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REVIEW

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Environmental and decontamination issues for human coronaviruses and their potential surrogates

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Abstract

Pandemic coronavirus disease-2019 (COVID-19) gives ample reason to generally review coronavirus (CoV) containment. For establishing some preliminary views on decontamination and disinfection, surrogate CoVs have commonly been assessed. This review serves to examine the existing science in regard to CoV containment generically and then to translate these findings into timely applications for COVID-19. There is widespread dissemination of CoVs in the immediate patient environment, and CoVs can potentially be spread via respiratory secretions, urine, and stool. Interpretations of the spread however must consider whether studies examine for viral RNA, virus viability by culture, or both. Presymptomatic, asymptomatic, and post-14 day virus excretion from patients may complicate the epidemiology. Whereas droplet spread is accepted, there continues to be controversy over the extent of possible airborne spread and especially now for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). CoVs are stable in body secretions and sewage at reduced temperatures. In addition to temperature, dryness or relative humidity, initial viral burden, concomitant presence of bioburden, and the type of surface can all affect stability. Generalizing, CoVs can be susceptible to radiation, temperature extremes, pH extremes, peroxides, halogens, aldehydes, many solvents, and several alcohols. Whereas detergent surfactants can have some direct activity, these agents are better used as complements to a complex disinfectant solution. Disinfectants with multiple agents and adverse pH are more likely to be best active at higher water temperatures. Real-life assessments should be encouraged with working dilutions. The use of decontamination and disinfection should be balanced with considerations of patient and caregiver safety. Processes should also be balanced with considerations for other potential pathogens that must be targeted. Given some CoV differences and given that surrogate testing provides experimental correlates at best, direct assessments with SARS-CoV, Middle East respiratory syndrome-related coronavirus (MERS-CoV), and SARS-CoV-2 are required.

KEYWORDS

coronavirus, COVID-19, disinfection, prevention, transmission

1 | INTRODUCTION

There has been considerable study of human coronaviruses (CoVs) preceding the onset of coronavirus disease-2019 (COVID-19). Included within that experience is knowledge that is quite relevant to environmental spread and related containment. For *Alphacoronavirus* and *Betacoronavirus* lineages, such information has variably included CoVs OC43, 229E, HKU-1, NL63, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome-related coronavirus (MERS-CoV). Other animal-sourced CoVs (eg, bovine coronavirus (BCoV), canine coronavirus (CCoV), feline coronavirus (FCoV), infectious bronchitis virus (IBV), murine hepatitis virus (MHV), porcine epidemic diarrhea virus (PEDV), porcine respiratory coronavirus (PRCV), transmissible gastroenteritis virus (TGEV)) have also been studied to various extents; the latter have included *Alpha*-, *Beta*-, and *Gammacoronavirus* lineages.[1] Whereas SARS-CoV-2 and SARS-CoV share many similarities, suggestions regarding environmental contamination and infection control can be made in reviewing these in the context of all CoVs. In this review, the science in this field is surveyed, and applicable inferences and conclusions for COVID-19 are drawn from the latter.

Given the severity of infections experienced with SARS-CoV, MERS-CoV, and SARS-CoV-2, many investigators have studied the science of prevention as is further illustrated herein. Similar studies have been previously published for nearly all known respiratory viruses.[2] There are many parallels that a priori would be applicable. Respiratory viruses are found in the immediate environment of patients and beyond. They may be spread by small and large particle aerosols and are particularly spread through close contact. Direct transmission from person-to-person contact is also well-established. Nevertheless, there is a need to establish CoV-specific science, especially now given the magnitude of COVID-19-associated morbidity and mortality.

Historically, it has generally been held that enveloped viruses such as CoVs are more susceptible to environmental factors and decontamination procedures compared with nonenveloped viruses.[3] While generally true, there is evidence to believe that CoVs are more stable than is generally believed as discussed herein. Despite reference to the presence of a viral envelope, surface proteins are sufficiently unique to expect that there could be some differences for decontamination compared with other respiratory viruses. Such differences may also potentially explain variations among CoVs.

Given the large number of studies for virus spread and control, one would generally believe that the state of the art for understanding microbial containment in both community and health care settings should be well-advanced. Our limitations for this topic have been repetitively identified by the numerous citations of nosocomial and public outbreaks for many pathogens. In this regard, the simple concept of physical cleaning is often underestimated.[4] COVID-19-related data are emerging albeit limited as we discuss.

2 | ENVIRONMENTAL SPREAD OF CORONAVIRUSES

Assessments for environmental spread of CoVs experimentally or naturally from their hosts have been chronicled. Many of these studies have included nonhuman CoVs in the veterinary field or as surrogates for SARS-CoV, MERS-CoV, or SARS-CoV-2. More benign human respiratory CoVs have also been used as surrogates for SARS-CoV, MERS-CoV, or SARS-CoV-2. Few studies have made comparative assessments. The sampling methodology used for environmental assessments has been considerably variable but generally includes a culture or genetic amplification technology. Where only genetic amplification technologies have been used to detect ambient virus, there is evidence of viral genome but not necessarily proof for the presence of infectious virus. The latter ambiguity then raises skepticism about the relevance of viral genome detection in itself for such assessments.

