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The epidemiology, diagnosis and treatment of COVID-19

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ABSTRACT

In December 2019, the outbreak of the novel coronavirus disease (COVID-19) in China spread worldwide, becoming an emergency of major international concern. SARS-CoV-2 infection causes clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus. Human-to-human transmission via droplets, contaminated hands or surfaces has been described, with incubation times of 2-14 days. Early diagnosis, quarantine, and supportive treatments are essential to cure patients. This paper reviews the literature on all available information about the epidemiology, diagnosis, isolation and treatments of COVID-19. Treatments, including antiviral agents, chloroquine and hydroxychloroquine, corticosteroids, antibodies, convalescent plasma transfusion and vaccines, are discussed in this article. In addition, registered trials investigating treatment options for COVID-19 infection are listed.

1. Introduction

There is a current worldwide outbreak of a new type of coronavirus (COVID-19), which originated from Wuhan, China and has now spread to 140 other countries, including Japan, Korea and Italy. The World Health Organization (WHO) declared that COVID-19 has become a global health concern, causing severe respiratory tract infections in humans. Current evidence indicates that SARS-CoV-2 spread to humans via transmission from wild animals illegally sold in the Huanan Seafood Wholesale Market. Phylogenetic analysis shows that SARS-CoV-2 is a new member of the Coronaviridae family but is distinct from SARS-CoV (identity of approximately 79%) and MERS-CoV (identity of approximately 50%) [1,2]. Knowing the origin of such a pathogen is critical to developing the means to block further transmission and vaccines [3]. Notably, SARS-CoV-2 shares a high level of genetic similarity (96.3%) with the bat coronavirus RaTG13, which was obtained from bats in Yunnan in 2013; however, bats are not the immediate source of SARS-CoV-2 [4].

The typical symptoms of COVID-19 are fever, sore throat, fatigue, cough or dyspnea coupled with recent exposure. As of March 16, 2020, the outbreak of COVID-19 generated 168 826 confirmed cases, including 6503 deaths worldwide. In China during the outbreak of the pandemic, 42 000 doctors and nurses from all over the country supported Wuhan. Moreover, the government shared the updated genome sequence of COVID-19 to the public, and scientists from China and overseas are working closely and efficiently on this public health emergency [5,6]. Due to interventions and control measures from the government (shutting down public transportation and implementing a treatment strategy) and the change in personal behaviors (wearing masks and reducing contact with others), the number of confirmed and suspected cases in China has started to decrease.

However, the transmission of pneumonia associated with SARS-CoV-2 has not yet been eliminated. The COVID-19 outbreak is still a major challenge for clinicians. The aim of this article is to describe the epidemiology, diagnosis, isolation, and treatment of COVID-19.

2. Epidemiology

2.1. Incubation period

A study of early transmission dynamics of COVID-19 revealed that the mean incubation period was 5.2 days (95% confidence interval [CI], 4.1-7.0), with the 95th percentile of the distribution at 12.5 days [7]. A later study using the travel history and symptom onset of 88 confirmed cases showed a similar mean incubation

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period of 6.4 days (95% CI, 5.6-7.7) [8]. An unusual case was also reported in which the incubation period was as long as 19 days [9]. Notably, a long incubation time means adjustments in screening and control policies [10]. The 19-day incubation period is a low probability event, and experts suggest 14 days for quarantine.

2.2. Basic reproduction number

The basic reproduction number is model-based, largely depends on the epidemiological setting, and is the most important parameter to determine intrinsic transmissibility. The early outbreak data largely follow exponential growth. Different models based on the clinical progression of the disease were devised to estimate the basic reproduction number. In the early stages of COVID-19, the pandemic doubled in size every 7.4 days, and the basic reproduction number was estimated to be 2.2 [7]. Another study estimated the basic reproduction number as ranging from 2.24 to 3.58 [11]. However, a deterministic compartmental model based on the likelihood and a model analysis showed that the control reproduction number may be as high as 6.47 [12]. The authors noted that this basic reproduction number was higher because the estimate accounts for 3-4 generations of viral transmission and intensive social contacts. The basic reproduction number estimated by the majority of studies ranges from 2.24 to 3.58 [13], which is slightly higher than that of SARS.

3. Diagnosis

Rapid and accurate detection of COVID-19 is crucial to control outbreaks in the community and in hospitals [14]. Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP) [15,16]. RT-LAMP has similar sensitivity to rRT-PCR, is highly specific and is used to detect MERS-CoV [17,18]. According to current diagnostic criteria founded by the China National Health Commission, laboratory examinations, including nasopharyngeal and oropharyngeal swab tests, have become a standard assessment for diagnosis of COVID-19 infection. To identify patients earlier, two one-step quantitative RT-PCR (qRT-PCR) assays were developed to detect two different regions (ORF1b and N) of the SARS-CoV-2 genome [19]. Three novel RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N) genes of SARS-CoV-2 were developed. Among the three novel assays, the COVID-19-RdRp/Hel assay had the lowest limit of detection in vitro; highly sensitive and specific assays may help to improve the laboratory diagnosis of COVID-19 [20]. The SARS-CoV E gene assay was more sensitive than the RdRp gene assay combined with the one-step RT-PCR system [21]. The E gene PCR was sufficient to diagnose a SARS-CoV-2 infection but the RdRp protocol was recommended to confirm a positive result [22,23]. The overall positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan was 38% [24]. The positive rate of PCR for oropharyngeal swabs is not very high: only 53.3% of COVID-19-confirmed patients had positive oral swabs tests [25]. In a series of 51 patients with confirmed COVID-19 infection, 71% patients were RT-PCR positive at the first time of testing of throat swab or sputum samples [26]. The RT-PCR results usually become positive after several days (2-8 days) [27]. Automated solutions for molecular diagnostics can handle large numbers of samples and can be scaled to keep pace with fluctuating demand [28-30]. The good analytical performance of a molecular assay for the detection of SARS-CoV-2 on a high-throughput platform, the cobas 6800, was observed with minimal hands-on time, while offering fast and reliable results [31,32].

