What You Need to Know About Infectious Disease

DETAILS

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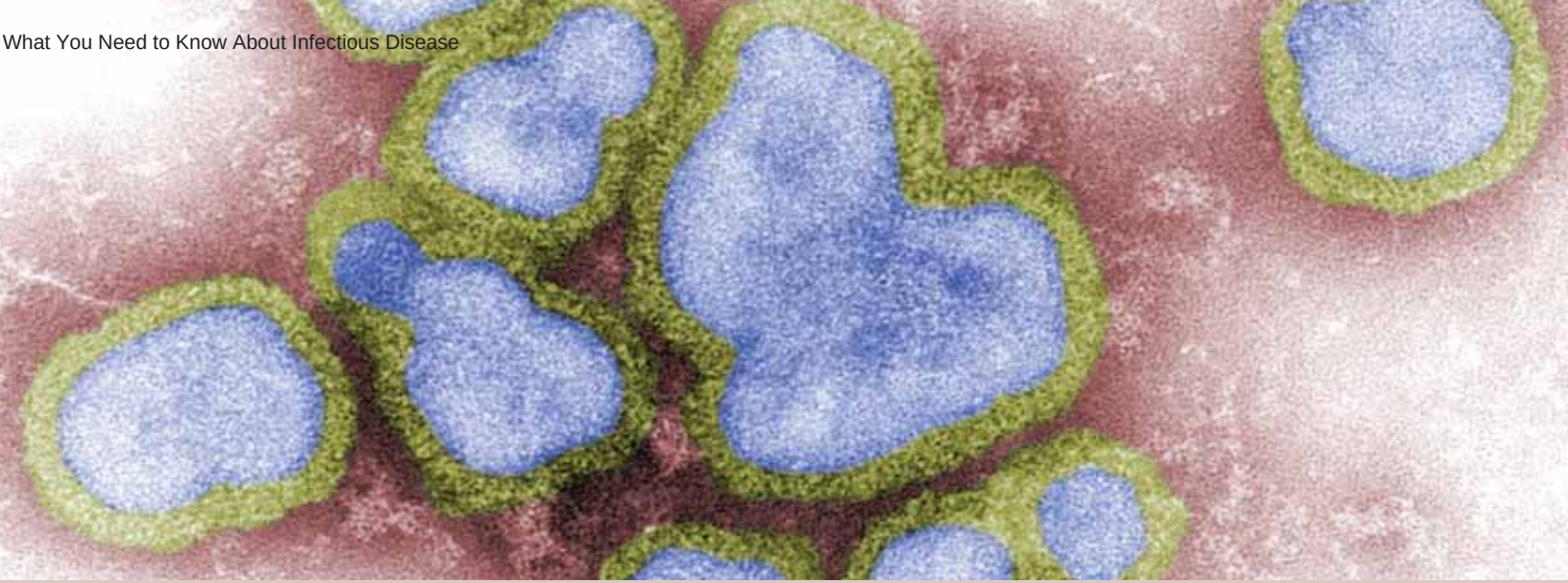

INFECTIOUS DISEASE

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Many people think of bacteria, viruses, and other microorganisms as our enemy. The germ theory of disease, first proposed in the 19th century, maintained that illness springs from the actions of infecting microorganisms. Such a view draws battle lines between “us” (the afflicted hosts) and “them” (the invading microbes). Germ theory was crucial in identifying many diseases caused by microbes and in finding ways to prevent them through such measures as immunization, sanitation, and improved living conditions. By the mid-1960s, many experts concluded that infectious disease was all but conquered, and researchers could shift their focus to chronic medical conditions such as heart disease and cancer. But this optimism was shaken in the mid-1970s and early 1980s with the appearance of Legionnaire’s disease, toxic shock syndrome, and HIV/AIDS.

It was dealt further blows with the development of antibiotic-resistant bacteria and the appearance of SARS, West Nile virus, and Lyme disease. Scientists began to re-examine the relationship between hosts and microbes.

Today, many scientists recognize the need for a more ecological view of the microbial world around us: Microbes and their hosts (including humans) ultimately depend on each other for survival. And although the microorganisms that cause disease often receive more attention, most microorganisms do not cause illness. In fact, many of them protect us, helping our bodies function properly and competing with harmful organisms in an eternal contest for habitable space in and on our bodies.

But there is a reason why the few microbes that cause illness draw so much interest. The World Health Organization (WHO) reports that new infectious diseases are continuing to emerge and old ones are appearing in new locations around the globe. About a quarter of deaths worldwide—many of them children—are caused by infectious organisms. What’s behind this trend? How can invisible organisms cause such harm? And to what extent has human behavior amplified the problem?

This booklet provides an overview of infectious disease, drawing on reports and studies from the Institute of Medicine. It describes the biology, history, and future trends of these infections. And it explains what we need to do—as individuals and as a society—to address the challenge of infectious disease.

I

How Infection Works

There is a close connection between microbes and humans. Experts believe about half of all human DNA originated from viruses that infected and embedded their nucleic acid in our ancestors' egg and sperm cells.

Microbes occupy all of our body surfaces, including the skin, gut, and mucous membranes. In fact, our bodies contain at least 10 times more bacterial cells than human ones, blurring the line between where microbes end and humans begin. Microbes in the human gastrointestinal tract alone comprise at least 10 trillion organisms, representing more than 1,000 species, which are thought to prevent the gut from being colonized by disease-causing organisms. Among their other beneficial roles, microbes synthesize vitamins, break down food into absorbable nutrients, and stimulate our immune systems.

The vast majority of microbes establish themselves as persistent "colonists," thriving in complex communities within and on our bodies. In many cases, the microbes derive benefits without harming us; in other cases, both host and microbe benefit.

From the moment we are born, microbes begin to colonize our bodies. Each of us has a unique set of microbial communities, which are believed to play an important role in digestion and in protection from disease.

Lactobacillus *bacteria, which produce lactic acid to help with digestion.*

And though some microbes make us sick and even kill us, in the long run they have a shared interest in our survival. For these tiny invaders, a dead host is a dead end.

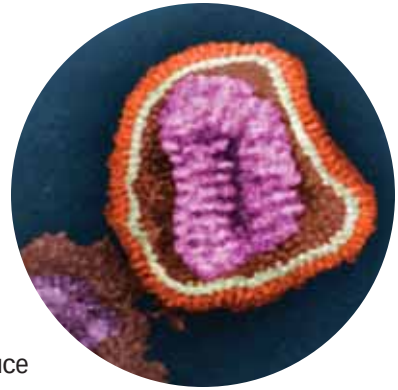
The success of microorganisms is due to their remarkable adaptability. Through natural selection, organisms that are genetically better suited to their surroundings have more offspring and transmit their desirable traits to future generations. This process operates far more efficiently in the microbial world than in people. Humans produce a new generation every 20 years or so; bacteria do it every 20 to 30 minutes, and viruses even faster. Because they reproduce so quickly, microorganisms can assemble in enormous numbers with great variety in their communities. If their environment suddenly changes, the community's genetic variations make it more likely that some will survive. This gives microbes a huge advantage over humans when it comes to adapting for survival.

Types of Microbes

There are five major categories of infectious agents: Viruses, bacteria, fungi, protozoa, and helminths.

Viruses

Viruses are tiny, ranging in size from about 20 to 400 nanometers in diameter (see page 9). Billions can fit on the head of a pin. Some are rod shaped; others are round and 20 sided; and yet others have fanciful forms, with multisided "heads" and cylindrical "tails."



An electron micrograph of an influenza virus particle, showing details of its structure.

Viruses are simply packets of nucleic acid, either DNA or RNA, surrounded by a protein shell and sometimes fatty materials called lipids. Outside a living cell, a virus is a dormant particle, lacking the raw materials for reproduction. Only when it enters a host cell does it go into action, hijacking the cell's metabolic machinery to produce copies of itself that may burst out of infected cells or simply bud off a cell membrane. This lack of self-sufficiency means that viruses cannot be cultured in artificial media for scientific research or vaccine development; they can be grown only in living cells, fertilized eggs, tissue cultures, or bacteria.

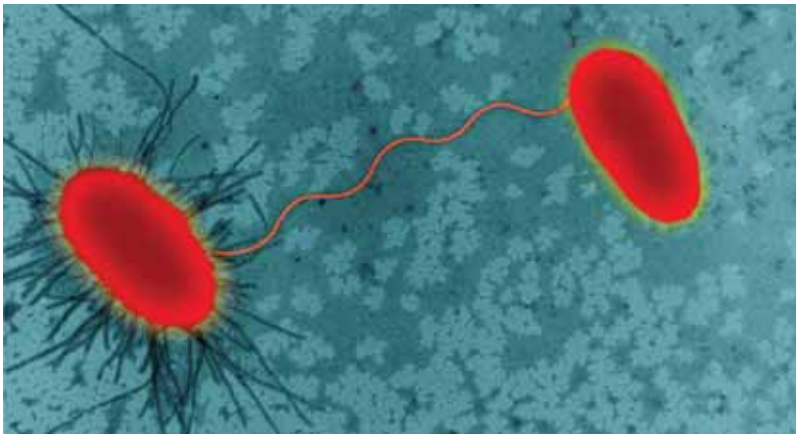
Viruses are responsible for a wide range of diseases, including the common cold, measles, chicken pox, genital herpes, and influenza. Many of the emerging infectious diseases, such as AIDS and SARS, are caused by viruses.

Bacteria

Bacteria are 10 to 100 times larger than viruses and are more self-sufficient. These single-celled organisms, generally visible under a low-powered

microscope, come in three shapes: spherical (coccus), rodlike (bacillus), and curved (vibrio, spirillum, or spirochete).

Most bacteria carry a single circular molecule of DNA, which encodes (or programs) the essential genes for reproduction and other cellular functions. Sometimes they carry accessory small rings of DNA, known as plasmids, that encode for specialized functions like antibiotic resistance. Unlike more complex forms of life, bacteria carry only one set of chromosomes instead of two. They reproduce by dividing into two cells, a process called binary fission. Their offspring are identical, essentially clones with the exact same genetic material. When mistakes are made during replication and a mutation occurs, it creates variety within the population that could—under the right circumstances—lead to an enhanced ability to adapt to a changing environment. Bacteria can also acquire new genetic material from other bacteria, viruses, plants, and even yeasts. This ability means they can evolve suddenly and rapidly instead of slowly adapting.



E. coli *bacteria directly transferring genetic material via a pilus (the thin strand connecting the two).*

Bacteria are ancient organisms. Evidence for them exists in the fossil record from more than 3 billion years ago. They have evolved many different behaviors over a wide range of habitats, learning to adhere to cells, make paralyzing poisons and other toxins, evade or suppress our bodies' defenses, and resist drugs and the immune system's antibodies. Bacterial infections are associated with diseases such as strep throat, tuberculosis, staph skin infections, and urinary tract and bloodstream infections.

