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RESEARCH ARTICLE

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Epidemiological features and viral shedding in children with SARS-CoV-2 infection

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Abstract

A pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection broke out all over the world; however, epidemiological data and viral shedding in pediatric patients are limited. We conducted a retrospective,

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multicenter study, and followed-up with all children from the families with SARS-CoV-2 infected members in Zhejiang Province, China. All infections were confirmed by testing the SARS-CoV-2 RNA with real-time reverse transcription PCR method, and epidemiological data between children and adults in the same families were compared. Effect of antiviral therapy was evaluated observationally and fecal-viral excretion times among groups with different antiviral regiments were compared with Kaplan-Meier plot. By 29 February 2020, 1298 cases from 883 families were confirmed with SARS-CoV-2 infection and 314 of which were families with children. Incidence of infection in child close contacts was significantly lower than that in adult contacts (13.2% vs 21.2%). The mean age of 43 pediatric cases was 8.2 years and mean incubation period was 9.1 days. Forty (93.0%) were family clustering. Thirty-three children had coronavirus disease 2019 (20 pneumonia) with mild symptoms and 10 were asymptomatic. Fecal SARS-CoV-2 RNA detection was positive in 91.4% (32/35) cases and some children had viral excretion time over 70 days. Viral clearance time was not different among the groups treated with different antiviral regiments. No subsequent infection was observed in family contacts of fecal-viral-excreting children. Children have lower susceptibility of SARS-CoV-2 infection, longer incubation, and fecal-viral excretion time. Positive results of fecal SARS-CoV-2 RNA detection were not used as indication for hospitalization or quarantine.

KEYWORDS

antiviral therapy, children, COVID-19, epidemiological characteristics, SARS-CoV-2, viral clearance, viral excretion

EVIDENCE BEFORE THIS STUDY

coronavirus disease 2019 is a highly contagious disease and has caused pandemics all over the world. Children had milder clinical symptoms, better clinical outcome, and more common fecal-viral excretion. However, their susceptibility for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a matter of debate, and if antiviral therapy affects viral shedding outcomes is unknown.

ADDED VALUE OF THIS STUDY

We investigated all contacts in the families with SARS-CoV-2 infected members, and analyzed the epidemical aspects in children in Zhejiang Province, China. We found that incidence of infection in children contacts was 13.2% (43/325, 95% confidence interval [CI]: 9.5-16.9), which was significant lower than that in adult contacts (21.2%, 108/510, 95% CI: 17.6-24.7) in the same families. The mean incubation period for children was 9.1 days. Fecal SARS-CoV-2 RNA detection was positive in 91.4% (32/35) cases and some children had viral excretion time exceeded 70 days. Viral clearance time was not different among the groups treated with different antiviral regiments. No subsequent infection was observed in family contacts of fecal-viral-excretion children.

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE

Children have lower susceptibility for SARS-CoV-2 infection, longer incubation, and fecal-viral excretion time. Positive results of fecal SARS-CoV-2 RNA detection are not used as indication for hospitalization or quarantine. No effect on fecal-viral clearance was observed when treated with antiviral regiments in the study.

1 | INTRODUCTION

Recently, a pandemic of coronavirus disease 2019 (COVID-19) broke out all over the world. By 10 June 2020, more than seven million cases infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were reported worldwide.[1] Reports on COVID-19 exploded and most of them were focused on adults.[2-6] Research involving pediatric cases with SARS-CoV-2 infection was rare.[5,7] A recent review of 72 314 cases by the Chinese Center for Disease Control and Prevention (CDC) showed that less than 2% of the patients were younger than 19 years.[8] Dong et al[9] analyzed the epidemiology of COVID-19 among children in China, reported that up to 8 February 2020, the total confirmed cases (≤16 years) were 574 national wide. The low incidence of pediatric COVID-19 has perplexed clinicians, epidemiologists, and

