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ORIGINAL ARTICLE

Basic Study

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ABOUT COVER

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COVID-19 compared to other epidemic coronavirus diseases and the flu

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Abstract

Coronaviruses are among the largest group of known positive - sense RNA viruses with a wide range of animal hosts as reservoir. In the last two decades, newly evolved coronaviruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV) which caused the infamous 2002 outbreak, the Middle East respiratory syndrome coronavirus (MERS-CoV) which caused an outbreak in 2012, and now the SARS-CoV-2 [responsible for the current coronavirus disease 2019 (COVID-19)] have all posed notable threats to global public health. But, how does the current COVID-19 outbreak compare with previous coronaviruses diseases? In this review, we look at the key differences between SARS-CoV, MERS-CoV, and SARS-CoV-2, and examine challenges in determining accurate estimates of the severity of COVID-19. We discuss coronavirus outbreaks in light of key outbreak severity indicators including, disease fatality, pathogen novelty, ease of transmission, geographical range, and outbreak preparedness. Finally, we review clinical trials of emerging treatment modalities and provide recommendations on the control of COVID-19 based on the mode of transmission of the coronaviruses. We also recommend the development and use of a standardized predictive epidemic severity models to inform future epidemic response.

Key words: Severe acute respiratory syndrome, SARS; Middle East respiratory syndrome, MERS; COVID-19; SARS-CoV2; Coronaviruses; Influenza, Flu; Respiratory viruses

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Core tip: In this review, we look at differences and similarities between severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, and severe acute respiratory syndrome coronavirus 2 and we discuss the challenges in the determination of case fatality rates in pandemics like the current and propose the need for standardization of predictive epidemic severity models that considers critical factors that can influence the severity of outbreaks.

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INTRODUCTION

In December 2019, a cluster of pneumonia was reported in Wuhan, China. Nucleotide sequencing of samples from patients revealed a novel beta coronavirus that was designated novel coronavirus and subsequently as severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)^[1,2,3]. The disease caused by this novel coronavirus has been designated by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) meaning coronavirus disease of the year 2019. Initial cases of this disease were epidemiologically linked to the Huanan Seafood and Wet Animal Wholesale Market in Wuhan, Hubei Province, China, suggesting a possible zoonotic spill over from wildlife to humans. The disease subsequently spread and the global expansion was facilitated by human to human transmission^[1].

On March 11, the WHO declared the current COVID-19 outbreak, a global pandemic. This is not the first time the world is experiencing a coronavirus epidemic in recent times^[4]. Severe acute respiratory syndrome coronavirus (SARSCoV) occurred in 2002, which reportedly infected 8098 people and caused 774 deaths worldwide. Ten years later, the Middle East respiratory syndrome coronavirus (MERS-CoV) emerged causing a total of 2494 infections, and 858 fatalities^[5]. SARS-CoV-2 is the third coronavirus epidemic to emerge in the human population in the past two decades. Preliminary laboratory investigations suggest that the virus grows in the same cell lines that are used for growing SARS-CoV and MERS-CoV, however, SARS-CoV-2 grows better in primary human airway epithelial cells than in standard tissue culture cells unlike SARS-CoV or MERS-CoV^[6].

But how exactly is COVID-19 different from the SARS or MERS? Initial reports have suggested that the SARS-CoV and MERS-CoV may be more severe than SARS-CoV-2 while the later may be more infectious^[7]. These observations are based on case fatality rates (CFRs), which to the opinion of the authors of this review, is yet to be definitively established for SARS-CoV-2 as we discuss later in this paper. Given how new SARS-CoV-2 is, there are still a lot of unknowns regarding its morbidity and mortality. Since the onset of the disease in late 2019, several important questions regarding the virus and its disease are still being investigated and studied, *e.g.*, what is the shape of the disease pyramid? What proportion of infected people develop the disease? What proportion of infected persons are asymptomatic? And, what proportion of those with the disease die? Furthermore, indices other than fatality and transmissibility are necessary to establish a comprehensive estimate of disease severity. For example, the psychosocial severity of COVID-19 is yet to be determined. Also, because COVID-19 and the flu share commonalities in initial signs and symptoms, questions have been raised on the difference between the two in the context of comparing which epidemic or disease is most serious. However, understanding the differences in seriousness between the COVID-19 pandemic and the seasonal flu needs a comprehensive estimate of epidemic/outbreak severity. Below, we discuss key concepts of epidemic severity including fatality, disease severity, pathogen novelty, preparedness, geographic range, and ease of transmission.