Other Infectious Agents

The other three major types of infectious agents include fungi (spore-forming organisms that range from bread mold to ringworm to deadly histoplasmosis), protozoa (such as the agents behind malaria and dysentery), and helminths (parasitic worms like those that cause trichinosis, hookworm, and schistosomiasis).

A newly recognized class of infectious agents—the prions, or proteinaceous infectious particles—consist only of protein. Prions are thought to cause variant Creutzfeldt-Jakob disease in humans and "mad cow disease" in cattle. These proteins are abnormally folded and, when they come in contact with similar normal proteins, turn them into prions like themselves, setting off a chain reaction that eventually riddles the brain with holes. Prions evoke no immune response and resist heat, ultraviolet light, radiation, and sterilization, making them difficult to control.

Grand Prismatic Spring, a geothermal hot spring in Yellowstone and home to microbes that have adapted to this extreme environment.

Encountering Microbes

Microbes have inhabited the earth for billions of years and may be the earliest life forms on the planet. They live in every conceivable ecological niche—soil, water, air, plants, rocks, and animals. They even live in extreme environments, such as hot springs, deep ocean thermal vents, and Antarctic ice. Indeed microbes, by sheer mass, are the earth's most abundant life form and are highly adaptable to external forces.

New Meeting Places

Any changes that create new intersections between microbes and people pave the way for disease-causing agents to enter our species. One such change that has put us at risk is the global human population explosion—from about 1.6 billion people in 1900 to nearly 7 billion today. Humans have cleared forests for agriculture and suburbanization, leading to closer contact with environments that may harbor novel (or newly introduced) pathogens. Through much of the world's developing tropical regions, the massive expansion of roads and human settlements has also created transition zones filled with opportunities for contact with potential disease-causing agents.

Human travel and commerce have brought other risks. Almost 2 million passengers, each a potential carrier of infection, travel daily by aircraft to international destinations. International commerce, especially in foodstuffs, adds to the global traffic

Evidence for why it is important to cover your mouth when you sneeze.

of disease-causing microbes. Because the transit times of people and goods are often shorter than the incubation periods of infection, carriers of disease can arrive at their destination before the infection they harbor is detectable. International trade and travel are associated with the emergence of such infectious agents as the SARS coronavirus and West Nile virus.

Changes in human demographics and behavior are linked with the emergence of infections such as AIDS and hepatitis C, through sexual activity and intravenous drug use. More broad-scale changes that raise the risk of infectious disease include the breakdown of public health systems, poverty, war, and famine.

Entering the Human Host

Microorganisms capable of causing disease—pathogens—usually enter our bodies through the mouth, eyes, nose, or urogenital openings, or through wounds or bites that breach the skin barrier. Organisms can spread—or be transmitted—by several routes.

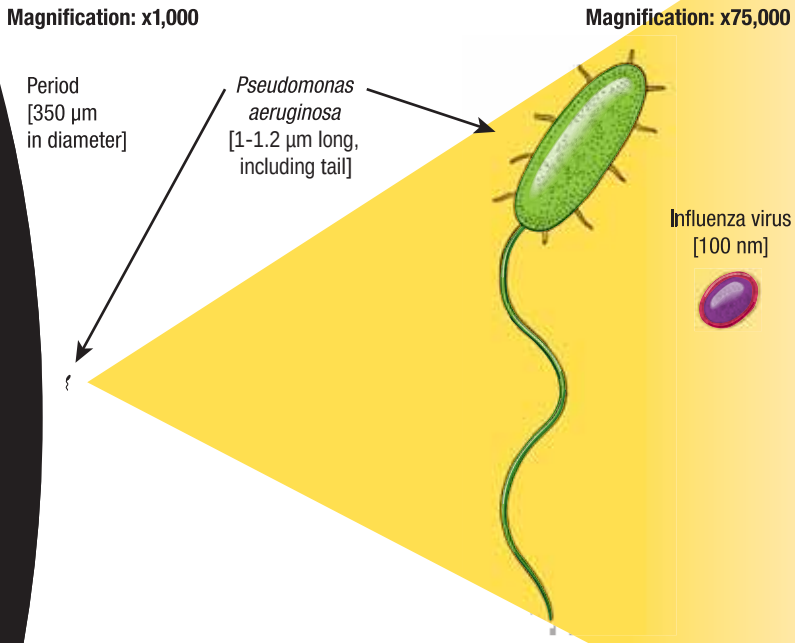
Contact: Some diseases spread via direct contact with infected skin, mucous membranes, or body fluids. Diseases transmitted this way include cold sores (herpes simplex virus type 1) and sexually transmitted diseases such as AIDS. Pathogens can also be spread by indirect contact when an infected person touches a surface such as a doorknob, countertop, or faucet handle, leaving behind microbes that are then transferred to another person who touches that surface and then touches his or her eye, mouth, or nose. Droplets spread by sneezes, coughs, or simply talking can transmit disease if they come in contact with mucous membranes of the eye, mouth, or nose of another person. SARS, tuberculosis, and influenza are examples of diseases spread by airborne droplet transmission.

Common vehicles: Contaminated food, water, blood, or other vehicles may spread pathogens. Microorganisms like *E. coli* and *Salmonella* enter the digestive system in this manner.

Vectors: Creatures such as fleas, mites, ticks, rats, snails, and dogs—called vectors—can also transmit disease. The most common vector for human infection is the mosquito, which transmits malaria, West Nile virus, and yellow fever.

Airborne transmission: Pathogens can also spread when residue from evaporated droplets or dust particles containing microorganisms are suspended in air for long periods of time. Diseases spread by airborne transmission include measles and hantavirus pulmonary syndrome.

HOW TINY ARE MICROBES?



Bacteria and viruses are almost unimaginably small. Bacteria are usually measured in microns (abbreviated "µm," 1 micron equals 1 one-millionth of a meter), while viruses are measured in the even more miniscule unit of nanometers (abbreviated "nm," 1 nanometer equals 1 one-billionth of a meter, or 1 one-thousandth of a micron). To give a sense of these measures, consider that the period at the end of this sentence is about 350 microns, or 350,000 nanometers, in diameter. If we magnify the period to one thousand times its actual size (see far left), a nearby *Pseudomonas aeruginosa*, the bacterium that causes hospital-acquired pneumonia and bloodstream infections, becomes visible. If, in turn, we magnify *Pseudomonas* 75 more times, or to 75,000 times its actual size, an adjacent influenza virus particle also becomes visible.

How Pathogens Make Us Sick

Infection does not necessarily lead to disease. Infection occurs when viruses, bacteria, or other microbes enter your body and begin to multiply. Disease, which typically happens in a small proportion of infected people, occurs when the cells in your body are damaged as a result of infection, and signs and symptoms of an illness appear.

In response to infection, your immune system springs into action. White blood cells, antibodies, and other mechanisms go to work to rid your body of the foreign invader. Indeed, many of the symptoms that make a person suffer during an infection—fever, malaise, headache, rash—result from the activities of the immune system trying to eliminate the infection from the body.

Pathogenic microbes challenge the immune system in many ways. Viruses make us sick by killing cells or disrupting cell function. Our bodies often respond with fever (heat inactivates many viruses), the secretion of a chemical called interferon (which blocks viruses from reproducing), or by marshaling the immune system's antibodies and other cells to target the invader. Many bacteria make us sick the same way, but they also have other strategies at their disposal. Sometimes bacteria multiply so rapidly they

A fever is often part of the immune system's response to infection.

crowd out host tissues and disrupt normal function. Sometimes they kill cells and tissues outright. Sometimes they make toxins that can paralyze, destroy cells' metabolic machinery, or precipitate a massive immune reaction that is itself toxic.

Other classes of microbes attack the body in different ways:

- *Trichinella spiralis*, the helminth that causes trichinosis, enters the body encased in cysts residing in undercooked meat. Pepsin and hydrochloric acid in our bodies help free the larvae in the cysts to enter the small intestine, where they molt, mature, and ultimately produce more larvae that pass through the intestine and into the bloodstream. At that point they are free to reach various organs. Those that reach skeletal muscle cells can survive and form new cysts, thus completing their life cycle.
- *Histoplasma capsulatum*, a fungus that transmits histoplasmosis, grows in soil contaminated with bird or bat droppings. Spores of the fungus emerge from disturbed soil and, once inhaled into the lungs, germinate and transform into budding yeast cells. In its acute phase, the disease causes coughing and flu-like symptoms. Sometimes histoplasmosis affects multiple organ systems and can be fatal unless treated.
- The protozoa that cause malaria, which are members of the genus *Plasmodium*, have complex life cycles. Sporozoites, a cell type that infects new hosts, develop in the salivary glands of *Anopheles* mosquitos. They leave the mosquito during a blood meal, enter the host's liver, and multiply. Cells infected with sporozoites eventually burst, releasing another cell form, merozoites, into the bloodstream. These cells infect red blood cells and then rapidly reproduce, destroying the red blood cell hosts and releasing many new merozoites to do further damage. Most merozoites continue to reproduce in this way, but some differentiate into sexual forms (gametocytes) that are taken up by the female mosquito, thus completing the protozoan life cycle.

These and many other ingenious pathways to causing disease demonstrate pathogens' rich evolutionary legacy and their continued inventiveness. In the next section, we look more closely at how some of these organisms have learned to thrive—often at humans' expense.

II

Disease Threats

Our "war" on infectious microbes has restricted the spread of several pathogens and drastically reduced the burden of human disease, but we are a long way from conquering infectious diseases.

During the past three decades, 37 new human pathogens have been identified as disease threats. An estimated 12 percent of known human pathogens have been recognized as either emerging or re-emerging. Having fallen steadily since the turn of the 20th century, the number of deaths attributable to infection in the United States began to increase in the early 1980s due, in large part, to the HIV/AIDS pandemic and increases in deaths attributable to pneumonia and bloodstream infections. Infectious disease continues to cause high morbidity and mortality throughout the world, particularly in developing countries. It accounts for about a quarter of deaths worldwide, and in 2008 caused more than two-thirds of the estimated 8.8 million deaths in children under the age of five. What are some of the most significant microbial threats we face?

Animal Carriers

Many of the diseases that afflict people today are caused by microbes whose ancestors came from animals first domesticated by early humans. Biologists believe that the measles virus stemmed from canine distemper and rinderpest, an affliction of cattle; that rhinoviruses, agents of the common cold, came to us from horses; and that smallpox is a close cousin of cowpox.

Infections transmitted from animals to humans are called *zoonoses,* or zoonotic diseases. Of the more than 1,700 known viruses, bacteria, and other pathogens that infect people, more than half either originated in or now come directly from animals;

Animals domesticated by early humans are believed to have been the source of microbes that eventually caused disease in people, as in the case of measles stemming from canine distemper and rinderpest.

the rest come from the environment around us, such as soil, water, and air. And of the 37 new infectious diseases identified in the past 30 years, more than two-thirds sprang from animals. The next deadly pandemic to sweep the world could very likely jump species in this way.

