Journal of Autoimmunity xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China

Yongshi Yang[a,1], Fujun Peng[b,c,1], Runsheng Wang[d,1], Kai Guan[a], Taijiao Jiang[b,c,****], Guogang Xu[e,***], Jinlyu Sun[a,**], Christopher Chang[f,g,*]

[a] Department of Allergy & Clinical Immunology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, National Clinical Research Center for Immunologic Diseases, Beijing, 100730, China
[b] Center for Systems Medicine, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100005, China
[c] Suzhou Institute of Systems Medicine, Suzhou, Jiangsu 215123, China
[d] Department of Respiratory Diseases, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing, 100853, China
[e] Department of Infection Prevention and Disease Control, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing, 100853, China
[f] Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis, Davis, CA, 95616, USA
[g] Division of Pediatric Immunology and Allergy, Joe DiMaggio Children's Hospital, Hollywood, FL, USA

ARTICLE INFO

Keywords:
Coronavirus
SARS-CoV-2
SARS-CoV
Epidemiology
Pneumonia
Flu
Bats
Human to human transmission
Epidemic
Pandemic
Pyroptosis

ABSTRACT

The 2019-nCoV is officially called SARS-CoV-2 and the disease is named COVID-19. This viral epidemic in China has led to the deaths of over 1800 people, mostly elderly or those with an underlying chronic disease or immunosuppressed state. This is the third serious Coronavirus outbreak in less than 20 years, following SARS in 2002–2003 and MERS in 2012. While human strains of Coronavirus are associated with about 15% of cases of the common cold, the SARS-CoV-2 may present with varying degrees of severity, from flu-like symptoms to death. It is currently believed that this deadly Coronavirus strain originated from wild animals at the Huanan market in Wuhan, a city in Hubei province. Bats, snakes and pangolins have been cited as potential carriers based on the sequence homology of CoV isolated from these animals and the viral nucleic acids of the virus isolated from SARS-CoV-2 infected patients. Extreme quarantine measures, including sealing off large cities, closing borders and confining people to their homes, were instituted in January 2020 to prevent spread of the virus, but by that time much of the damage had been done, as human-human transmission became evident. While these quarantine measures are necessary and have prevented a historical disaster along the lines of the Spanish flu, earlier recognition and earlier implementation of quarantine measures may have been even more effective. Lessons learned from SARS resulted in faster determination of the nucleic acid sequence and a more robust quarantine strategy. However, it is clear that finding an effective antiviral and developing a vaccine are still significant challenges. The costs of the epidemic are not limited to medical aspects, as the virus has led to significant sociological, psychological and economic effects globally. Unfortunately, emergence of SARS-CoV-2 has led to numerous reports of Asians being subjected to racist behavior and hate crimes across the world.

1. Introduction

Coronaviruses (CoVs) are named for the crown-like spikes on their surface and belong to the family Coronaviridae within the order Nidovirales. Coronaviruses broadly infect vertebrates including humans, birds, bats, snakes, mice and other wild animals [1,2]. Since the mid-1960s, seven known human coronaviruses (HCoVs) have been identified [3,4]. Four commonly detected HCoVs are 229E, OC43, NL63 and HKU1. In one study, 229E and OC43 accounted for approximately 15–29% of respiratory pathogens with relatively low virulence in

* Corresponding authors. University of California, Davis, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA.
** Corresponding author. No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing, 100730, China.
*** Corresponding authors. No.28 Fuxing Road, Beijing, 100853, China.
**** Corresponding author. No.9, Dongdan 3 rd, Dongcheng District, Beijing, 100005, China.
E-mail addresses: taijiao@ibms.pumc.edu.cn (T. Jiang), guogang_xu@qq.com (G. Xu), sunjinlv@pumch.cn (J. Sun), chrchang@ucdavis.edu (C. Chang).
[1] Yongshi Yang, Fujun Peng, Runsheng Wang contributed equally to this work.

https://doi.org/10.1016/j.jaut.2020.102434
Received 19 February 2020; Received in revised form 22 February 2020; Accepted 22 February 2020

humans [3,5]. Another epidemiological study in adults estimates that coronavirus causes about 15% of common colds [6]. Other significant causes of upper respiratory infections include influenza virus, rhinovirus, parainfluenza virus, Group A Streptococci, EBV and respiratory syncytial virus (RSV).

The three other strains of HCoVs, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have a different pathogenicity and lead to higher mortality rates in human populations. MERS-CoV was isolated from a male patient who died from acute pneumonia and renal failure in Saudi Arabia in 2012 [7], and was subsequently responsible for 2494 cases and 858 deaths from 27 different countries (case-fatality rate: 34.4%) [8]. Both SARS-CoV and SARS-CoV-2 were first recognized in China. SARS-CoV caused a total of 8422 probable SARS cases, 919 SARS-related deaths (case-fatality rate: 11%) and spread to 32 different countries or regions between November 2002 and August 2003 [9]. Since December 2019, the SARS-CoV-2 has infected 73,230 people and caused 1871 deaths (case-fatality rate: 2.6%) and has spread to 25 countries, according to the State Council Information Office in Beijing, China (updated as of Feb. 17, 2020) [10]. As of this date, the number of confirmed and suspected cases is still increasing, as is the number of deaths, although there is a significant increase in the number of recovered patients as well.

Coronaviruses were first identified in the 1960s. It is not known for how long they have existed. Most of the time they are associated with mild disease, but every few years a highly virulent strain appears. The pathogenesis of these deadly epidemics is unclear. An examination of the structure of the viruses and the mechanism of infection may help elucidate and provide information for the development of effective treatment and possibly vaccines. Our purpose of this review is to provide a brief summary of the epidemiology and history of SARS, as well as the lessons learned. The other aim is to review the epidemiology, pathogenesis, clinical characteristics, diagnosis and management of patients infected with SARS-CoV-2 to better understand this deadly coronavirus and suggest prevention, treatment and management strategies.

2. Characteristics of coronaviruses and coronavirus infections

2.1. Biology of the coronaviruses

CoVs are enveloped with a non-segmented, positive-sense, single-strand RNA, with size ranging from 26,000 to 37,000 bases. This is the largest known genome among RNA viruses [11]. The genomic structure of CoVs is as follows: 5′-leader-UTR-replicase-S (Spike)–E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTRpoly (A) tail. There are accessory genes interspersed within the structural genes at the 3′ end of genome [12], some of which have been shown to play an important roles in viral pathogenesis [13]. The S protein is responsible for receptor-binding and subsequent viral entry into host cells, the M and E proteins play important roles in viral assembly, and the N protein is necessary for RNA synthesis [12,14].

2.2. Coronavirus transmission

CoVs can transmit across species barriers. SARS-CoV originated from bats of the Hipposideridae family, using palm civets as intermediary hosts before dissemination to humans [15,16]. The earliest patients infected with SARS-CoV-2 in Wuhan ultimately caused the epidemic known as COronaVIrus Disease 2019 (COVID-2019). Some of these patients had a history of contact with a wholesale seafood market in the early stages, suggesting animal-to-person spread. Subsequently, a large number of patients reportedly did not have exposure to the markets, suggesting the development of person-to-person spread [17–20].

There are three primary ways to transmit the virus, including close person-to-person contact, aerosol transmission, and transmission by touch [21–23]. The virus is thought to be transmitted to other people by respiratory droplets during coughing or sneezing. Droplet spread can occur when an infected person sneezes or coughs, whereupon virus containing droplets are propelled up to 3 feet through the air and are deposited on the mucous membranes of the mouth, nose, or eyes of persons who are nearby. A recent report suggests that transmission through the ocular surface is also possible [24]. The other avenues for the spread of the virus are shaking hands with an infected person, touching an infected object/surface, frequent touching of the nose or mouth or coming into contact with a patient's excreta. Another avenue is through “hidden transmission” [19], in which asymptomatic infected individuals or carriers unknowingly transmit the virus to unsuspecting contacts.

2.3. Variability of clinical presentation

Before the first outbreak of SARS, a limited number of HCoVs such as HCoV-229E were frequently found to infect humans, and were widely circulating in human populations causing only mild illnesses like the common cold [3,25]. However, SARS, MERS and SARS-CoV-2 present with a spectrum of disease severity ranging from flu-like symptoms to acute respiratory distress syndrome [25,26]. Early on, these patients are usually treated with conventional medications which had no clinical benefit, resulting in spread to health care personnel. For those with flu-like symptoms or even more severe disease, it would not be immediately evident that this is an atypical and virulent form of a coronavirus. For comparison, influenza has an estimated mortality rate of 0.07%–0.2%. A high index of suspicion is helpful but not foolproof.

2.4. Genetic diversity

The various CoVs of animal origin undergo evolution and genetic recombination, thereby resulting in mutated CoVs that may be highly pathogenic and potentially be more deadly to humans [3,27]. For SARS-CoV, the mutation rate in the SARS-CoV genome was estimated to be 0.80–2.38 $\times$ 10^{-3} nucleotide substitutions per site per year, and the nonsynonymous and synonymous substitution rates were estimated to be 1.16–3.30 $\times$ 10^{-3} and 1.67–4.67 $\times$ 10^{-3} per site per year, respectively, which are similar to that of other RNA viruses [28]. The various CoVs of animal origin undergo evolution and genetic recombination either within the host species or upon jumping from one species to another. Such changes thus have the potential to lead to variants that have high pathogenic potential when transmitted to humans [29–31]. Recently, two mutations of the S protein and N protein SARS-CoV-2 may explain its zoonotic transmission [32]. Genomic alignment of 54 SARS-CoV-2 genomes identified two hotspots of hypervariability at positions 8789 (synonymous variant) and 28,151(Ser/Leu change), located in the polyprotein and ORF8 genes respectively [33].

2.5. Comorbidities

Most patients who have died from the virus had other chronic medical conditions, were elderly patients or were immunocompromised. One study reported that 6.7% of SARS patients had acute renal impairment and 84.6% had proteinuria [34]. Hematological abnormalities such as thrombocytopenia and lymphopenia were frequently observed in SARS [35,36]. Complications encountered for SARS-CoV-2 include acute respiratory distress syndrome (29%,12/41), anemia (15%, 6/41), acute cardiac injury (12%, 5/41) and secondary infection (10%, 4/41) [26]. In a SARS-CoV-2 descriptive study, 11 of 99 patients died of multiple organ failure, and seven were older than 60 years [37].

2.6. Lack of effective treatment

To date, there is no anti-viral therapeutics that specifically targets human coronaviruses, so treatment is only supportive. *In vitro*, interferons (IFNs) are only partially effective against coronaviruses [38]. *In vivo*, the effectiveness of IFNs combined with ribavirin requires further evaluation [39]. A variety of other agents, including antiviral peptides and corticosteroids have been shown to be effective *in vitro* and/or in animal models [40,41]. However, clinical evidence does not support the use of corticosteroid treatment for SARS-CoV-2 lung injury [42]. Vaccines that have been developed are either not effective, or in some cases have been reported to be involved in the selection of novel pathogenic CoVs via recombination of circulating strains [12,22,40]. Vaccine development can be a challenge. It is noteworthy that almost 20 years after SARS, there is still no vaccine for coronavirus.

3. A historical review of the epidemiology of SARS and how it was contained

It has been 17 years since the outbreak of severe acute respiratory syndrome (SARS) caused by the SARS coronavirus (SARS-CoV) [43]. This highly contagious atypical pneumonia first appeared in Guangdong Province, China, in November 2002. The initial cases were animal handlers in Guangzhou city having close contact with wild game food. It was suggested that civets could serve as an intermediate amplification host. Three months later, the SARS pandemic was rapidly and globally disseminated due to person-to-person transmission of the virus. On the February 21, 2003, a medical professor from Foshan in Guangdong province who was considered a “super-spreader” went to Hong Kong to visit his relatives. During his stay in Hong Kong, he transmitted the virus to 2 family members, 4 health care workers (HCWs) and 12 other nearby residents. Because of international travel and transmission to HCWs, these patients spread the SARS-CoV to Hong Kong and other countries including Vietnam, Singapore and Canada. Eventually, 8422 people were infected in 32 countries and 919 (11%) died [9]. In China, 5328 cases were reported and 349 (6.5%) perished between November 16, 2002 and June 3, 2003 [9].

At the beginning of the outbreaks in Hong Kong, mainland China and other areas, we were unfamiliar with the deadly SARS-CoV. It took about 3 months to complete the sequencing of this coronavirus [44]. The global success in the fight against SARS was partly based on epidemiological and biological characteristics of the infectious agent SARS-CoV. An understanding of transmission patterns and the ability to diagnose and confirm affected patients ultimately led to effective containment measures and a slowdown in the spread of the disease. Due to the lack of medications or a vaccine, the options for early intervention were limited to public health measures [45].

The steps that led to the containment of SARS can be illustrated by the events that occurred in Beijing. Beijing experienced the largest outbreak of SARS beginning on the March 5, 2003. The outbreak peaked within 6 weeks on the April 25, 2003 when 173 newly suspected SARS cases were hospitalized daily [46]. On the June 20, 2003, the last batch of 18 SARS patients recovered and were discharged from hospital, signaling the end of the pandemic in Beijing. The prompt resolution of the outbreak in Beijing was attributed to the rapid adoption of a series of effective control measures.

