COMMENTARY

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Pay attention to SARS-CoV-2 infection in children

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The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been prevalent for nearly two months. The first case of COVID-19 was reported in Wuhan, Hubei Province, China in mid-December, 2019. On January 9, 2020, Chinese scientists isolated and obtained the genome sequence of the new virus; they shared the genome information on relevant international websites one day later.[1,2] Announcement No. 1 of the National Health Commission of the People's Republic of China (on January 20, 2020) has categorized COVID-19 as a Class B infectious disease, in accordance with the Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases; however, the announcement urged public health authorities to undertake prevention and control appropriate for a Class A infectious disease.[3] As of January 31, 2020, there were 9720 confirmed cases of COVID-19 in China and a total of 9826 cases have been reported globally, involving 19 countries. WHO declared the outbreak to be a public health emergency of international concern on January 31 2020.[4] Thus far, the SARS-CoV-2 outbreak has not been well controlled and requires close attention.

Coronavirus (CoV) belongs to the family *Coronavirinae* of the order *Nidovirales*. Based on analysis of their genomic structure and phylogenetics, CoVs are divided into four genera: α, β, γ, and δ. Both α and β CoVs only infect mammals, whereas γ and δ CoVs mainly infect birds and rarely infect mammals. The genome of CoV is a complete single-stranded positive-sense RNA of approximately 30 kb in length, which is the largest of all RNA viruses. It also exhibits typical characteristics of RNA viruses, including a 5' cap and 3' poly-A tail.[5,6]

Based on currently available evidence, CoVs infecting humans include two α-CoVs (229E and NL63), and five β-CoVs (OC43, HKU1, Middle East respiratory syndrome coronavirus [MERS-CoV], severe acute respiratory syndrome coronavirus [SARS-CoV], and SARS-CoV-2).[5] SARS-CoV-2 is a new species of the β-coronavirus genera, which includes bat-SARS-like (SL)-CoV ZC45, bat-SL-CoV ZXC21, SARS-CoV, and, MERS-CoV. Phylogenetic analysis showed that SARS-CoV-2 is more closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21, whereas it is distantly related to SARS-CoV.[7] Current research has shown that SARS-CoV-2 came from wild animals, although its specific source requires further investigations.[5,7]

The currently reported cases of COVID-19 mainly occurred in adults, and there have been no large-scale studies of their clinical features.[8,9] Huang et al[8] described the clinical manifestations of disease in 41 hospitalized patients who were confirmed to have COVID-19; in these patients, Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea

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(one [3%] of 38). Dyspnoea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnoea 8.0 days [IQR 5.0–13.0]). Twenty-six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest computed tomography. Complications included acute respiratory distress syndrome (12 [29%]), RNAaemia (six [15%]), acute cardiac injury (five [12%]) and secondary infection (four [10%]). Thirteen (32%) patients were admitted to an ICU and six (15%) died. Notably, the proportion of critically ill patients and the case-fatality rate might have been biased in this report by Huang et al[8] due to its small sample size.

SARS-CoV-2 is a newly emerged virus that may have originated from wild animals, and further in-depth basic, clinical, and epidemiological research is necessary to identify and clarify its source, intermediate hosts, transmission routes and infectivity, susceptible populations, pathogenicity, and mortality.

Thus far, a notable feature is that only a small number of confirmed cases of SARS-CoV-2 infection have involved children.[10-12] Most patients with SARS-CoV-2 infection are middle-aged and elderly individuals; the majorities of patients who were critically ill and patients who died comprised frail older adults and individuals with underlying diseases. Importantly, the proportion of children with SARS-CoV-2 infection has been low. The virus enters human alveolar epithelial cells by binding to receptors on the cell surface and then replicates by using cellular components. Current research findings suggest that the expression levels of angiotensin-converting enzyme 2 (i.e., ACE2), which may serve as the SARS-CoV-2 receptor, do not differ among age groups.[13] Therefore, children are presumably equally susceptible to infection with SARS-CoV-2. Possible explanations for the lower rate of SARS-CoV-2 infections in children are as follows: a) children are less likely to be exposed to the virus, due to their daily activities; and b) pediatric patients did not undergo laboratory tests because of mild symptoms, leading to fewer laboratory-confirmed cases. Further observations are needed to test these hypotheses.

