

# COVID-19: A Risk Assessment Perspective

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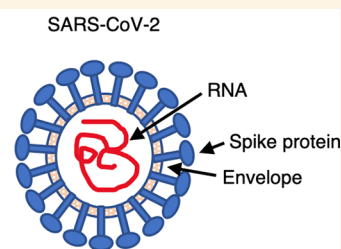
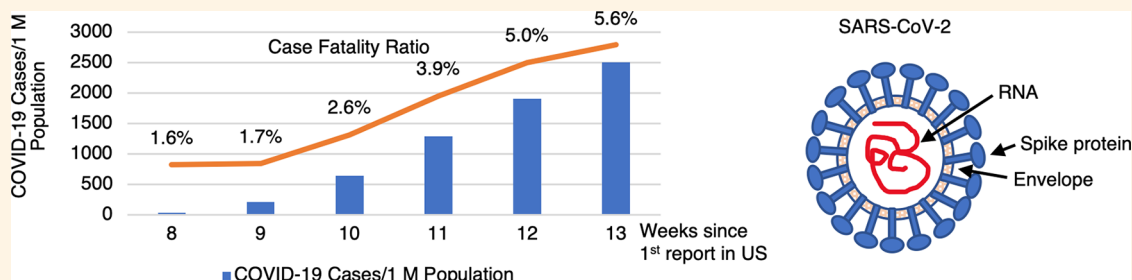
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**ABSTRACT:** COVID-19 is a newly emerging viral respiratory disease first identified in Wuhan, China, in December 2019. The disease is caused by the coronavirus SARS-CoV-2, which is related to the viruses that cause SARS and MERS. While the case fatality ratio for COVID-19 (5%) is far lower than that for SARS (11%) and MERS (34%), COVID-19 is spreading relatively uncontrolled at this time across the globe. In contrast, SARS appears to be contained, and MERS is controlled. This paper will explore why COVID-19 is able to progress to a global pandemic that affects our daily lives to an extent not known in recent history. The COVID-19 outbreak and spread will be examined based on the current literature, using a researcher's perspective of risk assessment and risk mitigation; this approach will be related to public health.

**KEYWORDS:** COVID-19, SARS-CoV-2, risk assessment, risk mitigation, pandemic

## INTRODUCTION

The first cases of COVID-19 became known in mid to late December when a clustering of patients with unusually severe respiratory disease was noticed in Wuhan, the capital of China's Hubei province, a city with roughly 11 million inhabitants. On December 31, 2019, China informed the World Health Organization (WHO), and the world took notice for the first time. While the Chinese government began to take restrictive actions to curb the spread of the virus, most people in the rest of the world did not comprehend then that this disease would change our daily lives as we know it. One might compare the onset of the COVID-19 outbreak with a looming storm and our inability to predict the extent of the storm's severity despite available data. Four months later, by the time this Review was written, COVID-19 was rapidly spreading out of control with alarming death rates worldwide. The outbreak has led to a global health and economic crisis with countries closing their borders and issuing travel bans, shuttering their schools and businesses, imposing strict quarantines, and more. In short, COVID-19 has posed severe economic strain on the world's economy. Furthermore, life-saving supplies and hospital beds are already limiting in most countries. What causes COVID-19, and why is this outbreak so different from other outbreaks such as SARS and MERS? In addition, why is the COVID-19 disease so difficult to contain?

This paper will address these questions using a risk assessment approach normally used by scientists working with pathogenic organisms or biohazardous materials and apply this approach to public health. Lessons learned from the SARS epidemic and guidelines for pandemics will be reviewed. Why are we so unprepared? In essence, the current COVID-19 pandemic appears to be an ongoing experiment on mitigating practices of a global emergency with broad implications for future health crises.

## LESSONS LEARNED FROM SARS

A coordinated multinational effort was able to contain the 2002 SARS pandemic that had spread to 26 countries. The global cost of SARS associated with economic losses was estimated at \$54 billion.<sup>1</sup> The following summarizes the lessons learned from that outbreak:<sup>2</sup>

- importance of early detection of a disease, surveillance, and effective communication to countries worldwide

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**Table 1. Recent Pandemic and Major Pandemic-Prone Emerging Diseases**

disease	pathogen	worldwide infected	worldwide deaths	case fatality ratio <sup>a</sup>
1918 Influenza pandemic <sup>6</sup>	Influenza A (H1N1)	500 million	>17.4 million (1% <sup>b</sup> )	>2.5%
1957 Influenza pandemic <sup>7</sup>	Influenza A (H2N2)	unknown	1.1 million (0.004% <sup>b</sup> )	<0.1%
1968 Influenza pandemic <sup>8</sup>	Influenza A (H3N2)	unknown	1 million (0.03% <sup>b</sup> )	<0.5%
1981 HIV/AIDS pandemic <sup>9</sup>	HIV	75 million	32 million	100% <sup>c,10</sup>
2002 SARS <sup>11</sup>	SARS-CoV-1	8422	916	11%
2009 Swine Flu <sup>12</sup>	Influenza A (H1N1) pdm09	unknown	151 700–575 400 (0.001–0.007% <sup>b</sup> )	0.1–5%
2012 MERS <sup>13</sup>	MERS-CoV	2494	11 325	34%
2014 Ebola <sup>14</sup>	Ebola virus	28 652	13 562	40%
2018 Ebola <sup>d,15</sup>	Ebola virus	3461	2279	66%
2019 COVID-19 <sup>e</sup>	SARS-CoV-2	2 714 942	190 395	7%

<sup>a</sup>Case fatality ratio (CFR) is the number of deaths/confirmed total cases. <sup>b</sup>Estimated percentage of world population. <sup>c</sup>If untreated; HIV by itself is not lethal, but mortality is caused by secondary infections in immunodeficient patients due to HIV infection. <sup>d</sup>As of 4/2020. <sup>e</sup>As of 4/22/2020, the CFR is the average from 213 countries reporting COVID-19.

