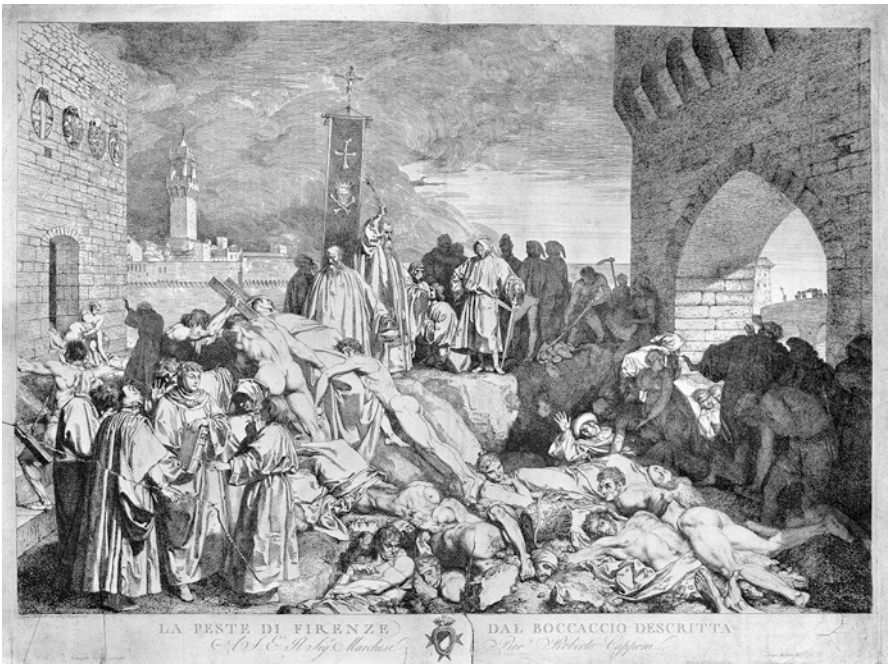
Chapter 4
Disease Now and Potential Future Pandemics



The plague of Florence in 1348, as described in Boccaccio's Decameron

A group of wealthy travelers enters your village, a day's ride outside of Florence, Italy, in 1348. They offer a handsome sum for housing and food, and are fed and given rooms. Later that evening one of them is overheard talking about a terrible disease that has started in Florence, expressing relief they have escaped. The next day, one of the travelers calls for a healer. He has pustules covering his body. Within 4 days of getting a high fever and vomiting blood, he has died. Soon others in his party and then people in the village start exhibiting the same symptoms. Within 2 months, 3/4 of the people in the village are dead. A few attempt to escape and travel to other villages. The Black Death (bubonic plague) has taken another village and continued to spread. This pandemic was the worst in recorded history and

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caused the death of roughly half of Europe's population. It killed one in five people on Earth, and caused drastic political changes [24].

Right now, a child lies weak in a hut in Africa. She has not been able to hold food for a week and is nothing but skin and bones. Only a moment later, the life passes from her eyes, another victim of diarrhea. This will happen again to four children under the age of 5 somewhere in the world in the next minute or two.

These two stories illustrate two huge problems related to disease. First, I discuss disease as a major ongoing cause of mortality in developing countries, particularly for children. Next, the potential for a pandemic disease that kills a large portion of the population is covered. As we shall see, a massive pandemic is becoming ever more probable based on predictions arising from simple scientific principles. I start the chapter with some basic biological information because this information is necessary to understand how diseases develop and how humanity might be able to control them. Once again, taking the bias out of confirmation with increased understanding of accurate scientific information improves clarity with respect to causes and solutions of problems.

What Causes the Deadliest Diseases?

Diseases have probably existed since soon after the first life evolved. All organisms known today have diseases. These infections harm bacteria, fungi, protozoa, plants, and animals. Many of our diseases have their own diseases. Disease is an inescapable feature of human life. Humans can contract communicable diseases from bacteria, fungi, helminthes, protozoa, viruses, and prions. A little biology, my favorite subject, is required to understand how they cause disease, how novel diseases can arise, and why some of them are so difficult to control.