The current laboratory test is time-consuming, and a shortage of commercial kits delays diagnosis. For patients suffering from fever, sore throat, fatigue, coughing or dyspnea that is coupled with recent exposure, COVID-19 infection should be diagnosed with typical chest computerized tomography (CT) characteristics despite negative RT-PCR results [33]. Of 1014 patients, 59% had positive RT-PCR results, and 88% had positive chest CT scans [34]. COVID-19 belongs to the Coronaviridae family; therefore, it is not surprising that COVID-19 has imaging findings that are similar to those for SARS-CoV and MERS-CoV [35]. Typical CT findings included bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and peripheral lung distribution [33]. Eighty-six percent of patients showed ground-glass opacities or consolidation, and more than one lobe (71%) with bilateral involvement (76%) was affected in the 21 initial chest CT scans [36]. Notably, lung cavitation, discrete pulmonary nodules, pleural effusions, and lymphadenopathy were absent [36]. Lung abnormalities on chest CT scan were most severe approximately 10 days after the initial onset of symptoms [37]. Chest CT scans can be used to assess the severity of COVID-19. COVID-19 also manifests with chest CT imaging abnormalities in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progressed to or co-existed with consolidations within 1-3 weeks. Combining assessment of imaging features with clinical and laboratory findings could facilitate early diagnosis of COVID-19 pneumonia [38-40]. As the diagnostic criteria expanded from laboratory examination to chest CT imaging, more than 14 000 patients were diagnosed on February 12, 2020.

4. Isolation

Classical public health measures, including isolation, quarantine, social distancing and community containment, can be used to curb the pandemic of this respiratory disease [41]. China has been preparing since 2003 to contain future pandemics by applying lessons learned from SARS [42]. In the COVID-19 pandemic, China issued the largest quarantine in history. All the residents living in mainland China were locked-in, and city public transportation, including buses, trains, ferries, and airports, were shutdown. Given the trajectory of this outbreak, the Chinese government scaled up such efforts to keep pace with the rapid increase in cases and geographical spread. The Wuhan government made full use of the gym and two convention centers and transformed them into makeshift hospitals with 3400 beds in only one night to isolate COVID-19 patients from healthy controls. More makeshift hospitals are under construction. Isolation beds were quickly expanded from only 137 at the beginning of the outbreak of COVID-19 to 56 000 to separate infected patients from non-infected individuals. The swift and decisive response of China contributed to reducing the control reproduction number and transmission risk. Due to the powerful and effective isolation measures taken by the Chinese government, the increase in COVID-19 began to slow down on February 14, 2020, according to the data released by the China National Health Commission.

5. Treatments

5.1. Antiviral agents

There is no current evidence from randomized controlled trials (RCTs) to recommend any specific anti-SARS-CoV-2 treatment for patients with a suspected or confirmed COVID-19 infection. Lopinavir (LPV) inhibits the protease activity of coronavirus in vitro and in animal studies. A retrospective, matched-cohort study

including 1052 SARS patients showed that LPV/ritonavir as initial treatment was associated with a reduced death rate (2.3% vs. 11.0%) [43]. The protease inhibitor LPV is an effective treatment based on the experience accumulated from the SARS and MERS outbreaks, indicating it is a potential treatment option for COVID-19 [44]. Ribavirin, a guanosine analogue, is an antiviral compound used to treat several virus infections, including respiratory syncytial virus, hepatitis C virus, and some viral hemorrhagic fevers. Promising results were obtained with ribavirin in a MERS-CoV rhesus macaque model [45]. In addition, SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) model is targeted by ribavirin after sequence analysis, modeling, and docking to build the model. This feature increases its potential as an antiviral against SARS-CoV-2 [46].

The antiviral agent, remdesivir was designed for the Ebola virus disease [47]. Remdesivir shows broad-spectrum antiviral activity against several RNA viruses, and it may compete for RdRp [48]. Remdesivir and IFNb have superior antiviral activity to LPV and ritonavir in vitro [49]. In a mouse model of SARS-CoV pathogenesis, both prophylactic and therapeutic remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology [50]. In a rhesus macaque model of MERS-CoV infection, prophylactic remdesivir treatment was initiated 24 h prior to inoculation, and MERS-CoV did not induce clinical disease and did not replicate in respiratory tissues, thus preventing the formation of lung lesions [51]. In cell-based assays, the triphosphate form of remdesivir incorporated at position i, and RNA chain termination was delayed, which explained the high potency of remdesivir against RNA [52]. Remdesivir was used to treat the first case of COVID-19 infection in the United States: the patient's clinical condition improved after only one day of remdesivir treatment [53]. A phase II clinical trial of remdesivir was performed by the University of Nebraska Medical Center, and a phase III clinical trial was performed by the China-Japan Friendship Hospital. The results of these clinical trials will be revealed in April 2020. Remdesivir improved pulmonary function, reduced lung viral loads, and ameliorated severe lung pathology. In contrast, prophylactic LPV/RTV-IFNb only slightly reduced viral loads and did not impact other disease parameters, and therapeutic LPV/RTV-IFNb improved pulmonary function, but did not reduce virus replication or severe lung pathology [49]. Overall, these results indicated that remdesivir showed more potential than LPV/RTV-IFNb [54]. In a case report, lopinavir/ritonavir (Kaletra®) and arbidol were associated with significant improvements in COVID-19 patients [55]. The efficacy and safety of these antiviral agents for COVID-19 will be assessed in further clinical trials. Thirty-four trials of antiviral agents in patients with COVID-19 have been registered up to March 15, 2020 (Table 1).

