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COVID-19 epidemic: disease characteristics in children

Short title: COVID-19 epidemic in children

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Abstract

In mid-December 2019, a disease caused by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which began in Wuhan, China, has spread throughout the country and many countries around the world. The number of children with coronavirus disease-2019 (COVID-19) has also increased significantly. Although information regarding the epidemiology of COVID-19 in children has accumulated, relevant comprehensive reports are lacking. The present article reviews the epidemiological characteristics of COVID-19 in children.

Key words: Children; SARS-CoV-2; COVID-19; Epidemiological characteristics

Since the middle of December 2019, a new type of coronavirus infection has been prevalent in Wuhan, China, and has rapidly spread to a large area[1]. To date, the disease epidemic caused by this virus has rapidly spread to all parts of China and 197 countries abroad. Genome sequencing of the virus isolated from a patient's lower respiratory tract on January 10, 2020, confirmed that this is a new type of coronavirus. Two days later, the World Health Organization (WHO) termed this pathogen "2019 novel coronavirus (2019-nCoV)". On January 20, 2020, the National Health Commission of the People's Republic of China (PRC) formally incorporated the disease caused by the virus, known as COVID-19, into the Class B infectious diseases stipulated in "the Law of the People's Republic of China on the Prevention and Control of Infectious Diseases", and adopted measures for the prevention and control of class A infectious diseases[2]. On February 7, 2020, the National Health Commission named the latest type of coronavirus-infected pneumonia as "novel coronavirus pneumonia". On February 11, 2020, the Coronavirus Study Group of the International Commission on Virus Classification named the new coronavirus "Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-CoV-2)". On the same day, the WHO named the disease caused by the new coronavirus as coronavirus disease-2019 (COVID-19). After evaluation, on March 12, 2020, the WHO announced that COVID-19 had reached pandemic status[3].

Current investigations have determined that SARS-CoV-2 belongs to a new type of coronavirus family, namely, genus β. Its genetic characteristics are distinctly different from those of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 is more than 85% homologous to bat SARS-like CoV (bat-SL-CoVZC45). The Wuhan Institute of Virology (Wuhan, Hebei province, China) also obtained evidence that SARS-CoV-2 originated from bats and confirmed that SARS-CoV-2, similar to SARS-CoV, enters cells by binding to the angiotensin converting enzyme 2 (ACE-2) cell receptor[1]. Subsequently, the South China Agricultural University (Guangdong, China) targeted pangolins as a potential intermediate host for SARS-CoV-2. A study by Matthew et al. reported that SARS-CoV-2 and Malay pangolin recombinant coronavirus share 98% amino acid homology and 89% nucleotide homology for the same receptor binding motif fragment[4]. Zhou et al. used cryo-electron microscopy to analyze the full-length structure of the SARS-CoV-2 receptor—namely ACE-2—for the first time[5], which will be helpful in developing inhibitors to block entry of the virus into cells. On February 21, 2020, Jorerg et al. proposed that active SARS-CoV-2 can be produced and transformed based on viral genetic structure, which is important in understanding and predicting development trends of the virus and the disease[6]. On March 3, 2020, Tang et al. described the genome evolution of 103 new coronaviruses and found that SARS-CoV-2 has evolved into two subtypes—L and S—and the virus strain has 149 mutation points more common in the early stages

of the Wuhan outbreak; as such, it is speculated that it is more infectious and capable of spreading[7].

COVID-19 was predominantly more prevalent among adults ≥15 years of age in the early stages of the outbreak, and the proportion of confirmed cases among children was relatively small. Since then, however, more regions have launched pathogen detection campaigns and, because younger children cannot wear masks and have not taken other special preventive and control measures, the number of child infection cases has increased significantly, especially in younger age groups and, therefore, should be given high attention[8]. On February 2, 2020, the PRC issued a notice on "doing a good job in the prevention and control of pneumonia outbreaks in children and pregnant women with new coronavirus infection", which clearly states that children are susceptible to SARS-CoV-2 due to the immaturity of their immune systems[1]. The latest guidelines also make it clear that all individuals—including children—are generally susceptible to SARS-CoV-2[9]. Furthermore, children exhibit certain particularities and cannot clearly describe their own health status or contact history, which has contributed to the severe challenge of protecting, diagnosing, and treating this population[10]. Due to the increasing global spread of SARS-CoV-2, China is now facing the risk for transmission of imported cases, which poses new challenges for the prevention and control of the COVID-19 epidemic among Chinese children. At the same time, children with other (i.e., co-morbid) diseases (such as congenital heart, lung and airway diseases, malnutrition, and tumors, among others) are vulnerable to infection with SARS-CoV-2; more specifically, "prone to severe illness"[11]. The present article reviews the epidemiological characteristics of COVID-19 in children.

