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Chapter 1

The Human Toll of Viral Diseases
Past Plagues and Pending Pandemics

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1. INTRODUCTION

This chapter profiles some examples of past and current viral infections that have levied a high toll in human misery and mortality. Viral epidemics can be very disruptive to civil society, and—conversely—civil disasters can trigger viral epidemics. Furthermore, viruses likely play an insidious role in initiating a number of chronic diseases whose burden is ever increasing. Evolving technologies have led to much more rapid detection of viral diseases emerging anywhere in the world (Lipkin, 2013a,b). However, current efforts to reduce the toll of viral diseases are less than satisfactory, and futurists predict the emergence of new pandemics particularly of zoonotic origin. Pathogenesis—the subject of this book—infoms ongoing efforts to mitigate the toll of viral disease.

Outbreaks of infectious disease have long been recognized as disruptive to civil society, and in their worst manifestations, human catastrophes. Epidemics and their toll on human society have been the subject of scholarly treatises, such as Plagues and People by William McNeill, novels such as I Promesi Sposi by Alessandro Manzoni, and artistic works such as representations of cholera by Honoré Daumier. Among major epidemics, some such as smallpox and influenza, are viral in origin. Less dramatic but perhaps more important are viral diseases of infancy and childhood. For instance, respiratory and diarrheal viral diseases among under-5-year-old children make a very significant contribution to the burden of human disease, and remain a major cause of short life expectancy in spite of the development of pediatric vaccines. As chronic diseases become more important, we are unraveling viral infections that are causal agents (such as oncogenic viruses) or are suspected to trigger immune-mediated illnesses (such as type 1 diabetes and multiple sclerosis).

New viral diseases continue to emerge, due to a wide variety of factors that are discussed in Chapter 16 (Figure 1). Viral diseases of animals that are transmitted to humans (zoonoses) are a significant cause of emerging infectious diseases, and constitute a future menace. Finally, viral diseases of animals of economic importance have an important impact on human food security. This chapter provides examples of these different ways in which viral disease takes a toll on humans and their civil societies. We conclude by a look into the future, making a few predictions about the ongoing toll of viral disease.
2. THE HUMAN TOLL OF SPECIFIC VIRAL DISEASES

2.1 Smallpox

Since the earliest recorded time (in ancient Egypt and subsequently), smallpox has been one of the most feared infectious diseases. In *Plagues and people*, McNeill describes a number of episodes in which smallpox altered the course of history. Introduced into a “virgin” population, smallpox is devastating. Historic reconstructions have suggested that smallpox did not exist in the western hemisphere when the Spaniards first invaded Central America. They inadvertently transmitted smallpox to the large and well-organized Mayan and Aztec populations, triggering a decimating epidemic. It was smallpox that permitted a small contingent of 600 invaders to overcome an indigenous population of millions. Even during the twentieth century, when vaccination was widely practiced, it is estimated that 300–500 million people died from smallpox or at least 2 million souls each year.

Smallpox is caused by variola virus, a poxvirus specific to humans. The virus is acquired by aerosol exposure, but spreads much less rapidly than many other viral infections since transmission usually occurs via face-to-face contact. Following infection, the incubation period is 10–20 days. Inhaled virus replicates first in the lungs, then spreads to internal organs causing a viremia and widespread dissemination. The virus replicates in skin and small dermal blood vessels, causing a rash that evolves into multiple blisters, which leave severe scars on the face and body; corneal infection may cause permanent blindness. Two different strains of variola virus circulated in humans, variola major with a mortality of 20–30% and variola minor, with a mortality of about 1%. The exact cause of death during smallpox infection is a bit murky, and has been attributed to “toxemia,” that is an overwhelming infection of lungs and many other organs.

The concept of immunization against viral diseases originated with variolation, the deliberate exposure to (hopefully)
smallpox-free in 1980 (Henderson, 2009; Foege, 2011). In smallpox was eradicated by 1977, and the world declared free of other countries with limited public health programs, more effective than population-wide immunization of children. “Ring vaccination” around individual outbreaks, which was confined to direct face-to-face contact between patients and susceptible persons; the incubation period was rather long, so that outbreaks spread slowly; and it was easy to identify immune individuals who had prominent scars due to prior infection or vaccination. A key to control was the strategy of “ring vaccination” around individual outbreaks, which was more effective than population-wide immunization of children and adults. Due to heroic efforts in India and a number of other countries with limited public health programs, smallpox was eradicated by 1977, and the world declared smallpox-free in 1980 (Henderson, 2009; Foege, 2011). In spite of the outstanding record of viral vaccines as effective public health tools, even today there remain a small group of nonbelievers.

