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COVID-19: Epidemiology

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Abbreviations

ACE2	angiotensin-converting enzyme 2
CDC	US Centers for Disease Control and Prevention
CFR	case fatality rate
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
mRNA	messenger RNA
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

On 1 December 2019, the first report of a pneumonia of unknown etiology was recognized in Wuhan, China, presenting with fever, malaise, dry cough, and dyspnea [1]. Based on clinical criteria, diagnostic tests, and imaging, this respiratory disease was determined most likely to be that of viral origin. Although its presentation resembled that of other well-known viral pneumonias in the region (i.e. influenza, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), it was clear this was a novel disease. The World Health Organization (WHO) announced an epidemic cluster of outbreaks of this disease in Wuhan, Hubei Province by 31 December 2019 [2]. This aggressive increase in cases understandably caught the attention of epidemiologists in the region, who conducted origin-related field studies in the community and nearby health facilities. Nose and throat specimens were collected for viral genomic sequencing and analysis. On 12 January 2020, the Chinese government publicly shared the genetic sequence of the causative agent, a novel coronavirus that the International Committee on Taxonomy of Viruses later would christen severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2).

SARS-CoV-2 is a novel coronavirus that belongs to the viral family Coronaviridae. A relatively large classification, these viruses are enveloped, positive-sense, single-stranded RNA viruses. Typically, these cause mild to moderate upper respiratory tract illnesses, but they can cause enteric, hepatic, and neurologic diseases as well [3]. Four of the seven known coronaviruses cause only mild to moderate disease. However, three new coronaviruses have emerged from animal reservoirs over the past two decades that cause widespread serious illness and death. The first of these is SARS coronavirus (SARS-CoV), which emerged in November 2002 and causes SARS. The second is known as the MERS coronavirus (MERS-CoV), which causes MERS. MERS was first identified in September 2012 and continues to cause sporadic and localized outbreaks largely in Saudi Arabia and South Korea [4]. The third and most recent novel coronavirus to emerge in this century is SARS-CoV-2; it is the seventh member of the coronavirus family known to infect humans.

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The first death from the novel SARS coronavirus was announced by Chinese health officials on 11 January 2020 [2]. The WHO named this illness coronavirus disease 2019 (COVID-19) according to its nomenclature on 11 February 2020 and would eventually declare the outbreak a pandemic on 11 March 2020 [5]. At the time of this writing in August 2021, the SARS-CoV-2 pandemic has left entire countries crippled and in desperate recovery. Worldwide spread has left more than 4 million people dead, ranking it among the top 10 most deadly pandemic illnesses in human history.

Origin

In the early stages of the pandemic, most cases were associated with individuals who had previously visited the Huanan wholesale seafood market in the city of Wuhan. It is important to note that in this market, along with seafood, large collections of various wild animals were also available for purchase and consumption during this time. SARS-CoV-2 was isolated from environmental samples of the market by Chinese Center for Disease Control and Prevention. Suspicions arose that this may have originated from the same animal host, masked palm civets (*Paguma larvata*), as SARS-CoV. Early viral sequencing showed that SARS-CoV-2 shares only 79.6% sequence identity with SARS-CoV based on full-length genomic comparisons. However, at the whole-genome level, it is highly identical (96.2%) to bat-CoV RaTG13, which was previously detected in the horseshoe bat *Rhinolophus affinis* from Yunnan Province, more than 1500 km from Wuhan [6]. In addition, similar strains of SARS-CoV-2 were found earlier in other regions of China. Bats are likely reservoir hosts for SARS-CoV-2; however, whether bat-CoV RaTG13 directly jumped to humans or transmitted to intermediate hosts to facilitate animal-to-human transmission remains inconclusive, and epidemiologic investigations are still being conducted.

Animal Host

In China, SARS-like viruses (SARS and MERS) have largely made bats their natural hosts. However, bat SARS, like other coronaviruses, will not normally directly infect humans unless mutation or recombination occurs in intermediate animal hosts. There are hundreds of different coronaviruses, most of which circulate among such animals as pigs, camels, and bats. Generally, bat habitats are far from human activity, so this recombination event rarely results in disease. However, further human encroachment into animal habitats has increased interaction between humans and animal hosts. Although this is still being studied, the first hypothesized mechanism by which this virus obtained virulence in humans is thought to be what is termed a zoonotic "spillover event," in which a virus reaches a certain mutagenic threshold and gains the ability to transmit from one species to another, which, in the case of humans, can lead to disease (Figure 1.1) [7].

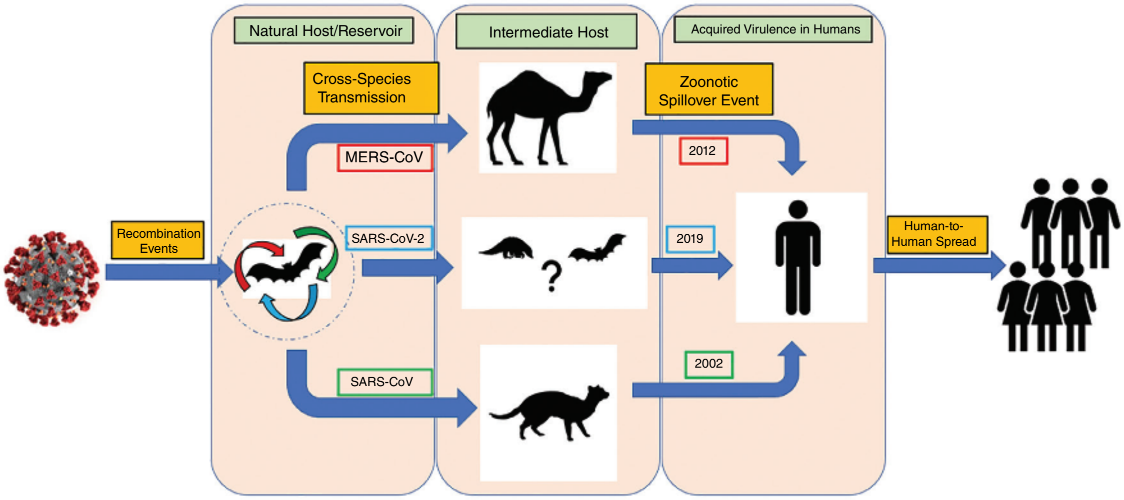

Figure 1.1 Diagram depicting historical examples, along with the proposed mechanism for SARS-CoV-2, of other Coronaviridae theorized recombination events leading to circulation in animals and zoonotic spillover into humans.

These events, although rare, are thought to have led to similar outbreak-type events several times in human history. Intermediate animal hosts of SARS-CoV and MERS-CoV were determined to be the masked palm civets (*P. larvata*) and the dromedary (*Camelus dromedarius*), respectively, before transmission to humans occurred [8, 9]. With respect to COVID-19, genomic evidence has pointed to the Sunda pangolin (*Manis javanica*) as a suspected intermediate host of SARS-CoV-2. Sequence identity between pangolin-origin coronavirus and SARS-CoV-2 is 99%, indicating that SARS-CoV-2 may have been passed on to humans as a result of exposure with these mammals [10]. In addition, SARS-CoV-2 and other coronaviruses from pangolins use receptors (angiotensin-converting enzyme 2 [ACE2] receptor) with similar molecular structures to infect cells, bolstering the argument for the virus being enzootic in these animals. However, others have questioned the relationship between pangolin and human infection, and this hypothesis is still being studied [11].