1. Thousands of local and military health workers were deployed for emergency management of the outbreak. Large quantities of emergency supplies including personal protective equipment (PPE) and medical apparat were sent to front-line medical sectors. These people and materials were key to winning the war against SARS.
2. More than 100 fever clinics were set up in all secondary and tertiary hospitals in Beijing. People visiting the fever clinics had a physical examination including body temperature, white blood cell count and chest radiograph. Fever clinics played an important role in screening and triage.
3. All actively ill patients with SARS were concentrated in designated hospital wards. On the May 1, 2003, a new 1000-bed SARS hospital (Xiaotangshan Hospital, Beijing) was built and put into operation immediately. The advantages of having such a facility was that it was more conducive to the centralized management of SARS patients, and at the same time, it reduced transmission of the virus to healthy people.
4. During the period of the SARS outbreak, more than 60,000 HCWs received medical training in the management of patients with SARS, infection control and the use of PPE.
5. Multiple measures were taken to reduce person-to-person transmission, including isolation of patients with SARS, tracing and quarantine of close contacts, transit site surveillance and closing poorly maintained facilities that could enhance spread of the virus.
6. Information dissemination was critical. Timely and accurate reporting of the status of the epidemic and scientific guidance on prevention and infection control played important roles in stabilizing people and overcoming the epidemic [45–48].

4. Lessons learned from the 2003 SARS pandemic

SARS was the very first coronavirus pandemic with the ability to spread from people to people mainly by droplets, but it would not be the last [49]. This section presents lessons learned from the SARS pandemic. Although the SARS-CoV rapidly spread throughout the world and caused great damages to human health, the global success in the fight against SARS ultimately demonstrated that containment was possible [50].

4.1. Animal source containment

Early on, there were clues suggesting the link between SARS-CoV and civets, bred for food in China [51]. Strengthening the monitoring of these wild animal sources was an important factor in controlling emergence of these virus and their spread in humans. Some scholars advocated that the trading of wild animals in wet markets in Southern China should be banned [52]. In fact, the Chinese government had issued bans on rearing, trading, transporting and slaughtering wild animals for dietary purposes over 10 years ago [53]. This however, did not stop the practice of illegal trading of wild animals.

4.2. Early detection and diagnosis

The nonspecific symptoms and signs of SARS and the long incubation period accentuated the transmission to HCWs and people in close communities [54]. Early identification of suspect cases is the key to inhibiting the spread of the virus. Rapid identification of the viral genome and the development of rapid diagnostic tests will facilitate the isolation of those who are confirmed as infected [50].

4.3. Rigorous infection control

a) Environmental hygiene in medical sectors and personal hygiene of health care workers should be maintained [55,56].
b) Contact tracing, strict isolation of actively ill patients and quarantine of close contacts should be implemented early [54].
c) Training in the use of personal protective equipment protects the safety of HCWs [57].
d) Establishing fever clinics, setting up designated hospital wards and SARS hospitals reduced human-to-human transmission [58].
e) Education of the public on communicable diseases and what measures to take on a personal basis to prevent spread.

4.4. Timely case report and rapid information dissemination

A number of studies have shown that clear and timely dissemination of information is essential in handling an outbreak [54]. Infection control is based on rapid information dissemination. Since SARS in 2003, China has implemented legislation on the surveillance, reporting and early warning system of infectious diseases, requiring the regular release of information during public health emergencies. There is a clearly defined procedure and schedule for reporting public health emergencies which requires designated medical centers to submit relevant information online. If confirmed, reports on SARS and other infectious diseases can be submitted and received directly within two hours through the Internet [53].

4.5. Vaccine development

After SARS, development of a vaccine appeared to be the best approach to prevent future SARS-CoV epidemics. However, there were many obstacles in SARS vaccine development. Firstly, researchers did not have a comprehensive understanding of the pathogenic mechanism of SARS-CoV. Secondly, animal models of SARS-CoV infection could not simulate human disease because of an incongruent pathogenesis. Thirdly, in order to test the efficacy, many people must be tested in areas where the virus is endemic. Once the SARS epidemic ended, human trials were not possible [59]. Although several candidate vaccines against SARS-CoV have been produced and tested, at present, unfortunately, there is no FDA approved vaccine against SARS.

5. The current SARS-CoV-2 infection in China

5.1. The origin of SARS-CoV-2

A cluster of cases of viral pneumonia of unknown etiology, now known as SARS-CoV-2 pneumonia, occurred in Wuhan, Hubei Province and were reported to health authorities on the December 29, 2019 [60]. This outbreak was associated with a large seafood and animal market [61]. Further investigations are ongoing to determine the origin of the infection. To date, many reports have described possible original and intermediate hosts (Fig. 1). Researchers found that the SARS-CoV-2 showed a higher sequence homology to Bat-CoV-RaTG13 that was previously detected in *Rhinolophus affinis* from Yunnan Province than Bat-SL-CoVZC21 and Bat-SL-CoVZC45, which suggested that the Chinese chrysanthemum bat is the origin of SARS-CoV-2. More recently, the pangolin was believed to be the likely intermediate host due to the fact that there appeared to be approximately 99% sequence homology between SARS-Co V-2 and the consensus sequence derived from >1000 metagenomic samples from the pangolin species [62].

5.2. New epidemiological developments

Currently, person to person transmission from patients with pneumonia or even asymptomatic patients during the incubation period are the main conduits for the spread of the infection [63]. Respiratory droplets are the main route of transmission, but the virus can also be transmitted through contact or through the fecal-oral route based on a study which demonstrated the presence of the virus in rectal swabs [64]. Fifteen health care workers in a Wuhan hospital were infected while caring for patients with confirmed or suspected infection [65,66]. As of February 11, 2020, a total of 1716 health care workers have become infected and 5 have died (0.3%) [67]. A study of a family cluster reported that five members of a family of six traveled to Wuhan, and four were infected with the SARS-CoV-2. The family member who did not travel became infected with the virus after several days of contact with the four infected members [19].

Li et al. [65] showed that human-to-human transmission among close contacts has been occurring since the middle of December 2019. Further dissemination has continued rapidly over the ensuing months. The authors estimated that the reproduction number (R_0) for SARS-CoV-2 is 2.2, meaning that every infected person can infect a mean of 2.2 people. In another study, the reproduction number of the SARS-CoV-2 was 2.68 with an epidemic doubling time of 6.4 days [68]. It is worth noting that a nucleic acid fragment of the SARS-CoV-2 was detected by Guangzhou Centers for Disease Control and Prevention (CDC) on a doorknob touched by a confirmed patient [69]. China Daily reported that scientists have discovered that stool samples from patients infected with the SARS-CoV-2 have also tested positive for the virus [70], and that the virus was also detected in the loose stool of the first patient in the US infected with the virus [71], meaning the virus has the potential to be spread through contaminated fecal material.

On the January 22, 2020, a member of the national expert panel on pneumonia reported that he was infected by SARS-CoV-2 during an inspection in Wuhan. He had worn an N95 mask but did not wear eye protection. Several days before the onset of pneumonia, he complained of redness of the eyes. Unprotected exposure of the eyes to SARS-CoV-2 in the Wuhan Fever Clinic may have allowed the virus to enter his body [24].

The situation with SARS-CoV-2 is evolving rapidly. According to the National Health Commission (NHC) of China update on February 17, 2020 [10], a total of 72,436 cases were confirmed in the Chinese mainland, including 11,741 severe cases and 1868 deaths. A total of 12,552 patients have recovered and have been discharged. An additional total of 6242 suspected cases remain. Most patients (59,989 cases) have been in Hubei province, where the outbreak began, including 10,970 severe cases and 1789 deaths. The Hong Kong and Macao Special Administrative Regions as well as Taiwan reported 92

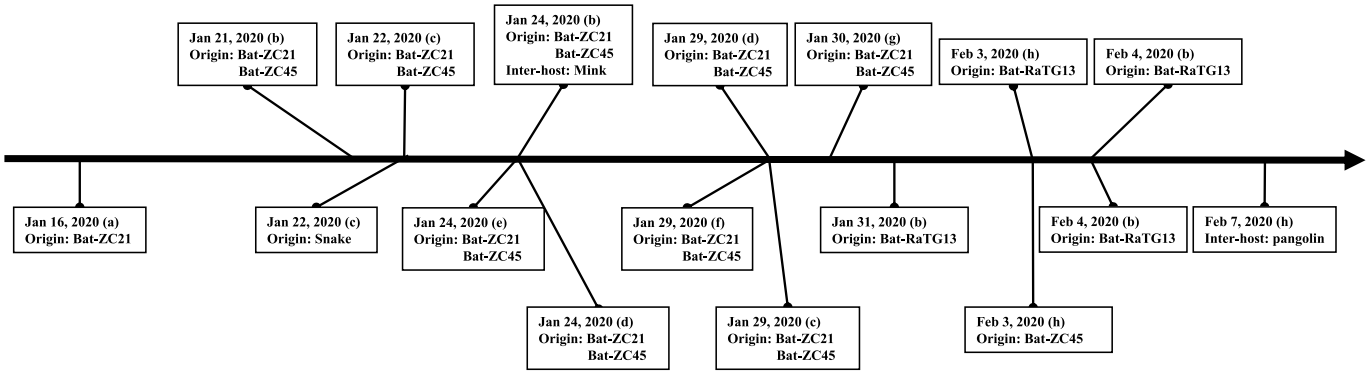

Fig. 1. The origin and inter-host timeline of SARS-CoV-2. All the information is derived from published data. Journal name: (a) Emerging Microbes & Infections, (b) bioRvix, (c) J Med Virol, (d) The Lancet, (e) the New England Journal of Medicine, (f) J Virol, (g) Chin Med J (Engl), (h) https://www.scau.edu.cn/2020/0207/c1300a219015/page.htm. Bat-ZC21: Bat-SL-CoVZC21, GenBank Accession MG772934; Bat-ZC45: Bat-SL-CoVZC45, GenBank Accession MG772933; Bat-RaTG13: yun-nan-Bat-CoV-RaTG13, GISAID accession EPI_ISL_402,131.

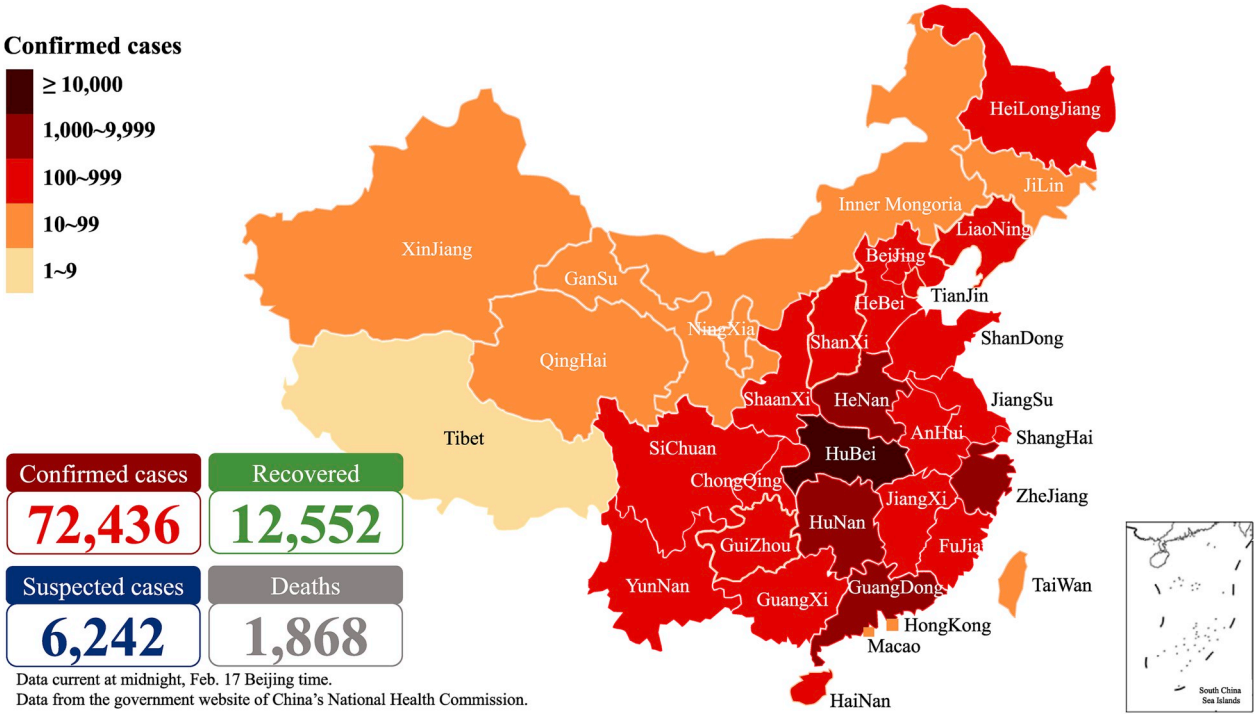

Fig. 2. Confirmed cases of SARS-CoV-2, February 17, 2020. (Data from the government website of China's National Health Commission).

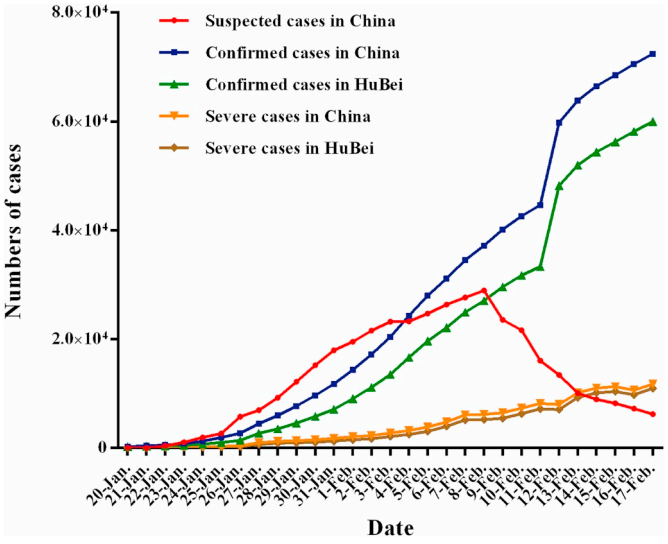

Fig. 3. Numbers of suspected, confirmed and severe cases of SARS-CoV-2 in China and Hubei province, February 17, 2020. (Data from the government website of China's National Health Commission. Since February 12, 2020, Hubei Province has included the number of clinical diagnosis cases into the number of confirmed cases).

