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Abstract

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan City, China, late in December 2019 is another example of an emerging zoonotic virus that threatens public health and international travel and commerce. When such a virus emerges, there is often insufficient specific information available on mechanisms of virus dissemination from animal to human or from person to person, on the level or route of infection transmissibility or of viral release in body secretions/excretions, and on the survival of virus in aerosols or on surfaces. The effectiveness of available virucidal agents and hygiene practices as interventions for disrupting the spread of infection and the associated diseases may not be clear for the emergent virus. In the present review, we recommend approaches for infection prevention and control for SARS-CoV-2 which can be invoked based on pre-existing data on microbicidal and hygiene effectiveness for related and unrelated enveloped viruses.

Late in December 2019, cases of pneumonia began appearing in Wuhan City, Hubei Province, China. By early January 2020, these cases were attributed to a novel coronavirus that was temporarily referred to as 2019 Novel Coronavirus (2019-nCoV)[1]. This member of the *Coronaviridae* family has now officially been named SARS-CoV-2[2]. As of April 17, 2020[3], there have been over 2,074,529 confirmed cases globally, with 139,378 deaths (mortality rate of ~6.7%). This emerging virus, and the associated disease (COVID-19), are not only impacting public health, but also international commerce and travel. As with the Middle East Respiratory Syndrome coronavirus (MERS-CoV) that emerged in Saudi Arabia in 2012 and the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) that emerged in China in early 2003, SARS-CoV-2 is considered a zoonosis, with bats suspected as the primary host species (Table 1)[4].

The *Coronaviridae* family is just one of several families of enveloped viruses that have emerged/re-emerged in recent years[5-9] (Table 1). While the list of viruses in Table 1 is not intended to be comprehensive, it contains most of the virus families attributed to the World Health Organization's current list of disease priorities needing urgent R&D attention[10] (i.e., MERS and SARS [*Coronaviridae*], Crimean Congo hemorrhagic fever (*Nairoviridae*), Rift Valley fever [*Phenuiviridae*], Ebola virus disease and Marburg virus disease [*Filoviridae*], Nipah and Hendra virus disease [*Paramyxoviridae*], and Lassa fever [*Arenaviridae*]).

Table 1. Characteristics of selected emerging/re-emerging viruses

Virus	Family	Particle size	Lipid Envelope	Genome* (segments)	Reservoir species	References
Lassa virus	*Arenaviridae*	110-130 nm	yes	±ssRNA(2)	rodent	6,61
SFTSV†	*Phenuiviridae*	80-100 nm	yes	-ssRNA(3)	tick	9
Hantaan virus	*Hantaviridae*	80-120 nm	yes	-ssRNA(3)	rodent	7,8,62
MERS-CoV	*Coronaviridae*	118-136 nm	yes	+ssRNA(1)	bat	2,18,63
SARS-CoV	*Coronaviridae*	80-90 nm	yes	+ssRNA(1)	bat	2,18,63
SARS-CoV-2	*Coronaviridae*	60-140 nm	yes	+ssRNA(1)	bat‡	4,15,64
Ebola virus	*Filoviridae*	80 × 14000 nm	yes	-ssRNA(1)	bat	61
Influenza H5N1	*Orthomyxoviridae*	80-120 nm	yes	-ssRNA(8)	avian	65
Nipah virus	*Paramyxoviridae*	40-1900 nm	yes	-ssRNA(1)	bat	5
EV-D68	*Picornaviridae*	~30 nm	no	+ssRNA(4)	unknown	16,66

*****Abbreviations used: ±, ambisense; -, negative sense; +, positive sense; ss, single-stranded. Segments (1) equates to a non-segmented genome. †Now referred to as Huaiyangshan banyangvirus.‡Suspected primary host based on >90% sequence homology to bat coronaviruses [63].

The emerging/re-emerging viruses shown in Table 1, with the exception of enterovirus D68, each are relatively large, enveloped, zoonotic viruses with single-stranded RNA genomes. Enterovirus D68 (EV-D68), a small non-enveloped virus of the *Picornaviridae* family is an example of a re-emerging virus from that family. While EV-D68, may also be zoonotic[11,12], a reservoir species has yet to be identified.

Aside from the characteristics described in Table 1, what other commonalities exist for these emerging/re-emerging zoonotic viruses? Can we use these commonalities as the basis for proposing approaches for infection prevention and control (IPAC)? In the remainder of this review, we examine various aspects of the emerging/re-emerging viruses that are important in formulating approaches for IPAC, namely transmissibility, infectivity, viral shedding, environmental survival, and expectations regarding microbicidal efficacy for targeted hygiene practices. This information may then be leveraged to effectively mitigate the health risks associated with SARS-CoV-2 and its associated disease (COVID-19), as well as with future emerging/re-emerging enveloped viruses.