Infectivity and Incubation

The precise interval that an individual with SARS-CoV-2 infection can transmit infection to others is uncertain. However, it is estimated that infected individuals are likely to be the most contagious in the earlier stages of illness when viral RNA levels from upper respiratory specimens are the highest. Modeling studies have estimated that infectivity begins two days before symptom onset, peaks, and then lasts for approximately seven days. Infectivity rapidly declines after 8–10 days after presentation of illness [12, 13]. Nucleic acid detection studies (reverse transcriptase-polymerase chain reaction) support this infectious period by demonstrating SARS-CoV-2 RNA detection in people one to three days before their symptom onset, with the highest viral loads observed around the day of symptom onset and a gradual decline over time [12]. The duration of nasopharyngeal reverse transcriptase-polymerase chain reaction positivity generally appears to be one to two weeks for asymptomatic persons, up to three weeks or more for patients with mild to moderate disease, and even longer for patients with severe COVID-19 disease and/or immunocompromise [12]. It is important to note that prolonged viral RNA detection does not indicate prolonged infectiousness, and that the duration of viral RNA shedding is variable and may increase with age and illness severity [14]. Furthermore, the short-term risk for reinfection (e.g. within the first several months after initial infection) is low, because prior infection has been shown to reduce the risk for infection in the subsequent six to seven months by 80–85% [15].

Modes of Transmission

Overview

The US Centers for Disease Control and Prevention (CDC) confirmed person-to-person transmission on 30 January 2020. Many transmission routes have been considered, such as surface-to-surface contact, fecal-oral, bloodborne, and sexual contact, but evidence points to droplet spread via the respiratory pathway to be the most likely principal mode of transmission [16, 17].

Respiratory Droplets

Inhalation of droplets allows the transmitted virus's spike (S) protein to bind to the host ACE2 receptor on respiratory epithelial tissue, a critical step for cell entry and infection [18]. Entry then allows for replication and, as the viral load increases, an increased risk for transmission when an infected individual coughs, sneezes, sings, or talks in the proximity of an uninfected individual. Viral load is highest in the upper respiratory tract (nasopharynx and oropharynx) early in disease and increases in the lower respiratory tract over time. This further suggests that the upper respiratory tract is the initial site of viral replication, with subsequent descending infection [17].

Aerosolization

Although transmission most likely occurs through prolonged close-range contact (i.e. within approximately 6 ft or 2 m) and involves large respiratory droplets, transmission also can occur more distantly via smaller respiratory droplets that can remain in suspension or be recirculated through ventilation systems. In addition, it is likely that during aerosol-generating procedures (e.g. fiberoptic bronchoscopy) the virus may be transmitted at a greater distance [17, 19]. Although SARS-CoV-2 also can be potentially transmitted over such longer distances via an airborne route, in a nonprocedural setting this would primarily occur in specific scenarios where proximity and viral load are optimized (i.e. sneezing and/or coughing in close contact). The precise extent to which aerosol transmission has contributed to the overall pandemic is uncertain and is not thought to be the major contributor to overall pandemic transmission [17, 20]. Regardless, there are numerous examples suggesting aerosol transmission in some settings and evidence supporting proximity as a key determinant of risk, along with duration of contact, indoor settings (i.e. households, healthcare settings, college dormitories, homeless shelters, detention facilities, superspreader events), and poor ventilation [17, 19, 21].

Direct Surface Contact and Fomites

Early reports of clustered infections from China raised concern of possible surface contact transmission of SARS-CoV-2. Although it is plausible that touching a contaminated surface and subsequently contacting a mucosal surface (the eyes, nose, or mouth) could lead to infection, there is currently no conclusive evidence for fomite or direct contact transmission in humans. Early concerns of events suggesting fomite transmission were circumstantial [22, 23]. In these early reports, individuals using shared facilities (such as elevators and restrooms) proposed either fomite or respiratory transmission in those settings. In a detailed investigation of a large nosocomial outbreak linked to 119 confirmed cases at a hospital in South Africa, fomite transmission was proposed given the separated distribution of cases in multiple wards [22]. However, the hospital did not have a universal mask policy, lacked adequate ventilation, and had a substantial burden of infection among health care workers. As a result, respiratory transmission from infected staff could not be excluded [24]. Among healthcare workers, poor hand hygiene has been shown to be associated with increased risk for infection with SARS-CoV-2. Although this might suggest increased risk for contamination via direct contact or fomite spread, it is difficult to separate this from other hygienic practices. As will be discussed in subsequent sections, hand hygiene precautions have been shown to be highly associated with practices that decrease risk overall (mask wearing, ventilation, adequate distancing, etc.) [17]. In addition, providers should always practice good surface hygiene, with the precautions that evidence may provide different conclusions in the future. In short, collective data suggest that live virus persists transiently on surfaces, and although it is beneficial to practice good sanitary hygiene overall, fomites are not thought to be a major route of transmission [17].

Fecal-Oral

SARS-Cov-2 has been detected in nonrespiratory specimens, including stool, blood, ocular secretions, and semen, but their role in infection also appears to be minimal. Fecal-oral transmission was theorized early in the outbreak because of the known high concentration of ACE2 receptors in the small bowel [25]. Although viral RNA is commonly detected in stool, live virus has only rarely been isolated. Currently, no evidence supports fecal-oral transmission in humans, and studies with intragastric inoculation of SARS-CoV-2 in macaques did not result in infection [17]. This is supported by an official joint report released by the WHO and China in February 2020 stating transmission through the fecal-oral route did not appear to be a significant contributing factor for viral spread [26].

Bloodborne

Bloodborne transmission was also hypothesized early on, but the proportion of persons with viral RNA detectable in blood is currently unknown and likely very small. An early study found viral RNA in only 3 of 307 blood specimens. However, no replication-competent virus has been isolated from blood samples to this date, and there have been no documented cases of bloodborne transmission [27]. Moreover, there have been documented reports of recipients of platelets or red blood cell transfusions from donors diagnosed with SARS-CoV-2 in which the transfused individuals did not experience COVID-19-related symptoms, nor did they test positive for SARS-CoV-2 [26, 28].

Semen and Vaginal Secretions

Sexual transmission of SARS-CoV-2 was also an initial concern. However, no current evidence supports sexual transmission of SARS-CoV-2 in semen or vaginal fluids. Although viral RNA has been found in semen, infectious virus has not been isolated [29]. In addition, vaginal fluid studies have been negative except for a small number of case reports showing RNA with low viral levels [30].

Asymptomatic Transmission

People who express symptoms convey the highest risk for transmission. However, one of the more insidious aspects of this virus is its ability to spread among individuals who are minimally symptomatic or asymptomatic. Multiple studies have demonstrated that asymptomatic or presymptomatic persons have the ability to spread infection, and this has been well documented throughout the pandemic [31–33]. Some models estimate the proportion of spread attributable to asymptomatic and presymptomatic transmission at greater than 50% [34]. However, it is important to note that the risk for transmission from an individual who is asymptomatic appears to be less than from a presymptomatic individual, who also carries lesser risk than that from one who is symptomatic [33]. The impact of asymptomatic spread on the pandemic is undoubtedly considerable and has led to difficulties in quantitatively tracking exposure in populations. Nevertheless, the concern for undetected spread has shaped policy and national decisions across the globe, forcing implementation of multiple unprecedented global infection prevention measures that will be briefly discussed in later sections.