1. Epidemic status

As of 24:00, March 26, 2020, China's 31 provinces (autonomous regions and municipalities) and the Xinjiang Production and Construction Corps had reported a total of 81340 confirmed cases, 3292 deaths, 74588 discharged patients, and 189 suspected cases of COVID-19. A total of 738 confirmed cases were also reported in Hong Kong (n = 453), Macao (n = 33), and Taiwan (n =252). The cumulative number of confirmed cases in America ranks first outside of China, reaching 83507[12]. After the nation's concerted efforts to fight the spread of the virus, the epidemic situation in China was gradually brought under control. On March 26, 2020, there were only 55 new confirmed cases across China, 54 of which were imported and one of which was from Zhejiang, China. Current case data in China reveal that children < 18 years of age accounted for only 2.4% of all reported cases[11]. As of February 15, 2020, incomplete statistics from China (excluding Hubei region) cumulatively reported 300 confirmed cases involving children[13] and, as of February 26, 2020, the total number of confirmed cases in Wuhan, China was 490[14]. Two children with COVID-19 were diagnosed in Germany on February 4, 2020[1] and a 5-year-old child in the Philippines was also diagnosed[15]. Canada reported the first confirmed case of COVID-19, who still carries the virus after rehabilitation and discharge, and is a possible communicator[16]. Zou et al. analyzed the relationship between viral load and symptoms of infection in 18 patients with COVID-19, and found that the pattern of viral nucleic acid excretion in those with SARS-CoV-2 infection was similar to that of influenza, and that the viral load determined in asymptomatic patients was similar to that of those with symptoms, which indirectly suggested potential transmission capacity in asymptomatic or mild cases with COVID-19[17]. Current studies have shown that the incubation period of SARS-CoV-2 is 1–14 days, and most commonly 3–7 days[9]. However, Guan et al. described a patient with an

incubation period of up to 24 days[18]. Subsequently, Bai et al. reported a patient with an incubation period of up to 19 days, who was also the first asymptomatic infection in China[19]. Children generally have low immunity and some exhibit a long incubation period after SARS-CoV-2 infection. Therefore, children should try to avoid contact with complex populations to avoid being infected by potential spreaders. COVID-19 is an acute, self-limiting disease; nevertheless, patients can die, with a mortality rate of 2%[20], and has also been reported in critically ill children[21]. Compared with the current COVID-19 epidemic, during the outbreak of SARS-CoV, the number of confirmed in children cases (4 months to 17 years of age) worldwide was < 0.02% of the total number of cases (no deaths were confirmed in children), and children with severe cases accounted for approximately 7.9%, and the vast majority of these had a history of family exposure or adult contacts, while a few had a history of travel in affected areas and a history of exposure in the hospital. Of the 1621 confirmed cases of MERS-CoV reported globally, children < 19 years of age accounted for approximately 2.2%. Of the 14 pediatric cases (8 months to 16 years of age), 9 (64%) were children infected after home exposure, but all were asymptomatic: 5 (36%) were in hospital and at home, with a history of internal exposure were symptomatic infections, of whom 2 (14.3%) exhibited mild respiratory symptoms, 3 (21.4%) had pneumonia; and 2 (14.3%) children with underlying diseases complicated by severe respiratory distress died from it[22]. Due to its rapid spread and the insufficient clinical analysis of children with SARS-CoV-2 infection, we reference the epidemic characteristics of children in the SARS-CoV and MERS-CoV period to provide clues for effective prevention.

2. Epidemiological characteristics

2.1 Patients with COVID-19 exhibit clustered infection characteristics

2.1.1 Children with COVID-19 exhibit characteristics of family-aggregated infections and a longer incubation period than adults

As the outbreak spread, it was gradually confirmed that SARS-CoV-2 could be transmitted from person to person in places such as homes or hospitals, and even from city to city, and country to country. Children are very special group, largely due to close family contacts, and may be susceptible to cross infection. According to existing epidemiological data, 56% (34/61) of children with COVID-19 demonstrated clear evidence of transmission through family gatherings [23]. China's first newborn COVID-19 patient was diagnosed at 17 days of age, first confirmed in the family nursing staff, followed by the parents, who were also diagnosed with COVID-19[24]. A 5-day-old neonatal COVID-19 patient, whose mother was also confirmed to be infected with SARS-CoV-2, and a newborn with suspected disease from cesarean delivery was confirmed to be infected with SARS-CoV-2 36 h after birth, followed by his mother who was diagnosed with COVID-19 shortly after giving birth[25]. On January 26, 2020, a 3-month-old baby and its parents in Hubei province, China, were both confirmed to be infected with SARS-CoV-2[26]. On January 19, 2020, a hospital in Shanghai, China, admitted a 7-year-old boy diagnosed with SARS-CoV-2 infection, whose father was diagnosed with COVID-19 earlier than the child[27]. On January 11, 2020, a case of asymptomatic infection was found in a 10-year-old boy in Shenzhen, Guangdong, China, whose parents, grandparents, and grandparents all developed fever, diarrhea, cough and other symptoms, and were diagnosed with COVID-19 earlier than the boy[28]. According to the epidemic situation described by Anhui Provincial Health Commission on January

28 and 29, 2020, a family of six in Huangshan city, Anhui, China, was confirmed to have COVID-19, including an 8-month-old baby and a 10-year-old child[1]. These cases were found in family clusters. Wei et al. performed a study on 9 infant COVID-19 patients, revealing that they all had at least one family member who had been infected with SARS-CoV-2 earlier, among which 7 infants lived in Wuhan, China or had family members who had traveled to Wuhan[8]. The parents of a 6-month-old baby in Singapore were infected with SARS-CoV-2. After the parents were diagnosed, the baby was initially asymptomatic but was admitted to hospital due to close contact. The baby was diagnosed with SARS-CoV-2 the day after admission[29]. The average incubation period for COVID-19 in children is approximately 6.5 days, which is longer than the 5.4 days reported in adults. The average number of secondary infections transmitted within the family was 2.43. The duration of nasal and pharyngeal detoxification in children is 6–21 days (average 12 days)[30]. An epidemiological analysis of 31 children with COVID-19 in six provinces (autonomous region) of northern China found that 21 (68%) had contact with an adult with confirmed disease. One (3%), who had contact with asymptomatic Wuhan return Township staff (without nucleic acid testing), became ill after 5 days, and 28 of these 31 children (90%) were clustered in families[31].