scientists.[10] Most of the researchers believe that children are susceptible for SARS-CoV-2 infection,[7,9,10] the absence of pediatric patients with COVID-19 should be attributed to low exposure to COVID-19 patients.[4] Xu et al[7] screened 745 children and 3174 adults by nasopharyngeal swab real-time PCR with reverse transcription (real-time reverse transcription PCR [RT-PCR]) for SARS-CoV-2 infection, found that confirmed cases were much fewer in children after exposure to COVID-19 patients than that in adults. Thus, if children have lower susceptibility for SARS-CoV-2 infection becomes a matter of debate. During the progress of COVID-19 outbreak, Zhejiang was one of the hard-hit provinces.[9] The number of confirmed cases rose rapidly along with the return of merchants and college students who lived in Wuhan before the Spring Festival, which made it possible to perform a family clustering study on the susceptibility to SARS-CoV-2 infection in children. During the preparation of our manuscript, a report on clinical and epidemiological features of 36 children (≤16 years) with COVID-19 in Zhejiang, China, the same region as our study, was published in the journal of Lancet Infectious Disease.[11] The data showed that children with COVID-19 had mild or asymptomatic disease accompanied by pneumonia in about half the cases. Certainly, there was some overlap of patients' population in both studies. Our study had enrolled all pediatric cases in Zhejiang Province, which were about 30% more cases (≤14 years) than the previous study.[11] In addition to the similar clinical characteristic as described by Qiu et al,[11] we have added analysis on the susceptibility of SARS-CoV-2 infection in children contacts and adult contacts in the same families, investigation on viral shedding and evaluation the effectiveness on viral clearance of different antiviral treatments by long time of follow-up. Our study addressed some of the most essential and unanswered questions that were not reported by Qiu et al[11] Thus, the objective of the current study was to describe the epidemiological and viral clearance aspects in all children from the families with SARS-CoV-2 infected members in Zhejiang province.

2 | METHODS

2.1 | Study design and participants

A retrospective, multicenter study including all pediatric cases (≤14 years) with SARS-CoV-2 infection, accompanied by follow-up, was designed in Zhejiang province, China. There was no selection of any sort on cases. Demographic information and epidemiological data of all pediatric cases were exacted from the electronic master database (updated daily) established by the Zhejiang Provincial CDC. All cases were confirmed based on positive results of an RT-PCR assay of SARS-CoV-2 RNA from respiratory specimens[12] and all cases with confirmed infection should be hospitalized at local designated hospitals according to the national policy. The epidemiological data were obtained from CDC records by Miao ZP (who were both health authorities from CDC and researchers in the study). Clinical data were obtained from the patients' medical records by the attending (who were researchers in the study too). Clinical outcomes were followed-up (till now) after the children were discharged (outpatients follow-up by attending and telephone follow-up by Hua CZ). Children's epidemiological information was confirmed again with children's guardians by direct telephone communication during the follow-up process. The incubation period was from the initial exposure to the illness onset day. Initial exposure was defined as the day when children were exposed to the confirmed patients for those who occasionally visited; or previous 3 days when the first patient had illness onset in the family for those who lived together.[13] All data were cross-checked by two researchers (Hua CZ and Miao ZP).

This study was approved by both the institutional ethics board of Zhejiang Provincial CDC (T-043-R) and ethics commission of all designated hospitals for recruiting COVID-19 patients. Individual privacy was protected during the study. Oral consents were obtained from the guardians of the children.

2.2 | Statistical analysis

SPSS software 20.0 (IMM) was used in the study. Age and time variables were described as mean (standard deviation [SD]) if they were normally distributed and compared with *t* test, or expressed as median (interquartile range) if they were not normally distributed and days in hospital among groups with different antiviral therapeutic regimens were compared with the Kruskal-Wallis test. Categorical variables were described as number (%) and the prevalence of SARS-CoV-2 infection was compared by χ^2 test between children group and adult group. Fisher's exact test was used in comparing the positive rates of RT-PCR results in feces among groups with different antiviral regimes. A two-sided α of less than .05 was considered statistically significant. Epidemic trend analysis was conducted with R software version 3.5.3 (R Foundation for Statistical Computing).

2.3 | Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3 | RESULTS

3.1 | Epidemiological features of SARS-CoV-2 infection in children

By 29 February 2020, 1298 cases infected with SARS-CoV-2 were confirmed in Zhejiang province, China. The patients aged from 3 months 20 days to 96 years old, 43 of which (3.3%, 43/1298) were children (≤14 years).The epidemic trend of SARS-CoV-2 infection in children and adults in Zhejiang Province was shown in Figure 1.