To understand environmental viral burden, it is critical to examine the pattern of CoV excretion. Human CoV illnesses generally, and COVID-19 particularly, are mainly respiratory infections.[5,6] Most transmission originates through shedding from the upper respiratory tract regardless of disease severity.[7-9] For SARS-CoV, live virus has been found not only in respiratory samples but also in urine and stool.[10-12] SARS-CoV-2 can also be found in the same sites but also in blood.[13-18] Enteric excretion has been less appreciated than the respiratory route, but is generally acknowledged now for all human CoV illnesses and associated with a variable frequency of associated gastrointestinal symptoms.[19-34] Much of the excretion data has depended on the detection of virus RNA. Although viral load can be approximated by reverse transcription polymerase chain reaction (RT-PCR) Ct values, extrapolation can be difficult given the variety of RNA detection methods that are currently used.[35] Patients with COVID-19 may become infected and then shed virus in a relatively asymptomatic state or presymptomatic state.[16,36-51] Viral RNA appears to be shed for a longer period in the symptomatic state, and higher loads are correlated with disease severity.[18,52] These issues are further complicated by the potential for prolonged or atypical virus shedding in some patients with complex underlying comorbidities.[9,53,54] Given the above, it is easy to understand how the patient and other environments may become contaminated with these viruses. There is also merit in further validating epidemiological parameters with culture technology.[55]

2.1 | Airborne transmission

The spread though airborne routes is controversial but of critical importance to health care workers and others for protection. For SARS-CoV, dynamic modeling studies from an apartment outbreak and the epidemiology of spread in an aircraft both initially suggested that airborne transmission occurred and that such transmission was directly related to proximity with the index case(s).[56,57] One study did not find SARS-CoV in air from a patient's room when assessed

with genetic amplification.[58] Another study found viral RNA in air samples within the patient room even though the patient was to remain five feet away from the air sampler.[59] For MERS-CoV, culture-positive samples were obtained from air in patient rooms, bathroom, and common corridor.[60] PRCV could be cultured from air samples during experimental porcine infection containment.[61] TGEV remained in an airborne state during experimental infection.[62] For PEDV, viral RNA could be detected up to 10 miles downwind from infected herds, and live virus could be detected in air some 1.2 m above experimentally infected swine.[63]

Early studies for SARS-CoV-2 also support aerosol transmission.[64-67] Aerosolization studies support the concept that virus is viable in aerosols for up to 3 hours.[65] In ferret experiments, uninfected and separated animals could acquire infection from infected animals in the same general confines.[66] Using techniques detecting viral RNA, SARS-CoV-2 could be found in air for 12.5% to 35% of the samples.[64] The latter included the finding of viral genome up to 2.5 to 4 m away from the source and in air from the patient corridor and contiguous doctors' office. In contrast, Wu et al[68] did not find viral RNA in a large number of air samples. Liu et al,[69] however, detected considerable viral RNA in aerosols.[69] They measured greater quantitations in high traffic environments and also found diminution when decontamination efforts were applied. Chia et al[67] found SARS-CoV-2 RNA in particles ranging from 1 to more than 4 μm size within an intensive care unit and among isolations rooms elsewhere even though there was apparent adequate air exchange implemented.[67] Smither et al[70] examined experimental aerosols of either a saliva construct or tissue culture medium and found that particles of 1 to 3 μm could carry virus.[70] Viable virus could be detected up to 90 minutes. The experimental finding that surgical mask partition could reduce animal model transmission speaks highly to the potential for aerosol spread and potentially airborne transmission.[71]

There are both logistic and etymological issues in understanding airborne spread. Like most if not all respiratory viruses, droplet spread occurs within a distance of approximately a meter from the patient source.[72] The latter is not absolute but a generalization. Risk increases proportionate to patient proximity.[73,74] CoVs are certainly capable of spread within such distance, but a concern is whether these viruses spread beyond the latter measures. "Airborne spread" is usually used to convey the potential for wider and more distant dissemination for microbes exemplified by varicella-zoster virus, *Mycobacterium tuberculosis* and *Coxiella burnetii* and for certain spore transmissions. The latter occurs with either small particles, dried microbe, or mobile spores. Isolation precautions have been more stringent for the latter than would be for typical respiratory viruses such as cold viruses or respiratory syncytial virus. Given the severity of SARS-CoV, MERS-CoV, and SARS-CoV-2 infections, there is concern whether more stringent airborne precautions should be maintained even when high-risk aerosolizing procedures are not being conducted. There is no doubt that the environmental spread discussed below can assure that virus is mobilized from sentinel sources by attendees especially health care workers. It appears that SARS-CoV-2 can be aerosolized and transferred for a longer distance than was originally assumed with other CoVs.[64] In effect, the airborne transmission is one of intermediacy as contrasted to conventional thoughts of how airborne transmission should be defined. The airborne transmission of PEDV as discussed above must also be seen in the context of the viral burden that is created when large herds of infected animals are pooled.[63] The topic of airborne transmission will continue to attract controversy and rightfully so.[75-77] In the context of discussing airborne spread, it is critical to remember that high touch surface contamination can occur regardless, and the potential for the latter to transmit virus can confuse the overall assessment.[67]

2.2 | Coronavirus survival in clinical samples

In respiratory samples, SARS-CoV has been found for 4 to 7 days at room temperature and nearly 3 weeks in refrigeration.[78,79] It can also survive the milieu of feces for up to 3 to 4 days especially if the sample is alkaline.[78-80] The timing for SARS-CoV stability in urine has ranged from 3 to 17 days.[79,80] For all CoVs, cold temperature has a stabilizing effect.