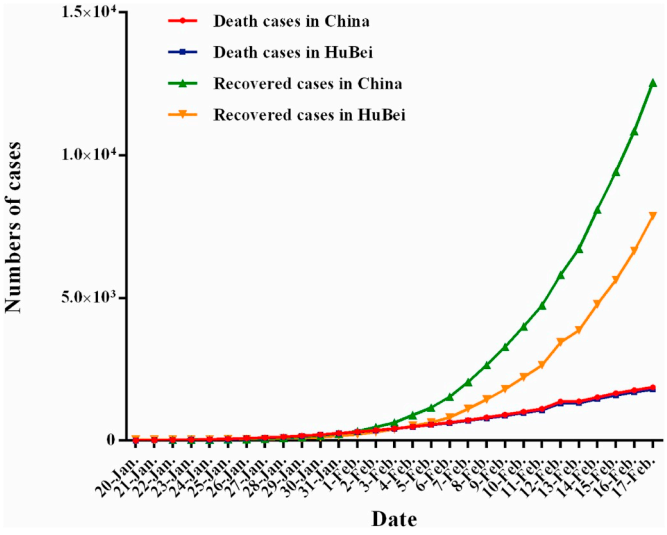

Fig. 4. Numbers of deaths and recovered cases of SARS-CoV-2 in China and Hubei, February 17, 2020. (Data from the government website of China's National Health Commission).

confirmed cases of the disease, including 2 deaths and 9 patients who have recovered. There are significantly more SARS-CoV-2 cases than SARS cases during the 2003 outbreak. The current spread of the epidemic in China is shown in Figs. 2–4.

According to World Health Organization (WHO) SARS-CoV-2 Situation Report [72], additional cases have been identified in a growing number of other international locations, including 25 countries outside China (Fig. 5). There are now three deaths that have been reported outside of China (one in the Philippines, one in Japan and one in France). The WHO declared the SARS-CoV-2 epidemic a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, citing that human-to-human infections have been confirmed in multiple countries [73].

According to Fang et al. [74], fifteen cases of childhood infection had been identified as of January 30, 2020, including 8 boys and 7 girls, ranging in age from 8 months to 12 years. Of the 15 pediatric cases, 13 had a clear history of family clustering in Wuhan. At present, several confirmed pregnant women in Wuhan have given birth during the illness. On February 2, 2020, Wuhan local media reported that a confirmed pregnant woman gave birth to a newborn by cesarean section under strict level three protection, but the newborn's throat swab was positive for the nucleic acid virus test [75]. However, Chen et al. tested the SARS-CoV-2 in amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six confirmed SARS-CoV-2 pregnant women, and all samples tested negative for the virus, which suggests that there is currently no evidence for intrauterine infection caused by

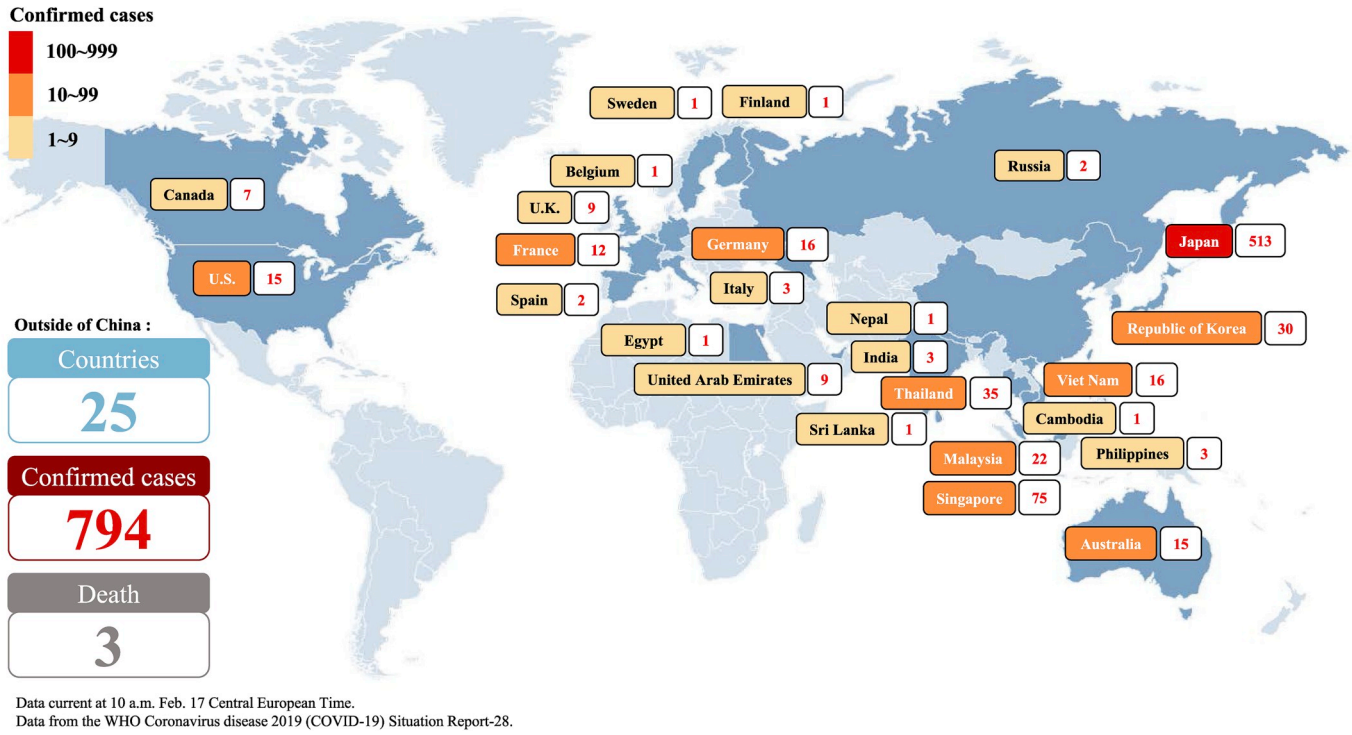

Fig. 5. Countries, territories or areas with reported confirmed cases of SARS-CoV-2, February 17, 2020. (Data from the WHO Coronavirus disease 2019 (COVID-19) Situation Report-28).

vertical transmission in women who develop COVID-19 pneumonia in late pregnancy [76]. No cases of newborns or child deaths have been reported. The NHC has called for close monitoring of outbreaks in children and pregnant women [77].

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team of the Chinese CDC reported the epidemiology characteristics of 44,672 confirmed cases as of February 11, 2020. Among the confirmed 44,672 cases (74.7% in Hubei Province), 51.4% were male, and 80.9% were mild or moderate cases. The majority of the cases were between 30 and 69 years old (77.8%), while 0-9 year-olds and 10-19 year-olds accounted for 0.9% and 1.2% respectively. Hypertension (12.8%), diabetes (5.3%), cardiovascular disease (4.2%) were the most common underlying diseases. A total of 1023 deaths occurred among confirmed cases for an overall case-fatality rate of 2.3%, and 81% of the deaths were over 60 years old. The mortality rates of those aged 60–69, 70–79 and over 80 years were 3.6%, 8.0%, and 14.8%, respectively. The mortality rate of critical cases was 49% [67].

Based on this evidence, the current SARS-CoV-2 is easily transmissible in humans, even in children and pregnant women. It should also be noted that most patients have a good prognosis. The symptoms in children are relatively mild, and only a minority are in critical condition. The death cases involved mostly the elderly and those with a chronic underlying disease. This fact, however, does not diminish the seriousness of the epidemic.

During the early stages of the epidemic, several hospitals, including Wuhan Union Hospital, Wuhan Tongji Hospital, and Peking Union Medical College Hospital, had created different diagnosis and treatment programs [37,78–80]. The WHO and the NHC of China have since then published guidelines for the diagnosis and clinical management of SARS-CoV-2 pneumonia [81,82].

6. Clinical presentation

6.1. Clinical manifestations

According to the guidelines published by the NHC and based on current epidemiological studies, the incubation period is typically 3–7 days, with a maximum of 14 days [82]. Common symptoms of COVID-19 include fever, fatigue, and dry cough. A few patients have symptoms such as nasal congestion, runny nose, sore throat, and diarrhea. Some patients only have a low fever, mild fatigue, and no pneumonia. In severe cases, the infection can cause pneumonia, shortness of breath and breathing difficulties occurring more than one week after infection. Critical patients may progress rapidly to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and even death. It is worth noting that during the course of severe and critical patients, there can be moderate to low-grade fever or even no obvious fever.

Huang et al. provided first-hand data regarding COVID-19 [26]. Their study reported the clinical features of the first 41 patients admitted to the designated hospital in Wuhan who were laboratory-confirmed COVID-19 by January 2, 2020. Twenty-seven (66%) of the 41 patients had been exposed to the Huanan seafood market. Common symptoms at the onset of illness were fever (98%), cough (76%), and myalgia or fatigue (44%). Less common symptoms were sputum production, headache, hemoptysis, and diarrhea. Dyspnea developed in 22 (55%) of 40 patients and 26 (63%) of 41 patients had lymphopenia. The median time from onset of symptoms to first hospital admission was 7.0 days, to shortness of breath was 8.0 days, and to ARDS was 9.0 days. Almost a third of patients developed ARDS requiring intensive care, 5 patients had acute cardiac injury, and 4 patients required assisted ventilation. Eventually 28 patients were discharged, 13 patients were admitted to the intensive care unit (ICU) and 6 patients died.

Chen et al. reported 99 patients with SARS-CoV-2 pneumonia admitted to the Jinyintan Hospital in Wuhan [37]. Forty-nine (49%) patients had a history of exposure to the local Huanan seafood market and 50 patients (51%) had chronic underlying diseases. Patients had clinical manifestations of fever (83%), cough (82%), shortness of breath (31%), muscle aches (11%), confusion (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), and diarrhea (2%). Eighty-nine (90%) patients had more than one symptom. According to their study, many cases presented with organ function damage, including 17 cases

with ARDS, 8 cases with acute respiratory injury, 3 cases with acute renal injury, 4 cases with septic shock, and 1 case with ventilator-associated pneumonia. Eventually 31 patients were discharged, 11 patients died, and the remaining 57 patients were still in hospital.

At Zhongnan Hospital of Wuhan University in Wuhan, Wang et al. [83] enrolled 138 hospitalized patients with SARS-CoV-2 pneumonia. Common symptoms included fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%), and dyspnea (31.2%). The median time from first symptom to dyspnea was 5.0 days, to hospital admission was 7.0 days, and to ARDS was 8.0 days. Major complications during hospitalization included ARDS, arrhythmia, and shock. Of the 138 hospitalized patients, 47 recovered and have been discharged, 36 patients were admitted to the ICU and 6 patients have died.

Chang et al. [84] reported 13 confirmed patients outside of Wuhan, including 2 children (aged 2 years and 15 years). Twelve patients (92%) had fever before hospitalization. Other symptoms included upper airway congestion (62%), cough (46%), myalgia (23%), and headache (23%). All the patients recovered.

Guan et al. [85] reported 1099 confirmed patients from 552 hospitals in the whole of China as of January 29, 2020. The most common symptoms including fever (87.9%) and cough (67.7%), whereas diarrhea (3.7%) and vomiting (5.0%) were rare. They also pointed out that only 43.8% of the patients had fever on presentation but 87.9% developed fever after being hospitalized. Moreover, compared with non-severe cases, any underlying diseases were significantly more common in severe cases. The most common complication was pneumonia (79.1%), ARDS (3.4%) and shock (1.0%). Of the 1099 patients, 55 patients were admitted to the ICU, and 15 patients died.

There were therefore a total of 41, 99 and 138 (total 278) cases of SARS-CoV pneumonia admitted in the 3 regional hospitals closest to the Huanan Seafood Market that resulted in 6, 11 and 6 deaths (23 deaths) or a case fatality rate of 0.82%.

6.2. Laboratory tests

In the early stages of the disease, the total number of leukocytes in peripheral blood is normal or decreased, the lymphocyte count is decreased, and some patients show increases in liver enzymes, muscle enzymes, and myoglobin. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are increased in most patients, and procalcitonin is normal. In severe cases, D-dimer increases, and peripheral blood lymphocytes decrease progressively. Coronavirus nucleic acid can be detected in the throat, sputum, lower respiratory tract secretions, blood and tool.