- effective communication to the general public to build trust in order to implement various social isolation approaches to slow the spread of a disease
- promotion of research and development of surge capacities for broad-spectrum antiviral drugs and vaccine production
- implementation of surge capacities for healthcare personnel and healthcare facilities
- coordination of such strategies by multinational collaboration

## WHO PANDEMIC GUIDELINES

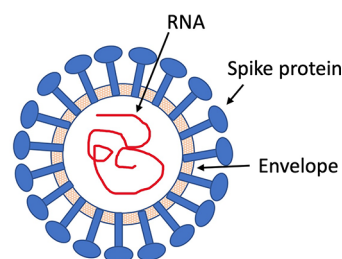
In 2009, the WHO published guidelines for preparing for the next influenza pandemic.<sup>3</sup> In their companion document on preparing the whole society for pandemic readiness, they state: “In the absence of early and effective planning, countries may face wider social and economic disruption, significant threats to the continuity of essential services, lower production levels, distribution difficulties, and shortages of supplies. ... The failure of businesses to sustain operations would add to the economic consequences of a pandemic. Some business sectors will be especially vulnerable (e.g., those dependent on tourism and travel) and certain groups in society are likely to suffer more than others.”<sup>4</sup> What was stated in 2009 equally applies to our currently limited global coordination efforts to curb COVID-19. A concerted global effort is needed to contain COVID-19.

## PANDEMICS AND EMERGING DISEASES

By definition, a pandemic is a disease that has spread from its country of origin, where it is considered an epidemic, to other countries worldwide. The World Health Organization (WHO) considers a pandemic a global illness caused by a new virus. As such, seasonal flu, which is caused by several influenza viruses having caused outbreaks previously, including those listed in Table 1, is not considered a pandemic disease. Table 1 lists some of the major emerging and re-emerging epidemics and pandemics in the 20th and 21st centuries to illustrate the constant threat that these types of diseases pose to the global population. It should be pointed out that the 1918 Influenza pandemic also known as the Spanish flu occurred before the discovery of antibiotics, and many deaths are now attributed to secondary bacterial infections.<sup>5</sup> Improvements in healthcare and the development of life-saving procedures and vaccinations have greatly reduced the number and outcomes of flu pandemics. Furthermore, epidemiological studies have provided guidance on how to limit the expansion of new diseases into pandemics.

## SARS-COV-2 VIRUS AND RELATED VIRUSES

SARS-CoV-2 is the causative agent of the coronavirus disease 2019 also termed COVID-19. It is an enveloped RNA virus, meaning it stores its genetic information as RNA packaged inside an envelope (see Fehr and Perlman for review on coronaviruses, Figure 1).<sup>16</sup> The envelope is composed of the



**Figure 1.** Schematic diagram of SARS-CoV-2. The virus consists of a phospholipid-bilayer, or envelope, which encloses the RNA genome. Spike proteins are embedded in the envelope.

host cell’s membrane and is decorated with viral proteins. The most prominent of the viral proteins, the spike protein, emanates from the infective virion (virus particle) giving it a crownlike appearance which has given this virus family the name coronaviruses. The spike protein serves to recognize and attach to the host cell’s receptor proteins and facilitates entry into the cell. Once inside the cell, the virus propagates by recruiting the host cell’s enzymes to produce numerous viral precursors. Mature virions are then released from the host cell’s surface by exocytosis.

The RNA sequence of SARS-CoV-2 became available in early January 2020 and revealed several important facts.<sup>17,18</sup> First, SARS-CoV-2 is a coronavirus very closely related to two coronaviruses found in Chinese bats (>99% and 98% sequence identity).<sup>17</sup> This finding explains why scientists believe that SARS-CoV-2 originated from a bat virus. Second, it is also related to SARS-CoV-1 (about 79%), which caused the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002, and more distantly to MERS-CoV (about 50%), which caused the Middle East Respiratory Syndrome (MERS) outbreak in 2012.<sup>17</sup> Third, RNA sequence comparison and protein modeling found that the domain of the spike protein that attaches the virus to the host cell receptor does so in a manner similar to that of SARS-CoV-1.<sup>17</sup>

Host cell invasion assays revealed that both viruses indeed recognize the human angiotensin-converting enzyme 2 (ACE2)

Table 2. Risk Group Assignments According to the NIH Guidelines<sup>24,25a</sup>

risk group	definition	examples
1	Agents that are not associated with disease in healthy adult humans. This group includes a list of animal viral etiologic agents in common use. These agents represent no or little risk to an individual and no or little risk to the community.	<i>Escherichia coli</i> K-12, nonpathogenic “wild-type” bacteria constituting <1% of human gut microbiome; derivatives are used for genetic manipulations in the laboratories.
2	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available. These agents represent a moderate risk to an individual but a low risk to the community.	<i>Escherichia coli</i> O157 causing severe diarrhea and death, antibiotic treatment is available; <i>Bordetella pertussis</i> causing whooping cough with associated death; antibiotic treatment and vaccination is available.
3	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available. These agents represent a high risk to an individual but a low risk to the community.	<i>Mycobacterium tuberculosis</i> causing tuberculosis; lengthy antibiotic treatment; no reliable vaccine is available; SARS-CoV-1 and MERS-CoV causing severe respiratory syndrome with high mortality; no vaccination and no effective treatment is available.
4	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available. These agents represent a high risk to the individual and a high risk to the community.	Ebola virus causing hemorrhagic fever associative with high mortality; while a vaccine for Ebola is now available (but not worldwide applied), an effective treatment is not.