Virulence and Mortality

Case Fatality Rate

Case fatality rate (CFR) is the total number of deaths from disease divided by the total number of confirmed cases. As of June 2021, there have been 178 180 208 confirmed cases and 3 859 722 deaths worldwide. This estimates the current worldwide CFR to be approximately 2.17%. There are limitations to using CFR as a measure of disease mortality. For example, this number is dynamic, because the denominator and numerator are based on documented cases and deaths and can rapidly change. For example, in the earliest stages of the outbreak, the CFR was much higher: 17.3% across China as a whole and greater than 20% in the center of the outbreak in Wuhan [35]. Underreporting of cases, such as from failure to test individuals with mild disease and asymptomatic infection, can greatly inflate the CFR. Conversely, there are concerns that during the rapid spread of disease during a pandemic, the CFR will underestimate disease, because the death counts do not account for any eventual deaths that may occur in the overall pool of cases. Wide variations (estimates ranging from <0.1% to >25%) in CFR can also arise from country to country as a result of extrinsic or societal factors [36]. CFR, furthermore, does not account for differences in age or sex; it is a cumulative population at-risk metric. Nevertheless, this method, along with others, was used to approximate disease mortality and was consistent with the initial CFR reports released from China in the early stages of the pandemic, outside of Hubei Province [36–38].

Serial Interval

In any infectious disease outbreak, the estimation of transmission dynamics is crucial to contain spread in a new area. Of the tools used in such estimations, the serial interval is one of the significant epidemiological measures that help determine the spread of infectious disease. It is required to understand the turnover of case generation and transmissibility of the disease and is defined as the time between which the infector and the secondarily infected show the symptoms, that is, the time interval between the onset of symptoms in the primary (infector) and secondary cases (infected). The estimated serial interval for SARS-CoV-2 is about 4.5–5 days [39].

Reproduction Number/Reproduction Ratio

Reproduction number (R_0) represents the number of people to whom an infected person passes the disease in its next generation, with length of time determined by the serial interval measure of the disease. This value has had wide variability throughout the pandemic. During the COVID-19 outbreak, the initial estimates of R_0 were between 2.0 and 3.0. However, later studies estimated the R_0 to be 3.82, with a mean reported R_0 range of 1.90–6.49 [40]. Importantly, it is estimated that R_0 is higher for certain variants of concern, such as the alpha or delta variants [40]. This increased transmissibility is of great concern as worldwide spread of variants of concern accelerates and more transmissible variants become the dominant circulating strains.

Excess Mortality

Excess mortality is a measure used by epidemiologists and public health experts to assess the overall impact of pandemic disease. Because not all cases and deaths can realistically be reported, this gives practical insight into overall impact. It is defined as the difference in mortality in a given year compared with the average number of deaths over a given number of previous years. In the United States, data from the National Vital Statistics System of the CDC estimated that 545 600–660 200 excess deaths occurred in the United States from 26 January 2020 to 27 February 2021 (Figure 1.2) [42]. The percentage excess mortality is this difference in mortality for a given time period divided by the average mortality in the same designated time frame during previous years. The estimated number of excess deaths peaked during the weeks ending 11 April 2020, 1 August 2020, and 2 January 2021 (Figure 1.2) [41], with approximately 75–88% of excess deaths directly associated with COVID-19 [42, 43].

Globally, it is difficult to accurately estimate the total number of excess deaths. Not all countries have the infrastructure to report nationwide mortality accurately and expeditiously, and representation from poorer countries is underreported. Keeping in mind these limitations, the WHO estimates, in 2020, a worldwide excess mortality of more than 1.8 million deaths attributed directly to COVID-19, with unofficial total pandemic deaths totaling more than 3 million people [43].

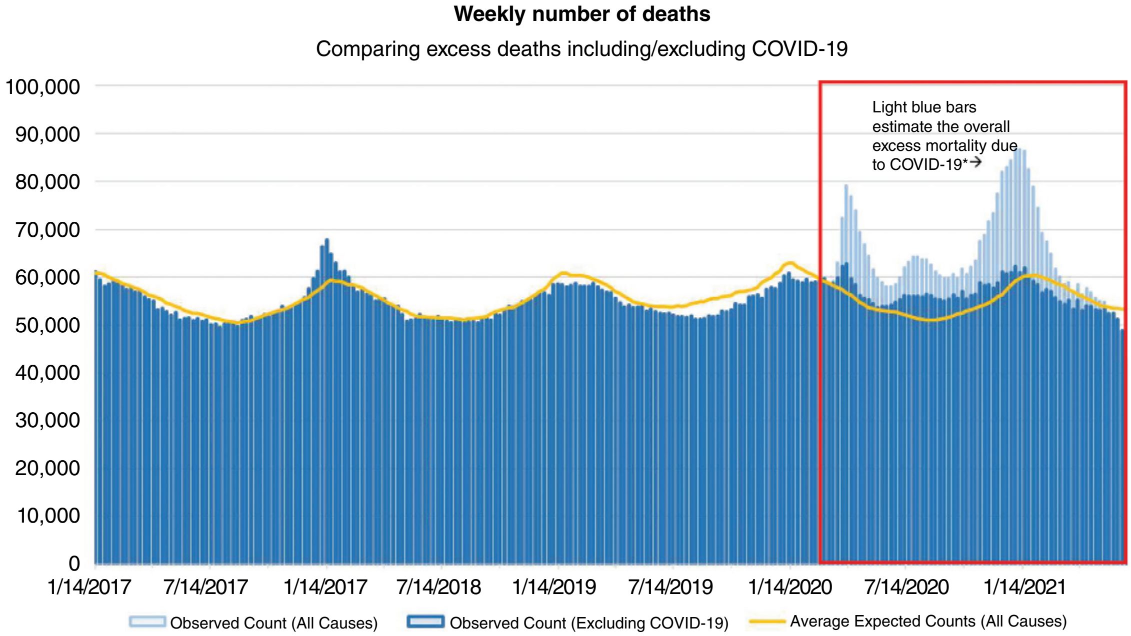

Figure 1.2 Excess mortality counts by week for observed all-cause mortality and observed mortality excluding COVID-19 (1 January 2017 to 1 July 2021). Overlaid trend line is average expected counts based on previous year trends. Red box: Counts may be incomplete because only 60% of death records are submitted to National Center for Health Statistics (NCHS) within 10 days of the date of death, and completeness varied by jurisdiction (1 February 2020 to 26 June 2021). *Number of deaths reported is the total number of deaths received and coded as of the date of analysis and does not represent all deaths that occurred in that period. Data are possibly incomplete because of the lag in time between when the death occurred and when the death certificate was completed, submitted to NCHS, and processed for reporting purposes. *Source:* Data are from the US Centers for Disease Control and Prevention [41].

