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REVIEW

Fecal-oral transmission of SARS-CoV-2: review of laboratory-confirmed virus in gastrointestinal system

Dajana Cuicchi[1] · Tiziana Lazzarotto[2] · Gilberto Poggioli[1]

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Abstract

Purpose The objective was to collect the data available regarding the presence of laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in gastrointestinal system and to evaluate whether the digestive system could contribute to viral transmission.

Methods Bibliographic databases were searched to identify all studies documenting, in adult patients with a confirmed diagnosis of coronavirus disease 2019 (COVID-19): (1) the presence of SARS-CoV-2 ribonucleic acid in the feces; (2) the presence of SARS-CoV-2 ribonucleic acid in the intestinal cells; (3) live SARS-CoV-2 in the feces.

Results Twenty seven met the inclusion criteria. In 26 studies, the presence or absence of SARS-CoV-2 ribonucleic acid in the feces of COVID-19 patients had been reported. Out of the 671 patients, 312 (46.5%) had a positive stool sample for viral nucleic acid. Of these patients, 63.9% remained positive for viral nucleic acid in the feces after pharyngeal swabs became negative; Three studies also evaluated the viral ribonucleic acid in the gastrointestinal tissues and the presence of SARS-CoV-2 nucleic acid was found in samples of 3 patients out of 8 examined (37.5%). The presence of the live virus in stool samples was confirmed in two studies but no in in a recent study from Germany. These results suggested that SARS-CoV-2 could infect gastrointestinal epithelial cells and it may be transmitted through the digestive tract.

Conclusion In order to control the pandemic, every effort should be made to understand all the possible routes of transmission of the infections, even the less important ones.

Keywords COVID-19 · Feces · Fecal-oral transmission · Gastrointestinal system · Severe acute respiratory syndrome coronavirus 2

> "Sed domus corporibus exanimis, itinera funeribus complebantur; non sexus, non aetas periculo vacua; servitia perinde et ingenua plebes raptim extingui, inter coniugum et liberorum lamenta, qui dum adsident, dum deflent, saepe eodem rogo cremabantur." Annales XVI, 13 Tacito

> "Yet the houses were filled with lifeless bodies, the streets with funerals. Neither sex nor age gave immunity from danger; slaves and the free-born populace alike were summarily cut down, amid the laments of their wives and children, who, themselves infected while tending or mourning the victims, were often burnt upon the same pyre." Annals Book XVI, 13 Tacitus

✉ Dajana Cuicchi
dajana.cuicchi@aosp.bo.it

[1] Surgery of the Alimentary Tract, Department of Medical and Surgical Sciences, Sant'Orsola- Malpighi Hospital, Alma Mater Studiorum University of Bologna, Via Albertoni 15, 40138 Bologna, Italy

[2] Operative Unit of clinical Microbiology, Department of Diagnostic Medicine and Prevention, Sant'Orsola Hospital, Alma Mater Studiorum University of Bologna, Via Albertoni 15, 40138 Bologna, Italy

Introduction

Since what would later be called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged for the first time in Wuhan, China, in December 2019, it has spread almost all over the world within a very short period of time and, on May 31, 2020, a total of 5,934,936 confirmed cases of coronavirus disease 2019 (COVID-19) including 367,153 deaths

were reported [1]. The World Health Organization (WHO) declared the outbreak of COVID-19 an international public health emergency at the end of January and, deeply concerned by the alarming levels of spread and severity, it made the assessment that COVID-19 should be characterized as a pandemic on March 11, 2020.

SARS-CoV-2 is an enveloped, positively charged, single-stranded RNA virus belonging to the beta coronavirus genus; it is one of seven known coronavirus species responsible for human diseases [2]. The genome sequence of SARS-CoV-2 is 82% similar to severe acute respiratory syndrome coronavirus (SARS-CoV). Human coronaviruses, such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), are known to cause respiratory and gastrointestinal (GI) symptoms [2, 3]. Since it has been shown that both viruses can be excreted in the stools of infected patients and remain viable under conditions which could facilitate fecal–oral transmission, it is possible that SARS-CoV-2 could also be transmitted via this route [3]. Moreover, SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV, to infect humans [4]; ACE2 is known to be abundant in the epithelia of the lungs and the intestine in humans which might add to the evidence of this possible route for COVID-19 [5]. In fact, although droplet and contact transmission are definitely the main routes of infection, studies regarding the presence of SARS-CoV RNA in the feces and in the colonic biopsy samples of infected patients have been published in recent months. Fecal-oral transmission poses very important public health implications and may partly explain the potential recurrence of the disease and its persistent transmission. Due to this concern, the authors sought to collect the data available and evaluate whether the digestive system could contribute to viral transmission.