<sup>a</sup>The reference to the healthy adult human population indicates that individuals outside this group can suffer greater adverse consequences.

as their target cell receptor for subsequent cell entry.<sup>19</sup> ACE2 is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels where it hydrolyzes the vasoconstriction hormone angiotensin II to angiotensin 1–7. Angiotensin 1–7 acts as a vasodilator, thus increasing blood flow and reducing blood pressure. Those individuals with hypertension are likely familiar with ACE-inhibitors such as lisinopril or the angiotensin receptor blocker losartan that inhibit the production of angiotensin II or block binding of angiotensin II to its receptor proteins, respectively. The expression of ACE2 was found to be increased in response to administration of ACE inhibitors, angiotensin receptor blockers, and also in response to some anti-inflammatory drugs such as ibuprofen, potentially providing more opportunities for SARS coronaviruses to enter the cell.<sup>20–22</sup> However, more research in this area is needed to produce conclusive results. Using a risk benefit approach, ACE inhibitors, angiotensin receptor blockers, and anti-inflammatory drugs have robust benefits to human health as compared to their risk based on unclear contributions to COVID-19 outcomes.

Not all human coronaviruses have severe outcomes. Besides the three shown in Table 1 that cause severe respiratory syndrome, four additional human coronaviruses are known,<sup>23</sup> coronaviruses 229E, NL63, OC43, and HKU1.<sup>23</sup> All are endemic globally and cause 10–30% of the upper respiratory tract illnesses like the common cold.

In addition to the human coronaviruses, hundreds of animal coronavirus variants exist with the greatest diversity observed in bats. Coronaviruses cause a variety of different diseases including enteritis in cows and pigs and upper respiratory disease in chickens.<sup>16</sup> Although these viruses rarely crossover to humans, occasional infections may occur if both share the same environment, for example, a farmer and their livestock.

## ■ RISK ASSESSMENT OF SARS-COV-2

A formal risk assessment procedure evaluates multiple aspects of a given pathogen, and how it interacts with the human and the environment. Risk assessments are commonly done in research environments, but they are also critical in public health to assess the dangers a newly emerging disease might pose to the population. Risks for emerging diseases should be evaluated similarly to new chemicals synthesized in drug development. The premise of risk assessment for biological research uses several well-defined criteria, including the pathogen, the human, and the context or environment, which affects policy decision making processes, including healthcare decisions in the public health realm.

**Pathogen Risk Groups.** The National Institutes of Health (NIH) and the World Health Organization (WHO) organize pathogens and toxins produced by certain pathogens into 4 risk groups based on the severity of the disease caused in humans, the adverse effect on the community, and the availability of preventative measures and treatment (Table 2).<sup>24,25</sup> The coronaviruses MERS-CoV and SARS-CoV-1 are classified as Risk Group 3 pathogens.<sup>24</sup> Clearly, SARS-CoV-2 carries a very high risk to the community based on the rapid, global spread of the virus and the impact it has on human health and the global economy. Furthermore, to date, no effective treatment nor vaccine exists. The high risk SARS-CoV-2 poses to the community makes this virus comparable to Risk Group 4 pathogens at this time. Since a risk group for SARS-CoV-2 has not yet been assigned, the National Institutes of Health (NIH) developed interim guidelines for handling specimens potentially containing the virus in the laboratory.<sup>26</sup>

**Host Range and Emerging Diseases.** The host range of a pathogen determines whether only a specific host or a broad range of hosts can be infected. How can a bat virus evolve into a human pathogen that creates a disease of such global dimensions? The answer to this question lies in a characteristic viral feature, the rapid viral genome mutation rate which then results in a variety of viral descendants with altered proteins responsible for attaching to and entering host cells of different animal species, including humans. RNA viruses such as the coronaviruses exhibit especially high mutation rates that allow rapid diversification at the cost of generating nonviable descendants.<sup>27</sup> Viral adaptation to new hosts is driven entirely by stochastic mutations and a stochastic, hit or miss host encounter. Expanding a viral host range creates additional reservoirs and is thus of evolutionary advantage to the virus. The spike protein is an important target for evolutionary changes as it allows recognition of different host cell target proteins, not only between different host species but also between different tissues within one host (tropism).<sup>28</sup> Dispersion as aerosolized particles to different species is especially efficient in creating new reservoirs of animals by mutated coronaviruses that can eventually reach a human host. As the virus is spreading across the world, it has already begun to mutate leaving a possibility for a recurrence of a SARS-CoV-2 variant.<sup>29,30</sup> More research will reveal the consequences of SARS-CoV-2 variants on host range and tropism.