Demographics

Overview

SARS-CoV-2 has shown the ability to infect all ages, races, and ethnicities across the globe. Notably, COVID-19 disproportionately affected different groups of individuals, with age, race, sex, and medical status all conferring varying levels of morbidity and mortality. In the United States, the virus has infected young adults most often. Elderly individuals (>65 years of age) were among the most vulnerable populations in terms of mortality [44]. Underlying comorbidities, immunocompromised status, and non-white race all are risk factors for progression of SARS-CoV-2 infection to more serious disease. In the United States, the most frequent comorbidities listed on death certificates of those with COVID-19 are influenza and pneumonia (45.8%), hypertension (19.8%), diabetes (16.0%), Alzheimer disease (13.5% of deaths), and sepsis (9.6%) [44].

Age

Data from the CDC, as well as other public health agencies around the world, demonstrated the ability of SARS-CoV-2 to infect individuals of all ages. Age groups for the CDC were reported in nine categories (Table 1.1). The overall trend showed that young adults make up most cases, with elderly individuals comprising the majority of deaths despite being a smaller percentage of the overall population (Figure 1.3). Most of these deaths occurred in those 85 years and older [45–47].

Table 1.1 CDC COVID-19 case and death percentages, by age, with respective percentages of the US population (data through July 2021).

Age group	Percent (%) of cases	Percent (%) of deaths	Percent (%) of US population
0–4 yr	2.1	<0.1	6
5–17 yr	10.4	0.1	16.3
18–29 yr	22.5	0.5	16.4
30–39 yr	16.4	1.2	13.5
40–49 yr	14.8	3.0	12.3
50–64 yr	20.2	15.3	19.2
65–74 yr	7.4	21.6	9.6
75–84 yr	3.8	27.4	4.9
≥85 yr	2.2	30.9	2

Of the 27 472 068 cases recorded, age group was available for 27 281 478 (99%) cases. Of the 495 907 deaths recorded, age group was available for 495 867 (99%) deaths.

Sex

Sex demographics reported by the CDC showed that females made up a slight majority (52.2%; males, 47.8%) of COVID-19 cases in the United States (Table 1.2) [45]. Worldwide, there was no significantly observed sex difference in proportion of COVID-19 cases [48]. Interestingly, in the United States, although COVID-19 affected more females than males, mortality disproportionately affected males, who account for approximately 54.2% of all COVID-19 deaths, with females comprising about 45.8% (Figure 1.4) [45]. This trend was also seen in other parts of the world [49]. It is unclear what drives this disparity, but the cause appears to be multifactorial [50–52].

Race and Ethnicity

Sadly, racial and ethnic disparities were apparent throughout the pandemic. Inadequate early prevention measures, testing, and social support and the need to work outside of the home disproportionately affected vulnerable and marginalized populations. This was very well displayed in data obtained from the Los Angeles Department of Public Health in California, where Hispanics were shown to be more than 2.5 times more likely to be infected with COVID-19 (Figure 1.5) than their white peers. Notably, the age-adjusted mortality rate for Hispanics from COVID-19 was more than three times greater than for non-Latino whites (Figure 1.6). For perspective,

Table 1.2 CDC data of COVID-19 deaths by sex (all age groups).

Sex	Percent (%) of cases	Percent (%) of deaths	Percent (%) of US population
Female	52.2	45.8	50.75
Male	47.8	54.2	49.25
Other	<0.1	<0.1	Not available

Data as of July 2021. Of the 495 907 deaths recorded, sex was available for 494 710 (99%) deaths.

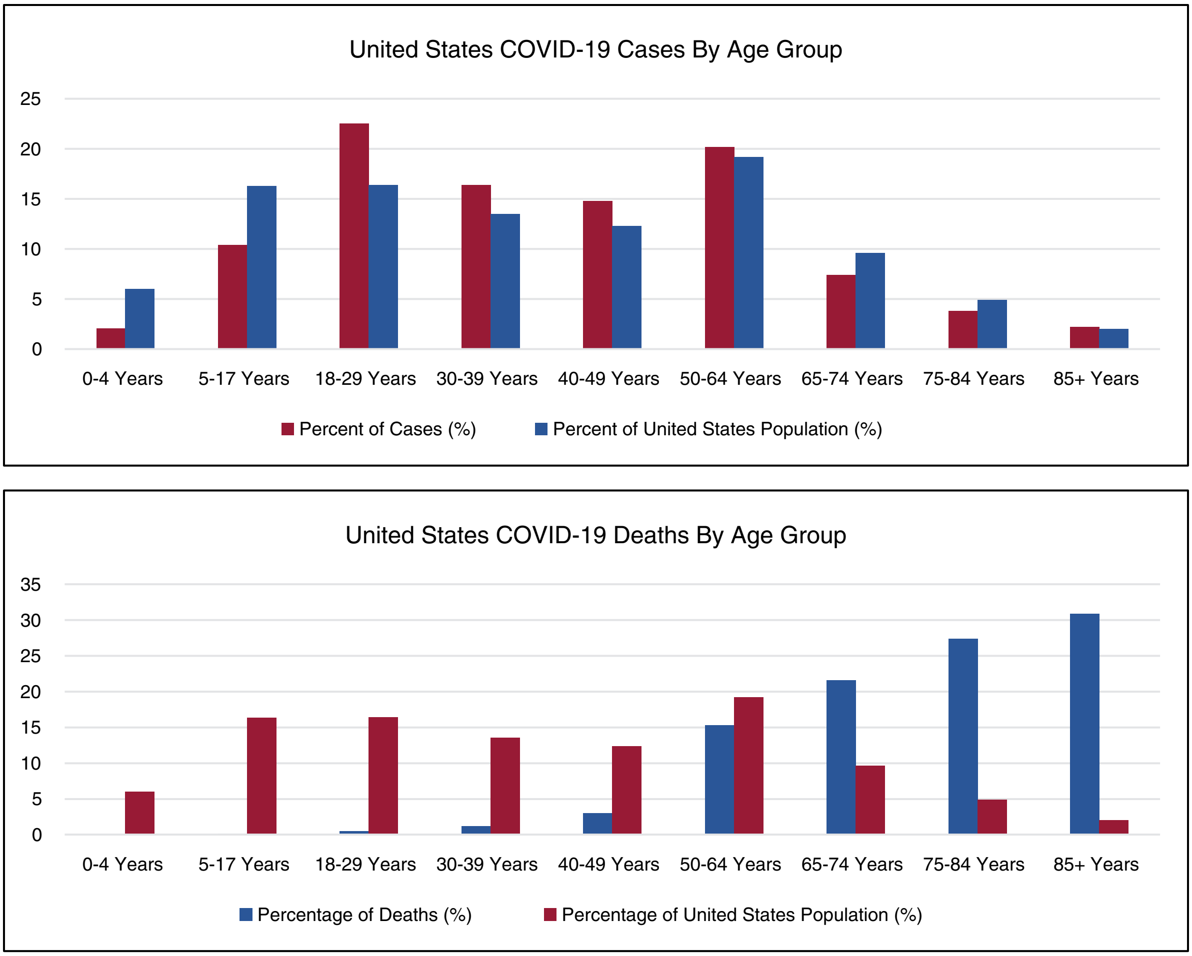

Figure 1.3 Case and death count distribution by age with corresponding percentage of US population for each respective age group. *Source:* Graph data are from the US Centers for Disease Control and Prevention [45].