2.2 HIV/AIDS

HIV/AIDS is the subject of a later chapter in this book, so the following brief account is focused on the human toll of this devastating epidemic, the first “great plague” of the twentieth and twenty-first centuries. Although HIV was probably first transmitted from chimpanzees to humans in Africa in the 1930s, it only assumed epidemic form about 1970 in Africa and 1–2 decades later in other regions of the world (Pepin, 2011). It is estimated that AIDS has caused over 30 million deaths, and that more than 30 million other humans are currently living with HIV/AIDS, while there are more than two million new infections each year.

In some of the countries with the highest prevalence of HIV infections, it is projected that AIDS resulted in a dramatic reduction of life expectancy, an impact that may be unique among viral diseases. Life expectancy in Botswana was reduced from a non-AIDS projection of 65 years to 45 years of age, prior to a massive rollout of antiretroviral treatment. Another unusual feature of the AIDS pandemic is its concentration in young adults who are the principal engines of society. This age selection has created a vast group of orphans and decimated the incomes and integrity of families, the social unit that is a major pillar of society.

In contrast to many other viral epidemics, HIV does not “burn out” or fade away by exhausting susceptible hosts, but is perpetuated by the continual recruitment of young adults as they become sexually active. Furthermore, the virus is transmitted in many ways, by blood and blood products, by use of contaminated needles and syringes, from mothers to their newborn infants, in addition to sexual contact. Finally, HIV infections tend to concentrate in social subgroups which can be marginalized, such as sex workers, injecting drug users, and gay men. All of these characteristics have made the pandemic a daunting public health challenge.

In contrast to many other viral diseases of public health importance, HIV causes a persistent infection with an incubation period (untreated) that averages about 5 years. The dramatic impact of mother-to-child transmission of HIV, incorporation
into microbicides to protect women from exposure to HIV-infected partners, and pre-exposure prophylaxis (PrEP) for subjects with high-risk of HIV contact.

However, the great potential utility of antiretroviral drugs is dependent upon access to expensive medications, highly specialized medical care, and robust public health programs. Even in high-income countries, there is a “treatment cascade” such that no more than 30% of HIV-infected persons have optimal diagnosis, treatment, and very low HIV blood levels (Figure 3). In Africa, the locus of about 75% of the global burden of HIV/AIDS, few countries have optimal HIV control programs. A significant impediment is the price of antiretroviral drugs, although this barrier has been substantially reduced. More important, few African countries have a health system that is sufficiently robust to provide adequate diagnosis and treatment for the whole population. A reduction in the incidence of new infections is likely the best measure for the success of an HIV control program (the reproductive rate, $R_0$, is less than 1). HIV incidence remains very high in the more heavily impacted countries, even though some have managed to somewhat reduce the year-on-year number of new infections. (It should be noted that a reduction in new infections has not been accomplished in the United States either, where new infections have plateaued for at least 20 years.)

### 2.3 Influenza

Mortality associated with influenza infection is carefully monitored by the Centers for Disease Control. Over a 30-year period, 1977–2006, annual influenza-associated deaths in the United States ranged from 3000 to 49,000.

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**FIGURE 3** In spite of the relative availability of antiretroviral treatment in the United States, only 30% of infected individuals are on optimal viral control. This is partly due to the complexity of treatment although simplified regimens have been introduced in the past few years. Top: HIV DRUG CHART, showing some of the single-pill antiretroviral options for HIV treatment, accessed online, from POZ, Health, Life, and HIV, [http://www.poz.com/](http://www.poz.com/), September 19, 2014. Bottom: Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care—United States. [Redrawn from Cohen et al. (2011), with permission.](http://www.poz.com/).
If it is assumed that on average, influenza caused 25,000 deaths in the United States and this death rate is applied to the global population (about 20 times the population of the United States), then there are—on average—at least 500,000 influenza-related deaths each year.

Influenza is caused by an eight-segmented negative-strand RNA virus. Influenza virions carry two external spikes, the hemagglutinin (H) and the neuraminidase (N); the hemagglutinin spike is responsible for attachment to the cellular receptor. The receptor is a sialic acid residue on cell surface proteins many of which are glycosylated. Importantly, sialic acid residues on human glycoproteins mainly have α2-6 linkages (the number two carbon on the sialic acid hexose ring is linked to the number six carbon on the galactose ring within the glycosyl moiety on the glycoprotein) while sialic acid residues on avian glycoproteins are mainly attached via α2-3 linkages. This has epidemiological implications because avian-derived type A influenza viruses preferentially attach to α2-3 linkages while type A influenza viruses that spread in humans preferentially attach to α2-6 linked sialic acid residues. Importantly, a few mutations on the viral hemagglutinin can change the sialic acid preference for the virus. There are many strains of type A influenza virus, and different strains circulate in different vertebrate species. Type A influenza virus strains are classified into subtypes by the antigenic determinants on the H and N spikes, which assort independently within the segmented viral genome. Thus, there are H1N1 subtypes, H1N2 subtypes, and so forth.