Methods

Eligibility criteria

Peer-reviewed articles documenting the presence of live SARS-CoV-2 or viral RNA either in the feces or in the intestinal cells of patients with a confirmed diagnosis of COVID-19 were included. The study population consisted of adult COVID-19 patients. Only studies in English were considered. Any study design was eligible; however, abstracts, review articles, and studies published on medRxiv and bioRxiv were excluded. Studies regarding patients without virological proof of SARS-CoV-2 infection were also excluded.

Information sources and search strategy

All articles published from December 2019 to May 31, 2020, in PubMed and in the Cochrane Library databases were consulted. The medical subject heading (MeSH) terms used for the research were: “coronavirus 2019”, “COVID-19”, “severe acute respiratory syndrome coronavirus 2”, “SARS-CoV-2”; different keywords were added to increase the sensitivity and specificity of the search (e.g., “pandemic”, “epidemic”, “outbreak”, “digestive”, “transmission”, “infection”,” enteric”, “intestinal”, “bowel”, “feces”, “stool”, “transcriptase polymerase-chain-reaction”, “biopsy”). Additional trials were identified by means of the accurate evaluation of the reference list of the studies included.

Study selection

The literature search was independently conducted by two authors to extract the relevant information. The results of the initial search strategy were first screened by title and abstract. The full texts of relevant articles were examined for inclusion and exclusion criteria (Fig. 1, PRISMA flow chart). When extracting information from the studies, the two researchers conferred to compare findings and reach a consensus. When a consensus was not reached, an independent researcher was consulted. The relevant information was then reported in a narrative review.

Data collection process and data items

Two investigators independently extracted, from the included studies, the following data: study authors, study designs, main results, and limitations.

Results

Twenty seven studies met the inclusion criteria [4, 6–31]. In 26 of all 27 studies, the presence or absence of SARS-CoV-2 RNA in the feces of COVID-19 patients had been reported (Table 1). The case-report regarding a COVID-19 patient with a positive result of viral nucleic acid in a fecal specimen and negative results on multiple pharyngeal and sputum samples was included [6]. The results of two studies conducted on COVID-19 patients who underwent detection of viral RNA in specimens from multiple sites including feces were also included [7, 30]. However, the results were excluded from the analysis of both the total number of patients evaluated and the prevalence of the positivity of the fecal tests as, in both studies, only the total number of stool tests carried out was specified but not the number of patients tested. In three studies, the intestinal mucosa was analyzed. Two of these 3 studies revealed the presence of a viral nucleotide in gastrointestinal tissue samples in 7 patients; all three studies had also tested SARS-CoV-2 RNA in the feces [8, 9, 20]. In 3 studies, researchers tried to isolate the virus from stool samples [7, 10, 11]. Two of these 3 studies had also tested SARS-CoV-2

