Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER SEVENTEEN

Panic and neglect—2000–2018

Abstract

Since 2000, multiple infectious threats to North America have been identified. The response to these threats has generally been one of initial panic. When major problems fail to develop, then the threat is rapidly forgotten. These threats include diseases arising within North America such as Lyme Disease, Rocky Mountain Spotted Fever, Legionnaire's Disease, and Norwalk virus, the cause of lethal diarrhea. Other diseases occurring in Latin America are moving northward. These include Dengue and Dengue Hemorrhagic Fever. The speed and efficiency of modern air travel have resulted in infections arriving from overseas. These include West Nile Fever, Chikungunya, and Zika Fevers, Ebola and Severe Acute Respiratory Syndrome (SARS) caused by a bat coronavirus. All of these affected relatively few people, and most were rapidly controlled.

Keywords: Outbreaks, SARS, Ebola, Zika, Dengue, West Nile virus, Preparedness, Surveillance, Air travel, Mosquitos

Deaths from infectious diseases dropped significantly in the United States after 1900. As a result, there was an increase in life expectancy of almost 30 years in white men, from 47 years in 1900 to 75 years in 2000 (Fig. 17.1). The increase in expectancy for black men has gone from 33 years to 68 years, for white women from 49 years to 80 years, and for black women from 34 years to 75 years. In 1900 a third of all deaths occurred in children under five and the three leading causes of death were all infections, pneumonia, tuberculosis, and enteric (intestinal) diseases. Together, these caused almost a third of all deaths. By the end of the 20th century, infectious diseases accounted for about 5% of deaths. Heart disease and cancer accounted for more than half the deaths. The leading lethal infections in 2000 were pneumonia, influenza, and AIDS.

These incredible improvements were largely a result of public health measures such as the availability of clean drinking water and effective sewage disposal systems, the development of antibiotics and the extensive use of vaccines, especially in children [1].

The previous chapters in this book have focused on the "Great diseases." Diseases that had killed hundreds of thousands or even millions of victims in the Americas. Even with COVID-19 circulating widely, AIDS continues its lethal process, tuberculosis is largely uncontrolled, while influenza, malaria,

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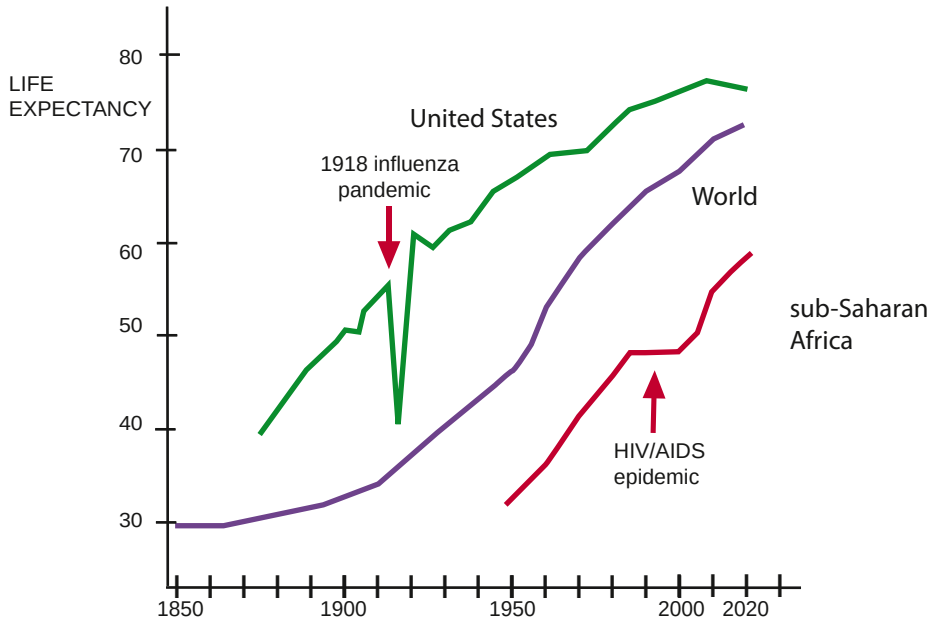

Fig. 17.1 The average estimated life expectancy in the United States, the world as a whole, and in sub-Saharan Africa from 1850 to the present. Two points are evident from this figure. First, life expectancy varies greatly among nations due to economics, political stability, and public health resources. Second, pandemics adversely affect life expectancy, though only temporarily. It has been projected that life expectancy in 2020 due to COVID-19 will drop by about 1–2 years in the United States. *(This figure is a compilation of data from the CDC, World Bank, and Our World in Data https://ourworldindata.org/grapher/life-expectancy.)*

and yellow fever lurk in the background. The decline in these great pandemic diseases does not however mean an absence of fear. Pandemic diseases emerge, disappear and reemerge. These emerging diseases have the potential to cause massive epidemics and pandemics if left unchecked. A prime example is the pandemic of COVID-19 caused by the SARS-CoV-2 coronavirus and discussed in the next chapter.

The prevalence and complexity of infectious diseases are increasing worldwide. There are several reasons for this. Changes in the climate, especially increasing temperatures are permitting arthropod vectors to move into areas that were previously too cold. Increasing populations have caused humans to move into previously unsuitable habitats such as forests, modify their environments, interact with wildlife, and set up conditions for the spillover of infectious agents, especially viruses. Indiscriminate antibiotic use has permitted resistant bacterial pathogens to resurface. In addition, the speed and rate of global travel have significantly increased the chances that infectious diseases will reach the United States and other developed countries. Everyone is at risk. Indeed, multiple examples of this have occurred in recent years. Most notably, West Nile virus, originally confined to the Middle East, was carried to New York and subsequently spread across the country infecting birds, horses, and humans. Mortality and morbidity have been low. None of these can be considered as great diseases—yet they should have served as a warning. Patients with Ebola disease have entered the United States after traveling from West Africa, the location of the most recent outbreak of this disease. Ebola has a mortality rate of 40%–80%. Severe acute respiratory syndrome (SARS-CoV-1) caused by a coronavirus also entered Canada by way of a returning tourist from China. In each of these cases, a prompt response by the Public Health Authorities prevented disease spread. Another recent example of an exotic foreign disease is Zika Disease. This viral disease originated in Africa and spread eastward around the world to reach the United States via Brazil in 2017. These were merely the taste of things to come. Dengue fever has reached south Texas and climate change will promote its northward spread. COVID-19 spread worldwide in less than 3 months and is not likely to go away completely.

In addition, terrorists are well aware of the ability of biological attacks to kill and cause panic. They have been planning these attacks and will only be controlled by rigorous surveillance and targeted preventive measures. It is abundantly clear that the risk of pandemic plagues has not gone away.

It is also fair to say that until the appearance of COVID-19, these emerging diseases failed to acquire the status of "great diseases." But it happened in

the past when, for example, poliomyelitis emerged at the beginning of the 20th century. AIDS was an emerging disease in the 1980s. The diseases discussed in this chapter reflect the American experience and can be considered as harbingers of the COVID-19 pandemic. In effect, the country has been in a cycle of panic then neglect or forget. When an epidemic is under way, be it Ebola, West Nile disease, or Zika, the public and the press give it a lot of attention. Once it fades away, people forget, and budgets shrink—until the next time.