Another feature of SARS-CoV-2 infection in children is that their symptoms are mild or clinically absent. Importantly, cases of infection in children during the outbreaks of SARS-CoV in 2003 and MERS-CoV in 2012 were also characterized by low rates of infection, mild symptoms, and good prognosis.[14-16] Memish et al[15] summarized the clinical manifestations of disease in 11 pediatric patients who were diagnosed with MERS-CoV infection after close contact with infected family members. Two patients with underlying disease were symptomatic and the other nine patients were asymptomatic. No clinical manifestations were noted during 6 months of follow-up. The ability of a pathogen infection to cause severe illness and death mainly depends on the following factors: 1) Pathogenicity and virulence of the pathogen itself, which are the primary factors that determine whether a pathogen causes serious infection; for instance, Ebola virus and avian influenza A (H5N1) virus caused serious diseases in both children and adults.[17-19] 2) Genetic predisposition of the host. 3) Underlying disease and immune status of affected patients; for example, infants/young children and elderly patients are at high risk of infection with common respiratory viruses (e.g., influenza virus and respiratory syncytial virus) and are more likely to develop severe disease due to their relatively low/poor immune function and—particularly among elderly patients—the presence of underlying diseases.[20-22] 4) Co-existing or secondary bacterial infections; for example, influenza co-infection with *Streptococcus pneumoniae* and *Staphylococcus aureus* can easily cause severe illness.[23,24] 5) Accurate early diagnosis and rational treatment, which are important for prevention of critical illness; for example, early diagnosis of influenza and timely antiviral treatment within 48 hours of onset of symptoms can reduce the risk of severe illness.[25,26]

The causes of mild symptoms in children infected with SARS-CoV, MERS-CoV, or SARS-CoV-2 are unclear, and the following potential explanations require further research to determine their validity. The pathogenic mechanism of CoVs infection may be related to immune maturity; the immature immune system in children may prevent a strong response to some infections. For instance, primary Epstein-Barr virus (EBV) infection typically causes subclinical or mild disease in immunocompetent young children, but can cause typical infectious mononucleosis in older children, adolescents, and young adults.[27,28] However, children are more susceptible than adults to infection with respiratory virus (including OC43, a β-CoV) and enterovirus;[29-32] they are also inoculated with a variety of antiviral vaccines in accordance with immunization schedules. As a result, there are multiple high-titer antibodies in the blood of children, which may offer cross-protection against SARS-CoV-2 infection.

Because SARS-CoV-2 is an emerging virus, there is no specific antiviral treatment for the disease caused by this virus. Currently, the therapy of SARS-CoV-2 infection is symptomatic and supportive. Inhaled interferon-alpha and oral lopinavir/ritonavir are recommended as antiviral treatment by the National Health Committee of the People's Republic of China. Interferon-alpha may have potential benefits for patients infected with SARS-CoV-2, as it is a broad-spectrum antiviral drug. The efficacy and safety of lopinavir/ritonavir in the treatment of SARS-CoV-2 infection have not been supported by robust clinical evidence. For children with mild symptoms, lopinavir/ritonavir treatment is not recommended.

Overall, there remain many questions regarding SARS-CoV-2 infection, including its source, transmission

pathway, and pathogenic mechanism, as well as humoral and cellular immune responses of infected patients, clinical features, populations at high risk, and prognosis of infected patients. The potential for SARS-CoV-2 infection in children is of particular concern. Further investigation and research are needed to explore the reasons for the fewer number of cases and the mild clinical manifestations in children with SARS-CoV-2 infection. Further monitoring and research are also necessary to determine whether SARS-CoV-2 will eventually cease to cause disease in humans, similar to the outcome of the SARS-CoV outbreak, or whether it will remain an important source of infectious disease.

CONFLICT OF INTEREST

None.

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