In Huang's study [26], the blood counts of patients on admission showed leucopenia and lymphopenia. Prothrombin time and D-dimer levels on admission were higher in ICU patients. Compared with non-ICU patients, ICU patients had higher plasma levels of IL-2, IL-7, IL-10, G-SCF, IP-10, MCP-1, MIP-1α, and TNFα. In Chen's study [37], all patients were tested for nine respiratory pathogens and nucleic acids of influenza viruses A and B, as well as bacteria and fungi. No other respiratory viruses were detected, but 4 cases of fungal and 1 case of bacterial infection were found. The absolute number of leukocytes was decreased in 9 patients and increased in 24 patients. The absolute neutrophil count was increased in 38 patients and the absolute lymphocyte count was decreased in 35 patients. Forty-three patients had varying degrees of liver dysfunction, seven patients had varying degrees of renal dysfunction, and most patients had abnormal myocardial zymograms. Seventy-three patients were tested for C-reactive protein which was increased in 63 patients. In Guan's study, 82.1%, 36.2%, and 33.7% of the patients had lymphopenia, thrombocytopenia, and leukopenia, respectively. Compared with non-severe cases, severe cases had more prominent laboratory abnormalities [85].

6.3. Imaging studies

In Huang's study [26], all 41 patients had pneumonia with abnormal findings on chest computed tomography (CT) and 40 (98%) had bilateral involvement. The ICU patients on admission had bilateral multiple lobular and subsegmental areas of consolidation. The non-ICU patients had bilateral ground-glass opacity and subsegmental areas of consolidation. Subsequent chest CT images showed bilateral ground-glass opacity, whereas the consolidation was resolved. In Chen's study [37], imaging showed that 74 patients had bilateral pneumonia, 14 patients had multiple mottled and ground-glass opacities, and 1 patient had a pneumothorax. In Wang's study [83], imaging showed that 138 patients had bilateral patchy shadows or ground-glass opacity. In Guan's study, 840 of 1099 patients received chest CT on admission which showed that 76.4% had pneumonia, but 23.9% of severe cases had no radiologic abnormality on initial presentation. Ground-glass opacity (50.0%) and bilateral patchy shadow (46.0%) were the most common findings [85].

7. Diagnosis

The earliest cases of SARS-CoV-2 were identified as “pneumonia of unknown etiology”, which was defined as an illness of unknown etiology with 1. Fever with or without a recorded temperature 2. Radiographic evidence of pneumonia 3. Low or normal leukocyte count or low lymphocyte count during the early stage of disease and 4. No improvement or worsening symptoms after 3–5 days of antimicrobial treatment per standard clinical guidelines [61]. With increasing research and knowledge of the disease, diagnosis and treatment guidelines have been continuously updated. At present, the NHC has issued the fifth edition of the guidelines. However, because of a shortage of diagnostic reagents for SARS-CoV-2 detection, different guidelines or programs emphasized comprehensive analysis based on epidemiological history, clinical manifestations and imaging examinations in diagnosis.

7.1. Diagnostic criteria [37,78–82]

The diagnostic criteria of suspected and confirmed cases were summarized in Table 1.

7.2. Differential diagnosis

The SARS-CoV-2 needs to be distinguished from other known viral pneumonias including influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS coronavirus, MERS coronavirus, as well as *Mycoplasma pneumoniae*, chlamydia pneumonia, and bacterial pneumonias. For patients with underlying diseases, attention should be paid to the detection of invasive fungal infections. The differential diagnosis also includes non-infectious diseases such as vasculitis, dermatomyositis, and organizing pneumonia. It should be noted that often patients with viral pneumonia may test positive to multiple viruses, and the potential lethality of a combined SARS-CoV-2/influenza virus infection should not be ignored.

8. The effectiveness of SARS-CoV-2 rapid diagnosis in preventing spread of disease

Several rapid and sensitive detection tests have been developed for the prevention and control of the SARS-CoV-2 outbreak. At present, seven products including the SARS-CoV-2 nucleic acid detection kit (fluorescent PCR method) and the SARS-CoV-2 nucleic acid sequencing system have been approved on an emergency basis by the National Medical Products Administration. Biological product companies have

Table 1
The diagnostic criteria for suspected and confirmed cases [37,77–81].

Case	Diagnostic criteria
Suspected case	Anyone with a history of epidemiology and any two of the clinical manifestations or anyone without epidemiological history and three of the clinical manifestations is considered to be a suspected case: (1) Epidemiological history: 1) within 14 days before the disease onset, there is a travel history or living history in Wuhan or other areas with local cases 2) within 14 days before the disease onset, there is contact with patients who had fever or respiratory symptoms from Wuhan or other areas with local cases 3) a clustering of patients or a contact with patients infected with the SARS-CoV-2 (2) Clinical manifestations: 1) fever and/or respiratory symptoms 2) with the above-mentioned imaging characteristics of pneumonia 3) the total number of leukocytes in the early stage of the disease is normal or decreased, or the lymphocyte count is decreased
Confirmed case	Any suspected case with one of the following pathogenic features is reclassified as a confirmed case: (1) Positive results of SARS-CoV-2 nucleic acids by RT-PCR of respiratory or blood specimens (2) DNA highly homologous to SARS-CoV-2 by genetic sequencing of viral genes in respiratory or blood specimens

RT-PCR: real-time reverse-transcriptase polymerase-chain-reaction.

expanded production of detection kits for the new coronavirus. The use of detection kits can accelerate accurate diagnosis of patients, help to determine quarantine and isolation requirements, assist in determining the treatment of patients and save limited medical resources. However, the rapidity of spread of the disease has led to an insufficient supply of detection kits.

It is worth noting that there have been confirmed patients whose viral nucleic acid tests are negative multiple times in the early stages, and there have also been confirmed cases whose throat swabs were negative for the viral nucleic acid test but positive in alveolar lavage fluid. Correlation of Chest CT and RT-PCR testing of 1014 cases showed that CT had a 88% had a positive CT scan but only 59% had positive RT-PCR. [86]. The poor sensitivity of the current tests makes diagnosis and epidemic control more challenging. Sampling techniques, extraction and detection of viral nucleic acids, and diagnostic reagents may affect the test results. More attention should be paid to the sensitivity and specificity of diagnostic reagents, and diagnostic decisions should rely on comprehensive judgment based on the clinical manifestations, laboratory results and imaging examinations of patients. According to the latest guideline of the NHC [82], if the suspected cases in Hubei Province have imaging characteristic of pneumonia, the CT image results can be used as a basis for “clinical diagnosis cases”.

9. The pathogenesis of COVID-19

Current understanding of the pathogenesis of HCoVs infection is still limited, especially for SARS-CoV-2. Before 2019, there were six CoVs that could infect humans and cause respiratory disease. HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 are sometimes attributed to the “common cold”, but in rare cases can cause severe infections in infants, young children and elderly people. On the other hand, SARS-CoV and MERS-CoV can infect the lower respiratory tract and cause a severe respiratory syndrome in human [3,12]. The new coronavirus SARS-CoV-2 is similar to SARS-CoV and MERS-CoV and can infect lower respiratory tract and cause severe pneumonia.

The origin of SARS-CoV-2 was thought to be wild animals in the Huanan Seafood Market in Wuhan. However, not all cases have an apparent connection with the Wuhan Huanan Seafood Wholesale Market. It is evident now that SARS-CoV-2 is capable of person-person transmission. We list the major pathogenic CoVs in Table 2 for better understanding of the pathogenesis of HCoV [87].

The term “cell pyroptosis” was first proposed in 2001 [88]. In recent decades, there has been increasing evidence suggesting that “pyroptosis” is a novel inflammatory form of programmed cell death. In 2019, Chen et al. found that SARS-CoV Viroporin 3a triggered the activation of the NLRP3 inflammasome and the secretion of IL-1β in bone marrow-derived macrophages, suggesting SARS-CoV induced cell pyroptosis [89]. Studies have shown that patients infected with SARS-CoV-2 have increased IL-1β in the serum [26]. As the rise of IL-1β is a downstream indicator of cell pyroptosis, this may suggest that cell pyroptotic activity is likely to be activated and involved in the pathogenesis of COVID-19 patients. Nevertheless, as both classical and non-classical pyroptosis signaling can induce the release of IL-1β, it is unclear which pathway is involved in COVID-19. Based on existing data, SARS-CoV-2 is likely to cause cell pyroptosis, especially in lymphocytes, through the activation of NLRP3 inflammasome. The pathways involved in the activation of the signaling between NLRP3m IL-1β, IL-18 and GSDMD are illustrated in Fig. 6 and are a subject of study in samples from SARS-CoV-2 patients [90].

Table 2
Partial list of important pathogenic human coronaviruses [87].

Virus	Genus	Symptoms
HCoV-229E	*alpha*	mild respiratory tract infections
HCoV-NL63	*alpha*	mild respiratory tract infections
HCoV-OC43	*beta*	mild respiratory tract infections
HCoV-HKU1	*beta*	pneumonia
SARS-CoV	*beta*	severe acute respiratory syndrome, 11% mortality rate
MERS-CoV	*beta*	severe acute respiratory syndrome, 34% mortality rate
SARS-CoV-2	*beta*	severe acute respiratory syndrome, 2.6% mortality rate

9.1. The genomic structure of SARS-CoV-2

The rapid sequencing of the nearly 30,000 nucleotide SARS-CoV-2 genome was accomplished in approximately 3 weeks from the time of the first hospitalized patient on the December 12, 2019 by Zhang's group and several others in China [91]. The genomic structure is shown in Fig. 7 and shows greater than 99.9% consistency [19,91–95].

The SARS-CoV-2 genome was found to possess 14 ORFs encoding 27 proteins. The orf1ab and orf1a genes are located at the 5′-terminus of the genome and encode 15 non-structural proteins (nsps) from nsp1 to nsp10, and from nsp12 to nsp16. The 3′-terminus of the genome contains 4 structural proteins (S, E, M and N) and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b and orf14). At the amino acid level, the SARS-CoV-2 is quite similar to that of SARS-CoV, but there are some notable differences. For example, the 8a protein is present in SARS-CoV and absent in SARS-CoV-2; the 3b protein is 154 amino acids in SARS-CoV but shorter in SARS-CoV-2 with only 22 amino acids. Further studies are needed to characterize how these differences affect the functionality and pathogenesis of SARS-CoV-2 [95].

The phylogenetic tree based on whole genomes showed that SARS-CoV-2 is most closely related to bat SARS-like coronavirus bat-SL-CoVZC21 (NCBI accession number MG772934) and bat-SL-CoVZC45 (NCBI accession number MG772933), which share ~89% sequence homology [91–93]. Their genomic organization is typical of a lineage B beta coronavirus. Further phylogenetic analysis has posited that SARS-CoV-2 is a product of recombination with previously identified bat

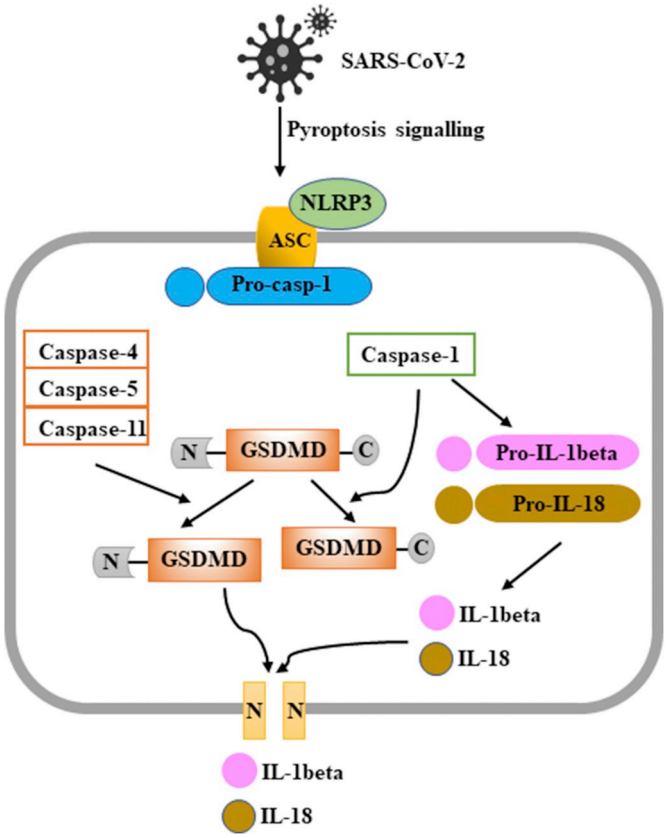

Fig. 6. A hypothesis of the relationship between SARS-CoV-2 and cell pyroptosis. The COVID-19 may be linked to cell pyroptosis, especially in lymphocytes through the activation of the NLRP3 inflammasome. Morphological changes in lymphocytes and macrophages, nucleic acid and protein levels in classical and non-classical cells, detection of NLRP3 and GSDMD, and the role of inflammatory cytokines IL-1β and IL-18 requires further research.

coronaviruses, but a recent report has subsequently identified a bat CoVs sequence, RaTG13, with 92–96% sequence identity with the novel virus, demonstrating that RaTG13 is the closest relative of the SARS-CoV-2 and forms a distinct lineage from other SARS-CoVs. This rejects the hypothesis of emergence as a result of a recombination event [94,96]. Even though there are high similarities between SARS-CoV-2 S and RaTG13 S, there are two distinct differences: one is an "RRAR" furin recognition site formed by an insertion residues in the S1/S2 protease cleavage site in SARS-CoV-2, rather than the single Arginine in SARS-CoV [97–101]; the other difference is the presence of 29 variant residues between SARS-CoV-2 S and RaTG13 S, 17 of which mapped to the receptor binding domain (RBD) [97].

The identities of 5′- and 3′-UTR sequences are more than 83.6% consistent between SARS-CoV-2 and other β-CoVs, such as SARS-CoV [102]. The replicase polyproteins ppla and pp1ab encoded by the largest genes orf1ab are proteolytic and have been reported to function in the replication of CoVs by regulatory elements located within the non-structural proteins [102]. Four structural proteins (S, E, M and N) contribute to virion assembly and infection of CoVs. The spike protein located on the surface of viral particles is made up of homotrimers of S proteins and is the key for the viral attachment to host receptors [103,104].

