Prolonged viral shedding in feces of children with COVID-19: a systematic review and synthesis of data

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Abstract
During the coronavirus disease 2019 (COVID-19) epidemic, many reports have indicated that children shed the virus longer than adults in stool, and that most of the children had mild or even asymptomatic infections, which increased the potential risk for feces to be a source of contamination and may play an important role in the spread of the virus. In this review, we collected relevant literature to summarize the duration of fecal viral shedding in children with COVID-19. We found that in about 60% of the cases, the fecal shedding time was between 28 and 42 days, which was much longer than that of adults. We further explored the possible reason for prolonged shedding and its the potential impact. The poor hand hygiene practices of children, their tendency to swallow sputum and/or saliva, the significant difference in expression of angiotensin-converting enzyme 2 (ACE2) in intestine between children and adults, and the variance in immune status and intestinal microbiome could be considered as potential casual agents of longer fecal viral shedding duration of children.

Conclusion: Children with COVID-19 show prolonged fecal shedding compared to adults. Several mechanisms may be involved in the longer fecal viral shedding. Viral shedding in the stool could be contributing to a possible route of transmission. Therefore, we think that further preventive measures in children should be taken to reduce the spread of the disease.

What is Known:
- Children with COVID-19 are more likely to have asymptomatic infections and to experience mild symptoms.
- Some patients continue to shed the virus in feces, despite respiratory samples testing negative.

What is New:
- Children with COVID-19 carried a longer-term fecal viral shedding than adults.
- The poor hand hygiene practices of children, their tendency to swallow sputum and/or saliva, the difference in expression of ACE2 in intestine between children and adults, and the variance in immune status and intestinal microbiome could be considered as potential casual agents of longer fecal viral shedding duration of children.

Keywords COVID-19 · Children · Stool · Viral shedding

Abbreviations
- ACE2: Angiotensin-converting enzyme 2
- COVID-19: Coronavirus disease 2019
- PCR: Polymerase chain reaction
- RNA: Ribonucleic acid
- SARS-CoV-2: Syndrome coronavirus 2
- 2019-nCoV: 2019 Novel coronavirus
- MERS-CoV: Middle East respiratory syndrome coronavirus

Introduction
COVID-19 continues to pose a global threat with the emergence of new variants. It has been reported that children with COVID-19 often had a milder disease course and they were possible sources of its spread [1]. Children have also reported to have prolonged shedding of syndrome coronavirus 2
(SARS-CoV-2) in feces compared to adults[2–4], which, combined with the possibility of fecal–oral transmission [5], lead to concerns that children may be potential sources of undetected community transmission. This study aims to summarize the existing data on the duration of fecal viral shedding in children with COVID-19 and explore the reasons for prolonged shedding and its potential effects.

**Method**

A systematic electronic databases search was performed in PubMed/MEDLINE and Web of Science using the search terms “COVID-19 or 2019-nCoV or SARS-CoV-2” and “pediatrics or children or infant or neonate or teenagers or adolescents” and “fecal or fecal or stool or rectal” between 2019 and the present time (i.e., January 6, 2022). In addition, the reference lists of all known primary and review articles were scrutinized to identify cited articles not captured by the electronic searches. Studies were included if they reported data on the duration of gastrointestinal viral shedding in children with COVID-19 in English.

The initial search produced 153 potentially relevant articles. After removing duplicates and excluding irrelevant articles, 70 full-text articles were assessed. Articles were further excluded because of the following: (1) the articles did not present original data (n = 7); (2) reported cases with incomplete information (n = 7); (3) review articles, meta-analyses, perspectives, comments, opinion articles, and letters (n = 21); (4) no original data (n = 7); (5) incomplete information (n = 7); (6) adult-only or including both adults and children but not presenting sufficient data for children (n = 10).

Studies included in data synthesis (n = 25) = 176 patients.
meta-analyses, perspectives, comments, opinion articles, and letters (n = 21); (4) studies including adult-only or including adults and children but not did not present sufficient data for children (n = 10); and (5) studies not written in English (Fig. 1).

