



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Editor's Note: This editorial was published online as a preprint proof on February 19, 2020, prior to a number of the clinical and scientific developments surrounding this fast-moving disease. The reader should seek more current information on diagnosis, treatment and prevention.

A Novel Coronavirus (COVID-19) Outbreak A Call for Action



Yi Zhang, MD, PhD

Jiuyang Xu, MDc

Hui Li, MD

Bin Cao, MD

Beijing, China

In December 2019, Wuhan, Hubei province, China, one of the six megalopolises with a population of 14 million, became the center of an outbreak of pneumonia of unknown cause. Because the early cases were linked to the Huanan Seafood Market, the market was shut down on January 1, 2020. One week later, on January 7, 2020, Chinese health authorities confirmed that they had identified a novel coronavirus (COVID-19). On January 30, 2020, the World Health Organization Director-General made the final decision on the determination of a Public Health Emergency of International Concern regarding the outbreak in China, with exportations to other countries.¹

As of mid-February, > 50,000 cases with laboratory-confirmed COVID-19 have been detected in China, of whom > 1,600 have died. It has spread to all 34 provinces in China within 1 month. The Spring Festival travel rush, in which an estimated 5 million people

traveled from Wuhan to throughout the country, was one of the key factors that led to the rapid intercity spread. Approximately 680 exported cases of COVID-19 infection have been reported in > 25 countries.

This outbreak is the third time in the past two decades that a zoonotic coronavirus has crossed species to infect humans. During the epidemics of the other two beta-coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and Middle East respiratory syndrome coronavirus [MERS-CoV]), > 10,000 cumulative cases occurred, with lethality rates of 10% for SARS-CoV and 37% for MERS-CoV.^{2,3} Learning from the 2003 SARS outbreak, Chinese health authorities have taken rapid measures to isolate suspected or confirmed patients, trace and quarantine their close contacts, educate the public on both food and personal hygiene, and alert and train health-care workers on compliance with infection control against emerging pathogens.

The Chinese Center for Disease Control and Prevention issued an epidemic update and risk assessment of COVID-19 in late January.⁴ The document describes evidence regarding what is known about the causative pathogen, the epidemiology and clinical features of the illness, diagnosis and management essentials, and public prevention measures. The Chinese Center for Disease Control and Prevention provided practical guidance for the public to protect themselves from the infection, including a recommendation (issued on January 27, 2020) that travelers avoid all nonessential travel to China.⁵

Molecular Characterization

Within 1 month of detection of the incident case, several Chinese scientists isolated the virus, sequenced its full-length genome, and described its specific morphology. The initial genome sequence was shared with the World Health Organization on January 12, 2020. Several investigative teams have independently isolated and characterized the viral genome, and the sequences were made publicly available on the Global Initiative on Sharing All Influenza Data platform (<https://www.gisaid.org>).

Zhou et al⁶ showed that COVID-19 shares 79.5% sequence identity with SARS-CoV. It was then isolated from the BAL fluid of a critically ill patient and was found to be neutralized by sera from similarly

AFFILIATIONS: From the Department of Pulmonary and Critical Care Medicine (Drs Zhang, Li, and Cao), Center of Respiratory Medicine, China-Japan Friendship Hospital; National Clinical Research Center for Respiratory Diseases (Drs Zhang, Li, and Cao); Department of Respiratory Medicine (Drs Zhang, Li, and Cao), Capital Medical University; and the Department of Basic Medical Sciences (Dr Xu), Tsinghua University School of Medicine.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Bin Cao, MD, No. 2, East Yinghua Rd, Chaoyang District, Beijing, China 100029; e-mail: caobin_ben@163.com

Copyright © 2020 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

DOI: <https://doi.org/10.1016/j.chest.2020.02.014>

infected patients. It was also confirmed that COVID-19 uses the same cell entry receptor, angiotensin-converting enzyme 2, as SARS-CoV, which is highly expressed in airway epithelial cells.

