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REVIEW

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
SARSCoV-2	Syndrome coronavirus 2
2019-nCoV	2019 Novel coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus

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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,

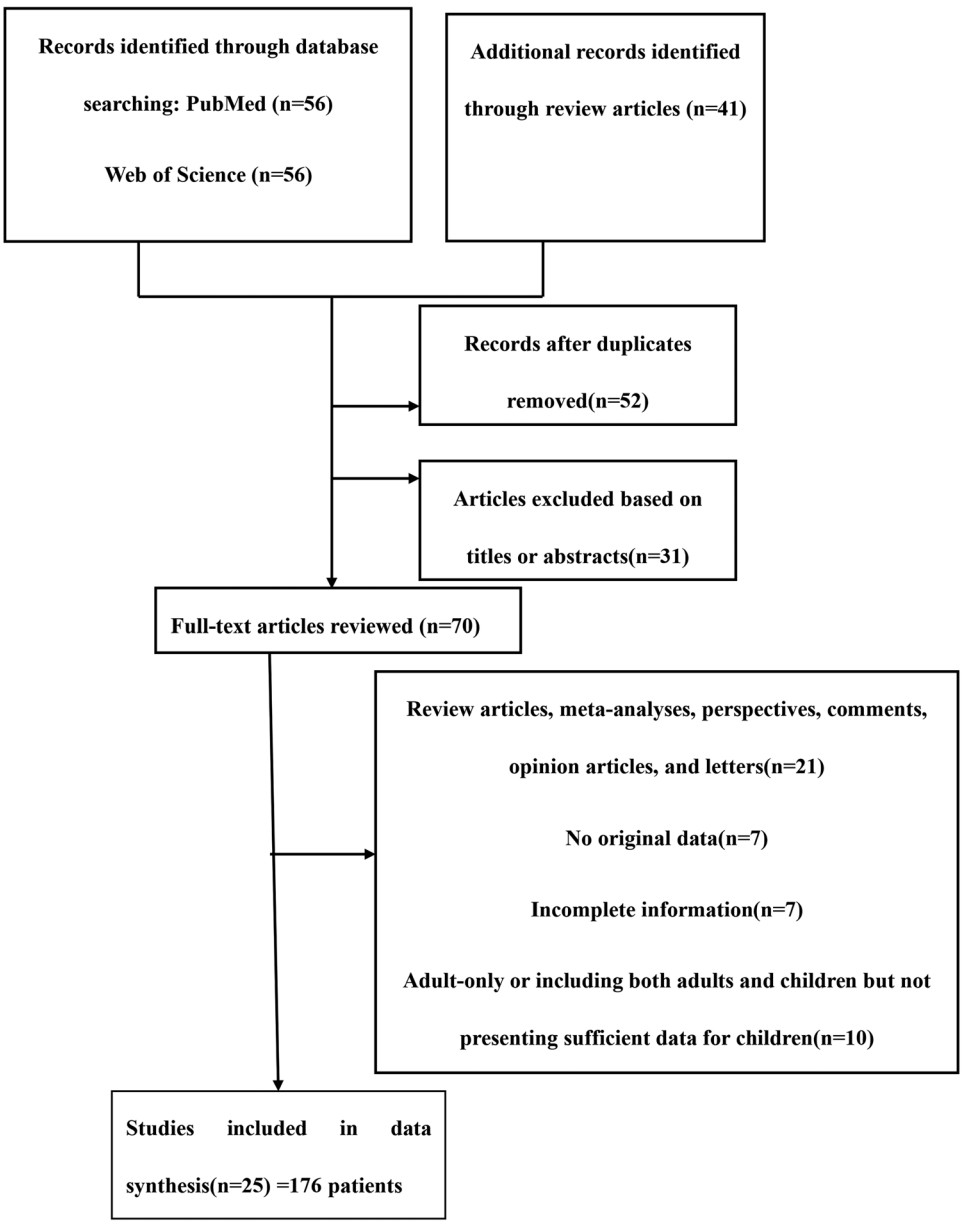

Fig. 1 Flowchart depicting the literature search and selection strategy. After applying the inclusion and exclusion criteria, a total of 25 articles were included in the final analysis

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 10 days	45 days 39 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 13 days 10 days	23 days 33 days 30 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 53 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/ throat swabs, fecal 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, stools	RT-PCR	4–13 days	43 days	N/A
17. Hua et al. 13	China, Hangzhou	8.2 years	43	Respiratory, fecal RT-PCR	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

Table 1 (continued)

Study	Setting	Age	Sample size	Specimens tested	Method	Duration of respiratory viral shedding	Duration of gastrointestinal viral shedding	Gastrointestinal symptoms
21. Park et al. [17]	Korea	10 years	1	Nasopharynx/throat, stool	RT-PCR	13 days	> 18 days	N/A
22. Tan et al. [19]	China, Changsha	8 years	1	Throat, stool swab samples	RT-PCR	10 days	24 days	Constipation
23. Tang et al. [20]	China, Zhou Shan	10 years	1	Nasopharyngeal swab, sputum samples, stool specimen	RT-PCR	0 days	11 days	N/A
24. Zhang et al. [22]	China, Guangdong	10 months, 13 and 14 years	3	Throat and rectal swabs	RT-PCR	6.3 days	27 days	N/A
25. Han et al. [12]	Korea	27 days	1	Nasopharyngeal swab, stool, urine	RT-PCR	17 days	18 days	Vomiting

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.

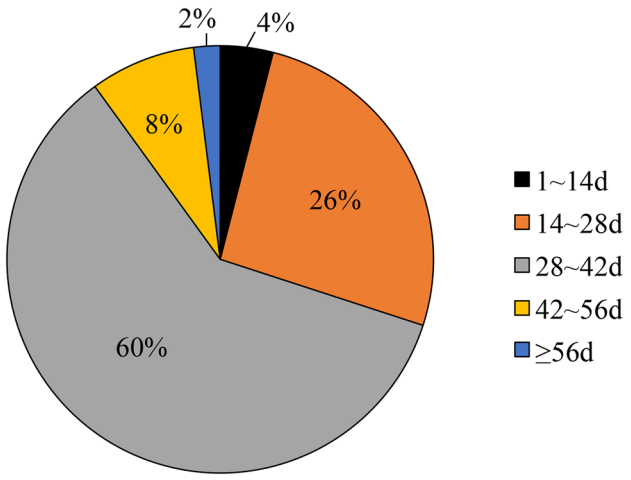

Fig. 2 Duration of gastrointestinal viral shedding

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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