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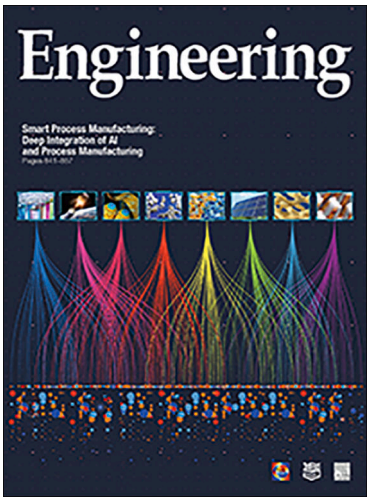


Review

# Strategies and Advances in Combating COVID-19 in China

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Research
Coronavirus Disease 2019—Review

# Strategies and Advances in Combating COVID-19 in China

Wei Liu, Wei-Jie Guan, Nan-Shan Zhong *
*State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou 510120, China*

* Corresponding author.
*E-mail address*: nanshan@vip.163.com,

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**ABSTRACT**

Coronavirus disease 2019 (COVID-19)—the third in a series of coronavirus infections—has caused a global public health event in the 21st century, resulting in substantial global morbidity and mortality. Building on its legacy of managing severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), China has played a key role in the scientific community by revealing the viral transmission routes and clinical characteristics of COVID-19 and developing novel therapeutic interventions and vaccines. Despite these rapid scientific and technological advances, uncertainties remain in tracing the original sources of infection, determining the routes of transmission and pathogenesis, and addressing the lack of targeted clinical management of COVID-19. Here, we summarize the major COVID-19 research advances in China in order to provide useful information for global pandemic control.

## 1. Introduction

Coronavirus disease 2019 (COVID-19), which emerged in December 2019, is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. According to the World Health Organization (WHO), COVID-19 has resulted in 34 495 176 laboratory-confirmed cases and 1 025 729 deaths as of 3 October 2020. SARS-CoV-2 shares at least 70% similarity of its genetic sequence with SARS-CoV [1,2]. Coming after SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), the SARS-CoV-2 outbreak is the third in a series of coronavirus outbreaks that have elicited heterogeneous clinical manifestations, ranging from asymptomatic response to fatal illness [3].

Like other common respiratory viruses (i.e., influenza virus, parainfluenza virus, respiratory syncytial virus, and rhinovirus), coronaviruses generally cause mild and self-limited upper respiratory tract infections with clinical manifestations of common cold or mild pneumonia [4]. Among all known coronavirus species, only six have been identified to cause human diseases as of 2019. The 229E, OC43, NL63, and HKU1 coronaviruses are well documented and mostly result in mild-to-moderate respiratory diseases [5]. However, the substantial genetic diversity, frequent recombination, and cumulative mutations of their RNA genomes, along with the notable increase in human-to-wildlife activities, have collectively resulted in a greater likelihood of the emergence of more transmissible and/or virulent pathogens.

Since the prevalence of COVID-19, China has been confronted with various uncertainties, including the infectivity and routes of transmission, clinical manifestations and immune responses, and possible effective treatments against SARS-CoV-2 infection. Determining how to best manage the surge of new cases, promptly triage patients based on the predicted disease development trajectory, and deploy practical management to improve the clinical outcomes has become the central task for the government and medical community. During the battle against COVID-19, based on the “life supremacy” policy, China has enforced rapid non-pharmaceutical interventions and played a crucial role in unraveling the viral transmission and clinical characteristics, and in developing novel therapeutic interventions and

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vaccine. Here, we summarize the strategies that have been used in China in different domains, which might help to increase our preparedness against future outbreaks and inform disease prevention and management across the globe.

## 2. Overview of the strategies for battling against COVID-19 in China

Epidemiological surveillance systems, which have been well established since the 2003 SARS epidemic in China, underpinned China's rapid identification of initial cases with a "pneumonia of unknown etiology" [6,7]. Within only one month, the Chinese government had declared the epidemic an "extremely serious public health incident." This familiar scenario, in which patchy shadows and ground-glass opacity on computed tomography (CT) images, even presenting with "white lung" in severe patients [8], surpassed the panic caused by the large-scale superspreading of SARS-CoV 17 years ago.

Defining the routes of transmission and sources of infection may inform the strategies for outbreak containment at a nationwide level, with the rapid deployment of non-pharmaceutical interventions [9,10]. In Wuhan, most cases had a history of recent travel to or contact with the people in a seafood wholesale market. Subsequent infections of medical staff and other sporadic cases showed no contact with this market. In cases of close contact, the human-to-human transmission potential of the virus was soon released, and the public was warned via multiple social media platforms. The declaration that Wuhan city—but not other regions—was the epicenter prompted the Chinese government to initiate an unprecedented and draconic measure: to lock down Wuhan and several other adjacent cities in Hubei province in order to rapidly curb the massive outflow of infected cases and enforce restrictions on movements to the epicenter [9]. To more rapidly achieve epidemic containment, non-governmental societies were soon mobilized to supervise and trace the paths of relevant individuals.

