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Coronavirus disease 2019 (COVID-19): A literature review

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Abstract

In early December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in Wuhan City, Hubei Province, China. On January 30, 2020 the World Health Organization declared the outbreak as a Public Health Emergency of International Concern. As of February 14, 2020, 49,053 laboratory-confirmed and 1,381 deaths have been reported globally. Perceived risk of acquiring disease has led many governments to institute a variety of control measures. We conducted a literature review of publicly available information to summarize knowledge about the pathogen and the current epidemic. In this literature review, the causative agent, pathogenesis and immune responses, epidemiology, diagnosis, treatment and management of the disease, control and preventions strategies are all reviewed.

Keywords: 2019-nCoV, COVID-19, outbreak, SARS-CoV-2, novel coronavirus

Background

On December 31, 2019, the China Health Authority alerted the World Health Organization (WHO) to several cases of pneumonia of unknown aetiology in Wuhan City in Hubei Province in central China. The cases had been reported since December 8, 2019, and many patients worked at or lived around the local Huanan Seafood Wholesale Market although other early cases had no exposure to this market [1]. On January 7, a novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified from the throat swab sample of a patient [2]. This pathogen was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group [3] and the disease was named coronavirus disease 2019 (COVID-19) by the WHO. As of January 30, 7,736 confirmed and 12,167 suspected cases had been reported in China and 82 confirmed cases had been detected in 18 other countries [4]. In the same day, WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC) [4].

According to the National Health Commission of China, the mortality rate among confirmed cases in China was 2.1% as of February 4 [5] and the mortality rate was 0.2% among cases outside China [6]. Among patients admitted to hospitals, the mortality rate ranged between 11% and 15% [7, 8]. COVID-19 is moderately infectious with a relatively high mortality rate, but the information available in public reports and published literature is rapidly increasing. The aim of this review is to summarize the current understanding of COVID-19 including causative agent, pathogenesis of the disease, diagnosis and treatment of the cases, as well as control and prevention strategies.

Discussion

The virus: classification and origin

SARS-CoV-2 is a member of the family *Coronaviridae* and order *Nidovirales*. The family consists of two subfamilies, *Coronavirinae* and *Torovirinae* and members of the subfamily *Coronavirinae* are subdivided into four genera: (a)

Alphacoronavirus contains the human coronavirus (HCoV)-229E and HCoV-NL63; (b) Betacoronavirus includes HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), HCoV-HKU1, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV); (c) Gammacoronavirus includes viruses of whales and birds and; (d) Deltacoronavirus includes viruses isolated from pigs and birds [9]. SARS-CoV-2 belongs to Betacoronavirus together with two highly pathogenic viruses, SARS-CoV and MERS-CoV. SARS-CoV-2 is an enveloped and positive-sense single-stranded RNA (+ssRNA) virus [16].

SARS-CoV-2 is considered a novel human-infecting Betacoronavirus [10]. Phylogenetic analysis of the SARS-CoV-2 genome indicates that the virus is closely related (with 88% identity) to two bat-derived SARS-like coronaviruses collected in 2018 in eastern China (bat-SL-CoVZC45 and bat-SL-CoVZXC21) and genetically distinct from SARS-CoV (with about 79% similarity) and MERS-CoV [10]. Using the genome sequences of SARS-CoV-2, RaTG13, and SARS-CoV [11], a further study found that the virus is more related to BatCoV RaTG13, a bat coronavirus that was previously detected in *Rhinolophus affinis* from Yunnan Province, with 96.2% overall genome sequence identity [11]. A study found that no evidence of recombination events detected in the genome of SARS-CoV-2 from other viruses originating from bats such as BatCoV RaTG13, SARS-CoV and SARSr-CoVs [11]. Altogether, these findings suggest that bats might be the original host of this virus [10, 11].

However, a study is needed to elucidate whether any intermediate hosts have facilitated the transmission of the virus to humans. Bats are unlikely to be the animal that is directly responsible for transmission of the virus to humans for several reasons [10]: (1) there were various non-aquatic animals (including mammals) available for purchase in Huanan Seafood Wholesale Market but no bats were sold or found; (2) SARS-CoV-2 and its close relatives, bat-SL-CoVZC45 and bat-SL-CoVZXC21, have a relatively long branch (sequence

identity of less than 90%), suggesting those viruses are not direct ancestors of SARS-CoV-2; and (3) in other coronaviruses where bat is the natural reservoir such as SARS-CoV and MERS-CoV, other animals have acted as the intermediate host (civets and possibly camels, respectively). Nevertheless, bats do not always need an intermediary host to transmit viruses to humans. For example, Nipah virus in Bangladesh is transmitted through bats shedding into raw date palm sap [12].

