SARS-CoV-2 and Coronavirus Disease 2019

Subjects: Infectious Diseases | Microbiology

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Coronaviruses, named for the crown-like spikes on their surface (Latin: corona = crown), are positive-sense RNA viruses that belong to the Coronvirinae subfamily, in the Coronaviridae family of the Nidovirales order. They have four main subgroups—alpha, beta, gamma, and delta—based on their genomic structure. Alpha- and betacoronaviruses infect only mammals, usually causing respiratory symptoms in humans and gastroenteritis in other animals. In December 2019, a cluster of fatal pneumonia cases presented in Wuhan, China. Based on clinical criteria and available serological and molecular information, the new disease was called coronavirus disease of 2019 (COVID-19), and the novel coronavirus was called SARS Coronavirus-2 (SARS-CoV-2), emphasizing its close relationship to the 2002 SARS virus (SARS-CoV).

Coronavirus COVID-19 SARS SARS-CoV-2 pandemic

1. Introduction

Coronaviruses, named for the crown-like spikes on their surface (Latin: corona = crown), are positive-sense RNA viruses that belong to the Coronvirinae subfamily, in the Coronaviridae family of the Nidovirales order [1]. They have four main subgroups—alpha, beta, gamma, and delta—based on their genomic structure. Alpha- and betacoronaviruses infect only mammals, usually causing respiratory symptoms in humans and gastroenteritis in other animals [2][3]. Until December of 2019, only six different coronaviruses were known to infect humans. Four of these (HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1) usually caused mild common cold-type symptoms in immunocompetent people and the other two have caused pandemics in the past two decades. In 2002–2003, the severe acute respiratory syndrome coronavirus (SARS-CoV) caused a SARS epidemic that resulted in a 10% mortality.

In late 2019, a cluster of pneumonia cases in Wuhan City, Hubei Province, China were identified as with a novel betacoronavirus, first called the 2019 novel coronavirus (2019-nCov) and often referred to as the Wuhan coronavirus. When the genomics of the 2019-nCov was sequenced, it shared 79.5% of the genetic sequence of the SARS-CoV that caused the 2002–2003 pandemic [4] and the International Committee on Taxonomy of Viruses renamed the 2019-nCov as SARS-CoV-2 [5]. Patients began to present in November and December with various degrees of respiratory distress of unknown etiology and treated at the time as possible influenza infections. As it became apparent that most cases had a shared history of exposure to the Huanan Seafood Wholesale Market (the so-called “wet market”), the Wuhan local health authority issued an epidemiologic alert on 30 December 2019 and the wet market was closed. About a week later, on 9 January 2020, Chinese researchers shared the full genetic sequence of the novel coronavirus, now called SARS-CoV-2 [6]. Since the novel coronavirus was recognized, the disease it caused was termed coronavirus disease 2019 (CoVID-19), and several reports on the clinical presentation, epidemiology, and treatment strategies have been published [7][8][9][10]. In addition, several websites have been setup to track the epidemic and the case detection rate,

which are being updated as often as hourly [11][12][13][14]. On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak to be a global public health emergency, sixth after H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019), and on 11 March 2020, the WHO characterized COVID-19 as a pandemic [15]. The timeline of events is summarized in **Figure 1**.