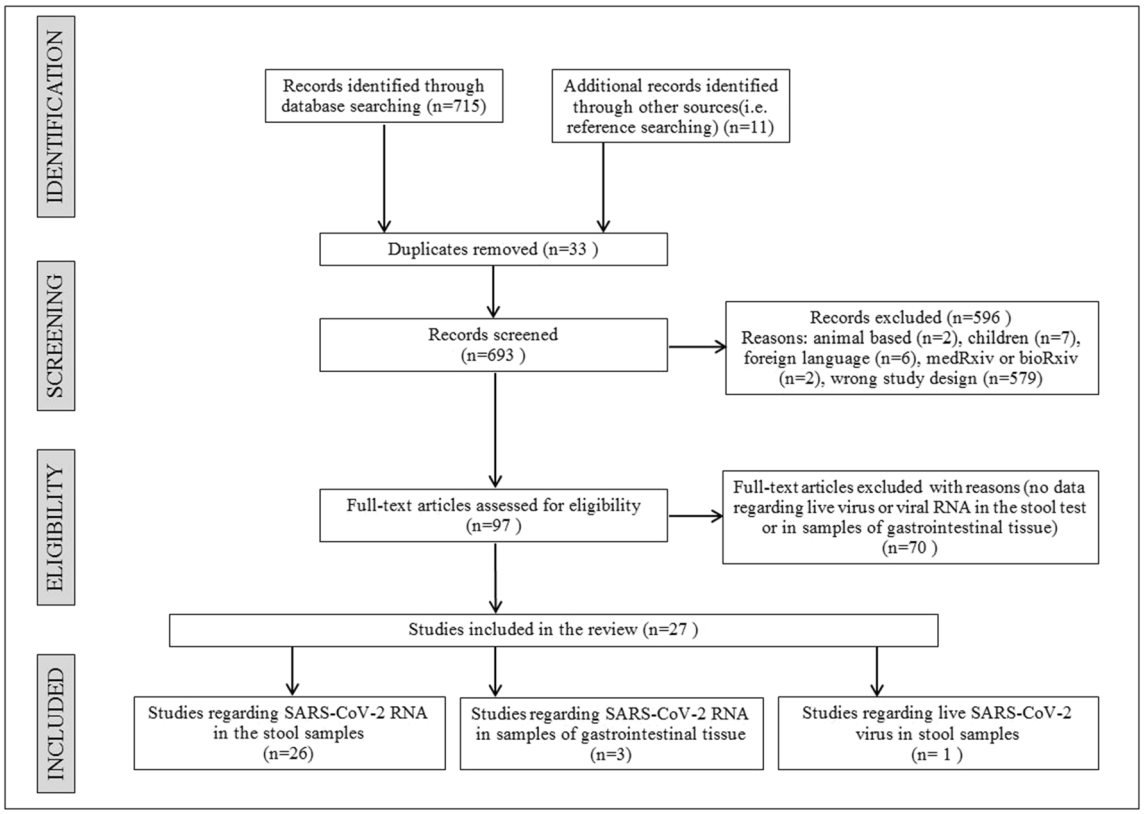

Fig. 1 Flow diagram of study selection

RNA in the feces. However, the study of Wolfel was excluded from the analysis of the rate of positive stool samples for viral RNA as it lacked some necessary information.

SARS-CoV-2 RNA in the stool

Overall, the authors evaluated data from 671 patients in order to determine the rate of viral shedding in the stool. Out of the 671 patients with laboratory-confirmed COVID-19, 312 (46.5%) had a positive stool sample for viral RNA. Of these studies, the rate varied from 6.5 to 66.7%. The cycle threshold (Ct) value of the stool samples ranged from 22.3 to 38.4 (Table 1). In the majority of studies, the nucleic acid positivity in the fecal samples was not related to gastrointestinal symptoms and severity of illness [4, 7, 9, 12, 13]. Interestingly, Han et al. [14] found that patients presenting with digestive symptoms were more likely to test positive for viral RNA in fecal specimens (73.3% vs. 14.3%, $p = 0.033$). Similarly Wei et al. [29] found that the frequency of positive rate for testing SARS-CoV-2 from stool was higher in patients with diarrhea, as compared with patients without diarrhea at admission (69% vs 17%, $p < 0.001$). Moreover Chen et al. [31] found that the presence of viral RNA in the anal swab was positively correlated with the severe disease stage. Of 183 Covid-19 patients with SARS-CoV-2 RNA in stool specimens, 117 (63.9%) remained positive for viral RNA in the feces after pharyngeal swabs became negative; the proportion varied from 10 to 81.8%. The stool viral clearance was longer in patients with steroid use as compared to those without steroid use [15].

SARS-CoV-2 RNA in samples of gastrointestinal tissue

To investigate the clinical significance of SARS-CoV-2 RNA in feces, Xiao et al. [8] examined the viral RNA in the feces of 73 patients with Covid-19; they also evaluated both the viral RNA and the viral nucleocapsid protein in the gastrointestinal tissues of one of these patients. They found SARS-CoV-2 RNA and viral nucleocapsid protein in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells. Moreover, their immunofluorescent data showed that ACE2 protein, which has been proven to be a cell receptor for SARS-CoV-2, was expressed in the cells of the gastric, duodenal, and rectal epithelia [8]. Lin et al. [9] also detected SARS-CoV-2 RNA in esophageal, gastric, duodenal, and rectal specimens in 2 out of 6 COVID-19 patients having gastrointestinal symptoms who underwent endoscopy. In this study, the presence of viral RNA in the gastrointestinal tissue was associated with severe disease; in fact, SARS-CoV-2 RNA was found in the samples of 2 patients with severe disease but not in those of 4 patients with nonsevere disease [9]. However in the case of SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis, histological examination of the colon and rectal