5.2. Chloroquine and hydroxychloroquine

Chloroquine is a widely-used antimalarial and autoimmune disease drug that has been reported to be a potential broad-spectrum antiviral drug [56-58]. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV [59]. The first results obtained from more than 100 patients showed the apparent efficacy of chloroquine in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects [60]. Chloroquine was included in the recommendations for the prevention and treatment of COVID-19 pneumonia [60,61]. The optimal dosage of chloroquine for SARS-CoV-2 will need to be assessed in future trials [62].

Hydroxychloroquine is a chloroquine analog for which there are fewer concerns about drug-drug interactions [63]. In the previous SARS outbreak, hydroxychloroquine was reported to have anti-SARS-CoV activity in vitro [64]. Using physiologically-based pharmacokinetic (PBPK) models, hydroxychloroquine was found to be more potent than chloroquine in SARS-CoV-2-infected Vero cells [65]. Cytokines IL-6 and IL-10 have been reported to be increased in response to SARS-CoV-2 infection [66,67]. This may progress to a cytokine storm, followed by multiorgan failure and death. Both chloroquine and hydroxychloroquine have immunomodulatory effects and can suppress the immune response [68,69]. Therefore, 21 clinical studies were launched by Chinese hospitals and the University of Oxford to evaluate the efficacy of these agents in COVID-19 infection (Table 2). It is also necessary to determine whether the benefit of chloroquine therapy depends on the age of the patient and the clinical presentation or stage of the disease [70]. If clinical data confirm the biological results, chloroquine and hydroxychloroquine may be used in prophylaxis as well as curative treatment for individuals exposed to SARS-CoV-2 [71].

5.3. Corticosteroids

In a study of 41 COVID-19 patients, 21% received corticosteroids, which could suppress lung inflammation [66]. The administered dose of methylprednisolone varied depending on disease severity. Current interim guidance from the WHO on the clinical management of severe acute respiratory infection when SARS-CoV-2 infection is suspected (released January 28, 2020) advises against the use of corticosteroids unless indicated for another reason. The clinical outcomes of coronavirus and similar outbreaks do not support the use of corticosteroids. In a retrospective observational study of 309 adults who were critically ill with MERS, patients who were given corticosteroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy [72]. For the management of SARS, corticosteroid treatment was more associated with psychosis, diabetes and avascular necrosis [73,74]. Overall, there is no unique reason to expect that patients with COVID-19 infection will benefit from corticosteroids, and such treatment may be harmful [75]. However, according to our clinical experience, corticosteroids could be prescribed at the right time for the right patients. The clinical trials involving corticosteroids are shown in Table 3.

5.4. Antibodies

The development of vaccines and therapeutic antibodies against COVID-19 has important implications. Considering the relatively high identity of the receptor-binding domain (RBD) in SARS-CoV-2 and SARS-CoV, the cross-reactivity of anti-SARS-CoV antibodies with the COVID-19 spike protein was assessed. The spike protein is the major inducer of neutralizing antibodies. Fortunately, the SARS-CoV-specific human monoclonal antibody CR3022 binds potently with the COVID-19 RBD [76]. However, other SARS-CoV RBD-directed antibodies 230, m396 and 80R cannot bind to the COVID-19 RBD [77]. CR3022 may be a potential therapeutic candidate, alone or in combination with other neutralizing antibodies, for the prevention and treatment of COVID-19 infections. Antibodies MAb114 and REGN-EB3 were designed for treatment of Ebola virus infection and significantly reduce mortality from Ebola virus disease [47]. Monoclonal antibodies can only recognize a single antigen epitope, which limits the use of MAb114 and REGN-EB3 in the treatment of COVID-19. However, the development of COVID-19-specific antibodies requires a long time. It is not easy to apply monoclonal antibodies for new pathogens to clinical practice in a short time.

Table 1
Clinical trials of antiviral agents in patients with COVID-19.

