Duration of Respiratory and Gastrointestinal Viral Shedding in Children With SARS-CoV-2: A Systematic Review and Synthesis of Data

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Background: Children with coronavirus disease 2019 (COVID-19) are more likely to have mild or no symptoms compared with adults and may represent important vectors for transmitting the virus. Little is known about the duration of respiratory and gastrointestinal viral shedding in children with COVID-19.

Objective: To determine the average shedding times of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via the respiratory and gastrointestinal tracts in children.

Methods: We performed a systematic search of Ovid MEDLINE, Embase and Cochrane CENTRAL databases for studies reporting real-time reverse transcriptase polymerase chain reaction (rt-PCR) results in children with COVID-19, then extracted and synthesized data on duration of viral shedding from symptom onset in respiratory and gastrointestinal samples.

Results: Based on data compiled from 69 pediatric cases, the duration of viral shedding through the respiratory tract is up to 24 days from symptom onset with a mean of 11.1 ± 5.8 days. Of the children who underwent testing with stool PCR, rectal swab or anal swab, 86% returned a positive result. The mean duration of viral shedding via the gastrointestinal tract was 23.6 ± 8.8 days from symptom onset. In 89% of cases, viral shedding via the gastrointestinal tract persisted after nasopharyngeal or throat swabs became negative, for as long as 4 weeks.

Conclusions: To our knowledge, this is the first attempt to systematically review the duration of respiratory and gastrointestinal viral shedding of SARS-CoV-2 in pediatric patients. These findings may have important implications for infection control strategies during the COVID-19 pandemic.

Key Words: coronavirus, COVID-19, SARS-CoV-2, children, viral shedding

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As of May 23, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 5 million people globally with an estimated 338,000 deaths.[1] Children represent 1%–5% of reported cases of COVID-19, the disease caused by SARS-CoV-2.[2] As with previous coronaviruses including SARS and Middle East respiratory syndrome (MERS), children are more likely to have mild disease or be asymptomatic compared with adults.[3–5] Children may therefore be important vectors for transmitting SARS-CoV-2.

Individuals infected by SARS-CoV-2 are known to shed the virus through both the respiratory and gastrointestinal tracts, as indicated by detection of SARS-CoV-2 RNA in the nasopharynx and feces via real-time reverse transcriptase polymerase chain reaction (rRT-PCR).[6,7]

Although SARS-CoV-2 is thought to predominantly be transmitted by respiratory droplets, growing evidence suggests that fecal-oral transmission is possible. High copy numbers (mean cycle threshold 31.4, similar to that of sputum and pharyngeal swabs) of SARS-CoV-2 RNA, as well as live virus, have been isolated from the feces of individuals with SARS-CoV-2.[6] Furthermore, ACE2 protein, a proven cell receptor for SARS-CoV-2, is abundantly expressed in the gastrointestinal tract.[8,9] Endoscopic sampling of patients with SARS-CoV-2 has recently demonstrated an intracellular staining of viral nucleocapsid protein in the gastric, duodenal and rectal epithelia.[8] Up to 79% of individuals with COVID-19 are known to exhibit gastrointestinal symptoms including diarrhea and vomiting, which can be present even in the absence of respiratory symptoms.[10] Compared with adults, children with COVID-19 have a higher incidence of gastrointestinal symptoms, particularly vomiting.[3,10] Fecal-oral transmission may therefore pose an important consideration for infection prevention and control practices, particularly in the pediatric population.

This systematic review compiles published data from pediatric cases of SARS-CoV-2 with the aim of determining the mean and upper limit of duration of viral shedding via both the respiratory and gastrointestinal routes.

MATERIALS AND METHODS

We searched Ovid MEDLINE, Embase and Cochrane Central for all published literature relating to SARS-CoV-2 viral shedding in the upper respiratory or gastrointestinal tract of children up until May 8, 2020 using the search strategies detailed below.

Ovid Medline and Embase

(Coronavirinae/OR coronavirus.mp. OR Coronavirus Infection/OR coronavirus infections.mp. OR novel coronavirus.mp. OR 2019 novel coronavirus infection.mp. OR covid-19.mp. OR covid 19.mp. OR SARS-CoV-2.mp. OR 2019-nCoV) AND (Pediatrics/ OR Child/ OR Infant/ OR ped*.mp. OR paed*.mp. OR child*.mp.) AND (Virus Shedding/ OR viral shedding.mp. OR shedding.mp. OR nasopharyn*.mp. OR throat.mp. OR oral.mp. OR fec*.mp. OR faec*.mp. OR stool*.mp. OR rectum.mp. OR rectal.mp. OR anal.mp.)