In order to more effectively manage the surge of mild-to-moderate cases, makeshift (Fangcang) hospitals with 13 000 beds were temporarily built in large-scale public venues to facilitate the isolation, treatment, and monitoring of confirmed cases, which would help to alleviate the shortage of medical supplies. The establishment of these low-cost hospitals obviated within-household and community transmission; it also helped to release the pressure of patient admissions to designated hospitals and made it possible to triage severe patients promptly. To minimize the risk of transmission, residents without symptoms and/or with a history of close contact yet a negative polymerase chain reaction (PCR) test were mandated to isolate at home. These measures eventually proved to be highly effective in flattening the epidemiologic curve. However, challenges in managing ongoing local outbreaks induced by imported cases remain due to the high risk of resurgence in regions such as Beijing, Xinjiang, Dalian, and Hong Kong, which have frequent population immigration.

## 3. Possible mechanisms underlying viral infection

SARS-CoV-2 was initially identified and isolated from a cluster of patients with similar symptoms (fever, cough, and dyspnea) and radiologic findings of ground-glass opacity on chest CT [6]. Next-generation sequencing and real-time reverse transcription polymerase chain reaction (RT-PCR) targeting to a consensus RNA-dependent RNA polymerase (RdRp) region of panβ-CoV demonstrated the pathogen to be a novel beta coronavirus [7]. Electron microscopy revealed the solar appearance of virion particles, whose morphology was consistent with that of the Coronaviridae family [7].

SARS-CoV-2 most likely originated from bats due to its substantially high homology (96% nucleotide sequence identity) with SARS-like bat coronaviruses (BatCoV RaTG13) [11,12]. A possible mechanism of the emergence of SARS-CoV-2 is that the accumulative mutations in its genome enabled the virus to cross the animal–human barrier. However, animal-to-human transmission is unlikely to have been the main driver for the COVID-19 pandemic.

SARS-CoV-2 employs mechanisms similar to those of SARS-CoV for receptor recognition and cell entry. The spike (S) protein on the virion surface facilitates the entry of the virus into the target cells by attachment to its cognate receptor, angiotensin-converting enzyme 2 (ACE2), on the cell surface. Transmembrane serine proteases of the target cells, such as FURIN or transmembrane protease serine 2 (TMPRSS2), induce cleavage of the S protein before membrane fusion for cellular entry [13]. Therefore, cells that co-express ACE2 and serine protease could be the primary targets of SARS-CoV-2. Single-cell RNA-sequencing studies have also confirmed the expression of ACE2 and TMPRSS2 in a vast array of cells, including lung alveolar epithelial type II cells, nasal goblet cells, cholangiocytes, colonocytes, esophageal keratinocytes, gastrointestinal epithelial cells, pancreatic β-cells, and renal proximal tubules and podocytes [14]. These observations have provided probable explanations for multiple-organ infection and injury via direct viral tissue damage. Moreover, clinical observations have demonstrated extrapulmonary manifestations, ranging from hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, and ophthalmologic to dermatologic systems [14].

SARS-CoV-2 attacks the host through direct tissue damage, endothelial cell damage and thrombosis, dysregulation of the immune response, and disorders of the renin-angiotensin-aldosterone system [15]. COVID-19 infection is accompanied by an aggressive inflammatory response with the release of massive pro-inflammatory cytokines in an

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event known as the "cytokine storm" [16,17]. Plasma collected from COVID-19 patients with pneumonia has shown markedly increased concentrations of pro-inflammatory cytokines (interleukin-1β (IL-1β), interleukin-1 receptor antagonist (IL-1RA), IL-7, IL-8, IL-9, IL-10, fibroblast growth factor, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), interferon-inducible protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β), platelet-derived growth factor (PDGF), tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF)) [18]. Critical illness in patients has also been associated with an elevated level of IL-2, IL-7, IL-10, G-CSF, IP10, MCP-1, MIP-1α, and TNF-α plasma concentrations as compared with mild cases. These events drive the recruitment of immune cells such as macrophages, neutrophils, and T cells into the sites of infection, causing destabilization of endothelial cell to cell and the vascular barrier and diffusing alveolar damage, and ultimately leading to multi-organ failure and subsequent death.

ACE2 is the key determinant of viral transmissibility. Recent studies have demonstrated that the receptor binding domain of the S protein from SARS-CoV-2 displays a 10- to 20-fold higher binding capacity with ACE2 compared with that of SARS-CoV [19,20], which may partially explain the increased transmissibility of SARS-CoV-2 [21]. SARS-CoV-2 shows a gradient of reduced infectivity from the proximal to distal respiratory tract, which coincides with the finding of progressively decreased expression of ACE2 from the oropharynx to the alveoli [22]. SARS-CoV-2 infection might be initiated from the nasal passages, followed by the aspiration of virions seeding along the respiratory tract to the lungs, rather than causing direct lung infection. A more possible process might involve high loads of virus shedding from the initially infected respiratory tract, along with the secretion of mucus accumulating at the oropharynx cavity, and finally arriving at the tracheobronchial tree via aspiration [23].