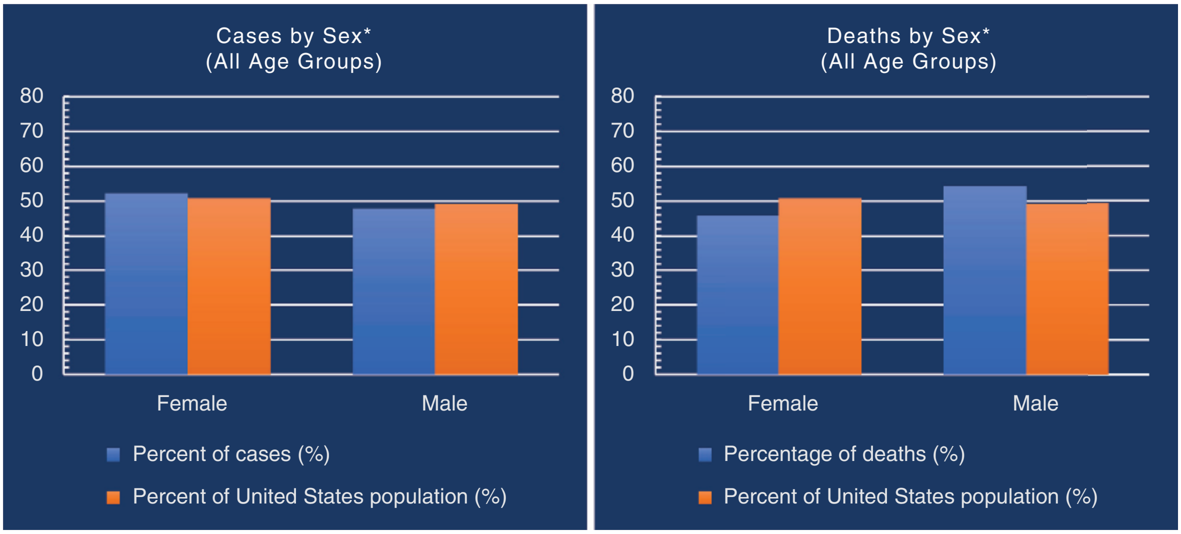

Figure 1.4 US COVID-19 cases and deaths for males and females for all age groups. *Those who were listed as "other" constituted less than 0.001% of cases, and deaths are not graphically represented here. *Source:* Case and mortality data from the US Centers for Disease Control and Prevention [45]. Data are as of July 2021.

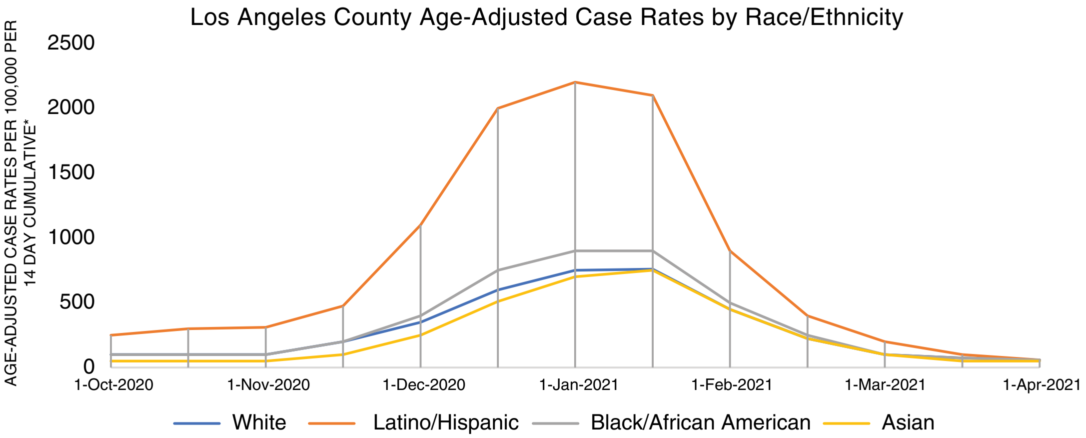

Figure 1.5 Los Angeles County age-adjusted COVID-19 case rate per 100 000 individuals by race/ethnicity, April 2020 to June 2021. *Data are estimated reported data from the Los Angeles County Department of Public Health and do not necessarily reflect exact amounts.

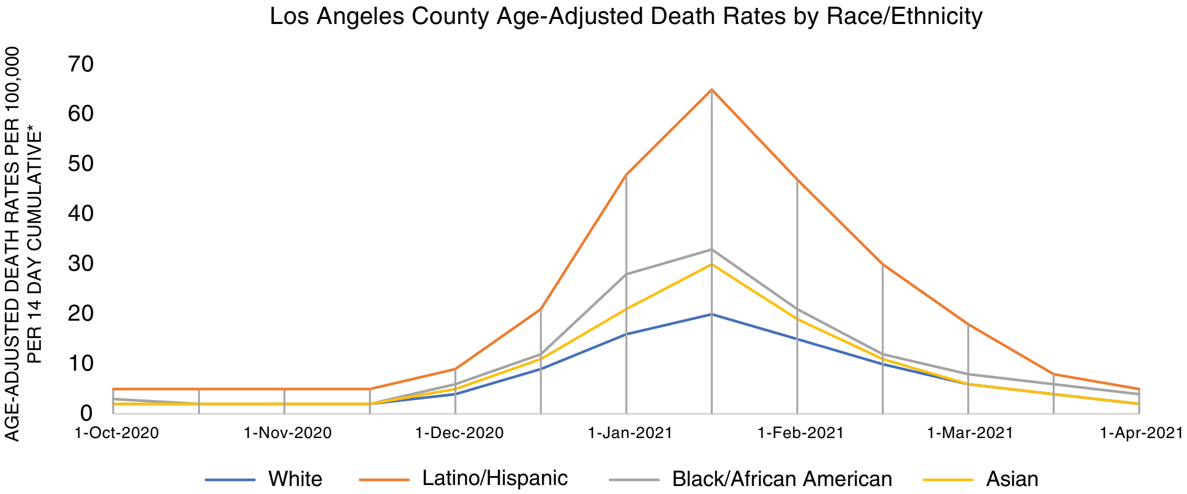

Figure 1.6 Los Angeles County age-adjusted mortality rate per 100 000 individuals by race/ethnicity, April 2020 to June 2021. *Data are estimated reported data from the Los Angeles County Department of Public Health and do not necessarily reflect exact amounts.

in 2020, COVID-19 became the leading cause of death in Los Angeles for Latino/Hispanics (where they account for 49% of the total population), outpacing mortality rates from heart disease, cancer, and diabetes [53].

In terms of the US population overall, crude data demonstrated that non-Hispanic whites accounted for the greatest percentage of morbidity, comprising approximately 50% of cases, with Hispanic and non-Hispanic blacks following at 29% and 11%, respectively (Table 1.3). However, when considering race-respective population percentages, Hispanics and non-Hispanic Blacks have been disproportionately affected in terms of disease morbidity and mortality, with both respective mortalities outpacing their proportions of the population (Figure 1.7) [54–56]. Furthermore, additional studies have reported that American Indian or Alaska Native, non-Hispanic persons were also disproportionately affected and more likely to be infected, hospitalized, or die with COVID-19 in comparison with their white counterparts [55–57].

Table 1.3 CDC data of COVID-19 cases by race/ethnicity.