Helminthes are simple animals, little microscopic worms. These animals often lack digestive systems, as they take nutrition directly from their hosts. They have complex life cycles and can inhabit several hosts. Evolution has stripped these animals down to only the basics required for living off others. Schistosomiasis is the most common helminth disease, causing widespread suffering. Initial infection can cause fever, chills, and liver and spleen enlargement. Chronic infections can lead to liver or kidney failure, bladder cancer, heart failure, and other symptoms. This disease is difficult to treat and causes major suffering in the world; at any one time, over 200 million people are infected, mostly in Africa. This disease is a major cause of suffering, but we don't know enough to eradicate it. We have studied most tropical diseases far less than those influencing populations in wealthier temperate countries. Worldwide cooperation in study of all major diseases is required to decrease the amount of suffering related to helminth diseases.

Fungal diseases are becoming more dominant as sources of mortality. They are particularly problematic for immune-compromised patients, but some of the diseases are endemic in environments around the world. They cause less mortality than many other diseases.

Protozoa are single-celled microbes that are tremendously diverse and play both positive and negative roles for humans. Protozoa cause a variety of nasty diseases including African sleeping sickness, *Giardia* and *Cryptosporidium* (two major causes of diarrhea). These diseases are difficult to control because protozoa are more like us than bacteria and chemicals that kill them tend to harm humans.

Of the diseases caused by protozoa, malaria is one of the top diseases causing death and suffering in the world. Mosquitoes carry this disease, and it is common in tropical areas worldwide. As global warming increases temperatures, mosquitoes will move into formerly colder climates, spreading malaria to new areas. There are over 200 million cases and a half million deaths each year from malaria. This is one of the major scourges of humanity, and it is a difficult disease to prevent and cure. More research is essential to control this disease.

Prions are strange disease agents that arise from proteins that cause other proteins to change shape and become ineffective. The mad cow disease is probably the best known of these diseases. This prion-caused disease arose when meat producers in Europe fed animals neural material (brain and spinal tissues) from other cattle. Cannibalism is not natural for cattle, but the practice arose because it stimulated growth when animals consumed waste by-products from other slaughtered cattle. Some of the sick animals had a protein in their brains that was defective and could infect the brains of other cattle when ingested. If people unknowingly eat beef contaminated with some of this infected neural tissue, they also become infected. The defective protein causes human neural proteins to lose their function slowly over time. People have died from this and related prion diseases. However, this number is small relative to other diseases and I will not consider it further.

Some of the worst diseases of humankind are bacterial, including the Black Death (plague), tuberculosis, cholera, salmonella, and coliform diseases. While antibiotics allow treatments for many of these diseases, they still infect and kill millions of people each year. Bacteria are very simple cells and can completely replicate themselves if provided the basic vitamins and compounds they require. The vast majority of bacteria are harmless to humans and even beneficial. For instance, if we did not have bacteria that decompose dead animals and plants, the Earth would rapidly fill with these and there would be no resources left for the living.

A very small number of bacteria, relative to the total millions of species on Earth, can cause significant disease in humans. Of these, some do so incidentally and can live indefinitely in the environment without ever interacting with a human in any way. However, a few can only live in animals and can lead to debilitating if not fatal diseases. Intermediate between these two strategies are the bacteria that opportunistically cause disease in humans, but can live freely without an animal host.

Viruses, like prions, are not individual life forms. They are more like information parasites that completely rely on their hosts for reproduction. Viruses take advantage of the fact that we use DNA as the blueprint containing the information we use to make all cellular components and RNA to translate that information from DNA into the structure and machinery of the cells (proteins). Viruses subvert the cell's reproductive machinery for their own nefarious purposes: the reproduction and dispersal of more viruses. All viruses, unlike bacteria, must take advantage of living

cells with DNA to reproduce. Viral diseases include HIV, smallpox, polio, hepatitis, influenza, Ebola, and rabies. Viral diseases also infect and kill millions of people per year.

The Biological Arms Race: Disease as an Evolutionary Process

Our bodies and our species are engaged in ongoing arms races against our diseases, just as all other species are in a biological arms race with their diseases. In the short-term, our immune systems learn to recognize and fight diseases. In the long-term, humans have evolved defenses against the diseases. For each defense humanity has evolved, the diseases have evolved ways to get around the defense.

The Red Queen Hypothesis describes this arms race. The Red Queen from Lewis Carrol's *Alice in Wonderland* needs to run as fast as she can just to stay in place. This hypothesis suggests that organisms need to evolve as fast as they can to keep up with the organisms with which they interact because they are evolving as well. This is a case of feedback, as both members of the interaction need to keep evolving to survive.