The hallmark of an emerging contagious disease is that it is not previously known to exist in humans but has now acquired the ability to spread from human to human. Diseases crossing the animal–human barrier are referred to as zoonotic diseases. Often peridomestic animals or wildlife serves as intermediate



stable reservoirs increasing the opportunity of the virus to inadvertently infect humans.<sup>31–33</sup> For MERS, camels were suggested as the intermediate reservoir.<sup>34</sup> COVID-19 spread from a Chinese seafood marketplace also selling live chicken and rabbits,<sup>33</sup> and SARS is thought to have originated from palm civets, exotic cats sold at Chinese marketplaces.<sup>35</sup> The exact intermediary animal for both SARS coronaviruses will become known once more viral sequences from various animal sources become available. This raises the question whether COVID-19 could spread from humans to domestic animals including pets and eventually wildlife, thus creating new reservoirs in countries without previous animal reservoirs. As of recently, there is evidence of inadvertent human to dog and cat (domestic and tiger) transmission of SARS-CoV-2.<sup>36</sup> In laboratory settings, cats as well as ferrets were also able to transmit the SARS-CoV-2 virus to their kind suggesting that cats and ferrets represent at least two new potential animal reservoirs in countries outside China. More research will examine whether either animal species can transmit the virus back to humans.

Interestingly, all viruses listed in Table 1 are RNA enveloped viruses and originated either in bats (i.e., coronaviruses, ebolavirus, and also zika virus not included in the table) or in birds or other animals (i.e., influenza viruses). An exception is HIV, which is thought to have originated in primates.

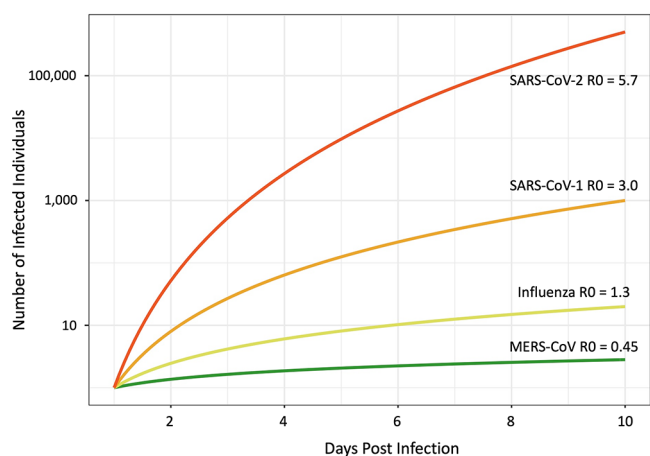
**Routes of Transmission.** COVID-19, SARS, and MERS are aerosol transmissible diseases that are thought to be transmitted via sneezing, coughing, and talking by an infected person. Droplets of various sizes are aerosolized and expelled with potentially great force, which allows them to travel relatively long distances. Larger droplets may be directly deposited to mucous membranes of unlucky bystanders in close proximity (direct contact, droplet transmission). Smaller droplets (<5  $\mu\text{m}$ ) can be directly inhaled (airborne transmission). These smaller droplets may remain airborne for hours while larger droplets more rapidly follow a trajectory path down toward a surface. Healthy individuals may become infected by touching contaminated surfaces and subsequently transferring viral particles to their mucous membranes of the eye, nose, and mouth (indirect contact or fomite transmission).

Person-to-person transmission of SARS-CoV-2 appears to occur most commonly in groups sharing close proximity including families and their friends, nursing and hospital environments, and other environments favoring close contact. This suggests that the main mode of transmission of SARS-CoV-2 is via droplet transfer by infected individuals during coughing, sneezing, or speaking.<sup>37</sup> However, a study found that, if aerosolized, SARS-CoV-2 remained viable for about 3 h in the air suggesting that airborne transmission could be possible.<sup>38</sup> SARS-CoV-2 RNA was also detected in stool, urine, and saliva of infected patients.<sup>39</sup> Furthermore, viral RNA was detectable in fecal samples for 33 days, even after patients' respiratory samples had tested negative.<sup>40</sup> This suggests continued viral shedding in feces. Therefore, alternative forms of transmission cannot be excluded, which may have ramifications for closed facilities such as nursing homes, hospitals, and cruise ships. More research on SARS-CoV-2 routes of transmission will inform additional protective measures.

**Infectious Dose.** The infectious dose is an important factor in assessing the ability of a pathogen to establish a successful infection in its host. It is expressed as  $\text{ID}_{50}$  and refers to the number of pathogens, including viruses and bacteria, that is sufficient to infect 50% of a given susceptible population. Some pathogens have lower infectious doses than others. For

influenza, a high infectious dose appears to correlate with a more severe disease.<sup>41</sup> The infectious dose for SARS-CoV-2 is currently not known. A study by Watabanbe et al. used animal studies and modeling of SARS spreading in an apartment complex in China to estimate the infectious dose for SARS-CoV-1 to be 280 viral particles to cause disease in 50% of the population.<sup>42</sup> This  $\text{ID}_{50}$  is similar to values determined for the human common cold coronaviruses and some animal coronaviruses belonging to the same genetic group as SARS-CoV-1.<sup>42</sup> Exact infectious dose estimations for human pathogens are difficult to obtain since human volunteer studies are rare. One such study for the Influenza A virus determined the  $\text{ID}_{50}$  to be 790 viral particles when administered intranasally. However, infection via aerosolization of Influenza A is believed to be much lower.<sup>43</sup> This suggests that the infectious doses for the human coronaviruses and Influenza A are in about the same range. In contrast, the  $\text{ID}_{50}$  of *Mycobacterium tuberculosis* is 10 bacteria by inhalation, which is far lower. How many SARS-CoV-2 viruses are expelled when people cough? The answer to this question is not yet known. However, viral shedding from the respiratory tract begins 2.5 days before the onset of symptoms and peaks already 0.6 day, on the average, before the onset of symptoms.<sup>44</sup> The authors speculate that 44% of transmission could already occur before people become aware of carrying the disease. Presymptomatic virus shedding is thus likely a major contributor to global COVID-19 spreading as it occurs undetected under the current limited testing practice. In contrast, SARS-CoV-1 and MERS-CoV virus shedding from the respiratory tract begins at the onset of symptoms, and infectivity is greatest in the second week of illness.<sup>45,46</sup> Thus, both of these diseases are easier to trace.

