

INFECTION OF GASTRO-INTESTINAL TRACT BY SARS-CoV-2 AND ITS POTENTIAL FOR FAECAL-ORAL TRANSMISSION: A LITERATURE REVIEW

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Abstract

Context: SARS-CoV-2, has already affected more than 180 countries. 3,175,207 confirmed cases and 224,173 deaths due to the disease were reported worldwide till 1st May 2020. WHO has declared it a Public Health Emergency of International Concern. **Aims:** To present information from worldwide literature on infection of gastro-intestinal tract by SARS-CoV-2 and its potential for faecal-oral transmission. **Material and Methods:** Literature search was carried out using Google Scholar and PubMed in 3rd week of April, 2020. Search terms used were "SARS-CoV-2" or "COVID-19" or "New Coronavirus" or "Coronavirus" in title and "Transmission" or "Faecal" or "Oral" anywhere in the article. Studies from the year 2019 to 2020 published in "English" language were included in the search. **Results:** 15 studies were found relevant and were included in the review. Studies reported that SARS-CoV-2 infects and replicates in gastro-intestinal tract and manifests enteric symptoms. Viral RNA is excreted in stool. Faecal samples were found to be positive for the viral RNA for many days even after respiratory samples become negative. Virus has been detected in anal swabs and live virus could be successfully isolated from stool specimen. The virus was also reported to be viable in the environment for many days. **Conclusions:** SARS-CoV-2 can potentially be transmitted by faecal-oral route. The transmission can occur even after respiratory symptoms subside and respiratory tract samples test negative for the virus. Appropriate policy response is needed for awareness, testing, discharge and quarantine of patients to prevent spread of the disease.

Keywords--SARS-CoV-2, Coronavirus Outbreak, COVID-19, New Coronavirus.

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BACKGROUND/RATIONALE

The world is fighting the latest Public Health Emergency of International Concern, unleashed by a new strain of coronavirus, the Severe Acute Respiratory Syndrome (SARS) Coronavirus-2 or SARS-CoV-2.¹

The SARS-CoV-2 outbreak was first reported on 31stDecember, 2019 from Wuhan city, located in Hubei province of China and spread quickly across the globe. ²By 1st May, 2020, more than 180 countries had reported 3,175,207 laboratory-confirmed cases of the disease and 224,173 deaths. ³India had reported 26,535 laboratory-confirmed cases and 1,223 deaths by 1st May, 2020.⁴

Clinical manifestations of SARS-CoV-2 are cough, expectoration, high body temperature, fatigue, dyspnoea, sore throat, vomiting, diarrhoea, and headache. ^{5,6}It is believed that SARS-CoV-2 was first transmitted from animals to humans and thereafter from humans to humans through respiratory droplets, fomites of the infected persons and direct or indirect contact.

^{7,8,9,10}Presently, the clinical diagnosis of SARS-CoV-2 is confirmed by real-time reverse transcriptase-polymerase chain reaction (rRT-PCR).

⁶Several aspects of SARS-CoV-2 outbreak, including its transmission dynamics and full spectrum of clinical illness, are yet to be fully understood.

¹¹It is, therefore, important to know whether the virus can be detected in specimens from sites other than nasopharyngeal region, and whether it can be transmitted in other ways than by respiratory droplets.

AIMS AND OBJECTIVES

Aim of this literature review was to present information from worldwide literature on infection of gastro-intestinal tract by SARS-CoV-2 and potential of transmission of the virus by faecal-oral route.

MATERIAL AND METHODS

Literature search for this study was carried out in 3rd week of April, 2020 using Google Scholar and PubMed. We used the search terms "SARS-CoV-2" or "COVID-19" or "New Coronavirus" or "Coronavirus" in title and "Transmission" or "Faecal" or "Oral" anywhere in the article. Studies from the year 2019 to 2020 published in "English" language only were included in the search.

Abstracts of studies yielded by using this search strategy were studied by the first two authors independently. A study was included if it was about enteric infection by SARS-CoV-2, shedding of the virus or viral RNA in stool, and survival of the virus in faecal matter.

If there was a dispute between the two authors, the decision on inclusion of the study in the review was taken in a meeting by a majority of the three authors. Citation search of selected studies was done to harvest additional relevant studies. Full texts of all the studies included in the review were studied. Grey literature was also searched using "Google" search engine.

RESULTS

Literature search yielded 15 relevant studies. 11 studies were from China, one from the United States of America while the remaining three studies were not country specific. A list of these studies showing Author(s), Year, Country, Title, and Brief Findings is given in Table-1.