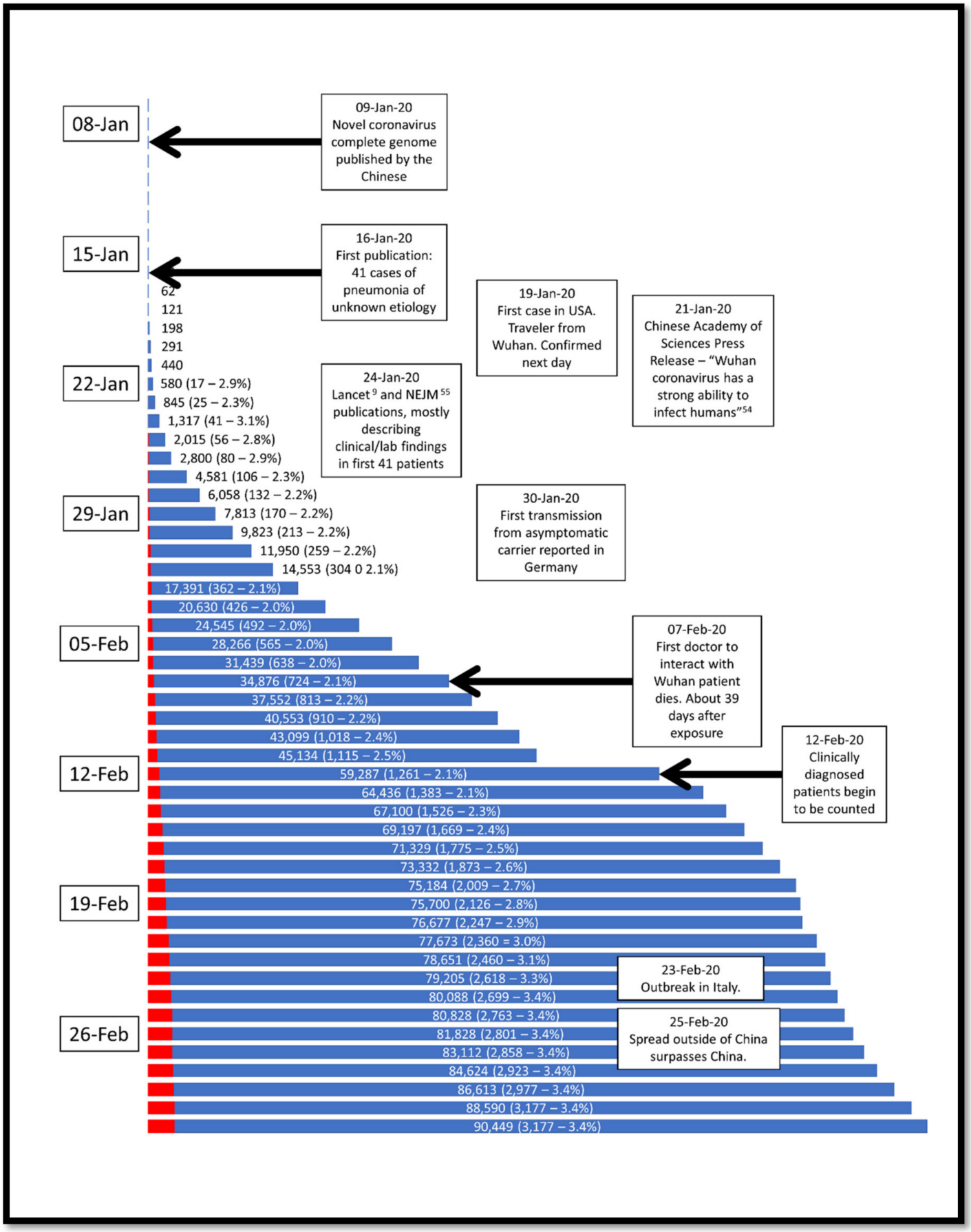
08-Jan
09-Jan-20
Novel coronavirus complete genome published by the Chinese
15-Jan
16-Jan-20
First publication: 41 cases of pneumonia of unknown etiology
19-Jan-20
First case in USA. Traveler from Wuhan. Confirmed next day
21-Jan-20
Chinese Academy of Sciences Press Release – "Wuhan coronavirus has a strong ability to infect humans"[54]
62
121
198
291
440
22-Jan
580 (17 – 2.9%)
845 (25 – 2.3%)
1,317 (41 – 3.1%)
2,015 (56 – 2.8%)
2,800 (80 – 2.9%)
4,581 (106 – 2.3%)
24-Jan-20
Lancet[9] and NEJM[55] publications, mostly describing clinical/lab findings in first 41 patients
6,058 (132 – 2.2%)
29-Jan
7,813 (170 – 2.2%)
9,823 (213 – 2.2%)
11,950 (259 – 2.2%)
14,553 (304 0 2.1%)
30-Jan-20
First transmission from asymptomatic carrier reported in Germany
17,391 (362 – 2.1%)
20,630 (426 – 2.0%)
24,545 (492 – 2.0%)
05-Feb
28,266 (565 – 2.0%)
31,439 (638 – 2.0%)
34,876 (724 – 2.1%)
07-Feb-20
First doctor to interact with Wuhan patient dies. About 39 days after exposure
37,552 (813 – 2.2%)
40,553 (910 – 2.2%)
43,099 (1,018 – 2.4%)
45,134 (1,115 – 2.5%)
12-Feb
59,287 (1,261 – 2.1%)
12-Feb-20
Clinically diagnosed patients begin to be counted
64,436 (1,383 – 2.1%)
67,100 (1,526 – 2.3%)
69,197 (1,669 – 2.4%)
71,329 (1,775 – 2.5%)
73,332 (1,873 – 2.6%)
75,184 (2,009 – 2.7%)
19-Feb
75,700 (2,126 – 2.8%)
76,677 (2,247 – 2.9%)
77,673 (2,360 = 3.0%)
78,651 (2,460 – 3.1%)
79,205 (2,618 – 3.3%)
23-Feb-20
Outbreak in Italy.
80,088 (2,699 – 3.4%)
80,828 (2,763 – 3.4%)
25-Feb-20
Spread outside of China surpasses China.
26-Feb
81,828 (2,801 – 3.4%)
83,112 (2,858 – 3.4%)
84,624 (2,923 – 3.4%)
86,613 (2,977 – 3.4%)
88,590 (3,177 – 3.4%)
90,449 (3,177 – 3.4%)