It is also pertinent to point out the obvious; recent epidemic panics have been driven by the deaths of very few individuals. None of the diseases discussed in this chapter could be considered significant when compared with the massive outbreaks of the past, or of COVID-19. Even mundane diseases such as pneumonias or gastroenteritis are not feared any more. In times past, death from infection was a constant threat and people knew it. This situation changed once again with the onset and spread of COVID-19.

Home-grown threats

The North American Continent is huge and there have been plenty of opportunities for pathogens to evolve here. Three notable "home-grown" examples are the bacterial diseases Lyme Disease, Legionnaires Disease, and Rocky Mountain Spotted Fever.

Lyme Disease

In 1975, two young boys in Old Lyme, Connecticut were taken to a doctor with complaints of persistent fever and aching joints. The doctor's initial diagnosis was juvenile rheumatoid arthritis. However, the boys' mothers heard that several other children in the neighborhood had developed similar symptoms. Subsequent investigations by Dr. Allen Steere from Yale University confirmed that there had been multiple similar cases in previous years. A unique feature of this disease was that some of the victims had developed a strange circular rash associated with a tick bite. Fortunately, one of these ticks had been saved and it was identified as *Ixodes scapularis*.

I. scapularis has a 2-year life cycle (Fig. 17.2). In its first year the tick feeds on white-footed mice. Once it develops into an adult in its second year, it feeds on white-tailed deer. It was not until 1981 that Dr. William Burgdorfer working at an NIH laboratory in Montana found a spirochete in an *I. scapularis* from Long Island. When injected into a rabbit this spirochete produced a skin rash similar to that seen in Lyme disease. Subsequently

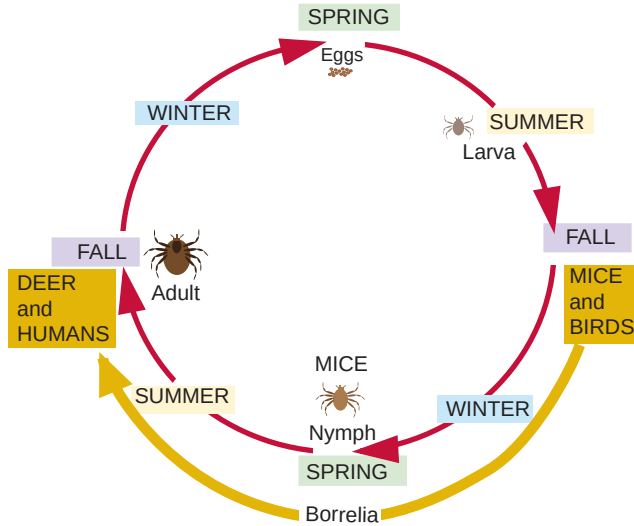

Fig. 17.2 The lifecycle of the deer tick, *Ixodes scapularis*. In its first year nymphal stage it feeds on mice and birds and may acquire *Borrelia burgdorferi*. As a result, in its second summer as an adult, it feeds on larger mammals and may transmit this organism to humans.

Dr. Steere found the same organism in his Lyme Disease patients. The bacterium was subsequently called *Borrelia burgdorferi*.

Beginning in communities around Long Island Sound, the number of cases of Lyme Disease increased and spread significantly. It is especially common in the Northeast and the Upper Midwest and it is the most prevalent vector-borne disease in North America. Over 30,000 cases of Lyme disease are reported annually but the true prevalence may be 10 times higher. Outbreaks are associated with a massive increase in the deer population in these areas as well as the encroachment of the urban suburbs into nearby forests where mice and deer are plentiful. However only nine lethal cases, all involving the heart, were reported by the CDC between 1985 and 2018. Lyme disease is treatable with appropriate antibiotics, especially tetracyclines.

Lyme disease is spread by the bites of infected ticks and it represents a case study on the destabilizing effects of human-caused environmental changes. As human populations have increased, the suburbs have expanded into nearby woodlands. These woodlands have been broken up into smaller and smaller fragments. White-tailed deer are browsers. They eat the nutrient-rich undergrowth that thrives under trees at the edge of the forest. (Deep in the forest there is insufficient light for undergrowth to prosper.) As a result, deer are "edge" species so that forest fragmentation, plus the elimination of predators, plus the decline in deer hunting, has resulted in a deer

population explosion. Likewise, the extirpation of predators such as foxes and eagles has allowed mouse and chipmunk populations to thrive. The movement of people into the woods has also provided the ticks with more opportunities to drink human blood. Tick eggs hatch in the leaf litter. The first life stages, the tick larvae, latch onto passing rodents and begin to feed. Once fed, they drop off and develop into the next stage called the nymph. The nymphs prefer larger prey and feed on deer, but, if deer are unavailable, any passing dog, or person will suffice.

Molecular studies on the genomes of *B. burgdorferi* from across the United States have determined its rate of evolution and thus revealed its history. It is now recognized to be an ancient infection that first spread, with its tick vectors, across North America at least 20,000 years ago [2]. Native American skeletons with arthritis that may be a result of Lyme disease and dated between 500 BC and AD 300 have been excavated in Louisiana. The development of this modern epidemic almost certainly reflects ecological and climate changes rather than changes in the bacterium.

Rocky Mountain Spotted Fever

Rocky Mountain Spotted Fever (RMSF), also called "black measles," was first recognized by an army physician, Major Marshall Wood, working in Boise, Idaho, in 1896. Subsequent reports described additional outbreaks in the Snake River valley of Idaho and the Bitterroot valley in Montana [3]. Of 111 cases studied at that time 76 were fatal. Patients rapidly developed fever, nausea, myalgias (muscle pains), gastrointestinal signs, and vomiting. It was followed in most patients, by the development of a characteristic spotted rash. The rash developed about 3 days after onset, first on the forearms, wrists, feet, and ankles. It eventually spread to the soles and the palms. This spotted rash results from damage to small blood vessels. This damage can interfere with the blood supply to critical organs and tissues. Thus, there may be residual brain or heart damage. Young children are especially vulnerable. The disease is currently treated with antibiotics such as doxycycline.

Beginning in 1901, efforts were made to investigate this problem and Rocky Mountain wood ticks were soon implicated as the vectors. The commonest ticks implicated in its transmission are the dog tick (*Dermacentor variabilis*) in the eastern United States and *Dermacentor andersoni* (the wood tick) in the Rocky Mountain states. Because of these dog ticks, it is possible to acquire RMSF at home from your pet dog without even venturing outdoors!