The incubation period of influenza is very short (1–4 days), and the shedding of aerosolized virus by infected patients leads to rapid spread of infection through a population. Since individuals who have recovered from infection are immune to re-infection by the same antigenic strain of virus, influenza virus exhibits a somewhat unique epidemiologic pattern. In the course of an influenza “season,” usually during the winter months, a specific antigenic strain may “exhaust” the majority of uninfected members of a human population and then fade away for the lack of susceptible hosts. Under these circumstances, influenza virus is subject to “antigenic drift,” whereby mutations in the H and N spike proteins generate a new virus, selected because it can escape neutralization by antibodies against the preceding epidemic strain of the virus.

Several times in a century, human influenza viruses undergo “antigenic shift” in which the prevalent H and N variant is replaced by a virus with different H and N proteins. Antigenic shifts are usually due to genetic recombination of strains of virus that are circulating in animal populations; the “new” strain of virus may have a mixture of genes derived from porcine, avian, and human viruses. Circumstantial observations suggest that genetic recombination occurs most frequently in pigs, which carry their own influenza strains and are often exposed to exogenous virus strains from both avian (wild and farmed) and human species. Less frequently, a nonrecombined animal influenza virus may jump the species barrier and become established in the human population. There are some stringent requirements for spread of a virus which represents an antigenic shift: (1) the new virus must be able to bind quite efficiently to the sialoprotein receptor on human cells, which differs slightly from the sialoprotein receptor on avian cells; (2) the new virus must be able to replicate efficiently in human cells, a property that is determined by several viral gene segments; (3) the new virus must be transmitted efficiently between humans, a property that is genetically distinct from the two preceding requirements.

Because the human population often lacks immunity to the newly emergent hemagglutinin, antigenic shifts can produce a “pandemic” with many more severe infections and deaths than are seen in a year where the prevalent strain is due to antigenic drift within the current H protein. Different variants of influenza virus vary widely in their virulence for humans, with case fatality ratios that range from 0.1% to 10%. Virulence is determined by several of the genetic segments—other than the H and N genes—of the virus acting in concert. Some highly transmissible viruses cause relatively mild disease while some highly virulent strains are poorly transmissible.

Rarely, there is a “perfect storm” in which antigenic shift is introduced by an influenza virus strain which meets all of the requirements for cellular infection, transmissibility, and virulence. It appears that this was the case only once in the last century, the “Spanish” influenza pandemic of 1918–1920 (Barry, 2004). It is estimated that the pandemic strain infected about 500 million persons, and resulted in about 50 million deaths (a case fatality ratio as high as 10%, compared to about 0.1% for a typical influenza season). This pandemic represented the largest single epidemic in recorded medical history, an unprecedented human catastrophe, which caused a transient drop in global life expectancy, an unprecedented phenomenon. Figure 4 shows a ward of influenza patients during this global pandemic.

![A ward of patients ill with influenza, Camp Funston, Kansas, 1918, accessed online, September 20, 2014](https://en.wikipedia.org/wiki/Camp_Funston)
Recent studies have reconstructed the genome of the 1918 virus from genetic fragments found in exhumed tissues of persons dying during the epidemic. The pandemic strain had an H1N1 phenotype, an antigenic pattern to which the human population was nonimmune since viruses of this type had not been prevalent in the human population for an estimated 35 years prior to the epidemic. Studies with the reconstructed virus in nonhuman primates have recapitulated the acute disease seen in humans. Diseases severity was associated with an extreme cytokine storm centered in the lungs, in contrast to the alternative theory that the virus had spread widely to many other tissues. Furthermore, studies with viral recombinants identified several viral genes (other than H and N determinants) that were associated with virulence. The unusual pathogenesis pattern may explain why the human pandemic produced a high case fatality ratio in young adults, in contrast to most influenza outbreaks where the toll is greatest in young children and elderly patients.

Of concern in 2014, there are several virulent strains of avian influenza virus that have infected a small number of humans in close contact with farmed poultry. To date these virulent animal influenza viruses have not been readily transmitted between humans, but—if they evolved to be transmissible—might have the potential to cause a pandemic, an issue discussed later in this chapter.

2.4 Measles

Measles is a ubiquitous acute transient illness of childhood. Infection is transmitted by inhalation of aerosolized virus, the virus spreads via circulating infected lymphoid cells, and many organs are involved. Although systemic, the infection is usually benign, and illness is confined to respiratory symptoms (coughing, and sneezing) and rash. Among well-nourished healthy children, measles has a low-case fatality ratio (about 0.1%). However, it is a much more serious disease among malnourished infants and children; the accompanying pneumonia may lead to a case fatality ratio as high as 10%. Prior to the introduction of measles vaccine, it is estimated that worldwide one to two million children died of measles each year (Moss and Griffin, 2012).