CORONAVIRUS DIVERSITY AND RESERVIORS

Coronaviruses belong to the family *Coronaviridae* which are enveloped, positive-sense, single-stranded RNA viruses of about 80-120nm diameter and 31 kb in size^[8]. There

are at least 7 types of human coronaviruses grouped into either alpha or beta coronaviruses. The alpha coronaviruses include 229E and NL63, and the beta include OC43, HKU1, MERS-CoV, SARS-CoV, and the novel SARS-CoV-2. Acute respiratory infections caused by 229E, NL63, OC43, and HKU1 are often mild while SARS-CoV, MERS-CoV, and SARS-CoV-2 cause both mild and severe disease and have been responsible for global epidemics that began in 2002, 2012, and 2019 respectively^[5]. Coronaviruses are ecologically diverse with the greatest variety seen in bats, which are known to be a reservoir for many emerging viruses. Peri-domestic animals may also serve as intermediate hosts, facilitating transmission to humans. Given the diversity of coronaviruses that infect animals and increasing human-animal interfaces, novel coronaviruses are likely to emerge periodically in humans through cross-species infections and occasional spillover events.

SYMPTOMS AND FATALITY OF SARS-COV-2 AND OTHER EPIDEMIC CORONAVIRUSES

Fatality is the most commonly used indicator to measure disease and outbreak severity. While the CFR is a well-known metric, standardized symptom-scoring metrics for coronaviruses are scarce. Nonetheless, the route of transmission, pathologies, and clinical manifestation of SARS-CoV-2 show resemblance to SARS-CoV and MERS-CoV^[3]. Symptoms of SARS-CoV include fever, cough, dyspnea, and occasionally watery diarrhea. During the epidemic in 2002 - 2003, the virus infected about 8098 individuals resulting in 774 fatalities, placing the CFR at 9.6%^[8]. MERS-CoV on the other hand caused explosive nosocomial transmission events, in some cases linked to a single super spreader. According to the WHO, as of November 2019, a total of 2494 persons had been infected with the MERS-CoV resulting in 858 deaths (CFR of 34.4%) with the majority in Saudi Arabia (Table 1). The clinical features of MERS share many similarities with SARS and COVID-19 such as severe atypical pneumonia, gastrointestinal symptoms, and acute kidney failure^[9]. With regards to the CFR for COVID-19, a recent study by researchers from China's Center for Disease Control and Prevention revealed some interesting clinical features on 44672 confirmed cases that were associated with 1023 fatalities (CFR of 2.3%) (Figure 1). The fatality was significantly higher in older patients (up to 14.8% in patients over 80). In critically ill patients, the death rate was over 49%. Interestingly, the majority of the cases, 81%, were classified as mild, meaning they did not result in pneumonia or resulted in only mild pneumonia, 14% were severe and 5% were critical. More than 87% of cases were aged 30 to 79 years and 2% less than 19 years of age, and 3.8% healthcare personnel were infected.

Finally, it is worth noting that most secondary transmission of SARS and MERS occurred in the hospital settings through super spreaders. Although, the transmission of COVID-19 is occurring in this context too, it appears that considerable transmission is occurring in communities^[10]. Caution should be applied when interpreting these head-to-head CFR comparisons as they might be impacted by confounding independent variables such as time and place.

GLOBAL SPREAD OF SARS-COV, MERS-COV, AND SARS-COV-2

The extent to which an outbreak spreads is dependent on human and environmental factors. Figure 2 shows the geographical distribution of cases of SARS, MERS, and COVID-19 (SARS in 29 countries, MERS in 27 countries, and COVID-19 in 185 countries/regions as of April 12, 2020). Of interest is that, COVID-19 has the largest geographic range. However, it has mostly impacted countries within Asia, Europe, and North America. Africa and South America have experienced the least impact of the coronavirus epidemics in general. Although COVID-19 pandemic has now expanded to these regions (Figure 2), the disease reproduction number is still relatively low. It is not entirely clear why there is limited impact of the disease in Sub Sahara Africa and Latin America, especially considering that transmission may be facilitated by sub-optimal health infrastructure and crowded communities in these regions. On the other hand, it may be construed that the low report of cases may be due to limited testing and surveillance mechanisms. Together, whether environmental factors contribute to the transmission of SARS-COV-2 is obviously an area that requires further research as we learn more about the transmissibility of epidemic coronaviruses. It was recently proposed that high temperature and high relative

Table 1 Comparison of severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus2

