Features of enteric disease from human coronaviruses: Implications for COVID-19

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Abstract
Coronaviruses have long been studied in both human and veterinary fields. Whereas the initial detection of endemic human respiratory coronaviruses was problematic, detection of these and newly discovered human coronaviruses has been greatly facilitated with major advances in the laboratory. Nevertheless, technological factors can affect the accuracy and timeliness of virus detection. Many human coronaviruses can be variably found in stool samples. All human coronaviruses have been variably associated with symptoms of gastroenteritis. Coronaviruses can occasionally be cultured from enteric specimens, but most detection is accomplished with genetic amplification technologies. Excretion of viral RNA in stool can extend for a prolonged period. Culture-positive stool samples have been found to exceed a fourteen day period after onset of infection for some coronaviruses. Virus can also sometimes be cultured from patients’ respiratory samples during the late incubation period. Relatively asymptomatic patients may excrete virus. Both viable and nonviable virus can be found in the immediate environment of the patient, the health care worker, and less often the public. These lessons from the past study of animal and human coronaviruses can be extended to presumptions for severe acute respiratory syndrome coronavirus 2. Already, the early reports from the coronavirus disease-2019 pandemic are confirming some concerns. These data have the cumulative potential to cause us to rethink some current and common public health and infection control strategies.

KEYWORDS
coronavirus, COVID-19, gastrointestinal, infection, SARS-CoV-2

1 | INTRODUCTION

Critical approaches toward the management of the emerging pandemic of coronavirus disease-2019 (COVID-19) require focused knowledge of the epidemiology that has been documented and is evolving. Given the absolute numbers of infections worldwide, study of the spread and containment of the virus will undoubtedly come forward from many countries in expeditious manner. In the interim, much has been learned from the human experience with other coronaviruses, and it is conceivable that the latter can provide some insight that can be used for the COVID-19 scenario. This review particularly examines the spectrum of enteric diseases that are associated with human coronaviruses and analyzes the published data to draw inferences that are relevant potentially to the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Early publications for SARS-CoV-2 are presenting what appears to be recurring themes.

2 | GENETIC SIMILARITY AND DIVERSITY AMONG HUMAN CORONAVIRUSES

Both animal- and human-linked coronaviruses were well known by at least the 1960s, and knowledge of their diversity quickly became apparent.

1 Differentiation of these viruses depended
largely on serological assessments of antigenicity and cross-reactions. Whereas human coronaviruses appeared initially limited to a few serologically distinct clusters, a larger spectrum became known in the veterinary field in short order. Before SARS-CoV-2, six human coronavirus groups were established in human infection represented by the designations OC43, 229E, NL63, HKU1, SARS-CoV, and MERS-CoV. Although antigenic and genetic distinctions prevail, these viruses nevertheless share many structural and behavioral characteristics that rightfully justify their inclusion in a common family of viruses, the Coronavirusidae. Four genus clusters have been proposed for coronaviruses generally, but the human coronaviruses, including the newly recognized SARS-CoV-2, all belong to two so designated Alphacoronavirus and Betacoronavirus. The origin and evolution of these pathogens has now been studied considerably, and there is good reason to believe that animal origins and recombination events have been instrumental in giving rise to the human coronaviruses that we find today. Four of these viruses were believed to have been endemic to humans—OC43, 229E, NL63, and HKU1; the remaining three (SARS-CoV, MERS-CoV, and SARS-CoV-2) putatively represent a more contemporary presence. The Betacoronavirus lineages can be further subdivided by comparative genomics; lineage A includes OC43 and HKU1, lineage B includes SARS-CoV and SARS-CoV-2, and lineage C includes MERS-CoV. Despite several differences in genome, phenotype, cellular attachment, or intracellular multiplication, there are equally many commonalities that are apparent thus giving justification to comparative discussions. One such commonality as we discuss herein is the ability for these viruses to be associated with enteric disease. As becomes apparent from this review, this aspect of pathogenesis may lead us to rethink the standard approaches taken thus far if not only provide for some stimulating and/or sobering thought.