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000029621	Clinical study of arbidol hydrochloride tablets in the treatment of novel coronavirus pneumonia (COVID-19)	Arbidol tablets + basic treatment (190 patients)	Basic treatment (190 patients)			Ruijin Hospital, Shanghai Jiao Tong University School of Medicine
ChiCTR2000029308	A randomized, controlled open-label trial to evaluate the efficacy and safety of lopinavir-ritonavir in hospitalized patients with novel coronavirus pneumonia (COVID-19)	Lopinavir-ritonavir tablets (each containing 200 mg of lopinavir and 50 mg of ritonavir), twice a day, 2 tablets at a time (80 patients)	Conventional standardized treatment (80 patients)		Clinical improvement time of 28 days after randomization, 7-point scale	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)
ChiCTR2000029387	Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate novel coronavirus pneumonia	Ribavirin + Interferon alpha-1b (36 patients)	Lopinavir / ritonavir + interferon alpha-1b (36 patients)	Ribavirin + LPV/r +Interferon alpha-1b (36 patients)	Time to 2019-nCoV RNA negativity in patients	Chongqing Public Health Medical Center
ChiCTR2000029468	A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of novel coronavirus pneumonia (COVID-19)	Lopinavir/ritonavir (LPV/r)+ emtritabine (FTC)/ Tenofovir alafenamide Fumarate tablets (TAF) in combination (60 patients)	LPV/r (60 patients)		Survival rate	Institute of Emergency Medicine and Disaster Medicine Sichuan People's Hospital, Sichuan Academy of Medical Sciences
ChiCTR2000029539	A randomized, open-label study to evaluate the efficacy and safety of Lopinavir-Ritonavir in patients with mild novel coronavirus pneumonia (COVID-19)	Conventional standardized treatment and Lopinavir-Ritonavir (164 patients)	Conventional standardized treatment (164 patients)		Incidence of adverse outcome within 14 days after admission: Patients with conscious dyspnea, SpO2 $\leq$94% or respiratory frequency $\geq$ 24 times/min in the state of resting without oxygen inhalation	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology
ChiCTR2000029541	A randomised, open, controlled trial for darunavir/cobicistat or Lopinavir/ritonavir combined with thymosin a1 in the treatment of novel coronavirus pneumonia (COVID-19)	DRV/c (800 mg/150 mg QD) + conventional treatment containing thymosin (40 patients)	LPV/r (400 mg/100 mg bid) + conventional treatment containing thymosin (40 patients)		Time to conversion of 2019-nCoV RNA result from RI sample	Zhongnan Hospital of Wuhan University
ChiCTR2000029548	Randomized, open-label, controlled trial for evaluating the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	BaloxavirMarboxil: 80 mg on day1, 80 mg on day 4; and 80 mg on day 7 as necessary (10 patients)	Favipiravir: 600 mg tid with 160 0mg first loading dosage for no more than 14 days (10 patients)	Lopinavir-Ritonavir: 2(200mg/50 mg), twice daily, for 14days (10 patients)	Time to viral negativity by RT-PCR,Time to clinical improvement	The First Affiliated Hospital, Zhejiang University School of Medicine
ChiCTR2000029600	Clinical study on safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19)	Alpha-Interferon atomization (30 patients)	Lopinavir and Ritonavir + alpha-Interferon atomization (30 patients)	Favipiravir + alpha-Interferon atomization(30 patients)	Negative time of novel Coronavirus by PCR, chest imaging, incidence rate of kidney damage	The Third People's Hospital of Shenzhen

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Table 1 (*continued*)

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000029603	A randomized, open-label, multi-centre clinical trial evaluating and comparing the safety and efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for confirmed cases of novel Coronavirus pneumonia (COVID-19)	Conventional standardized treatment and ASC09/Ritonavir (80 patients)	Conventional standardized treatment and Lopinavir/Ritonavir (80 patients)		The incidence of composite adverse outcome	The First Affiliated Hospital of Zhejiang University School of Medicine
ChiCTR2000029853	A randomized, open-label, controlled clinical trial for azvudine in the treatment of novel coronavirus pneumonia (COVID-19)	Oral administration of 5 tablets of 1 mg azvudine daily (10 patients)	Control group (10 patients)		Temperature, improvement of respiratory symptoms	People's Hospital of Guangshan County
ChiCTR2000029996	A randomized, open-label, controlled trial for the efficacy and safety of Farpiravir tablets in the treatment of patients with novel coronavirus pneumonia (COVID-19)	Tablets; 200 mg; oral; twice a day; adult dose is 1600 mg per time on first day (20 patients)	Tablets; 200 mg; orally; twice a day; adult dose is 1800 mg per time on first day (20 patients)	Tablets; 200 mg; oral; twice a day; adult dose is 2400 mg per time on first day (20 patients)	Time to clinical recovery	Beijing Chaoyang Hospital, Capital Medical University
ChiCTR2000030041	A single-arm, single-center clinical trial for azvudine tablets in the treatment of adult novel coronavirus pneumonia (COVID-19)	Azvudine tablets (40 patients)			The novel coronavirus nucleic acid negative rate	Zhongnan Hospital of Wuhan University
ChiCTR2000030113	Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir	Ritonavir/ritonavir treatment (15 patients)	Favipiravir (15 patients)		Blood routine tests, Liver function examination, Renal function examination, Blood gas analysis, Chest CT examination	The Third People's Hospital of Shenzhen
ChiCTR2000030254	A randomized, open-controlled trial for farpiravir tablets in the treatment of novel coronavirus pneumonia (COVID-19)	Farpiravir tablets (120 patients)	Abidole tablets (120 patients)		Pulse oxygen saturation parameters, respiratory support Nucleic acid test of novel coronavirus	Zhongnan Hospital of Wuhan University
ChiCTR2000030259	Evaluation Danorevir sodium tablets combined with ritonavir in the treatment of novel coronavirus pneumonia (COVID-19): a randomized, open and controlled trial	Danorevir sodium tablets/ritonavir oral (30 patients)	Symptomatic treatment (30 patients)		Rate of composite adverse outcomes: SpO2, PaO2/FiO2, respiratory rate	Shanghai Changzheng Hospital
ChiCTR2000030424	A single-center, single-arm clinical trial for azvudine in the treatment of novel coronavirus pneumonia (COVID-19)	Azvudine Tablet: D1: 10 mg/day,QD			Negative conversion rate of the new coronavirus nucleic acid	Henan Provincial People's Hospital
ChiCTR2000030472	An open and controlled clinical study to evaluate the efficacy and safety of Ganovo combined with ritonavir in the treatment of novel coronavirus pneumonia (COVID-19)	Ganovo/ritonavir oral + conventional treatment (10 patients)	Conventional treatment (10 patients)		Rate of composite adverse outcomes: SPO2, PaO2/FiO2 and respiratory rate	Shenyang Sixth People's Hospital
ChiCTR2000030487	A single-center, single-arm clinical trial for azvudine in the treatment of novel coronavirus pneumonia (COVID-19)	Azvudine Tablet: D1: 10 mg/day, QD			Negative conversion rate of the new coronavirus nucleic acid	The First Affiliated Hospital of Henan University of CM
NCT04244591	Glucocorticoid therapy for novel Coronavirus critically ill patients with severe acute respiratory failure (Steroids-SARI)	Methylprednisolone therapy and standard care	Standard care		Lower Murray lung injury score	Peking Union Medical College Hospital