	Severe acute respiratory syndrome (SARS-CoV)	Middle East respiratory syndrome (MERS-CoV)	Severe acute respiratory syndrome (SARS-CoV2)
Classification ^[5]	Beta coronavirus	Beta coronavirus	Beta coronavirus
Country of onset ^[4,5,7]	First reported in November 2002 in the Guangdong province, China	First reported in April 2012 in Saudi Arabia	First reported in December 2019 in Wuhan, China
Origin ^[2,4]	From bats, which infected civets and then humans	From dromedary camels to humans	Believed to have spread from contact with bats
Global spread ^[5,8]	29 countries worldwide	27 countries worldwide	185 countries and territories worldwide as of April 12, 2020 (ongoing)
Timeline ^[4,5,7]	Last case in 2004	Last case in 2019	Ongoing (as of May 7, 2020)
Cases and fatalities ^[5,8]	It infected 8098 persons and resulted in 774 deaths	It infected 2494 persons and resulted in 858 deaths	About than 3,836,215 cases and 268,999 deaths as of May 7, 2020
Transmission ^[5]	Droplets/contact In addition, it is possible that these viruses might be spread more broadly through the air (airborne spread) especially during an aerosol generating medical procedures.		
Incubation period ^[5]	Typically, 2-7 d or up to 10-14 d in some cases	2-14 d	1-14 d
Symptoms ^[3]	Fever, non-productive cough, sore throat, headache, myalgia, malaise, shortness of breath, chest pain, vomiting, and pneumonia	Fever, severe acute respiratory illness, cough, and shortness of breath, and pneumonia	Fever, cough, headache, body weakness and myalgia (fatigue), shortness of breath, and breathing difficulties. In severe cases, individuals may show symptoms of pneumonia
CFR ^[4,5,8]	9.6%	34.4%	2.2% (initial reports)
Treatment ^[4]	There are no antiviral drugs effective against coronaviruses. Supportive treatment using corticosteroids (methylprednisolone) to reduce lung injury induced by inflammation has been used to reduced acute respiratory distress		
Vaccines ^[4]	There is no approved and marketed vaccine against SARS-CoV, MERS-CoV, or SARS-CoV-2		

SARS-CoV: Severe acute respiratory syndrome coronavirus; MERS-CoV: Middle East respiratory syndrome coronavirus; CFR: Case fatality Rate; The ratio of deaths from a disease to the total number of people diagnosed with this disease for a certain period of time.

humidity significantly reduce the transmission of COVID-19. The authors suggested that one-degree Celsius increase in temperature and one percent increase in relative humidity lower R_0 (basic reproductive number) by 0.0383 and 0.0224, respectively^[11]. It is still unclear if this could be a reason for the low transmission in tropical regions. However, this hypothesis may suggest that the arrival of summer and rainy season in the northern hemisphere may affect the transmissibility of the virus. Sociocultural differences in human interactions in different parts of the world may also explain differences in transmission and epidemic expansion; *e.g.*, in contemporary Europe, salutation of friends and close acquaintances is often accompanied by hugging and a kiss on both cheeks. Such close and direct contact with infected persons who may be asymptomatic or unaware of their infections (given the long incubation period of the virus) may facilitate the spread of the virus. Similarly, the coincidence of the onset of COVID-19 outbreak, just prior to China's annual Lunar New Year holiday, was an important factor that had serious impact on the global spread of the disease. Because this is the largest and most important holiday of the year in China, millions of domestic and international trips are made by residents and visitors in often crowded planes, trains, buses, and local transit systems. Therefore, each infected person could have numerous close contacts over a protracted time and across long distances thereby, impacting the global expansion of the disease and complicating response efforts.

PATHOGEN NOVELTY, REPRODUCTION NUMBER, AND THE IMPACT ON TRANSMISSION

The extent to which a pathogen is novel can impact outbreak response, and consequently severity. Factors that determine the extent of pathogen novelty include, knowledge on the pathogen's primary and secondary reservoirs, transmission modes,