Fig. 17.3 Howard Ricketts working in his laboratory. *(Courtesy of the U.S. National Library of Medicine.)*

In 1906, Howard Ricketts from the University of Chicago was the first to characterize the causal agent, an exceedingly small intracellular coccobacillus (Fig. 17.3). He also demonstrated tick transmission to guinea pigs and showed that the organism was present in the blood of its victims. Ricketts died of typhus in 1910 (Chapter 9) and the organism was named after him—*Rickettsia rickettsii*—in 1919. Since that time, *R. rickettsii* has been found on all continents where ticks exist. It is present across the United States. North Carolina and Oklahoma account for about a third of US cases. The number of cases of RMSF diagnosed in the United States has increased in recent years from about 500 cases in 2000 to over 6000 in 2017. Most occur during the summer months. It kills about 14 people annually. The increase in diagnosed cases may well be an artifact resulting from the elimination of measles. It is believed that in the past, many of these RMSF rashes were often misdiagnosed as cases of measles!

RMSF belongs to a group of closely related spotted fever rickettsiosis, all transmitted by ticks, fleas, and mites. Other related diseases that occur naturally in the United States include Pacific Coast tick fever caused by *Rickettsia philipii* and transmitted by the Pacific Coast tick (*Dermacentor occidentalis*). This occurs in Northern California [4]. *Rickettsia parkeri* rickettsiosis is caused by its namesake and spread by the Gulf Coast tick, *Amblyomma maculatum*. This is found in the southeastern United States. There is also a very mild disease, called rickettsial pox caused by *Rickettsia akari* (Box 17.1).

BOX 17.1 Rickettsial pox.

In 1946 an outbreak of disease occurred in a large apartment complex in Queens, New York. The tenants developed a fever and rash that was initially diagnosed as chickenpox. The first sign of the disease was a small insect bite. Then the patient's lymph nodes enlarged, they developed a fever with chills and headaches, and eventually a rash. The rash would last about a week and all the victims recovered within about 3 weeks. The disease was restricted to that apartment complex and about 124 residents were affected.

One unique feature of the apartment complex was that it was infested with house mice. They were everywhere, both live and dead. It appeared that the garbage was not regularly collected so that the mice had plenty of food and thrived. When an entomologist, Charles Pomerantz examined the affected apartments he found enormous numbers of mouse mites hiding under the wallpaper! The mites were collected and a rickettsia, subsequently named *R. akari*, was isolated from them. Both mice and affected humans had antibodies against this bacterium. Pest control measures were rapidly adopted, and the garbage was cleaned up (Just like in San Francisco during the plague outbreak—Chapter 14). The disease was called Rickettsial pox. More cases of Rickettsial pox were identified in other areas of New York City between 1946 and 1951. In many of these, they too had been misdiagnosed as suffering from chickenpox.

Legionnaire's disease

On Wednesday, July 21, 1976, the Pennsylvania branch of the American Legion began their convention in Philadelphia to celebrate the bicentenary of the signing of the Declaration of Independence. More than 2300 Legionnaires and their families attended the convention. Afterward they returned home. Three days later, one died of an apparent heart attack, then four died, then six! Within a few weeks 149 legionnaires were sick as were 33 other guests and eventually 29 died! Common features of their illnesses were tiredness, chest pains, and fever. Some developed bronchopneumonia. Some had to be hospitalized.

Subsequent investigations showed that all of the victims had stayed at the Bellevue-Stratford Hotel on Broad Street. This was an old hotel, built in 1904 and beginning to show its age. On the second day of the convention, several participants had begun to experience a flu-like disease with fever, chills, and a dry cough. Once they developed severe pneumonia and began dying, physicians called repeatedly to the CDC and the authorities became seriously concerned. Swine flu, a major concern at that time,

BOX 17.2 The naming of new viruses.

It has long been convention that newly discovered viruses be named after the site of their original discovery. Hence virus names like Norwalk, Ebola, Zika, and West Nile. However not everybody is proud of having their neighborhood labeled in such a way. For example, the Navajo Nation in Arizona objected to the names given to the hantavirus isolated from their reservation and it was eventually named Sin Nombre virus—The nameless virus. This has become a contentious political issue in recent years. Thus, the coronavirus that originated in Wuhan, China, in late 2019 was originally designated the Wuhan virus, but was subsequently given the politically neutral name of SARS-CoV-2. It is the cause of COVID-19.

was suspected immediately but was soon excluded (Box 15.2). When the news of the outbreak broke, the remaining guests got out quickly. The hotel's water, food, and air were tested but no causal agent could be isolated. The epidemic peaked in August. By September, the outbreak had subsided, and the public relaxed. The disease was not contagious and there were no secondary cases. There was much debate regarding its cause. It was suggested that this was a terrorist attack involving some kind of poison gas. Careful epidemiological analysis of those affected indicated that they were primarily older men who had spent much time in the hotel lobby—but the hotel staff were unaffected!

CDC investigators were also searching for the cause and they received much criticism for their failure to identify it quickly. About 5 months after the outbreak around Christmas, Joseph McDade, a CDC bacteriologist, decided to look at the problem again. Lung tissues from four fatal cases had been inoculated into guinea pigs, the guinea pigs had sickened and were necropsied. Tissue smears from their lungs showed a few unidentifiable Gram-negative bacilli and these had been dismissed as contaminants. McDade looked at the slides again. He saw a few bacilli, but in one field he saw a cluster of them suggesting that they were growing. So, he injected infected guinea pig tissue into the yolks of fertile chicken eggs. The bacteria grew in enormous numbers. McDade showed that when these bacteria were mixed with a victim's blood serum a positive reaction occurred. (He used a fluorescent antibody test in which antibodies binding to the bacteria were tagged with a fluorescent dye. When viewed through a special microscope, the tagged antibodies caused the bacteria to fluoresce brightly.) In other

words, the victims had made antibodies against this bacterium. Serum taken from patients late in infection reacted much more strongly than serum taken early, confirming that antibody levels to this organism had increased in response to the infection. In January 1977, McDade was able to announce that he had found the causal agent—a hitherto unknown Gram-negative bacillus that he called *Legionella pneumophila* [5].

On inhalation, *L. pneumophila* grows in the lungs. It is especially lethal to cigarette smokers, the elderly, and immunosuppressed individuals. Person-to-person transmission has not been documented. The incubation period, as shown in the Philadelphia outbreak is about 2 weeks. The reason why the hotel staff were apparently unaffected was because they were immune as a result of prior exposure. They had high levels of antibodies in their bloodstream.

As news of this new organism was published, it became apparent that it was responsible for many other outbreaks of unexplained respiratory disease. Subsequent investigations found Legionella in large numbers in the cooling water of the air conditioning systems of many large, old buildings. In the case of the Philadelphia outbreak, this same water had been used to humidify the air-conditioning system, so it was distributed throughout the building. (Unfortunately, the Bellevue-Stratford hotel had closed so it was not possible to detect the bacterium in their system.) Further investigations suggest that Legionella grows well in stagnant, mineral-rich water. In order to infect humans however, it must somehow be aerosolized. Cases have been associated with drinking contaminated water. Other possible sources include swimming pools, hot tubs, humidifiers, spas, fountains, and even windshield wiper fluid. The bacteria are readily killed by chlorination of the water source. Many cases however of Legionnaire's disease go unreported since the victims recover uneventfully.

