Review of the risk factors for SARS-CoV-2 transmission

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which has lasted for nearly a year, has made people deeply aware of the strong transmissibility and pathogenicity of SARS-CoV-2 since its outbreak in December 2019. By December 2020, SARS-CoV-2 had infected over 65 million people globally, resulting in more than 1 million deaths. At present, the exact animal origin of SARS-CoV-2 remains unclear and antiviral vaccines are now undergoing clinical trials. Although the social order of human life is gradually returning to normal, new confirmed cases continue to appear worldwide, and the majority of cases are sporadic due to environmental factors and lax self-protective consciousness. This article provides the latest understanding of the epidemiology and risk factors of nosocomial and community transmission of SARS-CoV-2, as well as strategies to diminish the risk of transmission. We believe that our review will help the public correctly understand and cope with SARS-CoV-2.

Key Words: SARS-CoV-2; COVID-19; Transmission; Infection; Nosocomial; Risk

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is known for its high infectivity and pathogenicity, has lasted for nearly a year since the outbreak in the city of Wuhan, China at the end of 2019[3]. As of December 8, 2020, SARS-CoV-2 had infected 65872391 patients with 1523656 deaths (2.3% mortality rate) worldwide, with the largest number of cases in the United States (14191298 cases with 276503 deaths, 1.8% mortality), the largest number of recoveries (11,210,466), and the largest number of deaths (276,503) in the United States[8].

Unlike the two highly pathogenic coronaviruses previously identified, namely SARS-CoV in 2002-2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012[6], SARS-CoV-2 not only far exceeds them in the number of confirmed people with infection but has also overwhelmingly expanded to nearly 230 countries and regions in terms of spatial spread, posing great threats and challenges to social public health and medical systems[9].

In this review, we share the latest understanding of the epidemiology and risk factors of nosocomial and community transmission of SARS-CoV-2, and discuss the clinical characteristics of COVID-19, as well as strategies to diminish the risk of transmission and stress related to the pandemic.

EMERGENCE AND SPREAD OF SARS-COV-2

In late December 2019, a cluster of unidentified pneumonia cases occurred in the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China where live wild animal sales often occur before shutdown[4-7]. By January 7, 2020, the novel coronavirus was isolated from bronchoalveolar lavage fluid samples of confirmed infected pneumonia patients, and was later officially named SARS-CoV-2 by the International Committee on Taxonomy of Viruses on February 11, 2020[8]. At the same time, the World Health Organization (WHO) named this disease caused by SARS-CoV-2, COVID-19. Shockingly, in the following month, SARS-CoV-2 spread fast from Wuhan to Hubei province and even the whole country, and the number of confirmed and suspected cases increased by hundreds of thousands every day[4]. Due to the severity of the outbreak, on January 30, 2020, the WHO announced that the pandemic caused by SARS-CoV-2 is a public health emergency of international concern (PHEIC), which is the sixth time since the International Health Regulations (2005) took effect on June 15, 2007[9]. On March 11, 2020, the WHO officially declared the COVID-19 outbreak a global pandemic. An outline of the PHEIC announced by the WHO in the recent decade is listed in Table 1.

As the initial center of the SARS-CoV-2 outbreak, Wuhan combines multiple factors conducive to the emergence and spread of the virus such as convenient transportation facilities, more than 84 universities, and a floating population of 5 million. Another factor that cannot be ignored is that the outbreak coincided with the Spring Festival holiday at the end of the year, which is the largest annual population movement. A large number of people such as tourists, students, and migrants moved and consequently accelerated the spread of SARS-CoV-2. Most infections occurred as a result of person-to-person spread and the imported cases caused by these passengers leaving Wuhan via public transportation were responsible for the spread of SARS-CoV-2.
Table 1 Public health emergency of international concern announced by the World Health Organization

| Public health PHEIC announced by WHO |
|--------------------------------------|
| H1N1 influenza pandemic in 2009       |
| Polio eradication in 2014             |
| Ebola virus outbreak in West Africa in 2014 |
| Zika virus outbreaks in 2016          |
| Ebola outbreak in the Democratic Republic of Congo in 2018 |
| SARS-CoV-2 outbreak in 2020           |

H1N1: Influenza A; PHEIC: Public health emergency of international concern; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization.

CoV-2, which may explain the subsequent spread and outbreak of the international COVID-19 epidemic.

Although the number of newly confirmed cases in China has shown a downward trend since February 2020, the international epidemic situation is not optimistic. Italy is the second country that was hit hard by SARS-CoV-2 after China, and SARS-CoV-2 quickly spread across Europe and North America\[11\]. In the face of the spreading epidemic, many countries, such as those in Asia, have taken various measures to control its development including social isolation, closing public places, and non-essential outdoor activities. However, the effectiveness of these non-drug interventions varies from region to region. The overloaded medical system and the irrational and blind behavior of some people have significantly limited the government’s power and/or effectiveness in the battle against the epidemic\[12,13\]. In addition, although Africa has made significant progress in preventing and controlling infectious diseases since the Ebola outbreak in 2014-2016, the SARS-CoV-2 epidemic remains a huge challenge due to limited resources\[14\].

**SOURCE OF SARS-COV-2 INFECTION**

Previous studies have reported a close connection between wild animals and some confirmed cases, and it is presumed that SARS-CoV-2 may have been first transmitted from a wild animal to humans, after which it spread widely from person to person\[15,16\]. Since the SARS epidemic in 2003, extensive epidemiological investigations have shown that bats carry multiple coronaviruses that have the potential to infect humans\[17-19\]. The bat-derived coronavirus RaTG13 from the *Rhinolophus affinis* bat from Yunnan Province, China, shares up to 96.2% similarity of the gene sequence with SARS-CoV-2\[20\].

Pangolins are also thought to be a possible host for SARS-CoV-2. Earlier on October 24, 2019, Liu and colleagues first isolated SARS-like coronavirus from two dead Malayan pangolins illegally imported into Guangdong province, illustrating the diversity of pangolin virus using viral metagenomics analysis\[21\]. Subsequently, strong identity to SARS-CoV-2 in the receptor-binding domain was found from the pangolin lung samples\[22\]. In addition, researchers from the South China Agricultural University in Guangzhou proposed that pangolin could be the most likely intermediate host for SARS-CoV-2 based on the finding that a virus strain 99% similar to SARS-CoV-2 in genome sequence was isolated from pangolin\[23\].

Researchers have also tried to find possible intermediate hosts for SARS-CoV-2 in common animals such as cats, dogs, and pigs\[24\]. However, the available data have not led to identification of the specific source and intermediate host of SARS-CoV-2 transmission. Although patients diagnosed with COVID-19 are thought to be the main source of infection, all of these findings may help trace the origin and probable intermediate hosts of SARS-CoV-2 to block interspecies transmission.