Figure 1. Timeline of the SARS-CoV-2 epidemic, with significant dates noted. Each blue bar represents the cumulative number of COVID-19 patients diagnosed to that day, and the red bar the cumulative number of deaths. At each date, the actual numbers are present. Data from Worldometer [13].

2. The Origin of SARS-CoV-2

All coronaviruses that have caused diseases to humans have had animal origins—generally either in bats or rodents [16]. Previous outbreaks of betacoronaviruses in humans involved direct exposure to animals other than bats. In the case of SARS-CoV and MERS-CoV, they were transmitted directly to humans from civet cats and dromedary camels respectively (**Figure 2**).

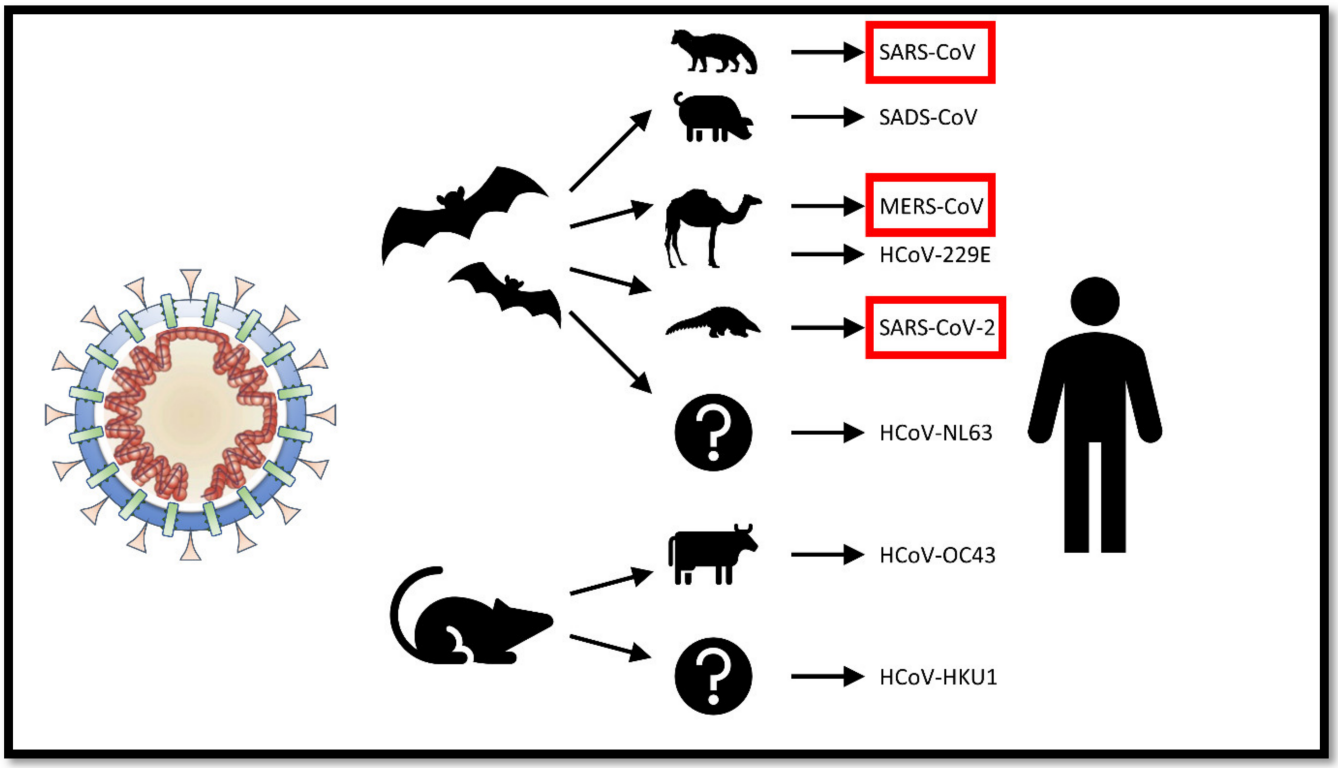

Figure 2. Animal origins of human coronaviruses. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) and were transmitted to humans from bats by civet cats and dromedary camels, respectively. The 2019 SARS-CoV-2 was likely transmitted to humans through pangolins that are illegally sold in Chinese markets [16][17].

The SARS-related coronaviruses are covered by spike proteins that contain a variable receptor-binding domain (RBD). This RBD binds to angiotensin-converting enzyme-2 (ACE-2) receptor found in the heart, lungs, kidneys, and gastrointestinal tract [18] thus facilitating viral entry into target cells. Based on genomic sequencing, the RBD of SARS-CoV-2 appears to be a mutated version of its most closely related virus, RaTG13, sampled from bats (*Rhinolophus affinis*) [19]. It is, therefore, believed that the SARS-CoV-2 also originated from bats and, after mutating, was able to infect other animals. The mutation increased the RBD affinity to ACE-2 in humans, but also other animals such as ferrets and Malayan pangolins (*Manis javanica*; a long-snouted, ant-eating mammal sold illegally for use in traditional

