeutic use of antibiotics in animal agriculture.¹¹ Other groups on record as opposing this practice include the American Public Health Association,¹² the Council of State and Territorial Epidemiologists,¹³ the National

In June 2001, the American Medical Association joined a growing roster of health organizations that have adopted formal resolution opposing routine use of important antibiotics in healthy farm animals.

A 1999 National Academy of Sciences report estimated that ending non-therapeutic antibiotic use in agriculture would cost U.S. consumers only about \$5 to \$10 per person per year.

Association of State Public Health Veterinarians,¹⁴ and the World Health Organization.¹⁵ In October 2001, the prestigious *New England Journal of Medicine* published a guest editorial concluding that the available data constitutes a “smoking gun” that warrants a ban on nontherapeutic uses and restrictions on certain therapeutic uses of antibiotics in animal agriculture.¹⁶

Consistent with the World Health Organization’s recommendations, in 1999 the European Union banned several medically important antibiotics from use as growth promoters in agricultural animals. Both Sweden and Denmark have gone even further: in 1986 Sweden banned *all* nontherapeutic uses of antibiotics,¹⁷ and Denmark phased them out between 1995 and 1999.¹⁸ Both countries instituted their bans largely at the initiation of farmers, in order to restore consumer confidence in meat-production systems. Both nations continue to have robust meat-production industries and use significantly lower quantities of antibiotics overall. Neither country, though, has restricted use of therapeutic antibiotics to treat sick animals. Finally, the European Union is reportedly considering phasing out the last four antibiotics and related compounds now approved for nontherapeutic use.¹⁹

To date, the United States has not placed any restrictions on the nontherapeutic use of antibiotics in animal agriculture based on resistance concerns. In 1999, the National Academy of Sciences estimated that the elimination of such uses in poultry, cow, and swine production would cost U.S. consumers only about \$5 to \$10 per person annually.²⁰

In addition to concerns about using antibiotics in healthy animals, those used to treat illness in agricultural animals can also present problems, particularly for antibiotics that play key roles in treating human illness. In October 2000, the U.S. Food and Drug Administration (FDA) proposed banning a class of antibiotics known as fluoroquinolones from use in poultry, based on evidence that resistance to this type of drug in some human pathogens has risen dramatically since 1995,²¹ when fluoroquinolones were approved for use in poultry. Fluoroquinolones are the drug of choice in treating severe foodborne illnesses in humans. Although one manufacturer of the drug (Abbott Laboratories) immediately phased out production, the other (Bayer Corporation) has contested the ban. As of November 2001, the drug remains in use on poultry farms despite concerns expressed by the American Medical Association and other health experts and advocacy groups.²²

Quantities of antibiotics used

Remarkably, no authoritative statistics are available on the overall quantity of antibiotics used annually in the United States, nor are there authoritative statistics on the quantity used in either human medicine or animal agriculture. Some experts estimate that agricultural use of antibiotics accounts for about 80 percent of all antibiotics sold in the United States, with the lion’s share—roughly 70 percent of the total—being used nontherapeutically.²³ More than half these antibiotics are now used in human medicine or are so closely related to human-use drugs that they trigger cross-resistance. Although agribusiness groups assert that the nontherapeutic agricultural use of antibiotics is substantially lower, they have not made public the basis for their calculations (other than as a one-page press release without explanatory methodology).²⁴ The summary data provided by the industry do, however, acknowledge the use of 20.5 million pounds of antibiotics

annually in animals (9.7 million pounds of which are compounds that are not antibiotics in the narrow sense of that term).²⁵

It is important to note that “use” does not equate directly with “contribution to resistance in human medicine.” Scientists cannot now determine what fraction of antibiotic resistance in human pathogens arises from agricultural versus medical use of antibiotics. Indeed, the complexity of the issue makes it unlikely that such an apportionment will be feasible any time in the reasonable future. But it is clear that while medical use of antibiotics is a major contributor to the emergence of antibiotic resistance, agricultural uses also pose a problem. The vast quantity of antibiotics used in agriculture unquestionably increases the numbers of resistant bacteria throughout the environment as well as on food products and thus contributes significantly to this growing health threat.

Pathways of exposure: from farm to human

When medical overuse of antibiotics gives rise to resistant bacteria, they do not have far to travel before colonizing or infecting humans. In addition to the individual in whom the resistant bacteria first emerge, such bacteria can spread to that person’s doctors, nurses, health-care aides, family, friends, and even nearby inanimate objects.²⁶ Although some types of bacteria are easily dislodged by washing one’s hands and taking similar precautions, others are far more tenacious and harder to control.