2.1.2 Patients with COVID-19 exhibit characteristics of exposure to infection in the foci

According to available epidemiological data, 43% of children with COVID-19 (26/61) exhibited characteristics of infection from epidemic exposure[23]. Wang et al. conducted an epidemiological analysis of 31 children with COVID-19 in six northern provinces of China (autonomous regions) and found that 9 (29%) lived in Hubei Province, China, for a long time[31]. China's

foremost critically ill child with COVID-19 was seen in several medical institutions at an early stage, and may have been exposed to infection in this process, with a history of endemic exposure[21]. Wang et al. analyzed 138 cases in Wuhan, China, and found that if a group of inpatients or medical personnel in the same ward were infected, the suggested source of infection was through hospital-related transmission[32]. Other studies have reported that the spread of SARS-CoV-2 from the township level also demonstrates obvious geographical aggregation (especially in Hubei, Beijing, Yangtze River Delta, Pearl River Delta, Hong Kong, "Diamond Princess" cruise ship, "Grand Princess" cruise ship, and other areas are more obvious)[33]. Therefore, as a susceptible population, children should try to avoid exposure to epidemic sources to reduce the risks for infection.

2.2 Age and sex distribution characteristics of COVID-19 patients

Patients with COVID-19 are distributed among all age groups. A study investigating 8866 cases of COVID-19 reported that the majority of patients were 36–65 years of age, with only 14 children < 10 years of age diagnosed with disease[33]. In an investigation of 72,314 cases, Wu et al. reported that children ≤ 9 and 10–19 years of age accounted for 1% of the total number cases, respectively[34]. The youngest of the confirmed child cases to date was merely 30 h of age, and the oldest was 18 years[1]. Studies have reported a higher incidence in men than in women (0.31/100,000 versus 0.27/100,000, respectively)[33]. In a study involving nine children with COVID-19 < 1 year of age, seven were girls[8]; however, it was not possible to determine whether girls or boys were more susceptible to SARS-CoV-2 infection due to the small sample size. Recently, the Chinese Center For Disease Control And Prevention (CDC) published a case analysis of > 70,000 cases of COVID-19 in which individuals 30–79 years of age

accounted 89.8% of the total number of confirmed cases in Wuhan, 88.6% in Hubei Province, and 86.6% of all cases in China. Among them, the ratio of men to women in confirmed cases was 0.99:1 in Wuhan, China, 1.04:1 in Hubei province, and 1.06:1 in all of China[35]. Nevertheless, there is still no direct evidence supporting whether men or women are more susceptible to SARS-CoV-2 infection.

2.3 SARS-CoV-2 is highly infectious

According to statistics from the WHO, four months after the outbreak of SARS-CoV in 2003, > 1000 cases accumulated worldwide; the MERS-CoV outbreak in June 2012, as of May 30, 2015, had accumulated 1180 cases. The total number of confirmed cases of SARS-CoV-2 infection in China reached 1297 in < 25 days since the first notification from the Wuhan Municipal Health Commission[36,37]. However, there is no clear evidence that adults are a source of infection in children[23].

The basic regeneration number (R0 value) represents the number of second-generation individuals that a patient can infect after entering a susceptible population under ideal conditions. The R0 value not only indicates the rate of transmission of the virus, but also reflects the potential and severity of the outbreak of infectious diseases[38]. Many research institutions have analyzed the R0 value of SARS-CoV-2, among which Du et al. calculated the R0 value of SARS-CoV-2 to be 2.56. A team headed by Adam Kuchrski reported that R0 fluctuated between 1.5 and 4[1]. Using a sample size of 8866, Yang et al. calculated a SARS-CoV-2 R0 up to 3.77 (95% confidence interval 3.51–4.05). That study demonstrated that the longer the infection period, the higher and longer the reported rate, the higher R0[33]. Based on these studies, it is clear that the estimated R0 values were all >1, indicating that SARS-CoV-2 is in an epidemic

phase and has a strong transmission capacity. Research data from Chen et al. showed that the R0 value for SARS-CoV was approximately 2–5 and < 1 for MERS-CoV [39]. As such, the R0 values of SARS-CoV-2 (1.4–5.5) and SARS-CoV (2–5) are similar, and significantly higher than that of MERS-CoV.

To measure the spread of the disease following the adoption of prevention and control measures, Yang et al. studied the effective reproductive number (Rt value), which represents the average number of follow-on cases of infection per infected person at time t. The Rt value after human intervention will decrease slightly with effective prevention and control measures. The results of the study revealed that from December 25, 2019, the Rt value of SARS-CoV-2 increased to > 1 around January 3, 2020, and peaked at January 8–15, but fell again to < 1 after January 16, 2020. However, the researchers believe that this did not necessarily indicate a decline in the transmission capacity of the virus, but may have been related to a delay in reporting epidemiological data[33]. According to a study involving 1099 patients, Bai et al. reported that there was asymptomatic transmission of infected patients without excluding the existence of "super-disseminators"[19].