2.3 | Coronavirus dissemination and survival in the health care environment

Surrogate CoVs have been used to assess survival on samples that mimic health care spaces. TGEV was found to survive on samples of gloves and hospital scrub dress for up to 4 hours and on N95 respirator and gown material for up to 24 hours.[81] TGEV and MHV survived on stainless steel templates for days to weeks at room temperature and longer under refrigeration.[82] Ambient humidity affected the latter. At room temperature, TGEV survived for much lesser time in the light than in the dark.[83]

229E showed temperature-dependent viability in buffer and suffered at higher ambient temperature.[84] The virus remained viable for up to 5 days at room temperature on surface materials such as polytetrafluoroethylene (Teflon), polyvinyl chloride, ceramic tiles, glass, silicone rubber, and stainless steel. It was susceptible to various copper alloys.[85] In another study, 229E was detectable for over 3 hours on aluminum, latex gloves, and sterile sponge, whereas OC43 appeared to be more susceptible.[86] Spontaneous inactivation of live 229E occurred on stainless steel, hard plastic, and glass over 1 week, but viable virus continued to be found.[87] NL63 was unstable on dry surfaces, but viral RNA could be detected for up to 1 week.[88]

SARS-CoV was more stable on disposable gown material than cotton, but was unstable on paper.[78] The virus was more labile in a dry environment and higher ambient temperature.[89] Viral RNA could be found in the emergency room setting on drinking fountains, bedside chair, table top, bedding, and book shelves.[90] The latter foci occurred both in areas with SARS-CoV patients and in presumed clean areas. Another study found viral RNA widely in patient rooms, nursing stations, and the emergency department, although viral cultures were negative.[91] The latter study also found viral RNA on a

hospital public area elevator hand rail. The association of mask use with protection from SARS as assessed serologically is also consistent with aerosol spread.[92]

MERS-CoV RNA could be found widely on fomites and fixed surface samples in patient rooms.[60,93] Viral RNA could yet be found after some surface cleaning with alcohol.[93] The virus survived on plastic and steel surfaces for up to 24 hours, although it was variably affected by ambient humidity.[94] Viable virus could be found on medical equipment, whereas viral RNA could be found both in patient rooms and the anteroom.[95]

One study of SARS-CoV-2 did not find viral RNA in the immediate patient environment nor on personal protective equipment.[96] Another study from a tertiary care hospital in Wuhan, China also did not find virus in the environment.[97] After disinfection, viral RNA could not be found in one patient's rooms.[98] The latter data has now been supplemented by further study, and viral RNA is ubiquitous on environmental surface sampling from medical rooms.[67,68,99,100] There is some variation in the nature and distribution of such environmental contamination, but this would be expected given the heterogeneity of health care settings. The finding of major floor contamination is often underappreciated.[67] Jiang et al[101] have also extended the findings of viral RNA to quarantine rooms elsewhere. The degree of infectivity of such spread remains to be precisely defined, but early indications from the publication of Chin et al[102] represent some initial findings which differentiate live and noninfectious virus in these environments. The latter study also found infectious virus remnants on the outer layer of a surgical mask by 1 week after inoculation. It is important, however, to recognize that a high titer of virus was initially applied. Fischer et al[103] have more recently examined decontamination processes for reuse of N95 respirators and report that several methods can be efficacious against SARS-CoV-2. The integrity of the respirator must be closely monitored nonetheless.

2.4 | Coronavirus survival in sewage

Both TGEV and MHV were stable in settled sewage water for many days at room temperature, and the stability could be extended considerably at refrigeration temperature.[104]

Although SARS-CoV was not detected in sewage directly, experimental seeding of sewage allowed for virus survival up to 2 days at 20°C, and viral RNA could be detected over 1 week at the same temperature.[105] Refrigerated, the virus could remain viable for up to 2 weeks.[105] In another study, SARS-CoV RNA could be found in sewage before and after chlorine treatment, but viable virus was never detected.[106] Under experimental conditions, SARS-CoV could survive in domestic sewage for 2 days, and viral RNA could be detected for 1 week.[80]

SARS-CoV-2 has been found in sewage with molecular techniques although not viable.[96] Viral RNA was found in waste-water intake at treatment plants but not in tertiary effluent.[107]

2.5 | Coronavirus survival in other environments

TGEV and MHV were stable in cold lake water and reagent-grade water for over 1 month, while lesser titers were found for up to 3 weeks when maintained at room temperature.[104] SARS-CoV has shown stability in soil and potable water.[79]

OC43 RNA was found with amplification methods on various surfaces during an airport surveillance including luggage boxes, stair rails, and payment buttons.[108]

PEDV RNA could be found both before and after disinfection from loading vehicles.[109] Several empty vehicles newly arriving to transport swine were found to have viral RNA in the latter analysis. Susceptibility of PEDV to environmental factors such as natural ultraviolet (UV) light and/or sunlight otherwise was suggested by the finding of less viral load in top layers of manure storage in contrast to deeper layers.[110] Live virus could be found in the latter milieu for up to 9 months. These studies illustrate the ability for such a virus to remain in the context of very high bioburdens.