Molecular dynamics simulations suggest that SARS-CoV-2 has a distinct binding interface to ACE2, with higher affinities and a different network of residue-residue contacts than other coronaviruses [2]. SARS-CoV-2 has a larger contact area than SARS-CoV with more conserved residues for ACE2 attachment. Unlike coronaviruses with low pathogenicity, SARS-CoV-2 exhibits enhancement of the nuclear localization signals in the nucleocapsid protein and distinct inserts in the spike glycoprotein, which appear to be associated with the high case-fatality rate [24].

SARS-CoV-2 could evolve into diverse lineages with different magnitudes of virulence and transmissibility via mutations [25]. Several studies have documented a SARS-CoV-2 variant, aspartic acid (D) with substitution of glycine (G) at codon 614 in the S protein [25–28], which is located on a B-cell epitope with a highly immunodominant region on the receptor binding domain. An *in vitro* study suggested that a D614G pseudotype variant was nine times more infectious than the D614 strains [29]. Strains carrying this mutation have become dominant since December 2019, and have been frequently observed in European countries (e.g., the Netherlands, Switzerland, and France) but not as frequently in China. Strikingly, the variant S-D614G distinguishes the SARS-CoV-2 strains that may have caused fatal infections in European populations [27]. A study on the alignment of 10 022 SARS-CoV-2 genomes from infected persons in 68 countries identified 6294 samples carrying the D614G mutation; almost all of these genomes also had another co-mutation in the proteins responsible for replication (ORF1ab P4715L; RdRp P323L) that might affect the speed of replication [28]. D614G was predicted to fine-tune the spike conformation and result in a loss of immunogenicity for B-cell recognition, a dominated process to stimulate adaptive immunity against SARS-CoV-2 infection.

## 4. Transmission routes

The major transmission route of SARS-CoV-2 is considered to be close contact with droplets containing exposed virus or contaminated fomites. Further studies have revealed the presence of viral RNA in various bodily fluid samples, including bronchoalveolar lavage fluid, sputum, nasal swabs, pharyngeal swabs, feces, blood, and urine [30], which suggest alternative routes of transmission. In fact, infectious SARS-CoV-2 virions have been isolated from fecal and urine samples. In line with these reports, SARS-CoV-2 productively infects the human gut enterocytes [31–34] and causes notable gastrointestinal symptoms, including abdominal pain and diarrhea in 20%–50% of patients [35–37]. Further investigations found that the viral load in feces was markedly higher than that in the respiratory tract between 17 and 28 d after symptom onset, and that RNA fragments—but not infectious virus—were detected in the feces [38]. During an episode of diarrhea, infectious virus could be more readily detected in the feces [37]. Moreover, infectious viruses have also been isolated from urine. Given these findings, appropriate precautions should be taken to avoid fomite transmission.

## 5. Advances in laboratory diagnosis

The development of rapid diagnosis is urgently needed during the early stages of an epidemic to enable community-based screening and consistent course development monitoring. During the early stage of the COVID-19 epidemic, diagnosis was based on symptoms and chest radiology. The majority of COVID-19 cases showed bilateral

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distribution of patchy shadows and ground-glass opacity on CT images. However, 17.9% of non-critically ill patients and 2.9% patients with severe illnesses showed no radiologic abnormality on hospital admission [39].

RT-PCR has been extensively deployed for the detection of SARS-CoV-2 RNA fragments, and has been recommended for the diagnosis of acute infection. However, false-negative results may be problematic, as they can jeopardize the whole community [40]. The fact that a patient who was RT-PCR negative developed clinical symptoms of COVID-19, suggesting that insufficient amounts of viral genome collection for amplification, or mutations in the NP and ORF of SARS-CoV-2, may lead to false-negative results [41].

Serological analysis is another typical method for COVID-19 diagnosis [42–44]. Accurate serological tests would enrich our understanding of the personal process of viral exposure, particularly in the monitoring of asymptomatic individuals. Nucleocapsid (N)- and S-specific immunoglobulin M (IgM) and IgG could be used for the detection of SARS-CoV-2 infection because of the progressively elevated titers after symptom onset (typically peaking at Days 7–10). The combined detection of N- and S-specific IgM and IgG may increase the detection rate at early stages. In fact, the combination of N- and S-induced IgM and IgG could be detected in up to 75% of infections within the first week of symptom onset [45]. The sensitivity of combined detection of N-IgM and N-IgG, or N-IgG and S-IgG, reached 94.7% within the second week [45]. At Week 3, S-IgG titers were significantly higher in non-intensive care unit (ICU) patients than in ICU patients [45]. Moreover, the expression level of N-IgG was significantly higher in ICU patients, although S-IgG titers were higher in patients with moderate illness. These findings provide hints for prognosis prediction [46].