**PATHOGENESIS OF SARS-COV-2**

SARS-CoV-2 targets the respiratory system as the main mechanism for attacking the
human body, and the patient can gradually progress to severe pneumonia, secondary infection, and even multiple organ failure[3,]. SARS-CoV-2 binds to the same receptor, angiotensin-converting enzyme 2 (ACE2), for cell entry as SARS-CoV[2,3,4]. Due to the high expression of ACE2 in nasal epithelial cells, SARS-CoV-2 enters epithelial cells through ACE2 in the upper respiratory tract and then begins to replicate and move into the lower respiratory tract of the lung[5]. Breakdown of the lung epithelial-endothelial barrier caused by viral replication drives a series of immune responses in the body[6]. The release of pro-inflammatory cytokines, such as interleukin 6 and tumor necrosis factor alpha, may stimulate the increase of reactive oxygen species in various organs or tissues, including vascular endothelial cells[7,8] and the respiratory system[9,10]. On the other hand, oxidative stress during respiratory viral infection may also exacerbate cytokine storms[11]. Cytokine storms are considered to be a major killer in patients with severe COVID-19 infection, and higher levels of pro-inflammatory cytokines have been found in these patients, indicating that they are closely related to disease severity[12,13]. Of note, compared to elderly patients, cytokine storms may be more severe in young patients because of their more developed immune system[14], which may explain why some otherwise very healthy young adults have died from COVID-19.

Histological examination has revealed that the typical pathological features in patients with severe COVID-19 are mainly located in the lungs, which are markedly similar to the pathological features of SARS and MERS[15,16,17,18]. The lung tissues mainly have bilateral diffuse alveolar damage, extensive interstitial fibrosis, hyaline membrane formation, and inflammatory infiltration of lymphocytes, indicating acute respiratory distress syndrome[19]. Recently, pathological findings of the extra-pulmonary organs have been reported including myocardial interstitial macrophage infiltration[20], lymphocyte reduction, and macrophage aggregation in spleen and hilar lymph nodes[21].

### NON-SPECIFIC CLINICAL FEATURES OF COVID-19

Apparently, to make a definitive diagnosis of COVID-19, a good understanding is needed about the occurrence and development of its clinical manifestations and the abnormalities of imaging and laboratory tests. The initial screening for SARS-CoV-2 usually begins at fever clinics, with fever, cough and shortness of breath being the most important symptoms in the majority of confirmed patients[22]. Other respiratory symptoms include expectoration, stuffy nose, and sore throat[22]. In addition, the appearance of patchy shadows or ground-glass shadows on chest X-rays or lung computed tomography scans is also a hallmark of COVID-19. However, similar to SARS and MERS, respiratory symptoms are not unique clinical manifestations of COVID-19, while some extra-pulmonary symptoms including myalgia, headache, fatigue and anorexia are common and most patients with COVID-19 have gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, and diarrhea[23,24,25,26]. Of note, compared to elderly patients, cytokine storms may be more severe in young patients because of their more developed immune system[27], which may explain why some otherwise very healthy young adults have died from COVID-19.

Clinically, these non-specific symptoms in the early outbreak of epidemic may be difficult to distinguish from many other common infectious diseases, especially in the winter and spring when influenza is highly prevalent. Some infected patients thought they had just caught a cold and did not pay enough attention at the early stage of symptoms, and thus no self-quarantine or other protective procedures such as mask wearing were exercised, indicating that everyone who came into close contact with them including family members, social service workers, and medical staff were at high risk of infection.

As an indicator of the transmissibility of a virus, the basic reproduction number (R₀) of SARS-CoV-2 differs between research groups and is updated as available and accurate information is increasing. Recently, the mean value of R₀ was estimated to be 3.28, with a median of 2.79, indicating the high infectiousness of SARS-CoV-2, which is consistent with the ongoing epidemic[28]. Furthermore, available evidence indicates that the median incubation period of SARS-CoV-2 is about 5 d, and 97.5% of patients develop symptoms within 11.5 d of infection[29]. Pre-symptomatic patients who tested positive prior to the onset of symptoms may unconsciously carry the virus into the surrounding environment during incubation time, thus accelerating the transmission cycle of SARS-CoV-2.
RISK FACTORS FOR POOR OUTCOMES

Based on many clinical studies, elderly COVID-19 patients with pre-existing chronic diseases are more prone to serious complications, progressively developing organ failure and even death\(^\text{[52,53]}\). As a result of relatively weaker immunity, the elders with chronic diseases are more prone to various bacterial and viral infections such as influenza, bacterial pneumonia, and even premature death\(^\text{[60,61]}\). Compared to patients without diabetes, COVID-19 patients with diabetes alone prior to the onset of illness have higher inflammation responses, which may be associated with the exacerbated progression and poor outcomes\(^\text{[62]}\). Apart from advanced age and comorbidity, laboratory examination indexes including elevated neutrophil count, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), and D-dimer all reportedly result in the poor prognosis of COVID-19\(^\text{[67]}\). Our previous study\(^\text{[68]}\) reported that 34 patients with COVID-19 were unintentionally scheduled for elective surgeries during the incubation period, of which 15 (44.1%) patients were transferred to the intensive care unit (ICU) for further treatment and 7 patients (20.5%) ultimately died after admission to the ICU. Another cohort study of 1128 patients from 24 countries showed that more than half of patients with perioperative SARS-CoV-2 infection had postoperative pulmonary complications and accounted for 81.7% of all deaths\(^\text{[5]}\). Putting aside the risk factors for poor outcomes mentioned above, the tissue trauma and inflammatory response caused by anesthesia, surgery and other invasive measures (transfusion of blood products, use of extracorporeal circulation) may further weaken the immunity of patients, which affect the disease progression and even increase mortality\(^\text{[69,70]}\). Moreover, administration of high-dose corticosteroids during hospitalization may indicate worsening of the condition in patients with severe COVID-19\(^\text{[71]}\).

Taken together, risk factors for poor prognosis (severity and death) of patients with COVID-19 are as follows: older age, male sex, comorbidity (hypertension, respiratory system disease, diabetes, cardiovascular and cerebrovascular disease), surgery-related trauma and laboratory biochemical indicators such as high D-dimer, increased neutrophil count, BUN, LDH and plasmin(ogen)\(^\text{[69]}\).

NOSOCOMIAL TRANSMISSION

In the early stages of the epidemic in China, 57 (41.3%) of 138 patients in a single center were suspected of nosocomial transmission, including 17 (12.3%) hospitalized patients and 40 (29%) medical staff\(^\text{[60]}\). A prospective cohort study from London reported that the rate of nosocomial infection among frontline medical staff was up to 44%\(^\text{[60]}\). Because SARS-CoV-2 can be transmitted through normal breathing, coughing, sneezing, talking and surface contact\(^\text{[60]}\), when interacting with patients in the hospital, especially in situations such as endotracheal intubation, manual ventilation before endotracheal intubation and bronchoscopy, medical staff and hospital cleaners are at higher risk of exposure to the virus and can transmit SARS-CoV-2 to patients with low immunity\(^\text{[60]}\). Compared to doctors working in fever clinics, doctors in other departments are less vigilant and have lower levels of personal protective equipment (PPE), and thus have a high chance of being infected. Patients with normal body temperature, who visited different outpatient clinics for non-respiratory symptoms, greatly drove the nosocomial spread of SARS-CoV-2.