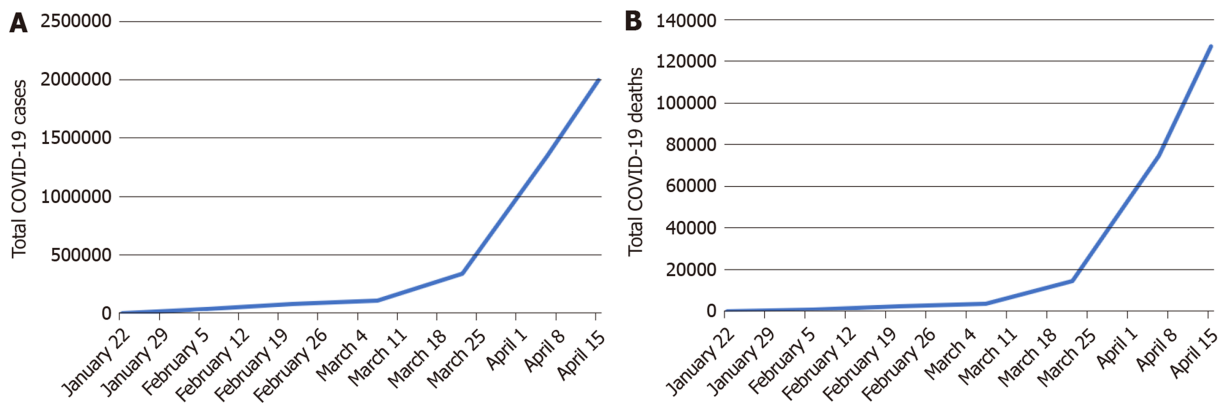


Figure 1 Number of cases of coronavirus disease 2019 and number of deaths due to coronavirus disease 2019 by April 15, 2020. A: Number of cases of coronavirus disease 2019 by April 15, 2020; B: Number of deaths due to coronavirus disease 2019 by April 15, 2020. COVID-19: Coronavirus disease 2019.

control measures, incubation time, diagnostic procedures and treatments, *etc*^[14]. In the case of SARS, the causative agent was only isolated and named after about 5 months into the outbreak, it was absolutely novel at the time^[15]. Unlike this first SARS outbreak, SARS-CoV-2's sequenced genome was already published less than a month after the first case in humans was reported^[15]. Similarly, MERS-CoV was identified at the onset of the outbreak^[14]. Hence it is fair to imply that, SARS was more novel than COVID-19 and MERS when it emerged.

Compared to the MERS outbreak, the SARS and COVID-19 outbreaks showed higher basic reproductive numbers (R_0 ; the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection). The R_0 for SARS and COVID-19 is similar (3 and 3.2 respectively) and MERS is < 1 ^[16-18]. The higher R_0 for SARS and COVID-19 may support the reason why their global spread is higher than MERS.

HOW DOES COVID-19 COMPARE TO THE SEASONAL FLU?

Human coronaviruses such as 229E, NL63, OC43, and HKU1 have long been considered inconsequential pathogens, causing the "common cold" and other mild respiratory symptoms in healthy people^[5,6]. However, in the last two decades highly pathogenic coronaviruses have emerged including the current SARS-CoV-2 causing widespread morbidity and mortality. Although the initial symptoms of both COVID-19 and the flu are associated with acute respiratory infection (Table 2), the global morbidity and mortality of the current COVID-19 pandemic is expected to surpass that of the seasonal flu. So far, the novel SARS-CoV-2 has led to about 3836215 illnesses and 268999 deaths as of May 7, 2020. This fatality is likely to increase before the pandemic resolves. The flu on the other hand sickens about 5 million people worldwide, killing up to 650000 people every year according to the WHO^[19]. Despite these figures, caution should be applied when interpreting global disease burden of these diseases. It is important to note that the burden of infections differ by place (country or region) and time (when). Hence, comparing the CFRs of COVID-19 and the seasonal flu without considering these differences is inappropriate. For example, this season (October 2019 to May 2020) the Centre for Disease Control estimates that as of March 28, 2020, about 24000-63000 of the 39-55 million people who contracted influenza in the United States have died. Historically, the CFR of influenza in the United States has always been $< 0.1\%$. As of May 7, about 76512 of the 1.29M confirmed cases of COVID-19 in the United States had died (CFR = 5.9%). Comparing the CFR of COVID-19 to the CFR of the seasonal flu from earlier years is inappropriate as place and time are independent variables that may influence disease transmission. Finally, it is essential to note that the occurrence of COVID-19 and the flu are not mutually exclusive. COVID-19 could potentially exacerbate the disease burden of the flu and vice versa. Despite the burden of the flu, a lot is known about the virus and the seasonal expectations and projections. In contrast, very little is known about SARS-CoV-2 (which obviously is not a flu), and the outbreak is yet to peak in several countries and jurisdictions. However, so far COVID-19 seems to have spread much faster than the flu causing severe illnesses and leading to a shutdown of the socio-economic activities worldwide. This seems to be a severe disease and its real burden will only be accurately reflected and evaluated post resolution of the