3 | DECONTAMINATION OF CORONAVIRUSES

Whether for surfaces or individualized items, decontamination of the environment can occur through a variety of potential methods. The validation for many of these approaches is variable even though some authorities have set some standards for assessment.[111-113] Such assessments include carrier tests, suspension studies, susceptibility of viable counts otherwise, detection of viral load through genetic amplification and detection, and field studies. Many such assessments do not test real-life situations but are rather generalized determinations of efficacy. For viruses in particular, there are many factors that affect the efficacy of a decontaminating agent. In the least, these include the initial virus titer, viral species, concomitant presence of more than one virucide, contact time, working dilution, pH, temperature, dry or wet state, relative humidity, concomitant bioburden, nature of the surface, and inactivation of the test agent by the materials. Contact times in practical use are often not fully considered. For example, the contact time after floor mopping or inanimate object wiping are characteristically brief and measured in less than 1 minute. Regardless of product residue, the decontaminated surface may also be unevenly exposed.

As viable virus is often determined through tissue culture methods, the residuum of the decontaminating agent may affect tissue culture eukaryotic cells directly. Such toxicity requires neutralization or removal through a variety of approaches before the detection of virus in tissue culture.[86,114-122] The latter issue is critical to some determinations of efficacy.[102] As illustrated with the caution provided by Chin et al[102] studying SARS-CoV-2, many disinfectant determinations can be compromised by the cytotoxic effect in cell lines for viral growth such that only a higher detection limit of virus is possible. Thus, while the disinfectant may seem efficacious to some extent of the experimentation, lower levels of infectious virus could not be ruled out.

3.1 | Radiation methods

Both ionizing (gamma irradiation) and nonionizing UV irradiation have been assessed for several CoVs, mostly those which are regarded as potential testing surrogates. Gamma irradiation is known for its ability to penetrate various biomaterials and packaging. Radiation doses of 2 to 3 Mrads (20-30 kGy) are generally effective to achieve sterility. UV light can be generated in a spectrum of 200 to 400 nm, but the narrower range of 200 to 280 nm (UVC) is the more virucidal. Commercial UV lights often produce ~250 nm emission. UV light is absorbed by plastic and glass products and does not penetrate solid substances well.

As far back as 1949, it was known that MHV was susceptible to UV light and that efficacy was time-dependent.[123] In viral culture medium and exposed in a Petri dish, cumulative reduction of 5 $logs_{10}$ of MHV quantitation could be achieved.[124] More intense UV exposure reduced MHV load in 15 minutes.[125] Under different conditions, CCoV could be significantly reduced in 15 minutes to several days.[125,126] The latter studies illustrate how the variance in testing methodology can affect the appreciation of efficacy. Other modifications of UV exposure have considerably reduced TGEV titers.[83] For OC43 and 229E, the rapidity of virus reduction was dependent on the contiguous organic load. Virus could be significantly reduced in seconds when exposure was made in the presence of 0.2% bovine serum albumin but required minutes in the presence of 2% fetal calf serum.[127] For 10^6 $TCID_{50}$ titers of SARS-CoV, nearly 1 hour was required to negate the virus in tissue culture medium/plastic wells with UVC at a distance of 80 cm.[79] In a similar setting, SARS-CoV could be inactivated with UVC whereas no effect was achieved with UVA in the same timing of 15 minutes.[128] Others have found UV exposure to be active against SARS-CoV.[129] For the recycling of N95 respirator masks, UV light was found to be sufficient for SARS-CoV-2 deactivation.[103] UV light provided by a commercial system in combination with riboflavin could considerably reduce SARS-CoV-2 titers in plasma and whole blood under experimental conditions.[130] Overall, UVC exposure is an effective virucidal method, but in the least, it is susceptible to exposure timing, distance from virus load, and burden of organic material in the virus milieu.

Gamma irradiation (^{60}cobalt) had a variable effect on SARS-CoV that was dose-dependent.[128,131] Darnell et al[128] found no effect of gamma irradiation in the range of 3 to 15 Krad. Feldmann et al[131] found that 2 Mrad was effective. For MERS-CoV, 3 Mrad was deemed effective to decontaminate up to 10^{10} pfu/mL.[132] Uniformity for assessing antiviral effects has not been established.

3.2 | Temperature modulation

Tests to assess the effect of temperature on viral load lack standardization. In addition, the starting inoculum has been variable (~10^5-10^7 $TCID_{50}$/mL) as has been the in vitro environment of the virus regarding organic load. Most common, viruses have been assessed in tissue culture medium with various animal serum quantitations. Efficacy of increasing temperatures can vary for "dry" heat vs "wet" heat.