3 | EPIDEMIOLOGICAL ASPECTS BEARING RELEVANCE TO ENTERIC DISEASE

As is evident from the plethora of scientific and medical publications that are arising for COVID-19, approaches to the detection, disease management, and prevention were very much dependent on lessons learned from the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics. The spread of SARS seems to have been terminated during 1 year, while MERS infections continued over a much longer period and are yet of lingering concern for relapse. The latter gives credence to the fact that, while there may be commonalities which suffice to assist us in these regards, there are nevertheless some virus-virus distinctions which must be considered.

Emerging data for COVID-19 have already corroborated or added to this concept sufficiently to cause some concern. The “incubation period” is typically less than 1 week, but any such calculation is bound by a confidence interval of earlier or later presentation. Lauer et al have estimated that the late 97.5% confidence outlier can be as long as 15 to 16 days. Extending their calculation to a higher percentile of confidence leads to an estimate that nearly one in 100 patients will have an incubation longer than 14 days. The actual practice seems to corroborate the latter. Wang et al provide clinical findings from the China experience that the incubation can occasionally extend up to 24 days. Backer et al, using data from travelers abroad that have returned from China, found a 97.5% confidence interval extending to 11.1 days, but a 99% confidence extending to possibly 17 to 32 days depending on the method of evaluation. The latter is also consistent with the transmission dynamics shown by Li et al. Qiu et al projected an incubation period of up to 32 days. Thus, while the majority of patients become ill in less than 2 weeks, outliers to this belief will inevitably occur when the population being affected is quite large as is occurring worldwide in several countries. These outliers therefore have the potential to promote viral transmission when it may not seem likely. A role for both respiratory and enteric reservoirs in this transmission could have relevance for prevention and control.

Typically, the “incubation period” is used to refer to the time from contact to the time of first clinical illness manifestation. As for SARS and MERS, and now documented for patients with COVID-19, some patients have been shown to harbor the virus in a relatively asymptomatic state. This may especially be true for infected children. It is of further concern when applicable to health care workers. Tang et al describe an asymptomatic child with prolonged SARS-CoV-2 genome excretion in the stool as detected with nucleic acid amplification technology. Respiratory samples from the child were negative by the same technique. Wang et al report that many of their patients were relatively asymptomatic. In the asymptomatic state, therefore, the typical application of “incubation period” takes on another dimension, that is, a time from exposure to the time of first positive diagnostic sample in the asymptomatic state. The latter will again have the potential to complicate control measures. These concerns may very well explain why some have proposed that SARS-CoV-2 could be transmitted during the incubation period in a presymptomatic state.

As for other human coronaviruses, SARS-CoV-2 can be found in both respiratory and stool (and urine and blood) patient samples. Thus, the potential patient sample source for transmission is likely to be more than simply respiratory. The enteric reservoir is further supported by symptoms of enteritis or abdominal complaint in some patients. Contamination of the patient environment can be widespread. Thus far, however, the majority of reports have depended on nucleic acid amplification techniques to define virus presence, and yet it is abundantly clear from past observations for coronaviruses, and other viruses generally, that viral genome presence does not equate consistently with live and hence infectious virus. The above is further complicated by several reservations in the use and verity of nonculture test methods and by variations in the quality of the clinical samples that are acquired.
All of these recent findings for SARS-CoV-2 then beckon the considerations made herein.