The Korean government confirmed a "super-spread incident" on February 20, 2020, in which a surge of 53 cases in a single-day was reported, of which 43 individuals from a church in Daegu were diagnosed[40]. In response to this epidemic, a new virus was found in the clinical front line before it spread, which is of great importance to early detection of pathogens and the implementation of effective prevention and control measures. Success in containing the SARS-CoV-2-triggered epidemic was largely due to the country's immediate measures at the beginning of the first spread of COVID-19, a very important "golden window" for disease control. A second-generation epidemic will be

exponentially larger. Therefore, the application of modern diagnostic technology can more effectively grasp the “golden window” period for infectious disease prevention and control[41].

2.4 SARS-CoV-2 infection is widespread

2.4.1 SARS-CoV-2 can be transmitted by respiratory droplets, close contact, aerosols, and through the conjunctiva

According to the latest release from the National Health Commission, PRC, SARS-CoV-2 is transmitted mainly through respiratory droplets and close contact(s). Spread is also possible through the conjunctiva, and the presence of SARS-CoV-2 in relatively closed environments with prolonged exposure to high concentrations of aerosols may also facilitate transmission. More specifically, the air-tightness of the environment and the density of viruses per unit volume can affect the spread of SARS-CoV-2[9]. Because SARS-CoV-2 binds to the ACE2 receptor, the virus must first come in contact with cells that express the receptor. Human mucosal cells express ACE2 receptors, and the lips, eyelids, nasal cavities, which are exposed to the air, have a large number of mucosal cells. SARS-CoV-2 binds to ACE2 receptors in close contact and conjunctival transmission without proper cleaning, disinfection and direct contact with eye, mouth and nose. Teams headed by Lu and Xia both have shown that infectious droplets and body fluids can contaminate the human conjunctival epithelium. Respiratory virus can cause ocular complications in infected patients, which in turn lead to respiratory tract infection; thus, exposure to SARS-CoV-2 may cause acute respiratory tract infection[42,43]. Similarly, ACE2 receptors are present in human lung AT2 cells[44]; as such, infection can be caused by exposure to respiratory droplets as well as aerosol transmission. To reduce the probability of SARS-CoV-2 infection in

children and avoid potential hospital transmission through aerosol the route, digestive endoscopy centers, fever clinics, and others have issued relevant emergency plans and management measures during the epidemic period[45,46].

2.4.2 SARS-CoV-2 may be transmitted through the digestive tract

SARS-CoV-2 must bind to ACE2 receptors to cause infection. Accordingly, Zhang et al. explored the infection pathway of SARS-CoV-2 and the role of ACE2 in the digestive system after identifying the cell composition and proportion of expression of ACE2 in normal human lung and the gastrointestinal system through single-cell transcription. They found that ACE2 was not only expressed in lung AT2 cells, but also in upper esophageal and stratified epithelial cells, as well as intestinal epithelial cells in the ileum and colon. Therefore, intestinal symptoms of SARS-CoV-2 may be associated with invasion of intestinal epithelial cells expressing ACE2[44]. In an earlier report from Wuhan, China, 2% to 10% of patients with COVID-19 experienced gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting. Patients with SARS-CoV-2 infection who were transferred to the intensive care unit exhibited a higher frequency of abdominal pain than those with SARS-CoV-2 infection who did not require intensive care, and 10% of patients with COVID-19 experienced diarrhea and nausea symptoms in the 1–2 days before the onset of fever and respiratory symptoms[47]. A study from the United States reported detected SARS-CoV-2 RNA in the feces of a patient[48]. Given that both SARS-CoV and MERS-CoV can be excreted through feces and remain viable under conditions conducive to transmission, it is speculated that SARS-CoV-2 may also be transmitted through this route. Guan et al. isolated SARS-CoV-2 from the urine of a COVID-19 patient[18]. This suggests that viral nucleic acids may persist in bodily fluids, secretions, and excreta of patients with COVID-19, and that the digestive tract is a potential route of

transmission. Viral nucleic acids may also be detected in the cerebrospinal fluid, pleural effusions, and additional specimens from patients with COVID-19 in the future. A study by Cai et al. revealed that viral RNA from feces of children with COVID-19 was detected at a high rate, and the detoxification period can be as long as 2–4 weeks[30]. Xu et al. performed nucleic acid testing on anal swabs from 10 children with COVID-19 and found that the duration of positivity in anal swabs and intestinal detoxification was longer. The longest time for the nucleic acid test to change from positive to negative in anal swabs from 10 children was 51 days; the time for a throat swab nucleic acid test in these 10 children to change from positive to negative was generally one week. At the same time, this study demonstrated that anal swab testing in children may be more useful than nasopharyngeal swab testing in determining the effectiveness of treatment and determining the timing of quarantine termination[49]. However, there was no direct evidence of fecal-oral transmission because the study did not capture live viruses.

2.4.3 There is no direct evidence that SARS-CoV-2 can be transmitted vertically from mother to child

Since the Wuhan Children's Hospital diagnosed COVID-19 in an infant at 30 h of age on February 5, 2020, it has been argued that SARS-CoV-2 may be transmitted vertically from the mother to the child[1]. Based on the potential mechanism of vertical transmission to the fetus, potential susceptible cell subsets of SARS-CoV-2 may not exist at the maternal-fetal interface, and the results show that there is no evidence of vertical transmission of SARS-CoV-2 to the fetus[49]. Chen et al. tested for the presence of SARS-CoV-2 in amniotic fluid, umbilical cord blood, and neonatal pharynx swab and breast milk samples at first lactation and detected no virus. All patients in the study were in the late stages of pregnancy; as such, evidence of intrauterine vertical transmission was insufficient.