Direct Transmission

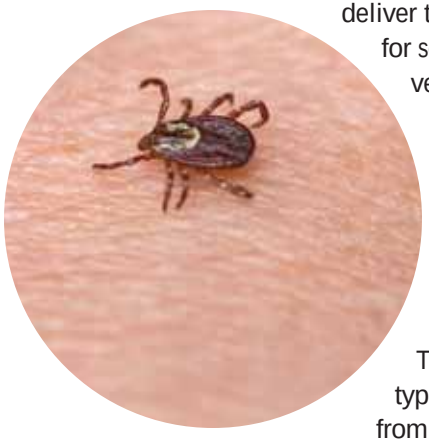
Some zoonotic infections move directly from animals to humans. In such cases, an animal is the natural host—or reservoir—for the pathogen, and through an evolutionary twist of fate, the pathogen moves from the natural host to humans. Severe Acute Respiratory Syndrome (SARS) is a recent example of this. In the spring of 2003 this new and deadly viral illness swept out from China's Guangdong Province and spread rapidly around the world before it was contained that summer. SARS originated in Chinese horseshoe bats, animals that are used for food and medicine in many parts of Asia, and was then "amplified" through the infection of civet cats, a step leading to a mutation that makes the disease transmissible to humans. The virus infected 8,098 people, of which 774 died—a nearly 10 percent mortality rate. Fortunately, no human infections have been found since early 2004.

There are many other examples of direct transmission. Toxoplasmosis, a parasitic disease that typically causes mild flu-like symptoms in humans (but potentially more serious illness in individuals with compromised immune systems), infects many warmblooded animals. Cats play an important role in spreading the disease when they become infected by eating infected rodents or small birds and then pass the parasite to humans through their feces. Leptospirosis, a bacterial disease spread through the urine of infected animals, or through soil or water contaminated by infected urine, can cause a wide range of symptoms in humans, including high fever, vomiting, and even meningitis and liver failure. The Nipah virus, which can cause fatal encephalitis (inflammation of the brain), emerged in 1998 in Malaysia. Harbored in fruit bats, the virus afflicted slaughterhouse workers who had caught it from pigs.

Fruit bat, which can transmit the Nipah virus.

Indirect Transmission

Diseases that are transmitted to humans indirectly via an insect, an arthropod (animals with jointed appendages and exoskeletons, such as ticks), or another animal (such as snails, which deliver the parasite responsible for schistosomiasis) are called vector-borne diseases. Vectors carry disease-causing viruses, bacteria, or parasites from one host to another, delivering these pathogens to humans and other warmblooded hosts. The vectors themselves typically suffer no ill effects from the organisms they carry.



American dog tick, potential vector of Rocky Mountain spotted fever.

In 1999, for example, a mosquito-borne infection—West Nile virus—suddenly began targeting New Yorkers. Seven people died and 62 were hospitalized. Until then the virus had been confined to Africa, West Asia, and the Middle East. Today, the infection caused by West Nile virus has fully established itself in North America, flaring up in the summer and continuing into the fall. Since 1999 the virus has spread rapidly across North America and into Latin America. In 2009 there were 720 reported cases of West Nile virus in the United States, of which 32 were fatal.

Wild or domestic animals are natural reservoirs for many vector-borne diseases. The main reservoir host for West Nile virus is wild birds. The New York City strain of the virus was virtually identical to a strain taken the previous year from a dead goose in Israel. Scientists speculate that an infected mosquito, human, or bird may have brought the pathogen to this country on a plane or ship.

A vector ecologist tests crows for the West Nile virus in a lab in St. Paul, Minnesota. Dead crows were one of the early signs of the virus's presence in North America.

Many other common infections, including malaria, yellow fever, Lyme disease, and typhus, are spread to humans from animals via the bites of insects and other arthropods. In fact, nearly half the world's population is currently infected with a vector-borne disease.

Foodborne Pathogens

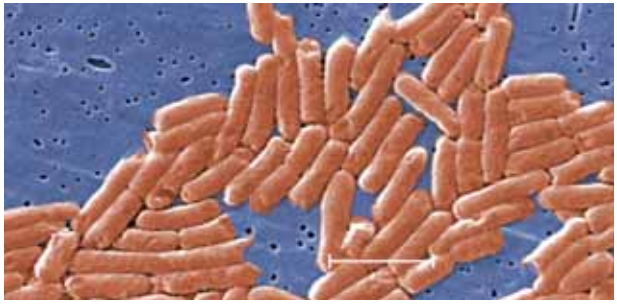
Each year an estimated 76 million Americans—about one in four—become infected by what they eat. Approximately 325,000 are hospitalized. More than 5,000 (14 a day) die. In April 2009 the U.S. Centers for Disease Control and Prevention (CDC) reported that progress in reducing foodborne infections had stalled, pointing to gaps in the existing food safety system and the need to develop improved food safety practices as products move from the farm to the table. The true magnitude of foodborne illness is likely to be much higher than even the official estimates because most people do not seek medical attention for its symptoms, such as abdominal cramps, vomiting, and diarrhea.

The Pathogens Behind Foodborne Illness

Foodborne disease occurs when a susceptible host consumes contaminated foods or beverages. Many different disease-causing microorganisms—bacteria, viruses, and parasites—can taint foods and liquids, each potentially associated with a different illness.

The most common causes of foodborne illness include the bacterial infections *Campylobacter,* the most frequently identified bacterial cause of diarrheal illness in the world; *Salmonella,* which spreads to humans through a variety of foods of animal origin, or through fecal contamination of plant-based foods, such as in the 2009 peanut-product outbreak; and *E. coli* O157:H7, the agent behind a serious and sometimes deadly complication called hemolytic-uremic syndrome (HUS). The most common viral cause of foodborne

Salad bars may harbor agents of foodborne illness, such as Salmonella *bacteria (below), if the food has not been handled properly.*



Outbreaks of norovirus (Calicivirus), *the most common form of viral foodborne illness, spread easily in places where large numbers of people are gathered together, such as cruise ships.*

Mangoes are sliced in preparation for exportation from South America. Global food distribution increases the risk of widespread epidemics if food becomes contaminated.

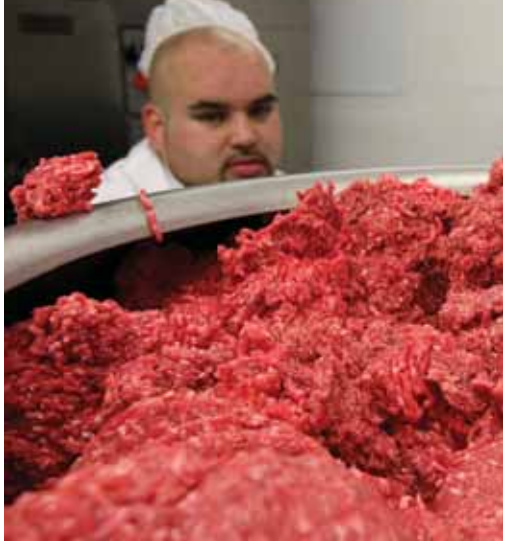
illness is *Calicivirus,* also referred to as Norwalk-like virus or norovirus. Unlike the previous three bacterial foodborne pathogens, noroviruses easily spread from one infected person to another and can contaminate an environment, making them extremely difficult to eradicate from hotels, hospitals, nursing homes, cruise ships, and similar establishments where large numbers of people congregate.

After you swallow a foodborne pathogen there may be a delay—the incubation period—before symptoms appear. This delay may range from hours to days. During the incubation period, the microbes pass through the stomach into the intestine, attach to the cells lining the intestinal walls, and begin to multiply there. Some types of microbes stay in the intestine; some, like cholera, produce a toxin that causes the body to secrete water, resulting in diarrhea. Others, like the typhoid bacillus, invade and replicate in the deeper body tissues.

Not all foodborne pathogens require an incubation period, however. Illness can result from toxins that form in the food before it is eaten—leading to true "food poisoning." In such cases, bacteria do not need to replicate in the body at all and the onset of symptoms can be more rapid.

What Causes Outbreaks?

In the past few decades, food production and distribution for the developed world have increasingly involved vast and intricate global networks. This sprawling system produces food that, if contaminated, increases the potential for widespread epidemics. In this giant food economy



Foods pooled from many sources, such as batches of raw ground beef, can become tainted if any of the meat in the batch is contaminated with a human pathogen.

opportunities abound for food to come in contact with pathogens. Meat and poultry carcasses can become contaminated during slaughter by contact with small amounts of intestinal contents. Fresh fruits and vegetables become tainted if they are washed or irrigated with water contaminated with animal manure or human sewage. (Outbreaks related to fresh produce have increased eightfold in the United States during the past several decades.) And increasingly, we don't cook our own meals, leaving food safety in the hands, literally, of others.

Raw foods of animal origin are the most likely to be contaminated—that is, raw meat and poultry, raw eggs, unpasteurized milk, and raw shellfish. Foods for which such products are pooled from many sources and batch processed are also hazardous, because a pathogen present in any one of the animals might contaminate the whole batch.

How to Protect Yourself

Consumers can reduce the risk of foodborne illness by adhering to the following safe food handling and preparation practices:

Wash hands thoroughly with soap and warm water before handling food.

Cook meat, poultry, and eggs thoroughly. Use a thermometer to measure the internal temperature of meat, to be sure that it is cooked sufficiently to kill bacteria. Ground beef, for example, should be cooked to an internal temperature of 160°F. Eggs should be cooked until the yolk is firm.

Separate: Avoid cross-contaminating foods by washing hands, utensils, and cutting boards after contact with raw meat or poultry and before they touch another food. Unless it is disinfected between each use, don't use a "universal" cleanup tool such as a sponge. Place cooked meat on a clean platter, rather than back on the one that held the raw meat.

Chill: Bacteria can grow quickly at room temperature, so refrigerate leftover foods if they are not going to be eaten within 4 hours. A large volume of food will cool more quickly if divided into several shallow containers for refrigeration.

Clean: Rinse fresh fruits and vegetables in running tap water to remove visible dirt and grime. Remove and discard the outermost leaves from a head of lettuce or cabbage. Because bacteria can grow on the cut surface of fruits or vegetables, be careful not to contaminate these foods while slicing them on a cutting board, and avoid leaving cut produce at room temperature for many hours.

Report suspected foodborne illness to your local health department.