4 | HUMAN CORONAVIRUSES AS ENTERIC PATHOGENS

4.1 | Considerations for animal coronaviruses

Many of the mammal- and avian-associated coronaviruses are well known to cause gastroenteritis in their host species. The long list includes agricultural and domestic examples such as poultry, swine, bovine, equine, canine, and feline hosts. Other examples of affected animals include rabbits, mink, ferrets, and dromedaries. Despite the latter, there is little evidence to support cross-over of these infections to humans with some exception. For example, infectious bronchitis virus (IBV) is a coronavirus of poultry that causes a respiratory disease typically in its natural host. Given human contact in commercial production facilities, serological studies were conducted to determine if exposure and hence IBV infection in humans could occur. Reactive sera were only found among those individuals who closely worked with poultry, albeit in low titers, but there were no purported human illnesses attributed including gastrointestinal. Furthermore, there is no good evidence at this time to prove that other animal enteric coronaviruses cause human disease. The latter is rather remarkable given the potential human contact with such viruses in animal husbandry in the least.

Other early studies examined a possible link between OC43 and neonatal calf diarrhea coronavirus (NCDCV). There were some commonalities in antigenic makeup, and both human and bovine antisera reacted with each virus although the two were not identical. OC43 also shared immunological cross-reactivity with an unknown human enteric coronavirus isolate, and the distinction from NCDCV was apparent. Some degree of immunological cross-reactivity was also found for 229E and some animal coronaviruses that were associated with diarrhea in their hosts. Further isolates of human enteric coronavirus (not then designated specific lineages) were found to be serologically distinct from OC43, 229E, mouse hepatitis virus-A59 (a murine coronavirus), and Breda virus (a bovine enteric torovirus). There were no further reports eventually characterizing these at the molecular level. The advent of molecular biology has since considerably changed the manner in which these viruses could now be compared with good precision. Such technology has since defined likely sources and vectors in nature for SARS-CoV and MERS-CoV.

4.2 | Evidence from electron microscopy

Knowledge of filterable albeit seemingly noncultivable agents in feces that could cause transmissible diarrhea in humans led in part to the use of electron microscopy (EM) for the detection of viruses in stool samples. Although initially and highly focused on rotavirus and enteric adenovirus, several presumed viral particles were identified in the stool of ill patients. In most laboratories, the coronaviruses constituted a considerable minority of such EM findings for humans. In the veterinary field, coronaviruses were found by EM in enteric specimens of many animals. Reports of the EM findings of coronavirus suggested that the putative pathogen(s) could be identified in outbreak settings of diarrhea. Studies from Argentina and Saudi Arabia respectively found the virus structure in 1.1% and 6% of samples from children with diarrhea. The coronavirus morphology was also found in outbreaks among neonates during manifestations of neonatal necrotizing enterocolitis. Patients with HIV infection, including some with a characteristic “wasting syndrome,” were also found to have coronaviruses in stool samples. Corroborative evidence for some of these findings was proposed by Gonzalez et al who found presumed viral antigen in stool specimens by enzyme immunoassays. Clarke et al who were among the leaders in this field at the time, suggested that enteric excretion of such viral coronavirus-like particles could continue for months. By 1980, a review of international proceedings on the subject had already acknowledged that coronaviruses could cause enteric disease. Up to 70% of presumed enteric viral particles could be coronaviruses. Confirmatory tests were generally unavailable at the time of the above publications, although immune electron microscopy from some studies suggested an infectious link given the use of convalescent patient sera.

Given the requirement of EM and given the nature of coronavirus morphology sought in such endeavors, there was some speculation that the laboratory findings could be over-represented. For some geographic regions, the frequency of EM-coronavirus morphotypes were equally found in symptomatic and control patients. In these regards, some investigators believed that coronaviruses could not be confirmed as enteric pathogens even by 2003. The discovery of Torovirus and its possible relationship to human disease also complicated the differentiation of viruses that could pose with the same morphological appearance to some observers.