Measles vaccine, introduced in the 1960s, is a live attenuated virus variant that is safe, effective, and inexpensive. The widespread use of vaccine has markedly reduced global measles mortality, but the virus still causes more than 100,000 deaths each year. This reflects the failure to immunize children due to the limitations of weak health maintenance systems, particularly in low income countries. Also, unimmunized children are more likely to be malnourished and prone to serious complications of the infection.

Global eradication of measles has been discussed for many years as a public health goal. It meets many criteria for potential eradication: the vaccine is safe, effective, long-lasting, and inexpensive, and humans are the only host for the virus. Endemic transmission of measles virus has been interrupted in the western hemisphere, demonstrating the plausibility of eradication in large populations. However, measles is very contagious, and transmission can be maintained in a well-immunized population where only 10% are susceptible. Therefore, very high levels of population immunity must be achieved to terminate spread of measles virus. It appears that the most realistic goal is reduction of measles mortality by maximizing immunization levels, particularly in low income countries.

2.5 The Global Toll of Viral Infections

At a global level, viral diseases take their greatest toll in developing countries, particularly in children under the age of 5 years. There are several reasons for this undue burden: A failure to immunize children with available vaccines due to weak health systems; and a markedly increased susceptibility to common childhood infections due to undernutrition which increases risk of death from infections. This relationship is evidenced in Figure 5 that plots death rates from pneumonia by countries sorted according to income.

3. EPIDEMICS AND SOCIETY

In epidemic form, viral diseases not only can decimate a population but also may have a major impact on civil society itself. Conversely, social catastrophes can produce a breeding ground for virus epidemics or impede the control of viral diseases. Several examples follow below.

3.1 Epidemic Yellow Fever in Philadelphia, 1793

Urban yellow fever is caused by a flavivirus that is transmitted by *Aedes aegypti*, a peri-domestic tropical mosquito that breeds in standing water. Both mosquito and virus are indigenous to the Caribbean and adjacent parts of Central and South America, since they cannot overwinter in temperate climates. The yellow fever epidemic of 1793 in Philadelphia, the most calamitous outbreak ever to strike an American city, was described in detail in the 1949 monograph, *Bring out your dead*, by J. M. Powell.

In 1793, Philadelphia was serving as the capital of the United States during George Washington’s first term as President. Thomas Jefferson was Secretary of State, and Alexander Hamilton was Secretary of the Treasury. The new government was less than 2 years old, and its fragile structure was threatened by the ongoing French Revolution and the incipient hostility between England and France. The tension increased with the arrival of “Citizen” Genet, the new ambassador from France, who effectively fomented pro-revolutionary sentiment among the inhabitants of
Philadelphia. Washington and Hamilton wished at all costs to avoid being drawn into an entanglement in a European conflict that would provide the British with an excuse to attempt to reclaim their colonies.

In 1793, the population of Philadelphia was about 50,000 and the annual mortality was about 2%. Water was supplied by individual shallow wells, and outside most houses there was a water barrel for drinking, cooking, and other needs. Mosquitoes bred in these containers, and they were notably plentiful in the hot and dry summer of 1793. This set the stage for the outbreak.

Neither *A. aegypti* nor yellow fever virus was native to Philadelphia. They were introduced in great numbers by a major social upheaval in the Caribbean. Following the French Revolution of 1789, there was an uprising among the slaves on the sugar plantations of Dominica (present Haiti and Dominican Republic), with the slaughter of many white plantation owners. This caused a mass exodus to various ports in the United States, including Philadelphia. The yellow fever cycle was maintained on board the crowded ships, where open water barrels permitted mosquitoes to breed during the voyage, while infections were continually transmitted among the human passengers. Following the arrival of large numbers of refugees in July, 1793 in Philadelphia, cases of a very severe often fatal febrile disease were first noted near the waterfront, and then spread to the rest of the city. After a slow beginning, the epidemic gathered force and increased at a rapid rate in September, to peak in mid-October.

The dimensions of the epidemic are hard to comprehend. About 20% of the population was stricken, half of whom, about 5,000, died, the largest single epidemic rate ever experienced in an American city. Washington, Jefferson, and Hamilton were all in Philadelphia. Hamilton was stricken, causing widespread consternation in the populace, but he recovered. The nascent government ground to a halt, when much of the population fled the city. Washington wanted to remain and was only persuaded by his wife to leave, along with Jefferson. A change in the weather slowed the epidemic in mid-October, then an early mosquito-killing frost in mid-November brought it to an end. It was only by chance that this epidemic did not alter the course of American history.