Even a SARS-CoV-2-infected patient with mild upper respiratory symptoms can cause extensive environmental contamination. In a COVID-19 ward, SARS-CoV-2 was detected in samples from 13 (87%) of 15 room sites (including air outlet fans) and 5 (60%) of 5 toilet sites (toilet bowl, sink, and door handle) before routine cleaning\(^\text{[71]}\). A study investigating the environmental contamination of SARS-CoV-2 in hospitals showed that self-service printers (20.0%), desktops/keyboards (16.8%) and doorknobs (16.0%) were the most contaminated in-hospital facilities, while hand sanitizer dispensers (20.3%) and gloves (15.4%) were the most contaminated in terms of PPE\(^\text{[72]}\). Another retrospective study evaluating risk factors for COVID-19 showed that poor hand hygiene after contact with a confirmed patient made the hands of healthcare workers a life-threatening tool to transmit SARS-CoV-2\(^\text{[73]}\). Under enormous pressure from the large number of confirmed cases, the shortage of protective equipment and irregular prevention measures may accelerate the spread of SARS-CoV-2 in hospitals.
COMMUNITY TRANSMISSION

Early confirmed COVID-19 cases were found to have a clear history of exposure to Huanan Seafood Wholesale Market, and it is not difficult to speculate that community transmission may have occurred first and subsequent human-to-human transmission contributed to the progress of the epidemic and even the outbreak of SARS-CoV-2. Notably, clusters of outbreaks in family and other communities such as office buildings or shopping malls is a frightening phenomenon of SARS-CoV-2 infection. The high transmissibility of SARS-CoV-2 may be linked to the viability and stability of the coronavirus in different environments, which is often overlooked by the general public. Table 2 summarizes the duration of survival for SARS-CoV-2, SARS-CoV, and MERS-CoV on the surfaces of different materials. SARS-CoV-2 can survive for several hours in aerosols and up to days on surfaces of plastic, stainless steel, copper and cardboard at temperature of 21-25 °C and 40% relative humidity. In comparison, MERS-CoV remained viable on different surfaces for 48 h at 20 °C and 40% relative humidity, while SARS-CoV can survive for 2 wk after drying, remaining viable for up to 5 d under similar conditions. The prolonged survival of these coronaviruses under various conditions increases the likelihood of contact and fomites transmission. Due to frequent contact with public facilities such as elevators and relatively closed spaces, SARS-CoV-2 can easily be transmitted in settings that have a defined population, especially in densely populated areas with poor sanitation.

EFFECT OF SOCIOECONOMIC STATUS ON THE TRANSMISSION

It is widely believed that people of lower socioeconomic status are in much worse physical health condition and at higher risk of premature mortality than those of higher socioeconomic status, mostly because most people with high socioeconomic status have a good educational background, basic health knowledge, and better healthcare services. Looking back at 2020 under the ravages of SARS-CoV-2, it is not hard to see that demographic and socioeconomic factors affect the spread of the virus. Data from the United States suggest that population density, gender ratio, low income and predominantly black communities are highly correlated with SARS-CoV-2-positive rates. To date, as a country with a large population, India has the second highest number of infections after the United States. In India, the undeveloped health care system and the lack of medical supplies including respiratory ventilators and protective equipment have weakened the government’s leadership and ability to respond to SARS-CoV-2 transmission. Strict social distancing measures and the lockdown of workplaces decrease the social labor force and put people at risk of unemployment, so vulnerable groups with financial difficulties may neglect to comply with physical distance measures because they need to work to survive, thereby increasing the risk of SARS-CoV-2 transmission. Conversely, a heavy medical burden has also led to severe economic recession and crisis. The rise in healthcare costs and drug prices have increased barriers for people with chronic and complex diseases, making this group of people at high risk of infection and disease progression during COVID-19 outbreaks. Additionally, the rapid progress of COVID-19 has exposed a serious problem that the majority of the world lack basic health care knowledge when facing infectious disease, for which they paid a painful price for their irrational and blind behavior, even in developed European countries.

STRATEGIES TO REDUCE THE RISK OF TRANSMISSION

At the peak of the epidemic, non-drug interventions, such as maintaining social distance and wearing masks, have shown considerable effectiveness. Although the outbreak gradually subsided in China, given the uncontrolled epidemic and current lack of confirmed effective treatments and vaccines for SARS-CoV-2, continuous prevention still depends heavily on compliance with public health measures. First, more attention should be paid to the hand hygiene of staff in hospital and they should be urged to clean their hands in the right way at the right time. Optimized hospital and community management system are urgently needed to centralize the management of confirmed and suspected cases, thereby reducing the spread of the virus to healthy people. All medical staff involved in the management should be equipped with standard PPE including gloves, gowns, eye shields, and N95.
| Ref.   | Year | Location | Virus | Load applied (TCID\(_{50}\)) | Substrate (s) | Temperature/RH | Viability | Reduction in infectious titer (TCID\(_{50}\)) | Half-life |
|--------|------|----------|-------|-------------------------------|--------------|----------------|-----------|-----------------------------------------------|-----------|
| van Doremalen et al\([78]\) | 2020 | United States | SARS-CoV-2, SARS-CoV | SARS-CoV-2: 10\(^{3.25}\) in aerosols, SARS-CoV-10 \(6.75-7.00\) in aerosols | Aerosols, plastic, stainless steel, copper, cardboard | 21-23°C/40% | Viable SARS-CoV-2 detected after 3 h in aerosols, no viable SARS-CoV-2 detected after 4 h on copper and 24 h on cardboard, stable after 72 h on plastic and stainless steel; no viable SARS-CoV detected after 8 h on copper and 8 h on cardboard | SARS-CoV-2: from 10\(^{1.3}\) to 10\(^{2.7}\) in aerosols, from 10\(^{3.7}\) to 10\(^{6.8}\) after 72 h on plastic, from 10\(^{3.0}\) to 10\(^{6.8}\) after 48 h on stainless steel; SARS-CoV: from 10\(^{3.4}\) to 10\(^{6.4}\) after 72 h on plastic, from 10\(^{3.6}\) to 10\(^{6.6}\) after 48 h on stainless steel | SARS-CoV-2 :1.1 h in aerosols, 6.8 h on plastic, 5.6 h on stainless steel, 0.8 h on copper, 3.5 h on cardboard; SARS-CoV :1.2 h in aerosols, 7.6 h on plastic, 4.2 h on stainless steel, 1.5 h on copper, 0.6 h on cardboard |
| van Doremalen et al\([80]\) | 2013 | United States | MERS-CoV | MERS-CoV tested after 48 h at 20°C/40% RH, 8 h at 30°C/80% RH and 24 h at 30°C/30% RH | Aerosols, steel, plastic | Variable | The viability of MERS-CoV decreased 7% at 40% RH and 89% at 70% RH in aerosols; Viable MERS-CoV tested after 48 h at 20°C/40% RH, 8 h at 30°C/80% RH and 24 h at 30°C/30% RH | The reduction in infectious titer was similar in solution compared with virus dried on surfaces | NA |
| Chan et al\([79]\) | 2011 | Hong Kong, China | SARS-CoV | 10\(^{3}\) on plastic | Plastic | Variable | SARS-CoV survived for 5 d at 22-25 °C relative humidity of 40%-50% with only 1 log10 loss of titer and was viable for more than 20 d; SARS-CoV was more stable at relatively low temperatures (28 °C vs 38 °C) and humidity (80%-89% vs > 95%) | SARS-CoV-2 :1.1 h in aerosols, 6.8 h on plastic, 5.6 h on stainless steel, 0.8 h on copper, 3.5 h on cardboard; SARS-CoV :1.2 h in aerosols, 7.6 h on plastic, 4.2 h on stainless steel, 1.5 h on copper, 0.6 h on cardboard |
| Rabenau et al\([82]\) | 2005 | Germany | SARS-CoV | NA | Polystyrene petri dish | Room temperature (21-25 °C) | SARS-CoV survived for more than 6 d and retained its infectivity for up to 9 d | The half-life of MERS-CoV ranged from 0.6 to 1 h on steel and from 0.4 to 1 h on plastic | NA |
| Lai et al\([83]\) | 2005 | Hong Kong, China | SARS-CoV | NA | Paper, disposable gowns, cotton gowns | Room temperature | SARS-CoV survived no more than 5 min to 24 h on paper, 1 h to 2 d on disposable clothing, and 5 min to 24 h on cotton clothing | The half-life of MERS-CoV: Middle East respiratory syndrome coronavirus; RH: Relative humidity; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. |
| Duan et al\([81]\) | 2003 | China | SARS-CoV | NA | Wood board, glass, mosaic, metal, cloth, paper, filter paper, plastic | Room temperature | SARS-CoV survived for > 72 h on the surfaces of eight materials, and > 120 h on metal, cloth and filter paper | NA |