Results

A total of 25 studies (n = 176 patients) were included in the final analysis [2–4, 6–27]. Among the selected studies, 14 (56%) were from China and 11 (44%) were from other countries (South Korea: three, Japan: one, Singapore: one, Italy: one, the Netherlands: one, Germany: one, India: one, and Iran: one). The number of cases enrolled in each study ranged from one to 49 and the age ranged from 7 days to 210 months. Of the 176 cases, 175 (99.4%) had a positive nasopharyngeal or throat swab (one case had positive stool specimens only). The duration of viral shedding via the respiratory route ranged from 0 day to at least 1 month, and the duration of gastrointestinal viral shedding ranged from 6 to 100 days. Several studies reported the duration of viral shedding as a range only, and thus, the mean value could not be calculated. The prevalence of all gastrointestinal symptoms was 24% (43/176), including diarrhea, vomiting, abdominal pain, liver function abnormality, nausea, gastric appetite, and constipation (Table 1).

According to the viral shedding time of anal/rectal swabs and stool specimens, these cases can be divided further into five groups: less than 14 days, 14–28 days, 28–42 days, 42–56 days, and more than 56 days. In 60% of the cases, the gastrointestinal shedding time was between 28 and 42 days, while only 4% of the cases presented shedding time shorter than 14 days, and only 2% of the cases reported shedding time longer than 56 days. The number of cases in the remaining two groups accounted for 26% and 8%, respectively (Fig. 2).

Discussion

SARS-CoV-2, SARS-CoV, and the Middle East respiratory syndrome-CoV (MERS-CoV) are three new species from the same coronavirus family, which are notorious to global people as they caused epidemics of serious respiratory disease. A clear difference between them was the detection of viral RNA in stool. It was reported that MERS-CoV RNA was detectable in only 14.6% of stool samples from infected patients [28], while for SARS-CoV and SARS-CoV-2, the RNA prevalence in stool samples was very high. Ling et al. found that the SARS-CoV-2 RNA can be detected in the stool of 81.8% (54/66) adult patients, and the median time from the onset of symptoms to first negative RT-PCR results for stool specimens was 11.0 (9.0–16.0) days [29]. Chen et al. found that the median duration time of positive RT-PCR test results for viral RNA in feces was 9, 8, and 14 days in uncomplicated, mild, and severe adult patients, respectively [30]. In one systematic review of 55 studies (1348 patients), the median duration of fecal RT-PCR positivity of children and adults was 22 days and 18 days, respectively [31]. Another meta-analysis suggested a median duration of 19.2 days for fecal viral clearance in adults [32]. In this study, we investigated the duration of gastrointestinal viral shedding in children and found that 60% of the cases were between 28 and 42 days, and some children presented viral excretion time of over 56 days. These findings demonstrated that children with COVID-19 have a longer-term fecal viral shedding than adults.

The reasons why children need a longer time to shed SARS-CoV-2 in their stool have not yet been fully understood. In the following, we summarize several possible mechanisms. First, SARS-CoV-2 gains entry to cells through the ACE2 receptor [33], which has been detected in intestinal cells [34]. Recently, in vitro models of SARS-CoV-2 infection show that the pediatric and late fetal gastric organoids are susceptible to infection with SARS-CoV-2, while viral replication is significantly lower in undifferentiated organoids of adult origin [35]. The different expression of ACE2 in the intestines from children and adults may play a role in the duration of gastrointestinal viral shedding. Second, the duration of viral shedding is related closely to the host immune status. Several studies have suggested that immunocompromised COVID-19 patients may have prolonged periods of SARS-CoV-2 viral shedding [36, 37]. A study of 104 COVID-19 patients by Hao et al. reported that a decrease in T cells and B cells was associated with prolonged viral RNA shedding [38]. For other respiratory viral infections, such as influenza [39], adenovirus [40], and norovirus [41], current data available suggest high rates of asymptomatic carriage in the stool and a prolonged carrier state in children, which are related in part to children’s current stage of immune development. It can be interpreted that prolonged fecal viral RNA shedding in children with COVID-19 may be related to the immaturity of their immune systems. Third, gut microbiota has been reported to play a key role in determining the sensitivity of patients to viral infection. An animal study showed that the bacterial microbiome prevented persistent murine norovirus infection via the replenishment of the bacterial microbiota related to host immune specificity [41]. Another research has confirmed that Coprobacillus spp. has been observed to upregulate ACE2 in the murine gut [42]. Recently emerging evidence has suggested a link between the infection of COVID-19 and gut microbiome status [43–45]. Studies show that when compared to the microbiota of adults, children have less...
Table 1 Characteristics of the included studies