**Communicability.** Communicability of a disease is another measure to determine the capability of a pathogen to be transmitted from one human or animal to another. The basic reproduction number ( $R_0$  or  $R_{\text{naught}}$ ) determines the severity of an epidemic. It indicates the average number of people that will be infected by a single person ("The Source"). Measles and pertussis (whooping cough) have an  $R_0$  of around 15 meaning one person can transmit the disease to an average of 15 other persons in a population that has not developed any immunity or has not been vaccinated. It is worth noting that both diseases are spread via airborne transmission.  $R_0$  is also a useful measure for explaining how a new, emerging disease spreads in a vulnerable population. If  $R_0$  is less than 1 the disease will die out, if it is equal to one the disease will remain stable in a population, and if it is greater than 1 it can cause an outbreak or epidemic. Based on data from early transmission of COVID-19 in an unprotected population in Wuhan, the average  $R_0$  for SARS-CoV-2 was estimated to be 2.2<sup>47</sup> but other studies suggest a higher  $R_0$  value.<sup>48</sup> A more recent analysis of the COVID-19 outbreak in China during the same time period, using mathematical modeling and including high-resolution domestic travel and infection data, determined  $R_0$  for SARS-CoV-2 to be 5.7.<sup>49</sup> This makes COVID-19 a far more contagious disease compared to SARS and MERS. The  $R_0$  value for SARS-CoV-1 was estimated to be 3.0<sup>50</sup> and for MERS-CoV 0.45.<sup>51</sup> Seasonal flu, for which herd immunity exists, has an  $R_0$  of 1.3. What are the practical implications of  $R_0$  values? The higher the  $R_0$  value, the faster a disease spreads through the population as the spread is exponential (Figure 2). Once the population approaches saturation, that is, everyone is diseased, the spread levels off. Social distancing can reduce  $R_0$  by lowering the probability of person-to-person transmission. Since individuals already shed



**Figure 2.** Exponential spread of emerging and re-emerging diseases based on their  $R_0$  values. The higher the  $R_0$  value, the faster a disease spreads through a population that has not yet built immunity or is not vaccinated. The label “Influenza” represents influenza viruses causing seasonal flu for which herd immunity exists.

SARS-CoV-19 viruses before becoming symptomatic, wearing masks to create a barrier and retain droplets should potentially also lower  $R_0$ . Once vaccines become available,  $R_0$  can likely be decreased effectively.

What else can change  $R_0$  of a disease? There is the possibility that a virus could mutate to become more or less efficient in establishing an infection, resulting in a higher or lower  $R_0$ , respectively. In addition, some infected individuals participate in superspreading events where excessive disease spreading is traced to a single person, who is also called a superspreader (reviewed by Stein 2011).<sup>52</sup> Well documented in the news is a woman in Korea traveling home from Wuhan and infecting 37 members during one large church event, who then went on to spread the disease to hundreds of other church members within a short period of time. At a birthday party in the US one person already ill with COVID-19 infected approximately 50 partygoers who subsequently scattered to different states in the US and traveled abroad infecting many people in their path.<sup>53</sup> Other documented cases of superspreader events are known for MERS and SARS.<sup>52</sup> A MERS superspreading event played a significant role in the outbreak of MERS in Korea in 2015. A businessman returning from the Middle East was treated at a hospital from which the disease was spread to other hospitals to which patients were transferred where MERS then became a nosocomial disease (that is, a disease originating in a hospital). Because of the superspreading hospital events, the  $R_0$  value for MERS was increased to 8.1.<sup>54</sup> In any case, whether it is the physiological nature of a certain individual or their social practices, superspreading events play a significant role in spreading emerging diseases. Examples of social gatherings that could become superspreading events contributing to rapid disease spread include major holidays that involve traveling such as the Chinese New Year, Thanksgiving, school or college holidays, and major gatherings such as sports events and concerts, etc.

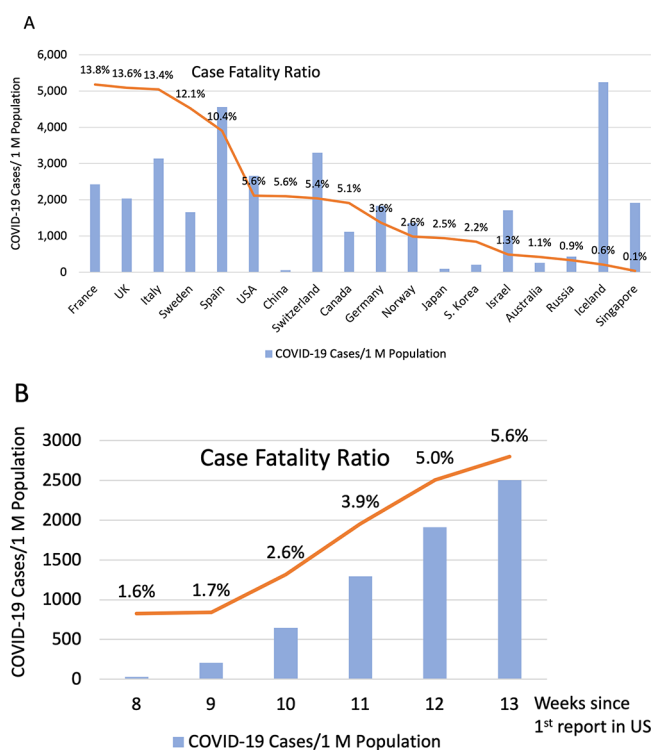
An additional important question is whether SARS-CoV-2 is present in asymptomatic persons, and if so, can these individuals transmit the virus? An analysis of the COVID-19 outbreak on the cruise ship *Princess Diamond* in Yokohama, Japan, showed that, of the 634 persons who tested positive for SARS-CoV-2, 50.5% had no significant symptoms.<sup>55</sup> Using mathematical modeling, Li et al. examined the spread of COVID-19 in 375