An outbreak of an acute but mild febrile respiratory disease resembling influenza but without pneumonia occurred in Pontiac, Michigan in 1967 although there were no fatalities and it resolved spontaneously. It was called Pontiac Fever and its cause was unknown. Analysis of stored serum samples from Pontiac indicated that they too contained high levels of antibodies against *L. pneumophila*. Since that time multiple other outbreaks of Legionella infection have been recorded. Some building closures associated with the COVID-19 pandemic have resulted in long-term cooling water stagnation and permitted the bacteria to multiply within unused cooling systems, including the offices of the CDC itself!

Legionella outbreaks continue to occur regularly. Thus between 2006 and 2010 14,574 victims required hospitalization for this disease. As expected, it affected primarily the elderly.

Norwalk virus

In November 1968, an outbreak of diarrhea and vomiting occurred in Bronson elementary school in Norwalk, Ohio. Fifty percent of pupils and teachers sickened as well as about a third of their family members. Electron microscopy of a filtrate from a stool sample from an infected child showed characteristic virus particles. The virus was therefore named after the town (Box 17.2) [6]. Further analysis indicated that the Norwalk virus belongs to a group of over 150 related viruses that are now called Noroviruses. Noroviruses are single-stranded, positive-sense, nonenveloped RNA viruses. They belong to the Caliciviridae family. The viruses replicate in the small intestine; however, they can survive for a long time outside their human hosts. They are spread by the fecal-oral route and are thus acquired by eating contaminated food or drinking contaminated water.

Within a couple of days of becoming infected, victims experience acute gastroenteritis with vomiting, nonbloody diarrhea, and abdominal pain. In some cases, a mild fever, lethargy, headache, and muscle aches may also occur. It lasts from 12 to 60 hours. The disease is often called "stomach flu" and tends to be most common during winter. It is a common cause of gastroenteritis on cruise ships. Most people feel better within a few days, but the very young, elderly, and immunosuppressed victims may develop life-threatening diseases. These viruses affect about 20 million persons annually in the United States. Up to 800 victims may die each year as a result. Noroviruses are responsible for more than half the food-borne disease outbreaks in the United States. Norovirus is very infectious. People contract the virus from food contaminated by food handlers or eating undercooked or raw foods. Oysters and clams, bivalve filter feeders, can be contaminated with the virus; it does not harm the oyster or clam. However, humans consuming these shellfish raw can become infected. A Norovirus outbreak in Colorado in December 2019 was linked to shellfish harvested from the Rappahannock River in Virginia. People who live to 79 may have experienced the infection about five times. One in 5000–7000 may die from the infection and it costs the country about $2 billion in health costs and lost productivity annually.

Across the southern border

South Texas has a tropical climate and there is no barrier to mosquito-borne viruses spreading north from Mexico [7]. Since 2013, the southern United States has experienced outbreaks of several arbovirus infections originating in Central and South America. (The term Arboviruses is a convenient contraction of "ARthropod-BOrne viruses.") The majority of diseases caused by these viruses in the Northern Hemisphere occur in the second, warmer half of the year. If climate change occurs as predicted, it is anticipated that insects will expand their range and disease transmission will spread with them. This would apply not only to mosquitos but also to sandflies, fleas, and ticks. The major group of pathogenic viruses that might benefit would be the arboviruses. Texas has large populations of Culex mosquitos, especially *Culex quinquefasciatus*, the vector of West Nile virus. Likewise, there are populations of Aedes mosquitoes, the vectors of dengue, chikungunya, and Zika virus in the state. All that would be needed to establish these diseases would be for these native mosquitoes to feed on an infected individual and transmit the virus to others.

Dengue and dengue hemorrhagic fever

Dengue fever is the most widespread mosquito-borne virus disease of humans. It occurs around the world in tropical and subtropical countries including both Central and South America. It causes over 100 million cases and 10,000 deaths annually and affects at least 63 countries. (The true figures are likely about three times this since most infections are asymptomatic, and the number of cases is very much underreported.) The Pan-American Health Organization reported that in 2014 in the Americas alone, there were 1,176,529 cases with 16,238 severe cases and 761 deaths. Over thirty thousand of these cases occurred in Mexico. It is estimated that its prevalence has increased 30-fold over the past 50 years so that half of the world's population is now at risk. Dengue virus is an RNA flavivirus. It is transmitted by those urban pests *Aedes aegypti* and *Aedes albopictus*.

Dengue causes a severe but usually nonfatal, flu-like illness. Symptoms usually develop 4–10 days after being bitten by an infected mosquito. Children generally develop a milder disease with rash, gastroenteritis, and a fever. Adults also develop a rash and sudden onset high fever but also severe

headaches and pain behind the eyes, as well as muscle, bone, and joint pains. Its other, older name is "breakbone fever" referring to the severity of these pains. Symptoms last for 2–7 days. The patients remain viremic for up to 12 days so that they can act as a source of infection for feeding mosquitos during that time. The effects of dengue may be prolonged and as a result may keep people from working and earning needed income for a long time.

Under some circumstances, patients infected with dengue virus for the second time may develop "severe dengue." This is a lethal dengue hemorrhagic fever (DHF) [8]. The mechanisms of this complication are unclear, but it is probable that antibodies induced by the first infection allow the virus to invade more (or different) cells. Affected patients develop a very high fever, bleeding from body orifices, severe abdominal pain, respiratory difficulty, liver enlargement, multiorgan failure, coma, and death. If diagnosed sufficiently early, careful fluid management can reduce the case fatality rate to less than 1%. Dengue shock syndrome develops if the patient's blood pressure drops excessively.

The prevalence of dengue has increased significantly over the past 50 years. There are many reasons for this. Population growth, uncontrolled urbanization, substandard housing, and climate change all play a role. As slums extend out from cities, sewage and water supplies become vulnerable and mosquito habitat increases. Intercontinental air travel can carry both infected mosquitos and infected people rapidly around the world. A vaccine has been developed but its usefulness may be limited by the possibility that it might trigger severe dengue in some sensitized patients.

Vectors

The role of mosquitos in the transmission of dengue was first described in 1906 after the discovery of their importance in yellow fever. The two prime vectors of these diseases are the mosquitos, *A. aegypti* and *A. albopictus*. *A. aegypti* tends to be restricted to tropical and semitropical climates and generally prefers to feed on humans. It likes to live in houses and often uses indoor breeding sites and man-made containers for breeding. *A. aegypti* is well adapted to urban living. (It can even breed in bottle caps.) It tends to feed early in the morning and just before dusk. The female may bite multiple people during each feeding period.