MERS-CoV: Middle East respiratory syndrome coronavirus; RH: Relative humidity; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.
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### Table 3 Measures to prevent the transmission of severe acute respiratory syndrome coronavirus 2

| Measures to prevent SARS-CoV-2 transmission |
|---------------------------------------------|
| Strengthen the environmental hygiene of the medical sector and the personal hygiene of medical staff |
| Standardize the management procedures for confirmed and suspected cases to reduce nosocomial transmission |
| Equip health-care workers with PPE to protect their safety |
| Strictly assess hospitalization criteria and limit nonessential visits |
| Increase public awareness and education on infectious diseases and measures to prevent the spread of diseases on an individual basis |
| Enhance supervision and management of the flow of people in public places to reduce large-scale gatherings |

PPE: Personal protective equipment; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Public facilities, which are effective in controlling clusters outbreak. Finally, in the fight against SARS-CoV-2, apart from the external factors, self-resistance and personal immunity are essential to defeat this global pandemic[^100,101]. Individuals must actively implement and comply with control strategies issued by sanitary authorities to strengthen personal protection including wearing a mask, developing a healthy lifestyle, and social distancing.

**CONCLUSION**

The prevalence of SARS-CoV in 2003, MERS-CoV in 2012 and now SARS-CoV-2 suggests that coronaviruses in the natural environment may pose a lasting threat to humans, for which people worldwide have paid a huge cost, and it remains unknown whether this will be the last. In view of the current pandemic, it is reasonably speculated that SARS-CoV-2, as an emerging coronavirus, is likely to establish a stable environment suitable for living in organisms and coexist with humans for a long time[^102]. With the gradual recovery of normal work, study and medical care, it is essential to accurately estimate the contribution of asymptomatic carriers to SARS-CoV-2 transmission[^103,104]. Meanwhile, although it is not clear whether SARS-CoV-2 transmission will be seasonal or year-round[^105], the strong sense of crisis aroused by this pandemic would promote the normalization of prevention and control measures.

Despite a great deal of studies trying to find the origin of SARS-CoV-2 and its molecular mechanism, our understanding of it is just the tip of the iceberg and several important questions on the epidemiology, pathogenesis and treatment of SARS-CoV-2 still remain unanswered (Table 4)[^106-108]. Although SARS-CoV-2 might be transmitted from bats via unknown intermediate hosts to infect humans, whether or not currently available existing animal models can accurately reflect the process of human infection with the virus remains to be determined[^109]. In addition, a series of major medical, economic and psychological problems caused by the rapid spread of SARS-CoV-2 need the cooperation of all mankind to solve[^110,111]. Relevant health authorities should maintain surveillance, release the latest situation of the epidemic timely and respond scientifically.
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Unanswered questions about SARS-CoV-2

Where does SARS-CoV-2 really originated from and how does it affect humans?

Will the spread of SARS-CoV-2 be a seasonal outbreak?

Why is the prevalence of SARS-CoV-2 infection lower in children than in adults?

Is the infectivity of a patient positively related to the severity of the disease?

What is the proportion of asymptomatic carriers worldwide and what role do they play in transmission?

Can animal experiments find out the specific pathogenesis of SARS-CoV-2 infection?

How does SARS-CoV-2 invade other organs than the lung?

What is the probability that a cured patient is re-infected with SARS-CoV-2?

How long will it take to develop effective vaccine or medicine against SARS-CoV-2?

What is the infectivity of a patient positively related to the severity of the disease?

Why is the prevalence of SARS-CoV-2 infection lower in children than in adults?

Will the spread of SARS-CoV-2 be a seasonal outbreak?

Table 4 Unanswered questions about severe acute respiratory syndrome coronavirus 2

| Unanswered questions about SARS-CoV-2 |
|---------------------------------------|
| Where does SARS-CoV-2 really originated from and how does it affect humans? |
| Will the spread of SARS-CoV-2 be a seasonal outbreak? |
| Why is the prevalence of SARS-CoV-2 infection lower in children than in adults? |
| Is the infectivity of a patient positively related to the severity of the disease? |
| What is the proportion of asymptomatic carriers worldwide and what role do they play in transmission? |
| Can animal experiments find out the specific pathogenesis of SARS-CoV-2 infection? |
| How does SARS-CoV-2 invade other organs than the lung? |
| What is the probability that a cured patient is re-infected with SARS-CoV-2? |
| How long will it take to develop effective vaccine or medicine against SARS-CoV-2? |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020; 395: 470-473 [PMID: 31986257 DOI: 10.1016/S0140-6736(20)30185-9]

3. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report. [cited December 12, 2020]. Updated 2020

4. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C. From SARS to MERS, Thrusting Coronaviruses into the Spotlight. Viruses 2019; 11 [PMID: 30646565 DOI: 10.3390/v11010059]