Spike glycoprotein consists of S1 and S2 subunits. The S1 subunit contains a signal peptide, an N-terminal domain (NTD) and RBD, while the S2 subunit includes the conserved fusion peptide (FP), heptad repeat 1 and 2 (HR1 and HR2), transmembrane domain (TM), and cytoplasmic domain (CP) [102,105]. Furthermore, the S2 subunit of SARS-CoV-2 is highly conserved and shares 99% similarity with those of Bat-SL-CoVZC45, Bat-SL-CoVZC21 and human SARS-CoV [102]. The S2 subunit is therefore targeted when screening broad spectrum antiviral peptides, which is an important piece of information that can be used to develop preventive and treatment measures. Most recently, the 3D structure of S protein was elucidated using Cryo-electron microscopy (Cryo-EM), and the RBD structure of the S protein is closer to the central location of SARS-CoV-2 compared to SARS-CoV [97].

The E protein plays a role in virus assembly and release, and is required for pathogenesis [106,107]. The N protein contains two domains, both of which can bind virus RNA genomes via different mechanisms. It has been reported that the N protein can bind nsp3 protein to help tether the genome to replicase-transcriptase complex (RTC) and package the encapsulated genome into virions [12,108,109]. The N protein is also an antagonist of interferon and viral encoded repressor (VSR) of RNA interference (RNAi), which benefits viral replication [110].

9.2. Entry into host cell

Cell entry is an essential component of cross-species transmission, especially for the β-CoVs. All CoVs encode a surface glycoprotein, spike, which binds to the host receptor and mediates viral entry [111]. For β-CoVs, the RBD of the spike protein mediates the interaction with host receptor. Upon binding the receptor, the spike protein is cleaved by nearby host proteases and releases the signal peptide to facilitate virus entry into host cells [112–115].

Angiotensin converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) are known host receptors for the β-CoVs SARS-CoV and MERS-CoV, respectively [116,117]. In similar fashion to SARS-CoV, SARS-CoV-2 also uses ACE2 to gain entry into host cells. Hoffmann et al. found that the cellular protease MPRSS2 blocks entry by cleaving the spike protein and may constitute a treatment option [118]. Zhou et al. also confirmed that SARS-CoV-2 is able to use all but mouse ACE2 as an entry receptor for ACE2-expressing cells, but not cells without ACE2, indicating that the cell receptor for SARS-CoV-2 could be ACE2, and not other coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase 4 [94]. Huang also showed that the affinity of the SARS-CoV-2 S-RBD binding to ACE2 is less than that of SARS-CoV

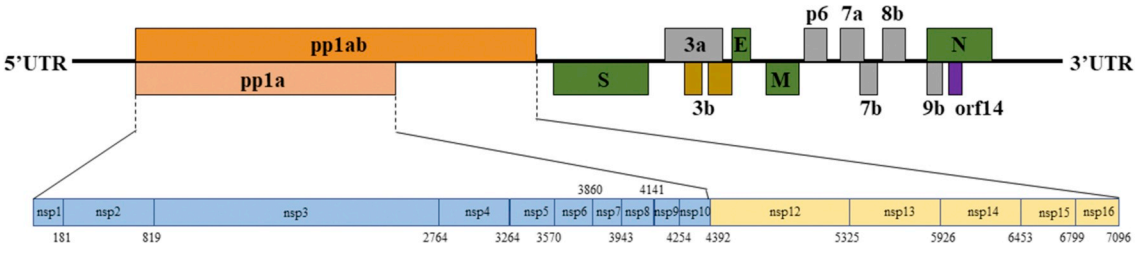

Fig. 7. Schematic diagram of the SARS-CoV-2 genome [95]. The genomic structure of SARS-CoV-2 is 5′-UTR-orf1a-orf1ab-S (Spike)–E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTRpoly (A) tail. Accessory genes are interspersed within the structural genes at the 3′ end of genome. The pp1a protein encoded by the orf1a gene and the pp1ab protein encoded by the orf1ab gene contains 10 nsps (nsp1-nsp10). The pp1ab protein also includes nsp12-nsp16.

through Monte Carlo algorithm [119]. However, Wrapp et al. found that SARS-CoV-2 S binding to ACE2 has approximately 10- to 20- fold higher affinity than SARS-CoV S, which can provide one explanation why SARS-CoV-2 has more human-to human spread compared to SARS-CoV [97].

The combination of SARS-CoV-2 S and ACE2 of host cells is similar to the combination of SARS-CoV and ACE2, indicating that they have the same mechanism to entry into host cells [97]. The S protein of metastable prefusion conformation undergoes a series of structural re-arrangements to combine with the viral membrane of host cells [111,120]. This process consists of the S1 subunit binding to the host cell receptor, triggering of the prefusion trimer's instability, and shedding of the S1 subunit, resulting in a highly stable post-fusion conformation of the S2 subunit [121]. During the binding of the subunit S1 to its cognate receptor, it is important to note that the S1 subunit exists in 2 different states, a “down” conformation and an “up” conformation state, which corresponds to a receptor-inaccessible state and an unstable receptor-accessible state, respectively [122–125]. Unfortunately, there are significant conformational differences between SARS-CoV and SARS-CoV-2 such that the commercially available monoclonal antibodies against SARS-CoV do not react with SARS-CoV-2 [97].

SARS-CoV-2 may directly bind to ACE2 positive cholangiocytes but not necessarily hepatocytes via specific expression of ACE2 in healthy liver tissues using cell RNA-seq data of two independent cohorts [126]. Though the respiratory systems is a primary target of SARS-CoV-2, bioinformatic analysis of single-cell transcriptomes datasets of lung, esophagus, gastric, ileum and colon reveal that the digestive system is also a potential route of entry for COVID-19, as ACE2 was not only highly expressed in lung AT2 cells, esophagus upper and stratified epithelial cells but also in absorptive enterocytes from the ileum and colon [127].

10. Recommendations

10.1. Preventing the spread of disease

In response to the outbreak of pneumonia caused by the SARS-CoV-2, China has activated Level I public health emergency response for the entire country. This activates the most comprehensive and rigorous prevention and control measures for health and safety. A team of professionals from the NHC and China CDC was sent to conduct field investigations and implement disease control and prevention measures. The virus was quickly isolated and sequenced. On January 3, 2020, the first complete genome of the SARS-CoV-2 was determined and shared internationally, which led to the rapid development and deployment of diagnostic tests [60]. The NHC announced that preventive and control measures of category A infectious diseases would be implemented to effectively fight SARS-CoV-2 and has also introduced public education campaigns. At the same time, all medical expenses of confirmed patients would be covered by central and local financial institutions.

10.2. Quarantine

Quarantine is a traditional but very effective measure to counter a deadly epidemic, but quarantine protocols can be hard to enforce. The local government in Wuhan announced the suspension of public transportation, with closure of airports, railway stations, and highways in the city, to prevent further disease transmission on January 23, 2020. Subsequently, the Chinese government imposed travel bans on several Chinese cities near Wuhan. At the same time, the Chinese government extended the Lunar New Year holidays and postponed the reopening of schools and factories to keep the nationwide migration of the population to a minimum. Travelers from Wuhan and other epidemic areas were advised to report their travel history and to self-quarantine for two weeks to prevent community transmission. In addition, most local governments required that all passengers must wear medical surgical masks or N95 masks when accessing public places, taxis or subways. Temperature screening checkpoints have been set up at subway stations, railway stations, high-speed rail exits and airports to screen passengers in an effort to curb the spread of the novel coronavirus.

10.3. Mobilize resources

With the rapid spread of the epidemic, more designated treatment hospitals and health care workers were needed to meet the growing number of patients. On January 24, 2020, the local government in Wuhan announced the construction of a 1000-bed infirmary, named Huoshenshan hospital, and a 1500-bed infirmary, named Leishenshan hospital within 10 days, to ease the shortage of beds and treat people diagnosed with the SARS-CoV-2. These facilities are specialty hospitals for infectious diseases, rather than simply units to receive and quarantine patients. Wuhan has also been building 11 mobile Fangcang hospitals (a Chinese name which came from Noah's Ark) and creating tens of thousands of beds, to centralize quarantine and provide medical treatment for confirmed patients with mild symptoms, suspected patients and those who need observation. The new facilities further enhance the local public health capacities. Hospitals offer online consultants and medical services to symptomatic patients and suspected patients, which help reduce the frequency that patients go to hospitals and thereby reduce the risk of being infected. Health care workers, including military medical teams, from across the Chinese mainland arrived in Hubei to provide much needed assistance. At present, more than 30,000 health care workers have arrived in Hubei to help fight the novel coronavirus epidemic. In order to prevent health care workers from being infected, the NHC ensured enough supplies of isolation gowns, gloves and masks and issued a technical guideline for the prevention and control of infection caused by the novel coronavirus [128].

10.4. Disseminate information

The NHC also formulated a community prevention and control program for SARS-CoV-2 pneumonia to strengthen community-level epidemic prevention measures to control the spread of the outbreak [129]. All communities screen patients with fever within the community and monitor and report suspected cases with COVID-19. Various forms of health education have been carried out in the community to disseminate knowledge of epidemic prevention and control, such as using masks and washing hands correctly. The NHC issued guidelines for the protection of people at different levels of risk for COVID-19 [130].

11. Treatment and management

There is no clear, unified and effective treatment plan for COVID-19. Most guidelines emphasize early identification, early isolation, early diagnosis, and early treatment. The treatment and management of SARS-CoV-2 pneumonia mainly include the following aspects (Fig. 8) [37,78–82].

Suspected and confirmed cases should be isolated and treated in designated hospitals with effective isolation and protective conditions as soon as possible. Suspected cases should be isolated in a single room. WHO suggests that patients with mild symptoms and without underlying chronic diseases (such as lung or heart disease, renal failure, or immunodeficiency) may be cared for in the home environment in isolation [131]. However, severe cases should be hospitalized, and critical cases should be admitted to the ICU as soon as possible.

Supportive therapy includes bedrest, adequate nutrition, monitoring vital signs and oxygen saturation, prevention of dehydration and maintaining water, electrolyte, and acid-base balance. For severe cases, it may be necessary to proactively prevent complications and secondary

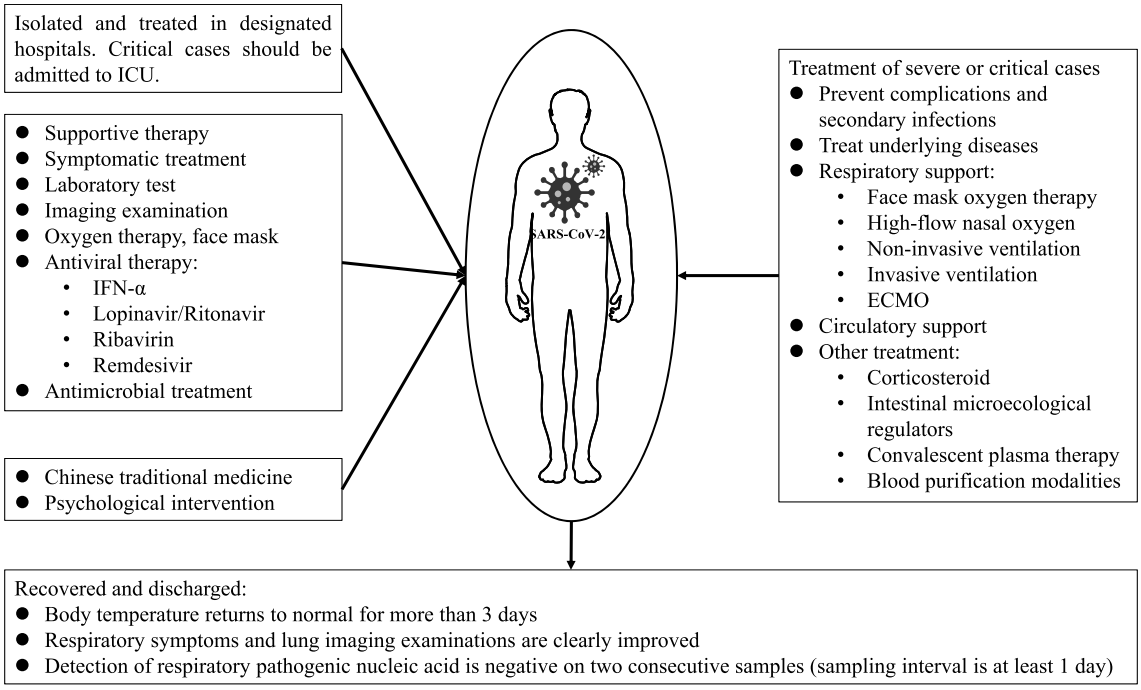

Fig. 8. The treatment and management of COVID-19 pneumonia. ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation.

infections, treat underlying diseases and provide organ function support according to the patients' condition such as that reported by Chen et all that involved the administration of intravenous immunoglobulin therapy to 27 of such patients [37].

Supplemental oxygen should be administered to patients with decreased oxygen saturation. In Huang's study [26], four (10%) patients needed invasive mechanical ventilation, and two received extracorporeal membrane oxygenation (ECMO). In Chen's study [37], 75 of 99 patients received oxygen therapy, 13 patients required non-invasive mechanical ventilation, four patients needed an invasive ventilator to assist ventilation, and three patients were treated with ECMO. In Wang's study [83], of the 36 patients in the ICU, four patients received high-flow oxygen therapy, 15 patients received non-invasive ventilation, and 17 patients received invasive ventilation (four patients switched to ECMO). In Guan's study, 418 of 1099 patients received oxygen therapy, 67 patients received mechanical ventilation, and ECMO was adopted in 5 severe cases [85].

