Editorial

2019 novel coronavirus disease in children: an insight and the next steps forward

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Introduction

The ongoing outbreaks of coronavirus disease 2019 (COVID-19) pose a major threat to global health. Since the middle of January 2020, there have been a rapidly growing number of COVID-19 cases across China, and thousands more have now been confirmed in countries around the world. The disease was first reported in December 2019, when a cluster of pneumonia cases of unknown cause emerged in Wuhan, the capital city of Hubei province. On 9 January 2020, the Chinese Center for Disease Control and Prevention (CDC) reported that a novel coronavirus had been identified as the causative agent of the outbreak, which was provisionally named as "2019 novel coronavirus (2019-nCoV)" by the World Health Organization (WHO) (1). Based on the new virus having a genetic structure similar to that of the 2003 SARS coronavirus, on 11 February 2020, the name "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" was announced by the International Committee on Taxonomy of Viruses (2). WHO officially declared the emergence of the novel coronavirus as a public health emergency of international concern (PHEIC) on 30 January 2020 (3). By 21 February 2020, 76,288 confirmed cases had been reported in China, with 2,345 (2.0%) deaths, and 1,200 confirmed cases had been reported in 26 countries outside of China, including 8 deaths (4,5). Approximately 20% of COVID-19 cases in China have been clinically diagnosed as severe (6). However, children have been less commonly affected by COVID-19 than adults. Understanding the SARS-CoV-2 infection in children is important to guiding appropriate prevention and management strategies for the possible sustained transmission of COVID in the pediatric population.

Epidemiology and clinical manifestations

As of 27 January 2020, almost all of the 4,515 confirmed COVID-19 cases reported to China CDC were among adults, with children aged <15 years old accounting for only 0.6% of cases (7). However, with the enhanced surveillance of COVID-19 and the accessibility and availability of rapid genetic amplification assays, a growing number of pediatric cases with COVID-19 have been confirmed in Wuhan and other areas. Of the 44,672 confirmed cases reported by 11 February 2020, children aged 0–9 years old and teenagers aged 10–19 years old accounted for 0.9% and 1.2% of cases, respectively (6). Of the 257 confirmed pediatric cases, 69 (26.8%) had recently traveled to or from the endemic areas, and 183 (71.2%) had a history of household cluster exposure (8). Predictably, the transmission of COVID in children occurred predominantly in a household setting.

The major transmission pattern of COVID in children is similar to that of SARS and MERS (9,10). During the first wave of outbreaks, epidemiological exposure is a key clue to recognizing COVID-19 in children at an early stage. In our field investigation of 8 children with COVID, the mean incubation period between a child's household exposure to a symptomatic adult case and symptom onset was 6.5 days, longer than the 5.4 days observed in adult cases (11,12). More epidemiological data are needed to support our finding.

The first reported pediatric case of asymptomatic COVID-19 was a 10-year-old child, who contracted the infection in a family cluster of pneumonia in Shenzhen (13). The first reported pediatric case with symptomatic COVID-19 was a 7-year-old child from Shanghai who developed mild acute respiratory infection after close contact

with his father and was confirmed with COVID-19 (14). Preliminary clinical data summarized by the Society of Pediatrics of the Chinese Medical Association and case series reports showed that the clinical manifestations of COVID-19 are usually milder in children than in adults (8,15,16). Among the 134 confirmed pediatric cases, 9 (6.7%) were asymptomatic, 87 (64.9%) presented with mild upper respiratory infection, 36 (26.9%) presented with non-severe pneumonia, and 2 (1.5%) critically severe cases with comorbidity survived after receiving mechanical ventilation and supportive care (8). Among the 117 confirmed cases for whom detailed clinical data were available, 89 (76.1%) children experienced a fever, with the duration of the fever usually lasting for 1-2 days, and a cough was also a common symptom. Other symptoms included fatigue, myalgia, a stuffy nose, rhinorrhea, headache, dizziness, nausea, vomiting, abdominal pain, and diarrhea. The disease usually resolved within 1 week after disease onset (8).

The laboratory findings of the majority of pediatric patients have revealed normal or slightly decreased white blood cell count, normal C-reactive protein (CRP) and procalcitonin (PCT) (8,12). At the earliest stage of infection, the radiographic characteristics of COVID-19 show small nodular ground-glass opacities or unilateral patchy infiltrate (8,17). The latest literature reported a critically severe case of COVID-19 that occurred in a 1-year-old child, who presented with intermittent fever, dyspnea, and oliguria 3 days after the resolution of diarrhea and vomiting. A CT scan revealed mixed diffused ground-glass opacification and consolidation in the right lung (18). This case serves as a warning to pediatricians to stay alert to the possibility of atypical severe COVID-19 in children and the potential role of chest radiographs, especially CT, in helping with the timely identification of COVID-19.