Nevertheless, the possibility of early or mid-gestational vertical transmission could not be determined. In addition, the study did not collect vaginal mucosal samples or birth canal shedding samples; therefore, it was not possible to analyze whether SARS-CoV-2 infection could be transmitted during vaginal delivery[50]. It is also uncertain whether breastfeeding leads to vertical transmission from mother to child. There is no direct evidence of vertical mother-to-child transmission; however, newborns can be infected through close contact. Zhu et al. considered neonates to be at high risk for SARS-CoV-2 infection if they met the following criteria: the mother experienced persistent fever before, during, or after childbirth, and routine laboratory investigations revealed a decrease in lymphocyte ratio; chest CT revealed lung infiltration, based on viral nucleic acid test results and epidemiological history suggesting that the mother is a confirmed/highly suspected case (remove other viral and bacterial infections, mycoplasma infections, puerperal fever, breast swelling, mastitis and other obstetric conditions); newborn whose mother has clinical manifestations or epidemiological history of infection, but not sufficiently suspicious to definitively diagnose; newborns with a history of infection epidemiology, including those from community sources and obstetric mother-infant same-room sources, family members or caregivers, and visitors who are diagnosed/highly suspected with SARS-CoV-2 infection; and, finally, newborns living in or visiting environments at high risk for SARS-CoV-2 infection[51].

In summary, although there is no direct evidence that SARS-CoV-2 can be transmitted vertically from mother to child, special attention should be devoted to the prevention of neonatal infection in pregnant women with confirmed COVID-19. “The Expert Recommendations for the Prevention and Control of the New-type Coronary Virus Infections in Neonatrics 2019” aim at strengthening preventive measures, effectively blocking the transmission of maternal, iatrogenic,

and community-derived SARS-CoV-2 infections, comprehensively promoting effective control of the epidemic and safeguarding lives and health. Hospitals must devote attention to the health of all neonatal medical staff and actively administer training and, at the same time, perform hospital cleaning and disinfection to ensure that newborns admitted for separate treatment are not exposed to infection risk[1].

2.5 Changes in incidence during the timeline

Before January 23, 2020, the incidence of COVID-19 increased exponentially, which basically corresponded to the spring transportation period, and the growth of suspected cases was slightly lower than that of diagnosed cases for 2–3 days[33]. According to incomplete statistics, as of 24:00 h on January, 31, 2020, China reported a total of 74 confirmed cases involving children[23]. As of February 15, 2020, incomplete statistics reported 300 cumulatively confirmed cases involving children nationally (excluding Hubei region)[13]. Thirty days after the report of the first confirmed case of COVID-19, the epidemic spread to the entire country (the first confirmed imported COVID-19 patient in Guangdong province on January 19, 2020, was the first confirmed patient outside Hubei province[35]). The first epidemic peak occurred between January 24 and 26, 2020, and then gradually decreased from February 1, 2020[35]. Shen et al. evaluated the role of the Wuhan “limit inflow and outflow” strategy in controlling the epidemic through mathematical models. The study predicted that “limit inflow and outflow” could reduce all cases of infection and by nearly 70%, assuming that all individuals wore a mask after “limit inflow and outflow” and that masks could reduce the risk for infection by 90%[52]. Limit inflow and outflow, the establishment of the Raytheon Mountain, Fire God Mountain and Fang Cabin

Hospitals, delayed resumption of work, suspension of classes[53], and enhanced etiological detection in various places all affected changes in morbidity.

2.6 COVID-19 mortality rate

According to preliminary statistics, the mortality rate among COVID-19 patients is 2.38% in China, 4.05% in Wuhan (China), and 0.25% in other countries and regions outside China. Comparing available mortality data of SARS-CoV-2 with that of SARS-CoV (9.6% [774/8098]) and MERS-CoV (34% [858/2494]), the mortality of patients with SARS-CoV-2 nationwide was lower [54]. A study analyzing the demographic and clinical characteristics of diagnostic cases using descriptive statistical medical records used the total number of confirmed deaths/diagnosed cases to indicate crude mortality. At the same time, the density of mortality was calculated using the number of deaths in diagnosed cases/cumulative number of days observed in diagnosed cases. In this study, which analyzed 44,672 confirmed cases, a total of 1023 died, corresponding to a crude mortality rate of 2.3% and a mortality density of 0.015/10 person days[35].

3. Clinical characteristics

In children with COVID-19, fever and cough are the most common clinical manifestations, with some accompanied by fatigue, myalgia, nasal congestion, runny nose, sneezing, sore throat, headache, dizziness, vomiting, and abdominal pain. A few children do not exhibit fever, but only manifest cough or diarrhea, and even fewer can be asymptomatic carriers. Some children and newborns exhibit atypical symptoms, manifested as vomiting, diarrhea, and other gastrointestinal symptoms, or only asthma and shortness of breath[10,55]. The first severe case of childhood infection reported in Wuhan, China, started with gastrointestinal symptoms, exhibited no obvious early respiratory manifestations, but progressed