A. albopictus, the Asian Tiger mosquito originated in the forests of Southeast Asia. It is a more aggressive biter and has a broader taste in blood than *A. aegypti*. It can withstand freezing and also hibernates. As a result, *A. albopictus*

can extend northward to temperate and even cold regions. *A. albopictus* also breeds in a greater variety of water sources than *A. aegypti* including coconut husks, bamboo and other tree stumps, rock pools, and even the saucers under plant pots. It can be abundant in both urban and rural areas. Its spread from Asia was due to its ability to breed in the water that collects in used tires. *A. albopictus* was first documented in Houston, Texas in August 1985; Houston is a major seaport and imported used rubber tires, most likely from Japan, contained sufficient water to support the larva or eggs. This species has become established in tropical and subtropical areas of Africa, Europe as well as the Americas.

Many viruses are maintained in mosquito populations by vertical transmission. That is, female mosquitoes transfer it to their young through their eggs. Once in crowded areas however, the disease can be amplified by transmission through the human population. The range of Aedes mosquitoes has also expanded greatly. *A. aegypti* is found in the coastal states from Texas to Florida and north to Virginia. *A. albopictus* is more cold-tolerant and so reaches as far as Illinois and Pennsylvania (Fig. 17.4). It is a less effective vector than *A. aegypti* but an aggressive biter.

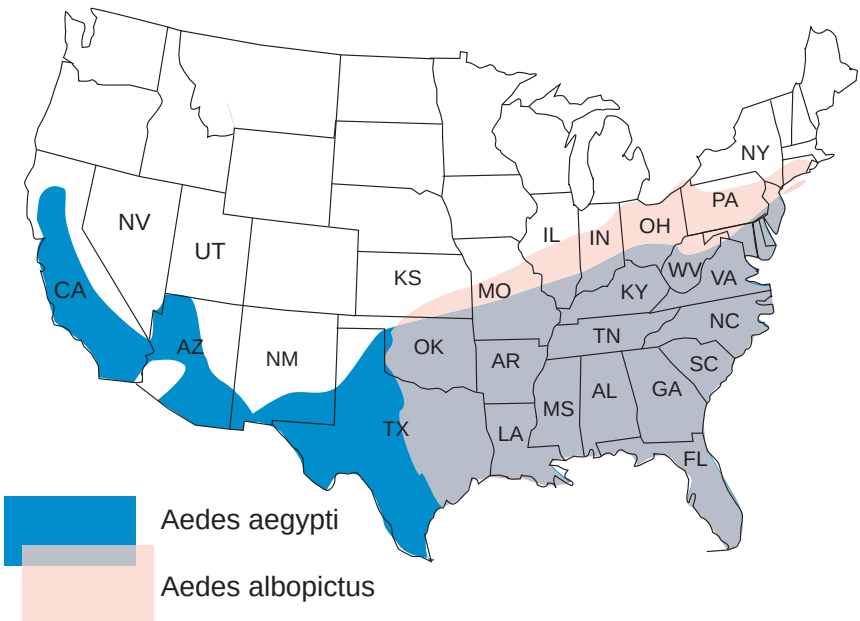

Fig. 17.4 The most probable ranges where *Aedes aegypti* and *Aedes albopictus* can live and breed in the United States as of 2017. *(Data courtesy of the CDC.)*

History

The first reported outbreak of dengue in the United States is believed to have occurred in Philadelphia in 1780 [9]. The term "Breakbone fever" appears to have been applied first by Dr. Benjamin Rush, the noted Philadelphia physician in 1789 [10]. He also used the more formal description of "bilious remitting fever." Beginning around 1827, the disease became more common, especially in southern ports such as Charleston, Savannah, Pensacola, and New Orleans. Outbreaks occurred again in 1850. (Given the vague nature of the disease and its similarity to other flavivirus infections, it is possible that some agent rather than dengue virus caused these outbreaks.) In 1873 it was claimed that 40,000 people were affected in New Orleans while an outbreak in 1879 again affected Charleston, Savannah, Augusta, and New Orleans. In the 1880s the disease spread westward and in 1885–86 caused 16,000 clinical cases in Austin, Texas. (The population of the city at that time was 22,000.) More outbreaks followed in 1898 and 1899 associated with the Spanish-American War. The Texas gulf coast cities of Galveston, Houston, and Brownsville suffered epidemics approximately every 10 years, in 1897, 1907, and 1918 [11]. The disease reappeared in a huge epidemic affecting the southern states in the summer of 1922 with over 500,000 cases in Texas (30,000 in Galveston, 30,000 in Houston, and 20,000 in Dallas), and a similar number in Savannah! In 1934 another outbreak affected Florida and Georgia. The most recent epidemics occurred in coastal Texas in 1941 and Louisiana in 1945. Sporadic outbreaks occurred in Hawaii (122 cases) in 2001–02, the Florida Keys (90 cases) in 2009–13, and Puerto Rico in 2010. There have been 11 reported cases in Key Largo, Florida in 2020.

Most recent cases of dengue in the United States have been introduced by travelers returning from tropical countries. Dengue also reappeared in 1977–79 in the Caribbean and Mexico and began to spread. Eventually it crossed into Texas and as a result, is now endemic in the lower Rio Grande Valley. Outbreaks have occurred since 1980 in both Brownsville and Laredo. It is believed that dengue infection rates may be relatively high in the impoverished shantytowns (colonias) that have grown up along the border. In 2005 the first warning of an outbreak developing in the Brownsville area was a locally acquired case of dengue hemorrhagic fever in a woman in late June. Unfortunately, the diagnosis was missed when she was admitted to hospital. Two months later, Mexican health officials informed their Texas counterparts that there had been 1251 cases in Tamaulipas state, just across the river from Brownsville. As a result, medical records were reviewed and 16 of 25 cases in Cameron County (at the southern tip of Texas) met the

BOX 17.3 Genetically modified mosquitoes?

Given the key role played by mosquitoes such as *A. aegypti* in the transmission of important diseases such as yellow fever, dengue, and Zika disease, it is clear that mosquito populations need to be controlled. Larvicide and pesticide spraying are effective but costly and environmentally damaging. What is needed is a method of selectively destroying a specific species of mosquito, and preferably just the females. This can be done by genetic engineering.

For example, it is possible to modify a specific essential gene expressed during the larval stage of female mosquitoes. The modification ensures that the gene only works in the presence of the antibiotic, tetracycline. In the absence of tetracycline, the gene will not function, and as a result, the female mosquito larva will die.

These mutated mosquitos can be raised in large numbers in the laboratory in the presence of the antibiotic so that they can survive and breed. Their eggs are then shipped out for release into the environment but in the absence of tetracycline only the nectar-feeding males will survive and fly away to mate. They will breed with the wild female mosquitos, but their offspring will carry the lethal gene and so any females will die. The modified males can survive for several months and breed with multiple females. Eventually however the supply of female mosquitoes will run out and the pest eliminated.

Field trials using modified *A. aegypti* have been successfully conducted in the Cayman Islands, Panama, and Brazil. A trial is currently underway in the Florida Keys despite local opposition.