All these 1298 cases were from 883 families excluding the prisoners, elderly people in gerocomium and students on campus, 714 families (80.9%) of which were successfully followed-up and

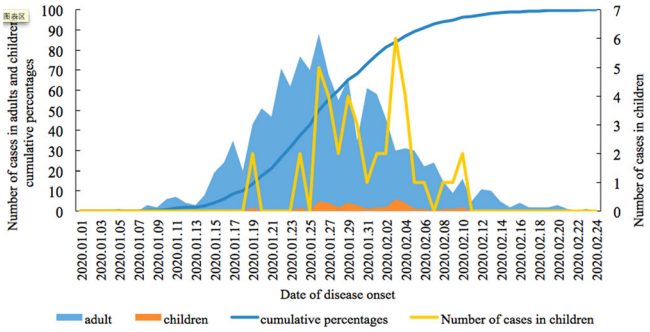

FIGURE 1 Epidemic trend of SARS-CoV-2 infection in children and adults in Zhejiang province. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

314 families had 417 children living together. Two of which were neonates born by pregnant women with COVID-19. Specimens evaluated from umbilical cord blood, neonatal blood, stool, and nasopharynx specimen, all were negative for SARS-CoV-2 RNA by RT-PCR.

The physical conditions of the children contacts and adult contacts from the 314 families with SARS-CoV-2 infected members in Zhejiang Province are shown in Table 1. All SARS-CoV-2 infection cases in the present study were confirmed by RT-PCR assay with respiratory specimen. Incidence of SARS-CoV-2 infection in children contacts (13.2%; 43/325; 95% confidence interval [C]I: 9.5-16.9) was lower than that in those adults contacts (21.2%; 108/510; 95% CI: 17.6-24.7), and the difference was statistically significant ($\chi^2 = 8.46$; $P = .004$).

The 43 cases who were not more than 14 years were analyzed, and 26 (60.5%, 26/43) were male. The children's ages were from 3 months 20 days to 14 years with a mean of 8.16 years (SD: 4.07). Forty children (93.0%) belong to family clustering cases and had long-term exposure (lived together with the family members with COVID-19 or had lived in epidemic areas, that is, Wuhan, or other cities in Hubei province). Three (7.0%, 3/43) children had shortterm exposure to COVID-19 patients directly (occasional visits or in public transportations). The incubation periods were ranging from 4 to 21 days, with a mean of 9.1 (SD: 3.7) days. Three patients (9.4%, 3/32) had incubation stages for more than 14 days. Twenty children (46.5%, 20/43) were imported cases[13]: children lived in Hubei province (12 in Wuhan city); six children were on vacation for 5 to 10 days in Hubei province (three in Wuhan); and one child lived in Henan province and came to Hangzhou for medical advice after his father, who is a doctor and treated suspected COVID-19 patients from Wuhan in his private clinic in countryside, thought they might have been infected by SARS-CoV-2. Feces were tested for SARS-CoV-2 RNA in 35 children by RT-PCR more than one time, and positive results were found in 32 (91.4%, 32/35) children.

3.2 | Clinical characteristics of pediatric COVID-19

Signs and symptoms in 43 children with SARS-CoV-2 infection are shown in Table 2. Two patients had vomiting, diarrhea, abdominal pain after receiving oral lopinavir/ritonavir and arbidol, and atomization inhalation with interferon-α2b in combination, and their gastrointestinal symptoms disappeared after lopinavir/ritonavir being removed or replaced with darunavir/cobicistat tablets. Liver function abnormality occurred in three patients after they received oral lopinavir/ritonavir and arbidol, and atomization inhalation with interferon-α2b (lopinavir/ritonavir was replaced with darunavir/cobicistat in one patient because of gastrointestinal symptoms). Thirty-six (83.7%, 36/43) children received chest computed tomography (CT) examination 1 to 8 times when they were in hospital or during the outpatient follow-up. Twenty children had imaging evidence for pneumonia, and nine had patchy shadow mainly in the peripheral lung fields. Three (15.0%, 3/20) children were asymptomatic and did not have imaging finding during the first week in hospital, but had patchy shadow or unilateral ground-glass opacity by chest CT when rechecked before being discharged (three patients) or after being discharged (one patient). Unilateral pneumonia were found by CT in three children whose chest X-rays were normal. Several time points in 20 patients with SARS-CoV-2 pneumonia are shown in Table 3.