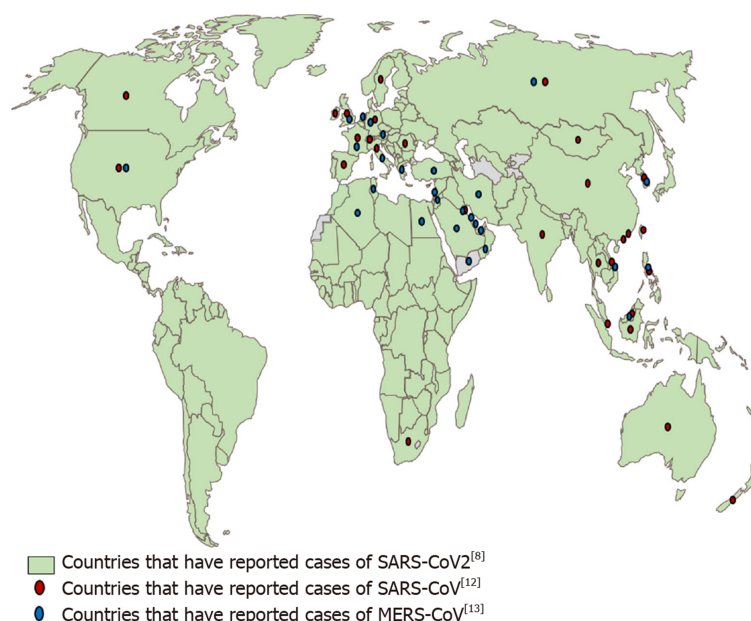


Figure 2 The global spread of severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus2 as of April 15, 2020. SARS: Several acute respiratory syndrome; MERS: Middle East respiratory syndrome; CoV: Coronavirus.

pandemic.

It should be noted that the above comparisons are made against endemic flu. However, the CDC estimates that 151700-575400 people worldwide died from the 2009 H1N1 flu pandemic during the first year the virus circulated. Strangely, > 80% of related deaths were estimated to have occurred in people younger than 65 years of age. This differs greatly from typical seasonal influenza epidemics about 70%-90% of deaths are estimated to occur in people 65 years and older.

THE CASE FATALITY RATIO OF COVID-19, AN UNRESOLVED DILEMMA

The CFR is the ratio of the number of deaths from a disease to the total number of people diagnosed with the disease for a certain period of time. For an emerging infectious disease like the COVID-19, CFR is a vital indicator to assess clinical severity. Initial reports from China and other global health agencies have reported that the CFR of COVID-19 is about 2.2%, relatively lower than SARS or MERS. In Canada and United States, the CFR as of April 6 is 2.2% and 3.4% respectively. However, in Spain and Italy during the same time, the CFR is 10% and 12.6%, respectively. For a disease that is in its nascent stage, we think it is far too early to definitively establish the crude fatality rate of COVID-19. We believe, these initial estimates are based on the intuitive calculation of dividing the death toll by the number of confirmed cases. For example, if we consider the estimate as of April 12, 2020 from Table 1, 113296 deaths divided by 1836338 confirmed cases (No. of deaths + recovered) multiplied by 100, we get a CFR of 6.1% while the CFR as of February 12 was 2.1%. As simplistic as this may be, biases in the estimate of population fatality rates during outbreaks may occur if critical confounding factors are not considered. It has been suggested that CFRs calculated from individual outcome data are likely to be more reliable than estimates calculated from population level data^[23]. If estimates from population-based data are used, they must include the lag time between reporting cases and reporting deaths in order to account for reported cases for whom the disease outcome is yet unknown. This is particularly important if there is a delay from symptom onset to case report or delay from death to fatality report^[24]. Moreover, from previous experience, equal reporting of cases and deaths is unlikely in an emergency pandemic situation, and even less likely to be consistent across multiple countries. This is because different reporting systems may be used by different countries to record confirmed cases and deaths, leading to inaccuracies in estimating the CFR. Simply dividing the total reported deaths by the total reported cases over multiple countries neglects such variability across countries and this may skew the calculation

Table 2 Comparison of coronavirus disease 2019 and the flu

Factors	COVID-19	Flu
Incubation period	2-14 d	1-4 d
Symptoms ^[3]	The most common symptoms are cough, sore throat, headache, body weakness and myalgia (fatigue) due to severe respiratory illnesses associated with shortness of breath and breathing difficulties. In severe cases, individuals may show symptoms of pneumonia	Typical flu symptom is characterized by a sudden onset of fever, cough (usually dry), headache, muscle and joint pain, severe malaise (feeling unwell), sore throat and a runny nose
Case fatality rate ^[8,20]	Initial reports from China suggest the case fatality rate is at least 2.2% (unresolved), and United States 3.9% as of April 12, 2020	The case fatality rate for the flu in the United States is < 0.1%
Virus transmission ^[17,21]	The basic reproduction number, R_0 is about 3.2	The production number of the flu is about 1.28
Characteristic	Pandemic	Endemic, potential for epidemic or pandemic
Prevention ^[19,22]	There is no approved vaccine for COVID-19	There is an annual flu vaccine

COVID-19: Coronavirus disease 2019; R_0 : the average number of people who catch the virus from a single infected person.

of the CFR^[25]. Countries specific variation in CFR is very prominent. As of April 12, 2020, the CFR of Italy was like ten times higher than that of most countries in Africa. Furthermore, the preferential reporting of apparently severe cases or symptomatic infections may neglect mild or asymptomatic infections and this bias can lead to faulty CFR calculation. Unfortunately, monitoring asymptomatic infections in an outbreak situation like the current one is not a public health recommendation and is not an area to prioritize resources during an active pandemic.