### 3.2 Eradication of Wild Polioviruses

It is estimated that, prior to the introduction of inactivated poliovirus vaccine (IPV or Salk vaccine), each year wild poliovirus caused about one million paralytic cases worldwide. Polio was a dread disease, since it struck at random and could leave a healthy child unable to walk or otherwise severely incapacitated. The public image of President Roosevelt, who was confined to a wheelchair, drove home this fear, as well as movies showing banks of children encased in iron lungs, without which they could not breathe (Figure 6). The horror of polio was captured by Philip Roth in his novel *Nemesis*.

Following the widespread use of IPV (inactivated poliovirus vaccine) and OPV (oral poliovirus vaccine or Sabin
vaccine), wild poliovirus was eradicated in the United States about 1973, and in the western hemisphere about 1990. As a result of these successes, WHO announced the goal of global eradication in 1988, at which time it was estimated that there were still about 350,000 paralytic cases annually. This initiative was so effective that paralytic polio was reduced to about 2000 cases by 2000. However, the eradication program has been stalled at that level for over a decade. Wild poliovirus was finally eliminated in India in 2011 as a result of a massive effort on the part of the government. But the virus has continued to circulate without interruption in three countries; Pakistan, Afghanistan, and Nigeria. Furthermore, for political reasons, polio vaccinators have been targeted and several have been killed by terrorist organizations. In 2013, wild virus spread from those locations to Syria as a by-product of the civil chaos in that country, and from there to Israel where it caused a “silent” outbreak recognized only by isolation of virus from sewage samples.

In Nigeria, poliovirus was long ago eliminated in the southern regions. But virus has continued to circulate in the northern regions, where the Muslim population has resisted public health immunizations sponsored by the central government which is Christian dominated. There is a current debate whether or not wild poliovirus will ever be eradicated (Nathanson and Kew, 2010). Clearly, the outcome will be determined by social and political forces rather than any scientific or public health impediments. However, writing in the Fall, 2014, there are several promising milestones: wild type 2 poliovirus disappeared in 1999; wild type 3 poliovirus has not been detected since 2012; and wild type 1 poliovirus—long endemic in three locations—was eliminated in India in 2011; it appears to be close to elimination in Nigeria in 2014; and only remains stubbornly circulating in the tribal areas of Pakistan and Afghanistan.

The foregoing examples vividly illustrate the impact of viral disease upon society and—conversely—how societal forces can influence viral epidemics and their control.

4. VIRUSES, PRIONS, AND CHRONIC DISEASE

In addition to overt outbreaks and pandemics, viruses can play a more insidious role, as instigators of chronic illnesses. In this context, the causal relationship is more subtle and may only be inferred from circumstantial data. Therefore, in many instances, the relationship is still controversial. Furthermore, research on transmissible agents that cause chronic illnesses has uncovered a novel group of infectious agents, now called “prions” (also designated “transmissible spongiform agents”). Although prions do not meet the traditional definition of viruses (“bad news wrapped in protein” according to Peter Medawar), they are included in the following discussion since they can be considered one of the simplest life forms.

It is now well established that several human viruses are major causes of specific cancers. Among these are hepatitis B virus, human papillomavirus, and Kaposi’s sarcoma virus (human herpesvirus 8), which are the subject of Chapter 8. In most of these instances, the causal relationship was heavily disputed and was only established by many years of research.

Multiple sclerosis and type 1 diabetes are examples of major chronic diseases whose pathogenesis is only partially understood. In both instances, there appears to be a major immunological mechanism involved, but it is not clear what triggers this pathological response. Genetic studies of identical twins in which one twin is afflicted with multiple sclerosis, indicate that a high proportion (perhaps 50%) of the cognate twins are also stricken. These data indicate that there are significant genetic determinants of risk. However, because many cognate twins do not have the disease, it has been inferred that there is also a “trigger” event that initiates the disease process. It has been suggested that—in some cases at least—an acute viral infection acts as this postulated trigger, although direct proof has not yet been uncovered.

4.1 Prion Diseases

Scrapie is a fatal progressive degenerative neurological disease of sheep, described at least 200 years ago by sheep herders in England. The pathological hallmark is a spongiform encephalopathy. A rare sporadic fatal human syndrome, Creutzfeldt-Jacob disease, was recognized to cause similar pathological lesions. Kuru, a similar affliction, was subsequently observed as an epidemic in a small stone-age linguistic group in the eastern highlands of New Guinea. Scrapie was shown to be transmissible from sheep to sheep by intracerebral injection of brain tissue from a diseased
animal, and a parallel experiment showed that kuru could be transmitted to chimpanzees.