To accelerate the clinical diagnostic testing of COVID-19 (particularly for population-based survey or point-of-care testing), a rapid, accurate, and portable detection method based on clustered regularly interspaced short palindromic repeats (CRISPR)/ CRISPR associate system (Cas) has been developed. The CRISPR/Cas system is an adaptive immune system in archaea and bacteria that defends against foreign genetic elements [47,48]. CRISPR allows a programmable protein to attach onto the target site assisted by a guide RNA for cleavage of the target sequence [47,49–51]. CRISPR/Cas12a-based detection has been established together with SARS-CoV-2-specific CRISPR RNAs (crRNAs) targeting the orf1a, orf1b, N, and E genes, and a single-stranded DNA (ssDNA) reporter labeled with a quenched green fluorescent molecule has been developed [48]. The fluorescent molecule is cleaved in the presence of a trace amount of SARS-CoV-2 sequences; more importantly, the results can be determined by the naked eye. This system also allows for simultaneous reverse transcription and isothermal amplification at a low temperature, independent of laboratory instruments, and thus could meet the urgent need for rapid diagnosis.

## 6. Clinical characteristics of COVID-19

Given the lack of knowledge regarding the manifestations of COVID-19 and the unclear targets for its prevention, efforts have been expedited to extract the clinical data from the first 41 cases, who were unanimously recruited from Wuhan [52]. To depict the clinical characteristics at the national level, a study was performed to analyze 1099 laboratory-confirmed cases from 552 hospitals across mainland China [39]. The most common symptoms were fever and cough on admission, while gastrointestinal illnesses such as nausea, vomiting, and diarrhea were uncommon (< 5%). The median incubation period was 4 d (interquartile range: 2–7 d). The case-fatality rate was 1.4%, which was comparable to the national official statistics in China as of 16 February 2020 [39]. However, the case-fatality rate cannot be precisely calculated due to the unclear total number of infected individuals. Importantly, fever was not present on admission in around half of the individuals, suggesting that fever cannot be the sole diagnostic standard for population-based screening of COVID-19. The fact that lymphopenia was common and more prominent in patients with greater disease severity has inspired clinicians to perform clinical trials to validate the effectiveness of interventions against lymphopenia. Furthermore, children are not immune to COVID-19 and most infected children have been found to have a history of recent infections in their families [53,54].

Multiple comorbidities have been found to be associated with the severity of disease and progression in SARS and MERS [55–57]. Similarly, recent studies have shown that COVID-19 patients with diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), hypertension, malignancies, and other comorbidities had a markedly higher mortality rate. Elevated levels of ACE2 that were proposed to be associated with an increased susceptibility have been observed in COVID-19 patients with diabetes, COPD, and CVD [58]. Persons suffering from hypertension may also have increased ACE2 levels induced by heavy dosages of ACE2 inhibitors and angiotensin receptor blockers (ARBs) during treatment. However, there has been no evidence that ACE inhibitors or ARBs affects the severity of COVID-19 [59–62]. Apart from hypertension, patients with cancer were found to be more susceptible due to their systemic immunosuppressive state [63]. Patients with cancer had a significantly higher risk of ICU admission, requiring invasive ventilation, and death [63,64]. Therefore, patient triage should be based on the presence and spectrum of comorbidities, which would allow for more intensive monitoring among patients at higher risk of developing severe clinical outcomes. Meanwhile, radiotherapy and chemotherapy may be postponed for cancer patients who are clinically stable in order to minimize the risk of acquiring nosocomial infections.

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The presence of systemic symptoms varied considerably among different countries. A recent meta-analysis of 29 studies, mainly from China, demonstrated that anorexia was present in 21%, nausea and/or vomiting in 7%, diarrhea in 9%, and abdominal pain in 3% of the cases, respectively. However, in a study from the United States, the systemic symptoms of anorexia (34.8%), diarrhea (33.7%), and nausea (26.4%) were found to be more common [14].

It is noteworthy that a small proportion of patients remained asymptomatic throughout the course of the disease [65]. Because of the atypical manifestations, contact tracing of asymptomatic patients is necessary after a positive viral RNA test [66,67]. The first report of an asymptomatic patient was anecdotal, based on a chest CT scan of an infected child in a familial cluster of cases. Further studies demonstrated that the proportion of asymptomatic patients ranged from 20% to 78% of positive cases [66,68]. Of the 166 new cases identified on 1 April 2020 in China, 130 (78%) were asymptomatic. Unlike symptomatic patients, hyposmia and nasal congestion were frequent among asymptomatic patients—regardless of whether they had positive CT scan findings or not—but uninfected patients could be excluded by RT-PCR. Asymptomatic patients remained contagious; viral shedding was found to be most prominent before symptom onset, and the duration of shedding might be extended in comparison with symptomatic patients [69,70]. However, the population of asymptomatic individuals may be highly heterogeneous, as such individuals may be in the earlier stages of the disease or could remain asymptomatic throughout the course of the disease.