In the case of human diseases, this arms race leads to a situation where humans are constantly adapting to their diseases, and the diseases are constantly evolving to take advantage of their hosts more effectively. To make things more complex, a disease that can jump from host to host, such as the flu that can move from pigs to humans, can escape the evolved defenses of one host by moving into another. We will consider this more completely when considering diseases arising from other animals. Sometimes these crossover diseases are too successful; in this case, the disease can completely kill off its new host leading to extinction of the disease itself. It is certainly a worst-case scenario that such a disease would arise in humans.

Humans have an immune system that can protect against most invasive diseases, but once an invader evolves a mechanism to skirt the human immune system, it can infect people everywhere. Infections will occur as long as humans do not evolve a way to keep the disease from reproducing or find a way to avoid exposure to the disease. Evolution to evade human immune defense is why viruses that cause colds move though human populations so readily. The group of cold viruses has evolved a way to swap genetic information, continuously creating new viruses. There are around 100 strains of cold virus, and each person gets a cold roughly twice a year. Thus, it would take you 50 years to go through all the cold viruses… and in that time new viruses could evolve.

The process of evolution is not "nice," because the very basis of natural selection is that some organisms die and others that are better adapted survive. When a novel deadly disease arises, it may not kill all the people that it infects, but could kill most and only the lucky few who survive can reproduce and pass their offspring resistance to the disease. Likewise, if humans become very resistant to a disease either through evolution or by technology (e.g., an effective vaccine), it might die out.

The ideas of humans evolving resistance to diseases, and of diseases becoming more effective at infecting people, lead to some of the major points in Jared Diamond's book *Guns, Germs, and Steel* [25]. He suggests that successful invading cultures are those that have evolved to be resistant to a larger array of diseases and as they evolve this resistance, the diseases become more virulent (infective) in order to spread. This evolution can lead to a situation where people are no longer killed by a disease, and some of them become disease carriers. Such a group of people will bring these diseases with them upon colonizing a new area. The disease that is not lethal to the colonists could be quite lethal to the colonized people that have no evolutionary experience with it.

European colonization of the Americas is a prime example of this form of migration and conquering other groups of people. Agriculture and technology made possible the large populations and cities in Europe and Asia. People living in dense urban environments, and trade routes connecting those groups of people across vast areas, created the perfect breeding grounds for new diseases to develop. Living in close proximity to domestic animals further stimulated the emergence of new diseases. The huge land mass of these two connected continents (and a modest connection to Africa as well) meant that there were many locations for diseases to develop then spread across the continents. Exposure to repeated waves of diseases allowed Europeans to develop immunity to those diseases while still chronically harboring many of them.

When Europeans encountered the indigenous peoples of the Americas, they gave them their diseases. These diseases probably moved across the American continents faster than the Europeans invaders did. The resulting wave of diseases could have killed even more people than the Black Death of Europe. We will never know exactly, because there are no written records and no accurate methods to estimate the exact causes of death of the pre-European human population in the Americas. However, archeologists have found evidence for a large crash in American Indian populations across both North and South America after first contact with Europeans; the estimates are 57% mortality. These estimates are based on genetic methods that can be used to indicate drastic population reductions (from all causes) in the past [26]. Thus, the European colonists entered a land with relatively low population density that was poorly defended with a huge amount of exploitable resources.

The endless cycle of disease, massive death, development of resistance, and resurgence of disease was the hallmark of human history until we developed the technology to control many of our diseases. Cultural evolution moved ahead of biological evolution and protected us by changing our behaviors and ultimately by allowing us to develop the tools to manipulate the biochemistry of our own cells to fight off diseases (inoculation with vaccines).

While many animals have adaptations that help them avoid disease, one of the earliest unique signs of human cultural technological developments to avoid disease (and make food more digestible) is the act of cooking food. Additional steps to avoid diseases included cultural changes such as dietary restrictions of religions, as well as guidance in matters of personal hygiene in ancient cultures and religions.

By the mid-1800s, John Snow used statistical methods to link a cholera outbreak in London to a particular well on Broad Street. The authorities shut down the well, probably helping end the outbreak. This understanding of the source of disease was the first case of using epidemiology (the science of incidence, distribution, and possible control of diseases) to help understand how to control disease [27].