Limited to English Language and Year 2019-Current.

Cochrane Central

([mh "coronavirinae"] OR "coronavirus" OR [mh "coronavirus infection"] OR "coronavirus infections" OR "novel coronavirus" OR "2019 novel coronavirus infection" OR "covid-19"

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OR "SARS-CoV-2" OR "2019-nCoV") AND ([mh "Pediatrics"] OR [mh "Child"] OR [mh "Infant"] OR "ped*" OR "paed*" OR "child*") AND ([mh "Virus Shedding"] OR "viral shedding" OR "shedding" OR "nasophryn*" OR "throat" OR "oral" OR "fec*" OR "faec*" OR "stool*" OR "rectum" OR "rectal" OR "anal")

In addition to the literature search, a single reviewer (C.X.) screened the reference lists of all relevant review articles to identify any further potentially relevant studies. The abstracts returned were screened for inclusion by two reviewers (C.X. and M.R.) independently in a Microsoft Excel spreadsheet for potential relevance to viral shedding in pediatric patients with COVID-19. The full texts of potentially relevant articles were then screened by the same reviewers with a third reviewer (J.S.) adjudicating any differences in accordance with the following inclusion criteria:

1. Case report, case series or other descriptive study reporting original data on patients <18 years of age with rRT-PCR-confirmed SARS-CoV-2.
2. Reports the timing of at least one positive rRT-PCR test on a respiratory or gastrointestinal sample in relation to the time of symptom onset OR reports the duration of positive rRT-PCR test on a respiratory or gastrointestinal sample in an asymptomatic individual.

From each included study, a single reviewer (C.X.) extracted the following data items: age, sex, symptoms, disease severity, types of specimens collected, duration of viral shedding from the respiratory tract from symptom onset (defined as the number of days from symptom onset until the day of the first negative nasopharyngeal or throat swab result after which no more positive results were recorded, not counting the day of the negative test) and, if available, the duration of viral shedding from the gastrointestinal tract from symptom onset (defined as the number of days from symptom onset until the day of the first negative rectal swab or stool PCR result after which no more positive results were recorded, not counting the day of the negative test).

We used the duration of viral shedding from symptom onset as opposed to true duration of viral shedding, which is not possible to ascertain without presymptomatic testing. This is a similar approach to other publications on this topic.[11] For asymptomatic cases, the total documented duration of viral shedding was calculated as the number of days from the first positive result until the day of the first negative result, after which no more positive results were recorded. We used IBM SPSS Statistics (24.0.0.0) to determine the normality of the shedding data and to calculate the principal summary measures (mean and standard deviation). A single reviewer (C.X.) assessed the risk of bias for each included study using the Joanna Briggs Institute Critical Appraisal Checklist for case series or case reports, depending on the type of study.[12]

Given the recency of the SARS-CoV-2 pandemic, we also performed a search of unpublished, non peer-reviewed literature in medRxiv and bioRxiv. The findings from this search are reported under the subheading "Unpublished Literature" in the results section.

RESULTS

A flowchart depicting study selection is given in Figure 1. The literature search returned 261 records; 210 unique records after 51 duplicates were removed. Twenty-four records appeared potentially relevant at the initial review. The most common reasons for study exclusion at the initial review were not studying SARS-CoV-2, not including patients <18 years of age and not reporting clinical data. After reviewing the full texts, 7 of the 24 studies were excluded: 2 studies did not contain original data on children with SARS-CoV-2 (did not meet criterion 1) and 5 studies did not report positive PCR tests in relation to symptom onset (did not meet criterion 2). The remaining 17 studies were included for data