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Table 1 (*continued*)

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
NCT04252274	Efficacy and safety of Darunavir and Cobicistat for treatment of pneumonia caused by 2019-nCoV (DACO-nCoV)	Darunavir, Cobicistat and conventional treatments	Conventional treatments		Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 7	Shanghai Public Health Clinical Center
NCT04252664	A Phase 3 randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with mild and moderate 2019-nCoV respiratory disease	Remdesivir	Remdesivir placebo		All cause mortality	Capital Medical University
NCT04254874	A prospective/retrospective, randomized controlled clinical study of interferon atomization in the 2019-nCoV pneumonia	Abidol hydrochloride	Abidol Hydrochloride combined with Interferon atomization		Rate of disease remission, Time for lung recovery	Tongji Hospital
NCT04255017	A prospective/retrospective, randomized controlled clinical study of antiviral therapy in the 2019-nCoV pneumonia	Abidol hydrochloride	Oseltamivir	Lopinavir/ ritonavir	Rate of disease remission	Tongji Hospital
NCT04257656	Severe 2019-nCoV Remdesivir randomized controlled trial (RCT)	Remdesivir	Remdesivir placebo		Time to Clinical Improvement (TTCI)	Capital Medical University
NCT04260594	Clinical study of arbidol hydrochloride tablets in the treatment of pneumonia caused by novel Coronavirus	Arbidol	Basic treatment		Virus negative conversion rate in the first week	Jieming QU
NCT04261270	A randomized, open, controlled clinical study to evaluate the efficacy of ASC09F and Ritonavir for 2019-nCoV pneumonia	ASC09F + Oseltamivir	Ritonavir + Oseltamivir	Oseltamivir	Rate of comprehensive adverse outcome	Tongji Hospital
NCT04261270	A randomized, open, controlled clinical study to evaluate the efficacy of ASC09F and Ritonavir for 2019-nCoV pneumonia	ASC09F + Oseltamivir	Ritonavir + Oseltamivir		Rate of comprehensive adverse outcome	Tongji Hospital
NCT04261517	Efficacy and safety of hydroxychloroquine for treatment of pneumonia caused by 2019-nCoV (HC-nCoV)	Hydroxychloroquine and conventional treatments	Conventional treatments		Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions	Shanghai Public Health Clinical Center
NCT04261907	Evaluating and comparing the safety and efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for novel Coronavirus infection	ASC09/ritonavir	Lopinavir/ ritonavir		The incidence of composite adverse outcome	First Affiliated Hospital of Zhejiang University
NCT04276688	Lopinavir/ Ritonavir, Ribavirin and IFN-beta combination for nCoV treatment	Lopinavir/ ritonavir	Ribavirin	Interferon Beta-1B	Time to negative NPS 2019-n-CoV RT-PCR	The University of Hong Kong
NCT04292730	Study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with moderate Coronavirus disease (COVID-19) compared to standard of care treatment	Remdesivir	Standard of care		Proportion of participants discharged by Day 14	Gilead Sciences

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Table 1 (*continued*)

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
NCT04292899	Study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with severe Coronavirus disease (COVID-19)	Remdesivir	Standard of care		Proportion of participants With normalization of fever and oxygen saturation through Day 14	Gilead Sciences
NCT04304053	Treatment of mild cases and chemoprophylaxis of contacts as prevention of the COVID-19 epidemic	Antiviral treatment and prophylaxis	Standard Public Health measures		Effectiveness of chemoprophylaxis assessed by incidence of secondary COVID-19 cases	Lihir Medical Centre
NCT04307693	Comparison of Lopinavir/Ritonavir or hydroxychloroquine in patients with mild Coronavirus disease (COVID-19)	Lopinavir / Ritonavir tablet	Hydroxychloroquine sulfate tablet		Viral load	Asan Medical Center

Table 2
Clinical trials of chloroquine and hydroxychloroquine in patients with COVID-19.