4.3 | Endemic human coronaviruses and enteric disease

The use of genetic amplification technologies has added considerably to the finding of coronaviruses from clinical samples, and this progression has allowed for considerable subsequent study. Of note, however, nearly all such studies of endemic coronaviruses have not used culture confirmation or secondary corroborative test methods. One collaborative group determined the presence of coronavirus with direct immunofluorescence of respiratory samples. In cohorts assessed for the presence of coronaviruses in respiratory and/or stool samples in the context of respiratory disease, these viruses have been found in variable frequencies. Depending on the study, gastrointestinal symptoms (variably diarrhea, abdominal pain, and/or emesis) proved to be common. Likewise, the viruses have also been found in cohorts of patients who have presented purely with...
gastrointestinal symptoms.\textsuperscript{94,90-92} One study found an equal proportion of patients with gastrointestinal symptoms in comparing groups that have been found to harbor either OC43 or NL63 in respiratory specimens.\textsuperscript{85} Others found a higher frequency of gastroenteritis among patients with NL63 in respiratory specimens versus those whose sample was negative for a respiratory virus generally.\textsuperscript{98} A significant association of gastrointestinal disease with respiratory coronavirus detection was found in France, but few of the patients had these viruses detected in stool.\textsuperscript{97} Coronaviruses were found more commonly in symptomatic gastroenteritis than controls.\textsuperscript{91}

Nevertheless, there are mitigating findings from others which would be taken together to counter the above data and that might lead one to conclude that these endemic coronaviruses are not veritable enteric pathogens.\textsuperscript{92-94} In Arizona, USA, patients with severe coronavirus-associated lower respiratory disease did not present with diarrhea.\textsuperscript{92} Among children with acute gastroenteritis, the frequency of coronavirus isolation was similar for those with disease and controls.\textsuperscript{92} In some studies, the detection of coronavirus in stools was commonly associated with the finding of another but commonly recognized viral enteric pathogen.\textsuperscript{85,90-93} In one such study, multiple simultaneous enteric viral pathogens (at times up to four) were said to have been codetected.\textsuperscript{90} The latter seriously raises the issue of the validity of the assays and of the need to have some form of confirmatory test. The latter would be applicable to the detection of coronaviruses let alone any other pathogen purely detected by real-time amplification processes.

The diversity of the endemic coronavirus group so understood at this time also raises the question as to whether any specific one may be more pathogenic than another, and whether any one may be more likely to cause gastrointestinal symptoms. For OC43, several studies had found enteric coronaviruses with some antigenic relationship.\textsuperscript{51,53,95} Among patients with acute OC43-related respiratory disease, over one-half of the patients has gastrointestinal symptoms.\textsuperscript{96} A smaller proportion of patients with the same virus had enteric symptoms in another study.\textsuperscript{97} When NL63 was isolated from patients with either respiratory or febrile illnesses, nearly one-third had diarrhea or abdominal pain.\textsuperscript{98,99} HKU-1 was also commonly associated with intestinal illnesses albeit mostly in common with acute respiratory infection.\textsuperscript{100-103} Some have suggested that the frequency of gastrointestinal symptoms was no different for comparisons of patients with OC43, NL63, and HKU-1.\textsuperscript{40}

The cumulative evidence in this field finds that endemic human coronaviruses can be found in patients with respiratory disease who have gastrointestinal symptoms or those with purely gastrointestinal disease. There is controversy as to the extent of the role for such illness.

4.4 | SARS-CoV and enteric disease

Gastrointestinal symptoms mainly in the form of diarrhea were common (~33%-73%) in patients with SARS-CoV infection.\textsuperscript{104-107} Although this manifestation may have been uncommon at the first day of presentation, these symptoms became apparent at a variable time later.\textsuperscript{107} In “atypical” presentations, a patient may have had no apparent respiratory symptoms while yet suffering from fever and/or diarrhea.\textsuperscript{108} When using RNA detection methods, stool samples were commonly positive at a later peak timing than respiratory samples, but not as late as urine reactive samples.\textsuperscript{107,109} Any such sampling that depends on amplification technology must bear in mind the diagnostic pitfalls inherent, and repeat sampling increases the positive and hence diagnostic yields.\textsuperscript{110} SARS patients diagnosed by one or several laboratory methods had a positive stool screen for the viral genome in approximately 28% to 78% of patients.\textsuperscript{105,111,112} The majority of these were found in the period of 9 to 14 days after the onset of clinical infection.\textsuperscript{105,107,111,113} By the third week after onset of infection, viral RNA could be amplified in almost 2/3 of patients.\textsuperscript{107} Detection in stool samples continued for up to 10 weeks.\textsuperscript{106,112,114,115} Prolonged excretion detected with genetic amplification correlated with increasing patient comorbidities.\textsuperscript{114} Increased viral load quantitated in stool samples correlated with greater likely for the patient to suffer with diarrhea.\textsuperscript{105} Most of the latter studies were not simultaneously assessing viral culture for pathogen viability.