Due to lack of valid evidence and possible adverse effects, routine use of corticosteroid should be avoided unless for specific reasons. Baillie JK et al. [42] suggested that corticosteroid should not be used for the treatment of SARS-CoV-2-induced lung injury or shock, because of the lack of evidence that patients with COVID-19 will benefit from corticosteroid. In the first 41 patients, only 22% (9/41) patients were given corticosteroid, with six of these in the ICU [26]. Chen et al. reported that 19% (19/99) patients received corticosteroid treatment for 3–15 days [37]. In Wang's study [83], 45% (62/138) patients received corticosteroid treatment. In Guan's study, 18.6% (204/1099) of patients were given systemic corticosteroids [85].

Indiscriminate or inappropriate antimicrobial treatment, especially the combination of broad-spectrum antibiotics, should be avoided. However, in Huang's study [26], all his 41 patients received antibiotic therapy. In Chen's study [37], 70 patients were given antibiotic treatment, among whom 25 patients were treated with a single antibiotic and 45 patients were given combination therapy. The duration of antibiotic treatment was 3–17 days. In addition, there were 15 patients who received antifungal treatment. In Wang's study [83], the 138 hospitalized patients all received antibacterial therapy, including moxifloxacin (64.4%), ceftriaxone (24.6%), azithromycin (18.1%). In Guan's study, 632 patients were given intravenous antibiotics, and 30 patients were given antifungal medications [85].

At present, there is no evidence-based medicine to support the effectiveness of antiviral drugs for COVID-19. The previous experience of treating SARS-CoV, MERS-CoV or influenza infections guides the selection of antiviral agents for COVID-19. The current guideline of the NHC recommends IFN-α, lopinavir/ritonavir, and ribavirin as antiviral therapy. In Huang's study [26], 38 of 41 patients were given antiviral therapy. The Jinyintan hospital has launched a randomized, controlled trial of the anti-HIV drug combination of lopinavir and ritonavir. In Chen's study [37], 75 patients received antiviral treatment, including oseltamivir, ganciclovir, and lopinavir/ritonavir, and the duration of antiviral treatment was 3–14 days. In Wang's study [83], there were 89.9% (124/138) patients who received oseltamivir. And in Guan's study, 35.8% (393/1099) of patients received oseltamivir [85]. The anti-viral drug remdesivir (Gilead®) is in clinical trials to treat COVID-19 in Wuhan [132]. Chloroquine phosphate has also been shown to be effective in some patients.

Identifying or developing novel drug treatment options as soon as possible is critical for the response to the SARS-CoV-2 outbreak. Based on the structural information of clinical effective medicines for SARS-CoV-2, Liu et al. predicted 10 commercial medicines which may function as inhibitors of SARS-CoV-2, including colistin, valrubicin, icatibant, bepotastine, epirubicin, etc. Some of these may be more resistant to viral mutation than lopinavir/ritonavir [133]. Stebbing et al. suggested that baricitinib may reduce both the viral entry and inflammation [134].

Lu reported that remdesivir may have the greatest potential for the successful treatment of SARS-CoV-2, but the efficacy and safety of remdesivir in COVID-19 needs further evaluation [135]. The antiviral efficiency of five FAD-approved drugs and two well-known broad-spectrum antiviral drugs have been studied and it has been found that remdesivir and chloroquine effectively inhibit SARS-CoV-2 *in vitro* [136]. The New England Journal of Medicine reported that the first case of COVID-19 confirmed in the United States was treated with intravenous remdesivir and demonstrated clinical improvement [71]. At present, a randomized, double-blind, placebo-controlled phase III clinical trial of remdesivir has been launched and already 761 confirmed

cases have been enrolled [132]. Lu also pointed out that there is no direct evidence that oseltamivir is effective in the treatment of SARS-CoV-2 [135]. However, we found that oral oseltamivir or abidol has been used for suspected or confirmed SARS-CoV-2 cases.

Favilavir, formerly known as Fapilavir, was the first anti-novel coronavirus drug that has been approved for marketing by the National Medical Products Administration since the outbreak. The drug was developed by Zhejiang Hisun Pharmaceutical Company and is expected to play an important role in preventing and treating the epidemic [137].

The role of intestinal microecological regulators that can be used to maintain intestinal microecological balance and prevent secondary bacterial infections is unclear. Chinese traditional medicine suggests Shufengjiedu and Lianhuaqingwen, which have played a role in the prevention and treatment of new infectious respiratory diseases, may be of benefit [138,139].

Anxiety and fear often exist in suspected or confirmed patients. Emergency psychological crisis intervention [140], and the implementation of classified intervention for different groups of people, is helpful in order to strengthen psychological counseling and reduce the psychological damage caused by the epidemic. Mass hysteria has also led to incidences of racial discrimination against Asians, particularly in non-Asian countries.

12. Development of vaccines for coronavirus

Research institutions and pharmaceutical companies worldwide are stepping up research and development for a coronavirus vaccine. Virus strains have been isolated from patients' samples and provide the basis for research and development of a vaccine for the novel coronavirus. Although vaccines have been developed for SARS-CoV and MERS-CoV, these are not commercially available [12,14,141]. Since the emergence of SARS-CoV and MERS-CoV, basic research on coronaviruses and advances in vaccine preparation technology can significantly shorten the development time of new coronavirus vaccines. However, the difficulties and challenges of developing an effective vaccine have been discussed earlier, and the key to a successful vaccine program is to vaccinate people before an outbreak occurs, not begin to develop the vaccine during the outbreak. Development of animal models that faithfully mimic SARS-CoV-2 infection in humans is critical not only in providing a more refined understanding of the pathogenic mechanisms involved but also to serve as a screening model for potential chemotherapeutic agents and vaccines.

13. Guidelines for the future

Recommendations for the prevention and management of coronavirus epidemics are summarized in Fig. 9. Since both SARS and SARS-CoV-2 appear to have an exotic animal origin, the purchase, trafficking, and sale of wild animals should be banned, and illegal activities should be prosecuted. Early recognition of the problem, early identification of infected patients and early mobilization of healthcare resources are critical in limiting morbidity and mortality. When an outbreak occurs, it is very important to rapidly identify and characterize the pathogen, in order to be able to develop diagnostic assays. In the early stage of the disease epidemic, summarizing the clinical characteristics and treatment efficacy, formulating the diagnosis procedures, defining suspected cases and locations, determining transmission patterns, isolating contagious patients and formulating the appropriate quarantine strategy are all necessary and need to be implemented promptly.

The strict control of cross-infection in medical institutions is also key to preventing the further spread of the epidemic. In addition, actively mobilizing the population to participate in epidemic prevention and control is critical, and this can be achieved by accurate information dissemination and ongoing updates. Real-time updating the information of the epidemic situation can help to alleviate panic and reduce societal anxiety. A strong public health surveillance system to guide the response to the outbreak is important in the face of a lack of effective therapeutics or vaccines. Big data and artificial intelligence systems are tools that can be used to fully integrate the information, conduct comprehensive research and analyze public health risks. Last but not least, use of the Internet and the media to conduct health education for the people, publicize the correct knowledge of prevention, and offer online consultation to guide patients to seek medical treatment correctly are additional strategies that can be implemented to achieve viral containment.

14. Discussion

14.1. The differences between SARS and SARS-CoV-2

Although SARS-CoV-2 and SARS-CoV have certain similarities in biological, epidemiological and pathological characteristics, there are some important differences. First, the most fundamental difference between the two viruses lies in their gene sequence. Second, during the SARS epidemic, a total of 8422 patients worldwide were infected with SARS-CoV, of whom 919 died, with a mortality rate of 9.5% [9]. A total of 5328 patients in China were infected with SARS-CoV, of whom 349 died, with a mortality rate of 6.5% [9]. As of February 17, 2020, there were 72,436 confirmed cases of 2019-nCoV in China, of whom 1868 have died, with a mortality rate of 2.6% [10]. Compared to SARS, there are more confirmed cases, suspected cases and deaths of SARS-CoV-2, but the mortality rate is lower than that of SARS.

From 2017 to 2018, influenza ravaged the world, affecting up to 45 million people and killing about 95,000 people, with a reported mortality rate of about 0.2%. Every year millions of people are infected by influenza despite the existence of a yearly vaccine. According to the United States CDC weekly report, the number of childhood deaths in the United States so far from influenza during this flu season alone is 105. Compared with influenza, the number of patients who have died of coronavirus infection is less, but the virulence and mortality rate of coronavirus is significantly higher.

Clinically, the patients with COVID-19 have no upper respiratory symptoms (such as runny nose, sneezing, sore throat). In 2003, a large number of medical personnel were infected, and iatrogenic

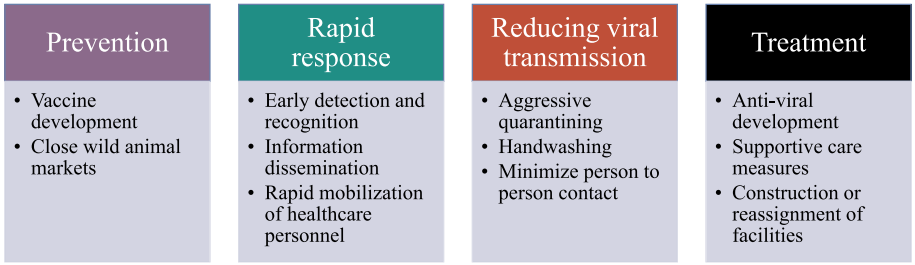

Fig. 9. Keys to the control of future hCoV epidemics. Lessons learned from both the SARS and SARS-CoV-2 epidemics.

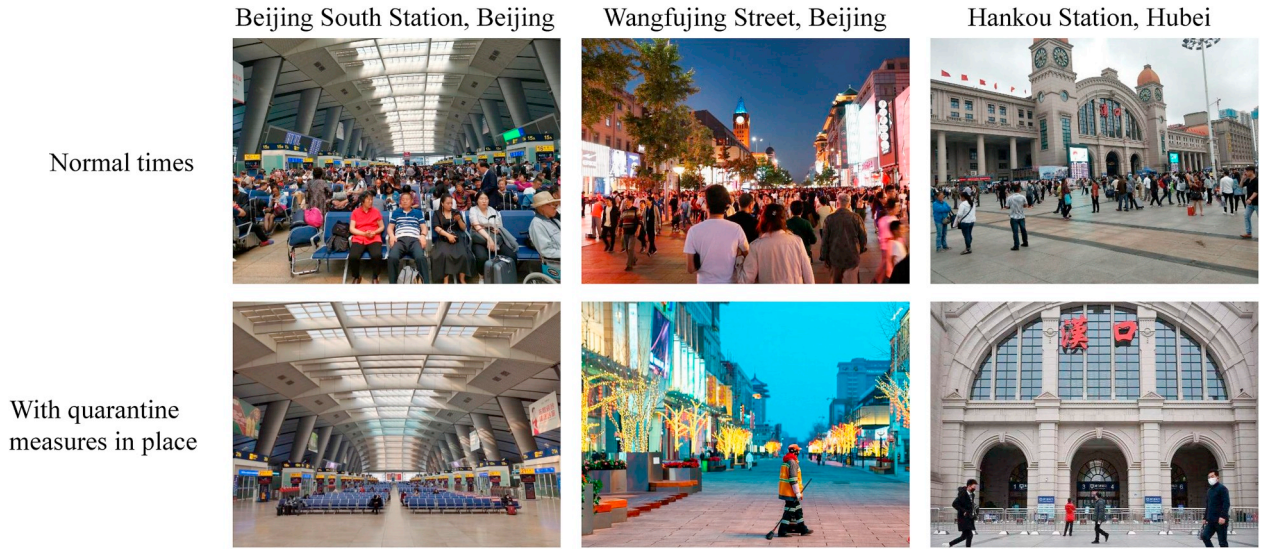

Fig. 10. Life in China in Beijing and Hubei during quarantine measures. Quarantine measures have led to empty streets and shopping centers.

transmission occurred in SARS. In contrast, although there are cases of nosocomial infection in SARS-CoV-2, most of them are out-of-hospital infections.

14.2. What can we learn from the 2020 nCoV epidemic in China?

The SARS-CoV-2 epidemic of 2020 in China is an international crisis, affecting human lives, the global economy, societal views and lifestyle. During times of crisis, misinformation, blame and conspiracy theories abound. It is probably prudent to not entirely trust the media, whether local, regional or international, as each most likely has their own agenda. On the other hand, it is the responsibility of doctors and scientists to evaluate the events to ascertain whether or not more effective management of the crisis could have been attained. This comes with its own set of challenges, as hindsight is always 20/20.

The quarantining of an entire country has been extreme, astounding and unprecedented. This not only involves quarantining measures within China but also internationally, as countries canceled flights into China, quarantined their own nationals as they returned from China and installed thermal scanners to detect ill people. But the quarantine measures inside China are certainly eye-opening. The entire city of Wuhan was shut off, and this was extended to every other city in China. In effect, the entire country was told to stay home, creating an enormous impact on the economy and on people's daily lives. Roads and stores became deserted (Fig. 10). In Ningbo, each household was only permitted to send one person out for groceries every other day. Schools were closed till the end of March. Everyone wears masks. The objective was to starve the virus, to eliminate hosts. Yet even with these measures, new cases continued to appear. The quarantine measures in China have obviously come under a great deal of scrutiny, with so called “experts” weighing in, some saying that it will not work, that isolating a city deprives it of medical resources. Whatever the criticism, it is humbling to think of what may have happened without these draconian measures. It is also difficult to comprehend if such measures could actually take place in other parts of the world, or if the implementation of these changes could have taken place as quickly. For example, hand shaking is not part of Chinese culture, but it is almost automatic in other parts of the world, and it is normally done without even thinking. This is the first thing that would have to stop to help contain the virus.