Table 1. Studies Included in the Literature Review

S No	Author(s)/(Year)/Country	Title	Brief Findings
SARS-CoV			
1	Yeo et al. (2020) Not country specific	Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible?	Genome grouping of SARS-CoV-2 has 82% closeness with SARS-CoV. Both SARS-CoV and MERS-CoV are discharged in faeces and stay alive in the faeces. This points towards the plausibility of transmission of SARS-CoV-2 by fecal-oral route.
2	Wang et. al. (2020) China	Clinical characteristics of 138 patients in hospital with 2019 new coronavirus contaminated pneumonia in Wuhan. China	Gastrointestinal symptoms in 10% of patients appeared 1–2 days before manifestation of high body temperature and respiratory symptoms
3	Wang et al (2020) China	Finding of SARS-CoV-2 in Multiple Types of Clinical Specimens	Live virus was detected in faeces, implying transmission of SARS-CoV-2 by faecal-oral route. Transmission of the virus by respiratory and extra respiratory routes may help explain the rapid spread of SARS-Cov-2.
4	Zhang et al (2020) China	Molecular and serological examination of 2019-nCoV contaminated patients: ramifications of different shedding courses.	Found 2019-nCoV in blood as well as anal swabs. In later stages of infections, positivity of anal swabs was higher than oral swabs. They suggested that the virus is shed in the faeces and can be potentially transmitted through the oral-faecal route.
5	Guan et. al. (2020) China	Symptoms of Coronavirus Disease 2019 in China	Diarrhoea and vomiting was reported by only 3.8%, and 5% of the SARS-CoV-2 patients respectively
6	Holshue et al (2020) USA	First case of 2019 new coronavirus in the USA	SARS-CoV-2 induces gut symptoms. Stool of the patients was found positive for the virus.
7	Xiao et al (2020) China	Evidence for gastro-intestinal infection of SARS-CoV-2	Detected viral RNA in gastrointestinal tissues and argued that SARS-CoV-2 infects gastro-intestinal tract and can be transmitted by fecal-oral route.
8	Guo et al (2020) Not country specific	The source, transmission and clinical treatments of coronavirus illness 2019 (COVID-19) flare-up a report on the states.	Summed up accessible research on the study of disease transmission, pathogenesis, and clinical qualities of SARS-CoV-2. The infection displays solid infectivity yet less destructiveness, contrasted with SARS and MERS, as far as grimness and mortality
9	Wu et al (2020) China	Extended presence of SARS-CoV-2 viral RNA in faeces	Positivity of fecal samples of patients for SARS-CoV-2 RNA was 55%. Fecal samples remained positive for viral RNA for an average of 27.9 days after the initial manifestation, which was 11.2 days longer than the duration of positivity for respiratory samples. Transmission by fecal-oral route could happen subsequent to the viral movement in the respiratory tract.
10	Xiao et al (2020) China	Evidence of SARS-CoV-2 Gastrointestinal Infection	53.42% of the SARS-CoV-2 patients tested positive for viral RNA in stool. Faeces of 23.29% of the patients were found positive even after viral RNA could not be detected in the respiratory tract.
11	Danchin et al (2020) Not country specific	A new transmission route for the proliferation of the SARS-CoV-2	Gut tropism and a secondary propagation route for SARS-CoV-2 suggested. Epidemic control measures should take into account both routes for epidemic control.
12	Zhang, Wang and Xue (2020) China	Faecal specimen diagnosis 2019 New Coronavirus–Infected Pneumonia	Viral RNA of 2019-nCoV detected in stool samples and its detection was comparable to pharyngeal swab specimens
13	Zhang, Y et al (2020) China	The 2019-nCoV removal from a feces sample of a research lab-confirmed coronavirus disease outbreak 2k19 (COVID-19)	The 2019-nCoV virus was detected live in stool samples. In addition to near exposure and interaction with patients' respiratory secretions, the virus can also spread through the possible fecal-oral route. The viruses' numerous distribution route may clarify in part its powerful and rapid transmitting rate.
14	Xu et al (2020) China	Traits of neonatal contamination with SARS-CoV-2 and possible evidence of chronic faecal viral spreading	Anal swabs of 8 out of 10 pediatric SARS-CoV-2 patients tested positive for the virus after adverse nasopharyngeal examination. Suggested gastrointestinal tract shedding of the virus and

			likelihood of faecal-oral transmission. Rectal swab-testing could be more useful in evaluating treatment efficacy and in deciding quarantine termination. There is, however, a lack of evidence of virus replication in faecal swabs needed to confirm faecal-oral transmission.
15	Pan et al. (2020) China	Viral load of SARS-CoV-2 in clinical samples	Positivity of Stool for SARS-Cov-2 was found to be 53% on RT-PCR analysis. Suggest precautionary measures when handling faecal samples.