## 7. Prognostic prediction of critical illnesses

COVID-19 is characterized by rapid progression in a number of patients. The case-fatality rate ranged from 1.4% in the general population by the statistic of 1099 cases, [39] to 49% in patients with critical illness in summary of a report of 72 314 cases from Chinese Center for Disease Control and Prevention [71]. Early identification of patients at risk of developing critical illness would allow for early triage, timely clinical management, and optimization of medical resources [72]. The overall problem encountered in China during the first few months of the epidemic was the difficulty of identifying patients who were more likely to develop severe illness out of the thousands of daily confirmed cases as soon as possible. However, no tool was available at the initial stage of the epidemic to inform clinicians in China.

To address this urgent issue, a predictive risk score estimating whether a hospitalized patient with COVID-19 would be inclined to develop critical illness was developed. A retrospective cohort of 1590 patients with COVID-19 from 575 hospitals in 31 provincial administrative regions was included. By using the least absolute shrinkage and selection operator model, 19 common clinical variables (clinical features and blood test results, chest X-ray (CXR) abnormality, age, exposure to Wuhan, first and highest body temperature, respiratory rate, systolic blood pressure, hemoptysis, dyspnea, skin rash, unconsciousness, number of comorbidities, COPD, cancer, oxygen saturation levels, neutrophils, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, direct bilirubin, and creatinine levels) remained to predict the likelihood of progressing to critical illness [72]. The deployment of an artificial intelligence (AI) system allowed a deep learning-based survival model to further establish an online calculation tool, which could differentiate patients with COVID-19 from those with other forms of common pneumonia [73].

A CT-based AI system could also assist in early diagnosis for triage, monitoring, and treatment, as well as in establishing a reference for longitudinal follow-up [74]. Since CT scanning provides more detailed information on pathology and gives a better quantitative measurement of the lesion's size and the extent or severity of lung involvement, it may be a preferred tool, especially for point-of-care testing. The rapid turnaround time of CT assessment, coupled with the application of an AI system, may help in the early triage of patients by significantly shortening the duration from clinical inspection to triage, especially when the healthcare system is overloaded [75,76].

Dynamic changes in hematologic and immunologic biomarkers might also be valuable for informing clinicians of the severity of COVID-19 and enabling them to postulate the most probable clinical outcomes [77]. Peripheral blood lymphocyte, eosinophil, and platelet counts could serve as predictors for disease recovery. Progressive increases in the numbers of neutrophils, basophils, and IL-6 levels have been found to be associated with a fatal outcome [18]. Regardless of the disease severity during the initial clinical visit, the absolute lymphocyte count remained substantially lower in non-survivors than in survivors. In addition, higher levels of neutrophil count, IL-6, pro-calcitonin, D-dimer, amyloid A protein, and C-reactive protein have been identified in deceased patients. Marked lymphopenia has also been associated with a fatal outcome; the platelet count was found to be significantly lower in severe patients and even lower in non-survivors. These findings provide a scientific basis for implementing therapeutic interventions targeted at restoring the inflammatory cell count and inflammatory mediators.

## 8. Advances in clinical management

Similar to the cases of SARS and MERS infection, no effective therapies with proven efficacy have been developed as yet against COVID-19. Therefore, recommendations for therapeutic intervention (including supportive therapy)

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have been based on extrapolation of published guidelines or expert consensus [78]. Most pharmacological treatments were extrapolated from treatments used during the SARS or MERS outbreaks. The main findings from the clinical trials of COVID-19 in mainland China were summarized in Table 1. However, at the initial stage of the COVID-19, few clinical trial findings were available to inform clinicians regarding which medications had the greatest efficacy in treating patients with COVID-19 and whether targeted therapies existed for COVID-19.

**Table 1**

Summary of the main findings from the clinical trials of COVID-19 in mainland China.

| Treatment | Target population | Reduces viral loads | Improvement in clinical outcomes | Main adverse effects |
|---|---|---|---|---|
| Lopinavir–ritonavir | Severe COVID-19 | Probable | No significant acceleration in the time to clinical improvement | Gastrointestinal tract symptoms; impairment of liver and kidney function |
| Remdesivir | Severe COVID-19 | Probable | No significant acceleration in the time to clinical improvement | Gastrointestinal tract symptoms; impairment of liver and kidney function |
| Favipiravir | Severe COVID-19 | Yes | Increase the rate of improvement of chest computed tomographic findings | Diarrhea; impairment of liver and kidney function |
| Chloroquine | Moderate-to-severe COVID-19 | Yes | No significant acceleration in the time to clinical improvement | Prolongation of Qt intervals; impairment of liver and kidney function |
| Convalescent plasma | Critical illness of COVID-19 | Yes | No significant acceleration in the time to clinical improvement | Unknown |
| Lianhuaqingwen capsule | Moderate COVID-19 | No | Accelerate symptom improvement and increase the rate of symptom improvement | impairment of liver and kidney function |
| Granulocyte colony stimulating factor | Lymphopenic patients with COVID-19 | No | Decrease the likelihood of disease progression and increase the rate of symptom improvement | Leukocytosis; osteodynia |
| Hydrogen oxygen mixed gas inhalation | Symptomatic patients with COVID-19 | Unknown | Rapidly ameliorate respiratory symptoms | Unknown |

