CHAPTER EIGHTEEN

COVID-19: Not just another respiratory virus—2020

Abstract

In late 2019, a new respiratory disease emerged in Wuhan, China. It was highly infectious and spread worldwide. It was caused by a new coronavirus; SARS-2 and was named Coronavirus Disease (COVID)-19. It reached the United States in early 2020. COVID is especially lethal for the elderly and within a year, over half a million victims had died in the United States. Attempts to control the spread by social distancing and mask wearing were unevenly applied and some places suffered more than others. Economic considerations affected the degree to which social distancing rules were enforced. The disease occurred in waves reaching its greatest prevalence in December–January of 2020–21. Fortunately, effective vaccines were developed rapidly, and mass vaccination began in January 2021. As a result, the number of new cases dropped rapidly and social restrictions were gradually restricted. The disease has not disappeared and will likely remain a common respiratory infection.

Keywords: COVID-19, Coronavirus, Elderly, Pneumonia, Vaccination, Social distancing, Face masks, China, Diagnostic tests

George Santayana's warning that "those who cannot remember the past are condemned to repeat it," while somewhat of a cliché, has been shown to be manifestly true in the case of the COVID-19 pandemic. The historical epidemics and pandemics described in the previous chapters provoked societal responses that have been repeated many times over the course of the coronavirus pandemic that spread to North America at the beginning of 2020. It is however also abundantly clear that this pandemic posed many unique problems.

As described in Chapter 13, when the first results of Jonas Salk's polio vaccine trial were reported, there was widespread rejoicing across the United States. Parents were truly grateful and awed. A terrible fear that had affected every parent was removed. Since that time the fear of infectious disease has receded. People lost not only their fear but also their respect for medical science, especially for public health measures. Experts have been discounted and their warnings dismissed. We had largely forgotten the toll that infectious diseases can take on human lives. As infectious disease threats

Great American Diseases
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appeared to decline, we no longer took public health seriously. The consequences of this lack of interest and concern have been seen in our response to the appearance of a new Coronavirus disease in late 2019, an outbreak that quickly grew into a pandemic.

Origins

The origins of this Coronavirus are unclear [1]. A study published in April 2021 suggested that the first human-to-human transmission of the virus had occurred in Hubei Province, China in mid-October 2019 [2]. However, the first "official" case of respiratory infection, the index case, reportedly developed in mid-November 2019, in nearby Wuhan. On December 1 this patient was admitted to a Wuhan hospital with severe breathing difficulty caused by pneumonia due to a previously unknown coronavirus. By December 17, 27 similar cases had been diagnosed. By December 27 there were more than 180 such cases. About two-thirds of these early cases were reportedly linked to the Huanan Seafood Wholesale Market in Wuhan. These "wet" markets are popular in China. They sell fresh fish and cheap meat from wild mammals that are housed in large numbers in close proximity. These animals may be sold as pets or for food. Viruses can spread readily within dense populations of stressed animals [3]. From the animals, they can readily jump to humans. This is called zoonotic spillover. The COVID-19 coronavirus most likely originated in horseshoe bats (*Rhinolophus*) [4, 5]. Surveys of bat samples from south China have identified several coronaviruses closely related to both SARS-CoV-2 as well as others related to SARS-CoV-1 [6]. However bats were not for sale at the Wuhan market although civets, a known intermediate host of coronavirus were. While many of the original cases were associated with the market it soon became obvious that the virus was also readily transmitted among humans. A similar event had occurred in 2002 when the SARS-1 coronavirus, transmitted by civets, escaped from another Chinese wet market and infected thousands of people (Chapter 17).

While the disease most likely originated from human-animal contacts in the wet market, it is also possible that the virus may have accidentally escaped from a nearby laboratory where research was being undertaken on bat coronaviruses. Three researchers from the Wuhan Virology Institute became sick in November 2019 and had to seek hospital treatment. The WHO investigated this possibility, accepted Chinese assurances, and reported that laboratory escape was unlikely.

Within a few weeks of the onset of the outbreak, the offending virus was identified, isolated, and its genome sequenced, something that could not have happened in prior pandemics. On January 7, 2020, the Chinese health authorities announced that the disease was caused by a novel betacoronavirus. Its complete genome was published on January 10 and development of the first diagnostic polymerase chain reaction (PCR) assay was reported on January 15. This was an incredibly rapid scientific response.

The virus was eventually named SARS-CoV-2. The disease that it causes was named Corona Virus Disease (COVID)-19 by the World Health Organization [7].

On January 15, 2020, a 35-year-old man returned to Washington State after visiting his family in Wuhan, China. On January 19, 2020, he presented at a clinic in Snohomish County, WA with a 4-day history of cough and fever; he sat in the waiting room for 20 min without any mask or face covering, prior to being seen by a physician. Oral and nasal pharyngeal swabs were tested by PCR assays at the CDC and found to be positive for SARS-CoV-2. The patient developed severe pneumonia but eventually recovered. He was almost certainly not the first case of the infection in the United States. Retrospective analysis of donated blood samples has found specific antibodies to SARS-CoV-2 in samples from Illinois donated on January 7, 2020. Since it takes about 2 weeks for antibodies to develop, that infection was likely acquired around Christmas 2019 [8]. The first confirmed COVID death in the United States occurred in California on February 6. Subsequent analyses also indicate that the virus reached New York City sometime in February by way of tourists returning from California, Iran, and Paris.