At about this time, Louis Pasteur developed the idea that bacteria spread disease. Once people had microscopes, they could see bacteria and assign them as potentially causative agents of disease. These observations by Pasteur and his contemporaries led to a rapid succession of ways to control diseases including purification of drinking water, preservation of food (pasteurization), and sterilization or sanitization during surgeries.

It was not until the discovery of antibiotics and vaccinations that humans really started to free themselves of some of the worst diseases in history, at least temporarily. People started looking for chemical agents to destroy bacteria once science confirmed that they caused diseases. Alexander Fleming discovered penicillin in 1928, and in 1942, Howard Florey and Ernst Chain developed the drug penicillin in an easily produced and administered form. Yet, humans still did not win the evolutionary battle between bacterial disease and humankind. When Fleming gave his Nobel acceptance speech in 1945, he noted that bacteria could develop that were resistant to penicillin if exposed to less than lethal concentrations. Within 2 years of the advent of clinical use of penicillin, clinicians had noted antibiotic-resistant bacterial infections in human patients.

Antibiotic resistance is a classic case of evolution. A very low proportion of bacteria in a population have the ability to survive exposure to the antibiotic. There is a low level of mutation leading to very small differences in the DNA in each bacterium. By chance, one or a few have a mutation that allows them to escape death from the antibiotic. These bacteria reproduce and soon take over the entire population.

Bacteria are particularly well suited to rapid evolution because their populations are so huge and grow so quickly that the chance that one cell has a mutation that makes it resistant is high, even though the chance that each individual cell is resistant is extremely low. There are about 100,000,000,000,000 (a hundred trillion) bacteria associated with each human. This is about 1000 times as many as there are stars in our galaxy, or 100,000 times as many as all the people on Earth.

There is an even more interesting, and insidious twist to this story. Bacteria have special little bits of DNA called plasmids. Since bacteria are not sexual organisms, they cannot exchange genetic material through sex like we, other animals, and many plants do. Instead, they trade these little plasmids. They can trade this genetic material within or among species. Thus, antibiotic resistance can move among different species of bacteria.

A recent spread of antibiotic resistance illustrates the problem [28]. The antibiotic colistin represents a last-ditch compound used to treat infections that are resistant to multiple antibiotics. The gene mcr-1 started showing up in bacterial infections in hospitals around the world, and this gene makes bacterial infections resistant to colistin. The antibiotic colistin had seen limited use in humans because

it has bad side effects. However, swine farmers use it. Researchers sequenced isolates of colistin-resistant bacteria from 31 countries, and the genetic data suggested the gene arose in a pig farm in China in 2006. It took less than 12 years for disease-causing bacteria containing the gene to move from livestock to humans globally.

Numerous plasmids for antibiotic resistance have spread readily around the world. Now microbiologists can take a sample from the center of the ocean and isolate bacteria that are resistant to antibiotics only synthesized by humans thousands of miles away. Thus, in the evolutionary battle, we cannot easily vanquish disease-causing bacteria.

Controlling the expansion of resistance to new and existing antibiotics requires an understanding of evolution. Taking a full course of antibiotics to be certain the drug completely clears the infection, only using antibiotics when they are necessary, and not allowing livestock producers to use antibiotics added to feed solely to increase growth rates of healthy animals are all necessary to decrease the probability that bacteria will become resistant to antibiotics. Cooperation not to overuse antibiotics, leading to antibiotic resistance, is necessary to control this threat. This cooperation needs to be worldwide given the propensity of diseases and antibiotic resistance to spread rapidly around the world. This is an evolutionary "arms" race, with bacteria rapidly evolving ways to resist antibiotics and humans developing new weapons against bacteria. We need science to win the "arms race" by coming up with novel antibiotics to stop diseases resistant to the current antibiotics. Otherwise, we end up back where humanity has been for most of its history, at the mercy of bacterial infection.

Chronic Diseases of Human Kind: Why Do So Many Children Die of Preventable Diseases?

We live in a world where millions of people die each year from preventable diseases. These diseases often only cause temporary illness to people in developed countries. For example, in developed countries, we do not generally consider diarrhea a fatal disease, and we successfully treat most severe cases with hydration and chemical therapy. In bad cases, intravenous fluids can prevent dehydration. Likewise, many cases of pneumonia can be treated, particularly bacterial-caused cases that are treatable with antibiotics. However, pneumonia is the top cause of death, diarrhea the second, and malaria and problems with childbirth are the next two top killers of children when considered worldwide.