Findings of the studies included in the review were categorized and analysed in four parts- infectivity of gastro-intestinal tract, presence of viral RNA in stool, viability of virus on different surfaces, and presence of live virus in faeces.

A. Infectivity of Gastro-Intestinal tract

Coronaviruses have been reported to impact the gastro-intestinal tract leading to enteric symptoms in some of the patients. Cases of both SARS-CoV and MERS-CoV which has high genome similarity with SARS-CoV-2, had also reported enteric symptoms.¹²Studies on SARS-CoV-2 informed that 2–10% of the confirmed cases presented gastro-intestinal tract symptoms such as diarrhoea, nausea, vomiting and pain in abdomen.^{2,6,13}10% of the patients presented gastrointestinal symptoms before manifestation of respiratory symptoms and development of fever.^{6,12}In a study of 1,099 patients whose laboratory tests had confirmed SARS-CoV-2 infection, Guan et al (2020) had informed that diarrhoea was manifested by 3.8% of the patients while vomiting was reported in 5.0% of the patients.¹⁴Zhang et al (2020) showed that SARS-CoV-2 was present not only in lungs of patients but also in their stratified squamous epithelial cells in oesophagus, and enterocytes of ileum and colon.¹⁵Holshue et al (2020) also informed that SARS-CoV-2 instance induces gut symptoms.¹¹Xiao et al (2020) suggested gastrointestinal infection by SARS-CoV-2 virus too.¹⁶Danchin et al (2020) also suggested gut tropism and a secondary propagation route for SARS-CoV-2.¹⁷Zhang et al (2020) also concluded that besides the respiratory systems, SARS-CoV-2 infects the digestive system as well.¹⁸Enteric symptoms, such as nausea, vomiting and diarrhoea induced by SARS-CoV-2 were reported to be even graver than those caused by other coronaviruses namely MERS-CoV and SARS-CoV.^{7,8,19}

B. Presence of viral RNA in stool

Studies have informed detection of SARS-CoV-2 viral RNA fragments in the faecal matter of patients.^{11,16}Wu et al (2020) had collected respiratory and faecal samples from SARS-CoV-2 patients in Zhuhai, China and reported that in 55% of the patients, faecal samples were found positive for the RNA of SARS-CoV-2.³²They had also reached the conclusion that SARS-CoV-2 RNA was first detected in samples taken from the respiratory tract and was subsequently detected in faecal sample.²⁰ Viral RNA could be detected in faecal samples for an average of 27.9 days as compared to the average of 16.7 days for respiratory samples.²⁰However, in one case the faecal sample tested positive for viral RNA continuously for 33 more days after viral detection had stopped in respiratory samples.²⁰Wu et al (2020) reached the conclusion that the virus replicated actively in the gastrointestinal tract of patients even after respiratory tract has been cleared of the virus.²⁰However, they sounded a caution that it was difficult to determine whether the virus detected through nucleic acid was viable or not.²⁰In another study, Xiao et al (2020) found 53.43% faecal sample positivity rate of SARS-CoV-2 RNA in hospitalized patients of SARS-CoV-2.¹⁶They had also found that even after the viral RNA in respiratory tract samples reduced to an undetectable level in patients, stool samples of 23.29% of the patients continued to remain positive for the viral RNA.¹⁶

C. Viability of the virus in environment

A recent analysis of the survival of human coronaviruses on surfaces had found considerable variation in their survival, ranging from 2 hours to 9 days.²¹Studies indicated that a variety of factors, such as surface texture, temperature, relative humidity, and particular virus strain, influenced their survival.²²SARS-CoV can stay alive for up to 15 days after drying.²²Chan et al (2011) reported that at a temperature of 22°C to 25°C and relative humidity of 40–50%, SARS-CoV was found viable for up to 5 days.²³ Thereafter, its infectivity gradually declined.²³MERS-CoV also preferred low temperature and low humidity.²⁴It was found viable on multiple surfaces for 2 days at 20°C and 40% relative humidity.²⁴In case of SARS-CoV-2, the literature search yielded only one study on survival of the virus in environment and it reported that SARS-CoV-2 could remain viable in the environment for days.²⁵