Whereas the virus could be obtained from some stools by culture, the vast majority were culture-negative by the end of the first week.\textsuperscript{113} Indeed most stools were culture-negative.\textsuperscript{105,115-117} Despite the latter, however, stools yielding virus in tissue culture have been found 14 to 21 days after onset of disease.\textsuperscript{115,116} Cultures for both respiratory and urine samples can extend beyond 14 days.\textsuperscript{113}

For purposes of hospital infection control and general prevention elsewhere, the above findings suggest that some patients remain infectious by at least that route for a longer period of time than is commonly thought. In experimental settings, SARS-CoV can survive in stool samples for 3 hours to 4 days, and the viability is greater when the sample has an alkaline pH.\textsuperscript{118} In contrast, virus can remain viable for up to 1 week at room temperature in respiratory secretions and up to 4 weeks when refrigerated.\textsuperscript{118} These findings are relevant to one outbreak in which it was believed that a sewer back-up facilitated some spread.\textsuperscript{117} Although reverse transcriptase-polymerase chain reaction positive, culture-negative sewage was found in such a context, the inoculation of sewage with live virus showed that viability could be found for 2 days when stored at room temperature but up to 14 days when refrigerated.\textsuperscript{117} All such assessments must be viewed with caution since even spiked samples of stool, urine, blood, and respiratory secretions may not yield fully positive amplification tests.\textsuperscript{109}

As for proof of enteric disease, some pointed studies have examined tissue pathology from biopsy or autopsy.\textsuperscript{104,120,121} Both intestinal mucosal epithelium and lymphoid tissue were shown to have the virus by in situ hybridization.\textsuperscript{120} Coronavirus-like particles were also visualized in the latter enteric epithelial tissue when viewed by electron microscopy. Other autopsy-based review found that SARS-CoV could infect multiple tissues which included intestinal mucosa, lymphoid tissue, and circulating lymphocytes.\textsuperscript{121} There is further corroboration in the finding of virus by culture from both small and large intestines whether from colonoscopy biopsy or postmortem tissue.\textsuperscript{106} In the latter study, over one-quarter of the
patients manifested diarrhea, several had findings of virus in the stool, and eight patients presented with fever and/or diarrhea in the absence of respiratory symptoms.

4.5 | MERS-CoV and enteric disease

Gastrointestinal symptoms, especially diarrhea, are common in MERS-CoV infections and occur in up to at least one-third of patients.\textsuperscript{122-126} What has been somewhat more important in this context, however, is that asymptomatic or relatively minor infections occur in a considerable number of people who test positive with genetic amplification technologies.\textsuperscript{127-129} One review proposed that some 12% to 25% of identified MERS-CoV infections are asymptomatic.\textsuperscript{130} These findings also need to be couched in the context of potential test fallibility for a variety of reasons.\textsuperscript{131}

From nasopharyngeal samples, both viral RNA and culture-viable MERS-CoV can be found in patients past 14 days.\textsuperscript{124,132} Viral RNA can be detected for up to 27 to 47 days (average 14 days) in stool samples.\textsuperscript{124,127,133} Some 14% to 50% of MERS infections will shed viral RNA in stool.\textsuperscript{124,133} Even those stool samples with the highest viral RNA load proved to be culture-negative in one study.\textsuperscript{133} Two studies that examined stool for viable virus were unsuccessful, but these reports included only a total of eleven stools tested.\textsuperscript{124,133}