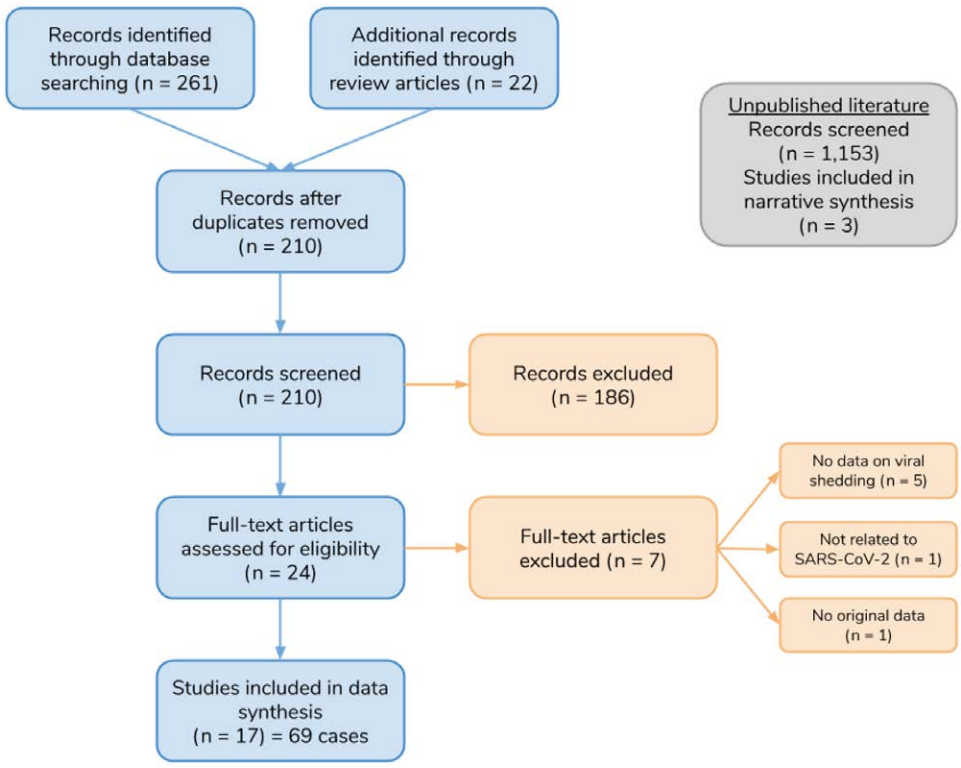

FIGURE 1. Peer-reviewed literature study selection.

extraction[13–29]: 6 studies were case reports and 11 were case series, defined by the Oxford Handbook of medical statistics as "a descriptive study involving a group of patients who all have the same disease or condition."[30] The 17 studies contained 73 individual cases of children with COVID-19. Data from 4 children were incomplete as they were still in hospital at the time of publication and were therefore excluded, leaving 69 individual cases for quantitative analysis. The age, sex, symptoms and durations of viral shedding for each individual case are given in Table 1.

Patient Characteristics

Age was reported for 67 of 69 cases and ranged from 36 hours to 15 years, with a mean age of 6 years. Sex was again reported for 67 cases, of which 37 (55.2%) were female. All cases were

TABLE 1. Demographic Data and Duration of Viral Shedding via Respiratory and Gastrointestinal Routes of 69 Pediatric Cases of SARS-CoV-2

Study	Age	Sex	Symptoms	Duration of Viral Shedding via Respiratory Route From Symptom Onset (d)	Duration of Viral Shedding via Gastrointestinal Route From Symptom Onset (d)	Gastrointestinal Specimen Type
Cai et al[13]	7 years	M	Fever Cough	12	>30	Stool
	10 years	F	Fever Coryza Sore throat	22	10	Stool
	10 years	F	Fever Cough Coryza Sore throat	8	>20	Stool
	9 years	M	Fever Cough Coryza Sore throat	8	>19	Stool
	7 months	F	Cough Coryza	6	>18	Stool
	6 years	F	Fever	15	Not tested	N/A
	3 months	F	Fever	8	>23	Stool
	4 years	F	Cough	12	Not tested	N/A
	8 years	M	Fever Sore throat	14	Not tested	N/A
	5 years	M	Fever Cough	15	Not tested	N/A
Danis et al[14]	N/A	N/A	Fever Cough	14	Not tested	N/A
	N/A	N/A	Fever Cough	11	Not tested	N/A
Fan et al[15]	3 months	F	Fever Diarrhea	13	≥28	Anal swab
Kam et al[16]	6 months	M	Fever	16	≥9	Stool
Lin et al[17]	7 years	F	Coryza	≥11	Negative	Anal swab
Ma et al[18]	8 years	F	Fever	8-14	22-28	Stool
	3 years	M	None[a]	1-7	≥35	Stool
	2 years	F	None[a]	8-14	≥35	Stool
	11 months	M	None[a]	1-7	≥28	Stool
	9 years	F	None[a]	1-7	≥28	Stool
	3 years	F	Fever	8-14	≥35	Stool
Park et al[19]	10 years	F	Fever Cough	13	≥18	Stool
See et al[20]	1 year	F	Fever Diarrhea	1	Negative	Rectal swab
	4 years	M	Fever Coryza	6	Not tested	N/A
	9 years	F	None[a]	8	Not tested	N/A
Shen et al[21]	1 years	F	None[a]	14	Not tested	N/A
	2 years	F	Fever	10	Not tested	N/A
	8 years	M	Fever	10	Not tested	N/A
	8 years	M	Diarrhea	0	Not tested	N/A
	9 years	F	Sore throat	0	Not tested	N/A
	11 years	F	Cough	10	Not tested	N/A
Song et al[22]	10 years	F	Headache Fatigue	14	Not tested	N/A
	9 months	F	Fever	12	Not tested	N/A
	6 years	F	Fever	20	Not tested	N/A
	10 months	M	Fever	10	Not tested	N/A
	5 years	F	Cough	23	Not tested	N/A
	3 years	F	Cough	18	Not tested	N/A
	2 years	F	Fever	14	Not tested	N/A