Coronaviruses

Coronaviruses are enveloped, nonsegmented positive-sense RNA viruses. They derive their name from the crown-like halo of spikes around each spherical virion. They have the largest genomes known among the RNA viruses. The *Coronavirinae* are subdivided into four groups, the alpha-, beta-, gamma-, and deltacoronaviruses. Alpha- and betacoronaviruses typically cause disease in mammals. Gamma- and deltacoronaviruses mainly infect birds. The first coronavirus, identified in 1937, was the virus that causes infectious bronchitis in chickens. As its name implies, this is a respiratory disease, but in cattle, pigs, dogs, and cats other coronaviruses usually cause severe gastroenteritis. Coronaviruses readily adapt to changes in their hosts. For example, it is likely that bats have provided the gene pools for the alpha- and betacoronaviruses while birds are the most likely sources of the gamma- and deltacoronaviruses. SARS-CoV-2 grows readily in ferrets, mink, and cats. Cats (and tigers) and dogs are susceptible to airborne infection.

SARS-CoV-2 is the seventh coronavirus known to infect humans. These coronaviruses cause respiratory diseases ranging from mild, such as some forms of the common cold, to seriously lethal, such as the diseases caused by the betacoronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2. Four human alphacoronaviruses (HCoV) cause about a third of common cold cases—a runny nose. It is as yet unknown why these viruses only cause mild disease when the betacoronaviruses are so lethal.

The spikes that cover coronaviruses are used by the virus to invade cells. Thus, the spike protein of SARS-CoV-2 binds strongly to a human cell surface protein, called angiotensin-converting enzyme-2 (ACE2). ACE2 is found on the cells that line our airways. As a result, inhaled virus can bind, enter, and kill these cells.

Clinical disease

Initial studies in China soon determined that the incubation period of COVID ranged from 2 to 14 days. Most symptoms appeared in 4–5 days. It appeared to be especially lethal for the elderly (The median patient age was 59 years) and those with underlying diseases. The number of cases in the early epidemic in China doubled every 7.2 days. The hospitalization rate was in the region of 20%. SARS-CoV-2 killed between 1% and 3.4% of these hospitalized patients.

Most respiratory viruses infect either the upper or lower respiratory tracts, but SARS-CoV-2 infects both simultaneously. After it kills the cells in the airways, the dead cells are shed into the bronchi, where they are drawn into the lungs and clog the airways resulting in severe breathing difficulty. Because it infects the upper airways, COVID-19 is readily shed in the airborne droplets generated by coughing, sneezing, singing, or even speaking loudly. Some of these droplets may be very small and may remain suspended in air for a long time.

SARS-CoV-2 causes a spectrum of illnesses ranging from asymptomatic to lethal pneumonia. It is estimated that about 40%–45% of infected individuals never show symptoms. This results in an "iceberg" effect where many infections are inapparent and thus not detected. On the other hand, in the

United States, it has been estimated that about 10 people in every thousand infected will die from the disease—a case mortality rate of around 1%. This is about 10 times more lethal than seasonal influenza.

These numbers are however affected by the age structure of the population since COVID-19 is especially lethal in older individuals with preexisting medical conditions. These medical conditions result in a two- to threefold increase in disease severity. They include chronic kidney disease, chronic obstructive pulmonary disease, immunosuppression, obesity, heart disease, sickle cell disease, and type 2 diabetes mellitus. Persons over 50 are about 2.5 times more likely to develop severe disease than the general population. The case fatality rate in the United States for persons over 75 is 13.83%. Smoking makes it worse. Males develop severe disease 1.3 times more frequently than females. This is not to say that younger individuals are not susceptible to lethal disease either. In China, children made up 2.5% of the early cases although almost none were severely ill. Deaths do however occur in infected children and teenagers.

In the United States, minorities have been disproportionally affected. Thus, the age-adjusted data show that their risk of being hospitalized with or dying from COVID-19 is greater for minorities than for Whites: Native Americans are 3.4 and 2.4 times more likely to be hospitalized or dying, respectively; Hispanics are 2.8 and 2.3 times more likely of being hospitalized or dying, respectively; and, African Americans are 2.8 and 2.0 times more likely to be hospitalized or dying, respectively. Asian and Pacific Islanders have approximately the same risk as Whites. These disparities are mainly due to inequalities in health care access, insurance rates, preexisting and predisposing health conditions, work demands, housing quality, and language barriers.

While the prime targets of the virus are the cells of the respiratory tract, other organs including the heart, kidneys, intestine, and brain may also be affected. Once inhaled, the virus gains access to the nose and throat where many cells carry ACE2. The disease commonly starts as a flu-like illness. The victim develops a fever, sore throat, loss of smell and taste, as well as headaches, body and muscle aches, intense fatigue, diarrhea, nausea, and vomiting. Some may develop skin rashes and painful "COVID-toes." Young people especially, develop chronic fatigue. The immune response to this invasion results in the migration of inflammatory cells into infected tissues. These in turn attract other cells by releasing molecules called chemokines. The accumulated cells and fluid fill the lungs and interfere with oxygen uptake. Patients often have great difficulty in breathing. If the chemokine production is excessive and prolonged, then this "cytokine storm" may result in damage leading to a loss of lung function and death.

About 20% of patients suffer heart damage; some develop clots in their bloodstream that can block vital arteries. About 25% of patients develop kidney failure. Five to ten percent develop brain damage and encephalitis. About half of affected patients develop diarrhea.

Many infected individuals continue to experience multiple symptoms after 12 weeks. This so-called long-COVID includes extreme fatigue, "brain fog" (an inability to think clearly), sleep disturbances, shortness of breath, heart abnormalities, and chest pain. The mechanisms of this long-COVID are complex. They probably include long-term damage to many organs, perhaps as a result of persistent inflammation.

The clinical signs of COVID-19 infection are thus entirely nonspecific. At its early stages it resembles any other respiratory infection. It cannot be diagnosed by clinical examination alone. The presence of the virus in the patient's respiratory tract must be demonstrated. This is done by swabbing the throat and detecting the presence of coronaviral RNA through the use of a reverse-transcriptase PCR test (Box 18.1).