4.6 | SARS-CoV-2 and enteric disease

The finding of SARS-CoV-2 RNA in stool samples by amplification is now accepted widely.\textsuperscript{134,135} Early data also suggests that a substantial portion of patients suffer gastrointestinal complaints.\textsuperscript{21,136-138} Wölfel et al\textsuperscript{43} did not find infectious virus in multiple samples. Zang et al\textsuperscript{139} also did not find live virus in stool samples. In contrast, others have now independently confirmed that the virus can be cultured from the feces from an active infection.\textsuperscript{140,141}

5 | EXPERIMENTAL ENTERIC TISSUE CAN BE PERMISSIVE TO HUMAN CORONAVIRUSES

The historic problem with finding endemic human coronaviruses from clinical specimens in the laboratory was the purported inability to detect the virus in tissue culture. We now recognize that only particular cell lines are permissive to infection and furthermore that only particular cell lines yield a visible cytopathic effect in tissue culture. In permissive cell lines that do not show cytopathic effects, viable virus growth can be demonstrated by passage, molecular techniques, and histopathology. Both SARS-CoV and MERS-CoV can replicate in a variety of cell lines including many that are not of gastrointestinal origin.\textsuperscript{109,142,143} OC43 was cultured in human colonic carcinoma cells (Caco-2), and other enteric coronavirus isolates (somewhat related to OC-43) could be cultivated in human fetal intestine explants.\textsuperscript{55,144,145} 229E has been cultivated in human embryonic intestinal fibroblast cell line MA-177.\textsuperscript{146} SARS-CoV has been propagated in Caco-2 and colon adenocarcinoma cell lines and small intestinal organoids.\textsuperscript{147,148} MERS-CoV can be passaged in Caco-2 cells, human primary intestinal epithelial cells, human small intestine explants, and human "intestinaloids."\textsuperscript{149}

The major cell surface receptor in the respiratory tract for both SARS-CoV and SARS-CoV-2 is angiotensin converting enzyme 2.\textsuperscript{2} Such receptors, however, are also plentiful in the gastrointestinal tract thus giving credence to the potential for these viruses to attach and infect gastrointestinal epithelium.\textsuperscript{21,150-152} Growth in human small intestinal organoids has been successfully achieved with both wild-type SARS-CoV-2 and a related chimeric virus.\textsuperscript{139,141,147} One such study included growth in bat intestinal organoids.\textsuperscript{141}

6 | ANIMAL MODELS FOR HUMAN CORONAVIRUS GASTROINTESTINAL INFECTION

Models of infection for gastrointestinal-associated coronaviruses in animals have been well established.\textsuperscript{153} For MERS-CoV, the presence of virus as detected by RNA amplification has been shown for other animals in addition to camels.\textsuperscript{154} An animal model of SARS in monkeys demonstrated the presence of virus in the intestines by day 7.\textsuperscript{155} The latter could be accomplished with inoculation through the respiratory or intravenous routes. Intragastric inoculation did not lead to infection. For MERS-CoV, infection of human DDP4 transgenic mice was associated with the finding of virus histologically in the intestines.\textsuperscript{149} Gastric fluid was also inhibitory in the latter model but not intestinal bile. The latter gastric fluid inhibition was evident in the nonfed (acidic) state. The Golden Syrian hamster model of SARS-CoV-2 infection is associated with histopathology of the gastrointestinal tract.\textsuperscript{156,157}