(From Curtis Z, Matzen K, Oviedo MN, et al. Assessment of the impact of potential tetracycline exposure on the phenotype of Aedes aegypti OX513A: implications for field use. PLoS Negl Trop Dis 2015. https://doi.org/10.1371/journal.ptnd.0003999.)

criteria for DHF. In order to determine the true prevalence of dengue infection in Brownsville, multiple blood samples were tested for the presence of antibodies against the virus. Forty seven of 141 (38%) blood samples tested were positive. Both *A. aegypti* and *A. albopictus* are well established in the region. The high prevalence of seropositivity also points to a high potential risk of second infections and DHF.

Dengue is not restricted to far south Texas. Outbreaks of dengue occurred in Houston in 2003–05. (There were 47 positive samples out of 3768 tested including 2 that were viremic [12].) During this same period, Texas reported 154 cases of dengue of which 27 were in Cameron County. It is unclear whether these were contracted within Texas or imported by travelers. Likewise, in 2019, 413 dengue cases, including 14 cases of severe dengue, were reported from Florida. While most cases were in returning travelers, 18 were locally acquired, predominantly in the Miami area (Box 17.3).

Flying in West Nile Fever

West Nile virus (WNV) is a mosquito-borne single-stranded RNA flavivirus that circulates naturally between birds, principally corvids (crows and jays), raptors (birds of prey), and passerines (songbirds), and infected Culex mosquitoes. Infected mosquitoes carry the virus in their salivary glands and so infect birds when they feed. When transmitted to a human by a mosquito bite, in most cases it is either nonsymptomatic or causes a mild fever. Some patients may however develop very serious illness and die. Ticks and American alligators may also play a role in the transmission of WNV. Mammals are incidental dead-end hosts. It is not directly transmitted between humans. Related flaviviruses include dengue, yellow fever, and St. Louis encephalitis. (A flavivirus is a virus that belongs to the same family as yellow fever virus.)

The disease

Most people infected with WNV do not develop clinical disease. However, about 20% of infected individuals develop relatively mild West Nile Fever. The symptoms are similar to those caused by other flaviviruses, namely fever, headache and body aches, a skin rash, and possibly swollen lymph nodes. About 1 out of 150 affected individuals develop West Nile neuroinvasive disease. This mainly occurs in immunosuppressed individuals and in the elderly. In these patients the virus can enter the brain to cause severe encephalitis, with a high fever and headache leading to convulsions, paralysis, coma, and even death. WNV neuroinvasive disease has long-term effects, including motor disturbances, hearing loss, eye damage (retinopathy), memory loss, fatigue, and depression. WNV can cause severe disease in horses (horses are dead-end hosts) and kills many birds.

History

West Nile virus was first identified in 1937 in the West Nile province of Uganda when it was isolated from a woman suffering from a mild fever, headaches, and muscle aches. Since that time the virus has spread to the Middle East, Europe, and Asia. It reached Egypt and Israel in the 1950s, and France in the 1960s [13]. It is believed that the spread of the virus out of Africa is a result of carriage by migratory birds. Some birds can maintain a high viremia for up to 4 days. Mosquitoes that feed on these birds will therefore ingest a high dose of virus. In Europe, WNV rarely kills infected birds. Molecular studies on the genetics of the virus suggest that the

European and North American viruses are variants of the original Uganda strain.

In 1999, West Nile virus arrived in New York probably by way of international flights arriving at Kennedy Airport. Kennedy handles 11,000 overseas flights and more than 20 million passengers disembark each year. (It has been estimated that on transatlantic flights, there are a mean of 5.2 mosquitos on each plane [14]. Spraying the passenger cabin is ineffective since the majority of Culex mosquitoes have been found in the cargo hold! Thousands of horses and other animals are also imported each year, and many mosquitoes may have accompanied them in their travels.)

In mid-August 1999, 60-year-old Enrico Gabrielli was admitted to Flushing Queens Hospital with fever, disorientation, and severe muscle weakness. He had to be put on a respirator for several days, but he recovered. Four days later an 80-year-old neighbor was admitted with similar symptoms but after multiple organ failure, he died. Over the next few weeks the hospital was admitting multiple such cases. The CDC investigated the outbreak [15]. The disease appeared to be mosquito-borne and mediated by a flavivirus. It looked like an outbreak of St. Louis encephalitis. This is a flavivirus found across the United States where it caused 30–40 cases annually. But St. Louis encephalitis had not been previously recorded in New York City and the numbers were unusually large. It has a reservoir in wild birds although prevalence has declined since West Nile arrived.

In late June of 1999 a veterinarian in Queens, New York had examined dozens of birds, primarily crows, suffering from a neurologic disease. About half of them died. In July and August dead crows were being found all around nearby Nassau County as well as the Bronx. There was a die-off of exotic birds; a cormorant, three Chilean flamingos, a pheasant and a bald eagle, at the Bronx Zoo. The zoo veterinarian, Dr. Tracy McNamara, questioned the diagnosis of St. Louis encephalitis since this is not normally lethal for birds. Also, most of the dead birds were Western Hemisphere species. She thought that it might be something more exotic—an introduced virus! The CDC was not interested in testing animal samples, so she sent them to the National Veterinary Services Laboratory in Ames, Iowa. They detected a Flavivirus in the samples. The CDC by now significantly alarmed, changed its mind and agreed to test her samples. In September, the CDC announced the presence of West Nile virus in New York. The flavivirus isolated from a flamingo at the zoo had its genome sequenced. The results indicated that it was West Nile virus and it was most closely related to one isolated from a dead goose that had died during a mass die-off of birds in Eilat

in Israel in 1998 (>99.8% similarity). At the same time human virus isolates sequenced at Columbia University were also identified as WNV.

In the ensuing epidemic in New York and Long Island there were 62 confirmed cases of West Nile encephalitis and 7 human deaths plus more than 600 suspected cases. By late 1999 the virus had been detected in New Jersey and three other states. It was assumed that the outbreak would stop with the arrival of freezing weather and the death of infected mosquitoes. Unfortunately, the mosquitoes found ways to survive a New York winter. The next year the disease continued to spread so that by October 2000 it was detected in 12 states killing humans, horses, and thousands of birds. Birds migrate south in the fall. Thus, the first cases outside the Northeast occurred in Madison County, FL in July 2001. By the end of that year it had been detected in 10 states, all in the East. In 2002 it hit Louisiana especially hard. It had reached 46 states by 2003 and spread to Canada and the Caribbean. In late 2003 there were 8567 human cases with 199 deaths in the United States. Most of these deaths were a result of systemic infection but about a quarter were due to neuroinvasive disease. It spread west and south, eventually reaching the West Coast and Mexico.

As a newly introduced virus, North American birds, like Native Americans in the past had very little resistance. Crows, ravens, blue jays, magpies, and raptors, especially owls, died in large numbers.