Early researchers assumed that the spongiform encephalopathies were caused by a new unknown group of viruses. However, years of experimentation failed to identify an RNA or a DNA associated with increasingly purified preparations of the transmissible material. Based on these observations, Stanley Prusiner proposed that the spongiform agents consisted solely of protein, in a specific molecular conformation that explained their unique properties, such as resistance to proteolytic digestion and ability to “replicate.” This hypothesis, which violated the central dogma of molecular biology (information is transmitted from DNA to RNA to protein), was gradually confirmed by many experiments conducted by numerous investigators over 30 years. Examples of prions (not all of which are associated with disease states) have been described in life forms as simple as yeasts, making them a more ubiquitous phenomenon than originally recognized.

Prion diseases have taken on an increasingly important role as a cause of animal and human diseases. In the 1980s, in the United Kingdom, there was an epidemic of spongiform encephalopathy in cattle (so-called bovine spongiform encephalopathy or “mad cow” disease) that involved at least 180,000 animals. Subsequently, there was a small outbreak (more than 150 cases) of “new variant Creutzfeldt–Jacob disease” in humans, presumed to have been caused by eating meat or offal from afflicted cows. It is now postulated that several degenerative neurological diseases of humans, including Alzheimer’s disease, may be caused by prions, although this is still controversial (Prusiner, 2012). If correct, prions will assume a very important role as disease agents in a globally aging population.

5. LESSONS LEARNED: THE ROOT CAUSES OF SIGNIFICANT VIRAL DISEASES OF HUMANS

From the foregoing litany of viral diseases that affect the well-being of humans, a number of generalizations can be made. Many of these concepts are developed in later chapters and are summarized in Sidebar 1. There are a multitude of viral infections of humans, but most of them are relatively innocuous and cause mild transient infections (for instance, rhinoviruses, one cause of the “common cold”). However, a few viruses cause major morbidity and mortality. In some instances, such as those viruses that are transmitted by aerosol, disease symptoms (such as coughing and sneezing) play a critical role in transmission, but in many other instances (for instance, many clinically silent enteric infections such as that caused by poliovirus) spread is unrelated to disease causation. Thus, there is no necessary relationship between the disease caused by a virus and its ability to perpetuate itself in the human population. A good example is the contrast between the two variants of smallpox virus both of which were maintained in human populations; variola major carried a 20–30% case fatality ratio while variola minor killed only 1% of its victims.

Some viruses cause acute infections while others persist. Among both groups, there are instances of serious disease. Smallpox, rabies, and polio viruses cause acute infections, while HIV, human papilloma, and Kaposi’s sarcoma viruses cause persistent infections. It is noteworthy that the severity of disease caused by a given virus is determined in part by the individual human host. As an extreme example of human genetic determinants, individuals who are homozygous for the delta 32 deletion (for expression of the CCR5 protein) are resistant to infection with HIV, and there are many other human genetic determinants that influence the course of HIV infection. The age of infected individuals can also have a dramatic influence on the course of infection with a specific virus. During the epidemic of measles in a “virgin” population in the Faroe Islands in 1846, measles had a fatality ratio of 20% in infants, 10% in the elderly, but only 1% in young adults.

There are several factors that conspire to create a major virus pandemic with high mortality. These include: a population that is immunologically susceptible to the specific viral invader; a virus that can spread widely in the susceptible population; a virus variant that is highly virulent.
in humans; and an infection that is not readily contained by human intervention once an ongoing epidemic is recognized. Most recent examples of severe viral diseases of humans, such as HIV/AIDS, SARS, and influenza pandemics, have been caused by zoonotic viruses. Although there are many zoonotic viruses that occasionally cross the species barrier and infect humans, relatively few of them are able to spread from person to person and infect large numbers of humans (Table 1).

### 6. VIRAL INFECTIONS OF ANIMALS

Many viral infections of animals can be transmitted to humans, and some of these zoonotic infections can cause serious illness in humans, such as several strains of avian influenza virus, Ebola and Marburg filoviruses, and Hendra and Nipah henipaviruses. In a few instances, such zoonotic infections can become established in human populations with devastating consequences, such as SARS (severe acute respiratory syndrome) coronavirus and HIV. These infections are dealt with in some detail in Chapters 9 and 16.

#### 6.1 SARS

SARS appears to be a natural infection of certain species of bats, but can be transmitted to other wild animals, some of which are eaten in southeast China. SARS first appeared as an acute severe sometimes fatal respiratory disease in humans in the Guangdong province of China in 2001. Many of the early human cases occurred in persons who had contact with a variety of wild animals, such as palm civets, sold in food markets. Unusually, for a zoonotic infection, SARS then spread by aerosol from human to human. From China it was carried to Hong Kong, and thence to many distant sites, including Southeast Asia and Canada. A stringent series of quarantine steps succeeded in terminating further spread. By the end of the epidemic, in 2003, there were over 8000 recorded cases with a case fatality ratio of almost 10%.