Global Killers

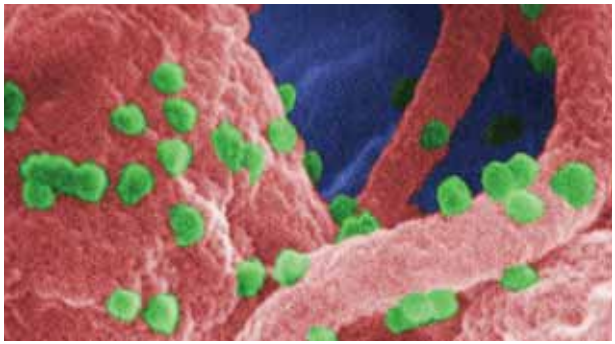
A handful of deadly infectious diseases claim millions of lives worldwide each year: lower respiratory tract infections, diarrheal diseases, HIV/AIDS, tuberculosis, and malaria. Together, they account for nearly one-fifth of deaths globally. Several of these diseases have plagued humankind throughout history, often decimating populations with greater efficiency than wars. In an age of vaccines, antibiotics, and dramatic scientific progress, these diseases should have been brought under control. Yet they continue to kill at an alarming rate, particularly in the developing world. In low-income countries the dominant causes of death are infectious and parasitic diseases (including malaria) and poor medical care surrounding childbirth. By contrast, in high-income countries the leading causes of death are noncommunicable diseases, such as heart disease and cancer. Infectious and parasitic causes of mortality are farther down on the list.

Lower respiratory tract infections (including pneumonia) account for more than 4 million deaths worldwide—the greatest global killer among infectious diseases. Pneumonia is also the leading cause of death of the very young, often striking children with low birth weight or those whose immune systems are weakened by malnutrition or other diseases. Most of these deaths occur in developing countries.

Diarrheal diseases are the second-leading cause of infectious disease deaths worldwide, accounting for more than 2 million deaths each year, and nearly one-fifth of all deaths of children under the age of five. These infections are so widespread in developing countries that parents often fail to recognize when symptoms become critical. Children die simply because their bodies are weakened—often through rapid loss of fluids and undernourishment. The burden of diarrheal diseases is highest in deprived areas where there is poor sanitation, inadequate hygiene, and unsafe drinking water.

HIV stands for *human immunodeficiency virus*, the virus that causes *acquired immunodeficiency syndrome* (**AIDS**), the final stage of HIV infection. HIV appears to have jumped to humans early in the 20th century from a type of chimpanzee in West Africa—most likely when humans hunted these animals for meat and came into contact with their infected blood. The virus slowly spread across Africa and later to other parts of the world.

In 2008 more than 33 million people worldwide were infected with HIV and an estimated 2 million died. Unlike most other viruses, HIV attacks the



HIV particles (green spheres).

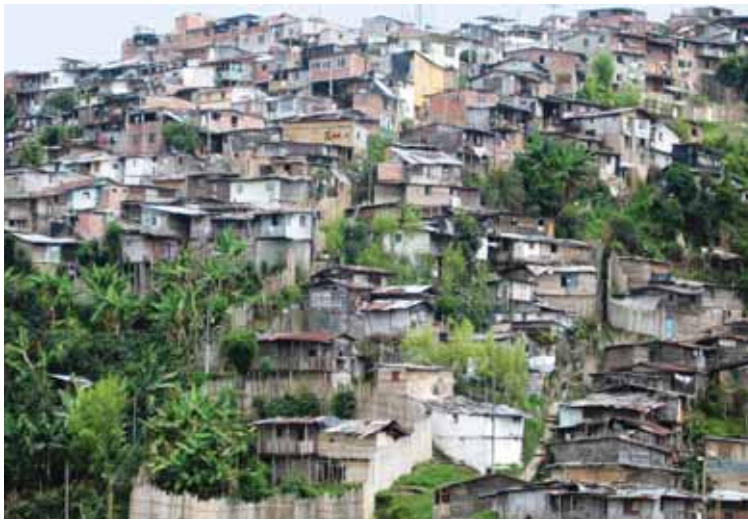
immune system, destroying a type of white blood cell (T cells or CD4 cells) that the immune system needs to fight disease. HIV is transmitted by having sex with someone infected with HIV, by sharing needles and syringes with an infected person, through blood or blood product transfusions, or by being exposed as a fetus or an infant to the virus before or during birth or through breastfeeding. HIV is not transmitted through casual contact, such as shaking hands, hugging, modest kissing, or drinking from the same glass.

Someone in the world is newly infected with the **tuberculosis** (TB) bacterium every second. In 2008 there were an estimated 9.4 million new cases of tuberculosis and 1.8 million deaths. The vast majority of TB deaths are in the developing world, and more than half of all deaths occur in Asia. In the United States, 12,904 TB cases were reported in 2008, a nearly 3 percent decline from the number reported in 2007.

TB, which is caused by the bacterium *Mycobacterium tuberculosis,* is a contagious disease that spreads through the air when an infected person coughs or sneezes and people nearby breathe in the bacteria. TB bacteria can live in the body without making an individual sick, a condition known as latent TB infection. More than 2 billion people—about one-third of the world's population—are infected, many asymptomatically, with TB bacilli. A person with active TB can be treated by taking several drugs for 6 to 12 months.

Multidrug-resistant TB (MDR-TB) is a new threat. It is difficult and expensive to treat and fails to respond to the standard first-line drugs that are most easily tolerated and have historically worked best against the disease. Extensively drug-resistant TB (XDR-TB) occurs when resistance to second-line drugs, which are typically more toxic and less effective, develops on top of MDR-TB. Such infections are highly lethal.

On the global stage, HIV/AIDS and TB are tragically interconnected. Among HIV-infected people whose immune systems are weakened by the effects of the virus, the risk of developing TB is much higher than for persons with normal immune systems. Indeed, TB is the leading cause of death worldwide among people infected with HIV. Likewise, among people with latent (inactive) TB infection, HIV infection is the strongest known risk factor for progressing to active TB disease.



Crowded housing with poor sanitation may enable the rapid spread of disease within a community.

Villagers in sub-Saharan Africa learn how to set up a mosquito bednet for protection against malaria.

Like the other global killers, **malaria** occurs mostly in poor, tropical, and subtropical areas of the world. Each year as many as 300 million people are infected with malaria worldwide, and up to 1 million die, most of them young children in sub-Saharan Africa. Malaria is a mosquito-borne disease caused by several different protozoan parasites. Humans infected with malaria parasites, depending on the type, can develop a wide range of illnesses, from mild infection that does not produce symptoms to the classic symptoms of malaria (fever, chills, sweating, headaches, muscle pains) to severe complications (anemia, kidney failure, coma) that can lead to death.

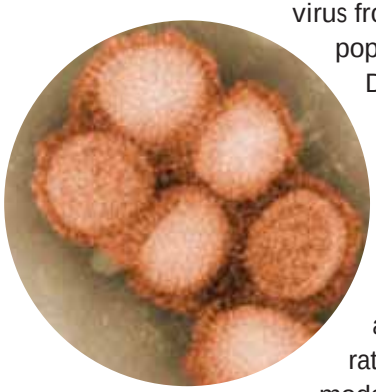
Malaria serves as a particularly dramatic example of infectious disease re-emergence and illustrates the challenges of controlling human vector-borne diseases. Following the drastic depopulation of *Anopheles* mosquitoes in the first half of the 20th century due to liberal use of the pesticide DDT, malaria began its resurgence in Asia in the late 1960s. In Sri Lanka, where only 17 cases of malaria were reported in 1963, a major epidemic of more than 440,000 cases erupted 5 years later, after preventive vector control was replaced with a strategy of identifying and treating new cases of the illness. Similarly, by the mid-1970s millions of new cases had occurred in India after mosquito eradication efforts ceased. In Africa, where vector control programs were never initiated, a more recent upsurge in infections, including several explosive epidemics, has erupted in endemic areas. A number of factors appear to be driving this global resurgence, including the rapid spread of drug resistance among malarial parasites, changing rainfall patterns, and water development projects, such as dams, which create new mosquito breeding sites.

Yet despite today's dire headlines, progress is being made against the world's modern infectious scourges. The scale-up of antiretroviral therapy has reduced the number of AIDS deaths and mother-to-child transmissions, and has improved survival and productivity. Wider access to antiretroviral treatments has also been accompanied by a dramatic reduction in prices. The prevalence of TB has declined since 2000, partly because the WHO's Directly Observed Therapy Short-Course strategy brought treatment and a cure to tens of millions of patients. And malaria deaths have fallen with the development of artemisinin-based drugs, distribution of insecticide-treated bed nets, and indoor residual spraying of insecticides. Alongside these efforts there have been major investments in health care systems—bolstering infrastructure, laboratories, and human resources.

Influenza

The "flu" has become a popular catch-all term to describe anything from a bad cold to stomach distress. But the real flu, influenza, is a defined illness that many public health officials dread most. Each year in the United States about 36,000 people die from flu-related complications, and more than 200,000 are hospitalized.

Of even greater concern is a flu pandemic—a worldwide epidemic of a new strain of influenza virus from which the human population has no immunity. Depending on its severity, an influenza pandemic could result in 200,000 to 2 million deaths in the United States alone. In 2009 the WHO declared the current H1N1 "swine flu" a pandemic, although its human mortality rate to date has been relatively modest, with about 18,000 confirmed deaths worldwide.



2009 H1N1 influenza virus.

How the Flu Spreads

Influenza viruses mainly spread when droplets from the cough or sneeze of an infected person are propelled through the air and land on the mouth or nose of someone nearby. Flu viruses may also spread when a person touches respiratory droplets on another person or on an object and then touches his or her own mouth or nose. The hardy influenza virus can survive on environmental surfaces, such as doorknobs and countertops, for 2 to 8 hours—one of the reasons that hand washing and surface hygiene is an important part of most flu control strategies.

Once the flu virus makes contact with mucous membranes in the eyes and nose, it heads to the cells along the upper respiratory tract, bronchial tubes, and trachea, where it swiftly multiplies. Scientists believe flu symptoms arise because growth of the virus damages the cells into which it has inserted itself and because the immune system, in trying to limit the damage, responds in ways that cause familiar discomfort: It sends out white blood cells, called cytokines, that cause muscle and joint pain, and it produces a fever, which is one of the body's ways of mobilizing its defenses against invaders.