rapidly to acute respiratory distress syndrome[21]. According to clinical characteristics of existing pediatric cases, children with COVID-19 can be divided into five clinical types: asymptomatic infection, mild, common, severe, and critically severe[11]. One published study reported that among 134 children diagnosed, 89 exhibited fever (high fever [n = 11], low and medium fever [n =17], and unknown [n = 61]), and 28 exhibited no fever. Fever duration was mostly 1 to 2 days, and the longest was 8 days. Most routine blood examinations were normal, and C-reactive protein (CRP) levels were normal or transiently increased (3 cases > 20 mg/L [23, 27, and 47 mg/L, respectively])[55]. Of 54 patients with pulmonary imaging data, 38 (70.4%) exhibited ground-glass opacities or exudates, infiltrative lesions; 4 (7.4%) exhibited enhanced lung texture; and 12 (22.2%) had no abnormalities. Five patients, who were negative at the time of throat swab virus nucleic acid testing, were children: two at 9 days after illness; and three at 12 days after illness. Two critically ill patients had a history of underlying disease, and 1 was after congenital heart disease 7 months with moderate malnutrition; the 1 other had bilateral hydronephrosis and left kidney stones. Of the 134 confirmed cases of disease in children, if chest imaging was used as the basis for the diagnosis of pneumonia, 36 patients exhibited the common type (26.9%, including 7 cases were subclinical); 2 cases were critically ill (1.5%); 9 cases were completely asymptomatic with normal lung imaging and asymptomatic infection (6.7%); 87 cases were mild (64.9%)[27]. The data show that the prevalence of disease in children ≤ 18 years of age is relatively low, accounting for approximately 2.4% of all reported cases[56], and clinical characteristics of adult cases (severe symptoms, long detoxification time). In comparison, most children diagnosed with the disease experience mild symptoms, faster recovery, shorter detoxification time, and good prognosis. Xu et al. conducted nucleic acid tests on 745 children and 3174 adults with a history of close contact with COVID-19

patients or whose family members have confirmed COVID-19. They found that only 10 children tested positive, accounting for 1.3% of the total number of children, and 111 adults tested positive, accounting for 3.5%. Among these 10 children with COVID-19, body temperature, routine blood tests, and chest CT tests showed that, compared with adults, children with COVID-19 were less ill and exhibited less obvious symptoms, and were not typical[49]. Although the incidence of critical illness in children is low, the current incidence is sufficient to alert pediatricians. In is important to identify children with COVID-19, especially those with underlying/co-morbid disease(s), and to treat them early.

In summary, special attention should be devoted to children because they are a special group of patients. Through analysis of the epidemiological history of a small number of child cases of COVID-19, and a fuller grasp of the epidemiological characteristics of SARS-CoV-2, it will be possible to provide more effective preventive measures and treatment policies, and lay a solid foundation for winning the battle against this epidemic.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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References

1. She Jiatong, Liu Wenjun. Epidemiological characteristics and prevention and control measures of Corona Virus Disease 2019 in children. Journal of Tropical Medicine, 2020.ISSN 1672-3619, CN 44-1503/R.

   http://kns.cnki.net/kcms/detail/44.1503.R.20200217.1638.002.html

2. National Health Commission of the People's Republic of China. Notice of the National Health Council of the People's Republic of China [EB/OL] (2020-01-20) [2020-01-20]. http://www.nhc.gov.cn/jkj/s7916/202001/44a3b8245e8049d2837a4f27529cd386.shtml

3. World Health Organization.WHOcharacterizesCOVID-19as a pandemic. 1.1 [EB/OL] (2020-03-12) [2020-03-12].

   https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen

4. Matthew C. Wong, Sara J. Javornik Cregeen, Nadim J. Ajami, et al. Evidence of recombination in coronaviruses implicating pangolin origins of 2019-nCoV [J]. bioRxiv, 2020. DOI: https://doi.org/10.1101/2020.02.07.939207.

5. Qiang Zhou, Renhong Yan, Yuanyuan Zhang, et al. Structure of dimeric full-length human ACE2 in complex with B^0ATI [J]. bioRxiv, 2020. DOI:https://doi.org/10.1101/2020.02.17.951848

6. Tran Thi, Nhu Thao, Fabien Labroussaa, Nadine Ebert, et al. Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform [J]. bio Rxiv, 2020.

   DOI: https://doi.org/10.1101/2020.02.21.959817

7. Xiaolu Tang, Changcheng Wu, Xiang Li, et al. On the origin and continuing evolution of SARS-CoV-2 [J]. National Science Review, nwaa036. https://doi.org/10.1093/nsr/nwaa036

8. Min Wei, Jingping Yuan, Yu Liu, et al. Novel coronavirus infection in hospitalized infants under 1 year of age in China [J]. JAMA, 2020.2.19. DOI:10.1001/jama.2020.2131 https://jamanetwork.com/journals/jama/fullarticle/2761659

9. National Health commission of the People's Republic of China.Diagnosis and treatment of novel coronavirus pneumonia (trial version 7 revised version). [EB/OL]. (2020-03-03) [2020-03-03]. http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml

10. Yang Lifen, Dai Zhenyuan, Duan Mengqi, et al.Suggestions for medical staff from

department of pediatrics during the treatment of 2019-nCoV infection/pneumonia [J].

Journal of New Medicine, 2020. ISSN 0253-9802,CN 44-1211/R.

DOI:10.3969/j. ISSN 0253-9802.2020.02.001

11. Jiang Yi, Lu Xiaoxia, Jin Runming, et al. Novel coronavirus infections: standard/protocol/guideline recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (the second edition) [J]. Chin J Appl Clin Pediatr, 2020, 35(2): 143-150. DOI: 10.3760/cma.j.issn.2095-428X.2020.02.012.