(*Continued*)

TABLE 1. (*Continued*)

Study	Age	Sex	Symptoms	Duration of Viral Shedding via Respiratory Route From Symptom Onset (d)	Duration of Viral Shedding via Gastrointestinal Route From Symptom Onset (d)	Gastrointestinal Specimen Type
Tan et al[23]	9 years	F	Cough Abdominal pain	24	Negative	Stool
	11 years	F	Cough	17	Not tested	N/A
	2 years	F	Fever Vomiting Convulsion	5	Not tested	N/A
	8 years	M	Fever Constipation	10	24	Stool
	1 year	F	Nonspecific	4	Not tested	N/A
	12 years	M	Fever	17	Not tested	N/A
	8 years	M	None[a]	7	Not tested	N/A
	9 years	F	Cough	14	Not tested	N/A
	3 years	F	Fever	14	14	Stool
	8 years	F	None[a]	17	≥15	Stool
Tang et al[24]	10 years	M	None[a]	0 (never positive)	11	Stool
Wang et al[25]	36 hours	M	None[a]	14	Negative	Anal swab
Xing et al[26]	1 year	M	Fever	15	23	Stool
	5 years	M	Fever Cough Coryza Abdominal pain Diarrhea	13	33	Stool
	6 years	F	Fever	10	30	Stool
Xu et al[27]	6 years	M	Fever Cough Diarrhea	9	≥29	Rectal swab
	12 years	F	Fever Sore throat Coryza	5	≥25	Rectal swab
	7 years	F	Fever Cough Sore throat Diarrhea	5	≥24	Rectal swab
	13 years	M	None[a]	2	6	Rectal swab
	1 year	M	Fever	4	≥24	Rectal swab
	3 years	M	Coryza	2	≥20	Rectal swab
	15 years	F	Fever	3	Never positive	Rectal swab
	13 years	M	Fever Cough Sore throat	17	≥20	Rectal swab
	2 months	F	Cough Sore throat	7	Never positive	Rectal swab
	1 year	M	Fever Cough Diarrhea	20	≥24	Rectal swab
Zhang et al[28]	14 years	M	None[a]	8	24	Rectal swab
	13 years	M	None[a]	5	26	Rectal swab
	10 months	F	Crying Wakefulness	6	31	Rectal swab
Zhang et al[29]	9 years	M	Fever Sore throat Coryza Nausea Loss of appetite Headache Myalgia	14	≥33[b]	Stool
	6 years	M	Cough	11	≥35[b]	Stool
	8 years	M	Fever Coryza Loss of appetite	7	≥29[b]	Stool

[a]In asymptomatic cases, the durations given are the number of days from the first positive result until the first negative result after which no more positive results were obtained, not counting the day of the negative result.

[b]Stool PCR results were not reported in relation to symptom onset. Durations are calculated as ≥length of hospital stay + time from discharge to stool PCR positive + time from readmission to stool PCR negative.