Then there is the matter of the ophthalmologist and others who voiced concerns in the media about a cluster of cases of a flu-like illness near the end of December. At the present time, it is difficult to say whether or not the response could have been faster than it actually was, as this corresponds to the time when work began on viral sequencing. It is possible that medical teams were already working on the sequence at that time. It is also quite possible that officials did not initially sound the alarm publicly because they did not want to cause a panic. Perhaps this was the wrong decision, but these decisions are difficult in times of crisis and it is of course easy to second guess. It is easy to understand that this can be perceived as withholding information and why the public would be frustrated. The lesson here is that dissemination of accurate and validated information and establishing guidelines to prevent the spread of infections is critical.

There are many “heroes” in these crises, people who have risked their lives and made incredible sacrifices to help society rid itself of this scourge, including those who work on the front lines, epidemiologists, scientists, doctors, first responders, and members of the public. Unfortunately, these events also bring out the worst in people. Numerous accounts of racial discrimination have been perpetrated against Asians across the world, many rising to the level of hate crimes. One must not forget the psychological impact of an infection such as this on people who are not even infected or who will never encounter an infected person.

The emergence of SARS-CoV, MERS-CoV, and now SARS-CoV-2, suggests that coronavirus will pose a lasting threat to human beings. The epidemic will eventually be contained, and people's memory of the coronavirus may gradually blur. But we must not forget the lessons learned from this crisis, and already begin to take measures to prevent the next new outbreak of Coronavirus or some other virus from appearing in the future. If it does appear, how will we respond to it? What if it does not happen in China? Will other countries have the fortitude to implement even more drastic measures and mobilize resources to prevent the spread of the virus and to care for the sick?

We can always improve on the handling of global pandemics or epidemics. From the lessons learned during the SARS and now the SARS-CoV-2 epidemics, we can nearly provide a roadmap for the response to future outbreaks. The development of a vaccine for coronavirus is a critical step in prevention, but it may not be effective for future strains, and we must be ready for the next epidemic.

Funding

Beijing Municipal Natural Science Foundation General Program (7,192,197).

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] S.R. Weiss, J.L. Leibowitz, Coronavirus pathogenesis, Adv. Virus Res. 81 (2011) 85–164.
[2] U.B.R. Balasuriya, et al., List of contributors, in: N.J. MacLachlan, E.J. Dubovi (Eds.), Fenner's Veterinary Virology, fifth ed., Academic Press, Boston, 2017, pp. xvii–xviii.
[3] S. Su, et al., Epidemiology, genetic recombination, and pathogenesis of coronaviruses, Trends Microbiol. 24 (6) (2016) 490–502.
[4] N. Zhu, et al., A novel coronavirus from patients with pneumonia in China, 2019, N Engl J Med, 2020.
[5] D. Isaacs, et al., Epidemiology of coronavirus respiratory infections, Arch. Dis. Child. 58 (7) (1983) 500–503.
[6] S.B. Greenberg, Update on human rhinovirus and coronavirus infections, Semin. Respir. Crit. Care Med. 37 (4) (2016) 555–571.
[7] A.M. Zaki, et al., Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. 367 (19) (2012) 1814–1820.
[8] W.H. Organization, Middle East respiratory syndrome coronavirus (MERS-CoV), [cited Jan 30, 2020; Available from: http://www.who.int/emergencies/mers-cov/en/.
[9] W.H. Organization, Summary table of SARS cases by country, November 1, 2002-August 7, 2003, Available from: http://www.who.int/csr/sars/country/2003_08_15/en/.
[10] C.N.H. Commission, Update on the Novel Coronavirus Pneumonia Outbreak, (2020) Available from: http://www.nhc.gov.cn/xcs/xxgzbd/gzbd_index.shtml.
[11] S.R. Weiss, S. Navas-Martin, Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus, Microbiol. Mol. Biol. Rev. 69 (4) (2005) 635–664.
[12] A.R. Fehr, S. Perlman, Coronaviruses: an overview of their replication and pathogenesis, Methods Mol. Biol. 1282 (2015) 1–23.
[13] L. Zhao, et al., Antagonism of the interferon-induced OAS-RNase L pathway by murine coronavirus ns2 protein is required for virus replication and liver pathology, Cell Host Microbe 11 (6) (2012) 607–616.
[14] Z. Song, et al., From SARS to MERS, thrusting coronaviruses into the spotlight, Viruses 11 (1) (2019) 59.
[15] S.K. Lau, et al., Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events, J. Virol. 84 (6) (2010) 2808–2819.
[16] W. Li, et al., Bats are natural reservoirs of SARS-like coronaviruses, Science 310 (5748) (2005) 676–679.
[17] H. Lu, C.W. Stratton, Y.W. Tang, Outbreak of pneumonia of unknown etiology in wuhan China: the mystery and the miracle, J. Med. Virol. 92 (4) (2020 Apr) 401–402, https://doi.org/10.1002/jmv.25678 Epub 2020 Feb 12.
[18] W. Ji, W. Wang, X. Zhao, J. Zai, X. Li, et al., Cross-species transmission of the newly identified coronavirus 2019-nCoV, J. Med. Virol. 92 (4) (2020 Apr) 433–440, https://doi.org/10.1002/jmv.25682.
[19] J.F. Chan, et al., A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Lancet 395 (10223) (2020 Feb 15) 514–523, https://doi.org/10.1016/S0140-6736(20)30154-9 Epub 2020 Jan 24.
[20] H. Nishiura, N.M. Linton, A.R. Akhmetzhanov, Initial cluster of novel coronavirus (2019-nCoV) infections in wuhan, China is consistent with substantial human-to-human transmission, J. Clin. Med. 9 (2) (2020) E488.
[21] Organization, W.H., Consensus Document on the Epidemiology of Severe Acute Respiratory Syndrome (SARS). 2003, World Health Organization: Geneva.
[22] H. Maier, E. Bickerton, P. Britton, Coronaviruses: Methods and Protocols, (2015), pp. 1–282.
[23] M. Malik, et al., Middle East respiratory syndrome coronavirus: current knowledge and future considerations, EMHJ-Eastern Mediterranean Health J. 22 (7) (2016) 533–542.
[24] C. Lu, X. Liu, Z. Jia, 2019-nCoV transmission through the ocular surface must not be ignored, Lancet 395 (10224) (2020 Feb 22) e39, https://doi.org/10.1016/S0140-6736(20)30313-5 Epub 2020 Feb 6.
[25] Y. Yin, R.G. Wunderink, MERS, SARS and other coronaviruses as causes of pneumonia, Respirology 23 (2) (2018) 130–137.
[26] C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020 Feb 15) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5 Epub 2020 Jan 24.
[27] J.S. Sabir, et al., Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia, Science 351 (6268) (2016) 81–84.
[28] Z. Zhao, et al., Moderate mutation rate in the SARS coronavirus genome and its implications, BMC Evol. Biol. 4 (2004) 21.
[29] P.C. Woo, S.K. Lau, K.Y. Yuen, Infectious diseases emerging from Chinese wet-markets: zoonotic origins of severe respiratory viral infections, Curr. Opin. Infect. Dis. 19 (5) (2006) 401–407.
[30] P.C. Woo, et al., Coronavirus diversity, phylogeny and interspecies jumping, Exp. Biol. Med. 234 (10) (2009) 1117–1127.
[31] P.C. Woo, et al., Comparative analysis of 22 coronavirus HKU1 genomes reveals a novel genotype and evidence of natural recombination in coronavirus HKU1, J. Virol. 80 (14) (2006) 7136–7145.
[32] D. Benvenuto, et al., The 2019-new coronavirus epidemic: evidence for virus evolution, J. Med. Virol. 92 (4) (2020 Apr) 455–459, https://doi.org/10.1002/jmv.25688 Epub 2020 Feb 7.
[33] C. Ceraolo, F.M. Giorgi, Genomic variance of the 2019-nCoV coronavirus, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25700.
[34] K.H. Chu, et al., Acute renal impairment in coronavirus-associated severe acute respiratory syndrome, Kidney Int. 67 (2) (2005) 698–705.
[35] J.S. Peiris, et al., Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study, Lancet 361 (9371) (2003) 1767–1772.
[36] C.M. Booth, et al., Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area, J. Am. Med. Assoc. 289 (21) (2003) 2801–2809.
[37] N. Chen, et al., Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: a Descriptive Study, Lancet, London, England), 2020 S0140-6736(20)30211-7.
[38] J. Cinatl, et al., Treatment of SARS with human interferons, Lancet 362 (9380) (2003) 293–294.
[39] L.J. Stockman, R. Bellamy, P. Garner, SARS: systematic review of treatment effects, PLoS Med. 3 (9) (2006) e343.
[40] A. Zumla, et al., Coronaviruses - drug discovery and therapeutic options, Nat. Rev. Drug Discov. 15 (5) (2016) 327–347.
[41] N. Lee, et al., Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients, J. Clin. Virol. 31 (4) (2004) 304–309.
[42] C.D. Russell, J.E. Millar, J.K. Baillie, Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury, The Lancet, 2020.
[43] J.S. Peiris, et al., Coronavirus as a possible cause of severe acute respiratory syndrome, Lancet 361 (9366) (2003) 1319–1325.
[44] Z. NS, Z. GQ, Our strategies for fighting severe acute respiratory syndrome (SARS), Am. J. Respir. Crit. Care Med. 168 (1) (2003) 7–9.
[45] R.M. Anderson, et al., Epidemiology, transmission dynamics and control of SARS: the 2002-2003 epidemic, Phil. Trans. Roy. Soc. Lond. B Biol. Sci. 359 (1447) (2004) 1091–1105.
[46] X. Pang, et al., Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing, JAMA, 2003 290 (24) (2003) 3215–3221.
[47] Centers for Disease, C. and Prevention, Efficiency of quarantine during an epidemic of severe acute respiratory syndrome-Beijing, China, MMWR. Morbidity Mortality Weekly Rep. 52 (43) (2003) 1037–1040 2003.
[48] R.F. Breiman, et al., Role of China in the quest to define and control severe acute respiratory syndrome, Emerg. Infect. Dis. 9 (9) (2003) 1037–1041.
[49] P. Sampathkumar, et al., SARS: epidemiology, clinical presentation, management, and infection control measures, Mayo Clin. Proc. 78 (7) (2003) 882–890.
[50] M.D. Christian, et al., Severe acute respiratory syndrome, Clin. Infect. Dis. 38 (10) (2004) 1420–1427.
[51] W. N, Learning from the sars outbreak, Curr. Biol. : CB 14 (3) (2004) R91–R93.
[52] D.S. Hui, P.K. Chan, Severe acute respiratory syndrome and coronavirus, Infect. Dis. Clin. 24 (3) (2010) 619–638.
[53] Z. NS, Z. GQ, Pandemic planning in China: applying lessons from severe acute respiratory syndrome, Respirology (2008) S33–S35.
[54] A. AS, et al., Lessons from the severe acute respiratory syndrome outbreak in Hong Kong, Emerg. Infect. Dis. 9 (9) (2003) 1042–1045.
[55] W. RP, E. MB, Listening to SARS: lessons for infection control, Ann. Intern. Med. 139 (7) (2003) 592–593.
[56] V.C. Cheng, et al., Clinical management and infection control of SARS: lessons learned, Antivir. Res. 100 (2) (2013) 407–419.
[57] U.D. Parashar, L.J. Anderson, Severe acute respiratory syndrome: review and lessons of the 2003 outbreak, Int. J. Epidemiol. 33 (4) (2004) 628–634.
[58] X. Pang, et al., Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing, JAMA, 2003 290 (24) (2003) 3215–3221.
[59] T. DR, Obstacles and advances in SARS vaccine development, Vaccine 24 (7) (2006) 863–871.
[60] T. Wenjie, et al., A novel coronavirus genome identified in a cluster of pneumonia cases — wuhan, China 2019 − 2020, China CDC Weekly 2 (4) (2020) 61–62.
[61] The -nCo, V.O.J.F.E.I.T. L. Qun, An outbreak of NCIP (2019-nCoV) infection in China — wuhan, Hubei province, 2019 − 2020, China CDC Weekly 2 (5) (2020) 79–80.
[62] S.C.A. University, Pangolin was found to be a potential intermediate-host of new coronavirus, Available from: https://www.scau.edu.cn/2020/0207/c1300a219015/page.htm.
[63] C. Rothe, et al., Transmission of 2019-nCoV infection from an asymptomatic contact in Germany, N. Engl. J. Med. (2020 Jan 30), https://doi.org/10.1056/NEJMc2001468 [Epub ahead of print].
[64] Clinical updates in women's health care summary: liver disease: reproductive considerations, Obstet. Gynecol. 129 (1) (2017) 236.
[65] Q. Li, et al., Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2001316.
[66] C.I. Paules, H.D. Marston, A.S. Fauci, Coronavirus infections-more than just the common cold, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.0757.
[67] T. Novel Coronavirus Pneumonia Emergency Response Epidemiology, The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China, Zhonghua liu xing bing xue za zhi = Zhonghua