Transmission

The role of the Huanan Seafood Wholesale Market in propagating disease is unclear. Many initial COVID-19 cases were linked to this market suggesting that SARS-CoV-2 was transmitted from animals to humans [13]. However, a genomic study has provided evidence that the virus was introduced from another, yet unknown location, into the market where it spread more rapidly, although human-to-human transmission may have occurred earlier [14]. Clusters of infected family members and medical workers have confirmed the presence of person-to-person transmission [15]. After January 1, less than 10% of patients had market exposure and more than 70% patients had no exposure to the market [13]. Person-to-person transmission is thought to occur among close contacts mainly via respiratory droplets produced when an infected person coughs or sneezes. Fomites may be a large source of transmission, as SARS-CoV has been found to persist on surfaces up to 96 hours [16] and other coronaviruses for up to 9 days [17].

Whether or not there is asymptomatic transmission of disease is controversial. One initial study published on January 30 reported asymptomatic transmission [18], but later it was found that the researchers had not directly interviewed the patient, who did in fact have symptoms prior to transmitting disease [19]. A more recent study published on February 21 also purported asymptomatic transmission [20], but any such study could be limited by errors in self-reported symptoms or contact with other cases and fomites.

Findings about disease characteristics are rapidly changing and subject to selection bias. A study indicated the mean incubation period was 5.2 days (95% confidence interval [95%CI]: 4.1 to 7.0) [13]. The incubation period has been found to be as long as 19 or 24 days [21, 22], although case definitions typically rely on a 14 day window [23].

The basic reproductive number (R_0) has been estimated with varying results and interpretations. R_0 measures the average number of infections that could result from one infected individual in a fully susceptible population [24]. Studies from previous outbreaks found R_0 to be 2.7 for SARS [25] and 2.4 for 2009 pandemic H1N1 influenza [26]. One study estimated that that basic reproductive number (R_0) was 2.2 (95% CI: 1.4 to 3.9) [13]. However, later in a further analysis of 12 available studies found that R_0 was 3.28 [27]. Because R_0 represents an average value it is also important to consider the role of super spreaders, who may be hugely responsible for outbreaks within large clusters but who would not largely influence the value of R_0 [28]. During the acute phase of an outbreak or prepandemic, R_0 may be unstable [24].

In pregnancy, a study of nine pregnancy women who developed COVID-19 in late pregnancy suggested COVID-19 did not lead to substantially worse symptoms than in nonpregnant persons and there is no evidence for intrauterine infection caused by vertical transmission [29].

In hospital setting, a study involving 138 COVID-19 suggested that hospital-associated transmission of SARS-CoV-2 occurred in 41% of patients [30]. Moreover, another study on 425 patients found that the proportion of cases in health care workers gradually increased by time [13]. These cases likely reflect exposure to a higher concentration of virus from sustained contact in close quarters.

Outside China, as of February 12, 2020, there were 441 confirmed COVID-19 cases reported in 24 countries [6] of which the first imported case was reported in Thailand on January 13, 2020 [6, 31]. Among those countries, 11 countries have reported local transmission with the highest number of cases reported in Singapore with 47 confirmed cases [6].

Risk factors

The incidence of SARS-CoV-2 infection is seen most often in adult male patients with the median age of the patients was between 34 and 59 years [20, 30, 32, 33]. SARS-CoV-2 is also more likely to infect people with chronic comorbidities such as cardiovascular and cerebrovascular diseases and diabetes [8]. The highest proportion of severe cases occur in adults ≥ 60 years of age, and in those with certain underlying conditions, such as cardiovascular and cerebrovascular diseases and diabetes [20, 30]. Severe manifestations maybe also associated with coinfections of bacteria and fungi [8].

Fewer COVID-19 cases have been reported in children less than 15 years [20, 30, 32, 33]. In a study of 425 COVID-19 patients in Wuhan, published on January 29, there were no cases in children under 15 years of age [34]. Nevertheless, 28 paediatric patients have been reported by January 2020 [35]. The clinical features of infected paediatric patients vary, but most have had mild symptoms with no fever or pneumonia, and have a good prognosis [35]. Another study found that although a child had radiological ground-glass lung opacities, the patient was asymptomatic [36]. In summary, children might be less likely to be infected or, if infected, present milder manifestations than adults; therefore, it is possible that their parents will not seek out treatment leading to underestimates of COVID-19 incidence in this age group.