Seasonal Versus Pandemic Flu

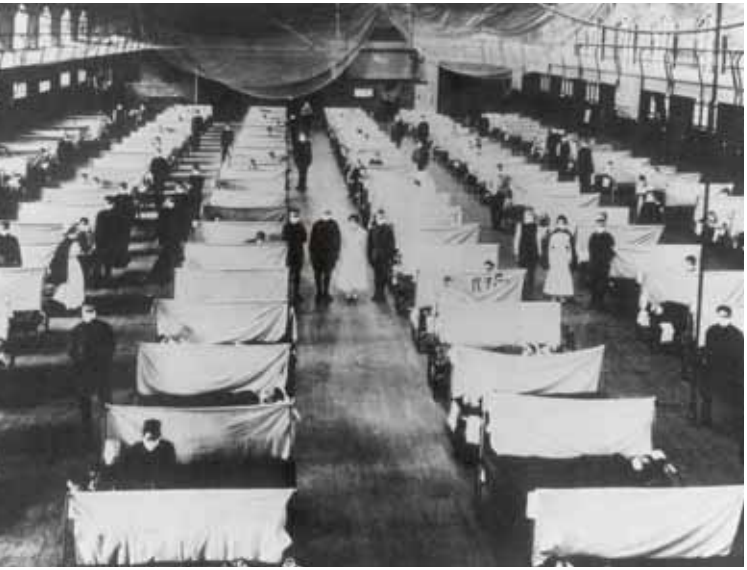
The genius of the influenza virus lies in its ability to alter itself. The virus uses RNA rather than DNA as its genetic material. RNA viruses make frequent mistakes while copying themselves. Their high mutation rate means that RNA viruses evolve far more rapidly than DNA viruses, because every successive generation is a little different from the previous one. The flu virus's surface proteins—hemagglutinin (H) and neuraminidase (N)—are also changeable. These proteins have a role in making it possible for a virus to invade and hijack cells. Hemagglutinin permits virus particles to gain access to the cell's interior, and neuraminidase helps newly produced copies of the virus break free of the cell in quest of other cells to invade.

There are three types of influenza viruses: A, B, and C. Only influenza A viruses are further

classified by subtype on the basis of the H and N surface proteins. Influenza A subtypes and B viruses are further classified by strains. Among influenza A viruses, there are 16 known subtypes of hemagglutinin and 9 of neuraminidase. Many different combinations of these H and N proteins are possible, each representing a different subtype.

According to the CDC, the subtypes of influenza that are currently circulating among people worldwide include A H1N1, A H3N2, and B strains. Usually only one subtype predominates in a given flu season. Epidemics break out every year because of slight genetic mutations in a virus subtype's surface proteins that result in a new strain of the virus—a process known as antigenic *drift.* New combination vaccines are formulated annually to protect against the three circulating strains of seasonal flu that experts predict will cause the most illness in the coming season.

Sometimes the virus's surface proteins undergo a radical change—a process known as antigenic *shift*—resulting in an altogether new influenza subtype against which most humans have no immunity. The result can be a pandemic. The extent and severity of a pandemic depend on the specific characteristics of the virus. While rare, pandemics sweep the world like wildfire. In addition to the recent H1N1 pandemic, three major pandemics broke out in the 20th century: an H1N1 in 1918 (the misnamed "Spanish" flu), an H2N2 in 1957 (the "Asian" flu), and an H3N2 in 1968 (the "Hong Kong" flu). Of these pandemics, the 1918–1919 virus was the most fearsome, killing 50 million to 100 million people worldwide (or between 0.5 and 1 percent of the global population at that time). Many of those deaths were due to the effects of pneumococcal pneumonia, a secondary complication of flu for which no antibiotics



During the 1918 flu pandemic, emergency hospitals were set up quickly for the huge influx of patients (left). A *CDC microbiologist works carefully with a recreated 1918 virus to identify the characteristics that made this organism such a deadly pathogen* (below).

existed in 1918. Diagnosis and treatment of this complication continue to be key to survival and recovery for flu patients.

Where Does the Flu Virus Come From?

The source of all flu strains is migrating aquatic birds, such as wild ducks, geese, and terns. Domestic birds—such as chickens, geese, and ducks—also carry a large variety of flu strains. New flu strains enter human populations in several ways. Sometimes genetic material is exchanged between human and avian flu viruses when a human or other mammal is infected with both viruses. Often this mixing and matching of viral genes happens in pigs, which are uniquely susceptible to both human and avian flu viruses. The process of swapping genes is called "reassortment." Today's H1N1, for example, is a triple reassortment virus containing genetic materials from avian, swine, and human viruses.

Sandpipers and other migrating aquatic birds are the source of all influenza strains.

Another process, known as adaptive mutation, is more gradual. In this case, the longer an avian flu virus infects humans, the more it is able to bind to human cells as the virus adapts to its new host. Recent investigations suggest that the 1918 flu virus was a bird virus that became a human virus by slowly accumulating genetic mutations that helped it survive in a human host.

On rare occasions, flu viruses leap directly from birds to humans. In 1997 a highly fatal H5N1 bird flu broke out in Hong Kong, infecting 18 individuals and causing 6 deaths—a potential pandemic that was averted when authorities ordered the slaughter of more than 1.5 million domestic birds. If H5N1 were to acquire the ability to spread easily from person to person, a new influenza pandemic could be possible.

Vaccines

Vaccines provide an effective means to prevent infection by the influenza virus. But as the world learned with the 2009 H1N1 "swine flu" pandemic, making vaccine is a time-consuming process that normally takes 5 to 6 months. For more than 50 years, flu vaccine has been produced by injecting the whole virus into fertilized hens' eggs. The virus is harvested, purified, chemically treated, and then weakened (attenuated) so that it cannot trigger infections. Despite appeals from scientists, governments have been slow to invest in newer and faster methods of producing flu vaccines, such as recombinant technologies or tissue culture–based production methods that bypass the need to grow a whole virus in eggs or cells. However, recent moves by the U.S. government and vaccine manufacturers toward utilizing some of these new technologies

provide hopeful signs. Scientists are also exploring ways to make a vaccine that is effective against all flu strains—a so-called universal vaccine. Such a development could dramatically improve the public's protection against influenza infection.

How to Protect Yourself

- Consider getting vaccinated against influenza. Vaccines are one of the best ways to reduce the morbidity and mortality associated with the disease. They do not themselves cause influenza in any form.
- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.
- Wash your hands often with soap and water, especially after coughing or sneezing. Alcohol-based hand sanitizers are also effective.

Injecting eggs with the flu virus to develop vaccines.

Alcohol-based hand sanitizers are effective in preventing the transmission of many pathogens. The Food and Drug Administration recommends a concentration of at least 60 percent ethanol. In healthy households, the use of other antibacterial agents, such as triclosan (common in many soaps and detergents), may contribute to the problem of antibiotic resistance and should be used prudently.

- Avoid touching your eyes, nose, or mouth, which can spread germs.
- If you do get sick, stay home from work or school and limit your contact with others to keep from infecting them.
- Ask your doctor whether you should take an anti-influenza drug, such as Tamiflu, which can be effective if taken within 48 hours of developing the symptoms of flu.

Antibiotic Resistance

Antibiotics—medicine's "magic bullets"—save tens of thousands of lives annually in the United States. But these magic bullets are losing their power. The problem is growing antibiotic resistance—the ability of bacteria to resist the effects of an antibiotic. Antibiotic resistance occurs when bacteria undergo a genetic change that reduces or eliminates the

effectiveness of drugs or other agents designed to cure or prevent infection. Resistant bacterial infections have inevitably followed the widespread use of every new antibiotic introduced.

The more we use antibiotics, the more widespread bacterial resistance to these drugs becomes. Every time a person takes an antibiotic, sensitive bacteria are killed while resistant germs are left to grow and multiply—a classic case of natural selection. Too-frequent and improper uses of antibiotics are the main causes of today's increase in drug-resistant bacteria.

Another source of antibiotic resistance originates with the way we raise livestock, fish, and orchard crops. Almost 70 percent of all the antibiotics produced in the United States are added to animal feeds—not to fend off disease but to boost growth. These non-therapeutic uses of antibiotics are a perfect way to cultivate resistant organisms, including *Campylobacter* and *Salmonella*, bacteria that can sicken people who eat meat and poultry products.

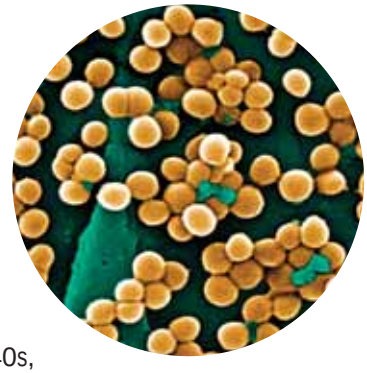
The Toll of Resistance

Antibiotic resistance has been called one of the world's most pressing public health problems. Almost every type of bacteria has become less responsive to the antibiotic treatment designed to combat it. And antibiotic resistance affects everyone's health in a way that no single disease does. It is a particularly serious problem for patients whose immune systems are compromised, such as people with HIV/AIDS and patients in critical care units. Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays.

But healthy people are also at risk. A child with an ear infection that in the early 1990s would have been instantly cured by penicillin may now need two, three, or four courses of different drugs. A new mother may contract a drug-resistant urinary tract infection that keeps her in the hospital an extra day or more.

How Bacteria Become Drug Resistant

Bacteria are able to resist drugs through one of several mechanisms. Some develop the ability to inactivate or destroy the antibiotic before it can do harm. Others can rapidly pump the antibiotic out of bacterial cells. Still others can change the place in the cell that antibiotics target so that the drugs are ineffective. The more these resistant organisms spread, the more they add to the pool of resistance genes in all bacteria, raising the odds that these genes will jump to more and more disease-causing microbes.



MRSA bacteria.

The story of staph bacteria and antibiotics illustrates the perils of drug resistance. Scottish bacteriologist Alexander Fleming discovered the first antibiotic, penicillin, in 1927, an achievement for which he was co-awarded a Nobel Prize in 1945. By the early 1940s, the drug was used in patients. But

penicillin-resistant staph bacteria emerged as early as 1942. Today, virtually all *Staphylococcus aureus* are penicillin resistant.

Staph bacteria are commonly carried on the skin or in the nose of healthy people. MRSA—methicillin-resistant *Staphylococcus aureus*—is a type of staph that is resistant to antibiotics called beta-lactams. In the past the majority of MRSA infections occurred among patients in hospitals or other health care settings. But drug-resistant staph is also showing up in healthy people who have not been staying in a hospital. If common staph bacteria were to become resistant to all readily available antibiotics, the practice of medicine would change dramatically. Any surgery or invasive procedure could bring life-threatening complications. As was the case in the pre-antibiotic era, even the most minor cuts in the skin could prove fatal.

Though this discussion focuses on the evolving resistance of bacteria to antibiotics, the issue of antimicrobial resistance is actually much broader. The resistance of viruses such as HIV and influenza to antivirals and of protozoan parasites to antimalarial drugs is a huge problem around the globe. Microbes have the capacity to develop resistance, whether they are bacteria, viruses, or protozoa.