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000029898	Evaluation of the efficacy and safety of hydroxychloroquine sulfate in comparison with phosphate chloroquine in severe patients with novel Coronavirus pneumonia (COVID-19): a randomized, open-label, parallel, controlled trial	Hydroxychloroquine sulfate Day1: first dose: 6 tablets (0.1 g/tablet) , second dose: 6 tablets (0.1 g/tablet) after 6 h ;Day2~5: 2 tablets (0.1 g/tablet), BID (50 patients)	Phosphate chloroquine Day 1-3:500 mg, BID Day 4-5:250 mg, BID (50 patients)		TTCI (Time to Clinical Improvement)	Peking University Third Hospital
ChiCTR2000029988	Clinical Study of Chloroquine Phosphate in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	Chloroquine phosphate (40 patients)	None (40 patients)		Time to Clinical Recovery	Zhongnan Hospital of Wuhan University
ChiCTR2000029542	Study for the efficacy of chloroquine in patients with novel coronavirus pneumonia (COVID-19)	Chloroquine (10 patients)	Conventional management (10 patients)		Viral-negative transforming time 30-day cause-specific mortality	Sun Yat sen Memorial Hospital of Sun Yat sen University
ChiCTR2000029559	Therapeutic effect of hydroxychloroquine on novel coronavirus pneumonia (COVID-19)	Hydroxychloroquine 0.1 oral 2/day (100 patients)	Hydroxychloroquine 0.2 oral 2/day (100 patients)	Starch pill oral 2/day (100 patients)		Renmin Hospital of Wuhan University
ChiCTR2000029609	A prospective, open-label, multiple-center study for the efficacy of chloroquine phosphate in patients with novel coronavirus pneumonia (COVID-19)	Oral chloroquine phosphate (59 mild-moderate patients and 14 severe patients)	Oral Lopinavir/ritonavir (59 mild-moderate patients and 14 severe patients)	Chloroquine phosphate plus Lopinavir/ ritonavir (59 mild-moderate patients)	Virus nucleic acid-negative transforming time	The Fifth Affiliated Hospital of Sun Yat-Sen University
ChiCTR2000029740	Efficacy of therapeutic effects of hydroxycholoroquine in novel coronavirus pneumonia (COVID-19) patients (randomized open-label control clinical trial)	Oral intake hydroxycholoroquine 0.2 twice a day (54 patients)	Conventional therapy (24 patients)		Oxygen index, lung radiography, temperature	The First Hospital of Peking University
ChiCTR2000029741	Compare the efficacy and safety of chloroquine and lopinavir/ritonavir in patients with mild/general CoVID-19 infection, and establish a standardized treatment plan.	Chloroquine phosphate (56 patients)	Control group (56 patients)		Length of stay, oxygenation index during treatment, all-cause mortality in 28 days	The Fifth Affiliated Hospital Sun Yat-Sen University

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Table 2 (*continued*)

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000029803	A prospective, randomized, open-label, controlled clinical study to evaluate the preventive effect of hydroxychloroquine on close contacts after exposure to the Novel Coronavirus Pneumonia (COVID-19)	Hydroxychloroquine, small dose and high dose (80 patients/group)	Abidol hydrochloride, small dose and high dose (80 patients/group)		Number of patients who have progressed to suspected or confirmed within 24 days of exposure to new coronavirus	Renmin Hospital of Wuhan University
ChiCTR2000029826	A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in serious/critically ill patients with novel coronavirus pneumonia (COVID-19)	2 tablets phosphoric chloroquine BID (80 patients)	2 tablets placebo BID (40 patients)		Mortality rate	Jingzhou Central Hospital
ChiCTR2000029837	A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in mild/common patients with novel coronavirus pneumonia (COVID-19)	2 tablets phosphoric chloroquine BID (80 patients)	2 tablets placebo BID (40 patients)		Time of conversion to negative novel coronavirus nucleic acid	Jingzhou Central Hospital
ChiCTR2000029868	Hydroxychloroquine treating novel coronavirus pneumonia (COVID-19): a multicenter, randomized controlled trial	Oral hydroxychloroquine sulfate tablets (100 patients)	Conventional treatment meeting the Guideline (100 patients)		Viral nucleic acid test	Ruijin Hospital, Shanghai Jiaotong University School of Medicine
ChiCTR2000029898	Evaluation the Efficacy and Safety of Hydroxychloroquine Sulfate in Comparison with Phosphate Chloroquine in Mild and Common Patients with Novel Coronavirus Pneumonia (COVID-19): a Randomized, Open-label, Parallel, Controlled Trial	Hydroxychloroquine sulfate Day1: first dose: 6 tablets (0.1 g/tablet) , second dose: 6 tablets (0.1 g/tablet) after 6 h ;Day 2~5: 2 tablets (0.1 g/tablet), BID (50 patients)	Phosphate chloroquine Day 1-3:500 mg, BID Day 4-5:250 mg, BID (50 patients)		Time to Clinical Recovery, TTCR	Peking University Third Hospital
ChiCTR2000029935	A Single-arm Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19)	Conventional treatment combined with Chloroquine Phosphate (100 patients)			Length of hospital stay	HwaMei Hospital, University of Chinese Academy of Sciences
ChiCTR2000029939	A Single-blind, Randomized, Controlled Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19)	Conventional treatment (50 patients)	conventional treatment combined with Chloroquine Phosphate (50 patients)		Length of hospital stay	HwaMei Hospital, University of Chinese Academy of Sciences
ChiCTR2000029988	Clinical Study of Chloroquine Phosphate in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	Chloroquine phosphate (40 patients)	None (40 patients)		Time to clinical recovery	Zhongnan Hospital of Wuhan University
ChiCTR2000029992	A prospective, randomized, open label, controlled trial for chloroquine and hydroxychloroquine in patients with severe novel coronavirus pneumonia (COVID-19)	Chloroquine phosphate 1.0 g x 2 days for the first dose, 0.5 g x 12 days from the third day (40 patients)	Hydroxychloroquine sulfate 0.2 g bid x 14 days (40 patients)	Recommended treatment plan for novel coronavirus pneumonia severe and critical cases (20 patients)	Clinical recovery time, changes in viral load of upper and lower respiratory tract samples compared with the baseline	Zhongshan Hospital Affiliated to Xiamen University

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Table 2 (*continued*)