Pathogenesis and immune response

Like most other members of the coronavirus family, *Betacoronavirus* exhibit high species specificity, but subtle genetic changes can significantly alter their tissue tropism, host range, and pathogenicity. A striking example of the adaptability of these viruses is the emergence of deadly zoonotic diseases in human history caused by SARS-CoV [37] and MERS-CoV [38]. In both viruses, bats served as the natural reservoir and humans were the terminal host, with the palm civet and dromedary camel the intermediary host for SARS-CoV and MERS-CoV, respectively [39, 40]. Intermediate hosts clearly play a critical role in cross species transmission as they can facilitate increased contact between a virus and a new host and enable further adaptation necessary for an effective replication in the new host [41]. Because of the pandemic potential of SARS-CoV-2, careful surveillance is immensely important to monitor its future host adaptation, viral evolution, infectivity, transmissibility, and pathogenicity.

The host range of a virus is governed by multiple molecular interactions, including receptor interaction. The envelope spike (S) protein receptor binding domain of SARS-CoV-2 was shown structurally similar to that of SARS-CoV, despite amino acid variation at some key residues [10]. Further extensive structural analysis strongly suggests that SARS-CoV-2 may use host receptor angiotensin-converting enzyme 2 (ACE2) to enter the cells [42], the same receptor facilitating SARS-CoV to infect the airway epithelium and alveolar type 2 (AT2) pneumocytes, pulmonary cells that synthesize pulmonary surfactant [43]. In general, the spike protein of coronavirus is divided into the S1 and S2 domain, in which S1 is responsible for receptor binding and S2 domain is responsible for cell membrane fusion [10]. The S1 domain of SARS-CoV and SARS-CoV-2 share around 50 conserved amino acids, whereas most of the bat-derived viruses showed more variation [10]. In addition, identification of several key residues (Gln493 and Asn501) that govern the binding of SARS-CoV-2 receptor binding domain with ACE2 further support that SARS-CoV-2 has acquired capacity for person-to-person

transmission [42]. Although, the spike protein sequence of receptor binding SARS-CoV-2 is more similar to that of SARS-CoV, at the whole genome level SARS-CoV-2 is more closely related to bat-SL-CoVZC45 and bat-SL-CoVZXC21 [10].

However, receptor recognition is not the only determinant of species specificity. Immediately after binding to their receptive receptor, SARS-CoV-2 enters host cells where they encounter the innate immune response. In order to productively infect the new host, SARS-CoV-2 must be able to inhibit or evade host innate immune signalling. However, it is largely unknown how SARS-CoV-2 manages to evade immune response and drive pathogenesis. Given that COVID-19 and SARS have similar clinical features [7], SARS-CoV-2 may have a similar pathogenesis mechanism as SARS-CoV. In response to SARS-CoV infections, the type I interferon (IFN) system induces the expression of IFN-stimulated genes (ISGs) to inhibit viral replication. To overcome this antiviral activity, SARS-CoV encodes at least 8 viral antagonists that modulate induction of IFN and cytokines and evade ISG effector function [44].

The host immune system response to viral infection by mediating inflammation and cellular antiviral activity is critical to inhibit viral replication and dissemination. However, excessive immune responses together with lytic effects of the virus on host cells will result in pathogenesis. Studies have shown patients suffering from severe pneumonia, with fever and dry cough as common symptoms at onset of illness [7, 8]. Some patients progressed rapidly with Acute Respiratory Stress Syndrome (ARDS) and septic shock, which was eventually followed by multiple organ failure and about 10% of patients have died [8]. ARDS progression and extensive lung damage in COVID-19 are further indications that ACE2 might be a route of entry for the SARS-CoV-2 as ACE2 is known abundantly present on ciliated cells of the airway epithelium and alveolar type II (cells (pulmonary cells that synthesize pulmonary surfactant) in humans [45].