5. Hui DS. Epidemic and Emerging Coronaviruses (Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome). Clin Chest Med 2017; 38: 71-86 [PMID: 28159163 DOI: 10.1016/j.ccm.2016.11.007]

6. Deng SQ, Peng HJ. Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China. J Clin Med 2020; 9 [PMID: 32093211 DOI: 10.3390/jcm9020575]

7. Jiang S, Du L, Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect 2020; 9: 275-277 [PMID: 32605086 DOI: 10.1008/jemr9020575]

8. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. Nature 2020, 579: 265-269 [PMID: 32015508 DOI: 10.1038/s41586-020-0208-3]

9. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma M, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020; 382: 1199-1207 [PMID: 31995857 DOI: 10.1056/NEJMoa2001316]

10. World Health Organization. IHR Procedures concerning public health emergencies of international concern (PHEIC). [cited April 30, 2020]. Available from: https://www.who.int/ihr/procedures/pheic/en/

11. Worobey M, Pekar J, Larsen BB, Nelson MI, Hill V, Joy JB, Rambaut A, Suchard MA, Wertheim JO, Lemey P. The emergence of SARS-CoV-2 in Europe and North America. Science 2020; 370: 564-570 [PMID: 32912998 DOI: 10.1126/science.abc8169]

12. Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, Whittaker C, Zhu H, Berah T, Eaton JW, Monod M; Imperial College COVID-19 Response Team; Ghani AC; Donnelly CA; Riley S; Vollmer MAC; Ferguson NM; Okell LC; Bhatt S. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature 2020; 584: 257-261 [PMID: 32512579 DOI: 10.1038/s41586-020-2405-7]

13. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; 395: 1225-1228 [PMID: 32178769 DOI: 10.1016/S0140-6736(20)30627-9]

14. Kapata N, Ihekweazu C, Ntoumi F, Raji T, Chanda-Kapata P, Mwaba P, Mukonkwa V, Bates M, Tembo J, Corman V, Mfinanga S, Asogun D, Elton L, Arruda LB, Thomason MJ, Mboera L, Yavlinsky A, Haider N, Simons D, Hollmann L, Lule SA, Veas F, Abdel Hamid MM, Dar O,
Edwards S, Vairo F, McHugh TD, Drosten C, Kock R, Ippolito G, Zumbà A. Is Africa prepared for tackling the COVID-19 (SARS-CoV-2) epidemic. Lessons from past outbreaks, ongoing pan-African public health efforts, and implications for the future. *Int J Infect Dis* 2020; 93: 233-236 [PMID: 32119980 DOI: 10.1016/j.ijid.2020.02.049]

15 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

16 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

17 **Su S**, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y, Gao GF. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. *Trends Microbiol* 2016; 24: 490-502 [PMID: 27021512 DOI: 10.1016/j.tim.2016.03.003]

18 **Hu B**, Zeng LP, Yang XL, Ge XY, Zhang W, Li B, Xie JZ, Shan XR, Zhang YZ, Wang N, Luo DS, Zheng XS, Wang MN, Daszk P, Wang LF, Cui J, Shi ZL. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLoS Pathog* 2017; 13: e1006698 [DOI: 29190287 DOI: 10.1371/journal.ppat.1006698]

19 **Foroni D**, Caglioni R, Clerici M, Sironi M. Molecular Evolution of Human Coronavirus Genomes. *Trends Microbiol* 2017; 25: 35-48 [PMID: 27743730 DOI: 10.1016/j.tim.2016.09.001]

20 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhi Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang L, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang Y, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-1217-7]

21 **Liu P**, Chen W, Chen JP. Viral Metagenomics Revealed Sendai Virus and Coronavirus Infection of Malayan Pangolins (*Manis javanica*). *Viruses* 2019; 11 [PMID: 31652964 DOI: 10.3390/v11110979]

22 **Zhang T**, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. *Curr Biol* 2020; 30: 1346-1351.e2 [PMID: 32197085 DOI: 10.1016/j.cub.2020.03.022]

23 **Xiao K**, Zhai J, Feng Y. Isolation and Characterization of 2019-nCoV-like Coronavirus from Malayan Pangolins. *bioRxiv* 2020.02.17. 951335 [DOI: 10.1101/2020.02.17.951335]

24 **Shi J**, Wen Z, Zhong G, Yang H, Wang C, Huang B, Liu R, He X, Shuai L, Sun Z, Zhao Y, Liu P, Liang L, Cui P, Wang J, Zhang X, Guan Y, Tan W, Wu G, Chen H, Bu Z. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. *Science* 2020; 368: 1016-1020 [PMID: 32269068 DOI: 10.1126/science.abb7015]

25 **Wan Y**, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol* 2020; 94 [PMID: 31996437 DOI: 10.1128/JVI.00127-20]

26 **Andersen KG**, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med* 2020; 26: 450-452 [PMID: 32284615 DOI: 10.1038/s41591-020-0820-9]

27 **Hou YJ**, Okuda K, Edwards CE, Martinez DR, Asakura T, Dinnon KH 3rd, Kato T, Lee RE, Yount BL, Macsenik TM, Chen G, Olivier KN, Ghio A, Tse LV, Leist SR, Graiinski LE, Schäfer A, Dang H, Gilmore R, Nakano S, Sun L, Fulcher ML, Livraghi-Butrico A, Nicely NI, Cameron M, Cameron C, Kelvin DJ, de Silva A, Margolis DM, Markmann A, Bartelt L, Zumwalt R, Martinez FJ, Salvatore SP, Borchuk A, Tata PR, Sontake V, Kipple M, Jaspers I, O’Neal WK, Randell SH, Boucher RC, Baric RS. SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. *Cell* 2020; 182: 429-446.e14 [PMID: 32526206 DOI: 10.1016/j.cell.2020.05.042]

28 **Teuwen LA**, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020; 20: 389-391 [PMID: 32439870 DOI: 10.1038/s41591-020-0434-0]

29 **Deng B**, Xie S, Wang J, Xia Z, Nie R. Inhibition of protein kinase C β2 prevents tumor necrosis factor-α-induced apoptosis and oxidative stress in endothelial cells: the role of NADPH oxidase subunits. *J Vasce Res* 2012; 49: 144-159 [PMID: 22269198 DOI: 10.1159/000332337]

30 **Lei S**, Su W, Liu H, Xu J, Xie ZY, Yang QJ, Qiao X, Du Y, Zhang L, Xia Z. Nitroglycerine-induced nitrate tolerance compromises propofol protection of the endothelial cells against TNF-α: the role of PKCβ2 and NADPH oxidase. *Oxid Med Cell Longev* 2013; 2013: 678484 [PMID: 24396568 DOI: 10.1155/2013/678484]

31 **Jiang Y**, Zhou Z, Meng QT, Sun Q, Su W, Lei S, Xia Z, Xia ZY. Ginsenoside Rb1 Treatment Attenuates Pulmonary Inflammatory Cytokine Release and Tissue Injury following Intestinal Ischemia Reperfusion Injury in Mice. *Oxid Med Cell Longev* 2015; 2015: 843721 [PMID: 26161243 DOI: 10.1155/2015/843721]