Table 1 Characteristics of the studies on stool viral RNA positivity included in the review

	Country	Total patients	GI symptoms (%)	F RT-PCR test + (%)	ct value of RT-PCR test (range)	F PCR test + in pts with GI symptoms (%)	F PCR test + in pts without GI symptoms (%)	R PCR test – and F PCR test + (%)	Time differences between F RT-PCR test -and R RT-PCR test (days)
Carvalho A [20] Gastroenterology	USA	1	1	1 (100)	–	–	–	–	–
Chan JFW [21] Lancet	China	4	2 (50)	0	–	–	–	–	–
Chen EQ [22] E J Clin Microbiol & Infectious diseases	China	1	0	0	–	0	0	–	–
Chen L [6] Am J Gastroenterol	China	1	–	1	–	–	–	–	–
Chen Y [13] J Med Virol	China	42	8 (19,0)	28 (66,7)	–	6/8(75.0)	22/34 (64,7)	18 (64,8)	6,5–7
Chen W [31] Emerg Microbes Infect	China	28	–	11 (39,3)	24–39	–	–	–	–
Cheng SC [23] JFMA	Taiwan	1	0	0	–	–	–	–	–
Cheung KS [18] Gastroenterology	Hong Kong	59	15 (25,4)	9 (15,3)	Median viral load = 4,7 Log 10 copies per mL (cpm) (range 3,4-7,6)	5/15 (33.3)	4/44 (9,1)	–	–
Guan W [24] NEJM	China	62	–	4 (6.5)	–	–	–	–	–
Han C [14] AJC	China	22	15	12 (54,5)	–	11/15 (73.3)	1/7 (14,3)	–	
Holshue ML [16] NEJM	USA	1	1	1	36–38	1	–	–	–
Kim JY [25] J Korean Med Sci	Korea	2	0	0	–	–	–	–	–
Lescure FX [26] Lancet	France	5	1 (20)	2 (40)	Range viral load = 6.8–8.1 Log 10 copies per g (cpm)	0	2 (50)	1 (50)	1
Ling Y [15] Chin Med J (Engl)	China	66[†]	–	66 (100)	–	–	–	54 (81,8%)	2 (+1 to +4)[‡]
Lin L [9] J Med Virol	China	65[§]	42 (64,6)	31 (47,7)	–	22/42 (52,4)	9/23 (39,1)	–	–
Lo IL [27] Int J Biol Sci	China	10	50	10 (100)	–	–	–	1 (10)	9
Pan Y [28] Lancet Infect Dis	China	17	–	9 (53)	Range viral load = 550–1.21 × 10^5 copies per mL (cpm)	–	–	–	–
Wang W [7] JAMA	China	205[¶]	–	44/153[4] (29)	22.3–38.4	–	–	–	–
Wei XS [29] Clinical gastroenterol and Hepatology	China	84	26 (30,9)	28 (33)	–	18 (69)	10 (17)	20 (71,4)	–
Wu J [30] Travel Med Infec Dis	China	132	–	24/244 (9,8)[¥]	–	–	–	–	–

Table 1 (continued)

	Country	Total patients	GI symptoms (%)	F RT-PCR test + (%)	ct value of RT-PCR test (range)	F PCR test + in pts with GI symptoms (%)	F PCR test + in pts without GI symptoms (%)	R PCR test – and F PCR test + (%)	Time differences between F RT-PCR test -and R RT-PCR test (days)
Wu Y [4] Lancet Gastroenterol Hepatol	China	74	–	41 (55,4)	–	–	–	–	11,2
Xiao F [8] Gastroenterology	China	73	26	39 (53,4)	–	17/26 (65,4)	22/47 (46,8)	17 (43,6)	–
Young BE [19] JAMA	Singapore	8[#]	2 (25)	4 (50)	26–36	1/2 (50)	3/6 (50)	–	–
Zhang JC [12] J Med Virol	China	14	0	5 (35,7)	–	–	5/14 (35,7)	0	–
Zhang W [17] Emerg Microbes Infect	China	15	–	4 (26,7)	30,2-33,6	–	–	2 (50)	–
		16	–	T0: 4 (25) T5: 6 (37,5)[¤]	T0:19,5-33,6 T5:17,8-30,0[¤]	–	–	T0: 2 (50) T5: 4 (66,7)	–