Diarrhea causes 15% of global deaths in children under 5 years of age even though it is treatable with access to basic medical care and many cases are preventable with clean food and water. Pneumonia causes even more childhood deaths (18%). Essentially all of these deaths occur in developing countries. Vaccines against some bacteria that cause pneumonia can help, and access to antibiotics for

bacterial cases can help cure the disease. Inoculations against measles and whooping cough (pertussis) can also help reduce mortality as these diseases can lead to pneumonia. Malnourished children are more susceptible as well as those are that are exposed to indoor air pollution (smoke from cooking fires). Only about 1/5 of the children with bacterial pneumonia even have access to antibiotics. Solutions are obvious and not tremendously expensive. Still the solutions to these diseases require global cooperation and a concerted effort.

There is good news; child mortality rates continue to fall, and diseases are decreasing worldwide [29]. However, in undeveloped countries, rates are still high and not declining rapidly enough. The following interventions could reduce childhood disease (in parentheses) by over 40%: (1) breastfeeding (diarrhea, pneumonia, neonatal sepsis), (2) insecticide-treated nets (malaria), (3) additional food for infants 6–12 months old (diarrhea, pneumonia, measles, malaria), (4) zinc supplements (diarrhea, pneumonia), (5) sanitary delivery (childbirth deaths), (6) Hib vaccine (pneumonia), and (7) clean water (diarrhea, pneumonia). Oral rehydration therapy, antibiotics, and antimalarial therapy could reduce deaths by another 31%. None of these steps seems that difficult.

Globally, including adults and children, the World Health Organization estimates that millions of people are afflicted by treatable diseases. These include (in millions), diarrheal disease (4620), lower respiratory infections (429), malaria (241), measles (27), pertussis (18), dengue (9), tuberculosis (8), and HIV (2.8). Many of these diseases are disproportionately harming people in less developed countries.

Spread of Successful Diseases: Why Epidemiology Matters

The study of epidemics is essential to understanding how diseases spread from one organism to another. Diseases can be passed from person to person, from animals to people, or from the environment to people. A firm set of general principles of the conditions under which harmful diseases will emerge, some of them already referred to here, are now widely agreed upon by epidemiologists. These general principles, in addition to a number of unique behaviors in humans, lead to the conclusion that the probability of global disease is increasing drastically.

Density of hosts is important in proliferation of disease. In diseases that move from person to person, the greater the frequency of contact between people, the more quickly disease can increase. We now live in a world where over half the people live in cities. The total number of people on Earth is still increasing, leading to ever-greater population density.

People move from city to city and around the globe more quickly and more frequently than ever. Many diseases have an incubation time of days to a week. Historically, long-distance travel across oceans took months. If somebody with a deadly disease boarded a boat, it could kill all the people on the boat, or they would be over the disease and no longer infective before they reached their destination.

Thus, conditions are more conducive than ever for the spread of a new deadly disease around the world.

New diseases are more likely to arise when there is opportunity for them to take hold. Stressed or unhealthy people are more likely to contract and transmit diseases than healthy individuals. We now have a greater absolute number of disease-prone malnourished people on Earth than at any time in history. People who live in cities, particularly the poor, are under constant stress from crowded living conditions, unhealthy environments, and the pressure to survive. A greater proportion of people live in cities now than any time in history, and the total number of people living in cities is also greater.

Novel diseases arise when humans come in contact with animals that can transmit diseases to humans (zoonotic diseases) [30]. We already have dozens of diseases that come from animals. We grow ever more animals to feed people as increasing population and standard of living increases demand for meat. We grow these animals under crowded conditions. Oftentimes we breed the animals for maximum growth, and they are genetically similar, conditions that can lead to greater disease susceptibility. We raise many pigs and birds in huge numbers in close proximity. Most diseases that arise in birds are not transmissible to people. However, they are more transmissible to pigs. Once the bird diseases establish in pigs, they are more likely to evolve ways to be infectious to humans.

Bush meat refers to wild animals killed by people for protein. As people move into more remote areas, they hunt wildlife to satisfy their protein needs. There is a particularly high chance of disease transmission from animals to humans when people butcher wild animals and make contact with fresh blood and organs from these animals. Human populations are growing and moving into more wild areas, particularly in the tropics.