Together, as the pandemic spreads rapidly through countries, and as country specific surveillance significantly differ, the CFR estimates may fluctuate substantially. Therefore, without adequate knowledge of the relative reporting of cases to deaths, estimates of CFR calculated from population level data should be interpreted with caution. A retrospective study that will assess the serostatus of close contacts of patients irrespective of symptoms would help to determine the proportion of asymptomatic and mild infections and help guide the calculation of the near true CFR. Until then, the exact reproduction number (R_0) estimate or CFR of COVID-19 still remains an issue to be thoroughly investigated.

OUTBREAK PREPAREDNESS AND THE IMPACT ON DISEASE CONTROL

There is an old adage that says, “luck favours the prepared mind”. Slow and ineffective responses can prolong an outbreak and consequently increase severity. In this section we use the 2019 Global Health Security (GHS) index domains, an outbreak preparedness metric, to explore the outbreak severity of coronavirus outbreaks. GHS is an index that contains 34 indicators organized across 6 domains that measure, (1) Prevention of the emergence or release of pathogens; (2) Early detection and reporting of epidemics of potential international concern; (3) Rapid response to and mitigation of the spread of an epidemic; (4) Sufficiency and robustness of health systems to treat the sick and protect health workers; (5) Commitments to improving national capacity, financing plans to address gaps and adhering to global norms; and (6) Overall risk environment and country vulnerability to biological threats^[26].

Although the GHS index was only recently developed and can't be used for the inferences of prior health events, it is important to note that the frequent emergence and re-emergence of epidemics with pandemic potential has increased outbreak awareness and preparedness in the global community. Between 2011 and 2018, the WHO tracked 1483 epidemics in 172 countries^[26]. The frequency of these outbreaks has led to improved outbreak preparedness globally. A testament to increased outbreak preparedness in the global community is the implementation and monitoring of International Health Regulations (2005), which aim to prevent and control the international spread of disease through committed national leadership, health system strengthening, financing to address gaps, and international collaboration.

The GHS Agenda through its partners in over 64 countries is helping to build capacities to prevent or respond to infectious disease threats. This initiative focuses on 11 areas of action (action packages). Prevent 1: Antimicrobial Resistance; Prevent 2:

Zoonotic Disease; Prevent 3: Biosafety and Biosecurity; Prevent 4: Immunization; Detect 1: National Laboratory System; Detect 2: Real-Time Surveillance; Detect 3: Reporting; Detect 5: Workforce Development; Respond 1: Emergency Operations Centers; Respond 2: Linking Public Health with Law and Multisectoral Rapid Response; Respond 3: Medical Countermeasures and Personnel Deployment Action Package.

Although some countries have achieved significant progress in capacity level improvement in areas like immunization, biosafety, and biosecurity, there is a limited focus on surveillance of zoonotic diseases, infection prevention and control, and early detection capacity of emerging pathogens.

It is also important to mention that the severity of the outbreak can differ significantly by country's readiness. For example, countries with low GHS index are likely to be highly impacted (*e.g.*, the GHS score of the Democratic Republic of Congo is 26.5). If a country such as this is badly hit while already struggling to contain re-emerging Ebola outbreaks, the consequences might be dire. Hence, caution must be applied when inferring the overall severity and impact of the COVID-19 outbreak, as country readiness, capacity level, resources, and context are essential independent variables that should not be neglected in the assessment.