Compared with SARS in children, pneumonia caused by SARS-CoV-2 is milder in its clinical and radiographic characteristics (9). Three neonates have been confirmed with SARS-CoV-2 infection based on virus RNA detected in throat swab samples (8,19,20). Among these cases, 1 neonate, who was 17 days old, contracted the infection 3 days after her mother developed the symptoms of COVID-19 (19), and the other 2 neonates, who were born to mothers with COVID, were confirmed with SARS-CoV-2 infection (1 developed a fever 5 days after birth and the other was asymptomatic) (8,20). However, there was no definitive etiological evidence to suggest mother-to-infant vertical transmission.

Diagnosis

Validated point-of-care real-time reverse transcription-polymerase chain reaction (RT-PCR) diagnostic tests specific for 2019-nCoV became available soon after the full genome sequence data of 2019-nCov was officially shared (21). Because the availability of diagnostic tools is limited and laboratory biosafety needs to be strictly implemented at all times, most diagnostic testing for SARS-CoV-2 is presently conducted at CDC reference laboratories. There are also some designated hospitals that have specific SARS-CoV-2 detection capacity, where RT-PCR can be conducted with approved commercial kits. All suspected COVID cases are required to be screened for SARS-CoV-2 by PCR assay and are laboratory-confirmed based only on the results of the local CDC reference laboratory. If respiratory, blood, or stool samples obtained from suspected patients test positive for both the ORF1ab gene and the nucleocapsid protein gene of SARS-CoV-2, the specimen is considered as positive and the case is considered to be laboratory-confirmed (22,23). To ensure the quality of respiratory samples, we recommend sampling both a nasopharyngeal swab and a throat swab for the initial PCR screen to reduce the false negative result, and both a respiratory swab and a lower respiratory secretion should be collected to conduct a PCR test on patients with suspected pneumonia.

Since 15 January 2020, the case definition for suspected COVID has been revised constantly, based on updates on the clinical information and the epidemiological situation from the expert working group of the National Health Commission of China. Before 28 January 2020, suspected cases had to display the radiological features of COVID-like pneumonia and a history of epidemiological exposure during the 14 days prior to symptom onset. Since 28 January 2020, the radiological characteristic of COVID-like pneumonia has not been considered essential for COVID to be suspected, and, since 4 February, nor has a history of epidemiological exposure. Since screening for suspected COVID was initiated across the country, either acute fever or acute respiratory symptoms have been considered as the warning signs for a suspected pediatric case who has a clear history of epidemiological exposure. This is based on both the initial observations of COVID in officially reported pediatric cases and observations of influenza and other viral respiratory infections in children. Due to the high vigilance with which pediatric professionals have approached COVID, many mild pediatric cases have been confirmed at

a timely stage, and Chinese pediatricians have accumulated their own practical experience in the early recognition of pediatric COVID.

Management

The epidemiological data from the early phase of the COVID outbreak in Wuhan has demonstrated that COVID can spread from human to human with high transmissibility (11). Managing suspected and confirmed cases of COVID in children poses a challenge in pediatric practice, especially in relation to infection prevention and control (IPC) during health care. Fever and respiratory infections are the most common reasons for children seeking medical care and visiting hospital, which often results in crowded hospital waiting rooms. Meanwhile, the fever clinics in many hospitals have limited space and are not well equipped. Moreover, negative pressure wards are not available in almost all specialized children's hospital and pediatric wards at general hospitals. These factors put healthcare workers at high risk of professional exposure to COVID patients if appropriate personal protection equipment (PPE) are not worn. Unfortunately, at least 1,688 healthcare workers were confirmed with COVID between 8 December 2019 and 11 February 2020 (6).

The coincidence of the peak of the COVID outbreak with Chinese Spring Festival resulted in mass population movement which inevitably widened the spread of COVID outside Wuhan. Thus, it is critical to immediately initiate infection prevention and control (IPC) strategies at a national level to prevent or limit the transmission of COVID in healthcare settings. As part of the action taken to combat the national outbreaks of COVID, IPC has been strictly implemented within the healthcare setting, and includes the following: (I) ensuring triage, early recognition, and source control (isolating patients with suspected COVID); (II) applying standard precautions for all patients; (III) implementing empiric additional precautions (droplet and contact and, whenever applicable, airborne precautions) for suspected cases of COVID; (IV) implementing administrative controls; and (V) using environmental and engineering controls (24,25). Triage practices to quickly identify suspected COVID cases and the appropriate application of transmission-based precautions should be placed as the highest priorities in the prevention of healthcare-associated transmission. This approach has proved effective in reducing opportunities for early transmission of MERS (26). Our hospital has set up a series of standard procedures to rapidly screen SARS-CoV-2 infection and to manage suspected and confirmed COVID in different settings; these have worked well and efficiently so far (27-29).