12. National Health Commission of the People's Republic of China. An update on the incidence of Corona Virus Disease 2019 infection as at 24:00 on 26 March [EB/OL].(2020-03-26)[2020-03-26].

http://www.nhc.gov.cn/xcs/yqfkdt/202003/c521093a01734df3b3fbc156064ba19f.shtml

13. Zhu Yueling, Yang BinBin, Wu Fang. Understanding of COVID-19 in children from different perspectives of traditional Chinese medicine and western medicine[J].Chinese Traditional and Herbal Drugs, 2020. ISSN 0253-2670, CN 12-1108/R

https://kns.cnki.net/kcms/detail/12.1108.R.20200218.1120.002.html

14. CCTV13. Diagnosis and treatment of children with new coronary pneumonia [EB/OL]. https://video.weibo.com/show?fid=1034:4476589245661189

15. Zhimin Chen, Junfen Fu, Qiang Shu, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus [J]. World Journal of Pediatrics, 2020. DOI: https://doi.org/10.1007/s12519-020-00345-5

16. William Kyle Silverstein, Lynda Stroud, Graham Edward Cleghorn, et al. First imported case of 2019novel coronavirus in Canada, presenting as mild pneumonia. The Lancet, 2020.

DOI: https://doi.org/10.1016/S0140-6736(20)30370-6

17. Lirong Zou, Feng Ruan, Mingxing Huang, et al. SARS-CoV-2 Viral load in upper respiratory specimens of infected patients [J]. Journal of the American Medical Association, 2020. DOI: 10.1056/NEJMc2001737

18. Wei jie Guan, Zheng yi Ni, Yu Hu, et al. Clinical characteristics of 2019 novel coronavirus infection in China [J]. medRxiv, 2020. DOI: https://doi.org/10.1101/2020.02.06.20020974.

19. Yan Bai, Lingsheng Yao, Tao Wei et al. Presumed asymptomatic carrier transmission of COVID-19. Journal of the American Medical Association, 2020. DOI:10.1001/jama.2020.2565

20. Zhe Xu,Lei Shi, Yijin Wang,et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [J]. The Lancet, 2020. DOI: https://doi.org/10.1016/S2213-2600(20)30076-X

21. Chen Feng, Liu Zhi Sheng, Zhang Furong, et al. First case of severe childhood novel coronavirus pneumonia in China [J].Chin J Pediatr, 2020,58(3):179-183. DOI: 10.3760/cma.j.issn.0578-1310.2020.03.003.

22. Zeng Mei, Zhai Xiaowen, Wang Jianshe. 2019 novel coronavirus infection: Pediatric professionals perspectives and action [J]. Chin J Infect Dis, 2020,38(00): E003-E003. DOI: 10.3760/cma.j.issn.1000-6680.2020.0003

23. Fang Feng, Luo Xiaoping, et al. Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives [J]. Chin J Pediatr,2020,58(2):81-85. DOI: 10.3760/cma.j.issn.0578-1310.2020.02.001

24. Zeng Lingkong, TaoXuwei, Yuan Wenhao, et al. First case of neonate infected with novel coronavirus pneumonia in China [J]. Chin J Pediatr, 2020,58(4):E009-E009. DOI:10.3760/cma.j.cn112140-20200212-00081

25. The Society of Pediatrics, Chinese Medical Association, the Editorial Board, Chinese Journal of Pediatrics. Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition) [J]. Chin J Pediatr, 2020,58(03): Epub ahead of print. DOI: 10.3760/cma.j.issn.0578-1310.2020.0004

26. Zhang Yuehua, Lin Daojiong, Xiao Meifang, et al. 2019-novel coronavirus infection in a three-month-old baby [J]. Chin J Pediatr, 2020,58 (3): 182-184. DOI:10.3760/cma.j.issn.0578-1310.2020.03.004

27. Cai Jiehao, Wang Xiangshi, Ge Yanling, et al. Novel coronavirus infections: case report first case of 2019 novel coronavirus infection in children in Shanghai [J]. Chin J Pediatr, 2020,58(02): 86-87. DOI:10.3760/cma.j.issn.0578-1310.2020.02.002

28. Chan J F W, Yuan S, Kok K H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster [J/OL]. The Lancet, 395(10223):514-523. DOI: https://www.thelancet.com/coronavirus. 30154-9

29. Kai-qian Kam, Chee Fu Yung, Lin Cui, et al. A well infant with Coronavirus Disease 2019 (COVID-19) with high viral load [J]. Clinical Infectious Diseases, ciaa 201. https://doi.org/10.1093/cid/ciaa201

30. Cai Jiehao, Xu Jing, Lin Daojiong, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features [J]. Clinical Infectious Diseases, ciaa198. https://doi.org/10.1093/cid/ciaa198

31. Wang Duan, Ju Xiuli, Xie Feng, et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous

region) of northern China [J]. Chin J Pediatr, 2020,58: Epub ahead of print. DOI: 10.3760/cma.j.cn112140-20200225-00138

32. Dawei Wang, Bo Hu, Chang Hu, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China [J]. JAMA 2020. DOI: 10.1001/jama.2020.1585

33. Yang Yang, Qingbin Lu, Mingjin Liu, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China [J].med Rxiv, 2020. DOI: https://doi.org/10.1101/2020.02.10.20021675

34. Zunyou Wu, Jennifer M. McGoogan. 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 [J]. JAMA. DOI:10.1001/jama.2020.2648

35. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China[J]. Chinese Journal of Epidemiology, 2020, 41(2): 145-151.