Race/ethnicity	Percent (%) of cases	Percent (%) of deaths	Percent (%) of US population
Hispanic/Latino	28.7	18.6	18.45
American Indian/Alaska Native non-Hispanic	1	1.2	0.74
Asian non-Hispanic	3.2	3.8	5.76
Black non-Hispanic	11.4	13.7	12.54
Native Hawaiian/Other Pacific Islander non-Hispanic	0.3	0.2	0.182
White non-Hispanic	50.1	58.6	60.11
Multiple/other non-Hispanic	5.3	3.8	2.22

Data as of July 2021. Of the 27 472 068 recorded cases, race/ethnicity was available for 17 382 837 (63%) cases.

Disease Prevention

Vaccinations

One year into the pandemic, vaccination-based prevention was developed and implemented. Numerous vaccines are currently in development, and several have been approved for official use. These largely fall under four technology categories: adenovirus vector vaccines, inactivated viral vaccines, protein subunit vaccines, and messenger RNA (mRNA) vaccines. Following is a brief overview of the more notable vaccines; these and others will be covered in greater detail elsewhere in the text.

Viral vector vaccines use a modified, nonreplicating virus that is taken up and processed by human cells, expressing a viral protein, generating an immune response. Several different viruses have been used as vectors, including influenza, vesicular stomatitis virus, measles virus, and human and nonhuman primate adenoviruses. This technology has been used historically to develop vaccines for many diseases, including malaria, Ebola, leishmaniasis, HIV, tuberculosis, and the common cold [58, 59]. Currently, the adenovirus vector technology has been used to produce publicly available SARS-CoV-2 vaccines, most notably, the Oxford–AstraZeneca and the Johnson & Johnson vaccines [60, 61]. The two-dose Russian Sputnik adenoviral vaccine has shown similar high efficacy [62].

Inactivated or weakened virus vaccines use a form of the virus that has been inactivated or weakened, so it does not replicate or cause disease but still contains sufficient cellular signals to generate an immune response. A caveat to this is that these vaccines typically do not provide as strong an immune response (protection) as live vaccines, so several doses may be required over time (booster shots) to obtain ongoing immunity against diseases [60]. Sinopharm (BBIBP), CoronaVac (Sinovac), and Covaxin are all examples of vaccines that use this technology. These are largely used internationally in countries throughout Asia and Latin America; currently, they have not been approved for use in the United States.

Protein-based vaccines use fragments of proteins or protein shells that mimic viral antigens to generate an immune response, which is enhanced by coformulation with an adjuvant substance. The antigen can be any molecule, such as structural proteins, other peptides, or polysaccharides. Like inactivated vaccines, the vaccine is completely “dead,” that is, replication incompetent, and therefore may be less risky [60]. Vaccines that have historically used this technology include the hepatitis B vaccine. Currently, the vaccines against COVID-19 that implement this technology include the Novavax NVX-CoV2373 vaccine, the Sanofi-GSK adjuvanted protein subunit vaccine Vidprevtyn, the Russian EpiVacCorona (Vector), and the Chinese RBD-Dimer (Anhui Zhifei Longcom and the Institute of Medical Biology of the Chinese Academy of Medical Sciences). The latter two are exclusively used in Russia, China, Turkmenistan, and Uzbekistan [60].

mRNA vaccines are a cutting-edge approach that use genetically engineered RNA to synthesize a structural protein and generate an immune response. Although

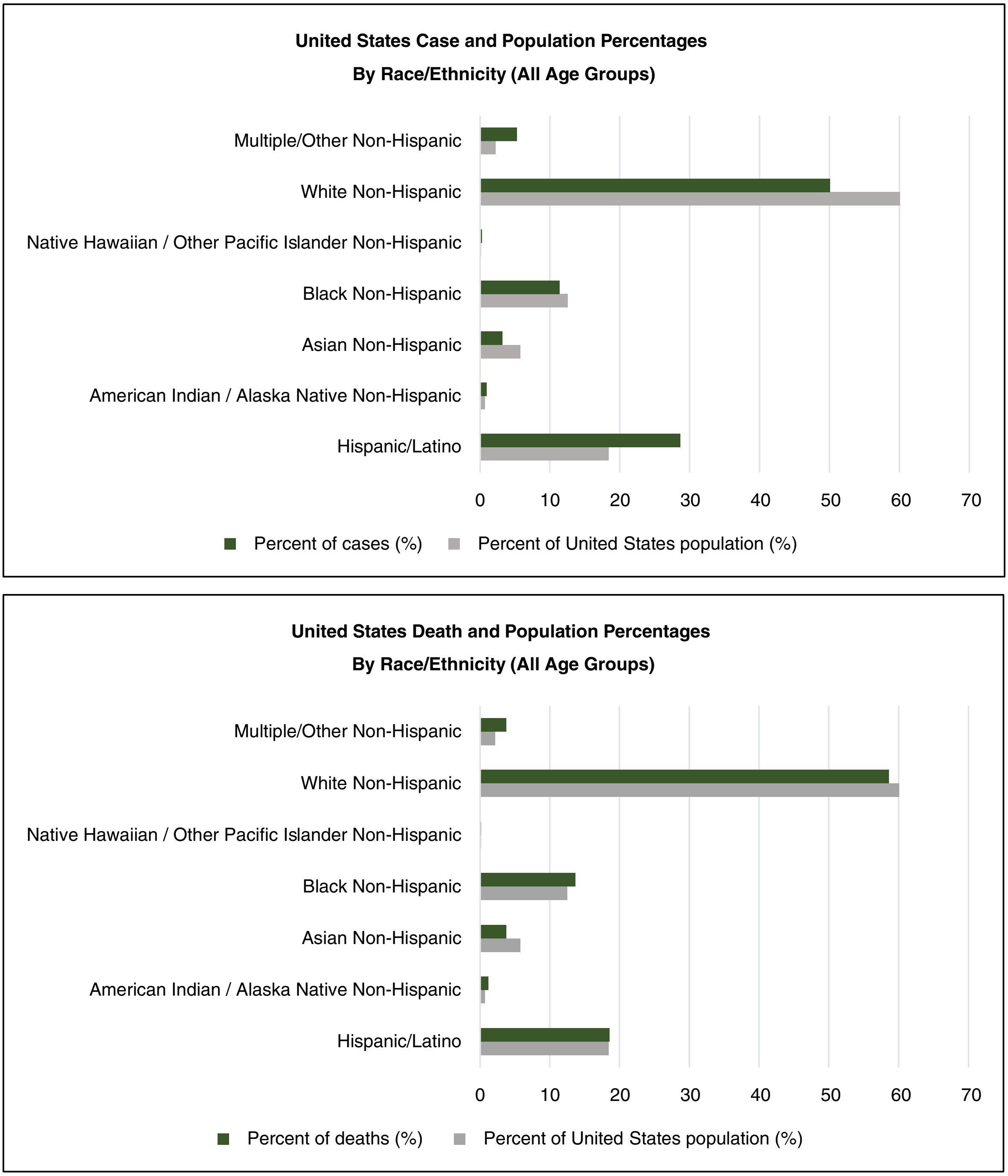

Figure 1.7 Case and death percentages by race/ethnicity with corresponding percentage of US population for each respective group. *Source:* Data are from the US Centers for Disease Control and Prevention [45]. Data are as of July 2021.

this is a relatively new method in the arsenal of vaccine development, this technology has been studied for at least a decade before this specific application, so the science is well understood. mRNA segments coding for the coronavirus spike protein are introduced into the body through an intramuscular injection to trigger an immune response. Using a protective lipid nanoparticle coating, these particles are taken up by cells, processed, coded for synthesis of spike protein, and presented to the immune system, triggering a humoral and a cellular immune response. The Pfizer-BioNTech and Moderna vaccines are examples of this technology and are the main vaccines used by the United States and many countries throughout Europe. These vaccines were approved by the US Food and Drug Administration for Emergency Use Authorization on 11 December 2020 for Pfizer and on 18 December 2020 for Moderna [60, 63]. The Pfizer vaccine received full US Food and Drug Administration approval on 23 August 2021.