Chinese cities during January 10–23, 2020.<sup>56</sup> This was a time period of extensive travel due to the Chinese Spring Festival, and before the Chinese Government implemented travel restrictions to curb the spread of the disease. The authors concluded that 86% of all infections were not documented during this time period because infected individuals displayed mild, limited, or no symptoms. While the infected but asymptomatic population was estimated to be less contagious, they were responsible for 79% of the symptomatic COVID-19 documented cases during that time period.<sup>56</sup> Therefore, SARS-CoV-2 transmission by asymptomatic or individuals with mild symptoms is a major contributor to the rapid global spread of COVID-19. In contrast, asymptomatic SARS-CoV-1 made up 7.5% of a healthcare worker population before infection control measures were implemented,<sup>57</sup> and the latest WHO estimation indicates that 10% of a MERS positive population is asymptomatic or has mild symptoms.<sup>58</sup> It is unclear to date whether SARS and MERS asymptomatic individuals can transmit the disease.

**Case Fatality Ratio.** The case fatality ratio (CFR, also called case fatality rate) is the ratio of deaths per total confirmed infected cases. It plays a significant role in assessing the severity of a disease. The case fatality ratio of COVID-19 was estimated to be 5.6% in China and 15.2% outside of China.<sup>59</sup> The high percentage of deaths was speculated to be due to the breakdown of the healthcare system, i.e., their inability to optimally treat seriously ill patients.<sup>60</sup> Furthermore, incomplete testing could contribute to high CFRs if the population of COVID-19 infected individuals is substantially larger than the cases confirmed by laboratory testing. Using the WHO estimate calculated from the ratio of death cases per total laboratory-confirmed positive cases, the CFR for COVID-19 is estimated worldwide to be 7.0% (as of 4/22/2020), which compares with 11% for SARS and 34% for MERS (Table 1). Analysis of the current CFRs by country illuminates significant differences in CFR (Figure 3A). Certain countries such as France, UK, Italy, Sweden, and Spain have substantially higher CFRs than other countries. In addition, CFRs in one country can increase over time (Figure 3B). Factors underlying high CFRs are under investigation, but the availability of an effective healthcare system may play a major role in curtailing the CFR within a country. This can occur when the total number of cases increases sufficiently to overwhelm the available hospital capacities for critical care. In particular, countries with less developed healthcare structures will be expected to have high CFRs. In a global pandemic, other communities/countries need to step up in order to provide critical life-saving support.

CFRs are also strongly influenced by underlying diseases and ages of infected patients. Older patients are exceedingly more prone to die of COVID-19 probably because of a diminished immune system and additional comorbidities such as cardiovascular disease, diabetes, hypertension, and cancer.<sup>61</sup> Conclusions might still be too early, and more research will provide better insight into factors contributing to COVID-19 morbidity and mortality.

**Persistence.** Viral persistence without losing viability on solid surfaces or while airborne plays an important role in the spread of pathogens. Both aerosol and fomite transmission were important drivers of superspreading events during the 2002–2003 SARS epidemic.<sup>52</sup> A recent study by Doremalen et al. revealed that both SARS-CoV-2 and SARS-CoV-1 can remain viable for hours in air and on solid surfaces but decayed exponentially.<sup>38</sup> Under controlled experimental conditions, the median half-life of SARS-CoV-2 small aerosolized particles was



**Figure 3.** Case fatality ratios (CFRs) for COVID-19 by select countries as of April 22, 2020. Data were obtained from Worldometer.<sup>62</sup> The case fatality ratio was calculated as the ratio of total deaths per total number of laboratory confirmed cases. Dependent on the country both numbers can be underestimated. COVID-19 cases were normalized to total cases/1 million population. (A) The graph illustrates that CFR is not a constant; some countries have a low percentage CFR in relation to a high number of cases, while other countries have a high CFR as compared to their total number of cases. (B) As shown here for the US, the CFR of a country can change within a relatively short period of time as the number of cases increases. This could be due to an overwhelmed healthcare system where personnel, hospital beds, and life-saving supplies become limiting.

2.7 h in air. SARS-CoV-2 has half-lives on copper, cardboard, steel, and plastic surfaces of 3.4, 8.5, 13.1, and 15.9 h, respectively. The environmental stability of SARS-CoV-1 was overall similar to that of SARS-CoV-2 suggesting that virus stability is not the cause for the explosive pandemic spread of COVID-19 as compared to the containable SARS outbreak.<sup>38</sup>

What is known about the environmental stability of other enveloped viruses? Because of their lipid membrane, enveloped viruses are generally more prone to desiccation and inactivation than nonenveloped viruses.<sup>63</sup> Once the envelope is disrupted, the virus loses its viability.

## ■ RISK MITIGATION

What are effective risk mitigation practices for emerging diseases? In laboratory research and high-risk manufacturing environments, risk mitigation relies on multiple safety measures including engineering controls to establish barriers between the hazard and humans, administrative controls that guide best practices for handling hazards, and personal protective equipment (PPE) considered to be the personal protection of last resort when engineering or administrative control measures fail. When working with radioactivity the ALARA principle is applied, which means to keep the exposure As Low As Reasonably Achievable. Redundant measures are operational-

ized in healthcare settings and could be expanded to the larger public health community.<sup>64</sup> However, this requires commitment from organizational leadership and appropriate resources for it to work well.