BOX 18.1 The reverse transcriptase polymerase chain reaction (PCR) test.

The standard test used for COVID-19 testing in the United States is the reverse transcriptase PCR. This test is designed to detect the presence of coronaviral RNA in a nasal or mouth swab. Because we know the complete gene sequence of the coronaviral RNA, we can select a short sequence that is unique to the coronavirus. We can then construct an artificial sequence that is complementary to this viral RNA and will bind only to that sequence—this is called the primer sequence. To perform the test, a nasopharyngeal swab is extracted in saline and any viral RNA is converted to DNA through the use of a reverse transcriptase enzyme. (This is the same type of enzyme used by retroviruses—Chapter 16.) A primer sequence is then mixed with the newly formed DNA. If the coronavirus-specific DNA is present it will react very specifically with the primer sequence. An enzyme called DNA polymerase is then added to the mixture and the conditions manipulated so that the selected DNA sequence is massively increased through many cycles of a polymerase chain reaction (PCR). Any newly generated DNA, if present, can then be detected by the process of electrophoresis. A positive result can be confirmed later by sequencing the newly formed DNA and confirming that it is indeed complementary to the coronavirus RNA.

Prevention and control

As discussed in Chapter 1, a simple measure of a virus's transmissibility is its basic reproductive rate (R_0). The R_0 is the average number of secondary cases arising from a single case in a nonimmune population. For COVID-19, the R_0 appears to be in the region of 2–2.5. This is an important number since any value greater than 1.0 means that the virus is spreading. All our efforts must be directed to getting the R_0 below 1.0 if the spread of the virus is to be stopped. For comparison, the R_0 of seasonal flu is 0.9–2.1 while the R_0 of the 1918 pandemic flu was about 1.4–2.8. It is of interest to point out however that further analysis also suggests that a high proportion of COVID cases are caused by a small fraction of infected individuals—so-called supershedders.

Given that SARS-2 has a lethality of about 1% and that initially, nobody had any immunity to it, it was easy to calculate that it could potentially infect all 340 million people in the United States and kill 3.4 million! This will not happen because, as the virus spreads through the population, individuals who recover develop immunity. As this "herd" immunity develops, the proportion of susceptible people in the population falls and the virus finds it increasingly difficult to encounter nonimmune victims.

The basic principle of infectious disease control is therefore to ensure that the R_0 drops below 1. In order to do this, the opportunities for viral spread must be minimized. This can be done by reducing the exposure of susceptible people by the use of isolation and quarantine, by wearing properly fitting masks, by avoiding indoor crowds, and by social distancing (staying 2–3 m apart) so that an infected victim cannot transmit the virus to other susceptible individuals. Additionally, if everyone is vaccinated and hence immune, then the virus will be unable to find any susceptible victims. Thus, logical control procedures consist of Step 1: Quarantine and social distancing and Step 2: Vaccination.

In the absence of herd immunity, the simplest method of dropping the R_0 below 1 is social distancing. Analysis of the 1918 influenza pandemic has shown that those cities that introduced and enforced social distancing had many fewer cases than those that delayed distancing or terminated it prematurely. Many cities and states also introduced social distancing measures in their efforts to fight COVID-19 but this was largely uncoordinated and adjacent jurisdictions may have had very different rules. Face masks also appear to be much more effective than first thought at reducing transmission. These masks, when properly fitted, help reduce transmission by a person shedding the virus from their nose and mouth. Other steps that help reduce disease spread include contact tracing and the identification of disease "hot-spots" as well as of asymptomatic infected individuals by testing.

The SARS-2 coronavirus, like other respiratory pathogens, spreads fast. Its long incubation period and the fact that large amounts of virus are shed prior to symptoms appearing means that infected persons can transmit it long before they begin to feel unwell. In addition, many of those infected never show clinical signs and so act as superspreaders. Obviously, it is critical to detect these healthy but infected persons in order to isolate them and prevent disease spread.

Time course

As described, the first recorded US case of COVID-19 was identified on January 19, 2020, in Washington state. More recent data however, suggests that the coronavirus had reached the major US cities by early January and had spread widely before the first wave of clinical cases appeared in late February and early March.

Restrictions on flights from China to the United States were put in place on January 31. On March 13, travel restrictions were placed on 26 European countries [9]. Unfortunately, travel restrictions are easily circumvented and did not apply to US citizens. As a result, they could only delay but not stop the spread.

The virus arrived about the same time on both the East and West coasts. The first wave of the pandemic centered primarily on the Northeast, especially New York City (NYC), while much of the rest of the country remained relatively unaffected. New York City was severely affected. Its hospitals were almost overwhelmed by the number of cases. To assist, the US Navy sent the hospital ship, USNS *Comfort*, with a 1000-bed capacity and 12 operating rooms, "to provide relief to frontline health care providers" and to increase local hospital capacity; the ship arrived in New York Harbor on March 30. By April 8 there had been 799 COVID-related deaths. By June, NYC, with a population of 8.6 million had had more than 23,508 confirmed and probable deaths from COVID-19. Thus in 3.5 months, the disease killed one in every 400 New Yorkers (Fig. 18.1).