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000030031	A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in mild/common patients with novel coronavirus pneumonia (COVID-19)	2 tablets phosphoric chloroquine BID 80 patients)	2 tablets placebo BID (40 patients)		Time of conversion to negative novel coronavirus nucleic acid	The Sixth Affiliated Hospital of Guangzhou Medical University
ChiCTR2000030054	A prospective, open label, randomized, control trial for chloroquine or hydroxychloroquine in patients with mild and common novel coronavirus pulmonary (COVIP-19)	Hydroxychloroquine sulfate 0.2 g bid x 14 days a day (30 patients)	First dose of chloroquine phosphate 1 g x 2 days, and the third day was 0.5 g x 12 days (30 patients)	Recommended treatment plan for novel coronavirus pneumonia diagnosis and treatment plan (20 patients)	Clinical recovery time	Zhongshan Hospital Affiliated to Xiamen University
ChiCTR2000030417	Efficacy and safety of chloroquine phosphate inhalation combined with standard therapy in the treatment of novel coronavirus pneumonia (COVID-19)	Chloroquine phosphate aerosol inhalation solution (15 patients)	Water for injection atomization inhalation (15 patients)		Temperature, respiratory symptoms	Harbin infectious diseases hospital
ChiCTR2000030718	Randomized controlled trial for Chloroquine Phosphate in the Treatment of novel coronavirus pneumonia (COVID-19)	Chloroquine phosphate (40 patients)	Regular treatment (40 patients)		Time to clinical recovery	Zhongnan Hospital of Wuhan University
NCT04303507	Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Chloroquine	Placebo		Number of symptomatic COVID-19 infections	University of Oxford

Table 3
Clinical trials of corticosteroids in patients with COVID-19.

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Group 3 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000029386	Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: a randomized controlled trial	Methylprednisolone, intravenous injection, 1-2 mg/kg·d for 3 days (24 patients)	Without any glucocorticoid therapy (24 patients)		SOFA score	Chongqing Public Health Medical Center
ChiCTR2000029656	A randomized, open-label study to evaluate the efficacy and safety of low-dose corticosteroids in hospitalized patients with novel coronavirus pneumonia (COVID-19)	Standard treatment and methylprednisolone for injection (50 patients)	Standard treatment (50 patients)		Chest imaging, complications	Wuhan Pulmonary Hospital
ChiCTR2000030481	The clinical value of corticosteroid therapy timing in the treatment of novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial	Early corticosteroid intervention (75 patients)	Middle-late corticosteroid intervention (75 patients)	No corticosteroid (50 patients)	Time of duration of COVID-19 nucleic acid RT-PCR test results of respiratory specimens change to negative	Zhongnan Hospital of Wuhan University
NCT0424459	The efficacy of different hormone doses in 2019-nCoV severe pneumonia	Methylprednisolone (<40 mg/d intravenous drip for 7 days)	Methylprednisolone (40~80 mg/d intravenous drip for 7 days)		Rate of disease remission, rate and time of entering the critical stage	Tongji Hospital

Table 4
Clinical trials of convalescent plasma transfusion in patients with COVID-19Searched on http://www.chictr.org.cn/ and https://clinicaltrials.gov/. As of March 15, 2020.

Register number	Title	Group 1 (sample size)	Group 2 (sample size)	Primary indicator	Primary sponsor
ChiCTR2000030039	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)	Conventional therapy with infusion of convalescent plasma: 200-500 mL (30 patients)	Conventional therapy (30 patients)	Viral load, SARS-CoV-2 antibody levels	Affiliated Hospital of Xuzhou Medical University
ChiCTR2000029757	Convalescent plasma for the treatment of severe and critical novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial	Conventional treatment and convalescent plasma therapy (100 patients)	Conventional treatment (100 patients)	Number of days between randomized grouping and clinical improvement	China-Japan Friendship Hospital
ChiCTR2000029850	Study on convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19)	Standardized comprehensive treatment combined with convalescent plasma treatment (10 patients)	Standardized comprehensive treatment (10 patients)	Fatality rate	The First Affiliated Hospital of Zhejiang University School of Medicine
ChiCTR2000030010	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	Anti-SARS-CoV-2 virus-inactivated plasma (50 patients)	Ordinary plasma (50 patients)	Improvement of clinical symptoms	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)
ChiCTR2000030046	A single arm trial to evaluate the efficacy and safety of anti-2019-nCoV inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19)	Anti-2019-nCoV virus-inactivated plasma (10 patients)		Changes to clinical symptoms, laboratory and radiological data	First People's Hospital of Jiangxia District
ChiCTR2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	Routine treatment + plasma treatment (50 patients)	Routine treatment (50 patients)	Cure rate, mortality	The First Affiliated Hospital of Nanchang University
ChiCTR2000030381	A randomized, open-label, controlled and single-center trial to evaluate the efficacy and safety of anti-SARS-CoV-2-inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient	Conventional treatment and anti-SARS-CoV-2 virus-inactivated plasma (20 patients)	Conventional treatment and ordinary plasma (20 patients)	Clinical symptom improvement	First People's Hospital of Jiangxi District, Wuhan
ChiCTR2000030627	Study for using the healed novel coronavirus pneumonia (COVID-19) patients plasma in the treatment of severe critical cases	Convalescent plasma therapy + routine treatment (15 patients)	Routine treatment (15 patients)	Temperature, virus nucleic acid detection	The First Affiliated Hospital of Zhengzhou University
ChiCTR2000030702	Plasma of the convalescent in the treatment of novel coronavirus pneumonia (COVID-19) common patient: a prospective clinical trial	Conventional treatment and convalescent plasma therapy (25 patients)	Conventional treatment (25 patients)	Time to clinical recovery after randomization	China-Japan Friendship Hospital
NCT04292340	Anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of COVID-19	Anti-SARS-CoV-2-inactivated convalescent plasma		Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions	Shanghai Public Health Clinical Center

5.5. Convalescent plasma transfusion

Convalescent plasma was administered early after symptom onset in the treatment of SARS, and the pooled odds of mortality following treatment was reduced compared with placebo or no therapy (odds ratio, 0.25) [78]. However, in Ebola virus disease, the transfusion of up to 500 mL of convalescent plasma in 84 patients was not associated with a significant improvement in survival [79]. In a laboratory test, the COVID-19 virus was isolated from the bronchoalveolar lavage fluid of a critically ill patient, and it could be neutralized by sera from several patients [80]. Current clinical trials involving convalescent plasma transfusion are shown in Table 4. The National Health Commission of China appealed to convalescent patients to donate blood for the treatment of COVID-19 infection. Convalescent plasma should be collected within two weeks after recovery to ensure a high neutralization antibody titer. The difficulty in obtaining plasma during convalescence limits its clinical application. Well-designed clinical trials are needed to further evaluate the efficacy and safety of convalescent plasma therapy in patients with COVID-19 infection.