Patients with SARS and COVID-19 have similar patterns of inflammatory damage. In serum from patients diagnosed with SARS, there is increased levels of proinflammatory cytokines (e.g. interleukin (IL)-1, IL6, IL12, interferon gamma (IFN γ), IFN- γ -induced protein 10 (IP10), macrophage inflammatory proteins 1A (MIP1A) and monocyte chemoattractant protein-1 (MCP1)), which are associated with pulmonary inflammation and severe lung damage [46]. Likewise, patients infected with SARS-CoV-2 are reported to have higher plasma levels of proinflammatory cytokines including IL1 β , IL-2, IL7, TNF- α , GSCF, MCP1 than healthy adults [7]. Importantly, patients in the intensive care unit (ICU) have a significantly higher level of GSCF, IP10, MCP1, and TNF- α than those non-ICU patients, suggesting that a cytokine storm might be an underlying cause of disease severity [7]. Unexpectedly, anti-inflammatory cytokines such as IL10 and IL4 were also increased in those patients [7], which was uncommon phenomenon for an acute phase viral infection. Another interesting finding, as explained before, was that SARS-CoV-2 has shown to preferentially infect older adult males with rare cases reported in children [7, 8]. The same trend was observed in primate models of SARS-CoV where the virus was found more likely to infect aged *Cynomolgus macaque* than young adults [47]. Further studies are necessary to identify the virulence factors and the host genes of SARS-CoV-2 that allows the virus to cross the species-specific barrier and cause lethal disease in humans.

Clinical manifestations

Clinical manifestations of 2019-nCoV infection have similarities with SARS-CoV where the most common symptoms include fever, dry cough, dyspnoea, chest pain, fatigue and myalgia [7, 30, 48]. Less common symptoms include headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting [7, 30]. Based on the report of the first 425 confirmed cases in Wuhan, the common symptoms include fever, dry cough, myalgia and fatigue with less common are sputum production, headache, haemoptysis, abdominal pain, and

diarrhoea [13]. Approximately 75% patients had bilateral pneumonia [8]. Different from SARS-CoV and MERS-CoV infections, however, is that very few COVID-19 patients show prominent upper respiratory tract signs and symptoms such as rhinorrhoea, sneezing, or sore throat, suggesting that the virus might have greater preference for infecting the lower respiratory tract [7]. Pregnant and non-pregnant women have similar characteristics [49]. The common clinical presentation of 2019-nCoV infection are presented in Table 1.

TABLE 1

Severe complications such as hypoxemia, acute ARDS, arrhythmia, shock, acute cardiac injury, and acute kidney injury have been reported among COVID-19 patients [7, 8]. A study among 99 patients found that approximately 17% patients developed ARDS and, among them, 11% died of multiple organ failure [8]. The median duration from first symptoms to ARDS was 8 days [30].

Diagnosis

Efforts to control spread of COVID-19, institute quarantine and isolation measures, and appropriately clinically manage patients all require useful screening and diagnostic tools. While SARS-CoV-2 is spreading, other respiratory infections may be more common in a local community. The WHO has released a guideline on case surveillance of COVID-19 on January 31, 2020 [23]. For a person who meets certain criteria, WHO recommends to first screen for more common causes of respiratory illness given the season and location. If a negative result is found, the sample should be sent to referral laboratory for SARS-CoV-2 detection.

Case definitions can vary by country and will evolve over time as the epidemiological circumstances change in a given location. In China, a confirmed case from January 15, 2020 required an epidemiological linkage to Wuhan within 2 weeks and clinical features such as fever, pneumonia, and

low white blood cell count. On January 18, 2020 the epidemiological criterion was expanded to include contact with anyone who had been in Wuhan in the past 2 weeks [51]. Later, the case definitions removed the epidemiological linkage.

The WHO has put forward case definitions [23]. Suspected cases of COVID-19 are persons (a) with severe acute respiratory infections (history of fever and cough requiring admission to hospital) *and* with no other aetiology that fully explains the clinical presentation *and* a history of travel to or residence in China during the 14 days prior to symptom onset; or (b) a patient with any acute respiratory illness *and* at least one of the following during the 14 days prior to symptom onset: contact with a confirmed or probable case of SARS-CoV-2 infection *or* worked in or attended a health care facility where patients with confirmed or probable SARS-CoV-2 acute respiratory disease patients were being treated. Probable cases are those for whom testing for SARS-CoV-2 is inconclusive or who test positive using a pan-coronavirus assay and without laboratory evidence of other respiratory pathogens. A confirmed case is one with a laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical signs and symptoms.