As ambient temperature increases from near 0°C, CoVs are increasingly labile in a time-dependent fashion.[69,102,123-125,133,134-137] At refrigeration temperature (~4°C), there is little loss of infectious virus, and relative stability may remain for some 20 to 72 days depending on the conditions.[90,123,124,134,135] The addition of virus stabilizers can extend the viability.[138] At typical working room temperatures (~20°C-22°C), virus titers decline, but detectable viable virus can last up to 3 to 14 days, or longer with preservatives.[78,80,94,123,133,137-139] Between room temperature and 56°C, progressive viral loss is observed.[79,83,89,94,123,124,127,135-137,139,140] Ambient humidity can have variable effects at given temperatures.[89,94,141] Extremes of humidity can be adverse to CoVs.[70,141]

IBV was susceptible to 56°C at thirty minutes (5-6 log10 reduction) but required some 2 hours to be fully inactivated.[142] It was also susceptible to steam when used as a surrogate for a mask decontamination study.[143] Lability for other CoVs at this temperature has been reproduced but again often required up to 2 hours for complete inactivation.[83,123,124,128,133-135,139,144,145] For SARS-CoV, 56°C inactivated the virus considerably in the absence of protein but not in the milieu of 20% protein.[133] For MERS-CoV, 1 to 2 hours. were required to negate 10^5 to 10^6 $TCID_{50}$ virus at 56°C, but only 15 minutes at 65°C.[144] At temperatures of 56°C to 72°C, exposure for 1 to 5 minutes is likely to be insufficient to inactivate coronavirus loads of 10^7 $TCID_{50}$.[79,125,128,136] For SARS CoV, inactivation times of 90, 60, and 30 minutes have been recommended for temperatures of 56°C, 67°C, and 75°C, respectively.[79,128] For SARS-CoV-2, there was considerable virus stability at 4°C up to 2 weeks, whereas 70°C exposure for 5 minutes led to the inactivation of a high titer.[102] In dry heat application for N95 mask resuse, 70°C inactivated SARS-CoV-2.[103] There is also progressive loss of SARS-CoV-2 RNA stability with increasing heat treatment; no viral RNA could be detected after either prolonged boiling or autoclaving.[146]

Comparative temperature stability studies are few.[127,133] Both OC43 and SARS-CoV (*Betacoronavirus*) are less susceptible to temperature inactivation than 229E (*Alphacoronavirus*). Few studies have examined more than one strain of the representative CoVs.

Temperature can have an effect on disinfectant efficacy.[147] For PEDV, efficacy in decontamination was apparent over a temperature range of −20°C to 37°C.[147] Temperature change can also affect the actions of extreme pH.[132,144] At higher temperatures, both increased acidity or alkalinity garner greater antiviral action.

The impact of bioburden on the efficacy of high temperature inactivation is best shown by the study of Thomas et al.[122] In the extreme bioburden of feces, the survival of PEDV was assessed with animal oral inoculation experiments. Virus could be inactivated in 10 minutes at 71°C and in 7 days at room temperature. In lesser circumstances, higher protein or solute concentrations in the virus sample protects viability.[124,133,135,138]

3.3 | Acidity and alkalinity

Acid lability was once a characteristic that was used to help in the classification of viruses.[140] For disinfection, both extremes of

hyperacidity and hyperalkalinity can have significant antiviral effects. These effects are time-accrued and vary according to the testing temperatures and virus medium.

For IBV, minimal inactivation was seen at room temperature for 30 minutes over the pH range of 2 to 9.[142] Over the pH range of 6 to 8, virus viability was mostly reduced at 37°C in contrast to 4°C or 23°C.[148] At pH 3 in room temperature for 4 hours, virus stability was variably reduced.[149] At 4°C, virus was inactivated at pH 11 but minimally at pH 3.[150]

TGEV was minimally affected by pH 5 to 8 at 4°C, but pH greater than 7.5 diminished titers at 37°C.[151] At 37°C, virus was relatively stable over pH 4 to 8 and variably inactivated at pH 3.[83,139,152] Sodium hydroxide inactivated TGEV.[153] For MHV at 37°C, virus was inactivated at pH less than 3 and more than 9, but conformational changes in the virus surface proteins were occurring as early as pH 8.[124,154] CCoV can be inactivated at low and high pH but more so in higher temperature.[126] FCoV was undetectable after exposure to pH greater than or equal to 9.7 at 4°C to 25°C, and virus diminished to a lesser extent with incremental temperature.[155] The application of acidic feed additives (such as citric, fumaric, malic, lactic, phosphoric, formic, propionic, and/or benzoic acids) to porcine diets minimally reduced porcine delta coronavirus survival.[156]

229E viability was significantly reduced below pH 5 and above pH 8 at low and high temperatures.[84,120] SAR-CoV was relatively stable over pH 5 to 9 and for temperatures varying from 4°C to 37°C, but pH less than or equal to 3 and greater than or equal to 12 totally inactivated the virus.[128] SARS-CoV was also susceptible to vinegar.[133] In fecal samples, SARS-CoV could survive for 1 to 5 days at pH 8 to 9, but only for several hours at pH 6.[78] Chin et al[102] find that a pH between 3 to 10 did not have much effect on SARS-CoV-2 at room temperature for 1 hour. Salicylic acid can also have some activity against SARS-CoV-2 in a liquid handwash formulation.[113]

Strain variation in pH susceptibility has been shown for TGEV and IBV.[142,149,152] OC43 was more acid tolerant than 229E.[127]

Bleach products are considerably alkaline (undiluted 5% bleach pH~11). Many other commonly tested and commercially available disinfectants have quite variable pH ranges from 1 to 12.[78,114,120,121] It then begs consideration as to how much the pH plays a role in claimed disinfection vs the direct action of one or more other ingredients in these products. Most commercial products do not post pH values regardless of how much other content descriptions are shown.