The fact that viral infection (including viral sepsis) [79] remains the key driver of the pathogenesis of COVID-19 has fueled research exploring the efficacy of antiviral medications in patients with severe or critical illness. Taking into account the findings from *in vitro* [80,81] and *in vivo* studies [82–84], lopinavir/ritonavir, remdesivir, and chloroquine (previously intended for the treatment of Ebola virus or human immunodeficiency virus (HIV) infections) have been repurposed for combating SARS-CoV-2 infection. In a randomized clinical trial conducted in the early stage of the epidemic in China, patients with severe COVID-19 were assigned to receive standard-of-care alone or in combination with a 14-day course of treatment with lopinavir/ritonavir [82]. Neither the duration from randomization to clinical improvement nor the mortality rate differed significantly between the treatment group and the control group. Subsequently, in another double-blinded clinical trial, patients with severe COVID-19 were randomly allocated to receive standard-of-care alone or in combination with 10 d of remdesivir [81]. Again, there was no significant difference in the time to clinical improvement, which was the primary endpoint of the study. Neither lopinavir/ritonavir nor remdesivir markedly reduced viral loads, as monitored dynamically throughout the two trials. Several reasons could have accounted for these negative findings. It was notable that patients entered the clinical trials after a median duration of 11–13 d, which could have diminished the efficacy as compared with earlier administration of the drugs. In fact, early administration of lopinavir/ritonavir (within 10 d of symptom onset) has been associated with a shorter course of viral shedding [83]. Moreover, both of these trials might have been underpowered for statistical analysis due to the emergency of the outbreak and the premature cessation of patient recruitment (there was difficulty in recruiting sufficient patients once the epidemiologic curve has flattened within Wuhan). Nevertheless, the results did not preclude the use of lopinavir/ritonavir and remdesivir for severe cases of COVID-19. Both trials indicated a numerically faster time to clinical improvement in the treatment group [82,85]

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and, in a more recent clinical trial, administration of remdesivir for 10 d was associated with a faster time to clinical improvement and a lower mortality rate by 14 d, as compared with the placebo group [86]. Furthermore, when administered in combination with IFN-β and ribavirin, lopinavir/ritonavir has been associated with a marked reduction in viral loads compared with usual care alone [87]. Therefore, combined antiviral medications might have a role in accelerating viral clearance in patients with COVID-19. Several other candidate medications have also been tested in clinical settings for COVID-19. The effects of chloroquine and hydroxychloroquine on patients with COVID-19 remain under debate. While chloroquine effectively reduced viral loads and achieved negative conversion of viral assays in hospitalized patients [88], the administration of hydroxychloroquine failed to increase the probability of achieving negative conversion of viral assays by 28 d in patients with mild-to-moderate COVID-19 [84]. In a pilot open-label study, favipiravir was shown to markedly shorten the time to viral clearance and increase the rate of improvement in chest imaging compared with a combination treatment with lopinavir/ritonavir plus IFN-α inhalation [89]. This finding added to the scientific evidence on candidate medications with potent antiviral activities.

Apart from heightened inflammatory response and viral infections, the aberrant immune response has been the canonical pathophysiological change leading to the poor clinical outcomes. Lymphopenia was identified in up to 80% of patients with COVID-19 and was significantly correlated with the risk of mortality [39,90]. Mobilizing the trafficking of lymphocytes to the peripheral blood with recombinant human granulocyte colony stimulating factor (rhG-CSF) might represent an appealing therapeutic approach for patients with COVID-19 who have lymphopenia. A recent randomized clinical trial revealed that, despite the failure to accelerate clinical improvement, rhG-CSF markedly increased $CD8^+$ T cell and natural killer (NK) cell count while reducing the risk of progression to critical illness or death compared with the usual care alone [91], particularly in patients with a blood lymphocyte count below 400 per cubic milliliter. Mechanistic studies unraveling the mode of actions of rhG-CSF in patients with COVID-19 are needed.

Corticosteroids confer powerful anti-inflammatory effects and hence may ameliorate inflammation-mediated lung injury, thus preventing progression to respiratory failure and death. In an observational study, the use of methylprednisolone was found to be associated with a markedly lower risk of mortality in patients with COVID-19 who had developed acute respiratory distress syndrome [92]. In an echo of these findings, a recent clinical trial recruiting hospitalized patients with COVID-19 showed that the oral or intravenous administration of dexamethasone ($6\ mg \cdot d^{-1}$) for up to 10 d resulted in a markedly lower 28-day mortality in comparison with the control group among patients receiving invasive mechanical ventilation at randomization or receiving oxygen without invasive mechanical ventilation [93]. The benefit was also clear in patients who were being treated more than 7 d after symptom onset, when inflammatory lung damage became more prominent. However, no significant effects were observed among patients not receiving any respiratory support, which was in line with the findings from a recent meta-analysis [94].