For patients who meet diagnostic criteria for SARS-CoV-2 testing, the CDC recommends collection of specimens from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) and, if possible, the lower respiratory tract (sputum, tracheal aspirate, or bronchoalveolar lavage) [52]. In each country, the tests are performed by laboratories designated by the government.

Laboratory findings

Among COVID-19 patients, common laboratory abnormalities include lymphopenia [8, 20, 30], prolonged prothrombin time, and elevated lactate dehydrogenase [30]. ICU-admitted patients had more laboratory abnormalities compared with non-ICU patients [30, 32]. Some patients had

elevated aspartate aminotransferase, creatine kinase, creatinine, and C-reactive protein [20, 32, 36]. Most patients have shown normal serum procalcitonin levels [20, 30, 32].

COVID-19 patients have high level of IL1 β , IFN- γ , IP10, and MCP1 [7]. ICU-admitted patients tend to have higher concentration of granulocyte-colony stimulating factor (GCSF), IP10, MCP1A, MIP1A, and TNF- α [7].

Radiology findings

Radiology finding may vary with patients age, disease progression, immunity status, comorbidity, and initial medical intervention [53]. In a study describing 41 of the initial cases of 2019-nCoV infection, all 41 patients had pneumonia with abnormal findings on chest computed tomography (CT-scan) [32]. Abnormalities on chest CT-scan were also seen in another study of 6 cases, in which all of them showed multifocal patchy ground-glass opacities notably nearby the peripheral sections of the lungs [36]. Data from studies indicate that the typical of chest CT-scan findings are bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities [7, 8, 20, 30, 32, 33, 54]. The consolidated lung lesions among patients five or more days from disease onset and those 50 years old or older compared to 4 or fewer days and those 50 years or younger, respectively [48].

As the disease course continue, mild to moderate progression of disease were noted in some cases which manifested by extension and increasing density of lung opacities [50]. Bilateral multiple lobular and subsegmental areas of consolidation are typical findings on chest CT-scan of ICU-admitted patients [7]. A study among 99 patients, one patient had pneumothorax in an imaging examination [8].

Treatments

Similar to MERS-CoV and SARS-CoV, there is still no specific antiviral treatment for COVID-19 [55]. Isolation and supportive care including oxygen

therapy, fluid management, and antibiotics treatment for secondary bacterial infections is recommended [56]. Some COVID-19 patients progressed rapidly to ARDS and septic shock, which was eventually followed by multiple organ failure [7, 8]. Therefore, the effort on initial management of COVID-19 must be addressed to the early recognition of the suspect and contain the disease spread by immediate isolation and infection control measures [57].

Currently, no vaccination is available, but even if one was available, uptake might be suboptimal. A study of intention to vaccinate during the H1N1 pandemic in the United States was around 50% at the start of the pandemic in May 2009 but had decreased to 16% by January 2010 [58].

Neither is a treatment available. Therefore, the management of the disease has been mostly supportive referring to the disease severity which has been introduced by WHO. If sepsis is identified, empiric antibiotic should be administered based on clinical diagnosis and local epidemiology and susceptibility information. Routine glucocorticoids administration are not recommended to use unless there are another indication [59]. Clinical evidence also does not support corticosteroid treatment [60]. Use of intravenous immunoglobulin might help for severely ill patients [8].

Drugs are being evaluated in line with past investigations into therapeutic treatments for SARS and MERS [61]. Overall, there is not robust evidence that these antivirals can significantly improve clinical outcomes. A. Antiviral drugs such as oseltamivir combined with empirical antibiotic treatment have also been used to treat COVID-19 patients [7]. Remdesivir which was developed for Ebola virus, has been used to treat imported COVID-19 cases in US [62]. A brief report of treatment combination of Lopinavir/Ritonavir, Arbidol, and Shufeng Jiedu Capsule (SFJDC), a traditional Chinese medicine, showed a clinical benefit to three of four COVID-19 patients [63]. There is an ongoing clinical trial evaluating the safety and efficacy of lopinavir-ritonavir and interferon- α 2b in patients with COVID-19 [56]. Ramsedivir, a broad

spectrum antiviral has demonstrated *in vitro* and *in vivo* efficacy against SARS-CoV-2 and has also initiated its clinical trial [64, 65]. In addition, other potential drugs from existing antiviral agent have also been proposed [66, 67].