Abbreviations: GI:Gastrointestinal; R RT-PCR: respiratory reverse transcriptase polymerase-chain-reaction; F RT-PCR: fecal reverse transcriptase polymerase-chain-reaction; RT-PCR: reverse transcriptase polymerase-chain-reaction; ct: cycle threshold; [†] convalescent patients, [‡] subgroup analysis of 55 pts. as the stool specimens of the remaining 11 patients still tested positive at the end of the study; [§] subgroup analysis of 95 pts., [¶] 153 is the number of specimens, [¥] 244 is the number of specimens, [#] subgroup analysis of 18 pts., [¤] T0 is day 0, T5 is day 5

biopsies showed normal cellularity and intact crypts but did not show virocytes [20].

Live SARS-CoV-2 virus in stool samples

The presence of the live virus in stool samples from patients with COVID-19 was first confirmed by Zang et al. [10] using electron microscopy, they observed virus particles with the typical morphology of coronavirus after inoculating stool suspension into Vero cells. This finding was confirmed in another study in which 4 SARS-CoV-2 positive fecal specimens with high copy numbers were cultured. Live virus was observed in 2 cases under electron microscopy [7]. Instead, in a recent study from Germany, virus isolation from stool samples was never successful, irrespective of viral RNA concentrations, in 13 samples taken between day six and day twelve from four patients [11].

Discussion

Respiratory droplets and contact transmission are considered to be the most important transmission pathways of SARS-CoV-2 and, in fact, they are. However, these transmission routes could not fully explain the occurrence of all cases of COVID-19 and the rapid spread of the virus.

The finding of SARS-CoV-2 RNA in the stool of an American patient raised the question of the fecal-oral transmission route [16]. Subsequently, a growing number of clinical studies were conducted to verify the presence of viral nucleic acids in the stool samples of COVID-19 patients. The first molecular study of SARS-CoV-2 RNA in anal swabs of Covid-19-patients was conducted in Wuhan Pulmonary Hospital. The authors carried out two different investigations. The first one was conducted on 15 patients who still carried the virus following days of medical treatment. The authors found that the anal swabs of 4 patients were positive (26.7%), and of these 4 patients, 2 had negative oral swabs. The aim of the second investigation was to determine the dynamic changes in viral presence in both the oral and the anal swabs in another group of 16 patients. The authors found more anal swab positives (6/8, 75%) than oral swab positives (4/8, 50%) in a later stage of infection [17]. High positivity rates for SARS-CoV-2 RNA in fecal specimens were also detected in subsequent studies with values ranging from 15.3 to 66.7% [4, 7–9, 12–14, 18–20, 26–29, 31]. Considering all the patients analyzed in this review, 46.5% had a positive stool sample for viral RNA. In contrast to the Ct value of 36–38 of the stool samples from the first US case, the Ct values in subsequent studies were, for the most part, below 34. This suggested that viral shedding from the gastrointestinal tract could be abundant [7, 16–19, 31]. The studies available also demonstrated that a nonnegligible percentage of

patients continued to have positive fecal tests while their respiratory specimens were negative [2–27, 29]. In a study of 66 convalescent patients, viral RNA in both oropharyngeal swabs and feces became negative at the same time in 12 cases (18.2%); in the remaining 54 patients (81.8%), the stool specimens became negative after a longer period of time than the throat swabs [15]. After the negative conversion of pharyngeal swabs, the duration of viral shedding from the feces varied from 2 to 11 days, regardless of COVID-19 severity [4, 13, 15, 27, 29]. In particular, one patient had positive stool samples for 33 days continuously after respiratory samples became negative [4]. Cheung et al. [18] reported data from a cohort of 59 patients with COVID-19 in Hong Kong; they carried out a systematic review and meta-analysis of 11 studies regarding the detection of the virus in the stool in a heterogeneous population of adults and children. They found similar results to those in the present study; RNA viral shedding in the stool was detected in 48.1% of patients, and 70.3% of these patients had persistent positive stool viral RNA, despite negative respiratory samples [18].