TREATMENT OPTIONS AND CLINICAL TRIALS FOR COVID-19

The emergence of SARS-COV-2 and COVID-19 has left the scientific community searching for potential therapeutics to manage the disease. There is no known effective antiviral against SARS-COV-2, however previously used antivirals and pharmacologics are currently being investigated and in some cases used in the clinical setting on an off-label basis to treat patients suffering from COVID-19. Chloroquine and its hydroxyderivative - hydroxychloroquine, are currently being used to treat COVID-19 patients in some countries across world (*e.g.*, China, France and United States). Chloroquine and hydroxychloroquine have been used for decades for the effective treatment of malaria with a well-known tolerability and safety record. Based on its known *in vitro* antiviral activities against diverse human viruses (reviewed in Devaux *et al*^[27], 2020) and SARS coronaviruses^[27-29], and the recent reports of its *in vitro* efficacy against SARS-COV-2^[30-32], a non-randomized trial to evaluate the clinical efficacy and safety was carried out in small cohort of hospitalized patients with COVID-19 pneumonia in China^[33,34]. Compared to control treatment (Lopinavir/Rotinavir), chloroquine demonstrated superior efficacy in the inhibition of the exacerbation of pneumonia both clinically and based on improved lung imaging findings, shortened disease course and promoted complete viral clearance. In these patients, 500 mg of chloroquine was administered orally twice daily for 10 d. Chloroquine has now been included in the Guidelines for the Prevention, Diagnosis and Treatment of Pneumonia Caused by COVID-19 by the National Health Commission of China^[34,35]. A non-randomized open label trial carried out in France treated hospitalized COVID-19 patients with variable disease severity with a combination of hydroxychloroquine (600 mg/d for 10 d) and azithromycin (500 mg on day one followed by 250 mg/d for four d) or no treatment^[36,37]. Results from this study indicated that hydroxychloroquine and azithromycin were effective treatments for COVID-19 patients resulting in faster clinical improvement and discharge; and complete viral clearance (based on a negative polymerase chain reaction test results or viral culture). Despite the encouraging findings from these studies, it is important to note that the trials were non-randomized, had design flaws with relatively few participants (less than a few hundred participants in each study). It is, therefore, prudent for the scientific community to carry out more well-designed clinical trials to assess the efficacy and safety of chloroquine for the treatment and management of COVID-19 patients prior to making a final recommendation for its use. This will allow for the development of appropriate treatment guidelines including dosage, patient monitoring, duration of treatment and expected outcomes. The United States Food and Drug Administration has since issued an authorization to permit the emergency use of chloroquine phosphate to treat adult and adolescent hospitalized COVID-19 patients for whom a clinical trial is not available, or participation is not feasible^[38]. More than 30 clinical trials are ongoing in different parts of the world on the use of chloroquine for COVID-19 treatment^[39-41]. While chloroquine may be well tolerated, safe and cheap, the drug has a narrow therapeutic index and long-term use may be associated with cardiomyopathy and retinopathy^[42,43]. Toxic concentrations can be lethal as such self-prescription is not recommended and administration should be done only in a hospital setting.

Another drug in clinical trials used for treatment of COVID-19 patients is remdesivir (GS-5734). It is a broad-spectrum antiviral nucleotide analogue with reported efficacy against SARS-CoV1 and MERS-CoV coronaviruses in cell culture and animal models that was used to treat a COVID-19 patient in the United States who showed significant improvement and tolerability one day after intravenous administration of the drug^[32,43,44]. Apart from chloroquine and remdesivir, several drugs both new and old being repurposed for the treatment of COVID-19 are now under clinical trials with the hope that they may be available at patients bed-side in the near future.

The most effective strategy to control the spread, eradicate and minimize the burden of infectious diseases is through mass immunization. Unfortunately, given the novelty of SARS-CoV-2 and COVID-19 and the speed with which the virus spread around the world, scientists have had little time to develop any vaccine candidates. As such there is no known effective vaccine against SARS-CoV-2 at this time, however emerging epidemiological data suggests that the Bacillus Calmette-Guérin (BCG) vaccine (the vaccine for tuberculosis) may be effective in decreasing spread of infection, disease severity and mortality from COVID-19^[45-48]. These reports suggest that there is a correlation between either universal or mandated BCG vaccination and morbidity and mortality from COVID-19. The evidence comes from historical vaccination data review and the current morbidity and mortality rates due to COVID-19 in different countries. Countries without historical universal policies of BCG vaccination at birth such as Italy, Netherlands, United States have been severely afflicted compared to countries with compulsory and long-standing BCG policies consistent with a possible protective role of the BCG vaccine against COVID-19^[45,47]. As promising and hopeful as these data may be, these are epidemiology studies and not controlled trials thus it is imperative for large scale randomized control trials be carried out to test this theory. The BRACE (Australia) and BCG-CORONA (Netherlands) randomized-controlled trials are currently in progress to assess the effectiveness of the BCG vaccine to enhance the immune systems of healthcare workers against COVID-19^[49,50]. Results from these studies will provide empirical data to support the epidemiological reports above and offer some hope to the world. As the pandemic escalates globally, basic infection prevention and control guidelines appear to be the best option to mitigate the spread of the disease.

INFECTION PREVENTION AND CONTROL FOR COVID-19

The route of transmission, pathologies, and manifestation of SARS-CoV-2 clearly show some similarities to SARS-CoV and MERS-CoV. Both SARS-CoV and MERS-CoV infect intrapulmonary epithelial cells better than cells of the upper airways making transmission to occur primarily from patients with recognized illness and not from patients with mild, nonspecific signs^[51]. The incubation period of SARS-CoV-2 is between 1-14 d and patients present with fever associated with flu-like symptoms including cough, sore throat, headache, body weakness and myalgia (fatigue) to severe respiratory illnesses associated with shortness of breath and breathing difficulties^[52]. In critical cases, individuals may show symptoms of pneumonia associated with complications of severe acute respiratory and cardiac distress, and kidney failure, which can eventually lead to death. The long incubation period facilitates the spread of the infection to others through contact and exposure to infected droplets.