**Engineering Controls.** Engineering controls provide a physical separation from infected individuals through mechanical means. The most effective examples are physical barriers and ventilation controls such as negative pressure isolation rooms in hospitals. Generally, hospitals do not equip these rooms with HEPA filters. HEPA filters are high-efficiency particulate air filters that retain 0.3  $\mu\text{m}$  particles with 99.97% efficiency. However, general room ventilation was also shown to reduce airborne viral particles load.<sup>65</sup> A study of isolation wards (rooms that can contain several beds and are located away from other hospital rooms) showed a significant correlation between the reduction of healthcare worker infections and increased room ventilation during the 2003 SARS epidemic.<sup>65</sup> Modeling the spread of influenza in schools demonstrated a significant reduction of airborne transmission when room ventilation was increased.<sup>66,67</sup> While effective room ventilation may not be an option for many schools, even opening windows was shown to significantly increase airflow and consequently decrease respiratory infection rates.<sup>68</sup> Additional engineering controls recommended by Centers for Disease Control (CDC) include physical barriers, partitions, and curtains to separate infected from healthy persons.<sup>37</sup>

**Administrative Controls.** Administrative controls guide—among other work practice controls—training and best practices including decontamination methods to prevent exposure to respiratory diseases. In addition, policies should direct a medical surveillance plan for healthcare workers and first responders, logistics for acquiring and storing needed materials required during an outbreak, and logistics for managing needed personnel. While this paper is not meant to detail all appropriate administrative controls needed for public health during a disease outbreak, two points should be emphasized. First, in the context of emerging diseases, administrative controls must optimally be put into place in anticipation of an outbreak or a pandemic rather than after a disease has already become established. Lessons learned from the SARS pandemic provide ample information for helping design administrative controls leaving sufficient flexibility for adaptation to different pathogens and regional needs.<sup>2</sup> Second, the importance of personnel training cannot be emphasized enough. Even if sufficient PPE is available it becomes useless if personnel are not trained in proper donning and doffing procedures. Improper PPE use was likely a contributing factor in superspreading hospital events during the SARS and MERS outbreaks.<sup>51,69</sup> In the 2003 SARS epidemic 20.5% of all healthcare providers treating SARS patients in Hong Kong hospitals became infected, and 36.7% in a Canadian hospital episode.<sup>69</sup> The incorrect removal of PPE, for example, gloves, not only endangers hospital personnel and first responders and their patients but also plays a role in spreading disease in other facilities such as nursing homes, airports, and grocery stores. Thus, instead of offering protection, PPE without guided training can instill a false sense of security and accomplish the opposite, the expansion of an outbreak.

Another important administrative control is the type of disinfectants to be used against SARS-CoV-2. Because of their phospholipid bilayer, enveloped viruses are highly sensitive to common household cleaners that contain detergent, bleach, or hydrogen peroxide as well as alcohol-based hand sanitizers and soap. These disinfectants dissolve the lipid layer and/or



denature viral proteins. Note that, in contrast to sterilization methods, which kill all pathogens, disinfectants greatly reduce the infectious dose by reducing the number of pathogens. A list of disinfectants recommended by the CDC for COVID-19 can be found at their website.<sup>70</sup>

**Personal Protective Equipment (PPE).** While PPE is generally considered to be the last line of defense in laboratory research and high-risk manufacturing industries, it appears that in healthcare environments PPE, when properly used in a patient setting, often serves as the initial barrier between healthcare providers or first responders and patients. This is because there are few or no physical barriers, unlike standard designs in laboratories and production facilities. PPE, therefore, should be given a much higher priority when dealing with infectious diseases equal to engineering controls. The CDC provides strict guidelines for PPE appropriate for hospital personnel treating patients with infectious respiratory diseases such as SARS-CoV-1 and SARS-CoV-2.<sup>37</sup> Included are disposable gowns, fit-tested N95 respirators or PAPRs (battery-powered air-purifying respirators), face shields or eye protection, and disposable gloves.

Why do N95 respirators need to be fit-tested and how are they different from standard face masks? N95 respirators filter 95% of all airborne particles if worn correctly. The respirator's flexible edge is designed to achieve a tight facial fit. Fit-testing determines the correct respirator size and model for the wearer and typically also trains the user in applying the respirator correctly so that the nose and mouth are effectively shielded from nonfiltered air. However, facial hair may not allow a tight seal, enabling infectious particles to be sucked in through the sides (as a point of least resistance).<sup>71</sup> Keeping in mind that the individual's health is of utmost importance; either facial hair must be removed, or an alternative respirator type should be used when available.

Face masks, in contrast, do not act as filters for airborne pathogens. Rather, they act as splash or spray barriers. For this reason, face masks are provided to infected persons as a barrier to dispersal of droplets generated by them. More information on respirators and masks can be found at the CDC.<sup>72</sup>

## ■ TESTING FOR SARS-COV-2

During an epidemic, it is critically important to monitor the spread of the disease agent. One could compare this to monitoring the whereabouts of radioactivity during an experiment or accident with radionuclides to prevent contamination. Testing generates data that informs public health policy makers in implementing administrative controls and then measures the effectiveness of those controls. However, insufficient numbers of tests in the US are currently hampering efforts to detect the spread and thus contain the expansion of COVID-19. An absence of testing could be equated to responding to the Chernobyl outfall hazard without having access to sufficient data from Geiger-Muller counters, and thus no information on the type and extent of exposure.