Since the obvious method of preventing the virus spread was social distancing, this principle was expanded to require an economic shut down in many communities [10]. Theaters, restaurants, bars, and gyms, were closed

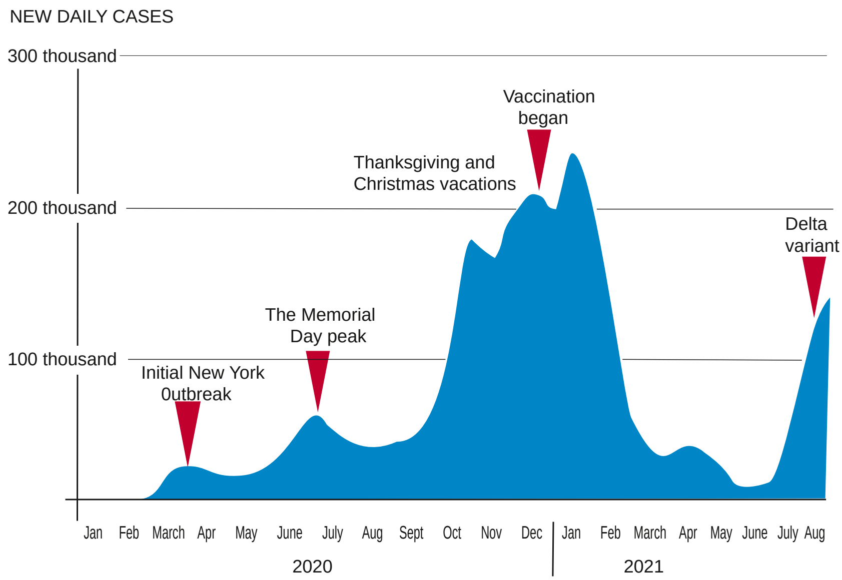

Fig. 18.1 The time course of the COVID-19 pandemic over its first year and a half. It has been marked by four peaks in mortality. The initial wave in April 2020 was largely restricted to New York City and the northeastern states. The second, in early summer 2020 was attributed to a premature relaxation of restrictions and social mingling around the Memorial day weekend. The third that began in the fall of 2020 was associated with the beginning of the school year, the arrival of cooler weather as well as the Thanksgiving and Christmas holidays. The rapid decline in new cases in early 2021 was probably a result of increased social awareness resulting in people taking more care to avoid contacts as well as the arrival and delivery of effective vaccines. Beginning in June 2021 however, case numbers in the United States began to rise again as a result of vaccine hesitancy and the spread of the much more infectious and lethal delta variant. *(Data courtesy of the CDC.)*

in many states at a time when case numbers were low. The early closure of events where crowds gather as well as schools and universities contributed to reducing disease spread and its associated mortality. The number of cases reported appeared stable. Nevertheless, by May 27, 2020, there had been 100,000 reported deaths from SARS-CoV-2 in the United States.

Following the April peak that was largely confined to the Northeast, the number of new cases began to decline giving rise to cautious optimism. By mid-June, the number of new cases had declined to such an extent that people began to gather in groups again and restaurants to reopen. Unfortunately, an economic disconnect also developed in relatively unaffected states. Few people knew a COVID patient, but many were adversely affected by the consequences of the shutdown. Political and economic pressure to reopen grew rapidly and by early May, many State governors, especially in Arizona, Texas, and Florida, lifted stay-at-home orders and ended many restrictions on business activities. Some declined to require people to wear face masks and prevented local governments from imposing such requirements. They ignored warnings regarding premature reopening.

The lifting of restrictions was welcomed by many, especially businesses and those who felt the need to gather and celebrate. Thus, beginning at the Memorial day holiday and recurring on July 4, large crowds of young people gathered, many in the belief that the young had little to fear from COVID. They were wrong. By the second week of June, case numbers began rising again. First in Arizona and subsequently in Texas, Florida, California, and other sun-belt states. This rise was attributed by many to increased testing, but while the number of tests performed indeed increased, so too did the percentage of positive results. As cases grew, so did hospital admissions. The demand for beds, intensive care units, and respirators began to sky-rocket. Some hospitals were overwhelmed by the demand. Many testing providers became backlogged. The time taken to produce and report test results increased significantly.

Interestingly while cases and the demand for hospital beds exploded, the rise in deaths, was not as great, reflecting increased success in treating patients, a decline in the average age of patients, and the availability of drugs to treat the most severe cases. As a result of this explosive surge of cases, many states responded by stepping back once again. They began to reimpose restrictions on businesses and mandating the wearing of face masks.

In a country such as the United States where each state was responsible for controlling COVID-19, there was a patchwork of responses. New York and adjacent states that suffered initially were hesitant to reopen and their cases continued to decline. In contrast, the early opening states in the South saw explosive outbreaks. Thus, the country was faced with the task of opening up one region while suppressing the pandemic in another.

Beginning however in mid-October, the numbers of daily COVID cases exploded nationally and climbed steadily to peak on January 2, 2021 at 300,462. The most COVID deaths occurred on January 12 when 4475 victims died. Both cases and deaths then declined rapidly. The reasons for the decline were a result of a combination of social distancing, enforcement of mask mandates, and most importantly, the rapid introduction of effective vaccines. Nevertheless, by mid-February the United States had already suffered 500,000 COVID-related deaths.

An aggressive vaccination campaign resulted in a significant decline in new cases and the country began to relax its restrictions once again. Unfortunately, by July 4 only about 67% of adults had been vaccinated. Many adults, especially in southern states declined the vaccine. As a result of this and the appearance of a more infectious virus variant, Delta, cases began to rise again. By mid August 2021, daily case totals had reached 121,000 and daily deaths averaged 655. Total US cases had reached 36,684,028 while total deaths had reached 621,051. The greatest increase in cases occurred in southern states such as Missouri, Louisiana, Texas, and Florida where hospitals were, once again, having great difficulties in handling the case load.

However further analysis has suggested that the actual number of deaths based on excess mortality estimates was about 905,000. If correct, this is significantly more than the 675,000 who died in the 1918 influenza pandemic. The official underestimates are attributed to local health systems being overwhelmed and to insufficient testing. This same analysis estimated that 9.4 million persons will have died worldwide by September 2021.