The route that resistant bacteria take from agriculture to humans, however, is more complex.²⁷ In a nutshell, these pathways can be summarized as food, environment, and the workplace.²⁸ Each is discussed below.

FOOD

Resistant bacteria can contaminate carcasses during slaughter and wind up on raw meat that reaches the consumer (whether in a private home, restaurant, or institutional kitchen).²⁹ If the meat is not cooked thoroughly, if cutting boards or knives are not thoroughly washed before being used for other food, or if raw meat juices are splashed onto other food or utensils, these bacteria can infect people who eat the food or use the utensils.

Foodborne illness is not uncommon. For example, *Salmonella* and *Campylobacter* from foodborne sources cause more than 3 million illnesses and 600 deaths annually.³⁰ Of course, disease-causing bacteria on meat are bad news even if they are not resistant, but at least antibiotics can be used to treat people who get seriously sick from such infections. (While most foodborne illnesses are of the “stomach bug” variety, a recent study in the *New England Journal of Medicine* found that one type of resistant *Escherichia coli*, potentially related to the ingestion of contaminated foods, was the cause of urinary tract infections in women located in several regions of the United States.³¹)

ENVIRONMENT

The nearly 2 trillion pounds of animal waste produced each year in the United States³² contain significant amounts of bacteria.³³ Moreover, because as much as 75 percent of an antibiotic may pass undigested through an animal, its waste can contain antibiotics as well as antibiotic-resistant bacteria and their genes.³⁴ Such

Resistant bacteria arising in agriculture can reach humans through a variety of pathways, including food, environment, and the workplace.

waste is often stored in open-air lagoons and/or spread on fields. Many of the lagoons are not lined and so are prone to leaking or breaking, thereby releasing the animal waste to surface and ground water.³⁵ In addition, manure spread on agricultural fields may contaminate vegetables and fruits, which can then transfer resistant bacteria to humans.

Many bacteria (pathogenic and otherwise) can live in both humans and animals, and many also can live in the general environment. Some cause disease in both humans and animals; others, in one but not the other. Animals and/or the environment may serve as “reservoirs” of human pathogens, or resistance genes that can be easily transferred from innocuous to pathogenic bacteria.

WORKPLACE

Workers at animal-agriculture operations may become infected with resistant bacteria in the course of caring for animals fed antibiotics, and they may then pass those bacteria along to their family and others in their community.³⁶ Some of the most dangerous multidrug-resistant “superbugs,” in fact, have been found in children and adults who have close contact with food animal production.³⁷

Combating antibiotic resistance

In the words of the Centers for Disease Control and Prevention, “Decreasing inappropriate antibiotic use is the best way to control resistance.”³⁸ Achieving this goal will require action by businesses, governmental leaders, and individuals, as patients, consumers, and citizens. The following paragraphs describe the steps that each of these groups can—and should—take to help combat this looming health crisis.³⁹

First, though, a short note on terminology. As used below, the phrase “medically important antibiotics” refers to those antibiotics that are currently used in treating human disease or similar antibiotics that trigger cross-resistance to human-use drugs. It also includes antibiotics that appear to be plausible candidates for medical purposes in the future (and those that promote cross-resistance to such drugs). The latter category is included because of recent experience with virginiamycin, which was used as a growth promoter beginning in 1974. Although virginiamycin had long been regarded as too toxic for use in humans, a close analog to virginiamycin was introduced for human use in the late 1990s. It was called Synercid and was critically important for treating certain pathogens that had become resistant to all other available antibiotics. Unfortunately, even before Synercid was approved for human use, Synercid-resistant bacteria were already showing up in people—a possible legacy of years of using virginiamycin in agriculture.⁴⁰ The lesson from Synercid is that some of the antibiotics used today only in animals may become tomorrow’s newest lifesaving drugs for humans—particularly as resistance continues to spread, thus shrinking the availability of other effective antibiotics.⁴¹

Actions by governmental and corporate decisionmakers

1. Producers of meat and poultry should discontinue the nontherapeutic use of medically important antibiotics, and pharmaceutical companies should stop producing antibiotics for such use in food animals.

As the Centers for Disease Control points out, “Decreasing inappropriate antibiotic use is the best way to control resistance.”