Chinese medicine), but also decreased the RBD affinity to ACE-2 found in rodents and civets. The pangolin is believed to be the intermediate host of SARS-CoV-2 [17].

There was some early speculation that SARS-CoV-2 emerged from a manmade manipulation of an existing coronavirus, but there is no evidence to support such a theory. In fact, Anderson et al. suggest that the particular mutation that was found in the RBD of SARS-CoV-2 is different to what would have been predicted based on previously used genetic systems.

3. Pathogenesis and Clinical Presentation

Since SARS-CoV and SARS-CoV-2 are so similar, the biochemical interactions and the pathogenesis are likely similar. Binding of the SARS-CoV to the angiotensin-converting enzyme 2 (ACE-2) receptors in the type II pneumocytes in the lungs triggers a cascade of inflammation in the lower respiratory tract [20]. It has been demonstrated that when the SARS spike protein binds to the ACE-2 receptor (**Figure 3**A), the complex is proteolytically processed by type 2 transmembrane protease TMPRSS2 leading to cleavage of ACE-2 and activation of the spike protein (**Figure 3**B) [21][22], similar to the mechanism employed by influenza and human metapneumovirus, thus facilitating viral entry into the target cell (**Figure 3**C). It has been suggested that cells in which ACE-2 and TMPRSS2 are simultaneously present are most susceptible to entry by SARS-CoV [23]. Early indications are that SARS-CoV-2 virus also requires ACE-2 and TMPRSS2 to enter cells [24].