Most new human diseases come from wild animals. As people stress natural ecosystems, the probability for such transmission could increase because we displace other animals from their natural habitats causing them to move longer distances, and they are more susceptible to disease because of the stress induced by human pressure. There is also a demand for live exotic meat in some Asian countries in particular. In this case, merchants bring caged animals into dense markets in close contact with other animals and many people. These are perfect conditions for a novel disease to spread from infected animals to livestock and people.

More people in the world are now immune compromised than ever, offering another reservoir for diseases. Around 40 million people are HIV positive and may become immune compromised. In areas where medical care is available, these people are receiving quite a few antibiotics leading to increased antibiotic resistance evolving in bacterial diseases. In addition, recipients of transplanted organs are generally immune compromised because drugs given to them to avoid rejection of the transplants also halt immunity to disease.

Humans have also developed some novel behaviors that further increase the probability of transmission of diseases, particularly those that require blood-to-blood contact. Intravenous use of illegal drugs leads to sharing of needles and has resulted in transmission of HIV and Hepatitis B and C. This behavior could also

lead to transmission of novel diseases in the future. Blood transfusions and organ transplants can also lead to movement of diseases. People receiving blood products were some of the first victims of the HIV pandemic.

Organ transplants from other species into humans could also lead to transmission of novel diseases. The most common species considered for organ transplants into humans are apes and pigs. Both these groups of animals carry viruses that may be harmless to them but cause extreme disease in humans. Such transplants are very rare currently, but given that the majority of people on organ transplant lists are not able to obtain an organ before they die, it is likely such transplants will increase as research progresses on ways to accomplish such transplants successfully.

The field of epidemiology tells us that it is becoming more probable that new diseases will develop, existing diseases could evolve into more deadly and virulent forms, all diseases will multiply more quickly, and they will continue to become resistant to human efforts to control them. These findings have ramifications for both chronic diseases and new diseases.

Emergent Pandemics and Superbugs

One of the worst worldwide pandemics was the "Spanish" flu that started in 1918. It killed about 3% of the world population and infected about 1/6 of all people. The bubonic plague in the 1300s infected about 1/4 of the Earth's human population and killed an estimated 13%. The "swine" flu (H1N1) started in 2009 and infected about 1/4 of humanity but killed less than a hundredth of 1% of our population. Scientists have traced the first widespread series of cases of HIV/AIDS to 1981, but the disease probably jumped into humans in the early 1900s. Since then, about 1% of people on Earth are living with HIV, and about 1.5 million people per year die because of AIDS. About 2% of the human population deaths each year is from AIDS-related causes worldwide. Waves of disease are a regular occurrence throughout human history and becoming more common.

Recently the world has been concerned (terrified) about Ebola. Symptoms include fever, severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abdominal (stomach) pain, unexplained hemorrhage (bleeding or bruising), and death. This disease has been simmering in Africa for decades. Outbreaks have occurred in sub-Saharan Africa regularly since 1976; in 2014, an outbreak started in Guinea and jumped to other African countries in weeks and then to countries around the world killing over 10,000 people. In 2019 almost 2000 people died in the Democratic Republic of the Congo, and stopping the disease there has been difficult because of warfare; this outbreak has spread to Uganda. The ease of global movement and increased travel continue to increase the potential for spread of the disease. What if this disease evolves to an even more easily transmitted form? There is no treatment or vaccine (although some promising vaccines are being developed).

Disease epidemics that do not kill a large proportion of the human population are common. In the 1700s there were 13 epidemics and in the 1800s 12, with 5 pandemic influenza epidemics in the 1900s. The data suggest that roughly every 10–20 years, there are epidemics with some mortality that infect a quarter to a third of the world's population.

You could argue that disease has not wiped out humans yet, so it will not in the future. Unfortunately, science has documented cases where diseases cause the extinction of an entire species. For example, people have inadvertently moved a fungal disease around the world that kills amphibians (frogs and salamanders). This disease is leading to numerous species extinctions globally. I have seen the effects of this disease first hand in Panama.

We studied the consequences of the fungal disease killing all adult frogs leading to loss of all the tadpoles in Panamanian mountain streams. Scientists had already documented that the disease was moving through North America to South America through Central America. The disease kills frogs in high-elevation areas and moves through lower-elevation areas without killing most animals. We knew that the area we were working in was going in the direct path of the disease, so we set up a before-after experiment to understand the effects.