TABLE 1 The prevalence of infection in the children contacts and adult contacts from the 314 families with SARS-CoV-2 infected members in Zhejiang province, China

Physical condition	Total n	Children n (%)	Adults n (%)	Statistic values
SARS-CoV-2 infection	151	43 (10.3%)[a]	108 (17.1%)	$\chi^2 = 9.36$, $P = .002$[b]
COVID-19	133	33 (76.7%)	100 (92.6%)	$\chi^2 = 7.35$, $P = .007$[c]
Asymptomatic infection	18	10 (23.3%)	8 (7.4%)	
Negative results of RT-PCR	684	282 (67.6%)	402 (63.6%)	$\chi^2 = 1.79$, $P = .18$[b]
Not tested	214	92 (22.1%)	122 (19.3%)	$\chi^2 = 1.18$, $P = .28$[b]
Total (n)	1049	417	632	

Abbreviations: COVID-19, coronavirus disease 2019; RT-PCR, real-time reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

[a]Eight of which were brothers and sisters from four families.

[b]Comparison on incidence between children contacts and adult contacts.

[c]Comparison on constituent ratio of COVID-19 between pediatric cases and adult cases with SARS-CoV-2 infection.

TABLE 2 Signs, symptoms, imaging finding, leucocytes, and lymphocytes counts in 43 pediatric patients with SARS-CoV-2 infection in Zhejiang province

Signs and symptoms	Initial symptoms or signs on admission (n)	During the whole course (n)
Asymptomatic	10	10
Fever	17	21
Highest temperature (°C)		
≤37.4°C	14	10
37.5-38.9°C	14	17
≥39°C	3	4
Cough	5	12
Stuffy running nose	4	7
Fatigue	1	3
Diarrhea	1	3
Vomiting and abdominal pain	0	2
Liver function abnormality[a]	1	4
Shortness of breath, chest tightness, and headache	0	1
Imaging finding	16	20
Bilateral involvement	3	4
Unilateral involvement	13	16
Bilateral or unilateral ground-glass opacity	7	9
Leucocytes $<4\times10^9$/L (n)	4	5
lymphocytes $<1.2\times10^9$/L (n)	1	3

[a]Alanine aminotransferase, ALT 54-112 U/L, aspartate aminotransferase, AST 57-124 U/L.

3.3 | Treatment and outcome

All children were treated in isolation, and stayed in designated hospitals for recruiting COVID-19 patients. Only seven (16.3%, 7/43) of the children were hospitalized in the infectious disease ward in the children's hospital or in pediatric ward in general hospitals. Thirty-eight children (88.4%, 38/43) received antiviral treatment, including 21 with monotherapy, 17 with two or more than two antiviral drugs (Table 4), The duration of antiviral treatment ranged from 5 to 31 days with a mean as 14.9 (SD: 7.4) days. Five patients were not prescribed with any antiviral drugs. No patient was administered with corticosteroidor intravenous immunoglobulin. Oral Chinese medicine was used in 20 cases for 2 to 35 days. By 6 March 2020, all of the 43 children were discharged with favorable outcome. Their hospital stay ranged from 3 to 32 days with a mean of 20.2 (SD: 7.9) days. Criteria for discharge were based on viral clearance in respiratory samples from upper respiratory tract, improvement of clinical symptoms and chest radiographic evidence. Eighteen children (51.4%, 18/35) had positive results of SARS-CoV-2 RT-PCR in feces when they were discharged. Alanine aminotransferase increased from normal to 106 U/L in one child after he was discharged and had received more than 30 days of oral Chinese medicine (he had liver function abnormality after receiving antiviral treatment in hospital and had recovered when being discharged). All children were kept in quarantine for another 2 weeks, which included arrangement at resorts by the government for 35 and home quarantine for the other eight patients.