| Study | Setting | Age | Sample size | Specimens tested | Method          | Duration of respiratory viral shedding | Duration of gastrointestinal viral shedding | Gastrointestinal symptoms |
|-------|---------|-----|-------------|------------------|-----------------|----------------------------------------|------------------------------------------|--------------------------|
| 1. Cho and Ha [8] | Korea   | 45 days | 1           | Nasal swab, urine and serum specimens, stool specimens | RT-PCR         | 21 days      | >12 weeks                  | Diarrhea                  |
| 2. Holm-Jacobsen et al. [24] | Denmark | 22 days | 1           | Pharyngeal and rectal swabs | RT-PCR         | 11 days      | 45 days                  | N/A                       |
| 3. Uda et al. [27] | Japan   | 21 months | 1          | Nasopharyngeal and stool samples | RT-PCR         | 13 days      | 61 days                  | N/A                       |
| 4. De Ioris et al. [9] | Italy   | 8 days–210 months | 22         | Nasopharyngeal swab, stool samples | RT-PCR         | 8 days       | 14 days                  | Diarrhea and vomiting     |
| 5. Wolf et al. [21] | Germany | 2 years, 5 years | 2           | Nasopharyngeal swabs, stools samples | RT-PCR         | 5–6 days     | >4 weeks                  | Vomiting                  |
| 6. Dong et al. [10] | China, Wuhan | 2 years | 2           | Nasopharyngeal, rectal specimen | RT-PCR         | 0 day       | 45 days                  | Vomiting (n=1)            |
| 7. Xing et al. [2] | China, Qingdao | 1.5 years, 5 years, 6 years | 3           | Throat swabs, fecal specimens | RT-PCR         | 15 days      | 23 days                  | Abdominal pain and diarrhea (n=1) |
| 8. Tariverdi et al. [26] | Iran     | 27 months | 1           | Nasopharyngeal and stool samples | RT-PCR         | >1 month     | >1 month                  | diarrhea                  |
| 9. Mohanty et al. [25] | India   | 17 months, 36 months | 2           | Nasal/throat swab, stool samples | RT-PCR         | Not tested        | 99 days                  | N/A                       |
| 10. Chen et al. [7] | China, Liaocheng | 11 months | 1           | Nasopharyngeal swab, fecal samples | RT-PCR         | 22 days      | 100 days                 | N/A                       |
| 11. Ma et al. [3] | China, Jinan | 11 months–9 years | 6           | Nasal/throat, stool swab | RT-PCR         | 1–14 days      | >22–35 days              | N/A                       |
| 12. Slaats et al. [18] | Netherlands | 7 days | 1           | Nasopharyngeal swab, stool samples | RT-PCR         | 19 days      | 42 days                  | N/A                       |
| 13. Cai et al. [6] | China, Shanghai | 11.5±5.12 years | 49         | Nasopharyngeal swab, pharyngeal swab, and stool specimen | RT-PCR         | 14.1±6.4 days (asymptomatic cases) 14.8±8.4 days (symptomatic cases) 28.1±13.3 days (asymptomatic cases) 30.8±18.6 days (symptomatic cases) | N/A                        |
| 14. Xu et al. [4] | China, Guangzhou | 2 months–15 years | 10          | Nasopharyngeal and rectal swab | RT-PCR         | 2–20 days      | 6–29 days                | N/A                       |
| 15. Jiehao et al. [14] | China, Shanghai | 3–131 months | 10          | Nasopharyngeal/ pharyngeal swabs, stool samples, urine, serum | RT-PCR         | 12 days      | 10–30 days               | N/A                       |
| 16. Liu et al. [16] | China, Shanghai | 7–139 months | 9           | Nasopharyngeal/ oropharyngeal swabs, stool samples | RT-PCR         | 4–13 days      | 43 days                  | N/A                       |
| 17. Hua et al. [13] | China, Hangzhou | 8.2 years | 43         | Respiratory, fecal swab | RT-PCR         | 14.5 days      | 30.6 days                | Diarrhea (n=3), vomiting and abdominal pain (n=2), liver function abnormality (n=4) |
| 18. Fan et al. [11] | China, Jingzhou | 3 months | 1           | Oropharyngeal swabs, the anal swabs | RT-PCR         | 14 days      | 28 days                  | Diarrhea                  |
| 19. Zhang et al. [23] | China, Tianjin | 6–9 years | 3           | Throat swab, stool | RT-PCR         | 10.6 days      | >24 days                  | Nausea (n=1), gastric appetite (n=2) |
| 20. Kam et al. [15] | Singapore | 6 months | 1           | Nasopharyngeal specimens, stool sample | RT-PCR         | 16 days      | >9 days                  | N/A                       |
diverse microbiota despite the higher bacterial load [46], and thus, the differences in the gut microbiota may alter the ability of the virus to gain cellular entry into the gut, which may further influence the duration of viral shedding. Four, other factors could also play a role. Ma et al. [3] think that children often have poorer hand hygiene practices, causing contamination of the gastrointestinal tract through repeated touching with hands containing the virus or its fragments, and they are more prone to silent aspiration, and thus, the virus in the sputum or saliva may enter the gastrointestinal tract through swallowing.