2. Companies that market meat and poultry, including supermarkets, restaurants, and fast-food chains, should voluntarily stop selling products that have been produced with medically important antibiotics; they should also inform consumers of the availability of products produced without such antibiotics.
3. Congress or the U.S. Food and Drug Administration (FDA) should mandate a phaseout of the nontherapeutic use of medically important antibiotics in animal agriculture.
4. FDA should promptly finalize its proposal to ban fluoroquinolone antibiotics from use in poultry, to help combat increased resistance to this antibiotic, which is crucial in treating severe cases of foodborne illness in humans. The Bayer Corporation, the only remaining manufacturer of fluoroquinolones for poultry, should stop opposing the ban and voluntarily withdraw its product from the market.
5. Congress or FDA should require the collection of accurate data on the production and use of antibiotics in both human medicine and animal agriculture, and that information should be made available to the public.
6. Congress should provide adequate funding to FDA, Centers for Disease Control and Prevention, U.S. Geological Survey,⁴² and other agencies that are involved in combating antibiotic resistance and/or gathering data on the problem.

Actions by consumers and citizens

1. Consumers should select meat, either at the grocery store or in restaurants, that has been produced without the use of medically important antibiotics. A directory of restaurants and grocers selling such meat is available at www.KeepAntibioticsWorking.com/guide.
2. Citizens should urge policymakers in Congress and FDA, as well as corporations, to take the steps listed above. All our voices are needed, especially those who have had personal experience—as a patient, family member, friend, or health-care professional—in dealing with an antibiotic-resistant infection.

Actions by patients

The Centers for Disease Control and Prevention offer the following tips for patients:⁴³

1. Antibiotics intended for bacterial infections should not be taken for viral infections such as colds, coughs, or the flu.
2. If your health-care provider determines that you do not have a bacterial infection, ask about ways to help relieve your symptoms. Do not pressure your provider to prescribe an antibiotic.
3. Take the medicine exactly as your health-care provider prescribes.
4. Take the antibiotic until you have finished it, even if you are feeling better before it is gone. Do not save the medication to treat yourself or others later.

Conclusion

Although antibiotic resistance poses a threat to everyone, several groups are especially vulnerable: children, seniors, and persons with compromised immune systems and

certain other medical conditions. These groups will be hardest hit if recent trends in the spread of resistant bacteria continue unchecked. Halting those trends will require curtailing the unnecessary and inappropriate use of antibiotics in both human medicine and animal agriculture. Unless we act now, we will face a future of untreatable bacterial infections, and children, seniors, and those with health problems will pay the biggest price.

¹ A related topic that is beyond the scope of this report is the use of antimicrobials in soaps and some plastics for consumer use. These chemicals are distinct from antibiotics, although they also kill bacteria and other microorganisms, and some experts are concerned that overuse of these compounds may create problems. See Alliance for Prudent Use of Antibiotics, “Overuse of the antimicrobial triclosan in antibacterial soaps may promote triclosan-resistance,” www.healthsci.tufts.edu/apua/News/Antibacterials.html; E. Susman, “Too Clean for Comfort,” *Environmental Health Perspectives* 109 (2001): A18.

² Prescriptions are not required for some antibiotic-containing ointments sold over-the-counter for use on minor scrapes and burns.

³ Other uses of antibiotics in agriculture include use on some fruit trees to control “blights” caused by bacteria, but such use of antibiotics accounts for far less than 1 percent of the antibiotics used in agriculture and is not further discussed in this report. See M. Mellon, C. Benbrook, and K.L. Benbrook, *Hogging It—Estimates of Antimicrobial Abuse in Livestock* (Cambridge, Mass.: Union of Concerned Scientists / UCS Publications, 2001), pp. 51, 52, www.ucsusa.org/publications.

⁴ Though the use of antibiotics in aquaculture is beyond the scope of this report, it is worth noting that such uses are of concern because the antibiotics are administered to the fish via food, thus releasing antibiotics directly into waterways. See generally, D.P. Weston, “Environmental Considerations in the Use of Antibacterial Drugs in Aquaculture,” in *Aquaculture and Water Resource Management*, D. Baird et al., eds. (London: Blackwell Science, 1996), pp. 140-165.

⁵ One notable exception is the agricultural use of fluoroquinolones, which are available only for use by or on the order of a licensed veterinarian. See U.S. Department of Health and Human Services, Food and Drug Administration, “Enrofloxacin for Poultry; Opportunity for Hearing,” *Federal Register* 65 (October 31, 2000): 64954-65.