F, female; M, male, N/A, not applicable.

hospitalized for the purposes of isolation or medical treatment, and all cases were classified as mild to moderate severity by the authors of the study in which they were reported. Of the 69 cases, fever was present in 39 (56.5%), cough in 22 (31.9%), gastrointestinal symptoms including diarrhea, nausea, vomiting, abdominal pain, constipation and loss of appetite in 12 (17.4%), coryzal symptoms

including nasal congestion, rhinorrhea and sneezing in 11 (15.9%), sore throat in 10 (14.5%), nonspecific symptoms including headache, malaise, fatigue, myalgia, crying and wakefulness in 4 (5.8%) and convulsion in 1 (1.4%). Most cases (38) had more than one symptom and 13 cases (18.8%) had no symptoms.

Viral Shedding via Respiratory Route

Of 69 cases, 68 (98.6%) had a positive nasopharyngeal or throat swab on rRT-PCR (1 case had positive stool specimens only). The duration of viral shedding via the respiratory route ranged from 0 to 24 days following symptom onset (some patients had a positive PCR test before symptom onset and were negative after symptom onset). Two studies (containing 7 cases in total) reported the duration of viral shedding as a range only and therefore could not be included in the calculation of the mean value.[17,18] The mean respiratory shedding time of the remaining symptomatic cases (n = 53) was 11.1 ± 5.8 days from symptom onset. The mean total documented respiratory viral shedding time among the remaining asymptomatic cases (n = 8) was 9.4 ± 5.1 days.

Viral Shedding via Gastrointestinal Route

Forty-two of 69 cases underwent testing with stool PCR (25/42), rectal swab (14/42) or anal swab (3/42), of which 36 cases (85.7%) tested positive. The indications for rectal swab or stool PCR were not provided, although only 24% of the children who were tested displayed any gastrointestinal symptoms. The duration of viral shedding via the gastrointestinal route ranged from 10 days to at least 5 weeks following symptom onset. In the majority of these cases, researchers did not repeatedly perform swabs or stool PCRs until the point of negative result; therefore, it was not possible to determine the upper limit nor the mean shedding duration for the 42 cases.

In 7 cases, the exact number of days between symptom onset and negative stool PCR, rectal swab or anal swab was reported. The mean duration of viral shedding via the gastrointestinal tract for these cases was 23.6 ± 8.8 days from symptom onset, with a range of 10–33 days. In 32/36 cases (89%), gastrointestinal samples were positive after respiratory samples had become negative. The maximum duration of gastrointestinal shedding after clearance from the respiratory tract was at least 28 days.[18] The mean total documented gastrointestinal shedding time among the asymptomatic cases (n = 4) was 16.8 ± 9.8 days from symptom onset. In one study, an asymptomatic child was found to have had persistently positive stool specimens for at least 26 days following contact with a confirmed case, despite having persistently negative respiratory specimens.[24]

Risk of Bias

The results of the bias assessment for each study using the Joanna Briggs Institute Critical Appraisal checklist is displayed in Figure 2A and B. For case reports, items 5–7 of the checklist were omitted as they pertained to interventions and were not relevant for observational studies. Overall, the quality of case series and reports in this review was high, with most studies clearly reporting case definitions, methods of diagnosis, demographic data and clinical details. However, most case series did not clearly report consecutive cases or all cases within a defined period, which may affect the study's reliability.[12]

Unpublished Literature

Using the search terms "COVID-19 Children," "COVID-19 Paediatric," "COVID-19 Pediatric" and "COVID-19 Shedding" on May 7, 2020, we identified 3 relevant studies of 1153 records returned. In one study from China, 8 of the 10 children tested for SARS-CoV-2 in fecal specimens showed prolonged detection in feces, with a mean time of 11 days and a range of 5–23 days after nasopharyngeal swabs turned negative.[31] Another study predominantly included adult data; however, it did report that 2 asymptomatic children had detectable SARS-CoV-2 RNA in nasopharyngeal swabs 50 days after admission.[32] Finally, a study of 32 children with SARS-CoV-2 from China reported a mean duration of positive throat PCR of 15.4 days.[33] In this study, 6 children had an anal swab after discharge from hospital, of which 5 were positive. None of the 3 studies reported shedding times for individual cases; therefore, it was not possible to pool the data to calculate an overall mean.