On our first visit to the mountain stream, there were frogs everywhere. We needed to be careful not to step on them as we walked the trails. Each square yard of stream bottom had up to a hundred tadpoles. Twenty frog species used the streams for reproduction, and many of these species were entirely restricted to cooler areas with high altitude on this particular volcanic mountain. From sunset to sunrise, the jungle was a riot of frog choruses. There were fantastically colored adult frogs including the stunning black and white Panamanian Golden Frog, a species that has special meaning for Panamanians. We made our measurements on the stream, and enjoyed the frogs.

Two years later the disease had swept through as it progressed through the country from Costa Rica. When we drove up to the stream for the "after disease infection" experiment, it was immediately clear that it was different. Hoping against hope, I went down to the stream, but there were no tadpoles and no adult frogs on the banks. It was very quiet and sad. The stream had dense growths of algae because no tadpoles were eating it and the absence of the tadpoles fundamentally changed the way the stream functioned. In the end, maybe 100 species will go extinct from this disease.

Through this and other examples, we know that some diseases have driven animals and plants to extinction [31]. In Hawaii, 16 cases of bird extinctions have come about at least in part because of diseases. Numerous mammals and birds have gone extinct from diseases alone or in combination with other factors such as habitat loss [32]. Thus, it is not impossible that humans could suffer the same fate. The conditions that could lead to such a tragedy are making it more likely that such a disease could infect the human population.

Throughout human history, new nasty diseases have arisen. Many of them have jumped into humans from other species. Whenever a particularly virulent disease has infected a human, and killed most of the people exposed to it, the population of

people infected was small and disconnected from the rest of humanity. Epidemiology tells us that the incidents that were formerly isolated now have the potential to sweep across the globe and cause massive death and suffering.

We are increasing the conditions under which such diseases can arise and transmit to people (ever more intimate contact with wildlife, dense livestock production). Losses of biodiversity caused by humans also are predicted to increase the transmission of infectious human diseases [33]. It is no wonder that new diseases like Avian flu, H1N1, Ebola, and SARS are popping up with alarming regularity. Adding to the worry, viral evolution is unpredictable, and a new deadly strain of virus could arise from laboratories working on viruses that are presumably safe and contained. In this case a newly virulent strain could arise, escape, and become a pandemic [34].

At the same time, new diseases challenge the safety of people and the ability to treat such diseases increases. We can develop vaccines rapidly. Antiviral drugs are available that work at least well enough to decrease mortality. However, only those people in developed countries are able to afford or even have access to methods to protect from sickness and death from these infections. As usual, the poorer people of the world will suffer the worst of globalization, increased population, greater chance of new diseases, and unequal distribution of basic health care.

Bioterrorism, Biological Warfare, and Accidents

In late 2011 and early 2012, two laboratories, one at the University of Wisconsin-Madison, USA, and the other at Erasmus MC in Rotterdam, the Netherlands, found out how to make avian flu (H5N1) transmissible in ferrets. This research ignited a firestorm of controversy because the deadly virus could also spread among humans much more easily. The researchers submitted the work for publication but journals held up the release of the papers because of fears that people with bad intent (bioterrorists or countries willing to employ biological warfare) could use the information to transform this and other viruses to more deadly forms. Ultimately, the journals published the work, as eventually the information would get out. This is the way science works, once the general concept for an important idea is out, somebody else is certain to replicate the experiment. Thus, information on how to create a deadly disease is ever more available.

Accidental release from existing research facilities is also a concern. The deadliest diseases known to humanity are stored and researched in containment facilities found around the world. Smallpox has killed people for at least 3000 years, and following vaccination, it was completely eradicated from human populations in the 1970s. A number of laboratories still keep cultures. In 1978, one person died from exposure to the virus in a British laboratory. After that, scientists transferred all cultures to two laboratories, one in Russia and one in the United States. Entire generations have reached adulthood with no exposure to the disease; if smallpox was ever released by accident or on purpose (a scientist with PhD-level training could

potentially re-create it from the known genetic sequence), it could cause massive mortality.

In 1979, the Sverdlovsk military facility accidentally released anthrax causing 100 human deaths. Soviet researchers probably isolated this highly virulent strain of anthrax from rodents in the Soviet city of Kirov. The facility had likely accidentally released the bacterium at least once previously. Anthrax is able to survive as dry spores, and Soviets were presumably producing it to arm biological weapons.