⁶ P.F. Harrison and J. Lederberg, eds., “Antimicrobial Resistance: Issues and Options,” workshop report, Forum on Emerging Infections, Division of Health Sciences Policy, Institute of Medicine (Washington, D.C.: National Academy Press, 1998), vol. 1, 39-41, 46; U.S. Congress, Office of Technology Assessment (OTA), “Impacts of Antibiotic-Resistant Bacteria,” OTA-H-629 (Washington, D.C.: U.S. Government Printing Office, September 1995), www.nap.edu/books/0309060842/html/R1.html.

⁷ See, for example, American Academy of Pediatrics and Centers for Disease Control, “Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections,” 101 (1998): 163-184; Center for Disease Control and Prevention’s “National Campaign for Appropriate Antibiotic Use,” www.cdc.gov/antibioticresistance/default.htm; and the “Save Antibiotic Strength” campaign by the Coalition for Affordable Quality Healthcare, a coalition of twenty-six of America’s largest health plans and insurers and three principal health plan associations, www.caqh.org/whatwedo_advance_sas.html. Also see S. Dent, “Deadly Risks of Antibiotic Overuse Warrant Widespread Education,” *American Academy of Family Physicians, Family Practice Report* 6 (2000) www.aafp.org/fpr/20000300/01.html; B. Schwartz, D.M. Bell, and J.M. Hughes, Editorial: “Preventing the Emergence of Antimicrobial Resistance: A Call for Action by Clinicians, Public Health Officials, and Patients,” *Journal of the American Medical Association* 278 (1997): 944-45.

⁸ For further information, see generally KeepAntibioticsWorking.com.

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¹⁰ S.B. Levy, “The Challenge of Antibiotic Resistance,” *Scientific American* 278 (1998): 46-56, www.sciam.com/1998/0398issue/0398levy.html.

¹¹ American Medical Association, Resolution 508, annual meeting, 2001, www.ama-assn.org/ama/pub/article/1818-5001.html.

- ¹² American Public Health Association, Resolution 9908: “Addressing the Problem of Bacterial Resistance to Antimicrobial Agents and the Need for Surveillance,” 1999, www.apha.org/legislative/policy/policysearch/index.cfm?fuseaction=view&id=179.
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- ¹⁵ World Health Organization, “Containing Antimicrobial Resistance: Review of the Literature and Report of a WHO Workshop on the Development of a Global Strategy for the Containment of Antimicrobial Resistance” (Geneva: World Health Organization, February 4–5, 1999), www.who.int/emc-documents/antimicrobial_resistance/docs/whocdscsrdrs992.pdf.
- ¹⁶ See S.L. Gorbach, Editorial: “Antimicrobial Use in Animal Feed—Time to Stop,” *New England Journal of Medicine* 345 (2001): 1202–03.
- ¹⁷ L. Backstrom, “Sweden’s Ban on Antimicrobial Feed Additives Misunderstood,” *Feedstuffs*, November 22, 1999. However, Sweden did not ban the use of a group of compounds called ionophores; though ionophores are not technically antibiotics, they are often referred to as such.
- ¹⁸ H.D. Emborg et al., “The Effect of Discontinuing the Use of Antimicrobial Growth Promoters on the Productivity in the Danish Broiler Production,” *Preventive Veterinary Medicine* 50 (2001): 53–70; see also F. Bager and H.D. Emborg, eds., DANMAP 2000—Consumption of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Foods and Humans in Denmark” (Copenhagen: Statens Serum Institut, Danish Veterinary & Food Administration, Danish Medicines Agency, and Danish Veterinary Laboratory, 2000), www.svs.dk/uk/Organization/Frm_org.htm (select Zoonosis Centre; DANMAP 2000). Like Sweden, Denmark has not banned ionophores.
- ¹⁹ European Federation of Animal Feed Additive Manufacturers, “EU Mulls Feed Antibiotics Ban,” February 7, 2001, www.fefana.org. (The compounds in question are avilamycin, monensin, flavomycin, and salinomycin).
- ²⁰ National Research Council, “Costs of Eliminating Subtherapeutic Use of Antibiotics,” in *The Use of Drugs in Food Animals: Benefits and Risks* (Washington, D.C.: National Academy Press, 1999), books.nap.edu/books/0309054346/html/R1.html.
- ²¹ U.S. Department of Health and Human Services, Food and Drug Administration, “Enrofloxacin for Poultry; Opportunity for Hearing.”
- ²² Letter to Helge H. Wehmeier, President and CEO, Bayer Corporation, dated November 21, 2000, www.environmentaldefense.org/programs/Health/BayerLetter.PDF; Letter to Helge H. Wehmeier, President and CEO, Bayer Corporation, dated October 31, 2000, www.environmentaldefense.org/pubs/Filings/BayerLetter.html.
- ²³ Mellon, Benbrook, and Benbrook, “*Hogging It.*”
- ²⁴ Animal Health Institute, “New Data on Antibiotic Use in Animals Available,” press release dated February 14, 2001, www.ahi.org/News%20Room/Press%20Release/2001/February/usage.htm.
- ²⁵ Ibid.
- ²⁶ S.J. Olsen et al., “A Nosocomial Outbreak of Fluoroquinolone-Resistant Salmonella Infection,” *New England Journal of Medicine* 344 (2001): 1572–79.
- ²⁷ See G.G. Khachatourians, “Agricultural Use of Antibiotics and the Evolution and Transfer of Antibiotic-Resistant Bacteria.”
- ²⁸ In addition, antibiotics absorbed by animals can end up in meat as residues. While the government has established maximum levels for the amount of antibiotic “residues” allowed in meat and poultry, it is far from clear that the amount of sampling and analysis that is done suffices to ensure that these standards are actually met. See U.S. Department of Agriculture, Food Safety and Inspection Service, 2000 FSIS National Residue Program “Blue Book,” www.fsis.usda.gov/OPHS/blue2000/index.htm. Moreover, even if all residues were well within the standards for every piece of meat and poultry produced in the United States, it would not solve the problems of antibiotic use in agriculture, in light of the foodborne, worker, and environmental pathways by which resistant bacteria can spread.