3.4 | Peroxides

Accelerated hydrogen peroxide formulations have been assessed for 229E and PEDV.[121,157,158] In full strength exposure with one formulation, greater than 4log$_{10}$ reduction in 229E was achieved at 20°C for 1 minute in the presence of 5% serum. Virus-product exposure required Sephadex neutralization. The pH of the product was ~3, and surfactants had also been included.[121] For PEDV and with a similar product, 1:16 and 1:32 dilutions have been assessed to inactivate virus.[157,158] Major reductions in titer have been observed for virus-laden feces. After exposure for 40 to 60 minutes, pig inoculation bioassays confirmed lack of infectivity.

Hydrogen peroxide vapor automation was highly virucidal against TGEV on stainless steel templates.[159] It was also capable of sterilizing N95 masks for reuse in the context of SARS-CoV-2.[103] Hydrogen peroxide has also been added to ethanol and propanol hand sanitizers that have been internationally subscribed.[160,161]

A different form of oxidizing agent, potassium peroxymonosulfate or oxone, has been mixed with other ingredients which in combination were effective against SARS-CoV and PEDV.[78,147]

3.5 | Halogens

For SARS-CoV, 1:50-1:100 dilution of household bleach (50 000 ppm chlorine equivalent of undiluted) can reduce virus by greater than or equal to 3 log$_{10}$ in 5 minutes at room temperature.[78] In other study, the virus was susceptible after exposure for 30 minutes at 20°C to chlorine solution (from sodium hypochlorite) in a dose and time responsive manner.[80] Others have found 0.1% hypochlorite to be active against SARS-CoV.[129] Chlorine-based solution was more effective than chlorine dioxide. Chlorine-based solution could negate virus in the context of waste water.[80] When applied to a patient environment, a 1:100 dilution of 5% sodium hypochlorite prevented MERS-CoV detection by genetic amplification.[93] 229E was also inactivated with 0.10% to 0.5% hypochlorite, and some strain variation was noted in one study.[120,162] MHV was inactivated with 0.21% sodium hypochlorite.[163] Another study with sodium hypochlorite 100 ppm was effective for MHV and CCoV but not when diluted to 10 ppm.[125] In contrast, a 1:100 dilution of 6% sodium hypochlorite minimally inactivated MHV and TGEV on stainless steel carriers.[115] Others found hypochlorite inactivation of TGEV.[153] Hypochlorite solutions ranging from 0.17% to 2.06% inactivated PEDV at 4°C and 37°C when the virus was suspended in either cell culture medium or fecal slurries, and virus genome was difficult to detect by molecular methods at the highest concentration.[147] Household bleach dilutions of 1:49 and 1:99 were found to inactivate high titers of SARS-CoV-2 after 5 minutes of exposure.[102]

Chloramine T functions like hypochlorite solutions but is also highly oxidizing. In concentrations of 0.10%, it inactivates 229E.[120] Sodium chlorite (0.23%) was not active against the latter viruses in the same study, but it should be recognized that the action of sodium chlorite is considerably different than that of sodium hypochlorite.

For MERS-CoV and SARS-CoV, povidone-iodine preparations were assessed for antiviral action.[118,120,145,164] In 1:1 dilution of several such preparations, virus activity was lost after 2 minutes, and some product was effective as early as 1 minute.[145] Other povidone-iodine preparations were tested in the milieu of bovine serum albumin with or without added red blood cells.[118,163] Marked virus reductions were found at 15 seconds, and complete inactivation occurred at 30 seconds for 1:30 dilutions. An iodophor was effective against MHV and CCoV in 50 ppm but not 5 ppm.[125] The pH of 10% povidone-iodine in one product was 3.[120] With SARS-CoV-2, 7.5% povidone-iodine was found to inactivate high titers of virus after 5 minutes.[102]

Combination halides (hypochlorite and potassium bromide) in 0.05% solution are alkaline and have activity against 229E.[120] Halogen activity can be augmented by creating working solutions that also have surfactants or have low pH.

3.6 | Aldehydes and solvents

MERS-CoV, SARS-CoV, MHV, and CCoV are formaldehyde/formalin intolerant, and effective concentrations can be as low as 0.7%.[116,126,128,132-134,153] Concentrations as low as 0.009% have antivirus activity but require several days and temperatures at or above room.[126,128] Paraformaldehyde and ortho-phthalaldehyde are also strongly antiviral.[115,132,134]

Glutaraldehyde at concentrations as low as 0.7% is also very active and has been assessed with SAR-CoV, 229E, and TGEV.[114,120,133,153] Again, lower concentrations (0.001%-0.009%) may require several days and above room temperature.[126,128] Concentrations typically used for endoscopy decontamination are effective when properly used. Combinations of glutaraldehyde with other agents have been effective against SARS-CoV and PEDV.[114,147]

229E and MHV were ether and/or chloroform susceptible.[124,140]