Control and prevention strategies

COVID-19 is clearly a serious disease of international concern. By some estimates it has a higher reproductive number than SARS [27], and more people have been reported to have been infected or died from it than SARS [68]. Similar to SARS-CoV and MERS-CoV, disrupting the chain of transmission is considered key to stopping the spread of disease [69]. Different strategies should be implemented in health care settings and at the local and global levels.

Health care settings can unfortunately be an important source of viral transmission. As shown in the model for SARS, applying triage, following correct infection control measures, isolating the cases and contact tracing are key to limit the further spreading of the virus in clinics and hospitals [69]. Suspected cases presenting at healthcare facilities with symptoms of respiratory infections (e.g. runny nose, fever and cough) must wear a face mask to contain the virus and strictly adhere triage procedure. They should not be permitted to wait with other patients seeking medical care at the facilities. They should be placed in a separated, fully ventilated room and approximately 2 meters away from other patients with convenient access to respiratory hygiene supplies [70]. In addition, if a confirmed COVID-19 case require hospitalization, they must be placed in a single patient room with negative air pressure - a minimum of six air changes per hour. Exhausted air has to be filtered through high efficiency particulate air (HEPA) and medical personnel entering the room should wear personal protective equipment (PPE) such as gloves, gown, disposable N95, and eye protection. Once the cases are recovered and discharged, the room should be decontaminated or disinfected and personnel entering the room need to wear PPE particularly facemask, gown, eye protection [70].

In a community setting, isolating infected people are the primary measure to interrupt the transmission. For example, immediate actions taken by Chinese health authorities included isolating the infected people and quarantining of suspected people and their close contacts [71]. Also, as there are still conflicting assumptions regarding the animal origins of the virus (i.e. some studies linked the virus to bat [72, 73] while others associated the virus with snake [74]), contacts with these animal fluids or tissues or consumption of wild caught animal meet should be avoided. Moreover, educating the public to recognise unusual symptoms such as chronic cough or shortness of breath is essential therefore that they could seek medical care for early detection of the virus. If large-scale community transmission occurs, mitigating social gatherings, temporary school closure, home isolation, close monitoring of symptomatic individual, provision of life supports (e.g. oxygen supply, mechanical ventilator), personal hand hygiene, and wearing personal protective equipment such as facemask should also be enforced [75].

In global setting, locking down Wuhan city was one of the immediate measure taken by Chinese authorities and hence had slowed the global spread of COVID-19 [75]. Air travel should be limited for the cases unless severe medical attentions are required. Setting up temperature check or scanning is mandatory at airport and border to identify the suspected cases. Continued research into the virus is critical to trace the source of the outbreak and provide evidence for future outbreak [75].

Conclusions

The current COVID-19 pandemic is clearly an international public health problem. There have been rapid advances in what we know about the pathogen, how it infects cells and causes disease, and clinical characteristics of disease. Due to rapid transmission, countries around the world should increase attention into disease surveillance systems and scale up country

readiness and response operations including establishing rapid response teams and improving the capacity of the national laboratory system.

Competing interest

The authors declare that they have no competing interests.

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Reference

1. Lu H, Stratton CW, Tang YW: Outbreak of Pneumonia of Unknown Etiology in Wuhan China: the Mystery and the Miracle. *J Med Virol* 2020.
2. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, McHugh TD, Memish ZA, Drosten C *et al*: The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020, 91:264-266.
3. Gorbalenya AEA: Severe acute respiratory syndrome-related coronavirus: The species and its viruses - a statement of the Coronavirus Study Group. *Biorxiv* 2020, <https://doi.org/10.1101/2020.02.07.937862>.
4. Burki TK: Coronavirus in China. *Lancet Respir Med* 2020.
5. NHS Press Conference, Feb. 4 2020. Beijing, China. National Health Commission (NHC) of the People's Republic of China. <http://www.nhc.gov.cn/xcs/xwbd/202002/235990d202056cfcb202043f202004a202070d202007f209703b202113c202000.shtml>.
6. WHO: Coronavirus disease 2019 (COVID-19) Situation Report - 23. Geneva, Switzerland: World Health Organization; 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200212-sitrep-20200223-ncov.pdf?sfvrsn=20200241e20200219fb20200278_20200212 (Assessed online 20200213 Feb 20202020).
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y *et al*: Epidemiological and clinical characteristics of 99 cases of 2019

- novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020.
9. Burrell C, Howard C, Murphy F: Fenner and White's Medical Virology 5th Edition. United States: Academic Press; 2016.
 10. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N *et al*: Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020.
 11. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL *et al*: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020.
 12. Hughes J, Wilson M, Luby S, Gurley E, Hossain M: Transmission of human infection with Nipah virus. *Clin Infect Dis* 2009, 49(11):1743–1748.
 13. Yufika A, Wagner AL, Nawawi Y, Wahyuniati N, Anwar S, Yusri F, Haryanti N, Wijayanti NP, Rizal R, Fitriani D *et al*: Parents' hesitancy towards vaccination in Indonesia: A cross-sectional study in Indonesia. *Vaccine* 2020.
 14. Yu W, Tang G, Zhang L, Corlett R: Decoding the evolution and transmissions of the novel pneumonia coronavirus (SARS-CoV-2) using whole genomic data. *ChinaXiv* 2020:Preprint.
 15. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW *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.
 16. Kramer A, Schwebke I, Kampf G: How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infect Dis* 2006, 6:130.
 17. Kampf G, Todt D, Pfaender S, Steinmann E: Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. *J Hosp Infect* 2020.
 18. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W *et al*: Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med* 2020.
 19. Kupferschmidt K: Study claiming new coronavirus can be transmitted by people without symptoms was flawed. In: *Science News*. 2020.
 20. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, Wang M: Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA* 2020.
 21. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020, 395(10223):497-506.
 22. Chu DKW, Pan Y, Cheng SMS, Hui KPY, Krishnan P, Liu Y, Ng DYM, Wan CKC, Yang P, Wang Q *et al*: Molecular Diagnosis of a Novel Coronavirus (2019-nCoV) Causing an Outbreak of Pneumonia. *Clin Chem* 2020.
 23. Global Surveillance for human infection with novel coronavirus (2019-nCoV). In.: World Health Organization; 2020.

24. Bauch C, Oraby T: Assessing the pandemic potential of MERS-CoV. *Lancet* 2013, 382(9893):662-664.
25. Riley S, Fraser C, Donnelly CA, Ghani AC, Abu-Raddad LJ, Hedley AJ, Leung GM, Ho LM, Lam TH, Thach TQ *et al*: Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. *Science* 2003, 300(5627):1961-1966.
26. Yang Y, Sugimoto JD, Halloran ME, Basta NE, Chao DL, Matrajt L, Potter G, Kenah E, Longini IM, Jr.: The transmissibility and control of pandemic influenza A (H1N1) virus. *Science* 2009, 326(5953):729-733.
27. Liu Y, Gayle A, Wilder-Smith A, J. R: The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020, <https://doi.org/10.1093/jtm/taaa021>.
28. Kucharski A, Althaus C: The role of superspreading in Middle East respiratory syndrome coronavirus (MERS-CoV) transmission. *Euro Surveill* 2015, 20(25):pii=21167.
29. Chen HEA: Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020, [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3).
30. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y *et al*: Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
31. Sookaromdee P, Wiwanitkit V: Imported cases of 2019-novel coronavirus (2019-nCoV) infections in Thailand: Mathematical modelling of the outbreak. *Asian Pac J Trop Med* 2020, 13(3):139-140.
32. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020.
33. Chang, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, Sharma L: Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* 2020.
34. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY *et al*: Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020.
35. Shen KL, Yang YH: Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. *World J Pediatr* 2020.
36. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, Xing F, Liu J, Yip CC-Y, Poon RW-S *et al*: A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet* 2020.
37. Peiris JSM, Guan Y, Yuen KY: Severe acute respiratory syndrome. *Nature Medicine* 2004, 10(12):S88-S97.
38. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA: Isolation of a novel coronavirus from a man with pneumonia in Saudi