How to Protect Yourself

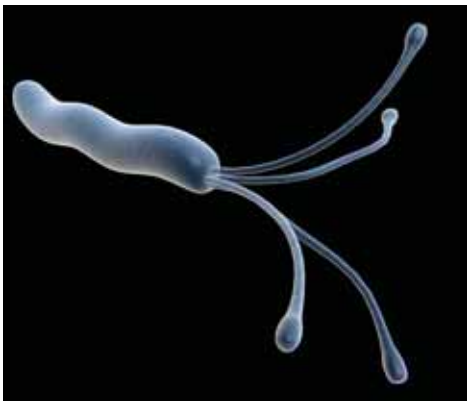
To avoid contracting an antibiotic-resistant infection:

- Do not demand an antibiotic when a health care provider says it is not needed.
- Do not take an antibiotic for a viral infection, such as the common cold.
- If your health care provider prescribes an antibiotic for you, do not skip doses and do not save any for the next time you get sick. Complete the prescribed course of treatment, even if you are feeling better.
- If you are a hospital patient or have a loved one in the hospital, make sure that you and the doctors, nurses, support staff, and all visitors wash their hands or use a hand sanitizer prior to touching the patient.

Chronic Illness and Cancer

In the United States, 70 percent of all deaths are due to chronic diseases. Until recently their biological causes were mostly unknown. Today, growing evidence suggests that infections are behind many chronic diseases once thought to be caused by genetic, environmental, or lifestyle factors.

The human papillomavirus (HPV), for instance, causes more than 90 percent of cervical cancer cases. The hepatitis B virus accounts for more than 60 percent of liver cancer cases. The hepatitis C virus causes cirrhosis, end-stage liver disease, and liver cancer. Human herpesvirus 8 causes Kaposi's sarcoma, a malignant complication of AIDS. *Helicobacter pylori*, a spiral-shaped bacterium, is the agent of peptic ulcers and gastric cancer. These examples may be just the tip of the iceberg.



Helicobacter pylori.

Clues to Infection

For scientists there are tantalizing clues that a seemingly chronic disease may be infectious. When an illness arises mostly in people whose immune systems are weak, it suggests infection (such as in Kaposi's sarcoma following organ transplants). When a disease gets better with antibiotics (as does strep-induced rheumatic fever), it's likely to be infectious. Another sign of possible infection is chronic inflammation, which is a common denominator in such diseases as multiple sclerosis, rheumatoid arthritis, lupus, and other autoimmune diseases. It remains to be proven that any of these diseases have infectious origins, though the possibility certainly exists.

The traditional standards for establishing a microbial cause of disease were developed in the 19th century for acute infections such as tuberculosis and anthrax. When it comes to tracking down an infectious source of chronic disease, however, traditional standards may prove to be too restrictive. Sometimes the suspect bacteria or viruses are difficult to detect or grow in the lab. Or there may be long delays between infection and disease, so that by the time symptoms appear, the agents that caused the original infection may be gone. Some psychiatric illnesses, such as schizophrenia, may have been triggered by infections that occurred just before or after birth. Studies are in progress to address this possibility.

New Treatment Approaches

Proof that certain infections cause chronic diseases raises the promise of treatment with antibiotics or vaccines. The discovery that infection with *H. pylori* was associated with peptic ulcers is a well-known example. Doctors used to assume that stress and spicy foods caused ulcers—and recommended bland diets. Today they simply cure the condition by prescribing a pair of antibiotics.

Another advance in prevention is the hepatitis B vaccine. Liver cancer is one of the most common cancers in the world and the most common cancer in some parts of Asia. With the hepatitis B vaccine now included in universal childhood immunization programs, new cases of this cancer are expected to drop.

As even this brief survey of disease threats shows, trends in infectious disease are never stagnant. They reflect dynamic forces in the world, some of which are the subject of the next section. The microbe–human relationship continues to evolve in ways that may not always be predictable, especially as we exert ever-greater stresses on the planet in our endless quest to survive and prosper.

III

Global Challenges

The rate of growth of the world's population is predicted to slow in the 21st century, but since the beginning of the 20th century the number of people in the world has more than quadrupled—from 1.6 billion to nearly 7 billion—and world population is expected to rise to more than 9 billion by 2050.

The sheer fact of all those people striving to achieve a suitable quality of life means that stress on the resources of our planet is bound to increase. Climate change, with its attendant effects on weather patterns; the displacement of human populations due to political conflict or worsening environmental conditions; and the expansion of settlements into former wilderness areas are all global trends that carry with them significant implications for the nature of humans' relationship with microbes.

Globalization

Today's world is a global village, with growing concentrations of people in huge cities, mass migrations forced by social or economic pressures, and accelerating commerce and travel. An estimated 1.8 million airline passengers cross international borders daily, creating routes by which human infections can radiate around the world within hours. The crates and containers in which goods are shipped worldwide provide safe passage for disease vectors and animal pathogens. Building roads in previously roadless areas brings people into contact with new environments and potentially new pathogens. Cruise ship travel has increased, bringing together—often in confined spaces—thousands of people from diverse geographic regions (including countries with immunization requirements that differ significantly from those of the various sites where ships disembark). And as adventure travelers intrude on new environments and make contact with exotic wildlife, they may encounter microbes that have never before been recognized as human pathogens.

The movement of people around the globe, depicted here in a map of air traffic among the 500 largest international airports, can lead to the rapid spread of infectious disease.

In this rapidly shifting and interconnected world, infectious agents continually find new niches. The 2009 "swine flu" pandemic starkly illustrated the impact of globalization and air travel on the movement of infectious diseases—with the infection spreading to 30 countries within 6 weeks and to more than 190 countries and territories within months.

The human population is undergoing a mass migration from the countryside to "megacities." Throughout history, big cities have been great incubators of infections—with outbreaks of respiratory, gastrointestinal, meningeal, and skin infections becoming common in crowded urban settings. Substandard housing and inadequate sewage and water management systems incubate disease vectors such as mosquitoes and rats. Poor access to health care services worsens the spread of infection.

Globalization of the food supply has spread disease caused by bacteria such as *Salmonella* and *E. coli* O157:H7. The United States, for example, imports about 20 percent of its fresh vegetables, 50 percent of its fresh fruits, and more than 80 percent of its fish and seafood. As wealthy nations demand such foods year-round, the increasing reliance on producers abroad means that food may be contaminated during harvesting, storage, processing, and transport—long before it reaches overseas markets.

Sao Paulo, Brazil—a modern megacity.

Food is not the only globally traded product to set off waves of infection. In 1999 the fungus *Cryptococcus gattii* emerged on Vancouver

Island, British Columbia, Canada, causing a growing epidemic of human and animal infections and deaths. It has since spread to the Pacific Northwestern United States. The fungus, which causes deadly infections of the lung and brain, had previously been found only in tropical or subtropical climates in such regions as Africa, Australia, Southeast Asia, and the South Pacific. The exact origins of this outbreak remain a mystery, but some researchers suggest that the fungus may have been introduced through the importation of contaminated trees, shoes, wooden pallets, or shipping crates.

Climate Change

Global climate change is expected to contribute to the worldwide burden of disease and premature deaths. Scientists predict that rising average temperatures in some regions will change the transmission dynamics and geographic range of cholera, malaria, dengue fever, and tick-borne diseases. Increased precipitation may raise the number and productivity of breeding sites for vectors such as mosquitoes, ticks, and snails. Rising atmospheric and surface temperatures are also increasing the intensity, frequency, and duration of heavy precipitation and flooding events, which may raise the risk of diarrheal diseases and vector-borne infections.

A number of diseases—such as malaria, dengue fever, and viral encephalitis infections—are highly sensitive to changes in the environment. The 1993 outbreak of hantavirus pulmonary syndrome (a severe acute respiratory disease) in the Southwestern United States provides a dramatic example of how acute weather events can promote disease transmission. The outbreak was traced to a steep increase in the population of deer mice that carry the virus—an increase caused by heavy rains after 6 years of drought, which led to an abundance of food sources for the deer mice. West Nile virus emerged in the Eastern United States in 1999, during the hottest and driest summer in a century. Subsequent outbreaks in the Midwest in 2003, 2005, and 2006 also coincided with heat waves. Scientists believe that hot weather may speed up both the breeding cycle of mosquitoes and replication of the virus in insects' guts.

Several recent studies have examined the relationship between the occurrence of infectious diseases and short-term climate variation, in particular the influence of the El Niño-Southern Oscillation (ENSO) cycle on the transmission of vector-borne and nonvector-borne infections such as malaria, dengue fever, and cholera. ENSO is the irregular cycling of surface water temperatures between warm and cool phases across parts of the Pacific Ocean. Global climate change is expected to intensify ENSO-related climate variability.

Scientists are currently debating the future effects of climate change on vector-borne disease. Some

experts predict that many vector-borne diseases will expand their range to higher elevations and latitudes in response to global warming; others claim that human impacts on the local ecology, such as deforestation and water use and storage, have a far stronger influence on the frequency and range of vector-borne infections.

A secondary effect of climate change also promotes infectious disease. Human migration often follows extreme weather or weather-associated events, including hurricanes, cyclones, fires, drought, and floods. The risk of disease outbreaks increases after such disasters due to population displacement, resulting in unsafe food and water, crowding, and poor access to health care.

Ecosystem Disturbances

Whenever animals (including humans), plants, and microbes are introduced into new places, they can disrupt ecosystems in ways that increase the potential for infectious disease outbreaks. Such changes can be difficult to predict and even more daunting to prevent. The term "invasive species" is widely used to describe plants and animals that, when introduced to and established in new environments, spread aggressively. Invasions of disease-causing microbes play out in similar ways.

The edges or transition zones between two adjacent ecological systems appear to be "hot spots" for disturbance-induced disease emergence. Examples of such transition zones include the border of human settlements, as well as natural transitions between forests and plains, shorelines, and tree lines. Because of the massive expansion of human settlements into natural, uninhabited ecosystems, these ecological transition zones now dominate much of the geography of the world's tropical developing regions.

When humans move into new environments, microbes that occur in the native wildlife population without causing apparent ill effects may adapt and jump to people. Scientists believe that the Ebola virus—first identified in a western equatorial province of Sudan and in a nearby region of Zaïre (now the Democratic Republic of the Congo) in 1976—naturally resides in the rainforests on the African continent and in the Western Pacific. Laboratory observation has shown that bats experimentally infected with Ebola do not die, and this has raised speculation that these mammals may play a role in maintaining the virus in the tropical forest. Closer to home, Lyme disease surfaced when abandoned farmland in the Northeastern United States reverted to fragmented forest land—a perfect home for deer and the deer tick that carries the bacterium associated with Lyme disease.

The clearing and settlement of tropical rainforests has exposed woodcutters, farmers, and ecotourists to new vector-borne diseases. Deforestation also creates new habitats for pathogens and vectors. In South America, for instance, epidemic malaria has broken out in recently clear-cut areas where mosquitoes now thrive.

The construction of large dams can cause profound ecological changes that increase vector-borne diseases. In tropical and subtropical nations the development of large water projects has been associated in some areas with a rise in malaria and schistosomiasis, both parasitic infections.