Global significance

According to the World Health Organization, as of August 14, 2021, 207 million people were known to have been infected and more than 4.3 million had died of COVID-19 worldwide. Of these at least 17,000 health workers had died from the disease. Economically the world lost US$ 10 trillion in output by the end of 2021, and it was estimated that this would compound to US$ 22 trillion over the 2020–25 period. At the peak of the pandemic in 2020, 90% of schoolchildren were unable to attend school. Ten million more girls were at risk of early marriage, gender-based violence increased fivefold and 115–125 million people were pushed into extreme poverty.

The victims

As an airborne virus, it is much easier to become infected by inhaling the still air within a building than in the breezy, sunny outdoors. It was estimated that the coronavirus was 19 times easier to catch indoors than outdoors. As a result, the disease occurred predominantly in dense indoor populations. These included cruise ships, church halls, prisons, and especially long-term care and nursing homes for the aged.

In December 2020, an average of 1.7 individuals died from COVID-19 every minute in the United States. Through December 2020 it is estimated that Americans collectively lost about 4.5 million years of life. It was estimated that US life expectancy fell by 1 year, to 77.8 years in the first half of 2020. This was the largest drop since World War II (Fig. 17.1). Life expectancy for the Black population dropped by 2.7 years over the same period. The death rate for Black Americans was twice as high as for White Americans. About one in 800 Black Americans had died and one in 1325 White Americans.

Among the most severely affected groups of individuals were physicians, nurses, and caregivers exposed to the virus on a daily basis. If they were sickened or forced into quarantine, this also increased the stress and the burden on their colleagues. This was also a consistent feature of historical plagues where those ministering to the sick were seriously overworked and often contracted the disease themselves. Health care workers were significantly affected during the COVID-19 outbreak, especially when appropriate protective equipment was not always available. However, once the new vaccines became available these workers were prioritized and became the first to receive their shots.

The effectiveness of the immune system declines with age and as a result, the elderly become increasingly susceptible to infectious diseases. Pneumococcal pneumonia killed so many elderly that it was once called "the old man's friend." Seasonal influenza is also a well-recognized killer of the elderly. COVID-19 is no different. Given both their aged immune system as well as the relatively crowded conditions under which the institutionalized elderly live, it is unsurprising that a very high proportion of lethal cases occurred in those over 70. While nursing homes and care facilities hold less than 1% of the US population, by mid-June they had accounted for 40% of COVID deaths. In New Jersey the early wave of disease killed one in every eight nursing home residents. As with health care workers, the elderly living in care homes and assisted living were among the first to receive the new vaccines that became available in December and January 2020–21.

About 30 million Americans under the age of 65 have no health insurance. Of these uninsured, half are persons of color and 15% are Black. This was reflected in COVID-19 mortality figures where Blacks died at twice the rate of whites (as discussed earlier). As a result of a lack of a social safety net, many workers in low-paying service jobs were forced to remain working in order to maintain their income. As a result, they too were more likely to spread and be exposed to the virus [11].

One of the consistent themes of this book is the frightful damage done to Native Americans by European diseases. From smallpox and measles to malaria and yellow fever, they have suffered disproportionately. COVID-19 was no exception. It has had a major impact on tribal nations across the United States. In 2020, the Navajo nation had a higher death rate than most American states—62 deaths/100,000 people. The Navajo nation had over 50% of the confirmed cases in New Mexico despite the fact that they only account for 11% of that state's population. These local clusters proved difficult for small tribal clinics and hospitals to handle. Many live in crowded multigeneration homes and poor quality water is a critical issue. Much of the problem lay in the high prevalence of preexisting conditions in these communities. Similar problems confronted native peoples elsewhere in the Americas, especially in Brazil.

Even politicians could become infected, especially if they resisted mask wearing and social distancing. Thus, President Trump and Prime minister Boris Johnson of the United Kingdom were both hospitalized for a short time as a result of severe respiratory difficulty caused by COVID-19.

The vaccines

It was obvious, almost from the beginning of the pandemic, that the only long-term solution to this disease was the development of effective vaccines [12,13]. Funding for vaccine production infrastructure has rarely been available in the absence of an imminent disease threat. As a result, coronavirus vaccine development started belatedly and from scratch. Eventually however, massive funds were made available in an effort to accelerate the vaccine development process [14]. On May 15, the Federal government instituted "Operation Warp Speed," a national private/public partnership program to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. One aim of the program was to deliver 300 million doses of a safe, effective vaccine by January 2021—it succeeded through hard work, clever ideas, and dedication [15].

Vaccines are tested through a multistage process. For example, a trial batch of vaccines must first be tested in a small group of individuals (Phase 1 trials). If successful it can then be tested in a small number of human volunteers to assure their safety. This group should have the same characteristics such as age and physical health as the proposed target population (Phase 2 trials). If all appears well and no significant adverse events have occurred, then the vaccine undergoes large-scale clinical trials involving thousands of people (Phase 3 trials). The recipients are monitored looking for adverse events and to determine if they are protected against the naturally acquired disease. It is imperative that any vaccine be both safe and effective. These trials normally take many months or even years. Once developed, any vaccine will then have to be manufactured in huge amounts and this itself may be difficult to achieve. Even mundane items such as syringes, glass vials, and rubber stoppers may be in short supply. Despite these constraints, the vaccine industry took up the challenge and developed several different, and remarkably effective COVID-19 vaccines in an incredibly short time.

The first two COVID vaccines, one produced by Pfizer-BioNTech and one by Moderna, were approved by the FDA for emergency use in November 2020 and began to be administered to those in the highest priority groups, health care workers, and the elderly living in institutions, by mid-December [16]. These two vaccines contained messenger RNA (mRNA) encoding the SARS-2 coronavirus spike protein incorporated in lipid nanoparticles (fat droplets). Once injected, these lipid particles are readily taken up by cells, the mRNA is then translated into the viral spike protein. This foreign protein is presented on the cell surface and recognized by the recipient's immune system. As a result, it triggers a protective immune response involving both T and B cells. The initial trials showed, and follow-up studies confirmed, that both these vaccines were 94%–95% effective after two doses in preventing disease and death and had remarkably few adverse side effects. As manufacturing ramped up, initial vaccine shortages were overcome, and the vaccine became available to a second priority group; those over 65 and those with a predisposing medical condition as described earlier.