Zhu et al⁷ also identified and characterized COVID-19. They reported the isolation of the virus and provided the initial description of its specific cytopathic effects and morphology. COVID-19 seems to be the seventh member of the family of coronaviruses that infect humans. Notably, COVID-19 grew more readily in primary human airway epithelial cells than in standard tissue culture cells, unlike SARS-CoV or MERS-CoV, suggesting the potential for increased infectivity. Homology modeling revealed that COVID-19 had some amino acid variations at key residues benchmarked with SARS-CoV.⁸ It is not clear whether these changes lead to the facilitation of virus infection.

The information produced by this research allows the medical and scientific communities to better understand the transmission of COVID-19, to develop rapid diagnostic tests and efficient epidemiologic control, and to facilitate the development of antiviral therapies and vaccines.

Clinical Features

Ren et al⁹ reported the clinical manifestations of the infection caused by the novel bat-origin of the human-infected coronavirus, including its potential lethality. On January 24, 2020, Huang et al¹⁰ reported in *The Lancet* on the epidemiologic, clinical, laboratory, and radiologic characteristics, as well as treatment and outcomes, of the virus. An understanding of the clinical features will help clinicians to recognize the infected patients and minimize the risk of exposure to others. It was inferred that the target cells might be in the lower airway, due to features of presentation such as the lack of prominent upper respiratory tract signs and symptoms and the ground-glass opacities on chest CT images. Older male subjects with comorbidities have been reported to have more severe and even fatal respiratory diseases.¹¹ Additional studies will help in assessing for host risk factors for disease severity and mortality. Laboratory evaluation has found lymphopenia in 63% of patients and a cytokine storm profile in those who are critically ill. The combination of viral replication in the lower respiratory tract and an aberrant immune response may have an impact on the severity of illness, similar to what has been proven in SARS and MERS.¹⁰ Translational research may

discover biomarkers and other cofactor triggers in infected patients with different risk stratification.

A familial cluster of pneumonia due to COVID-19 has been reported. This finding is consistent with person-to-person transmission, highlighting the risk of spread, which is further supported by reports of infected travelers in other geographical regions.¹² In the last 2 weeks of January 2020, thirteen children were diagnosed, fortunately with a mild clinical presentation. This information suggests the possibility that coronavirus transmission is evolving. The basic reproductive number of COVID-19 was estimated to be 2.2,¹³ lower than that of SARS-CoV (around 3).^{14,15} However, host virus interactions may hasten the birth of potential super spreaders, leading to major outbreaks.

Treatment of Coronaviruses

Due to the severe lung injury caused by SARS-CoV and MERS-CoV, patients who were infected and required invasive mechanical ventilation and extracorporeal membrane oxygenation had a very high mortality.^{2,3,16} Unfortunately, no specific coronavirus antiviral agents or vaccines have been proven to be effective. In a historical control study, a combination of protease inhibitors (lopinavir and ritonavir) was associated with substantial clinical benefit among patients with SARS-CoV.¹⁷ Results from in vitro cell and in vivo animal studies suggest that a combination of lopinavir/ritonavir and interferon- β 1 may be effective against MERS-CoV. A placebo-controlled trial of interferon- β 1 and lopinavir/ritonavir was initiated in patients with laboratory-confirmed MERS requiring hospital admission in Saudi Arabia.¹⁸

Remdesivir, a 1'-cyano-substituted adenosine nucleotide analogue prodrug with broad-spectrum antiviral activity against several RNA viruses, may be evaluated.¹⁹ The first reported patient with COVID-19 infection in the United States was administered remdesivir. Based on worsening clinical status, IV remdesivir was given for compassionate use on hospital day 7 (illness day 11).²⁰ Two randomized controlled trials have been registered to evaluate the safety and efficacy of remdesivir in mild/moderate or severe patients with COVID-19 viral pneumonia.^{21,22} Kirchdoerfer and Ward²³ noticed that nonstructural proteins (nsp)12 polymerase may be a template for the design of novel antiviral therapeutic agents to interrupt the assembly of the SARS-CoV core RNA-synthesis machinery. COVID-19 has full-length genome sequences with > 75% nucleotide identity with that of SARS-CoV,⁷ which allows the molecular

structure information to be used as a model for coronavirus antiviral design. Clinical studies should assess the effectiveness and safety of monoclonal and polyclonal neutralizing antibody products and aim to discover therapeutic targets against immunopathologic host responses.