It has been suggested that SARS-CoV-2 uses the same cellular receptor (human angiotensin-converting enzyme 2) as SARS-CoV, making transmission to occur mainly after signs of lower respiratory tract disease has developed^[53]. Similar to SARS-CoV and MERS-CoV, the transmission of SARS-CoV-2 occurs by means of droplets and contact with infected persons. Therefore, public health measures and strict adherence to standard precautions in health care settings, are critical in controlling the pandemic^[54]. Together, breaking the chain of transmission of a pandemic like COVID-19 is a shared responsibility; the population and the state have unique roles to play.

Population

Individuals must practice physical distancing (staying 2 metres apart from other people at all times). Anyone who is ill, including mild respiratory symptoms, must stay home and monitor their health for fever, cough or difficulty breathing and based on national legislation, report their symptoms to the public health authorities for tracing and eventual testing. All returning international travellers must stay home for 14 d. The population must be encouraged to practice good hand hygiene and cough etiquette. For example, washing of hands often with soap and warm running water,

or alcohol-based hand sanitizers and covering mouth and nose with the arm when coughing or sneezing to avoid the expulsion of droplets to others. People should avoid touching their eyes, nose, and mouth unless they have just washed their hands. Unnecessary movements should be restricted and if someone should go out for essential visits, he or she should wear a mask that covers the nose and mouth and care should be observed when handling the mask.

Health care establishments

All healthcare establishments should perform active and passive screening. Persons conducting screening should ideally be behind an impermeable barrier to protect them from droplet from sneezing/coughing patients. If a patient screens positive, he or she should immediately be asked to don a surgical mask and be isolated. From this time onwards, healthcare workers should apply standard and transmission-based precautions including the appropriate use of personal protective equipment such as gloves, gown, surgical/procedure masks and eye protection (goggles or face shields) for patient care^[54]. As a general rule, health care workers should use a risk assessment approach before and during each patient interaction to evaluate the likelihood of exposure. In the event that an aerosol generating medical procedure has to be done, droplet, contact and airborne precautions should be observed, and the procedure should be done in an airborne infection isolation room that is under negative pressure. These precautions include wearing the following personal protective equipment - gloves, gown, N95 fit-tested respirators and eye protection (goggles/face shields)^[55,56]. Patients who test positive for SARS-CoV-2 should not be cohorted with non-COVID-19 patients, but may be cohorted with other patients confirmed to have COVID-19. It is essential to routinely clean and disinfect care equipment, surfaces and environment using approved hospital-grade disinfectants.

Governments and public health authorities

It is the responsibility of every nation to protect the lives of its citizens. Once an outbreak of a disease with pandemic potential is determined, there should be declaration of a state of emergency to help contain the spread and protect the public. Consequently, the following establishments are required to closed to prevent congregation of persons; bars and restaurants (except to the extent that such facilities provide takeout and deliveries), indoor recreational centers, public libraries, churches, schools, child care centres, movie cinemas, theatres, concert venues and other communal or shared public or private centres. Additionally, all organized public events of over 5 people (or when a 2 m separation cannot be maintained) should be prohibited, including parades, funeral, weddings, and other social gatherings. As much as possible employees should be encouraged to work from home if feasible. Travel restrictions should be put in place to discourage the population from international travels especially to highly impacted countries. Returning travellers must self-isolate and monitor for symptoms for 14 d.

Also, it is absolutely necessary that the right information is given to the population to avoid the dissemination of false and inaccurate information and all rumours and conspiracies should be debunked with scientific evidence. The population through community leaders should be involved in decision making as an inclusive approach will results in better compliance and positive outcomes.

CONCLUSION

From 2002, there has been a pattern of coronaviruses emerging and causing epidemics every 8-10 years. The SARS-CoV, MERS-CoV, and now SARS-CoV-2 that have been responsible for global epidemics starting in 2002, 2012, and 2019 respectively^[57]. It is known that coronaviruses reside in animal reservoirs but the spillover mechanism into human population is not fully understood. In our opinion, coronaviruses will continue to emerge periodically and unpredictably, spreading and inducing serious infectious diseases of huge global health impact.

Although the first vaccine against COVID-19 is being developed and a chain of therapeutic clinical trials are underway, there are no approved drugs or vaccine for the treatment or prevention of coronavirus infections^[58]. Furthermore, the range of animal reservoirs for coronaviruses makes the threat to the human population worse. A starting point in the prevention of future coronavirus outbreak is the regulation of wildlife meat trades in order to reduce the risk of animal to human spillover of the virus, surveillance and development of laboratory capacities for early detection.

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