Targeted therapy has been very limited among critically ill patients with COVID-19. By extrapolating from experience in managing patients with SARS and MERS, efforts have been made to treat critically ill patients with COVID-19 with convalescent plasma. In a pilot single-arm study with five patients, convalescent plasma with high-titers neutralizing antibodies appeared to improve the overall clinical status [95]. On the basis of usual care in a randomized clinical trial, convalescent plasma therapy did not confer additional benefits in terms of the time to clinical improvement within 28 d [69]. However, convalescent plasma did show clinical benefits in the subgroup of severe patients, albeit not in critically ill patients. [96] Nevertheless, the bona fide therapeutic benefits of convalescent plasma cannot be precluded, as the trial was underpowered for analysis due to the difficulty in recruiting patients at later stages of the outbreak. Although there was no statistically significant difference, a possible clinical benefit was observed for patients with severe COVID-19 but not for patient subgroups with a life-threatening level of illness.

Several studies in China have observed disseminated intravascular coagulation (DIC) in most non-survivors [97,98]. Significantly higher levels of D-dimer and fibrin degradation products, as well as a longer prothrombin time, suggested that coagulopathy might be associated with poor prognosis [99]. The dynamic changes in D-dimer levels correlated positively with the prognosis of COVID-19 [98]. Patients with a sepsis-induced coagulopathy score greater than or equal to 4, or a D-dimer level greater than six times the upper limit of normal, exhibited a lower mortality rate when receiving low molecular weight heparin for 7 d or longer [100]. When given anticoagulant treatment, attention should be paid to avoid the development of diffuse alveolar hemorrhage, which is a life-threatening complication that may occur after the administration of warfarin [101].

Non-pharmacological interventions might have a role in the clinical management of COVID-19. Patients with COVID-19 have been characterized by increasingly laborious breathing as a result of greater airway resistance. Due to smaller molecular weight, helium-oxygen mixed gas has been applied to ameliorate dyspnea in patients with respiratory failure [102] and chronic obstructive pulmonary disease [103]. However, due to the low cost-effectiveness ratio, helium–oxygen mixed gas has not been extensively adopted in clinical practice. In contrast, hydrogen/oxygen mixed gas ($H_2$–$O_2$) could be generated via the direct electrolysis of water with the use of a commercialized instrument,

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and could be adopted for home use [104]. $H_2$–$O_2$ inhalation has recently been shown to markedly ameliorate dyspnea in patients with central airway stenosis [104]. It is essential to determine whether $H_2$–$O_2$ inhalation would result in a major clinical improvement in symptomatic patients with COVID-19. In an open-label multicenter clinical trial, $H_2$–$O_2$ inhalation led to a marked and rapid amelioration of the key respiratory symptoms (including dyspnea, chest pain, and cough scale) and improved the resting oxygen saturation and disease severity in patients with COVID-19 who had dyspnea at enrollment [105]. Based on these findings, $H_2$–$O_2$ inhalation has been endorsed by the National Health Commission of the People's Republic of China for COVID-19 patients with dyspnea or those in facilities without sufficient oxygen supplies [106].

Traditional Chinese medicine has been a treasure trove of complementary medicine. Efforts have been made to explore the effects of a panel of herbal formulas for the management of SARS and influenza. For example, Lianhuaqingwen (LH) capsule has been approved for the treatment of mild-to-moderate SARS [107,108]. Therefore, priority could be given to the development of LH capsules, because off label marketing medications would help reduce the time for research and development (R&D) against other candidate medications in the pipeline. In an in vitro study, LH capsule yielded potent antiviral effects against SARS-CoV-2 [109]. Based on these observations, a multicenter randomized clinical trial was undertaken to determine the effectiveness of LH capsule plus usual care, versus usual care alone [110]. At Day 14, treatment with LH capsule was associated with a significantly higher rate of symptom recovery and a markedly shortened time to symptom recovery, although no differences in the viral loads were observed between the two groups. It is notable that these therapeutic effects might not be related to the antiviral effects because the serum concentrations of LH capsule were markedly lower than those reported in the *in vitro* study in which the antiviral effects were potent [109]. LH capsules also exhibited anti-inflammatory and anti-oxidative effects via suppressing cytokine release, according to the results from an *in vitro* study [110]. These findings have resulted in the endorsement of LH capsules by the National Health Commission of the People's Republic of China for the treatment of mild-to-moderate COVID-19 [106]. Apart from LH capsules, other candidate herbal formulas such as Xuebijing injection and Liu Shen capsule have demonstrated antiviral activities against SARS-CoV-2 [111,112]. Multicenter clinical trials to determine the efficacy of these herbal formulas (i.e., Xuebijing injection for severe or critically ill cases with COVID-19) are now underway.