32 **Yao W**, Li H, Luo G, Li X, Chen C, Yuan D, Chi X, Zia X, Hei Z. SERPINC1 ameliorates acute lung injury in liver transplantation through ERK1/2-mediated STAT3-dependent HO-1 induction. *Free Radic Biol Med* 2017; 108: 542-553 [PMID: 28427999 DOI: 10.1016/j.freeradbiomed.2017.04.011]

33 **Liu Q**, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol* 2016; 13: 3-10 [PMID: 26189369 DOI: ]
Liu Y. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool 2020; Li T, Xu G, Hu Q, Ding M, Li G, Zheng ZJ, Qiu SQ, Luo J. Clinical Characteristics of COVID-19 Patients With Severe and Critical COVID-19 Pneumonia. Li K. Characteristics of Coronavirus Disease 2019 in China. Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus-Infected Pneumonia in Wuhan, China. Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Wu Z, Zhang J, Huang S, Yao X, Zhou Y, Wang C, Zhang D, Wang G, Liu L, Bian XW. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Xu Z. Pulmonary pathology of early-phase COVID-19 pneumonia in a patient with a benign lung lesion. Zeng Z, Xu L, Xie XY, Yan HL, Xie BJ, Xue W, Liu XA, Kang GJ, Jiang WL, Yuan JP. Pulmonary pathology of early-phase COVID-19 pneumonia in a patient with a benign lung lesion. Histopathology 2020; 77: 823-831 [PMID: 32374419 DOI: 10.1111/his.14138] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zou L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X] Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. Eur Heart J 2020; 41: 3827-3835 [PMID: 32968776 DOI: 10.1093/eurheartj/ehaa664] Liu Q, Shi Y, Cai J, Duan Y, Wang R, Zhang H, Ruan Q, Li J, Zhao L, Ping Y, Chen R, Ren L, Fei X, Zhang H, Tang R, Wang X, Luo T, Liu X, Huang X, Liu Z, Ao Q, Ren Y, Xiong J, He Z, Wu H, Fu W, Zhao P, Chen X, Qu G, Wang Y, Wang X, Liu J, Xiang D, Xu S, Zhou X, Li Q, Ma J, Li H, Zhang J, Huang S, Yao X, Zhou Y, Wang C, Zhang D, Wang G, Liu L, Bian XW. Pathological changes in the lungs and lymphatic organs of twelve COVID-19 autopsy cases. Natl Sci Rev 2020; 7: 1868-1878 [DOI: 10.1093/nsr/nwa2247] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648] Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, Ling Y, Jiang Y, Shi Y. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020; 295: 210-217 [PMID: 32027573 DOI: 10.1148/radiol.2020200274] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069 [PMID: 32305170 DOI: 10.1001/jama.2020.1583] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa200232] Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. Invest Radiol 2020; 55: 327-331 [PMID: 32118615 DOI: 10.1097/RLI.0000000000000672] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol 2020; 115: 766-773 [PMID: 32287140 DOI: 10.14309/agj.0000000000000620] Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, Zhang L, Lin R, Liu J, Ding Z, Hou X. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. Am J Gastroenterol 2020; 115: 916-923 [PMID: 32301761 DOI: 10.1038/s41395-020-03836-1] Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher...
compared to SARS coronavirus. *J Travel Med* 2020; 27 [PMID: 32052846 DOI: 10.1093/jtm/taaa021]

51 Lauk SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med* 2020; 172: 377-382 [PMID: 32150748 DOI: 10.7326/M20-0504]

52 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475-481 [PMID: 32105632 DOI: 10.1016/s2213-2600(20)30079-5]

53 Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. *PLoS Med* 2020; 17: e1003321 [PMID: 32911500 DOI: 10.1371/journal.pmed.1003321]

54 Kontis V, Mathers CD, Bonita R, Stevens GA, Rehm J, Shield KD, Riley LM, Poznyak Y, Jabbour S, Garg RM, Hennis A, Fouda HM, Beaglehole R, Ezzati M. Regional contributions of six preventable risk factors to achieving the 25 × 25 non-communicable disease mortality reduction target: a modelling study. *Lancet Glob Health* 2015; 3: e746-e757 [PMID: 26497599 DOI: 10.1016/S2214-109X(15)00179-5]

55 Richardson CR, Franklin B, Moy ML, Jackson EA. Advances in rehabilitation for chronic diseases: improving health outcomes and function. *BMJ* 2019; 365: i2191 [PMID: 3120954 DOI: 10.1136/bmj.i2191]

56 Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020: e3319 [PMID: 32330313 DOI: 10.1002/dmr.3319]

57 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

58 Li L, Zhang B, He B, Gong Z, Chen J. Critical patients with coronavirus disease 2019: Risk factors and outcome nomogram. *J Infect* 2020; 80: e37-e38 [PMID: 32272120 DOI: 10.1016/j.jinf.2020.03.025]

59 Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternalmed.2020.0994]

60 Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, Zhan L, Yi J, Zhang L, Liu D, Xia ZY, Xia Z. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine* 2020; 21: 100331 [PMID: 32292899 DOI: 10.1016/j.eclinm.2020.100331]

61 COVID Surg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet* 2020; 396: 27-38 [PMID: 32479829 DOI: 10.1016/S0140-6736(20)31182-X]

62 Schilling T, Kozian A, Kretzschmar M, Huth C, Welte T, Bühling F, Hedenstierna G, Hachenberg T. Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. *Br J Anaesth* 2007; 99: 368-375 [PMID: 17621602 DOI: 10.1093/bja/aem184]

63 Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubes P, Lilford RJ. The systemic immune response to trauma: an overview of pathophysiology and treatment. *Lancet* 2021; 384: 1455-1465 [PMID: 25390327 DOI: 10.1016/S0140-6736(14)60867-5]

64 Rossaint J, Zarbock A. Perioperative Inflammation and Its Modulation by Anesthetics. *Anesth Analg* 2018; 126: 1058-1067 [PMID: 29222235 DOI: 10.1221/ane.0000000000002484]

65 Nazer RI. Outbreak of Middle East Respiratory Syndrome-Coronavirus Causes High Fatality After Cardiac Operations. *Ann Thorac Surg* 2017; 104: e127-e129 [PMID: 28734432 DOI: 10.1016/j.athoracsur.2017.02.072]

66 Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, Renz H, Liu X, Xie J, Xie M, Zhao J. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020; 146: 110-118 [PMID: 32294485 DOI: 10.1016/j.jaci.2020.04.006]

67 Ji HL, Zhao R, Matalon S, Matthey MA. Elevated Plasmin(ogen) as a Common Risk Factor for COVID-19 Susceptibility. *Physiol Rev* 2020; 100: 1065-1075 [PMID: 32216698 DOI: 10.1152/physrev.00013.2020]