While research on diseases is necessary to learn about causes and cures of the diseases that influence humans, such research comes with a cost. The ability to contain these diseases in research settings is plagued with the problem of potential human error. In addition, the possibility of terrorist attacks on such facilities is perhaps remote, but real.

In 1984, followers of Bhagwan Shree Rajneesh in Oregon released salmonella into 10 restaurant salad bars sickening 751 people in an attempt to keep them from voting in a local election in which the cult had candidates. Luckily, nobody died in this incident, but it does illustrate that people can be capable of bioterrorism.

In June of 1993, members of the Aum Shinrikyo cult sprayed anthrax from the top of an eight-story building in the heart of Tokyo. Fortunately, the disease did not take hold. The strain they used was not very deadly, and they had problems with a sprayer so the dispersion of the disease was not as effective as they had hoped. This group had previously set up multiple laboratories and had experimented with the toxin for botulism, cholera, and Q fever (a dangerous bacterial disease carried by livestock). They also previously sponsored a trip to the Democratic Republic of Congo that was an attempt to bring back an isolate of Ebola. This apocalyptic cult eventually released the chemical weapon Sarin in the Tokyo subway killing 12 people and sickening thousands.

While both these examples are unusual cases, we are entering a world where a few crazy people or one crazy country could do tremendous damage to humanity if they had access to the right materials and knowledge. Such knowledge is becoming commonplace. Every year academia cranks out numerous PhDs around the world with the technical expertise to build a deadly virus with the right equipment, chemicals (reagents), and knowledge of the sequence. At the same time, technology to work with DNA sequences is getting cheaper, easier to use, and more broadly available. With a million dollars and proper training, it is now possible to create designer diseases.

We should consider motives in this discussion as well. A terrorist who wanted to kill many people but wanted to discriminate victims would not only need to create a disease but also vaccinate or protect all the people they did not want to die. While a few doses of a disease placed appropriately could quickly spread around the world, creating many doses of vaccine is a far more daunting and expensive task. Thus, it seems unlikely that any of the major terrorist groups would be able to create a disease and vaccinate large numbers of people before releasing the disease without being detected first. Such a task is not completely out of the question for a small country such as North Korea.

There are insane people who just might try to take down the entire human race. The mass shooting in a movie theater in Denver in 2012 was carried out by a neuroscience PhD student. This individual could have had the technical ability to create a novel disease. A scenario where such a person creates and releases a deadly virus is conceivable. Quite a bit of preparation and disaster training would be necessary to stop transmission of an infectious agent once it was released [35].

How Can We Stop Pandemics?

Active surveillance of disease outbreaks is necessary to react to a pandemic in time. Currently the World Health Organization keeps track of disease outbreaks, but we need new methods to detect pandemics in time to respond. An effort called Global Viral [30] is also helping move the international community toward predicting viral outbreaks by promoting science and education about viral outbreaks.

Responses could include rapid development of vaccines to protect a population, antiviral drugs to decrease the probability of mortality, and increased capacity to produce these treatments. Public health officials are developing novel methods using social media and networks of cell phones to create an early warning system of disease outbreaks from remote areas. Additional improvements are possible in safety of livestock production, safer practices in killing and butchering wild animals, and education on behaviors that discourage the transmission of diseases.

There are several things that we can do to thwart bioterrorism. The easiest way to obtain a disease would be for a terrorist to attack one of highest-level containment facilities in the world that has cultures of the deadliest diseases known to humankind. These laboratories should be resistant to attack and have established procedures to quickly destroy all the diseases in them if they are compromised.

Several historic agreements are present to stop the use of biological and chemical warfare and terrorism. The 1925 Geneva Protocol, the 1972 Biological Weapons Convention, the 1976 Environmental Modification Convention, and the 1993 Chemical Convention all strove to have all countries agree to not develop or use chemical or biological weapons [36]. The Obama administration was involved in international efforts to stop the spread of biological weapons to terrorists. The United Nations is developing other treaties. Measures might include careful accounting of the reagents that molecular biologists can use to produce diseases and barring companies from providing DNA or RNA synthesis for particular sequences known to be associated with disease organisms. Careful international monitoring of biological laboratories capable of handling pathogenic microbes is also necessary, as well as protecting the laboratories that hold the deadliest human diseases. All of these require modest cost, but a substantial degree of international cooperation. For example, if even one country allows synthesis of dangerous virus sequences and will sell those to individuals, control elsewhere is pointless.