What types of testing are used to monitor the spread of COVID-19? The most commonly used diagnostic test for SARS-CoV-2 is done by RT-PCR (reverse transcriptase polymerase chain reaction). Briefly, viral RNA is first purified from samples, transcribed into DNA which is then amplified in a PCR reaction to achieve easily detectable amounts. In the laboratory, the RNA isolation and the RT-PCR reaction and analysis can be automated, processing 100 or more samples at a time on one machine with a turnaround time of a few hours.

Multiply that by several machines per lab and many laboratories per country and, theoretically, this should provide hundreds of thousands of tests per day. But that is not what the current reality looks like. At this time, COVID-19 test availability is limited, and it often takes days to obtain results. What is limiting testing, and why does it take so long to get results? Before answering these questions, let us ask how other countries solve this problem. Recall the images of drive-by testing stations in South Korea? Healthcare personnel fully protected by appropriate PPE (Tyvek suits, respirators, eye or face protection, and gloves) took swabs and personal information from concerned citizens who could then expect the result via text or email message the next day. The testing procedure in South Korea and elsewhere currently relies on the same type of RT-PCR assay. Some countries such as South Korea have more test reagents available to them than other countries because they already produced them and rapidly increased production as soon as they learned of the emergence of COVID-19.<sup>73</sup> Other countries had to import them.<sup>73</sup> As more and more countries dealt with increasing numbers of COVID-19 cases, the supply of swabs, test reagents, other laboratory supplies, and PPE became limited, and the ability to test for COVID-19 was disrupted. Some companies are already working on offering tests that combine the RNA purification and RT-PCR procedures into one step that can be accomplished by a small portable machine. These quick tests reduce testing time and allow for personalized testing by medical offices affording the price. An effective response to an outbreak would be to ramp up production of all needed materials as soon as there is a threat of a potential pandemic.

As of April 22, the testing density of populations ranges from 1.4% in the US to 1.6% in Canada, 0.9% in the UK, 2.6% in Italy, and 1.1% in South Korea.<sup>62</sup> Early testing in South Korea guided immediate social isolation approaches, in accordance with the SARS lessons learned,<sup>2</sup> and likely contributed to a lower CFR as compared to other countries (Figure 3A). Note that no country has yet been able to test 10% of its total population for COVID-19 with the exception of Iceland.<sup>62</sup> Increased levels of testing would be ideal, as it better informs healthcare planning, treatment, and quarantine measures. The combination of testing, extensive contact tracing, and follow-up controls such as quarantine was effective in controlling the SARS, MERS, and other outbreaks.<sup>74</sup>

Other monitoring tests currently in development include human antibody and viral antigen tests. Most infected persons develop antibodies as part of their immune response to most pathogens. These antibodies can be detected with synthetic peptides designed to mimic specific portions of a pathogen's surface that is exposed to the immune system. Such antibody tests are available to detect SARS-CoV-1 and MERS-CoV in the serum of previously infected patients. Antibody tests are effective weeks to months to years after an infection depending on the immunity to a given pathogen. They are useful to survey the spread of a disease and provide insight into the scale of an outbreak. The test may also be effective in screening for nonsymptomatic carriers that could be part of a yet unknown transmission chain during an outbreak. Finally, they can be used after the crisis phase passes to better measure the true infection rate. The antigen test works similarly except that antibodies generated against a pathogen are used to directly detect this pathogen in the serum or other bodily fluids of infected patients. Like RT-PCR, this test is a diagnostic test but is less sensitive than the RT-PCR test and is generally applied several days after a patient becomes symptomatic. However, the antigen test is

generally less expensive than RT-PCR, administered more conveniently, and has a fast turnaround time.

## CONCLUSION

All influenza and coronavirus outbreaks have two factors in common: (a) human proximity to farm and wildlife animals that facilitates interspecies transmission and emergence of disease in humans, and (b) global travel. However, several factors set the COVID-19 pandemic apart from the SARS and MERS outbreaks. These include the high infectivity as indicated by a recently estimated  $R_0$  of 5.7 for SARS-CoV-2, peaking of viral shedding before the onset of symptoms, and a large population of asymptomatic carriers still capable of infecting others. Thus, COVID-19 is a highly contagious disease that can easily spread undetected in a society with high population density and mobility.

It is only a matter of time for new diseases to emerge or reemerge and cause pandemics. It would appear that coronavirus-associated diseases have been underestimated thus far, and the time since the SARS and MERS outbreaks was not used effectively to develop infrastructure to rapidly mobilize diagnostic tests, vaccinations, antiviral therapies, and policies to control outbreaks and to coordinate healthcare systems worldwide. Countries are struggling to save lives while attempting to limit damage to their economies in order to preempt a potential local and worldwide recession. What will be the lessons learned from COVID-19 that will convince policy makers to treat the next emerging disease with scientific rationale? Risk assessment for emerging hazards is essential to employ optimal engineering and administrative controls and inform appropriate PPE decisions. Constant surveillance is essential for the detection of emerging diseases and their containment by contact tracing and social isolation. The same risk assessment principles for work with hazardous chemicals, radioactivity, or encounters apply to newly emerging diseases:

- decrease the time of exposure to reduce the dose;
- increase the distance to the source (i.e., infected persons); and
- use shielding to protect from direct contacts.

The lessons learned from the COVID-19 pandemic will only be valuable if they result in actions to prepare our global society for the next pandemic to come.

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