68 Houlihan CF, Vora N, Byrne T, Lewer D, Kelly G, Heaney J, Gandhi S, SPyer MJ, Beale R, Cherepanov P, Moore D, Gilson R, Gamblin S, Kassiotis G, McCoy LE, Swanton C; Crick COVID-19 Consortium; Hayward A; Nastoulai E; SAFER Investigators. Pandemic peak SARS-CoV-2 infection and seroconversion rates in London frontline health-care workers. *Lancet* 2020; 396: e6-e7 [PMID: 32653078 DOI: 10.1016/S0140-6736(20)31484-7]

69 Public Health Ontario. COVID-19 — what we know so far about routes of transmission. 2020. 1: 14. [cited July 24, 2020]. Available from: https://www.publichealthontario.ca/
Li X et al. Risk factors for SARS-CoV-2 transmission

/mediadocuments/ncov/wkksf-routes-transmission-mar-06-2020.pdf?la=en. opens in new tab

70 Calò F, Russo A, Camaioni C, De Pascalis S, Coppola N. Burden, risk assessment, surveillance and management of SARS-CoV-2 infection in health workers: a scoping review. Infect Dis Poverty 2020; 9: 139 [PMID: 33028400 DOI: 10.1186/s40249-020-00756-6]

71 Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, Marimuthu K. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA 2020; 333: 1610-1612 [PMID: 32129805 DOI: 10.1001/jama.2020.3227]

72 Ye G, Lin H, Chen S, Wang S, Zeng Z, Wang W, Zhang S, Rehmann T, Li Y, Pan Z, Yang Z, Wang Y, Wang F, Qian Z, Wang X. Environmental contamination of SARS-CoV-2 in healthcare premises. J Infect 2020; 81: e1-e5 [PMID: 32360881 DOI: 10.1016/j.jinf.2020.04.034]

73 Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk Factors of Healthcare Workers With Coronavirus Disease 2019: A Retrospective Cohort Study in a Designated Hospital of Wuhan in China. Clin Infect Dis 2020; 71: 2218-2221 [PMID: 32179890 DOI: 10.1093/cid/ciaa287]

74 Nishiura H, Linton NM, Akhmetzhanov AR. Initial Cluster of Novel Coronavirus (2019-nCoV) Infections in Wuhan, China Is Consistent with Substantial Human-to-Human Transmission. J Clin Med 2020; 9 [PMID: 32054045 DOI: 10.3390/jcm9020294]

75 Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsai HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus during person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-523 [PMID: 31986261 DOI: 10.1016/S0140-6736(20)31054-9]

76 Huang R, Xia J, Chen Y, Shan C, Wu C. A family cluster of SARS-CoV-2 infection involving 11 patients in Nanjing, China. Lancet Infect Dis 2020; 20: 534-535 [PMID: 32119823 DOI: 10.1016/S1473-3099(20)30147-X]

77 Pan X, Chen D, Xia Y, Wu X, Li T, Ou X, Zhou L, Liu J. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. Lancet Infect Dis 2020; 20: 410-411 [PMID: 32087116 DOI: 10.1016/S1473-3099(20)30114-6]

78 van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. Adv Virol 2020; 2005; 1-6 [PMID: 32179823 DOI: 10.1155/2020/734690 DOI: 10.1186/s40249-020-00756-6]

79 van Doremalen N, Bushmaker T, Munster VJ. Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. Euro Surveill 2013; 18 [PMID: 24084338 DOI: 10.2807/1560-7917.es2013.18.38.20590]

80 Duan SM, Zhao XS, Lin H, Chen S, Wang S, Zeng Z, Wang W, Zhang S, Rebmann T, Li Y, Pan Z, Yang Z, Wang Y, Wang F, Qian Z, Wang X. Environmental contamination of SARS-CoV-2 in healthcare premises. J Infect 2020; 81: e1-e5 [PMID: 32360881 DOI: 10.1016/j.jinf.2020.04.034]

81 Lai MY, Cheng PK, Lim WW. Survival of severe acute respiratory syndrome coronavirus. Clin Infect Dis 2005; 41: e67-e71 [PMID: 16142653 DOI: 10.1086/433186]

82 Yuan J, Chen Z, Gong C, Liu H, Li B, Li K, Chen X, Xu C, Jing Q, Liu G, Qin P, Liu Y, Zhong Y, Huang L, Zhu BP, Yang Z. Sewage as a Possible Transmission Vehicle During a Coronavirus Disease 2019 Outbreak in a Densely populated Community: Guangzhou, China, April 2020. J Infect Dis 2020; 32182409 DOI: 10.1056/NEJMec2004973

83 Chan KH, Peiris JS, Lam SY, Poon LL, Yuen KY, Seto WH. The Effects of Temperature and Relative Humidity on the Viability of the SARS Coronavirus. Adv Virol 2011; 2011: 734690 [PMID: 22312351 DOI: 10.1155/2011/734690]

84 van Doremalen N, Bushmaker T, Munster VJ. Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. Euro Surveill 2013; 18 [PMID: 24084338 DOI: 10.2807/1560-7917.es2013.18.38.20590]

85 Duan SM, Zhao XS, Lin H, Chen S, Wang S, Zeng Z, Wang W, Zhang S, Rebmann T, Li Y, Pan Z, Yang Z, Wang Y, Wang F, Qian Z, Wang X. Environmental contamination of SARS-CoV-2 in healthcare premises. J Infect 2020; 81: e1-e5 [PMID: 32360881 DOI: 10.1016/j.jinf.2020.04.034]

86 Liu MY, Cheng PK, Lim WW. Survival of severe acute respiratory syndrome coronavirus. Clin Infect Dis 2005; 41: e67-e71 [PMID: 16142653 DOI: 10.1086/433186]

87 Yuan J, Chen Z, Gong C, Liu H, Li B, Li K, Chen X, Xu C, Jing Q, Liu G, Qin P, Liu Y, Zhong Y, Huang L, Zhu BP, Yang Z. Sewage as a Possible Transmission Vehicle During a Coronavirus Disease 2019 Outbreak in a Densely populated Community: Guangzhou, China, April 2020. J Infect Dis 2020; 32182409 DOI: 10.1056/NEJMec2004973

88 Kivimäki M, Batty GD, Pentti J, Shipley MJ, Sipilä PN, Nyberg ST, Suominen SB, Oksanen T, Stenholm S, Virtanen M, Marmot MG, Singh-Manoux A, Brunner EJ, Lindbohm JV, Ferrie JE, Vahtera J. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. Lancet Public Health 2020; 5: e140-e149 [PMID: 32007134 DOI: 10.1016/S2468-2667(19)30248-8]

89 The Lancet Public Health. Income, health, and social welfare policies. Lancet Public Health 2020; 5: e127 [PMID: 32135154 DOI: 10.1016/S2468-2667(20)30034-7]

90 Whittle RS, Diaz-Artiles A. An ecological study of socioeconomic predictors in detection of COVID-19 cases across neighborhoods in New York City. BMC Med 2020; 18: 271 [PMID: 32883276 DOI: 10.1186/s12916-020-01731-6]