Chikungunya and Zika fevers

Chikungunya fever is a mosquito-borne viral disease that was first described in 1952 during an outbreak in Tanzania, East Africa [16]. Its name means "to become contorted" describing in the local Kimakonde language, the appearance of sufferers with acute joint pain. It is transmitted by the same mosquito species, *A. aegypti* and *A. albopictus*, that transmit dengue and Zika viruses. Its incubation period is 3–7 days. The signs and symptoms of chikungunya are totally nonspecific and as a result the diagnosis is likely to be missed. They include an abrupt onset of fever, headache, muscle pains, painful swollen joints, fatigue, and depression as well as a rash that can occur anywhere on the body. There is no rapid diagnostic test yet. Most people recover in about a week, but the joint pain may persist for months. It is rarely fatal, and most patients recover fully. On the other hand, many cases are mild or inapparent. As in so many cases the very young and the elderly are at greater risk of severe disease. Chikungunya has very similar symptoms to dengue but has a longer incubation period and victims tend to have much more severe and intense joint and tendon pain. There are no specific drugs to cure the disease nor

is there a vaccine. As with other mosquito-borne diseases, prevention and control depend upon elimination of mosquito breeding sites as well as minimizing exposure to the day-flying mosquitos. Since its first appearance in 2004, Chikungunya has caused major disease outbreaks in Asia and Africa and affected more than 2 million people. The first case of autochthonous disease in the Americas was reported in 2013. (The term "autochthonous" refers to a case of disease acquired within the community, in other words, not imported.) An individual with autochthonous disease was diagnosed with Chikungunya fever in Cameron County, Texas, in November 2015. Prior to that the only US cases had been acquired overseas [17].

Zika virus was, until recently, a very obscure arthropod-borne virus restricted to the tropics that had never been known to cause an epidemic. It is named after Zika forest in Uganda where it was first identified in 1947. However, beginning in 2014 its behavior changed. It began a pandemic that spread eastward across Asia and the Pacific to eventually reach Brazil and North America. It is believed that the cause of this behavioral change was a change in a single amino acid in the viral envelope glycoprotein [18]. The mutation resulted in increased virulence as well as increased mother-to-fetus transmission and a higher viremia (virus levels in the bloodstream).

Zika is both a mosquito-borne and sexually transmitted disease. It can be spread by both *A. aegypti* and *A. albopictus*. Most people develop inapparent infections but may still transmit the virus to others. The clinical signs are very nonspecific. They include fever, joint pain, conjunctivitis, and an itchy rash. It is difficult to distinguish it clinically from dengue, but this is important, especially for pregnant women. If infected while pregnant, the Zika virus may infect the unborn child and prevent proper growth of the child's brain. This results in microcephaly (a smaller than normal brain) leading to fetal losses, severe neurologic defects, and developmental delays. Now the surviving children are getting older, they cannot walk or talk, and their families are overwhelmed.

Most of the 200 cases of Zika fever in the United States occurred in 2016 in travelers returning from countries where the disease is prevalent, especially Brazil. They were largely restricted to Texas and Florida. Fourteen people were diagnosed with Zika in Miami and the CDC advised pregnant women to avoid the area. In December 2017 it was reported that Zika virus had been transmitted by mosquitoes between individuals in Cameron and Hidalgo counties in deep south Texas. Another such case was reported a year later in the same area. In much of the developing world, the conditions for an epidemic are already there; huge numbers of densely packed people who cannot afford insect repellent or window screens.

Zika virus can also be transmitted from person to person by sexual contact and by blood transfusions. Infected men may potentially transmit Zika virus in their semen for up to 3 months after infection. Texas and Florida both have large populations of both *A. aegypti* and *A. albopictus*. Malaria eradication efforts in the 1950s involving the widespread use of DDT and other insecticides succeeded in markedly reducing the populations of *A. aegypti* in many countries but once these efforts were relaxed in the 1970s, back came the mosquito and its companions, yellow fever, dengue, chikungunya, and Zika. *A. aegypti* is especially prospering in the densly populated urban slums of the large Brazilian cities [19].

Ebola

Ebola is a viral disease of African origin. It is named after the Ebola River in the Democratic Republic of the Congo (Zaire) where the first recorded outbreaks occurred. Ebola virus is classified as a filovirus and looks worm-like on electron microscopy. The virus's natural hosts are probably various species of fruit bats [20]. It was first described in 1976 in both South Sudan and the Democratic Republic of the Congo. An outbreak in Zaire in 1995 resulted in 244 deaths out of 316 persons infected—a death rate of 77%. In December 2013, in the village of Meliandou in Guinea, children playing disturbed a colony of bats roosting in a nearby tree [21]. At least one child was exposed to bat droppings containing Ebolavirus. The disease rapidly spread to other West African countries. It was not brought under control until mid-2016. Outbreaks have occurred most recently in 2018–20 in Uganda and the Democratic Republic of the Congo. They resulted in 3481 reported cases and 2299 deaths. New outbreaks were reported in the eastern Congo in January 2021 and Guinea in February 2021. It is of relevance to note also that while Ebola was first described in 1976, 90% of all known Ebola cases have occurred since 2014.

Ebola virus causes a highly lethal hemorrhagic fever. In this disease the virus invades and kills the endothelial cells that line small blood vessels. As a result, the vessels leak and rupture. They leak internally into the body cavities and into the lungs, liver, kidney, and heart. They leak from the intestine, mouth, skin, and eyes. Eventually this blood loss results in death. The infection is spread by persons touching contaminated body fluids or fomites. Thus, it primarily affects persons providing medical and nursing care as well as funeral attendants. The R_0 of Ebola virus ranges, according to population density, from 1.3 to 2.0.

West Africa is only a day's flight away from North America. In August 2014, two American missionaries, Kent Brantly and Nancy Writebol who contracted the disease in Monrovia, Liberia were flown to Emory University Hospital in Atlanta. They recovered. On September 20, 2014, a Liberian citizen, 42-year-old Thomas Duncan, flew to Dallas, Texas to visit his family. On September 24 he began to sicken, developed a fever, abdominal pain, and nausea. He went to the Emergency Department at Texas Health Presbyterian Hospital in Dallas on September 25; sinusitis was diagnosed, and he was sent home with an antibiotic prescription and Tylenol! When he was readmitted to the hospital on September 28, he had a high fever, abdominal pain, and diarrhea. He was vomiting copiously. When it was noted that he had come from Liberia, he was placed in isolation and tested for Ebola. The test result was positive. A team from the CDC arrived in Dallas later that night and began tracing exposed contacts. Thomas Duncan died on October 8, 2014. On October 10, one of the nurses, Nina Pham, who had treated Duncan developed a fever and sore throat and tested positive for Ebola. She survived however and was declared Ebola-free on October 22 and 24. Though it is uncertain if pets can transmit the virus, Ms. Pham's dog, Bentley, was placed in quarantine; he was reunited with Nina Pham after 21 days. Four days later another nurse, Amber Vinson, had similar clinical signs and also tested positive for Ebola. Ms. Vinson had traveled to Akron, Ohio ("no one told her not to fly") so contacts there had also to be monitored. Three weeks is the maximum incubation time for Ebola, so all her contacts had to be monitored for 21 days. The outbreak was declared over on November 7. This case reflects just how easy it is for an infectious disease to travel the globe. No one is safe as the events related to COVID-19 demonstrate!