- Arabia. *The New England journal of medicine* 2012, 367(19):1814-1820.
39. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ *et al*: Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 2003, 302(5643):276-278.
 40. Alagaili AN, Briese T, Mishra N, Kapoor V, Sameroff SC, Burbelo PD, de Wit E, Munster VJ, Hensley LE, Zalmout IS *et al*: Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. *mBio* 2014, 5(2):e00884-00814.
 41. Brennan G, Kitzman JO, Rothenburg S, Shendure J, Geballe AP: Adaptive gene amplification as an intermediate step in the expansion of virus host range. *PLoS Pathog* 2014, 10(3):e1004002.
 42. Wan Y, Shang J, Graham R, Baric RS, Li F: Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *Journal of Virology* 2020:JV1.00127-00120.
 43. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC *et al*: Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003, 426(6965):450-454.
 44. Tatura AL, Baric RS: SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. *Current opinion in virology* 2012, 2(3):264-275.
 45. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H: Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of pathology* 2004, 203(2):631-637.
 46. Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, Lit LC, Hui DS, Chan MH, Chung SS *et al*: Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clinical and experimental immunology* 2004, 136(1):95-103.
 47. Smits SL, de Lang A, van den Brand JM, Leijten LM, van IWF, Eijkemans MJ, van Amerongen G, Kuiken T, Andeweg AC, Osterhaus AD *et al*: Exacerbated innate host response to SARS-CoV in aged non-human primates. *PLoS Pathog* 2010, 6(2):e1000756.
 48. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R *et al*: A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020.
 49. Chen H GJ, Wang C, *et al*: Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020.
 50. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA *et al*: CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020:200230.
 51. CDC China: Epidemic update and risk assessment of 2019 Novel Coronavirus. *Chinese Center for Diseases Control and Prevention* 2020,

- <http://www.chinacdc.cn/yysrdgz/202001/P020200128523354919292.pdf> (Accessed 22 Feb 2020).
52. Patel A JD: Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak—United States, December 31, 2019–February 4, 2020. *MMWR Morb Mortal Wkly Rep* 2020, 69:140.
 53. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q *et al*: A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020, 7(1):4.
 54. Lei J, Li J, Li X, Qi X: CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology* 2020:200236.
 55. Tang JW, Tambyah PA, Hui DSC: Emergence of a novel coronavirus causing respiratory illness from Wuhan, China. *The Journal of infection* 2020.
 56. Habibzadeh P, Stoneman EK: The Novel Coronavirus: A Bird's Eye View. *The international journal of occupational and environmental medicine* 2020, 11(2):65-71.
 57. Organization WH: Global Surveillance for human infection with novel coronavirus (2019-nCoV). In.; 2020.
 58. Gidengil C, Parker A, Zikmund-Fisher B: Trends in risk perceptions and vaccination intentions: a longitudinal study of the first year of the H1N1 pandemic. *Am J Public Health* 2012, 102: 672–679.
 59. Organization WH: Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. In.; 2020.
 60. Russell C, Millar J, Baillie J: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020, 395(10223):473-475.
 61. Paules CI, Marston HD, Fauci AS: Coronavirus Infections-More Than Just the Common Cold. *JAMA* 2020.
 62. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A *et al*: First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020.
 63. Wang Z, Chen X, Lu Y, Chen F, Zhang W: Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends* 2020.
 64. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G: Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020.
 65. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H: Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proceedings of the National Academy of Sciences* 2020:201922083.

66. Liu X, Wang X-J: Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. *bioRxiv* 2020:2020.2001.2029.924100.
67. Lu H: Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends* 2020.
68. Mahase E: Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ* 2020, 368:m641.
69. Chan JFW, Lau SKP, To KKW, Cheng VCC, Woo PCY, Yuen K-Y: Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clinical microbiology reviews* 2015, 28(2):465-522.
70. Centers for Diseases Control and Prevention: Coronavirus Disease 2019 (COVID-19). 2020.
71. Wang C, Horby PW, Hayden FG, Gao GF: A novel coronavirus outbreak of global health concern. *The Lancet* 2020.
72. Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S: Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infection, Genetics and Evolution* 2020:104212.
73. Randhawa GS, Soltysiak MPM, El Roz H, De Souza CP, Hill KA, Kari L: Machine learning analysis of genomic signatures provides evidence of associations between Wuhan 2019-nCoV and bat betacoronaviruses. *BioRxiv* 2020.
74. Ji W, Wang W, Zhao X, Zai J, Li X: Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. *Journal of medical virology* 2020.
75. David L Heymann & Nahoko Shindo: COVID-19: what is next for public health? *THE LANCET* 2020.

Table 1. Clinical symptoms of patients with 2019-nCoV infection

Study	Chen et al. [8]	Huang et al. [7]	Chung et al. [50]
Patient count	99	41	21
Age (mean, year)	55.5	49	51
Fever	83%	98%	67%
Cough	81%	76%	43%
Shortness of breath	31%	55%	-

Myalgia	11%	44%	3%
Haemoptysis	-	5%	-
Sputum production	-	28%	-
Confusion	9%	-	-
Sore throat	5%	-	-
Rhinorrhoea	4%	-	-
Chest pain	2%	-	-
Diarrhoea	2%	1%	-

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