91 Guha A, Bonu J, Dey A, Addison D. Community and Socioeconomic Factors Associated with COVID-19 in the United States: Zip code level cross sectional analysis. medRxiv 2020 [PMID: 32511646 DOI: 10.1101/2020.04.19.20071944]

92 Chetterje P. Gaps in India's preparedness for COVID-19 control. Lancet Infect Dis 2020; 20: 544 [PMID: 32311328 DOI: 10.1016/S1473-3099(20)30300-5]

93 The Lancet. COVID-19 in India: the dangers of false optimism. Lancet 2020; 396: 867 [PMID: 32979962 DOI: 10.1016/S0140-6736(20)32001-8]

94 Raffman MA, Raffman JR. Disparities in the Population at Risk of Severe Illness From COVID-19 by Race/Ethnicity and Income. Am J Prev Med 2020; 59: 137-139 [PMID: 32430225 DOI: 10.1016/j.amepre.2020.03.020]
The 2019 novel coronavirus outbreak is urgently needed. Xiang YT, Psychiatry Duan L [PMID: Chan JFW, García-Sastre A, Neyts J, Perlman S, Reed DS, Richt JA, Roy CJ, Segalés J, Vasan SS, Salguero FJ, Schotsaert M, Stittelaar KJ, Thibaut HJ, Tseng CT, Vergara-Alert J, Beer M, Brasel T, Munster V, Oreshkova N, Rasmussen AL, Rocha-Pereira J, Rockx B, Rodríguez E, Rogers TF, Andersen H, Baric RS, Carroll MW, Cavaleri M, Qin C, Crozier I, Dallmeier K, de Waal L, de Wit DOI: 10.1016/j.tmaid.2020.101619

Recovered From COVID-19. Lan L [PMID: 10.1001/jama.2020.2565

Transmission of COVID-19. Bai Y Med [PMID: 10.1001/jama.2020.2789

perspective. Simpson RJ Infect Dis 2001; 200-202 [PMID: 10.1016/S2468-1253(20)30182-5

measures implemented in the severe acute respiratory syndrome outbreak in Beijing, 2003. JAMA 2003; 290: 3215-3221 [PMID: 14693874 DOI: 10.1001/jama.290.24.3215]

Infection control measures for operative procedures in severe acute respiratory syndrome-related patients. Anesthesiology 2004; 100: 1394-1398 [PMID: 15166557 DOI: 10.1097/00000542-200406000-00010]

Park J, Yoo SY, Ko JH, Lee SM, Chung YJ, Lee JH, Peck KR, Min JJ. Infection Prevention Measures for Surgical Procedures during a Middle East Respiratory Syndrome Outbreak in a Tertiary Care Hospital in South Korea. Sci Rep 2020; 10: 325 [PMID: 31941957 DOI: 10.1038/s41598-020-57216-x]

SARS safety and science. Can J Anaesth 2003; 50: 983-985, 985 [PMID: 14656774 DOI: 10.1007/BF03018360]

Barry A, Apsisanthanaras S, O’Kane GM, Sapisochin G, Beecroft R, Salem R, Yoon SM, Lim YS, Bridgewater J, Davidson B, Scorratti M, Solbiati L, Diehl A, Schuffenegger PM, Sham JG, Cavallucci D, Galvin Z, Dawson LA, Hawkins MA. Management of primary hepatic malignancies during the COVID-19 pandemic: recommendations for risk mitigation from a multidisciplinary perspective. Lancet Gastroenterol Hepatol 2020; 5: 765-775 [PMID: 32511951 DOI: 10.1016/S2468-1253(20)30182-5]

High KP. Nutritional strategies to boost immunity and prevent infection in elderly individuals. Clin Infect Dis 2001; 33: 1892-1900 [PMID: 11692301 DOI: 10.1086/324509]

Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the Regulation of Immune Functions. Prog Mol Biol Transl Sci 2015; 135: 355-380 [PMID: 2647922 DOI: 10.1016/bs.pmbts.2015.08.001]

The hallmarks of COVID-19 disease. PLoS Pathog 2020; 16: e1008536 [PMID: 32442210 DOI: 10.1371/journal.ppat.1008536]

Chunk M, Sothmann P, Bretzel G, Froschel G, Wallrauch C, Zimmer T, Thiel V, Janke C, Gugmemos W, Steilmaier M, Drosten C, Vollmarr P, Zwirglmaier K, Zange S, Wölfel R, Hoelscher M. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med 2020; 382: 970-971 [PMID: 32003351 DOI: 10.1056/NEJMca2001468]

Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, Wang M. Presumed Asymptomatic Carrier Measures for Surgical Procedures during a Middle East Respiratory Syndrome Outbreak in a Tertiary Care Hospital in South Korea. Sci Rep 2020; 10: 325 [PMID: 31941957 DOI: 10.1038/s41598-020-57216-x]

Park J, Yoo SY, Ko JH, Lee SM, Chung YJ, Lee JH, Peck KR, Min JJ. Infection Prevention Measures for Surgical Procedures during a Middle East Respiratory Syndrome Outbreak in a Tertiary Care Hospital in South Korea. Sci Rep 2020; 10: 325 [PMID: 31941957 DOI: 10.1038/s41598-020-57216-x]

SARS safety and science. Can J Anaesth 2003; 50: 983-985, 985 [PMID: 14656774 DOI: 10.1007/BF03018360]

Barry A, Apsisanthanaras S, O’Kane GM, Sapisochin G, Beecroft R, Salem R, Yoon SM, Lim YS, Bridgewater J, Davidson B, Scorratti M, Solbiati L, Diehl A, Schuffenegger PM, Sham JG, Cavallucci D, Galvin Z, Dawson LA, Hawkins MA. Management of primary hepatic malignancies during the COVID-19 pandemic: recommendations for risk mitigation from a multidisciplinary perspective. Lancet Gastroenterol Hepatol 2020; 5: 765-775 [PMID: 32511951 DOI: 10.1016/S2468-1253(20)30182-5]

High KP. Nutritional strategies to boost immunity and prevent infection in elderly individuals. Clin Infect Dis 2001; 33: 1892-1900 [PMID: 11692301 DOI: 10.1086/324509]

Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the Regulation of Immune Functions. Prog Mol Biol Transl Sci 2015; 135: 355-380 [PMID: 2647922 DOI: 10.1016/bs.pmbts.2015.08.001]

The hallmarks of COVID-19 disease. PLoS Pathog 2020; 16: e1008536 [PMID: 32442210 DOI: 10.1371/journal.ppat.1008536]

Chunk M, Sothmann P, Bretzel G, Froschel G, Wallrauch C, Zimmer T, Thiel V, Janke C, Gugmemos W, Steilmaier M, Drosten C, Vollmarr P, Zwirglmaier K, Zange S, Wölfel R, Hoelscher M. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med 2020; 382: 970-971 [PMID: 32003351 DOI: 10.1056/NEJMca2001468]