3.7 | Alcohols

Ethanol and variations of propanol have been used against CoVs in a variety of formulations. Ethanol concentrations varying from 30% to 95% have been active against SARS-CoV-2, SARS-CoV, MHV, CCoV, TGEV, 229E, and BCoV.[102,103,113,114,115,120,123,125,129,153,160,161] In particular, ethanol-based hand rubs have fared well albeit some preparations were enhanced with low levels of hydrogen peroxide.[114,115,160,161] Isopropanol (2-propanol) and n-propanol (1-propanol) have also been active against CoVs when the concentration is over 30%.[98,125,133,160,161] For MHV, a 79% ethanol mixture with a quaternary ammonium compound was effective over thirty seconds.[164] SARS-CoV-2 infectious virus was reduced on standardized surfaces and suspensions when used alone or with a quaternary ammonium compound.[113] For the aforementioned alcohol products, the effect is time accrued. While there are considerable viral reductions, some assessments do not necessarily find complete inactivation especially when the initial starting point is a high titer. Both ethanol and propanol mixtures can be active in the presence of organic loads.[114] Working dilutions of alcohol-based products have been generally recommended to start at 70% when there is no other active product combined.[111]

Methanol in its niche uses is effective against MERS-CoV and SARS-CoV.[132,145]

3.8 | Detergents/surfactants

It has generally been held that detergents can have antimicrobial activity in addition to their benefit for assisting in the removal of associated organic debris (surfactant activity). For viruses in particular, the ability for detergents to interact with lipids gave the impression that activity should be greater against enveloped viruses in contrast to nonenveloped viruses. There are many potential detergent varieties (cationic, anionic, or neutral). One or more have been compounded with other antimicrobial products in the wide array of commercially-available disinfection products. The studies which have examined these products are quite variable in their description of working dilutions, temperature of use, pH, and contact times.

For TGEV, 0.1% sodium dodecyl sulfate (SDS) was highly active after 1 hour at 37°C.[83] SDS also appeared to enhance the effect of a phenolic.[120] For CCoV, benzalkonium chloride (BAK) was ineffective, but two other detergents were effective at a 1:100 dilution.[165] BAK (1%) was also ineffective against OC43 in 1 minute.[119] In yet another format, BAK (0.05%) reduced MHV and CCoV quantitations by 3.7 to 4.1 $\log_{10}$.[125] For SARS-CoV, 1% BAK had antiviral activity but was inferior to sodium hypochlorite.[129] Live titers of SARS-CoV-2 were reduced with 0.1% BAK, but the sensitivity of the assay was compromised by cell line toxicity of the product.[102] Three individual quaternary ammonium compounds showed activity against SARS-CoV-2 either alone or with ethanol at room temperature.[113]

Detergent-added complexed solutions were active against for SARS-CoV, MHV, and 229E.[78,114,120,164] Some of the latter solutions have also been of an acidic (pH 3.2) or alkaline nature (pH 8-9).[114] An alkaline mixture of quaternary ammonium compounds, surfactants, and glutaraldehyde inactivated PEDV.[147]

It is uncommon to find practical assessments of these agents in the field. One such study found that, despite the regular daily use of a combination of nonionic and anionic surfactants for disinfection, 229E continued to be found by culture from high-risk environmental surfaces in a university classroom.[87] Another study examined the efficacy of cleaning toys with a solution combination of two quaternary ammonium compounds and an alcohol ethoxylate.[166] As assessed with measures of viral RNA presence, CoV presence was not significantly altered, and CoV was much more resilient to the cleaning than most other respiratory viruses so tested.

3.9 | Phenolics

There are many phenolics which have been used generally in commercial disinfectants. Some of these solutions have had one or more such chemicals with or without other disinfectants added and at variable pH. Generalizing, the effects of phenolics alone have at times underperformed in comparisons to other agents.

Chloroxylenol (0.24%) did not reduce OC43 titers over 10 minutes at 20°C.[119] 229E was not reduced in titer more than 99.9% when exposed to a three phenolic combination on stainless steel carriers, but the solution could be sufficiently augmented with the addition of either SDS or ethanol.[120] A combination of two phenolics moderately reduced MHV and TGEV titers on steel carriers.[115] Moderate reductions in titers of MHV and CCoV were achieved with Cresol (methyphenol), and the latter underperformed when compared with ethanol.[125] MHV and SARS-CoV

were susceptible to chloroxylenol (0.12%) and phenol (2%), respectively.[134,164] Chloroxylenol (0.05%) was said to be efficacious against SARS-CoV-2, but the lower end of test sensitivity for live virus was compromised by toxicity in cell culture.[102] In other studies, chloroxylenol (0.018%-0.094% dilution) showed activity against SARS-CoV-2 at 21°C to 38°C.[113] Triclosan 0.05%, which has some phenolic properties (a bisphenol), could considerably reduce high titers of MHV.[164]

MHV was suspended in murine brain tissue and retained infectivity for mice despite exposure to 1% phenol for 4 hours at room temperature.[123] In another study, a solution of phenol did not reduce PEDV RNA load in cell culture or in a fecal slurry.[147]