A third vaccine also received conditional approval from the FDA. This was a single-dose vaccine manufactured by Johnson and Johnson. It differs from the previous two in that it uses a slightly different technology. It employs a harmless adenovirus into which, the genetic code for the coronavirus spike protein has been inserted. When this "recombinant" adenovirus enters cells, the infected cells use this code to make coronavirus spike protein that in turn triggers an immune response. The J&J vaccine is reported to be 85% effective against severe COVID.

The Oxford-AstraZeneca vaccine was developed in the United Kingdom. It too contains a genetically modified, harmless recombinant adenovirus. It has been reported to be 65%–85% effective. Vaccines were also developed in Russia, India, and China. Many other vaccines are currently under development.

As has been made clear in previous chapters, not everyone is convinced that vaccines are effective or safe. As a result, many individuals hesitate to be vaccinated. This is not a new phenomenon as was seen in the cases of smallpox and measles. Unfortunately, in the case of COVID, distrust of science and government as well as a constant stream of misinformation emanating online has accentuated the problem. This has been especially the case in conservative southern states. As a result of this vaccine hesitancy as well as the emergence of the Delta variant, COVID case numbers and hospital admissions in the United States began to rise rapidly again in June 2021. By August new case numbers had once again exceeded 100,000 cases daily.

New viral variants

Coronaviruses, like most RNA viruses, make no effort to ensure that they replicate faithfully. Thus, as these viruses grow within cells and their RNA is copied, gradual errors and changes creep in [17]. This means that, over time, their RNA sequences change as do the viral proteins encoded by this RNA. As a result, new variants are continuously emerging. Some make little difference. Others may have completely new properties that can negate our control procedures. The new coronavirus variants are identified by Greek letters. Of these, the Delta variant that originated in India is more virulent and more transmissible than earlier strains. (It is 40%–60% more transmissible than the original Alpha strain. It can enter cells faster and generate many more viral particles. As a result victims may contain a thousandfold more viruses than previous variants.) Delta has rapidly become the dominant strain in the United States. People infected with Delta are about twice as likely as people infected with the Alpha variant to require hospitalization. If these changes are great enough, then it is possible that antibodies directed against the parent strain may not be able to bind and neutralize these new variants. This "immune escape" is similar to that seen in influenza and is the reason why flu vaccines have to be made and administered annually. It is also why the mild coronavirus infections that cause the common cold can recur after several years. It is possible that a similar situation may occur with the COVID-19 coronavirus vaccines and that we may eventually require annual booster vaccinations to maintain immunity [18]. It is still too early to know if this will be the case (Box 18.2).

BOX 18.2 The first Promed-Mail Posts.

Promed is the Program for Monitoring Emerging Diseases published online by the International Society for Infectious Diseases. This consists of a website that promptly reports on any new disease outbreaks. Here is the first Promed Mail Post regarding the Coronavirus outbreak dated December 30, 2019.

ProMED
INTERNATIONAL SOCIETY
FOR INFECTIOUS DISEASES

Published Date: 2019-12-30 23:59:00
Subject: PRO/AH/EDR> Undiagnosed pneumonia - China (HU): RFI
Archive Number: 20191230.6864153

UNDIAGNOSED PNEUMONIA - CHINA (HUBEI): REQUEST FOR INFORMATION
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A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

[1]
Date: 30 Dec 2019
Source: Finance Sina [machine translation]
https://finance.sina.cn/2019-12-31/detail-iihnzahk1074832.d.html?from=wap

Wuhan unexplained pneumonia has been isolated test results will be announced [as soon as available]

On the evening of [30 Dec 2019], an "urgent notice on the treatment of pneumonia of unknown cause" was issued, which was widely distributed on the Internet by the red-headed document of the Medical Administration and Medical Administration of Wuhan Municipal Health Committee.

On the morning of [31 Dec 2019], China Business News reporter called the official hotline of Wuhan Municipal Health and Health Committee 12320 and learned that the content of the document is true.

12320 hotline staff said that what type of pneumonia of unknown cause appeared in Wuhan this time remains to be determined.

According to the above documents, according to the urgent notice from the superior, some medical institutions in Wuhan have successively appeared patients with pneumonia of unknown cause. All medical institutions should strengthen the management of outpatient and emergency departments, strictly implement the first-in-patient responsibility system, and find that patients with unknown cause of pneumonia actively adjust the power to treat them on the spot, and there should be no refusal to be pushed or pushed.

Continued

BOX 18.2 The first Promed-Mail Posts.—cont'd

The document emphasizes that medical institutions need to strengthen multidisciplinary professional forces such as respiratory, infectious diseases, and intensive medicine in a targeted manner, open green channels, make effective connections between outpatient and emergency departments, and improve emergency plans for medical treatment.

Another piece of emergency notification, entitled "City Health and Health Commission's Report on Reporting the Treatment of Unknown Cause of Pneumonia" is also true. According to this document, according to the urgent notice from the superior, the South China Seafood Market in our city has seen patients with pneumonia of unknown cause one after another.

The so-called unexplained pneumonia cases refer to the following 4 cases of pneumonia that cannot be diagnosed at the same time: fever (greater than or equal to 38C); imaging characteristics of pneumonia or acute respiratory distress syndrome; reduced or normal white blood cells in the early stages of onset The number of lymphocytes was reduced. After treatment with antibiotics for 3 to 5 days, the condition did not improve significantly.