Transmissibility of Emerging/Re-emerging Viruses

According to several authors[13,15], sustained person-to-person transmission of viruses is favored by certain viral characteristics, including lack of a lipid envelope, small particle size, limited

genomic segmentation, and low mortality of the associated disease[13-15]. Tropism of the virus for the liver, central nervous system (CNS), or the respiratory tract, and lack of vector-borne transmission also appear to favor sustained person-to-person transmission[13,14]. On the other hand, possession of an RNA vs. a DNA genome was not found to contribute to the likelihood of such sustained transmission[13,14].

It is of interest that many of the viral characteristics mentioned above that are considered predictive of sustained person-to-person transmissibility are not shared by the viruses associated with the World Health Organization (WHO) diseases of concern[10]. Namely, all of the emerging/re-emerging diseases mentioned in the WHO list[10] involve relatively large enveloped viruses with ssRNA genomes, many of which are segmented. Of the emerging/re-emerging viruses listed in Table 1, only EV-D68 is a small, non-enveloped virus. In addition, many of the listed viruses exhibit high human mortality (Tables 1 and 2).

Table 2. Transmission and mortality of emerging/re-emerging viruses

Virus	Tropism for organs	Mode of transmission*	Mortality	Reference
Lassa virus	Vascular system	Contact, aerosols	15-20%	25,61
SFTSV	Vascular system	Vector (tick)	12-30%	9,67
Hantaan virus	Lower respiratory, renal	Contact, Aerosols	1-15%	61,62,68,69
MERS-CoV	Lower respiratory, GI	Contact, aerosols	34-36%	25,42,70,71
SARS-CoV	Lower respiratory	Contact, aerosols	15 ± 11%	25,72
SARS-CoV-2	Lower respiratory, GI	Contact, aerosols	7%	3,19
Ebola virus	Vascular system	Contact, aerosols	41%	25,42,73
Influenza H5N1	Upper respiratory	Contact, aerosols	>60%	25,74
Nipah virus	CNS, respiratory	Contact, ingestion	65 ± 28%	5,27
EV-D68	Respiratory, CNS	Aerosols, contact	Up to 10%	66,75

*"Contact" refers to contact with bodily fluids or with fomites; "aerosols" equates to respiratory aerosols/droplets. CNS, central nervous system, GI, gastrointestinal

Certain predictive factors[13-15] that do seem to be shared by the emerging/re-emerging viruses in the list in Table 1 include tropism for the respiratory tract or the CNS, and lack of vector-borne transmission. While most enteroviruses are less susceptible to acid and are disseminated by the fecal-oral route, EV-D68 is acid-labile and has a lower temperature optimum, reflecting its tropism for the upper respiratory tract rather than the gastrointestinal tract (i.e., EV-D68 acts more like a rhinovirus than an enterovirus)[16].

It is unknown if sustained person-to-person transmissibility necessarily equates to a high level of concern for an emergent zoonotic virus. For instance, there appears to be no evidence that Hendra virus (another zoonotic enveloped virus) has shown person-to-person transmission[17], yet this virus is similar to Nipah virus in many respects and is of concern, due its high mortality rate in humans.

As mentioned in Table 2, the most common modes of transmission for the emerging/re-emerging viruses discussed in this review are contact with infected bodily secretions/excretions and contaminated fomites, especially high-touch surfaces (HITES), and inhalation of respiratory

droplets/aerosols containing infectious virus (Fig 1). The intermediacy of hands in transmission through contact is emphasized in Fig. 1.