By the end of 20 April, 41 were followed-up by telephone for at least twice, and one patient still had positive fecal RT-PCR results. On days 7 and 14 after being discharged, the results of fecal RT-PCR switched to negative in 17.6% (3/17) and 33.3% (6/18) of the children, respectively. Positive fecal-viral excretions were confirmed by RT-PCR for more than 70 days in one child since illness onset (As of 20 April 2020, follow-up are going on). Figure 2 shows the clearance curves of SARS-CoV-2 in feces in cases treated with different antiviral regiments. None of their family contacts developed new infection during the quarantine periods. Imaging evidence for pneumonia was found in one child (he was asymptomatic at that time) when he was rechecked by CT 7 days after being discharged.

4 | DISCUSSION

Currently, a few studies on pediatric SARS-CoV-2 infection were reported accompanied by the global pandemic of COVID-19 in the world, though the numbers of cases included in these studies were usually small because of the low incidence in children. Xu et al[7] studied 745 children and 3174 adults who had either close contact with diagnosed patients or had family clusters and found that positive rate in adults was 2.7-fold higher than that in children. Similarly, in the present study, we investigated all of the contacts in the same families and found that the incidence of SARS-CoV-2 infection in children contacts was 13.2%, which was much lower than that in

TABLE 3 Several time points in 20 patients with SARS-CoV-2 pneumonia

	Minimum	Maximum	Mean (SD) or Median (IQR)
Days from illness onset to visit	1	10	3.3 (2.0)
Days from being exposed to illness onset	4	21	9.2 (4.1)
Symptomatic duration, d	1	10	4.6 (2.4)
Days from exposure to imaging finding	5	36	7 (6, 10)
Days from illness onset or positive RT-PCR finding to imaging finding	1	30	3 (1, 6)
Days in hospital	3	32	20.2 (7.9)
Days from the illness onset to results of RT-PCR in respiratory samples turned to negative	3	28	14.0 (6.6)

Note: Four children had "asymptomatic" pneumonia, one of which was diagnosed after being discharged.
Abbreviations: IQR, interquartile range; RT-PCR, real-time reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation.

adults contacts and was in accordance with the finding by Xu et al[7] and Lu et al,[14] and indicated that children are less susceptible to SARS-CoV-2 infection. SARS-CoV-2 uses the cell receptor angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) for infecting cells. Children were found to have significantly lower expression of SARS-CoV-2 receptors-ACE2 and TMPRSS2 in the upper and lower airways than that of adults,[15] and the reduced airway tissue expression of ACE2 and TMPRSS2 may be the reason why children had lower risk of infection.[16,17] With the implementation of policy to restrict the movement of people, the epidemic trend of COVID-19 in children was controlled much better than that in adults, and no new cases were confirmed since 10 February 2020, which may be due to the low susceptibility, as well as the reduced exposure. Most of the children were at school ages and were in family clusters. The epidemic peak in children was 2 weeks later than that in adults, which might be associated with the longer incubation stage.[7,18] The median incubation period in adults usually was 3.0 to 6.4 days.[2-6,19] Conversely, it was much longer in children.[7] The median incubation period was 9.1 days with a range as 4 to 21 days in the present study, which could partly explain why the number of pediatric cases was peaked 2 weeks after that of adult cases. A long incubation period in children indicated that quarantine period for children who had contacted confirmed patients should be longer.

Similar with the findings in previous studies,[5,7,20] symptoms in most of the pediatric patients with COVID-19 were mild, or even none. Most of patients did not seek medical care, and they were diagnosed because of their exposure history. Fever and cough were the most common symptoms, which were milder or even transient. Headaches, fatigue, and chest tightness, which were common symptoms in adults, were rare in children in our study. All of the patients recovered soon. Leukopenia and lymphocytopenia were not common and most of the children had normal C-reactive protein, which indicated the inflammatory response was mild.

Although children with SARS-CoV-2 infection had mild symptoms or even were asymptomatic, chest CT was still widely used. Most of the children received chest CT more than one time. Accordingly, more pneumonia, including "asymptomatic pneumonia," was confirmed based on abnormalities in chest CT imaging. Image manifestation was found upon admission in most adult patients, and the typical findings of chest CT images were bilateral pneumonia, multiple lobular ground-glass opacity, and subsegmental areas of consolidation.[2-6,17,21] Twenty percent of the children with pneumonia in our study were confirmed at the second week in hospital, or even after being discharged. The most common findings were unilateral pneumonia, isolated ground-glass opacity. Transient fever or respiratory symptoms were not present in half of the patients when pneumonic images were found by chest CT or X-ray, indicating that change in pulmonary image might be later than the appearance of clinical symptom. The possible progress of SARS-CoV-2, an emerging virus, in children was not clear, which might lead to the over examination by chest CT. Chest CT helps to find more cases with COVID-19 from children with mild symptoms or even without any symptoms.[21] Even so, when we look back on these children with SARS-CoV-2 infection, we question the necessity of chest CT in most cases with mild symptoms or even without any symptoms.