#### 6.2 Rinderpest

Virus diseases of animals of economic importance can also take a toll on humans, by compromising food security. Examples are rinderpest of cattle, influenza of chickens and turkeys, and foot-and-mouth disease virus in cattle, swine, and sheep.

Rinderpest (cattle plague in German) is caused by a morbillivirus that infects cattle and other even-toed ungulates but not humans. It can cause devastating epidemics that kill a large proportion of animals in a herd. In areas where cattle are a key to the economy, rinderpest epidemics have led to widespread famines. As summarized in Wikipedia “Cattle plagues recurred throughout history, often accompanying wars and military campaigns. They hit Europe especially hard in the eighteenth century, with three long pandemics which, although varying in intensity and duration from region to region, took place in the periods of 1709–1720,
1742–1760, and 1768–1786 (Figure 7). There was a major outbreak covering the whole of Britain in 1865/66. Later in history, an outbreak in the 1890s killed 80–90% of all cattle in southern Africa, as well as in the Horn of Africa.” A global program to immunize cattle led to the eradication of wild rinderpest virus in 2001, a first for virus diseases of animals. As a result, the threat of epidemics has been eliminated enhancing food security for human populations.

7. SCORE CARD: ARE WE CONTROLLING MAJOR VIRAL DISEASES?

Life sciences have advanced to an extraordinary degree in the last century, and have produced a large number of preventive and therapeutic modalities that have had a major impact on human health. As example, life expectancy in the United States was about 47 years in 1900 but is now close to 80 years, a change greater than that seen in all of recorded history. Congruent with this, there are now safe and effective vaccines against more than 15 individual virus diseases of humans. This has led to a dramatic reduction in child mortality, which in turn has made an important contribution to the increase in life expectancy. Another example is antiretroviral therapy for young adults infected with HIV, which has increased life expectancy to an estimated 50 years compared to an average 5 years prior to treatment.

However, balanced against these triumphs of medical science, there still exist some outstanding current failures. Here are two examples. First, underutilization of both vaccines and antiviral drugs remains a major challenge in developing countries. It has already been noted that an estimated 150,000 unvaccinated children die unnecessarily of measles each year. HIV/AIDS is even a more serious problem. On a global level, there are still more than two million new human infections with HIV annually. And in the United States, the annual number of new HIV infections (estimated 60,000) has not dropped in the last 20 years. Second, the lack of an HIV vaccine. More than 30 after the isolation of HIV, progress toward an effective HIV vaccine is still very slow and research has yet to solve some daunting scientific challenges that impede vaccine development.

More recently, in the high income countries, an anti-vaccine movement has left some children without recommended immunizations (Offit, 2011). As an example, a 2015 measles outbreak originating in Disneyland in southern California has been triggered by children whose parents declined to have them vaccinated (Zipprich et al., 2015).

8. PANDEMICS YET TO COME: WHAT DOES THE FUTURE HOLD?

What does the future hold as to new viral diseases that could take a toll on human health? Events of the last 50 years justify some predictions, although the specifics remain hazy (Sidebar 2). In recent decades, a considerable number of new viral diseases of humans have emerged (Figure 1). Of these, the most significant are HIV/AIDS, influenza, and SARS. All of these viruses share three properties: they are zoonotic infections, transmitted from animals to humans; they produce a high level of morbidity and mortality in their human hosts; and they have adapted to spread directly from human to human. Zoonotic infections such as Sin Nombre, Ebola, Marberg, Nipah, and Hendra viruses are also highly virulent, but they have limited ability to spread from human to human; therefore, they have caused small outbreaks albeit with high mortality.

8.1 Modern Diagnostics and Global Surveillance

Since the turn of the century, there have been two important developments relevant to the rapid detection of emerging viral diseases. First, the Internet and mobile phones have facilitated the rapid exchange of health information around the world, and there are a number of open access Web sites dedicated to disease surveillance. In addition to conventional reporting of unusual disease events, it is now possible to monitor many human activities on a massive scale, such as the volume of communications on social networks like Facebook and Twitter; spurts in activity may reflect an incipient disease threat. Second, the use of evolving laboratory methods, such as PCR and next generation genome sequencing, has permitted the identification of novel viruses with lightning speed.