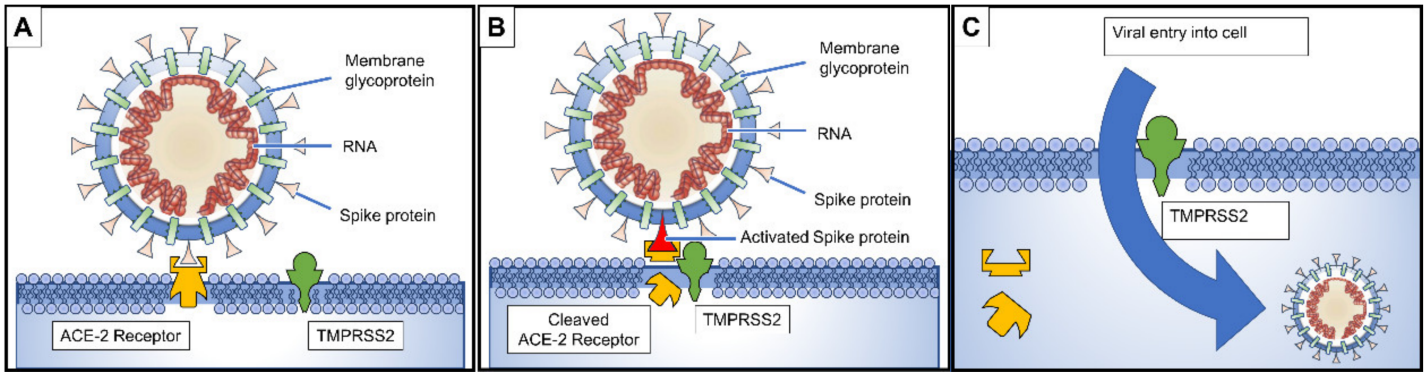

Figure 3. (**A**) Spike proteins on the surface of the coronavirus bind to angiotensin-converting enzyme 2 (ACE-2) receptors on the surface of the target cell; (**B**) The type II transmembrane serine protease (TMPRSS2) binds to and cleaves the ACE-2 receptor. In the process, the spike protein is activated; (**C**) Cleaved ACE-2 and activated spike protein facilitate viral entry. TMPRSS2 expression increases cellular uptake of the coronavirus [20][21][22].

4. Epidemiology

As of March 16, 0700 GMT, there were 169,930 confirmed cases, about half of which (80,860 cases, 47.6%) were within mainland China. About 18% of ill people had severe disease, and 82.0% had mild disease and a total of 889 tested-positive cases were asymptomatic [13][25]. While initially confined to China among those who visited the Wuhan wet market, over the course of about 3 months the SARS-CoV-2 has to date been confirmed in 157 countries and one cruise ship [13]. The Chinese CDC published the epidemiologic characteristics of the COVID-19 outbreak as of 11

February 2020 (**Table 1**) [26]. Initial data suggests that the majority of patients (73%) were over age 40 years, and that the risk of death increases with age. No deaths were reported in patients younger than 10 years old, and only 2.6% of the total fatalities were in patients younger than 40 years of age.

Table 1. Epidemiologic characteristics of the first 44,672 confirmed cases in China [26].

	No. Cases (%)	Deaths (%)	CFR (%)
Overall	44,672	1023	2.3
Age			
0–9 yrs	416 (0.9)	-	-
10–19 yrs	549 (1.2)	1 (0.1)	0.2
20–29 yrs	3619 (8.1)	7 (0.7)	0.2
30–39 yrs	7600 (17.0)	18 (1.8)	0.2
40–49 yrs	8571 (19.2)	38 (3.7)	0.4
50–59 yrs	10,008 (22.4)	130 (12.7)	1.3
60–69 yrs	8583 (19.2)	309 (30.2)	3.6
70–79 yrs	3918 (8.8)	312 (30.5)	8.0
≥ 80 yrs	1408 (3.2)	208 (20.3)	14.8
Wuhan related exposure			
Yes	31,974 (85.8)	853 (92.8)	2.7

	No. Cases (%)	Deaths (%)	CFR (%)
No	5295 (14.2)	66 (7.2)	1.2
Case Severity			
Mild	36,180 (80.9)	-	-
Severe	6168 (13.8)	-	-
Critical	2087 (4.7)	1023 (100)	49.0
Missing	257 (0.6)	-	-

[11][13]

rch 2020, been 6522 ntainment strategies in China, including a mass quarantine of the entire 11 million population of Wuhan, the acceleration of new cases in China has slowed whereas that outside of China has increased. As of March 2nd, the number of daily new cases outside of China was nine times higher than those within China. Many countries have instituted travel bans and/or quarantine procedures for incoming travelers. Closures of public schools and social gatherings have been instituted in many countries in an effort to contain the spread of COVID-19 and decrease the public health burden [27][28] and the CDC has released recommendations on school closure criteria [29].

In comparison, the 2002 SARS pandemic, which also originated in China, resulted in 8096 people infected and 774 deaths (9.6%). On the other hand, the 2012 MERS pandemic infected 2494 people causing 858 deaths (34.4%). Therefore, although MERS and SARS had higher mortality, the much larger number of people infected with SARS-CoV-2, and the rate at which the number is increasing, raises red epidemiologic flags.