A fourth US case was identified on October 23 in Dr. Craig Spencer in New York. He had worked for Doctors without Borders on Ebola patients in West Africa. He knew about the disease and when he developed a fever he called ahead. He was transported to Bellevue hospital by a team in full protective garb. Bellevue was ready for him. He recovered and was declared Ebola-free on October 11.

Dr. Martin Salia, a US resident who had been treating patients in Sierra Leone had tested positive for Ebola on November 10 and flew to Omaha, Nebraska on Nov 15 in critical condition with renal failure. He died 2 days later in the Nebraska Medical Center. He was the third Ebola patient to be treated there and was the only one that died.

Another outbreak of Ebola (the Kivu outbreak), began in the Democratic Republic of the Congo in August 2018. By the summer of 2020 it

had resulted in 3500 cases and over 2200 deaths. The control of the outbreak was severely hampered by social unrest in the region that resulted in the murder of several health workers and attacks on health care centers. On the other hand, a new vaccine was available. More than 300,000 people have received the vaccine. Anyone known to be in contact with a case was tracked down and vaccinated within 24–48 h. The strategy appears to have worked and the outbreak may be over. It is important to note that in the case of Ebola, local funeral practices were the prime mode of transmission. It emphasizes the importance of cultural understanding in these situations.

As a result of these major epidemics, much recent effort has been put into developing vaccines against Ebola. These are generally virus-vectored vaccines in which Ebola virus antigens are expressed in a nonpathogenic viral vector. The first approved vaccine uses Ebola virus antigens expressed in a vesicular stomatitis virus vector. Clinical trials indicate that it is safe and highly effective. A second candidate vaccine uses Ebola genes expressed in a chimpanzee adenovirus vector to deliver the antigens. Other vaccines are still in development (Box 17.4).

BOX 17.4 The Reston virus.

August 2014 was not the first occasion that an Ebola virus had entered the United States. In October 1989, a group of monkeys, crab-eating macaques (*Macaca fascicularis*) were imported from the Philippines to a quarantine facility in Reston, VA—a suburb of Washington DC.

In early November, the monkeys started developing subcutaneous hemorrhages, bloody diarrhea, and stopped eating. They began to sicken and die. The cause was identified as a viral disease, simian hemorrhagic fever. However, they were also infected by an Ebola virus! By the end of the outbreak, over 600 monkeys either died or were euthanized and 6 workers from the facility were seropositive (had antibodies against Ebola virus), The Ebola virus proved to be a new species—the Reston virus. Fortunately, none of the workers sickened. It seems that Reston virus causes asymptomatic infections in humans.

This was not a one-off incident, however. Reston Ebola returned to the United States in 1996, again in monkeys imported from the Philippines. This time they were housed at a facility in Alice, Texas. As before, no humans got sick, but nine employees who had handled the animals, became antibody positive indicating exposure to the virus!

These incidents raise important questions: How many times have this, or other potential pathogens been imported into the United States and gone unrecognized? Will the Reston Ebola virus become pathogenic to humans? (All the other known Ebola viruses are pathogenic and deadly.) What is to stop future animal importations resulting in zoonotic spillover?

(From Preston R. The hot zone: A terrifying true story. Anchor Books; 1995.)

Severe acute respiratory syndrome (SARS)

In November 2002, an outbreak of "atypical pneumonia" broke out in Guandong province of southern China. Dozens of people experienced headaches, muscle pains, and a severe cough. The disease rapidly developed into lethal pneumonia. It spread across the province, but the authorities tried to keep the outbreak secret to prevent civil unrest and to protect tourism. (Of course, a similar problem had arisen during the San Francisco plague outbreak in 1900.) The disease was initially assumed to be H5N1 bird flu but within a few months was found to be caused by a unique betacoronavirus and the disease was named Severe Acute Respiratory Syndrome or SARS. The virus is now called SARS-CoV-1. Coronaviruses are large, positive-stranded RNA viruses. The coronavirus reservoir animal was at first believed to be the masked palm civet (*Paguma larvata*). Subsequent studies have indicated that it probably originated in several species of horseshoe bats (*Rhinolophus* spp.) . It is spread by bat saliva to the civets who eat fruit chewed by bats [22]. The civets shed the virus in their feces. The virus affects both the cells lining the airways as well as the cells lining the alveoli in the lungs. It also affects other internal organs including the liver, intestine, and kidneys.

The first cases of SARS were detected in Hong Kong in February 2003. A physician who worked at a hospital in Guangdong traveled to Hong Kong in mid-February to attend his nephew's wedding. He went shopping but soon developed a cough and sore throat. He developed breathing difficulty, was admitted to hospital but despite intensive care he died in early March. That individual succeeded in infecting 16 other guests staying at the same hotel. The guests went their separate ways. One of them, a 78-year-old Chinese-Canadian woman, Mrs. Kwan, returned to Toronto, Canada. Two days later she developed a fever and respiratory distress and died at home on March 5 but not before infecting her son who developed respiratory distress two weeks later and went to Scarborough Grace Hospital's emergency room. He sat in a crowded waiting room for 16 hours before being admitted. Two patients waiting with him contracted SARS. He also infected doctors, nurses, and other patients before dying on March 13. Nobody had checked on his wife and she was permitted to pass freely through the corridors. She infected 12 more health care workers and patients. One such patient appeared to suffer a heart attack and was transferred to the York Central Hospital in mid-March where he initiated a cluster of about 50 cases and forced both hospitals to close. Everyone who had entered the hospital after March 16 was asked to observe a 10-day quarantine at home. Despite taking

precautions, by March 26 there were another 18 confirmed SARS cases in Ontario. Toronto hospitals suspended all nonessential services. The World Health Organization issued a travel advisory, warning tourists not to visit Toronto unless absolutely necessary—a move that enraged Ontario politicians.

In May another cluster of 26 cases occurred in Toronto and more than 5000 people were quarantined in Canada. When the travel advisory was lifted in July there had been 257 cases and 44 deaths in Toronto and Vancouver. Not a lot when compared to the "great diseases" but a major economic disruption for the city as well as a disaster for the families that had lost loved ones.

In the United States only 137 suspected and 19 probable cases of SARS (with antibodies) were detected. There were eight laboratory-confirmed cases. All had traveled in infected areas such as Ontario. Local transmission took place in San Francisco. There were no deaths.

This first SARS outbreak was not brought under control until 2004. In the meantime, it spread to 33 countries and infected over 8422 humans; 916 died. SARS caused a true pandemic and with hindsight, was a harbinger of things to come. While SARS appears to have been eradicated in humans—for now, SARS-CoV-1 probably remains circulating in the wild, in bats and palm civets, and could re-emerge at any time. We must maintain our guard.

Middle East respiratory syndrome (MERS)

MERS, like SARS, is a respiratory disease also caused by a betacoronavirus. Its primary hosts are camels and it is largely confined to the Arabian Peninsula. In May 2014 two imported cases were detected, one in Indiana and one in Florida. Both cases were in healthcare providers who had worked in Saudi Arabia. Both were hospitalized and recovered fully.

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