As previously mentioned, COVID-19 is an emerging disease and little was known about it in children when it broke out. Thus, an effective treatment has not been established. Symptoms in adults were severer, and antiviral drugs, such as oral lopinavir/ritonavir, oral arbidol, and atomization inhalation with interferon, were widely used in adults in Zhejiang province. Accordingly, pediatric cases, including asymptomatic children, most of which were hospitalized in infectious disease ward in general hospitals, were given antiviral drugs. It was difficult to analyze the effectiveness of antiviral therapy in children by the duration it needed to improve clinical symptoms, because their symptoms were mild and transient. As an alternative, we evaluated the outcome of treatment by analyzing the persistent respiratory and fecal-viral shedding, and found that there was no difference among the groups received no antiviral therapy, or received one, two, three, or more than three antiviral drugs. Furthermore, gastrointestinal reactions and liver function abnormality occurred in some children after receiving ≥3 antiviral drugs. Given that no

TABLE 4 Effectiveness on potential viral excretion time in children treated with different therapeutic regimens

	Without antiviral therapy (n = 5)	Antiviral monotherapy[a] (n = 21)	With two or more than two antiviral drugs[b] (n = 17)	Statistic values
Days in hospital	18.0 (11.0)	19.9 (6.2)	18.5 (8.8)	$\chi^2 = 0.14$, $P = .69$
Days of the course when antiviral treatment initiated	…	2.4 (1.9)	2.3 (1.3)	$t = 0.12$, $P = .90$
Days for antiviral treatment	…	13.2 (7.7)	15.9 (7.3)	$t = 1.12$, $P = .27$
Days when results of respiratory RT-PCR turned to negative	11.2 (5.2)	16.8 (7.7)	12.7 (6.6)	$\chi^2 = 5.62$, $P = .06$
Days when results of fecal RT-PCR turned to negative	38.0 (17.8)	30.2 (9.4)	28.8 (14.7)	$\chi^2 = 1.37$, $P = .51$
Numbers of the patients with positive RT-PCR results in feces when being discharged	2/3	9/18	6/12	$P = .34$

Note: A, atomization inhalation with interferon-α2b; B, oral lopinavir and ritonavir tablets; C, oral arbidol; D, oral or intravenous ribavirin.

Abbreviation: RT-PCR, real-time reverse transcription PCR.

[a]19 Cases with A, one case with B and D, respectively.

[b]Six cases with A and B; five cases with A and C; one cases with A and D. Two cases with A, B, and C; one cases with A, C, and D; one case with A, B, and C as initial treatment, and switched to A, C, and oral darunavir/cobicistat in combination later because of serious vomiting, abdominal pain, and diarrhea; one case with A, B, C, and oral oseltamivir.

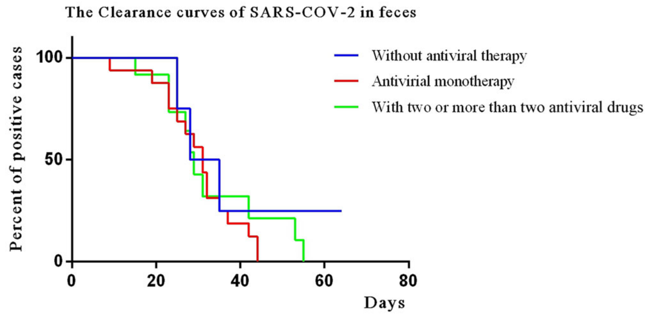

FIGURE 2 The clearance curves of SARS-cov-2 in feces in cases treated with different antiviral regiments. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

antiviral treatment for coronavirus infection has been proven to be effective, we advise that antiviral treatment might not be necessary for COVID-19 children without severe symptoms.[22] The best way to treat pediatric mild SARS-CoV-2 infection might be doing nothing except close monitoring and isolation.