Poverty, Migration, and War

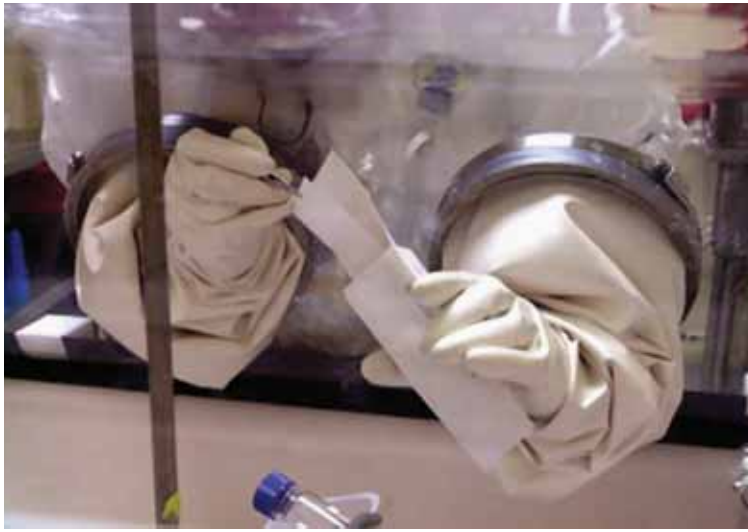
Throughout history, poverty and infectious disease have been intimately connected. In makeshift and overcrowded shantytowns and slum neighborhoods located on the outskirts of major cities in the developing world, lack of access to clean water and improper sanitation services spread diarrheal diseases. Worldwide, 884 million people do not have access to an adequate water supply, and about three times that number lack basic sanitation services. An estimated 2 million deaths a year can be attributed to unsafe water supplies; about 90 percent of those who die from diarrheal diseases are children in developing nations.

People in poor nations often suffer from more than one infection, because poverty breeds many diseases at once, including HIV/AIDS, malaria, tuberculosis, respiratory and intestinal infections, and neglected diseases of poverty such as intestinal worms, Chagas disease, and dengue fever. Pneumonia, diarrhea, and malaria are among the leading causes of death in the developing world in children under the age of five. When there is a lapse in political will to support disease prevention efforts, such as childhood vaccinations, disease can emerge rapidly, as seen in the spread of polio from northern Nigeria to more than 20 other countries.

Refugee camp in Sudan.

In addition, developing nations face public health hurdles such as weak health care systems and long distances to health care facilities. Limited availability of drugs, or widespread use of poor-quality or counterfeit medications, has led to drug resistance in the poverty-associated infections of HIV, tuberculosis, and malaria.

Growing numbers of people are moving within and across national borders after being forced from their homes by war, poverty, or famine. According to some estimates, 1 billion people could be displaced by 2050. Displaced people often bring their livestock, plants, or companion animals with them, increasing the variety of pathogens and vectors that accompany such journeys. Such refugees frequently live in crowded, unsafe conditions that exacerbate the transmission of infectious diseases. Rural to urban migration, for example, has led to increased HIV transmission in Africa.

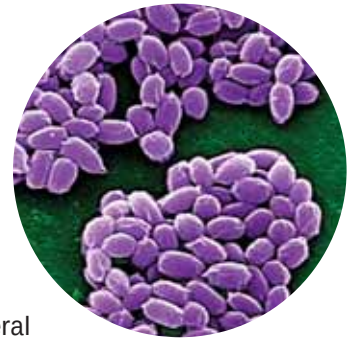


An investigator carefully examines one of the letters tainted with anthrax following the 2001 attack in the United States.

Bioterrorism

Bioterrorism is the deliberate release of viruses, bacteria, toxins, or other agents to cause illness or death in people, animals, or plants. According to experts, the threat of global bioterrorism is increasing. In October 2001, bioterrorism became a reality when letters containing powdered anthrax were sent through the U.S. Postal Service. The attack caused 22 cases of illness, 5 of which resulted in death, and widespread fear.

Biological agents are in some ways the perfect weapon of terror. They can be spread through the air, water, or food. Terrorists may choose these agents because they can be extremely difficult to detect and do not cause illness for several hours to several days after exposure, meaning that public health officials may not notice the attack until it is too late. Deadly pathogens are highly accessible. With the exception of smallpox, they all occur naturally in the wild—in soil, air, water, and animals. And the skills and equipment for making a biological weapon are widely known because they are the same as those required for cutting-edge work in medicine, agriculture, and other fields.



Bacillus anthracis,
the agent of anthrax.

High-priority organisms or toxins that pose the greatest risk to national security are known as Category A agents, according to the National Institute of Allergy and Infectious Diseases (NIAID). These deadly pathogens could be readily spread in the environment or transmitted from person to

person, triggering public panic and requiring special public health precautions.

Many public health officials believe that anthrax is the bioweapon of greatest concern—although in the case of the 2001 anthrax mailings in the United States there was less morbidity and mortality than many feared would occur. The infection is caused by *Bacillus anthracis,* a bacterium that forms spores. Anthrax does not spread from person to person but rather by hard-coated bacterial spores that spring to life under the right conditions. Anthrax can cause skin lesions and gastrointestinal disease. Inhalation anthrax is the rarest form of the infection—and may be the most difficult to treat.

Another disease of concern is smallpox, a serious, contagious, and sometimes fatal infection. Smallpox was officially declared eradicated from the globe in 1980, after an 11-year WHO vaccination campaign—the first human disease to be eliminated as a naturally spread contagion. Once the disease was gone, routine vaccination of the general public was stopped. Today, the virus remains only in laboratory stockpiles. But in the aftermath of the events of September and October 2001, concern has grown that the smallpox virus might be used as an agent of bioterrorism.

Another threat—the botulinum toxin—is the most lethal compound known. The nerve toxin is produced by the bacterium *Clostridium botulinum.* Researchers estimate that as little as a gram of aerosolized botox could kill more than 1.5 million people.

NIAID is developing tools to detect and counter the effects of a bioterrorist attack, including vaccines to immunize the public against diseases caused by bioterrorism agents, diagnostic tests to help first responders and other medical personnel rapidly detect exposure and provide treatment, and therapies to help patients exposed to bioterrorism agents regain their health.

Awareness of disease threats fostered by changing patterns of human existence and behaviors is the first step toward mitigating their effects. The following section explores what we can do, individually and collectively, to address risks posed by this evolving relationship between humans and microbes.

IV Prevention and Treatment

Infectious disease may be an unavoidable fact of life, but there are many strategies available to help us protect ourselves from infection and to treat a disease once it has developed.

Some are simple steps that individuals can take; others are national or global methods of detection, prevention, and treatment. All are critical to keeping communities, nations, and global populations healthy and secure.

Vaccines and Medicines

Medicines have existed in human society probably as long as sickness itself. However, with the advent of the modern pharmaceutical industry, biochemical approaches to preventing and treating disease have acquired a new level of prominence in the evolving relationship between microbes and their human hosts.

Vaccines

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe or its toxins. The agent stimulates the body's immune system to recognize it as foreign, destroy it, and "remember" it, so that the immune system can more easily identify and destroy any of these microorganisms that it encounters later. The body's immune system responds to vaccines as if they contain an actual pathogen, even though the vaccine itself is not capable of causing disease. Because vaccines are widely used in the United States, many once-common diseases—polio, measles, diphtheria, whooping cough, mumps, tetanus, and certain forms of meningitis—are now rare or well controlled.

Vaccinated people produce antibodies that neutralize a disease-causing virus or bacterium. They are much

less likely to become infected and transmit those germs to others. Even people who have not been vaccinated may be protected by the immunity of the "herd," because the vaccinated people around them are not getting sick or transmitting the infection. The higher the proportion of vaccinated people in a community, the lower the likelihood that a susceptible person will come into contact with an infectious individual—leading to greater herd immunity.

In the past, thimerosal, a preservative that contains mercury, was used in some vaccines and other products. Use of this product became the subject of controversy, with some arguing that the substance caused autism in children. Extensive, independent research has presented no convincing evidence of harm associated with the low levels of thimerosal present in vaccines. Since 2001, thimerosal has not been routinely used as a preservative in recommended childhood vaccines.

Antibiotics and Antivirals

Antibiotics are powerful medicines that fight bacterial infections. They either kill bacteria or stop them from reproducing, allowing the body's natural defenses to eliminate the pathogens. Used properly, antibiotics can save lives. But growing antibiotic resistance is curbing the effectiveness of these drugs. Taking an antibiotic as directed, even after symptoms disappear, is key to curing an infection and preventing the development of resistant bacteria.

Antibiotics don't work against viral infections such as colds or the flu. In those cases, antiviral drugs, which fight infection either by inhibiting a virus's ability to reproduce or by strengthening the body's immune response to the infection, are used. There are several different classes of drugs in the antiviral family, and each is used for specific kinds of viral infections. (Unlike antibacterial drugs, which may cover a wide spectrum of pathogens, antiviral medications are used to treat a narrower range of organisms.) Antiviral drugs are now available to treat a number of viruses, including influenza, HIV, herpes, and hepatitis B. Like bacteria, viruses mutate over time and develop resistance to antiviral drugs.

New Treatments

Modern medicine needs new kinds of antibiotics and antivirals to treat drug-resistant infections. But the pipeline of new drugs is drying up. For example, nearly 40 years elapsed between introduction of the two newest molecular classes of antibiotics: fluoroquinolones (such as Cipro) in 1962 and the oxazolidinones (such as Zyvox) in 2000.

Major pharmaceutical companies have limited interest in dedicating resources to the antibiotics market because these short-course drugs are not as profitable

as drugs that treat chronic conditions and lifestyle-related ailments, such as high blood pressure or high cholesterol. Antibiotic research and development is also expensive, risky, and time consuming. Return on that investment can be unpredictable, considering that resistance to antibiotics develops over time, eventually making them less effective.

New antiviral drugs are also in short supply. These medicines have been much more difficult to develop than antibacterial drugs because antivirals can damage host cells where the viruses reside. Today, there are more antiviral drugs for HIV than for any other viral disease, transforming an infection that was once considered a death sentence into a manageable chronic condition. But novel drugs are needed to combat other epidemic viral infections, such as influenza and hepatitis B and C.

Several programs have been developed to stimulate research and development of new vaccines and medicines. The U.S. Department of Health and Human Services recently formed the Biomedical Advanced Research and Development Authority, which provides an integrated, systematic approach to the development and purchase of the vaccines, drugs, therapies, and diagnostic tools necessary for public health medical emergencies. The Cures Acceleration Network provision of the Patient Protection and Affordable Care Act, signed into law by President Obama in March 2010, is designed to move research discoveries through to safe and effective therapies by awarding grants through the National Institutes of Health to biotech companies, universities, and patient advocacy groups. And nonprofit organizations dedicated to accelerating the discovery and clinical development of new therapies to treat infectious diseases are bringing together philanthropists, medical research foundations, industry leaders, and other key stakeholders to forge effective collaborations.