5.6. Vaccines

The structure of SARS-CoV-2 S protein has been revealed, and this should enable the rapid development and evaluation of medical countermeasures to address the ongoing public health crisis [77]. These findings provide the basis for further studies to optimize vaccination strategies for this emerging infection. The majority of the vaccines being developed for coronaviruses target the spike glycoprotein or S protein [81]. Vaccine development is a long process, and no vaccines are available at the time of a pandemic outbreak. For example, the Ebola epidemic outbreak occurred in 2013, and three years later, the rVSV Ebola Vaccine was selected for phase I clinical trials for its safety and immunogenicity in Africa and Europe [82]. In November 2019, the European Commission granted marketing authorization to Merck Sharp and Dohme B.V. in Europe for their Ebola vaccine, Ervebo. Fortunately, Moderna company announced on February 24, 2020 that the company's experimental mRNA COVID-19 vaccine, known as mRNA-1273, is ready for human testing. It is a remarkably fast development cycle to develop an initial vaccine just weeks after identifying the SARS-CoV-2 genetic sequence. The clinical trial of safety and immunogenicity of mRNA-1273 in the treatment of COVID-19 is under investigation (ClinicalTrials.gov Identifier: NCT04283461). Moreover, a new oral SARS-CoV-2 vaccine has been successfully developed at Tianjin University, which uses food-grade safe *Saccharomyces cerevisiae* as a carrier and targets the S protein. There are 18 biotechnology companies and universities in China working on SARS-CoV-2 vaccines. Vaccines for SARS-CoV-2 have been developed much faster than those for Ebola because of the collaborative efforts of scientists around the world and the fast-track approval of SARS-CoV-2 vaccine development efforts by the Chinese health organizations.

6. Conclusions

Bats have been recognized as a natural reservoir and vectors of a variety of coronaviruses, and these viruses have crossed species barriers to infect humans and many different kinds of animals, including avians, rodents, and chiropters [83,84]. While the origin of COVID-19 is still being investigated, COVID-19 has features typical of the Coronaviridae family and was classified in the beta-coronavirus 2b lineage. COVID-19 can be transmitted between humans. Interventions, including intensive contact tracing followed by quarantine and isolation, can effectively reduce the spread of COVID-19, with the effect of travel restrictions. Wearing masks, washing hands and disinfecting surfaces contribute to reducing the risk of infection. Human coronaviruses can be efficiently inactivated within 1 min using surface disinfection procedures with 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite [85].

Identification of the causative viral pathogens of respiratory tract viral infections is important to select an appropriate treatment, control the pandemic, and reduce the economic impact of COVID-19 on China and the world. In acute respiratory infection, RT-PCR is routinely used to detect causative viruses from respiratory secretions. The positive rate of PCR from oropharyngeal swabs is not very high. In this situation, more swab testing is needed to clarify diagnosis. Typical CT findings can help early screening of suspected cases and diagnosis of COVID-19.

The COVID-19 infection has a clustering onset and is more likely to affect older males (average age 51 years) with comorbidities [86]. No evidence supports adverse birth outcomes, intrauterine infection, or vertical transmission of COVID-19 [87]. However, viral infections can be acquired when the infant passes through the birth canal during vaginal delivery or through postpartum breastfeeding [88]. The most common symptoms were fever, cough, expectoration, headache, myalgia or fatigue, diarrhea, and hemoptysis [89]. Some people may experience severe acute respiratory distress syndrome. Histological examination of lung biopsy samples showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates [90]. Other organs are also susceptible to COVID-19. The single-cell RNA-seq data was used to analyse receptor ACE2 expression to reveal the potential risk of different human organs to COVID-19 infection [91]. COVID-19 uses the same cell entry receptor as SARS-CoV, ACE2, which regulates both cross-species and human-to-human transmissions [80]. Proximal tubular cells also express higher levels of the ACE2 receptor, which leads to susceptibility to COVID-19 [91] and induces kidney injury. Data from 33 patients with a complete clinical course were analysed, and the levels of blood urea and creatinine were higher in non-survivors than in survivors [92].

All patients with COVID-19-infected pneumonia received antibacterial agents, 90% received antiviral therapy, and 45% received methylprednisolone [92]. Clinical trials are underway to investigate the efficacy of new antiviral drugs, convalescent plasma transfusion, and vaccines. Most of the trials were initiated by investigators and the study period is 1 to 11 months. Although the final results of these studies will take a long time to complete, the interim research data may provide some help for the current urgent demand for therapy [93].

The COVID-19 pandemic is a public health emergency of international concern, and all countries need a coordinated international effort to fight COVID-19. The transmission of pneumonia associated with SARS-CoV-2 has not yet been eliminated. In the absence of vaccines and antivirals, isolation and quarantine are achieving remarkable results. It is necessary to strengthen the monitoring of COVID-19 and to develop drugs and vaccines against the COVID-19 infection as soon as possible.

Declarations

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