In this study, 18 children were discharged with positive results of fecal SARS-CoV-2 RNA detection. All of them were quarantined for another 2 to 4 weeks at resorts or at home. No new patient was found among their family members with close contact. According to previous studies, no evidence of fecal-oral transmission has been found for respiratory virus, the human coronavirus SARS or MERS. Similarly, there is no conclusive evidence that SARS-CoV-2 can cause illness by ingesting contaminated food or water to date. Therefore, we believe that a negative result of SARS-CoV-2 RNA detection in feces is not necessary for patients, whose clinical signs and symptoms had disappeared, to be discharged or released from isolation.[23] The level of expression of the viral receptor (ACE2) and TMPRSS2, especially in the nasal tissue, may be critical for the ability of the virus to transmit and replicate. The reason for prolonged viral shedding in feces in children is unknown yet. As the receptor of SARS-CoV-2, ACE2, was abundantly expressed in gastric, duodenal and rectal epithelia in COVID-19 patients,[24] which may lead to virus internalization and accumulation in these organs. It might explain the prolonged fecal virus shedding but needs to be further investigated.

In the present study, there were two neonates delivered by mothers with COVID-19, fortunately, neither clinical nor laboratory evidence for SARS-CoV-2 infection was confirmed in these babies. Till now, no case with vertical transmission was identified among pregnant women infected with SARS-CoV or MERS-CoV.[25] However, during the epidemic of COVID-19 in China, a neonate, delivered by a SARS-CoV-2 infected pregnant woman in Wuhan, was confirmed with COVID-19 at the age of 30-hour-old. The baby had shortness of breath together with abnormal chest imaging and liver function abnormalities.[26] The possible route of SARS-CoV-2 transmission between the mother and neonate was not conclusive.[25]

Our study has some limitations. First, the size of the cases was small, and all of the 43 children with SARS-CoV-2 infection were hospitalized in 15 local designated hospitals according to the

principle of localization management, the program for pediatric cases was not run across hospitals. The diagnosis was confirmed with respiratory tract specimens and paired rectal swabs or feces specimens were not obtained for all children. The interval time of SARS-CoV-2 RNA detection was also variable. Therefore the durations of viral excretion through the gastrointestinal and respiratory tracts were not accurate. Second, not all children in the family with infected members were checked by real-time RT-PCR for SARS-CoV-2 RNA. Adolescent was not separated from the adult group because of the small sample size. Finally, the finding that antiviral therapy did not affect viral shedding outcomes was evaluated observationally, further study based on clinical trials of antiviral therapies is needed.

In conclusion, we found that susceptibility of SARS-CoV-2 infection in children was lower, and the incubation periods were longer than that in adults. The clinical symptoms in pediatric cases were mild. Chest CT or X-ray is helpful for diagnosing SARS-CoV-2 pneumonia; however, the necessity is questionable because most patients had mild symptoms and would be self-healing. Benefit of antiviral treatment on improving the clinical signs or shortening the duration of potential viral excretion was not conclusive and further study is needed. At last, positive results of fecal SARS-CoV-2 RNA detection should not be used as indication for hospitalization or quarantine.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

HCZ and MZP contributed to writing of the paper and took responsibility for the integrity of the data and the accuracy of the data analysis. ZJS, HQ, SQF, LHP, SFF, WWH, HLP, XZW, JLD, ZHP, YXW, LMH, MYY, YMZ, and YS contributed to treatment of the patients, acquisition and interpretation of clinical data. LJF contributed to analysis of data. WW and CZM contributed to critical revision of the paper. SQ, CEF, and FJF conceived the idea for and designed the study and had full access to all data in the study. All authors reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Participant data without names and identifiers will be made available after approval from the corresponding authors and Zhejiang Provincial CDC. All authors declare that this submission could be shared directly with the WHO.

ETHICS STATEMENT

The study was approved by both the institutional ethics board of Zhejiang Provincial CDC (T-043-R) and ethics commission of all designated hospitals for recruiting COVID-19 patients. Oral consents were obtained from the guardians of children.

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