## 9. Vaccine development

Despite tremendous global efforts to contain the outbreak and rapid advances in therapeutics, few targeted approaches have been available. Given the rapid transmission and the rapid decay of antibody titers [113], vaccines that can induce strong anti-SARS-CoV-2 immune responses are urgently needed to achieve global containment of COVID-19.

Vaccine development has benefited from the early release of the complete genome sequence of SARS-CoV-2. As of 3 September 2020, according to the WHO, 33 vaccine candidates are at different stages of clinical development, six of which are at phase III clinical trials [114]. On 22 July 2020, China approved the use of two inactivated COVID-19 vaccines developed by Sinovac Biotech Co. Ltd. [115]. Another adenovirus vector-based SARS-CoV-2 vaccine was approved by the administrative office of Russia on 10 August 2020. U.S. authorities have recently announced the pending approval of a vaccine by the end of this year.

In public health emergencies, such as the COVID-19 pandemic, regulators are expected to act quickly to support accelerated vaccine development through the introduction of increased regulatory flexibility. To guide the accelerated vaccine development and approval for COVID-19, the Chinese regulatory agencies and the National Medical Products Administration (NMPA) have issued seven guidelines since March 2020 to provide a roadmap and requirements [116]. Moreover, the Chinese NMPA has formulated a special scheme to synchronize the protocol reviewing process with the research and development processes. Consequently, completion of the vaccine development and the review may take place simultaneously so that the vaccine development can proceed to clinical application without major delays. For example, the NMPA completed the review process of the Sinopharm COVID-19 vaccine application within just 24 h, although such a review would normally take 60 d. Thus far, there have been ten Chinese COVID-19 vaccine candidates in the pipeline of clinical trials [114,117–123], in four of which international phase III clinical trials have been initiated. Furthermore, more than 21 preclinical projects may have the potential to move into clinical trials.

Nearly all of the current human vaccines are based on two major platforms: the virus-based (inactivated/attenuated) vaccine platform and the recombinant protein-based (subunit/virus-like particle (VLP)) vaccine platform [124–126]. Four "inactivated virus vaccines" are in post-phase II clinical trials, and two of these have been approved for emergency use. This major achievement from the "inactivated virus vaccine platform" in China was made possible by the early development of the inactivated enterovirus 71 and inactivated poliovirus vaccines in China. A replication-defective human adenovirus type-5-based COVD-19 vaccine encoding the full S protein of SARS-CoV-2 as a subunit-based vaccine was found to successfully elicit cellular immune responses via single-dose inoculation through

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the intramuscular or intranasal administration. This vaccine could effectively prevent SARS-CoV-2 infection in the higher and lower respiratory tracts [127]. Moreover, mucosal vaccination might be more effective in preventing viral replication in the upper respiratory tract, as compared with intramuscular vaccination.

## 10. Summary

The COVID-19 pandemic is an unprecedented global threat that has resulted in substantial morbidity and mortality and has dramatically disrupted socioeconomic activities. Building on its experience in fighting against SARS and MERS, China has quickly adopted effective measures to curb the surge of cases and ultimately contain the epidemic (as shown in Table 2). The principles of early detection, early isolation, early management, and early prevention are the key steps to achieve effective containment of this rapidly spreading global pandemic.

**Table 2**
Summary of the advances and interventions contributing to COVID-19 containment in mainland China.

| Advance/intervention | Measures |
|---|---|
| Non-pharmaceutical interventions | Announcing the potential of human-to-human transmission |
| | Lockdown of Wuhan and other adjacent cities in Hubei province |
| | Imposing restrictions on all social activities |
| | Enforcing national and international travel restrictions |
| Clinical characterization and epidemiologic advances | Comprehensive characterization of the viral ultrastructure |
| | Revealing the route for SARS-CoV-2 transmission (including fomite transmission) |
| | Defining the clinical and epidemiological characteristics of COVID-19 |
| | Demonstration of the immune regulation network of COVID-19 |
| | AI prediction of the epidemics trend of COVID-19 under public health interventions |
| Therapeutic interventions | Validation of the efficacy and safety of repurposed drugs, especially traditional Chinese medicines (Lianhuaqingwen capsule, Xuebijing injection, and Liu Shen capsule), for accelerating symptom recovery |
| | Validation of the efficacy and safety of $H_2$–$O_2$ inhalation and endorsement by the National Health Commission of the People's Republic of China for COVID-19 patients with dyspnea or those in facilities without sufficient oxygen supplies |
| | Validation of the efficacy and safety of granulocyte colony stimulating factor for patients with marked lymphopenia |
| Diagnosis | Development of PCR- and serology-based rapid detection method |
| | Development of the portable, laboratory-instrument-independent CRISPR/Cas method for detection |
| Prognostic prediction | Identification of hematologic and immunologic biomarkers that correlate with the disease severity |
| | Establishment of AI model to predict the likelihood of developing into critical illness |

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## Compliance with ethics guidelines

Wei Liu, Wei-Jie Guan, and Nan-Shan Zhong declare that they have no conflict of interest or financial conflicts to disclose.

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