All pediatric suspected cases are required to be isolated at hospital until they are ruled out as having COVID based on the negative results of nucleic acid testing for SARS-CoV-2 on 2 respiratory samples collected at least 24 hours apart (22,23). Clinical assessment of the severity of the disease is necessary before an appropriate treatment regimen can be decided. Non-severe COVID is usually self-limited and symptomatic treatment is recommended. In the meantime, close observation is extremely important for children who have either non-severe symptomatic or asymptomatic infection as, based on the clinical findings of COVID in adults, the disease can worsen within 5–8 days after onset (15,16). For severe and critically severe COVID in pediatric patients, early supportive care and monitoring is the mainstay of the treatment regimen, which may refer to adult protocol (22). Empirical antibiotic initiation is not routinely recommended for the treatment of COVID-associated pneumonia without evidence of super bacterial infection. Given that no evidence has shown the currently available antiviral agents to be effective for treating COVID and that their potential adverse effects are a concern in children, antiviral agents should not be routinely recommended for the treatment of COVID at this stage, although antiviral agents including lopinavir, arbidol, ribavirin, and α-interferon inhalation have been tried as part of the treatment of COVID in adults (22). So far, the effect of these antivirals on COVID is not clear and they are still under clinical evaluation. For the treatment of severe COVID, ribavirin could be considered because it is often used in pediatric patients in China and severe adverse events have rarely been reported. National treatment protocol recommends the combination use of Western and traditional medicines, although the use of Chinese traditional medicine depends on the child's compliance with taking medicine (22). In addition, influenza virus screening is necessary to rule out possible coinfection and to avoid unnecessary empirical overuse of oseltamivir.

On the basis of national standard recommendations (22,23), the hospitalized patient should be isolated until 2 consecutive respiratory samples (collected at least 24 hours apart) test negative for the nucleic acids of SARS-CoV-2. Individuals who have asymptomatic infection should be isolated for 14 days or for at least 7 days if the respiratory samples test negative for the nucleic acids of SARS-

CoV-2. All close contacts should be strictly quarantined and monitored closely for symptoms for 14 days after last contact with the infected person, for whom COVID should be evaluated once symptoms develop. Based on our clinical observations, the nucleic acids of SARS-CoV-2 in nasopharyngeal/throat swabs is undetectable within 6–22 days (mean: 12 days) after illness onset (12). Of particular attention, the nucleic acids of SARS-CoV-2 are frequently detected in stool samples from pediatric patients with mild COVID-19, and the virus shedding phase in feces could last for at least 2 weeks and even exceed 1 month (12,14,30). China CDC has reported that live SARS-CoV-2 was found to be isolated in stool specimens from COVID-19 patients, which suggests that SARS-CoV-2 may replicate in the gastrointestinal tract (31). However, the impact on SARS-CoV-2 shedding in feces on the transmission model and IPC strategies should be further assessed.

Preparedness for the possible sustained epidemic of COVID in children

COVID appears to be severe, with a case-severity rate of 18.5%, as well as highly transmissible, with an estimated basic reproductive number (R0) of 2.2–2.68 in the early stages of the outbreak without effective control measures (11,32). In light of the information currently available and the global situation of COVID-19, sustained transmission of 2019-nCoV could be possible among community populations. As the next step, preparedness plans should be readied for potential epidemics of COVID-19 at a global level and the sustained circulation of SARS-CoV-2 in the population.

Despite children and teenagers having been only marginally affected as a group in this wave of COVID-19 outbreaks, this does not necessarily translate to them being less susceptible. Theoretically, all age groups are susceptible to this novel coronavirus. It is important to bear in mind that the time of kindergarten / school vacation and closures overlapped with the time when COVID-19 started to spread in Wuhan (between 11–21 January 2020) and outside of Wuhan (from 22 January 2020), which may have reduced the risk of exposure for children and protected them from infection so far. In addition, mild infection and subclinical infection have been underdiagnosed, especially in Hubei, and so the real figure for children infected with the virus may be higher.

Kindergartens, schools, and universities have not yet reopened, mainly due to the uncertainty surrounding the potential impact on the epidemic trend of SARS-CoV-2 among children. Simulation studies have suggested that school closures can serve as a useful control measure during an influenza pandemic, particularly for reducing peak demand on health services (33). The existing epidemiological data shows that the transmission of COVID among children can mainly be attributed to close household contact with adult patients. In the long term, without vaccines, school closures would be unlikely to prevent the COVID epidemic spreading among children. Continuous epidemiologic monitoring of SARS-CoV-2 is necessary in understanding the natural history of this novel virus infection in the pediatric population. Candidate therapies and vaccines urgently need to be developed to allow for tailored appropriate antiviral treatment and effective prevention strategies. Pediatric healthcare workers must also stay alert to the possibility of sustained sporadic cases and cluster cases of COVID in communities and in schools. Standard precautions in healthcare settings should be followed strictly, to prevent healthcare-associated nosocomial infection.

Conclusions

Once the first wave of COVID outbreak in China comes to an end, some important questions will remain unanswered. The need to closely monitor the subsequent epidemic trend of SARS-CoV-2 among the pediatric population should be highly prioritized. By doing this, a full understanding may be gathered of susceptibility, transmission routes, the role of asymptomatic virus shedding in the respiratory tract and stools on dynamic transmission, age-specific clinical severity, and the outcomes of SARS-CoV-2 infection in children. A vaccine against SARS-CoV-2 infection to effectively protect children and adults from COVID is expected in the near future.

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