It is understood that the 1st patient with unexplained pneumonia that appeared in Wuhan this time came from Wuhan South China Seafood Market.

12320 hotline staff said that the Wuhan CDC went to the treatment hospital to collect patient samples as soon as possible, specifically what kind of virus is still waiting for the final test results. Patients with unexplained pneumonia have done a good job of isolation and treatment, which does not prevent other patients from going to the medical institution for medical treatment. Wuhan has the best virus research institution in the country, and the virus detection results will be released to the public as soon as they are found.

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The problems

Unfortunately, the United States was unprepared for the COVID pandemic. Public Health funding has never been a high priority, especially in the absence of an imminent disease threat. There were very few individuals with Public Health expertise in the White House. The disease struck in an election year when the President's and senior politician's attention was often focused elsewhere, and no one was in charge of the response. As a result, the pandemic response became politicized as exemplified by fights over face masks and vaccine mandates.

Consequently, while the United States has just 4% of the world's population, it has had 25% of its reported COVID cases. (These data are greatly influenced by the number of tests performed and reported, but nevertheless, the United States initially had a majority of the COVID cases. Major outbreaks in India, Brazil, and Indonesia will likely change this.)

The world reacted slowly to the Coronavirus. Though the disease had reached epidemic proportions in China by the end of 2019, the World Health Organization did not declare a Public Health Emergency of International Concern until January 30, 2020. On January 31, Health and Human Services Secretary Alex Azar declared a Public Health Emergency. This declaration provided funds and federal assistance for state, local, and tribal health departments in their COVID-19 responses, and as noted earlier, a limited travel ban was instituted. However, federal and state governments, and emergency preparedness programs, did little to prepare the country, accumulate supplies, or establish an effective surveillance system. No diagnostic tests were available nor were any in development, thus testing and tracing capabilities were lacking.

A severe shortage of personal protective equipment developed in the early months of the pandemic. Hospitals, like many modern businesses, operate on a "just-in-time" basis and do not stockpile large quantities of equipment. In an interconnected world, complex supply chains often originate in distant countries with cheap labor. For example, half of the world's face masks were made in China. As a result of supply chain failures, a serious shortage of masks and other protective equipment developed early. The Federal authorities decided that solving the problem was a role for the States and individual hospitals. In order to obtain access to limited supplies, hospitals were forced to depend on capitalism and connections. Inevitably, rich hospitals were more successful.

Ongoing problems included not only a lack of protective equipment but also testing failures. There were, at times, a shortage of the nasopharyngeal swabs used to swab the airways; a shortage of extraction kits for obtaining the purified RNA from the swabs; a shortage of the required chemical reagents; and a shortage of individuals trained to perform the tests. Supply was quite unable to keep up with demand. Unfortunately, the first diagnostic tests were produced by the CDC, and they failed as a result of seeking to establish a very complex test and the use of contaminated chemicals that resulted in false-positive results. Thus, in the early weeks of the pandemic, effective tests were in short supply. By the end of February 2020, tens of thousands of Americans were infected but only several hundred had been tested.

There was no shortage of scientists, pseudoscientists, politicians, and commentators willing to pontificate on the pandemic. In an era of 24-h news cycles, the Internet, podcasts, and social media, "experts" jockeyed to be seen and heard. Events, information, and scientific studies were reported in nearly real-time and repeatedly reported and discussed. Little time was allowed for evaluation, interpretation, and objective consideration of the material; thus, the general population was continuously bombarded with conflicting messages, some correct, some with various inaccuracies, some irrelevant, some grossly misleading, some intentionally inflammatory. This led to a wide misunderstanding, confusion, and mistrust regarding many aspects of the pandemic.

People progressively lost their fear of the disease while the economic shutdown took its toll. As a result, the strict isolation and social distancing progressively lapsed. States with relatively few cases opened up first but within weeks the isolation consensus broke down. Many, perhaps most, individuals, remained cautious and practiced social isolation and mask wearing. A growing minority however dismissed the threat. States felt compelled to reopen even if prevalence was high and tests were unavailable. Businesses reopened. Life began to return slowly to normal and the virus took advantage of these changed circumstances!

As the population of the United States became aware of the severity of the COVID-19 pandemic and its possible consequences, people naturally avoided social contact. Some obvious sites to avoid were doctor's and dentist's offices as well as hospital emergency rooms. As a result, people simply stopped going to such places. Patient loads dropped dramatically. But as the pandemic continued, the medical profession and patients adapted. There was a massive increase in the use of telemedicine/telehealth services for primary care delivery.

One feature of American society and culture is that it prioritizes individual freedoms over government regulations. There is thus a strong aversion to mandating collective behavior. This aversion was reflected in the decision to wear face masks or be vaccinated. Some states required it; others resisted. Mask wearing became a partisan issue and as a result, inconsistent. In a Gallup poll on July 13, 2020, 34% of men and 54% of women reported that they always wore a mask outside the home; 20% of men and 8% of women said that they "never" wore a mask!

When the news of an epidemic is first released, there has always been a tendency to blame others such as immigrants, foreigners, gays, or other disfavored groups. Besides the obvious casting of blame for sexually transmitted diseases on others (the "French pox," for example), the great epidemics of the 19th century such as cholera and typhoid were routinely blamed on the most recent group of immigrants; the Irish, the Italians, or the Russian Jews. On the southern border, Mexicans were blamed for introducing typhus. The plague outbreaks in San Francisco in the early 1900s promoted extreme anti-Chinese prejudice. Not only had the plague originated in China but it reinforced perceptions of the Chinese being "dirty." These perceptions were totally inaccurate but reflected the ongoing prejudice of many against others who they saw as competitors, just as many in the United States view China today. Thence the pejorative terms the "Chinese virus" and "Kung Flu" for COVID-19.