In addition to the reasons for prolonged viral shedding in feces, the infectivity of these particles and whether they harbor the potential to be spread fecally orally have yet to be discussed. During the SARS-CoV-1 outbreak in 2003, high concentrations of SARS CoV were found in the feces and urine of a patient, which, leading to the formation of viral aerosols, and later studies suggest that the plumbing and ventilation systems interacted to transmit the SARS-CoV at an apartment complex in Hong Kong rapidly [47]. Recent studies have been able to isolate live viruses from stool or rectal swabs [5, 48, 49]. Lin et al. demonstrated that gastrointestinal symptoms can be more severe when the SARS-CoV-2 is present in gastrointestinal tissue confirming by endoscopy [50]. Moreover, it has been reported that viral particles in environmental settings may remain viable for up to 3 h in aerosols and 72 h on solid surfaces [51]. These findings suggested that viral shedding in the stool could be contributing to a possible route of transmission.

Recently, a new SARS-CoV-2 variant called Omicron was first reported in South Africa and quickly spread to other countries [52]. Compared with the previous variants, Omicron appears to be more infectious but causes a milder disease with younger patients and fewer hospitalizations [53, 54]. Given the situation, mild and atypical presentations of the infection in children may make early discovery difficult, and combined with the prolonged viral shedding in their feces and poorer hand hygiene practices, it may lead to further transmission of the disease.

### Conclusion

Children with COVID-19 show prolonged fecal shedding compared to adults. The poor hand hygiene practices of children, their tendency to swallow sputum and/or saliva, the significant difference in expression of ACE2 in the intestine between children and adults, and the variance in immune status and intestinal microbiome could be considered as potential casual agents of longer fecal viral shedding duration of children. Viral shedding in the stool could be contributing to a possible route of transmission. Therefore, to reduce the spread of the disease, further preventive measures in children should be taken, including hand hygiene and disinfection of public areas and health places.
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Declarations

Ethical approval This is a review article. No ethical approval is required.

Conflict of interest The authors declare no competing interests.

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