Microbe Awareness

Daily habits provide some of the strongest defenses against infectious diseases. Among the sensible actions you can take:

- Keep immunizations up to date.
- Wash your hands often. Washing with regular soap and rinsing with running water, followed by thorough drying, is considered the most important way to prevent disease transmission. Routine consumer use of residue-producing antibacterial products, such as those containing the chemical triclosan, have not been proven to confer health benefits and may actually contribute to antibiotic resistance.

- Prepare and handle food carefully. (See "How to Protect Yourself" in the Foodborne Pathogens section on page 16.)
- Use antibiotics only for infections caused by bacteria. Viral infections cannot be treated with antibiotics. Your doctor may prescribe an antiviral medication if your condition warrants it.
- Report to your doctor any rapidly worsening infection or any infection that does not get better after taking a course of antibiotics, if prescribed.
- Be careful around all wild animals and unfamiliar domestic animals. After any animal bite, cleanse the wound with soap and water and consult a clinician for further evaluation. Enjoy wild animals with your eyes, not by touching them.
- Avoid insect bites whenever possible by using insect repellent and wearing long-sleeved shirts, long pants, and a hat outdoors.
- Protect yourself by using safe sex practices. You and your partner should be tested for sexually transmitted diseases, including HIV, if there has been any risk of exposure. Consistently and correctly use condoms when having sex with a partner of unknown status. Avoid sex with an injecting drug user.
- Stay alert to disease threats when traveling or visiting underdeveloped countries. Seek advice from a reliable source, such as the WHO or the CDC, if you are going to areas of moderate-to-high disease risk.
- Acquire healthy habits such as eating well, getting enough sleep, exercising, and avoiding tobacco and illegal drug use.

Government Policies

Keeping our nation safe from disease outbreaks depends on effective and well-coordinated programs that monitor public health. What are some of the key efforts at work in the United States?

Public Health Capacity

The mission of public health is to safeguard and improve the health of the community as a whole. Effectively responding to infectious disease threats therefore requires a robust public health system. In the United States, public health surveillance for infectious diseases is conducted through a variety of agencies. Health care providers and others report cases of notifiable infectious diseases (as defined by local and state health codes) to state health departments. State health department officials, in turn, verify disease reports, monitor disease incidence, identify possible outbreaks, and forward their findings to the CDC. The CDC and other federal agencies, including the Food and Drug Administration, the U.S. Department of Agriculture, and the U.S. Department of Defense, independently gather and analyze information for disease surveillance.

CDC headquarters in Atlanta, Georgia.

Public health advocates have called for improved surveillance to better monitor infectious diseases across the country. Among their recommendations: a national electronic infectious diseases reporting system; innovative methods of disease surveillance (such as automated laboratory reporting of infectious disease or systematic gathering of informal reports of disease from the Internet); and fortifying the entire public health system, which historically has been underfunded compared to biomedical research.

Syndromic surveillance—the near- or real-time monitoring of nonspecific pre-diagnostic signs of disease outbreaks—is an innovative surveillance method that is being explored by some cities and states with assistance from the federal government as a means of providing early warning of infectious disease outbreaks. Syndromic surveillance rests on the idea that, following large-scale exposure to infectious disease in an epidemic or bioterrorist attack, people will first develop symptoms, stay away from work or school, and attempt to treat themselves before seeing a doctor. These systems therefore monitor school and work absenteeism, sales of over-the-counter medications, illness-related 9-1-1 calls, and other patterns that suggest an outbreak. However, most surveillance still focuses on tracking reported infections.

Food Safety

Foodborne diseases are largely preventable—but the goal requires vigilance in every step from the farm to the table. Good agricultural and manufacturing practices can reduce the spread of microbes among animals and prevent contamination

of foods. Monitoring the entire food production process can pinpoint hazards and control points where contamination can be prevented, limited, or eliminated. A formal method for evaluating risk control is called the Hazard Analysis Critical Control Point, or HACCP (pronounced "*has*-sip") system. First developed by NASA to ensure that the food eaten by astronauts was safe, HACCP safety principles are now being applied to a widening range of foods, including meat, poultry, seafood, fruit juices, and other products.

In recent years the U.S. Government Accountability Office, food safety advocates, and legislators have documented problems resulting from the fragmented nature of the nation's food safety system. At least a dozen federal agencies, implementing at least 30 different laws, have roles in overseeing the safety of the nation's food supply. Advocates have

recommended that all food safety activities be consolidated into a single federal agency with a unified mission.

International Cooperation

National borders offer trivial impediment to infectious disease threats. In the highly interconnected and readily traversed global village of our time, one nation's problem soon becomes every nation's problem. Therefore, many of the strategies described above must be implemented worldwide, not just nationally, in order to have a true impact.

Global Surveillance

Just as national surveillance is critical to controlling outbreaks within a nation, global surveillance is a critical component to responding to infectious disease worldwide. Among the strongest measures promoting worldwide infectious disease surveillance are the WHO's revised International Health Regulations, which entered into force in 2007. These require WHO member states to report certain diseases and outbreaks that may represent public health emergencies of international concern to the WHO and to strengthen their capacities for public health surveillance, diagnosis, and response. In addition, the CDC's Division of Global Migration and Quarantine, an integrated and comprehensive partnership of local, national, and global health authorities, works to prevent, detect, and contain infectious diseases in countries of origin and at U.S. ports of entry.

Technological advances in disease surveillance and detection such as regional syndromic surveillance, bioinformatics, and rapid diagnostic methods, have strengthened infectious disease control and prevention efforts. The global response to SARS, for example, was triggered by a report posted to the Program for Monitoring Emerging Diseases—or ProMED Mail—a global electronic reporting system for outbreaks of emerging infectious diseases and toxins.

Other networks are beginning to listen in on what scientists call "viral chatter"—the seemingly commonplace transmission of animal viruses to humans in parts of the world where the two populations overlap, such as live-animal markets or urban areas carved out of tropical rainforests. By identifying viruses, bacteria, and parasites in animals where they naturally live, and monitoring

those organisms as they move from animals into people, it may be possible to prevent deadly new infections of animal origin from entering and racing through human populations. The One Health Initiative, a worldwide movement to forge collaborations among physicians, veterinarians, and other related disciplines, is an example of efforts to improve communication about human and animal diseases.

Public Health in Developing Nations

The gaps in life expectancy between the richest and poorest countries now exceed 40 years—in large measure owing to the toll of infectious diseases. Safe water supplies, sewage treatment and disposal, improved food safety, and vaccination programs are urgently needed in developing nations. A major barrier to achieving these improvements is the underlying weakness of public health systems in resource-poor countries, including a shortage of health care workers, which hinders efforts to immunize, treat, and monitor the status of patients. Poor nations also lack disease surveillance programs and up-to-date laboratories, which are essential in the mission to find, diagnose, and contain infectious diseases.

Distribution of Medicines

Life-saving vaccines and medications are not distributed equitably around the world. More than half of those suffering from HIV/AIDS who need drug treatment are not receiving it. Only 2 percent of people with multidrug-resistant TB receive the right medications. And while children in wealthy countries are routinely immunized with vaccines that protect against childhood pneumonia and diarrhea, children in poor countries are not; for each child who dies from pneumonia in an industrialized country, more than 2,000 children die from the infection in developing countries.

Many factors influence whether poor nations can obtain affordable drugs of good quality. Most drug research and development is not geared toward the needs of people in poor countries because they are not a large market. As a result, a large percentage of the money spent worldwide on health care research is dedicated to problems affecting a small percentage of the world's population. Social and political challenges to the distribution of medicines are factors as well. Efforts are being made by foundations, pharmaceutical companies, and other organizations to overcome these challenges, providing funding, research, and donations of medications. The tragedy of global infectious disease is not only that so many lives are lost or damaged, it's that so many of these infections could be prevented or treated effectively with low-cost drugs.

Two health workers give a child polio vaccine during a vaccination campaign in the Democratic Republic of the Congo.

A Look Ahead

Although the vast majority of the microbes we encounter every day cause no harm, those that do lead to illness or death cannot be ignored. Dramatic advances in sanitation, as well as science, technology, and medicine, have enabled us to make great strides in our struggle to prevent and control infectious diseases. Yet pathogens—old and new—are endlessly resourceful in adapting to and breaching our defenses. In addition, factors related to society, the environment, and our increasing global interconnectedness enhance the likelihood of disease emergence and spread. Moreover, it is a sad reality that today we must also grapple with the potential use of biological agents to do harm, human against human.

Prevention and control of infectious diseases are fundamental to individual, national, and global security. Failure to recognize—and act on—this essential truth will surely lead to disaster. The magnitude of the problem requires renewed and sustained commitment from policy makers, public health officials, and a concerned public. Despite past achievements, we have still not done enough in our own defense or in the defense of others. But in looking at our prospects, it is clear that the best defense against any disease outbreak will be a robust public health system, both in its science and practice. Sustained attention, dedication, and support will be essential. Only in this way will we be able to ensure the health and safety of our nation—and the world.

The information in this booklet is based largely on the following Institute of Medicine reports and workshops. More specific citations can be found in the "About this Website" section of the online version: **www.needtoknow.nas.edu/infectiousdisease**.

Addressing Foodborne Threats to Health: Policies, Practices, and Global Coordination (Workshop Summary) **(2006)**

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic: Global Challenges, Global Solutions (Workshop Summary) **(2010)**

Ending the War Metaphor: The Changing Agenda for Unraveling the Host-Microbe Relationship (Workshop Summary) **(2006)**

Global Climate Change and Extreme Weather Events: Understanding the Contributions to Infectious Disease Emergence (Workshop Summary) **(2008)**

Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions (Workshop Summary) **(2007)**

The Impact of Globalization on Infectious Disease Emergence and Control: Exploring the Consequences and Opportunities (Workshop Summary) **(2006)**

Infectious Disease Movement in a Borderless World (Workshop Summary) **(2010)**

The Infectious Etiology of Chronic Diseases: Defining the Relationship, Enhancing the Research, and Mitigating the Effects (Workshop Summary) **(2004)**

Microbial Evolution and Co-Adaptation: A Tribute to the Life and Scientific Legacies of Joshua Lederberg (Workshop Summary) **(2009)**

Microbial Threats to Health: Emergence, Detection, and Response **(2003)**

Vector-Borne Diseases: Understanding the Environmental, Human Health, and Ecological Connections (Workshop Summary) **(2008)**

Reports from the National Academies are available from the National Academies Press, 500 Fifth Street, NW, Washington, DC 20001; 800-624-6242; www.nap.edu. Reports are available online in a fully searchable format.

Credits

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