Disease is bad for business. Thus, it has been common for business and political leaders to seek to downplay the significance of a disease outbreak, especially in its early stages. This was most obvious in the 1900 outbreak of plague in California where the business community and the State denied the existence of plague in San Francisco. There was a great reluctance to close down most businesses during the 1918 influenza pandemic not just for morale reasons but also because of the effects that it would have on business. This is by no means a strictly American phenomenon. Similar responses have occurred elsewhere including a 1599 outbreak of the plague in Valladolid in Spain, a 1996 outbreak of plague in Surat, India, and the 2002 SARS-1 outbreak in China. The risks of malaria were once downplayed since it posed a threat to Florida tourism.

There are unquestionably severe economic issues associated with disease epidemics that are of legitimate concern. Thus, social distancing, while reducing viral transmission and saving lives, also deprives individuals of their livelihoods. While it is overly simplistic to seek to regard this as a dichotomy of money versus lives, it is also clear that there are diverse opinions of the relative importance of each. This is also translated into taking chances—in effect, gambling. What are my chances of acquiring infection relative to any economic benefits I might gain by forgoing social distancing? The reader of this book may have noticed that certain behavior patterns repeat themselves when serious infectious disease outbreaks occur. This concern for economic consequences often results in a resistance to stringent quarantine measures. Quarantine is frustrating and people do not like it.

However, the consequences of the COVID shutdown were uneven. Some large organizations have been able to adapt to the new opportunities.

Conversely, many small businesses such as restaurants, shops, and bars, were forced to close with no alternative income sources. The markets for retail products, entertainment, and even food, moved online. Cash largely disappeared. The foods once provided by restaurants were taken over by supermarkets. They had the supply chains, the storage capacity, the staff, and the ability to deliver. Online retailers also benefited. Small stores and malls had been suffering from a shrinking market share for years and were unable to compete so that bankruptcies climbed. Shopping malls were deserted, and much retail space closed. Shopping was rerouted to the Internet. Thus, the shutdown accelerated long-term trends so that big companies increased their market share. Delivery companies dominated product delivery.

While most individuals are obliged to socially distance themselves at home, many people, those who can afford it, often seek to isolate themselves from disease by, for example, moving to remote locations. This was well recorded in the middle ages during the plague. Indeed, Giovanni Boccacio's great novel, the Decameron, describes the outcomes of such self-imposed isolation in rich young people fleeing the plague in Florence. The pope left Avignon and moved to his country estate. In 1625, the English parliament moved out of London where the plague was raging to nearby towns. It was clear then as now, that not everyone could afford to withdraw from society and escape to the Catskills or the Hamptons to avoid the miasma. In many cases these disease refugees carried the disease with them. Edgar Allen Poe's great short story: The Masque of the Red Death, makes this very clear (Chapter 4).

Predicted outcomes

COVID-19 has caused a typical, "virgin soil" pandemic. Since no human had encountered the virus previously, then nobody had any immunity, either antibody- or cell-mediated. Thus, unless controlled, SARS-2 will spread from individual to individual until a majority of the world's people are infected and subsequently either dead or immune. This will take at the very least 2 years to happen. The final proportion of those who become infected will depend ultimately on the development of herd immunity, but it is estimated that this will likely need to reach at least 60%–70% of the population to be effective in preventing significant disease outbreaks. We have been fortunate in that young people are largely resistant or it could have been very much worse.

If the new vaccines are as efficient as the data suggests, then the virus will eventually be unable to find susceptible hosts and its rate of spread will drop.

However, CoV-SARS-2 will not go away. The pandemic will end but the virus will continue to circulate. Like the plague, outbreaks will continue to flare. In addition, as an RNA virus the coronavirus will continue to mutate. Much will depend upon the degree and rate of antigenic change. There will, in effect be a race between the level of vaccination in a population and the emergence of new variants. New variants will be more likely to emerge in populations where the level of infection is high. Thus the greater the level of vaccination the less the risk of new variants arising.

Much depends on the duration of immunity. If vaccine-induced protective immunity is transient, then severe COVID-19 outbreaks may become an annual event. If immunity is persistent then outbreaks will likely be milder and less frequent. Much will depend upon the availability, acceptance, and effectiveness of vaccines [19]. With a good vaccine, widespread vaccination, and reasonable immunity COVID-19 will likely become another seasonal respiratory virus. Models also suggest that the infection will persist globally and flare up at intervals in different countries. In the most pessimistic models, if SARS-CoV-2 infects 60% of the world's population and its case fatality rate is 1% then 40 million will die, almost matching the number of deaths from the 1918 pandemic. (The case fatality rate is simply calculated; the total number of individuals that die from the disease is divided by the number of diagnosed cases multiplied by 100 and expressed as percent.)

To date, we have only succeeded in eradicating one human viral disease—smallpox. Smallpox eradication, in hindsight was easy—easy to diagnose, trace contacts, vaccinate against, and lifetime immunity. Polio has been much more difficult, and eradication has not yet been achieved. COVID-19 is a respiratory disease, and the most appropriate and relevant historical model is the 1918 influenza pandemic. That disease spread widely because of the special circumstances at the end of World War I. It likewise declined eventually as a result of two phenomena, social distancing and herd immunity. Flu has not disappeared, but we manage it.

It is essential to emphasize that COVID-19 is not just a North American disease. The disease is much more serious in other countries such as Brazil and India. The United States has resources to help it weather the pandemic. These other countries have much less. Lock-downs do not work in countries where there is no social safety net and workers are obliged to go to work or starve. Many live in large, overcrowded cities where effective social distancing is impossible. New variants are much more likely to emerge in these undervaccinated societies and once they appear we will be hard pressed to keep them out.

Perhaps the world will recognize that epidemic diseases have not gone away and prepare for the inevitable next one. We can be sure that there will be another pandemic, sometime.

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