D. Presence of live virus in faeces

Coronaviruses are present in the intestinal tracts of infected humans and are shed into the environment through faeces.^{26,27}Zhang et al (2020) had reported that they could successfully isolate live SARS-CoV-2 virus from faecal specimen of a patient whose respiratory tract sample had tested positive for SARS-CoV-2.²⁸They established occurrence of SARS-CoV-2 in both blood as well as anal swabs.²⁸Wang et al et al (2020) also claimed finding of live virus in faeces in 29% of the 153 cases studied.²⁹Zhang et al (2020) found existence of 2019-nCoV in both blood as well as rectal swabs.¹⁸ They had also found that in the later stages of infection, the positivity rate of rectal swabs was higher than the samples taken from blood or respiratory tract thereby suggesting the possibility of shedding of the virus in the faeces and its potential for transmission via oral-faecal route.¹⁸Pan et al (2020) did rT-PCR analysis and found that out of 17 cases of SARS-CoV-2, in nine (53%) patients, stool samples were found positive for the virus.³⁰Xu et al (2020) tested rectal swabs of child patients of SARS-CoV-2 and found that eight out of ten children studied tested positive even after nasopharyngeal testing was negative.³¹However, in faecal swabs, they could not obtain confirmation of a replication-competent virus that is needed to validate the capacity for faecal – oral transmission.³¹

DISCUSSION

a. Key Findings

Gastrointestinal symptoms have been manifested in about 5% of SARS-CoV-2 patients and in some of the patients these symptoms were manifested before onset of high body temperature and respiratory symptoms. The RNA of SARS-CoV-2 has been found in gastro-intestinal tissues, suggesting gastrointestinal infection of SARS-CoV-2. Live virus has been detected in rectal/anal swabs and stool samples suggesting shedding of virus in faeces and potential for its faecal-oral transmission. As faecal samples have been found positive for a duration much longer than respiratory samples, studies suggest that transmission of the virus by faecal-oral route could even occur subsequent to clearance of the virus from respiratory tract. Some studies attribute rapid spread of SARS-CoV-2 to multiple routes of transmission of this virus.

SARS-CoV-2 is an emerging infectious disease and there are limited studies in literature about shedding of live virus in stool.

However, existing studies suggest that the virus is shed in stool and can survive in sewage. The virus could also remain viable for days in the environment. Stool samples may contaminate hands, food, and even water leading to infection through oral cavity, respiratory mucosa, or conjunctiva. Therefore, the epidemic control measures must take into account both respiratory and gastro-intestinal routes of virus transmission. These would include health education and publicity, environmental health and personal hygiene, frequent hand washing, drinking boiled water, avoid consumption of raw food, disinfection of surfaces. Precautionary measures must be taken by the staff while handling faecal samples.

Shedding of SARS-CoV-2 RNA in stool for an extended period has implications for testing, discharge and quarantine policies. Negative oral swabs when virus is still being shed in the faeces may pose threat to other people. Such patients either had no symptoms of the disease or manifested mild symptoms of the same. Therefore, a possible shift in testing strategy from testing of oral swabs during early period of infection to the testing of anal swabs in later stages of the disease has been suggested. Decisions on discharge of patients and determination of quarantine period should be guided by the results obtained by the modified testing strategy. Strict precautions are necessary for both self-quarantined as well as hospitalized patients if their faecal sample has tested positive for the viral RNA to break the cycle of transmission of the virus.

b. Areas of future research

There are gaps in epidemiology and transmission of SARS-CoV-2 which need to be filled up by future research. The present nucleic acid detection approach makes it difficult to determine whether the virus shed in stool is viable or not. To define transmission potential, more research is needed into the viability of SARS-CoV-2 in faeces and potential for spreading the infection, particularly in patients who excrete the virus in faeces. More evidence is also needed on potential for transmission of the disease by patients who test negative for the virus in the respiratory tract but their stool samples test positive for the virus. Moreover, there is need for more studies to establish viability of the virus in environment and conditions which would facilitate its transmission by faecal-oral route.

LIMITATIONS

This literature review was conducted using only two search engines, Google Scholar and PubMed. Therefore, studies not listed in these two databases have not been included in the review. As SARS-CoV-2 outbreaks were reported from China, it is possible that there are many research studies on the virus published in the Chinese language which also got missed out in our search.

CONCLUSION

SARS-CoV-2 infects the gastro-intestinal tract, replicates there and is shed in the faeces. Live virus has also been isolated from stool samples and rectal swabs. The virus can survive in sewage and environment for days. The response to the epidemic, testing strategy, quarantine period and discharge policy should be formulated taking into consideration the faecal-oral transmission potential of the virus.

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