liuxingbingxue zazhi 41 (2) (2020) 145–151.
[68] J.T. Wu, K. Leung, G.M. Leung, Nowcasting and Forecasting the Potential Domestic and International Spread of the 2019-nCoV Outbreak Originating in Wuhan, China: a Modelling Study, Lancet, London, England), 2020 S0140-6736(20)30260-9.
[69] Prevention, G.C.f.D.C.a. The virus on the doorknob is not a live virus, Available from: http://www.gd.xinhuanet.com/newscenter/2020-02/04/c_1125528591.htm.
[70] ZH, Z. Fecal matter of patients tests positive for coronavirus, Available from: https://www.chinadaily.com.cn/a/202002/02/WS5e35b026a310128217274206.html.
[71] M.L. Holshue, et al., First case of 2019 novel coronavirus in the United States, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2001191.
[72] Organization, W.H. Novel Coronavirus, (2019-nCoV) situation reports to data, Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.
[73] Organization, W.H. Statement on the Second Meeting of the International Health Regulations (2005) Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV). . 2020, World Health Organization, Geneva, 2020 Available from: https://www.who.int/newsroom/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-healthregulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov.
[74] Z.D. Fang, Y. Chen, et al., Diagnosis and prevention of 2019-nCoV virus infection/pneumonia in children (in Chinese) Available from: https://www.cma.org.cn/art/2020/1/29/art_1822_32177.html.
[75] Technology, T.H.T.M.C.H.U.o.S.a. Be Alert to the Risk of Mother-To-Child Vertical Transmission and the First New Coronavirus Infection of a Newborn Was Diagnosed in Tongji Hospital, ChuTian Metropolis Daily, 2020, p. 2020.
[76] H. Chen, et al., Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records, The Lancet, 2020.
[77] C.N.H. Commission, Notice on prevention and control of pneumonia in children and pregnant women with new coronavirus infection, China National Health Commission, Beijing, 2020 (in Chinese), http://www.nhc.gov.cn/xcs/zhengcwj/202002/de2d62a5711c41ef9b2c4b6f4d1f2136.shtml 2020; Available from:.
[78] Technology, M.e.g.o.T.h.a.t.T.M.C.o.H.U.o.S.a. A rapid guideline for the diagnosis and treatment of pneumonia with new coronavirus infection (Third edition). . Herald of Medicine 2020 1004-0781,CN 42-1293/R]; Available from: http://kns.cnki.net/kcms/detail/42.1293.r.20200130.1803.002.html.
[79] Union Hospital, T.M.C., Huazhong University of Science and Technology., Wuhan union hospital manage the 2019 new coronavirus infection strategies and instructions (in Chinese),, 2020. https://mp.weixin.qq.com/s/d7btF9g1wMhNgFnHy5vY1Q.
[80] L.C. Yinghui Jing, Zhenshui Cheng, Hong Cheng, et al., Diagnosis and Clinical Management of 2019 Novel Coronavirus (2019-nCoV) Infection: an Operational Recommendation of Peking Union Medical College Hospital. (In Chinese), Medical Journal of Chinese People's Liberation Army, 2020 0577-7402,CN 11-1056/R.
[81] Organization, W.H., Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (nCoV) Infection Is Suspected, (2020).
[82] C.N.H. Commission, New Coronavirus Pneumonia Prevention and Control Program, fifth ed., China National Health Commission, 2020, Beijing, 2020 (in Chinese), http://www.nhc.gov.cn/xcs/zhengcwj/202002/3b09b894ac9b4204a79db5b8912d4440.shtml Available from:.
[83] D. Wang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.1585.
[84] D. Chang, et al., Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside wuhan, China, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.1623.
[85] W.-j. Guan, et al., Clinical Characteristics of 2019 Novel Coronavirus Infection in China, medRxiv, 2020 2020.02.06.20020974.
[86] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao, Z. Sun, L. Xia, Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of **1014** Cases. Radiology (2020 Feb 26) 200642, , https://doi.org/10.1148/radiol.2020200642 [Epub ahead of print].
[87] Y. Chen, Q. Liu, D. Guo, Emerging coronaviruses: genome structure, replication, and pathogenesis, J. Med. Virol. 92 (4) (2020 Apr) 418–423, https://doi.org/10.1002/jmv.25681 Epub 2020 Feb 7. Review.
[88] B.T. Cookson, M.A. Brennan, Pro-inflammatory programmed cell death, Trends Microbiol. 9 (3) (2001) 113–114.
[89] I.Y. Chen, et al., Severe acute respiratory syndrome coronavirus Viroporin 3a activates the NLRP3 inflammasome, Front. Microbiol. 10 (2019) 50.
[90] M. Yang, Cell Pyroptosis, a Potential Pathogenic Mechanismof 2019 nCoV Infection, (2020).
[91] L.E. Gralinski, V.D. Menachery, Return of the coronavirus: 2019-nCoV, Viruses 12 (2) (2020).
[92] R. Lu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (10224) (2020) 565–574, https://doi.org/10.1016/S0140-6736(20)30251-8 Epub 2020 Jan 30.
[93] F. Wu, et al., A new coronavirus associated with human respiratory disease in China, Nature (2020 Feb 3), https://doi.org/10.1038/s41586-020-2008-3 [Epub ahead of print].
[94] P. Zhou, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature (2020), https://doi.org/10.1038/s41586-020-2012-7.
[95] A. Wu, et al., Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China, Cell Host Microbe (2020 Feb 7), https://doi.org/10.1016/j.chom.2020.02.001 [Epub ahead of print].
[96] D. Paraskevis, et al., Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event, Infect. Genet. Evol. 79 (2020) 104212.
[97] D. Wrapp, et al., Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation, bioRxiv, 2020 2020.02.11.944462.
[98] W. Li, et al., Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature 426 (6965) (2003) 450–454.
[99] B.J. Bosch, W. Bartelink, P.J.M. Rottier, Cathepsin L functionally cleaves the severe acute respiratory syndrome coronavirus class I fusion protein upstream of rather than adjacent to the fusion peptide, J. Virol. 82 (17) (2008) 8887–8890.
[100] S. Belouzard, V.C. Chu, G.R. Whittaker, Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites, Proc. Natl. Acad. Sci. U. S. A 106 (14) (2009) 5871–5876.
[101] I. Glowacka, et al., Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response, J. Virol. 85 (9) (2011) 4122–4134.
[102] J.F. Chan, et al., Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan, Emerg. Microb. Infect. 9 (1) (2020) 221–236.
[103] B. Delmas, H. Laude, Assembly of coronavirus spike protein into trimers and its role in epitope expression, J. Virol. 64 (11) (1990) 5367–5375.
[104] D.R. Beniac, et al., Architecture of the SARS coronavirus prefusion spike, Nat. Struct. Mol. Biol. 13 (8) (2006) 751–752.
[105] S. Xia, et al., Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein, Cell. Mol. Immunol. (2020), https://doi.org/10.1038/s41423-020-0374-2.
[106] M.L. DeDiego, et al., A severe acute respiratory syndrome coronavirus that lacks the E gene is attenuated in vitro and in vivo, J. Virol. 81 (4) (2007) 1701–1713.
[107] J.L. Nieto-Torres, et al., Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis, PLoS Pathog. 10 (5) (2014) e1004077.
[108] C.K. Chang, et al., Modular organization of SARS coronavirus nucleocapsid protein, J. Biomed. Sci. 13 (1) (2006) 59–72.
[109] K.R. Hurst, C.A. Koetzner, P.S. Masters, Identification of in vivo-interacting domains of the murine coronavirus nucleocapsid protein, J. Virol. 83 (14) (2009) 7221–7234.
[110] L. Cui, et al., The nucleocapsid protein of coronaviruses acts as a viral suppressor of RNA silencing in mammalian cells, J. Virol. 89 (17) (2015) 9029–9043.
[111] F. Li, Structure, function, and evolution of coronavirus spike proteins, Annu. Rev. Virol. 3 (1) (2016) 237–261.
[112] S. Belouzard, V.C. Chu, G.R. Whittaker, Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites, Proc. Natl. Acad. Sci. U. S. A. 106 (14) (2009) 5871–5876.
[113] S. Matsuyama, et al., Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2, J. Virol. 84 (24) (2010) 12658–12664.
[114] S. Bertram, et al., Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease, J. Virol. 85 (24) (2011) 13363–13372.
[115] G. Simmons, et al., Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research, Antivir. Res. 100 (3) (2013) 605–614.
[116] J.H. Kuhn, et al., Angiotensin-converting enzyme 2: a functional receptor for SARS coronavirus, Cell. Mol. Life Sci. : CMLS 61 (21) (2004) 2738–2743.
[117] V.S. Raj, et al., Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC, Nature 495 (7440) (2013) 251–254.
[118] M. Hoffmann, et al., The Novel Coronavirus 2019 (2019-nCoV) Uses the SARS-Coronavirus Receptor ACE2 and the Cellular Protease TMPRSS2 for Entry into Target Cells, bioRxiv, 2020 2020.01.31.929042.
[119] Q. Huang, A. Herrmann, Fast Assessment of Human Receptor-Binding Capability of 2019 Novel Coronavirus (2019-nCoV), bioRxiv, 2020 2020.02.01.930537.
[120] B.J. Bosch, et al., The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex, J. Virol. 77 (16) (2003) 8801–8811.
[121] A.C. Walls, et al., Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion, Proc. Natl. Acad. Sci. U. S. A 114 (42) (2017) 11157–11162.
[122] M. Gui, et al., Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding, Cell Res. 27 (1) (2017) 119–129.
[123] J. Pallesen, et al., Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen, Proc. Natl. Acad. Sci. U. S. A 114 (35) (2017) E7348–E7357.
[124] Y. Yuan, et al., Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains, Nat. Commun. 8 (2017) 15092-15092.
[125] A.C. Walls, et al., Unexpected receptor functional mimicry elucidates activation of coronavirus fusion, Cell 176 (5) (2019) 1026-1039.e15.
[126] X. Chai, et al., Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage after 2019-nCoV Infection, bioRxiv, 2020 2020.02.03.931766.
[127] H. Zhang, et al., The Digestive System Is a Potential Route of 2019-nCov Infection: a Bioinformatics Analysis Based on Single-Cell Transcriptomes, bioRxiv, 2020 2020.01.30.927806.
[128] C.N.H. Commission, Technical Guideline in Medical Institutions for the Prevention

and Control of Infection with the Novel Coronavirus, China National Health Commission, Beijing, 2020 (in Chinese), http://www.nhc.gov.cn/xcs/zhengcwj/202001/b91fdab7c304431eb082d67847d27e14.shtml Available from:.
[129] C.N.H. Commission, Community Prevention and Control Program for the 2019-nCoV Infected Pneumonia, China National Health Commission, Beijing, 2020 (in Chinese), http://www.nhc.gov.cn/xcs/zhengcwj/202001/dd1e502534004a8d88b6a10f329a3369.shtml Available from:.
[130] C.N.H. Commission, A Guideline for the Protection of People at Different Risk of New Coronavirus Infection, China National Health Commission, Beijing, 2020 (in Chinese), http://www.nhc.gov.cn/xcs/zhengcwj/202001/a3a261dabfcf4c3fa365d4eb07ddab34.shtml Available from:.
[131] W.H. Organization, Home care for patients with suspected novel coronavirus (nCoV) infection presenting with mild symptoms and management of contacts: interim Guidance (in Chinese), https://www.who.int/publications-detail/home-carefor-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-withmild-symptoms-and-management-of-contacts, (2020) Available from:.
[132] China., M.o.S.a.T.o.t.P.s.R.o. Clinical trial of antiviral drug remdesivir starts in Wuhan. (in Chinese) http://www.most.gov.cn/kjbgz/202002/t20200206_151440.htm, (2020) Available from:.
[133] X. Liu, X.-J. Wang, Potential Inhibitors for 2019-nCoV Coronavirus M Protease from Clinically Approved Medicines, bioRxiv, 2020 2020.01.29.924100.
[134] P. Richardson, et al., Baricitinib as potential treatment for 2019-nCoV acute respiratory disease, Lancet 395 (10223) (2020 Feb 15) e30–e31, https://doi.org/10.1016/S0140-6736(20)30304-4 Epub 2020 Feb 4.
[135] H. Lu, Drug treatment options for the 2019-new coronavirus (2019-nCoV), Biosci. Trends (2020), https://doi.org/10.5582/bst.2020.01020.
[136] M. Wang, et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell research, 2020, https://doi.org/10.1038/s41422-020-0282-0.
[137] C. Daily, First antiviral drug approved to fight coronavirus, Feb.17,2002] http://global.chinadaily.com.cn/a/202002/17/WS5e49efc2a310128217277fa3.html, (2020) Available from:.
[138] S. Ji, et al., Unique synergistic antiviral effects of Shufeng Jiedu Capsule and oseltamivir in influenza A viral-induced acute exacerbation of chronic obstructive pulmonary disease, Biomed. Pharmacotherapy = Biomed. Pharmacotherapie 121 (2020) 109652-109652.
[139] Y. Ding, et al., The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function, BMC Compl. Alternative Med. 17 (1) (2017) 130-130.
[140] Commission, C.N.H, Guiding Principles for the Intervention of Acute Psychological Crisis in Pneumonia Cases with New Coronavirus Infection. (In Chinese), China National Health Commission, Beijing, 2020 Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202001/6adc08b966594253b2b791be5c3b9467.shtml.
[141] A. Zumla, et al., Coronaviruses - drug discovery and therapeutic options, Nat. Rev. Drug Discov. 15 (5) (2016) 327–347.