36. Wuhan Municipal Health Commission. Wuhan Health and Health Commission on the current situation of pneumonia in our city [EB/OL].(2019-12-31) [2020-02-01]. http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989.

37. National Health Commission of the People's Republic of China. An update on the incidence of Corona Virus Disease 2019 infection as at 24:00 on 31 January [EB/OL] (2020-02-01) [2020-02-01].

http://www.nhc.gov.cn/xcs/yqtb/202002/84faf71e096446fdb1ae44939ba5c528.shtml

38. Zhang Lei, Cao Qing, Wang Ying, et al. Experts proposal and frequently asked questions of

rapid screening and prevention of novel coronavirus pneumonia in children [J]. Chin J Appl

Clin Pediatr, 2020, 35(2): 105-111. DOI: 10.3760/cma.j.issn.2095-428X.2020.02.005

39. Jieliang Chen. Pathogenicity and transmissibility of 2019-nCoV−A quick overview and comparison with other emerging viruses[J]. Microbes and Infection, 2020.

DOI: https://doi.org/10.1016/j.micinf.2020.01.004

40. Health News. Invisible transmission is worse? How "bad" is the new coronavirus? Experts point out "see recruit to dismantle recruit"[EB/OL]. (2020-02-22)[2020-02-22].

https://mp.weixin.qq.com/s/NqmCEaOW9HRa69iGJ8TwUg

41. Zhang Wenhong. Identification of a novel coronavirus and the landscape of prevention and controlof emerging infectious diseases [J]. Chin J Infect Dis, 2020, 38(01): 3-5. DOI: 10.3760/cma.j.issn.1000-6680.2020.01.002

42. Chengwei Lu, Xiufen Liu, Zhifang Jia. 2019-nCoV transmission through the ocular surface must not be ignored [J]. The Lancet, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)30313-5

43. Jianhua Xia, Jianping Tong, Mengyun Liu, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection [J]. J Med Virol, 2020. DOI:https://doi.org/10.1002/jmv.25725

44. Hao Zhang, Zijian Kang, Haiyi Gong, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes [J]. bioRxiv, 2020. DOI: https://doi.org/10.1101/2020.01.30.927806

45. The Subspecialty Group of Gastroenterology, the Society of Pediatrics, Chinese Medical Association. Prevention and control program on 2019 novel coronavirus infection in Children's digestive endoscopy center [J]. Chin J Pediatr, 2020, 58(3):169-172. DOI: 10.3760/cma.j.issn.0578-1310.2020.0003

46. Zhang Guocheng, Cheng Xiaoning, Ding Hui, et al. Guidance on strengthening the management processes of children′ s fever in outpatient department during the novel coronavirus pneumonia epidemic period (First Edition) [J]. Chin J Appl Clin Pediatr, 2020,35(02): 97-104. DOI: 10.3760/cma.j.issn.2095-428X.2020.02.004

47. Charleen Yeo, Sanghvi Kaushal, Danson Yeo, et al. Enteric involvement of coronaviruses: is fecal-oral transmission of SARS-CoV-2 possible? [J]. The Lancet Gastroenterology & Hepatology, 2020. DOI: https://doi.org/10.1016/S2468-1253(20)30048-0

48. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States [J]. New England Journal of Medicine, 2020. DOI:10.1056/NEJMoa2001191.

49. Qingliang Zheng, Tao Duan, Liping Jin.Single-Cell RNA Expression Profiling of ACE2 and AXL in the Human Maternal–Fetal Interface [J]. Reproductive and Developmental Medicine,2020. DOI: 10.4103/2096-2924.278679. http://www.repdevmed.org/preprintarticle.asp?id=278679

50. Huijun Chen, Juanjuan Guo, Chen Wang, et al. Clinical characteristics and intrauterine Vertical transmission potential of COVID-19 infection in nine pregnant women: a Retrospective review of medical records [J]. The Lancet, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)30360-3

51. Zhu Huaping, Peng Sicong, Li Hua, et al. Common problems and countermeasures in the management of new coronavirus infection in high risk neonates [J].Chinese Journal of Neonatology, 2020, 35.

52. Mingwang Shen, Zhihang Peng, Yuming Guo, et al. Lockdown may partially halt the spread of 2019 novel coronavirus in Hubei province, China [J]. medRxiv, 2020.

DOI: https://doi.org/10.1101/2020.02.11.20022236

53. Foster Kofi Ayittey, Christian Dzuvor, Matthew Kormla Ayittey, et al. Updates on Wuhan 2019 novel coronavirus epidemic [J]. J Medical Virology, 2020. DOI: 10.1002/jmv.25695

54. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association. An update on the epidemiological characteristics of novel coronavirus pneumonia (COVID-19) [J]. Chinese Journal of Epidemiology, 2020,41(2):139-144.

DOI: 10.3760/cma.j.issn.0254-6450.2020.02.002

55. Tuo Hu, Liu Fang, Wang Junling, et al. Clinical characteristics of 2019 novel coronavirus (2019-nCoV) infection in children and family prevention and control [J]. Medical Journal of Wuhan University. DOI: 10. 14188/j. 1671-8852. 2020. 6020

56. National Health Commission of the People's Republic of China.China-WHO new coronavirus pneumonia COVID-19 joint inspection report [EB/OL] (2020-02-29) [2020-02-29]

http://www.nhc.gov.cn/jkj/s3578/202002/87fd92510d094e4b9bad597608f5cc2c.shtml