The goals of vaccination are grounded on two key concepts: bolstering individual immunity to prevent severe disease and hospitalization and to limit population-wide spread. "Herd immunity" is an indirect form of protection resulting from enough individuals obtaining immunity, via vaccination or infection, to the point where it minimizes further disease circulation within a population. This threshold varies from pathogen to pathogen. Herd immunity to SARS-CoV-2 has been estimated, giving circulating strain considerations, to require immunity in approximately 70–80% of the population. However, this number will increase as newer variants arise with higher R_0 and increased transmissibility [64].

For many viruses, the more it circulates in a population, the more opportunities it has to replicate and/or mutate; SARS-CoV-2 has demonstrated this ability [65]. These mutations have the potential to produce more transmissible and more virulent strains of SARS-CoV-2. For example, the 501Y mutation (present in the B.1.1.7 or alpha variant) and the L452R mutation (present in the B.1.617.2 or delta variant) are both associated with higher levels of transmissibility [66]. Fortunately, preliminary reports of current vaccine effectiveness have demonstrated protection, albeit reduced, to such variants and emphasize their need against more virulent strains [67].

The importance of vaccines cannot be understated. Successful historical examples, such as the polio, measles-mumps-rubella, and smallpox vaccines, have underscored the profound importance of this technology in achieving herd immunity. Vaccine-mediated herd immunity is an essential tool in public health and directly protects vulnerable populations with lesser vaccine responsiveness (i.e. elderly adults, individuals with chronic disease, and immunocompromised persons). The alternative "natural immunity" method would be impractical. Although preventing circulation of virus through naturally acquired herd immunity would occur eventually, it would also result in unnecessary cases and deaths and has possibly been achieved only in close situations such as prisons [68].

Current COVID-19 vaccinations have been shown to not only decrease viral load but also decrease risk for asymptomatic transmission [69–71]. However, emerging variants have the potential to escape some of these benefits of vaccination. Reducing transmission via vaccination carries important implications for reopening and shaping public health guidelines going forward, as the CDC and national governments relax recommended prevention measures for vaccinated individuals [72]. This is a monumental finding because, as mentioned in previous sections, SARS-CoV-2 and its variants carry significant mortality and disproportionately affect the marginalized and the disadvantaged [73]. Given the availability and promising results of this technology, immunity via natural circulation of the virus would be not only medically irresponsible but also potentially morally unacceptable.

Personal Protective Equipment: Respirators and Masks

In the United States, hospitals are required to provide personal protective equipment for staff working with patients with suspected or confirmed COVID-19, which includes the use of a gown, gloves, a respirator or medical mask, and eye or face protection for preventing transmission. N95 masks confer the greatest protection, especially in conditions of greater patient aerosolization, such as during aerosol-generating procedures and certain types of environmental cleaning. However, in the event that N95 masks are not available or are in limited supply, surgical masks are acceptable in many hospital settings [72, 74, 75].

In the community, mask wearing with social distancing as an alternative to widespread lockdown was officially endorsed by the CDC in March 2020. The CDC subsequently issued a mandate requiring masks on public transportation and areas or times of gatherings (including taxis and rideshares) and at transportation hubs (e.g. airports, bus or ferry terminals, railway stations, seaports) [76]. The rationale for community mask wearing is, regardless of symptoms, preventing transmission while maintaining the day-to-day functions for individuals and the country. In the United States, cloth masks or disposable masks (e.g. commercially available surgical masks) were recommended for the general public or in public settings with individuals outside the household to reduce transmission of SARS-CoV-2. In addition, guidance criteria for approved homemade masks were given to the public, stating that masks should be made with several layers, fit snugly over the face, and should not contain respiratory valves [74, 76].

Strategies to improve mask fit include using a mask with an adjustable nose bridge, wearing a cloth mask over a disposable mask, knotting the ear loops of a disposable mask to secure it against the face, using masks with ties rather than ear loops, and using a mask brace. Some individuals may opt to wear commercially available KN95 respirators, but many do not meet the advertised filtration standards. Furthermore, due to necessity in the healthcare setting, N95 respirators are not indicated or necessary for the general public and should generally be reserved for healthcare workers who work in higher-risk environments [74, 75].

Physical Distancing

In the effort against COVID-19 spread, countries across the globe used various physical distancing measures to keep clustering of individuals to a minimum. This included, but was not limited to, limiting the number of individuals in closed spaces, temporarily shutting down schools and universities, and limiting the number of people during indoor shopping, gymnasium use, personal services (e.g. hair cutting, manicures), and dining.

Distancing guidelines were implemented to minimize prolonged close-range contact with an infected individual, which, as previously mentioned, is thought to be the principal risk factor for transmission of SARS-CoV-2. This method was taken from previous data preventing SARS and MERS infections. In a meta-analysis of observational studies evaluating the relationship between physical distance and transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV, proximity and risk for infection were closely associated, and the infection rate was much higher with contact within 3 ft (1 m) compared with contact beyond that distance (12.8% versus 2.6%) [77].

Optimal distance is uncertain, but physical distancing is likely independently associated with a reduced risk for SARS-CoV-2 transmission. Current guidance suggests at least 6 ft. In the United States, the CDC recommends a minimum distance of 6 ft (2 m), whereas the WHO recommends a minimum distance of 1 m. In locations where there is community transmission of SARS-CoV-2 (including throughout the United States), individuals are advised to practice social or physical distancing in both indoor and outdoor spaces by maintaining a minimum distance from other people outside their household.

Widescale shelter-in-place orders and lockdowns were the most aggressive form of these distancing methods. During peak outbreaks, when daily case rates and deaths were the highest, governments strongly encouraged or required individuals to quarantine inside their homes, only leaving for necessities such as food and other items. Although one of the most controversial forms enacted by prevention taskforces, given societal and mental health considerations, studies can speak to the impact of distancing on viral transmission. One such study involving multiple countries showed a significant decrease in viral transmission when individuals were distanced 1 m or more from each other. Moreover, protection was increased as the distance was lengthened [77]. Other studies have shown that, after cases began to emerge, longer time periods for which countries waited to implement quarantine measures were associated with greater CFRs [78].