5. Risk Factors for Mortality

At such an early phase of the COVID-19 pandemic, it is difficult to accurately describe the populations most at risk, especially when teasing out risk factors for infection from risk factors for death from disease. Early on, it became clear that those who have visited the Wuhan wet market were most at risk of infection, but the population visiting the market is not an accurate reflection of the general population. The Chinese CDC published the epidemiologic characteristics of the COVID-19 outbreak along with associated risk factors for death [26].

The largest risk factor for death is age. Other risk factors include male sex and the presence of comorbid conditions. However, in addition to real age-specific mortality, the age-based risk could reflect underlying comorbidities among the elderly and the distribution of the underlying population in Wuhan, where the outbreak initiated.

Early in the COVID-19 epidemic, it appeared that children were a protected group, but this may have been because they were less likely to have frequented the Wuhan wet market, or because they were more likely to have asymptomatic or mild disease and thus less likely to have been tested. COVID-19 has affected infants as young as 1 month of age [30], most with mild or asymptomatic disease. There have been no reported cases of adverse infant outcomes for mothers who developed COVID-19 during pregnancy.

Second to the Hubei population, the other population at increasing risk is healthcare workers. As of February 17, 2020, total of 1716 healthcare workers in China have been infected, five of whom fatally [25].

6. Treatment

The current best strategy of treatment of patients with COVID-19 is purely supportive. Clinicians and intensive care specialists are applying much of what they have learned during the SARS epidemic to guide current therapy of COVID-19. Recommendations for admission to critical care units, guidelines for infection control, and procedures to minimize nosocomial transmission are being established [31]. However, there are several fronts that are being studied to develop targeted treatments.

The most efficient approach to the treatment of COVID-19 is to test whether existing antiviral drugs are effective. In previous betacoronavirus epidemics, several antiviral drugs, such as ribavirin, interferon, lopinavir-ritonavir, and darunavir/cobicistat (prezcobix) were tested, with some showing promising in vitro results [32]. Remdesivir, an adenosine analog used against RNA viruses (including SARS and MERS-CoV), was a candidate Ebola treatment with promising in vitro results but disappointing in vivo effects against Ebola [33][34]. There is currently in vitro evidence that remdesivir may be effective in controlling SARS-CoV-2 infection [35]. In fact, compassionate use of remdesivir was employed in the treatment of the first COVID-19 case in the United States, during a period of rapid clinical deterioration, and within one day there was dramatic improvement of the clinical condition [36]. Randomized double-blinded, placebo-controlled clinical trials are currently underway in China and USA to evaluate the efficacy of remdesivir and initial results are expected by the end of April 2020 [37][38].

Other existing drug candidates include chloroquine and camostat mesylate. Chloroquine is a widely used anti-malarial drug that is known to block virus-cell fusion and has been shown to interfere with the glycosylation of SARS-CoV and ACE-2 cellular receptors, rendering the ACE-2-SARS-CoV interaction less efficient [39]. There is also in vitro evidence that chloroquine may be effective in preventing SARS-CoV-2 cellular entry [35]. Camostat mesylate, also known as FOY 305 [40], was initially developed and currently approved for the treatment of chronic pancreatitis in Japan [41][42]. Camostat mesylate targets the TMPRSS2 protease, theoretically preventing viral entry. Researchers in Germany showed that camostat mesylate reduced the amount of SARS-CoV-2 viral replication [43].

A simple but very effective treatment modality is the use of convalescent plasma, or serum from patients who have recovered from the virus, to treat patients. Patients with resolved viral infection will have developed a specific antibody response which may be helpful in neutralizing viruses in newly infected individuals. This modality was successfully employed during the 2014–2015 Ebola outbreak [44][45]. However, the use of convalescent sera is of limited benefit in an

outbreak situation since the exponential growth of infected patients exceeds the ability of previous patients to provide donor plasma.

A second strategy is to create an ACE-2-like molecule that would bind to the S protein of the coronavirus itself. Again, research in to the 2002 SARS virus demonstrated that soluble ACE-2 proteins blocked the SARS virus from infecting cells in vitro [46][47]. The additional benefit to using this strategy lies in the possible prevention of S protein-mediated ACE-2 shedding that has been shown to induce the pulmonary edema characteristic of SARS [48][49]. A phase II clinical trial of recombinant ACE-2 in ARDS reported significant modulation of inflammatory proteins, but no significant differences in respiratory parameters [50]. Further research is necessary to assess if the animal studies will translate to clinical benefit.

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