DISCUSSION

To our knowledge, this is the first attempt to systematically review the duration of respiratory and gastrointestinal viral shedding of SARS-CoV-2 in pediatric patients. In this review, the longest duration of viral shedding from the respiratory tract in children was 24 days after symptom onset, with a mean of 11.1 days. This is shorter than the reported durations of adult patients, in whom the longest observed duration of viral shedding after illness onset is 60 days with a mean viral shedding duration of 20.0 days.[11,34]

Importantly, our literature search did not identify any studies on children with severe disease that met the inclusion criteria. There is evidence to suggest more severe cases have a longer respiratory viral shedding time,[11,35] which may at least partially explain why the duration is shorter in our review. The differences may also be partly explained by inherent differences in pediatric studies compared with adult studies; children may be less likely to be recruited into studies than adults as they have milder symptoms and are less likely to require medical care, with fewer cohort studies published than in adults. There may be a proportion of children with COVID-19 who remain undiagnosed and are therefore not included in shedding studies. Differences in sampling and PCR targets may also have resulted in different findings to adults, though more systematically collected data emerging from around the world may overcome these biases.

Among children tested for SARS-CoV-2 by rectal swab or stool PCR, 89% returned a positive result, despite the fact that the majority of these children (82.6%) had no gastrointestinal symptoms. This appears to represent a higher rate than in adults; a meta-analysis of COVID-19 cases (n = 4243) with a median age of 45.1 years found that 48% of patients had positive stool specimens.[36] The prolonged gastrointestinal shedding observed in the children in this review is known to also occur in adults, but perhaps to a less dramatic extent: Wu et al[7] reported that among 41 adult patients who had both positive fecal and respiratory samples, respiratory samples remained positive for a mean of 16.7 days, while fecal samples remained positive for a mean of 27.9 days. Small studies involving both adults and children, including a study included in this review, have noted a higher incidence of positive stool PCR after negative respiratory swab in children compared with adults.[18,37]

The clinical significance SARS-CoV-2 viral shedding, particularly via the gastrointestinal tract, remains unclear. Previous coronavirus epidemics have raised the possibility of fecal oral transmission: live SARS coronavirus has been isolated from stool[4] and faulty plumbing is thought to have played an important role in the transmission of SARS-CoV at an apartment complex in Hong Kong,[38] while MERS-CoV RNA is detectable in approximately 15% of stool samples from infected patients, with viral loads remaining stable in stool for at least 3 weeks.[39] Gastrointestinal viral shedding in the pediatric population is of particular concern given the increased prevalence of fecal incontinence in young children, which may increase the risk transmission to their caregivers and to other children via fomites. However, the presence of SARS-CoV-2