Hand and Surface Sanitation

Inanimate surfaces may be potential sites for the transmission of COVID-19 infection. Depending on the nature of the surface and conditions of the surrounding environment (temperature, pH, humidity, etc.), the virus can remain viable for several hours [78]. Concern mainly stems from potential contaminated surfaces contacting hands, which then pass the virus to upper respiratory tract mucous membranes (conjunctivae, nose, mouth, etc.) through touch. Although surface contact spread is only theoretical and has not been definitively documented, studies have shown that SARS-CoV-2 has extended longevity on certain surfaces and through skin-to-skin contact [79, 80]. The US Environmental Protection Agency recommends disinfectants that contain quaternary ammonium compounds, hydrogen peroxide, alcohol (ethanol, isopropyl alcohol, phenol), aldehyde, hypochlorous acid, octanoic acid, citric acid conjugate with silver ions, sodium hypochlorite, sodium bicarbonate, etc., all of which contain key virucidal activity. Specifically, alcohols ethanol (78–95%) and isopropanol (70–100%) have been used as reliable and relatively safe disinfectant options because they show potent virucidal activity with a negligible toxic effect on human skin [81]. In autopsy studies, SARS-CoV-2 remained viable on the skin for about nine hours but was completely inactivated within 15 seconds of exposure to 80% alcohol [81].

Adequate Ventilation of Indoor Spaces

A healthy amount of literature emphasizes the importance of air quality and ventilation in the healthcare setting. There is substantial evidence, drawn from prior studies on pandemics, that emphasizes an effective combination of air filtration and circulation can reduce risk for infection. However, much of the data surrounding ventilation and SARS-CoV-2 infection are model based, drawing conclusions from theoretical scenarios and calculated behaviors of similar-size microbes. Using the Wells–Riley equation, a study implementing calculated risk associated with various rates of ventilation concluded a significant theoretical reduction in COVID-19 infection risk with adequate ventilation of an enclosed space. Furthermore, these beneficial effects were compounded by those who concurrently wore a medical-grade mask [82]. A large literature review addressing air recirculation also drew on historical examples and the behavior of similar microorganisms to frame the need for adequate ventilation and concluded that specific filters and air ventilation flow rates can lead to lower viral air concentrations and a decreased risk for exposure and transmission of virus [83]. Although conclusions of ventilation effects on SARS-CoV-2 transmission are largely drawn from historical and theoretical models, they nonetheless highlight the need for improved air circulation to lower airborne viral concentrations and decrease the risk for transmission.

Use of Outdoor Spaces

Where possible, use of outdoor spaces can further reduce aerosol transmission [84]. Outdoor spaces typically offer greater physical distancing and airflow than indoor spaces. Relatively few SARS-CoV-2 transmissions have been linked to outdoor setting [85]. Although outdoor transmission can occur, and the precise settings in which this can be minimized are still being investigated, the odds of indoor transmission have been shown to be significantly greater [86]. Limiting the duration and frequency of personal contact, using personal protective equipment, and avoiding any indoor contacts may increase the safety of outdoor gatherings [84].

Global Impacts

Distribution

At the time that this was written, the WHO had estimated the total confirmed counts to be more than 200 million cases worldwide, with more than 4 million deaths. As discussed previously, these are confirmed cases only, such that the number of cases (i.e. overall disease burden) has likely been underreported [43]. Geographic distribution is worldwide, as cases have been found in nearly every country. The countries that had the highest disease burden were the United States of America, India, and Brazil. In terms of mortality, the countries with the highest mortality burden were the United States of America, Brazil, India, and Mexico [83].

International Response

This begs the questions, what countries had the most success against the COVID-19 pandemic, and why were they successful? Conversely, what was common among those who were not? There is a public health consensus that limiting the number of contacts between persons can slow COVID-19 transmission in a community and give time for healthcare systems to respond and vaccines to be developed. Factors such as population density, leadership, national wealth, infrastructure, and equitable healthcare resources influence a nation's capacity to do so [87].

Before vaccination, the most meaningful approaches governments took to stop community spread were stay-at-home-orders. These guidelines requested or required people to quarantine in their homes, to leave only for absolute necessities, such as food and healthcare needs [88]. Although there are multiple theoretical and practical models about how stay-at-home orders and travel restrictions slowed COVID-19 transmission, it is clear that consistency in communication and early implementation were key [89]. Retrospective data show that a longer amount of time before implementation of physical distancing measures was associated with worse CFRs [77]. Widespread testing efforts were valuable in the identification of cluster outbreaks. South Korea is a good example of the impact of early and effective measures, in which large-scale testing efforts in combination with contact tracing and social distancing measures led to one of the most successful pandemic responses in the world [90, 91]. Countries such as New Zealand succeeded by enacting strict border control. Of course, having the wealth and resources to accommodate such a large and rapid disease response is crucial to improving individual and population outcomes. Countries with an adequate physician workforce and technological capacity to accommodate pandemic-level crises were able to detect disease earlier and fared better in terms of overall mortality [77].

Future Outbreaks

Global trade, travel, climate change, urbanization, and national wealth all play a part in global infrastructure and the ability to address worldwide pandemics. Lessons learned over the course of the COVID-19 pandemic, compiled from multiple national responses, have created a type of framework, or a "pandemic playbook," in which governments and public health agencies can model policy to stave off future pandemic emergencies. Such a pandemic playbook has previously been proposed by the CDC to help coordinate pandemic influenza response [92]. This includes, but is not limited to, concepts such as swiftly tightening international borders to travel and trade, supervised traveler isolation and well-coordinated quarantines, early implementation of physical distancing requirements, encouraging good hand hygiene (frequent handwashing, use of alcohol hand sanitizers as an alternative, cough etiquette), and having the infrastructure for quick and widespread testing and contact tracing [91, 93]. In addition to these policies, nations must also possess the capacity to provide social supports in the future, to provide mental health services, adequate resources, and economic assistance to those in need. This is obviously a more attainable goal for wealthier countries, but nevertheless, it is imperative that nations and their leaders come together and offer mutual aid in times of crisis. Sharing of wealth, information, resources, intellectual property, and financial support are all necessary to maximize the safety and well-being of citizens.

Conclusions

This novel SARS-CoV-2 virus was unique in many ways. An insidious, yet defining, characteristic of this disease was its ability for asymptomatic spread. Without efficient widespread testing measures, we saw a virus, seemingly isolated to a limited region of China, stretch to every corner of the globe in a matter of months. In coordination with international leaders, our global health institutions developed guidelines to help contain spread, including isolation, mask wearing, hand hygiene practices, and nationwide shutdowns of business and mass gatherings. However, the aftermath of the outbreak cannot be ignored; shortcomings must be addressed. Hospitals quickly filled to capacity, and we saw our healthcare infrastructure woefully ill-equipped to handle the volume of individuals affected by this disease.

Indeed, the pandemic has revealed shortcomings in our health systems, notably highlighting, in the United States, the systemic racial and economic inequities that plague them. Moreover, this virus has profoundly reshaped how we must think about global public health and emphasizes the magnitude of work needed to be done. This pandemic illness has forced us to reevaluate our approach to disease epidemiology, outbreaks, and how further progress can be made under these new norms. Conversely, we have also seen the capacity for global coordination in an unprecedented time frame. Massive mobilization of manufacturing, testing resources, healthcare workforce, and biomedical engineering allowed us to address the novel challenges of the pandemic. It is essential for us to build on this progress, for the sake of the most affected dense and poor populations around the world. Our institutions, physicians, and healthcare leaders must take the lessons from this unprecedented event to facilitate change with decisive action and prevent any future catastrophes like the COVID-19 pandemic from occurring again.

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