3.10 | Other potential disinfectants

Both OC43 and 229E were not sufficiently inactivated with combinations of cetrimide (containing quaternary ammonium compounds) and chlorhexidine (biguanide), but the addition of 70% ethanol was beneficial.[119,120] Hexamidine did not affect 229E, and chlorhexidine gave mild antiviral activity after prolonged exposure.[116,117] Chlorhexidine (0.02%) had minimal effect on MHV and CCoV.[125] The assessment of chlorhexidine's action on SARS-CoV-2 was limited by cytotoxicity of the cell line, but virus inactivation was nevertheless noted to reduce high titers.[102] Deoxycholate 0.1%, but not 0.01%, was active against MHV and TGEV.[83,124] β-propiolactone (0.4%) was active against MHV. Two macrocytic compounds of the calixarene group had little to moderate activity against 229E.[116] A combination of glucoprotamine, surfactant, and a phenolic at pH 9 was weakly active against 229E and SARS-CoV compared to alcohol solutions.[133]

4 | DECONTAMINATION COMPOUNDING

There is some jeopardy in translating old studies to the current day. Many name-brand disinfectants have changed their formulations over time. Some have listed several different products with nearly the same name albeit with varying ingredients. It may be underappreciated that disinfectants could contain chemicals that are not generally understood to be antiviral. For example, PineSol may initially be conceived as a "pine oil" product but yet may simultaneously contain several different surfactants, isopropanol, benzoic acid, glycolic acid, and/or either acidic or basic pH.[164] As pH variation in itself can have differential antiviral effects, these pH extremes should be considered for products that are promoted for their antiviral properties on the basis of other ingredients. It is therefore important to perform tests with working dilutions rather than with the presumed individual active ingredients.

5 | CAVEATS FOR EFFECTIVE USE

Given the inherent variability of the aforementioned studies and for whichever antiviral approach, definitive statements for absolute efficacy cannot be made for many products. Nevertheless, the existing science can allow for some cautious applications. The following generalizations should be considered at this time:

1) Studies with surrogate CoVs generally provide good screening prediction for the success of decontamination and disinfection procedures with SARS-CoV, MERS-CoV, and SARS-CoV-2.
2) Differences among CoVs have been found for some decontamination and disinfection procedures. It is ultimately the virus of concern that should be exposed under real or experimental conditions to understand the applications in greater relevance.
3) Mechanical cleaning and removal of associated organic debris in the immediate environment will enhance the opportunity for decontamination and disinfectants to function effectively. The addition of detergents and surfactants to compounds fulfills this role in part. Precleaning before final method exposure is recommended.
4) Exposure times for decontamination or disinfection are critical. It is desirable therefore to use active agents that have more rapid onset of action when exposure times are likely to be brief.
5) National and international standards for product claims or efficacy provide a best-guess estimate for product impact. While of great value, efficacy of any decontaminating or disinfection approach is very much dependent on the real-life conditions for application. The context of the various foci where virus can reside complicates real-time efficacy. The use of different decontamination and disinfectant approaches for different intents or surfaces is inherent.
6) Temperature of exposure and working local pH can have significant impacts on virus stability in addition to effects achieved with specific products.
7) Aerosol and airborne spread continue to attract scientific analysis, but the existing science in the interim supports greater stringency for personal protective equipment. Where capable, negative pressure ventilation for patient rooms is recommended. In public and in patient homes, standard precautions of proper hygiene, distancing, mask use, and environmental cleaning are recommended.
8) Materials in the immediate vicinity of patient care should be protected or covered if possible. Computer keyboards are underrecognized sources for health care spread.
9) The immediate environment of patient care should be decluttered for nonessential items since their presence complicates the application of disinfectants.

6 | CAVEATS FOR SAFE USE

Just as there are potential perils for efficacy of decontamination or disinfection procedures, there are also safety concerns that can tip the balance when choosing any one or more methods. Among these safety issues are:

1) While concern may be made especially for a CoV with high infectivity and considerable associated clinical morbidity, decontamination, and disinfection must also simultaneously consider other pathogens (eg, bacterial or other) that require eradication in the same context.
2) CoV spread in the health care and/or patient setting is associated with considerable environmental burden as measured by both live virus and viral RNA. The surface perhaps most disregarded for spread is flooring where virus burden is considerable and where foot traffic is underestimated to play a role.
3) Use of any chemical or physical approach must take into consideration the potential for corrosion or disintegration otherwise of the treated material.
4) Use of a chemical should consider whether there is likely to be an accumulation that could be harmful to patients or caregivers.
5) Use of a chemical should consider whether there are likely to be significant risks of a caustic or flammable nature. In this regard, the use should consider the potential for direct skin contact or for volatility or inhalation.
6) Use of a chemical should consider problems that may arise with imposing potential allergens or scents.

7 | FUTURE NEEDS

Commonly-used disinfectants are often underlabeled for active ingredients, pH, and working dilutions. Preferred temperatures of diluents such as water should also be indicated. SARS-CoV-2-specific data are preferred. It is also preferential to examine decontamination and disinfection protocols in real-life situations of the patient environment. Directed investigative studies have the opportunity to assess the impact of many variables experimentally. Whether studying environmental and fomite viability or aerosol and airborne spread, future assessments should attempt to determine the presence of live and hence infectious virus. Experimental efficacy studies should examine both high and low virus burdens for quantitative reduction but should also consider whether any determinable viable virus is present.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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