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- ³⁰ P. S. Mead et al., “Food-Related Illness and Death in the United States,” *Emerging Infectious Diseases* 5 (1999): 607–25, www.cdc.gov/ncidod/EID/vol5no5/mead.htm.
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- ³² Environmental Defense, based on USDA data, www.scorecard.org/env-releases/aw/.
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- ³⁶ R.W. Lyons et al., “An Epidemic of Resistant *Salmonella* in a Nursery—Animal to Human Spread,” *Journal of the American Medical Association* 243 (1980): 546–47; S.B. Levy, G.B. Fitzgerald, and A.B. Macone. “Changes in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline-supplemented Feed on a Farm,” *New England Journal of Medicine* 295 (1976): 583–88.
- ³⁷ P. Fey et al., “Ceftriaxone-Resistant *Salmonella* Infection Acquired by a Child from Cattle,” *New England Journal of Medicine* 342 (2000): 1242–49.
- ³⁸ Centers for Disease Control and Prevention, “Background on Antibiotic Resistance” (2001), www.cdc.gov/antibioticresistance/default.htm.
- ³⁹ Because this report is directed toward policymakers and interested citizens, rather than health-care practitioners in their professional capacity, this section does not address the steps that can be taken by such professionals. Such steps are, however, of considerable importance in controlling the spread of antibiotic resistance. See generally www.healthsci.tufts.edu/apua/Practitioners/health-care.html, and www.cdc.gov/drugresistance/technical/clinical.htm.
- ⁴⁰ S. Rossiter, et al., “Isolation of Quinupristin-Dalfopristin-resistant *Enterococcus faecium* from Human Stool Specimens and Chickens Purchased from Grocery Stores in the U.S.—Use of Virginiamycin May Compromise New Human Antibiotic,” 137th American Veterinary Medical Association Annual Meeting, Salt Lake City, UT, July 2000. (The authors note that “the use of virginiamycin to promote the growth of chickens and other food animals may compromise the effectiveness of QD, a new antibiotic for the treatment of life-threatening infections in humans.”)
- ⁴¹ Certain animal-use drugs, such as ionophores and arsenicals, appear relatively unlikely to be candidates for human use, and thus reducing their use appears to be a lower priority. However, it is important to determine whether these compounds might have a cross-resistance impact.
- ⁴² The Toxic Substances Hydrology Program conducted by the U.S. Geological Survey (USGS) is analyzing for 22 human and veterinary antibiotics in samples from approximately 200 water bodies across the country (streams, wells, etc.). See toxics.usgs.gov/regional/emc.html.
- ⁴³ See Centers for Disease Control and Prevention, National Center for Infectious Diseases, “Antimicrobial Resistance: Prevention Tips” (2001), www.cdc.gov/drugresistance/general/prevention_tips.htm.

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