7 | ENVIRONMENTAL ASSESSMENTS WITH CORONAVIRUSES

The environmental viability and susceptibility to various conditions and cleaning agents have been reviewed.\textsuperscript{158-160} As surrogates, various animal-sourced coronaviruses have been studied.\textsuperscript{161-164} Porcine transmissible gastroenteritis virus survives on a variety of health care equipment for at least 4 hours and up to 24 hours.\textsuperscript{162} Mouse hepatitis virus can survive in both water and sewage fluid and can be inactivated by many disinfectants and antiseptics.\textsuperscript{163,164} Porcine epidemic diarrhea virus can be found in air samples and over a prolonged distance downwind.\textsuperscript{161} OC43 can survive on hospital surfaces for hours and has been found on airport commodities.\textsuperscript{165,166} 229E can also survive on hospital surfaces and remained infectious on public surface materials for days.\textsuperscript{165,167} SARS-CoV was found in patient rooms, nursing stations, emergency department, and public service areas of a hospital by RNA amplification.\textsuperscript{168} None of the latter could be confirmed with culture.
TABLE 1  Findings supporting enteric replication and potential transmission of human coronaviruses

| Animal coronaviruses | Endemic human coronaviruses | SARS | MERS | COVID-19 |
|----------------------|----------------------------|------|------|---------|
| RNA detection in feces | ✓ | ✓ | ✓ | ✓ | ✓ |
| Viral culture | ✓ | ✓ | ✓ | ✓ | ✓ |
| Permissive enteric cell lines | ✓ | ✓ | ✓ | ✓ | ✓ |
| Growth in intestinal organoids | ✓ | ✓ | ✓ | ✓ | ✓ |
| Histopathology of intestinal tissue | ✓ | Not reported | ✓ | Not reported | ✓ |
| Animal models of infection | ✓ | ✓ | ✓ | ✓ | ✓ |

Abbreviations: COVID-19, coronavirus disease-2019; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

In a study, SARS-CoV was more resilient to decontamination than 229E under experimental conditions. In the context of MERS-CoV, sources in the patient room, medical equipment, and the isolation anteroom all bore evidence of the virus by both detection of viral genetic amplification and culture.

Environmental contamination with SARS-CoV-2 is also becoming quite apparent. Although there are differences for specific surfaces more at risk among these reports, there is consistency that environmental spread is a significant problem. The latter may include personal protective equipment. Most such studies, however, have used viral RNA detection. The finding of viral RNA in municipal wastewater has been cited.

8 | RELEVANCE TO INFECTION CONTROL

All human coronaviruses can be found in stool samples, but the role of the endemic coronaviruses in diarrheal disease, while suggestive, requires further corroboration. Nevertheless, all human coronaviruses have been variably associated with symptoms of gastrointestinal enteritis. Coronaviruses can be cultured from enteric specimens, but most detection is accomplished with genetic amplification technologies. Excretion of viral RNA in stool can extend for a prolonged period. Culture-positive stool samples have been found to exceed a 14 day period after onset of infection. Virus can also be cultured from patients during the late incubation period. Relatively asymptomatic patients may excrete virus. Both viable and nonviable virus can be found in the immediate environment of the patient, the health care worker, and less often the public. As we are finding now early with COVID-19 infections, many of these past realizations are repeating themselves (Table 1).

In addition to the above concerns and their direct application to nosocomial infection control epidemiology, there is direct relevance to gastrointestinal endoscopy, and several pragmatic guides have emerged early.

Whereas infection control practices are groomed for many circumstances on the basis of likelihoods or risk management, we are finding that the presence of, persistence of, and resilience of the human coronaviruses is somewhat beyond initial and some past expectations. Accordingly, we may need to rethink detection and protection timings for the purposes of infection control especially in circumstances where spread is lesser tolerated. There is no doubt that the currently and commonly implemented infection control practices make a significant impact on the spread of SARS-CoV-2. The implementation of infection control measures both for basic and respiratory techniques will have an impact to control COVID-2. Beyond such mitigation, there remains some skepticism about the immediacy and extent of full suppression of virus spread both in the community and health care facilities. To improve on the latter, the role of enteric disease in the overall aspects of an effective infection control program, as well as other new considerations, should be taken into context for possible revisions to culture timing, samples taken, incubation period, length of illness, quarantine, and definitions of infected patients. In this regard, it would be prudent to garner more data. The lessons from the history of human coronavirus infection otherwise should continue to be compared with COVID-19 infection as the pandemic continues to unfold.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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