The mere presence of SARS-CoV-2 RNA in the stools of infected patients is not, however, sufficient to demonstrate virus infectivity by means of the fecal-oral route. In fact, it is uncertain whether these nucleic acids are live virus particles or just RNA fragments released from the intestinal cells. Stronger, though more limited, evidence derives from the detection of virus nucleotides in the samples of gastrointestinal tissue of COVID-19 patients [8, 9]. These results suggested that SARS-CoV-2 could infect gastrointestinal epithelial cells.

Recently, the isolation of three cases of infectious SARS-CoV-2 viruses from stool samples of COVID-19 patients has directly proven that SARS-CoV-2 could be transmitted via fecal-oral route [7, 10]. Nevertheless, live virus was not isolated from stool samples in 4 patients in spite of very high virus RNA concentrations in the stool and the occasional detection of viral subgenomic messenger RNAs directly in the clinical samples, factors which would indicate active replication in the gastrointestinal tract [11].

These results are preliminary and have some limitations; the majority of the data are from only one country, China, since the initial epicenter for this outbreak was this region; the analyses reported are mostly retrospective, single-center series with few cases or case reports. The viral shedding in the feces was not the primary aim in the studies analyzed. The heterogeneity was not formally assessed. Although only studies relating to adult population were analyzed, the studies are heterogeneous for type of sample (fecal specimens and anal swabs), sample timing, and follow-up testing. Nevertheless, this is currently the review with the largest number of articles relating to laboratory-confirmed virus in gastrointestinal system in adult population. This evidence has suggested that SARS-CoV-2 may be transmitted through the digestive tract. Although additional studies are needed to confirm fecal-oral transmission, this possibility should be taken into consideration because it has several implications. First, more attention should be paid to the five "F" factors of the fecal–oral route: fingers, flies, fields, fluids, and food. Hand cleansing with soap and disinfectants is frequently the better way to prevent transmission. Suggestions should however include maintaining environmental and personal hygiene, drinking mineral or boiled water, and avoiding raw food consumption. Strict precautions must be observed when handling the stools, vomitus, other bodily fluids, and stoma of infected patients or when disinfecting the environments of patients in medical facilities. In fact, the discharge into the toilet of feces of COVID-19 patients can generate infective aerosols which can lead to fomite transmission. The sewage of hospitals and houses of COVID-19 patients may serve as a source of infection. Rigorous protective measures are important to avoid cross-infection during endoscopic examination in epidemic areas. In the same way in the surgical theater is crucial that staff are properly trained and in particular they use appropriate tools and follow recommendations strictly to avoid increasing the risk of contamination. Both laparoscopic or open surgical procedures in fact, may potentially cause aerosolization of the virus and therefore infection of the personnel, probably even in absence of intestinal perforation or ischemia, due to presence of SARS-CoV-2 in peritoneal fluids [32–35]. The major concern is, however, the potential recurrence of the disease and persistent transmission from treated patients who meet discharge criteria with 2 sequential negative oropharyngeal swab tests collected 24 h apart since the clearance of viral RNA in patient stools is delayed as compared to oropharyngeal swabs. After discharge, the patient should pay close attention to hand hygiene and try to avoid sharing toilets with family members. Moreover a test for fecal nucleic acid could be useful to understand when to discontinue precautions.

SARS-CoV-2 probably has many routes of transmission which could explain its strong and rapid spread. In order to control the pandemic, every effort should be made to understand all the possible routes of transmission of the infections, even the less important ones. More studies regarding gastrointestinal involvement and viral excretion in feces are required.

Authors' contributions D.C.: conceptualized and designed the study in partnership with T.L. and P.G., conducted the literature search, collected data, carried out the initial analyses, and drafted the initial manuscript; T.L.: conceptualized and designed the study in partnership with D.C. and P.G., conducted the literature search, collected data, carried out the initial analyses, made substantial contributions to all aspects of the writing of the manuscript, which included contribution to conception, design, analysis and interpretation of the article, and review and revision of the manuscript. P.G.: conceptualized and designed the study in partnership with D.C. and T.L., interpreted data, reviewed and revised the manuscript, and supervised and provided mentorship throughout all stages of the project and writing of the manuscript.

Data availability Bibliographic databases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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