8.2 Influenza: Will It Cause the Next Human Pandemic?

Which viruses constitute the most likely threats in the near future? Influenza looms on the horizon as the most obvious candidate.
In 2009, a novel H1N1 type A influenza virus of swine origin crossed into humans and caused a worldwide epidemic, which was estimated to have infected over 100 million people in over 200 countries, with at least 20,000 confirmed deaths. Genetic analysis of this virus showed that it contained individual genes from four different sources, avian, human, and two swine influenza virus lineages. The critical genes for the H and N proteins were derived from the 1918 pandemic strain which had persisted in pigs since that time. Although this virus was much less virulent than the 1918 influenza virus, it demonstrated the potential for recombination as a source of new influenza viruses with the ability to spread rapidly in the human population.

Wild waterfowl are infected with a large number of type A influenza viruses, which cause asymptomatic enteric infections in these birds. These viruses are regularly transmitted to domestic poultry (chickens, turkeys, geese) and pigs, where they may recombine to take on new virulence and transmission phenotypes. Most of these viruses show a preference for the α2-3-linked sialic acid receptors on avian cells and are poorly infectious for human cells which mainly express α2-6-linked sialic acid residues. However, a number of avian type A viruses have been transmitted to humans in contact with domestic poultry, including H5N1, H7N2, H7N3, H7N7, H7N9, H9N2, H10N7, and H10N8 viruses.

In particular, H5N1 and H7N9 avian viruses have been of particular concern. Type A H5N1 virus appeared as a cause of deadly outbreaks among poultry in southeast Asia about 2003, and has continued to cause high mortality in domestic birds. This virus has spread to poultry in many countries in the region, and as far west as Pakistan, Iraq, and Egypt. It has also been transmitted to humans in contact with infected poultry, and has caused over 500 reported cases with a high mortality (about 50% of reported cases). However, H5N1 virus (which preferentially binds to avian-type cellular receptors) has not spread directly from human to human.

In controversial experiments, Yoshihiro Kawaoka and Ron Fouchier independently investigated the potential for the H5N1 virus to acquire the ability to spread among humans (Herfst et al., 2012; Imai et al., 2012). An H5 gene from the avian virus (with four point mutations that changed its receptor preference from avian-like to human-like), when recombined with seven other segments from the 2009 human pandemic H1N1 virus, was able to spread by aerosol between ferrets (a surrogate for human to human spread). Alternatively, an H5N1 avian virus, with four point mutations that changed its receptor preference from avian-like to human-like, was passaged in ferrets and ultimately acquired the ability to spread between experimental animals by aerosol; however, the evolved laboratory strain was not highly pathogenic in ferrets. Both of these studies—although artificial laboratory exercises—did demonstrate the theoretical potential for a pathogenic avian virus to adapt to spread in humans.

In China, during the period March to September, 2013, the avian H7N9 virus caused more than 100 infections among humans in contact with poultry, with a case fatality ratio about 30%. Since this virus causes only mild infections in poultry (in contrast to H5N1 virus) its geographic distribution has been difficult to track. Recent studies showed that this virus preferentially attached to avian-type sialic acid receptors and was poorly transmitted by aerosol between ferrets, consistent with its failure to spread from human to human.

In summary, outbreaks in the first decade of the present century illustrate the pandemic potential of type A influenza viruses. On the one hand, the 2009 H1N1 swine virus spread widely in the human population but caused a low mortality (less than 0.1% of overt cases). On the other hand, both H5N1 and H7N9 viruses are highly virulent in humans but have not spread directly from person to person. Should a virus evolve that combined both virulence and transmissibility, it could once again create the “perfect storm” of 1918. In spite of the tremendous scientific advances since 1918 in our understanding of influenza virology and immunity, it is unlikely that an effective vaccine could be produced and administered in time to abort an ongoing global pandemic. It is this nightmare scenario that concerns influenza investigators.

8.3 Ebola Pandemic

The Ebola pandemic that started in West Africa emerged as we wrote this book. It is discussed in Chapter 16 but deserves a brief comment here. Sidebar 3 sets forth the makings of a “perfect storm” that can lead to an emerging pandemic, which—unfortunately—we have witnessed during 2014.
9. FINAL COMMENTS

Although hard to quantify, viral diseases continue to take
a significant toll of human life and well-being. The rela-
tively recent emergence of diseases like HIV/AIDS and
SARS demonstrate the potential for new unpredicted viral
infections to appear in epidemic and endemic form. The
story of SARS, which was barely contained through the
application of the ancient practice of quarantine, points out
the potential dangers of new viral plagues. Likewise, the
inability—to date—to successfully control the AIDS pan-
demic underlines the power of a viral disease to defy the
formidable armamentarium of modern biomedical science.
While it is possible to identify emerging viral threats with
unprecedented speed and precision, some new infections
spread before an adequate response can be formulated and
deployed. The study of viral pathogenesis—in addition to
its intrinsic interest—will continue to be of practical impor-
tance as a critical contribution toward the control of present
and future viral plagues.

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