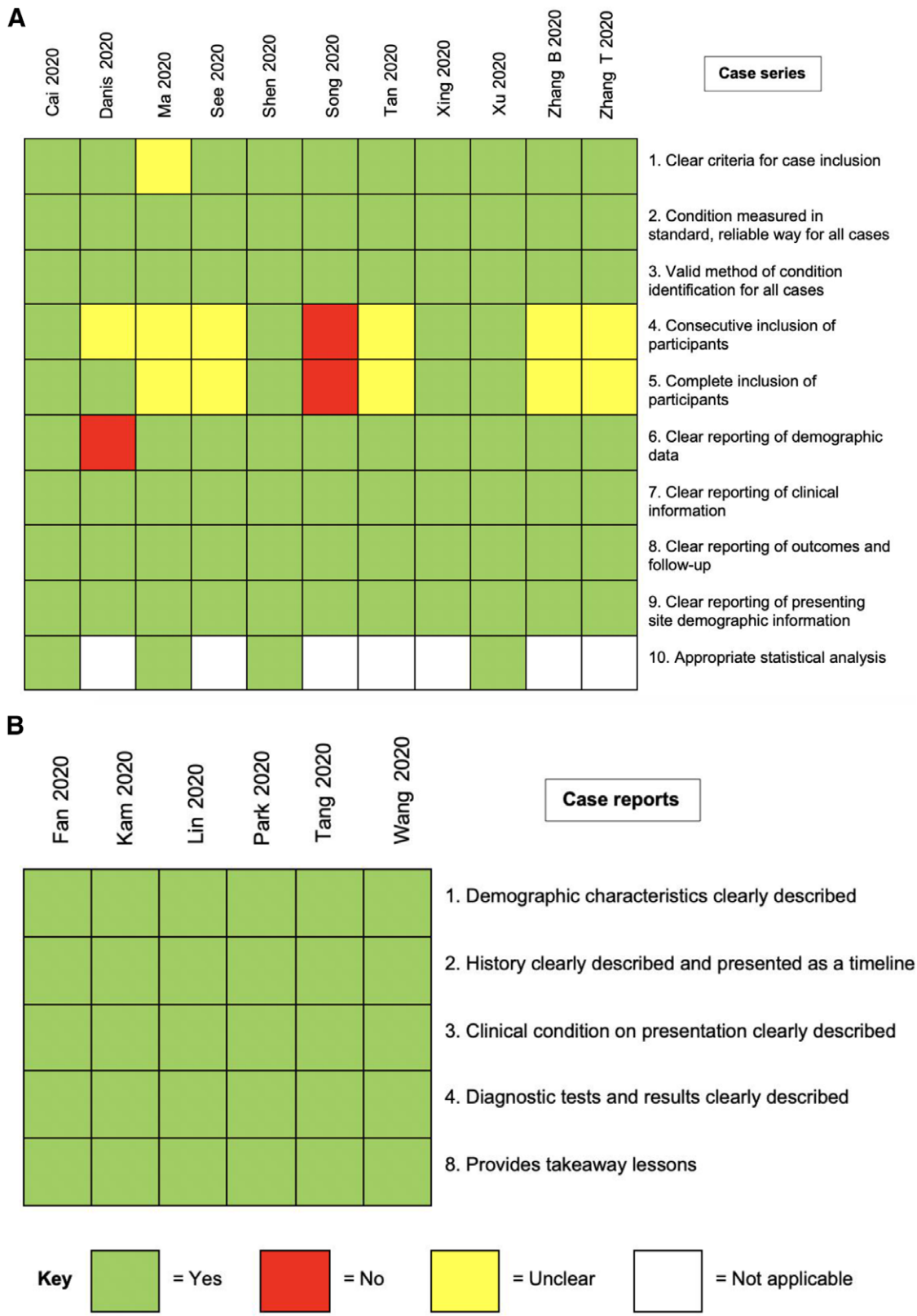

FIGURE 2. Assessment of risk of bias within studies. A: Risk of bias within individual studies (case series) assessed using the Joanna Briggs Institute critical appraisal tool. B: Risk of bias within individual studies (case reports) assessed using the Joanna Briggs Institute critical appraisal tool. Items 5–7 of the tool were not used as they were not relevant to noninterventional studies.

RNA in a patient's respiratory or gastrointestinal specimens does not necessarily equate to infectiousness of that individual. A recent study analyzing specimens from patients with COVID-19 found that live virus was not isolated in respiratory samples beyond day 8 of symptoms, despite ongoing high viral loads.[40] In the same study, no live virus was isolated from stool specimens, again despite high viral loads. Another study found that the highest concentrations of viral RNA in nasal and throat swabs were detected within the first week of symptom onset, comparable to the shedding pattern of influenza.[41] This evidence suggests that despite a potentially prolonged duration of shedding, the most important period of infectivity remains the early stages of the disease.

Limitations

This review has multiple limitations. Currently, all data on viral shedding in children with SARS-CoV-2 come from case reports and case series, and the total number of published cases is low. Case reports and series are subject to publication bias, in that unusual cases are more likely to be reported and published. Second, this review only reports on viral shedding from the time of symptom onset, not total duration of viral shedding (which likely begins 2–3 days before symptom onset).[42] It was not possible to calculate the true duration of viral shedding as most studies did not test pre-symptomatic children. Third, all cases included in this review were nonsevere. Therefore, the durations are not generalizable to children with severe disease. Finally, given this search was limited to articles in English only and that SARS-CoV-2 originated in Wuhan, China, there may be relevant non-English studies not included in this review.

Despite these limitations, this review demonstrates that viral shedding of SARS-CoV-2 is prevalent and prolonged in the feces of children across the current literature. This has potential implications for infection prevention in healthcare settings with regards to recommendations for isolation precautions and personal protective equipment use.

CONCLUSION

Based on the limited case data, children may display a shorter duration of viral shedding of SARS-CoV-2 through the upper respiratory tract compared with adults. Children exhibit prolonged viral shedding via the gastrointestinal route after clearing the virus from the respiratory tract, possibly more frequently than in adults, and stool PCR in recovering children may therefore play an important role in infection control and prevention of SARS-CoV-2. Larger studies are required to characterize the pattern and clinical significance of viral shedding in both children and adults with COVID-19.

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