China established an effective detection network in response to an outbreak of infectious diseases after the SARS pandemic. It is of great significance to share what is known of COVID-19 genome sequences, the epidemiology, and clinical features of the illness. In this social media era, when an epidemic occurs, a great deal of misinformation is readily available.²⁴ Hopefully, the early suggestion that COVID-19 infection is of lower lethality than SARS holds true. In contrast, a low health threat on the individual level means there is potential to cause disruptions of global public health systems and a long duration of person-to-person transmissibility. Mild illnesses and asymptomatic carriers may be potential sources of infection, sustaining a local epidemic and global spread. To reduce panic and economic loss, and to manage and save the infected, much remains to be done. The goal is to break the transmission chain of COVID-19. This will require effective programs to trace, diagnose, and cure every infected patient. We all need to be aware of the risks of another zoonotic virus crossing species to infect the human population in the future. It is of great imperative that we call for global action to deal with this major public health emergency.

References

- World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). [https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). Accessed February 1, 2020.
- World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. https://www.who.int/csr/sars/country/table2004_04_21/en/. Accessed February 1, 2020.
- World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). <http://www.who.int/emergencies/mers-cov/en/>. Accessed February 1, 2020.
- Chinese Center for Disease Control and Prevention. Epidemic update and risk assessment of 2019-nCoV. <http://www.chinacdc.cn/yyrdgz/202001/P020200128523354919292.pdf>. Accessed February 1, 2020.
- Centers for Disease Control and Prevention. 2019 Novel coronavirus (2019-nCoV), Wuhan, China. <https://www.cdc.gov/coronavirus/2019-nCoV/summary.html>. Accessed February 1, 2020.
- Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin [published online ahead of print February 3, 2020]. *Nature*. <https://doi.org/10.1038/s41586-020-2012-7>.
- Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019 [published online ahead of print January 24, 2020]. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2001017>.
- Lu RJ, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding [published online ahead of print January 29, 2020]. *Lancet*. [https://doi.org/10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8).
- Ren LL, Wang YM, Wu ZQ, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study [published online ahead of print February 11, 2020]. *Chin Med J (Engl)*. <https://doi.org/10.1097/CM9.0000000000000722>.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
- Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395(10223):514-523.
- Li Q, Guan XH, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia [published online ahead of print January 29, 2020]. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2001316>.
- Bauch CT, Lloyd-Smith JO, Coffee MP, Galvani AP. Dynamically modeling SARS and other newly emerging respiratory illnesses: past, present, and future. *Epidemiology*. 2005;16(6):791-801.
- de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523-534.
- Alshahrani MS, Sindi A, Alshamsi F, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. *Ann Intensive Care*. 2018;8(1):3.
- Chu CM. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256.
- Arabi YM, Allothman A, Balkhy HH, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials*. 2018;19(1):81.
- Mulangu S, Dodd LE, Davey RT, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med*. 2019;381(24):2293-2303.
- Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States [published online ahead of print January 31, 2020]. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2001191>.
- National Institutes of Health Clinical Center. Mild/moderate 2019-nCoV Remdesivir RCT. NCT04252664. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2020. <https://clinicaltrials.gov/ct2/show/NCT04252664?term=remdesivir&draw=2&rank=2>. Updated February 24, 2020.
- National Institutes of Health Clinical Center. Severe 2019-nCoV Remdesivir RCT. NCT04257656. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2020. <https://clinicaltrials.gov/ct2/show/NCT04257656?term=remdesivir&draw=2&rank=1>. Updated February 24, 2020.
- Kirchdoerfer RN, Ward AB. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun*. 2019;10(1):2342.
- Vincent JM, Marion K, van Neeltje DA, van Riel D, de Wit E. Novel coronavirus emerging in China—key questions for impact assessment [published online ahead of print January 24, 2020]. *N Engl J Med*. <https://doi.org/10.1056/NEJMp2000929>.