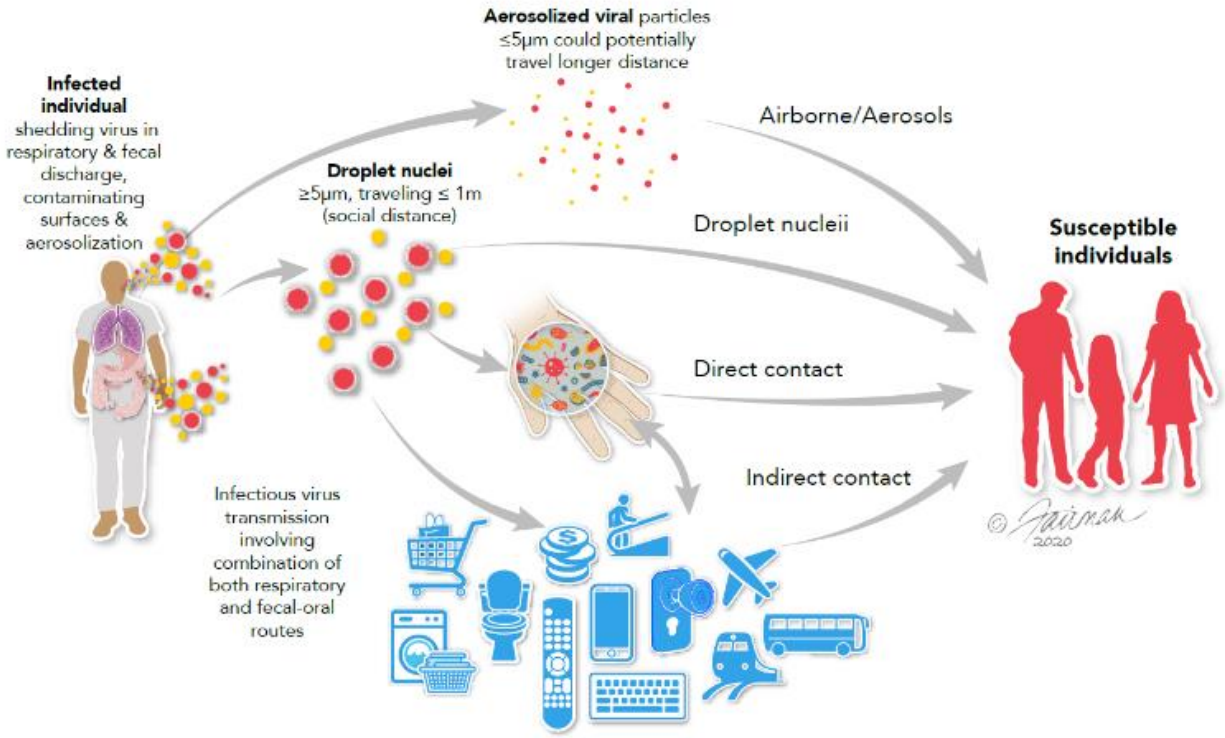

Figure 1. Modes of transmission of viruses, emphasizing respiratory infections such as SARS-CoV, MERS-CoV, and SARS-COV-2 (modified from Otter et al.[18]).

The animal-to-human and person-to-person transmission of SARS-CoV-2 and associated COVID-19 disease appears to occur in a manner similar to that described for MERS-CoV and SARS-CoV.

Infectivity and Virus Shedding of Emerging/Re-emerging Viruses

The infectivity of a virus refers to its ability to initiate infection of host cell with production of viral progeny. The infectious dose$_{50}$ (ID_{50}) is the smallest number of infectious virus particles that will lead to infection of 50% of an exposed population[20], and is dependent a number of factors, such as the species, age, or race of the host, the receptor, immune, and nutritional status of the host or host tissues, and the portal of entry of the virus. In the case of most viruses, only a percentage of those infected actually develop clinical illness[21]. Those who remain asymptomatic represent subclinical cases of the infection in whom the virus may still replicate and be released into the environment. IPAC may be difficult in the face of such silent disseminators (virus carriers/shedders). Exposure to as low as one infectious viral particle has a probability of causing an infection leading to disease, although that probability varies from virus to virus[22]. Typically, infectious doses are empirically derived and reported in units of 50% infective dose (ID_{50}) values

that reflect the doses capable of infecting half of the subjects exposed. As prospective studies in humans of highly pathogenic viral diseases with potentially fatal outcomes cannot ethically be performed, very limited data exist on the infectivity of the emerging/re-emerging viruses in Table 1. Where studies have been performed using animals, extrapolations of such data to humans must be made with caution.

The estimates that have been reported for viruses listed in Tables 1 and 2 are discussed below, acknowledging the unavoidable variability in literature with regard to such assessments of infectivity. It has been stated that 1-10 infectious aerosolized Ebola virus particles can cause an infection in humans[23,24]. A similar range has been reported for the Lassa virus[25]. Influenza virus infectivity values specific to the H5N1 and H7N9 strains are not known[22] but estimates of 100 to 1000 infectious viral particles have been reported[22,25]. The human infective dose for SARS-CoV has been estimated at 16 to 160 plaque-forming units[26]. Data on the human infectious doses for MERS-CoV, SFTSV, Nipah virus, and EV-D68 have not been reported. Until such data become available, it should be assumed that these emerging/re-emerging viruses, including SARS-CoV-2, have relatively low ID_{50} values.

Once infected with one of these emerging/re-emerging viruses, during the prodromal period before actual appearance of symptoms, as well as once symptoms appear, the infected individual may become a shedder of infectious particles. The extent to which virus shedding might lead to dissemination of the associated disease depends upon a number of factors, including the amount of virus released (shed), the infectivity of the virus within the released matrix (droplets/aerosols, fecal/diarrheal discharge, and other excretions including respiratory secretions), and the survival of the released viruses within such matrices once dried on HITES. Extent of virus shedding, unfortunately, is commonly measured through detection of genomic material[e.g., 18,22,27,28], rather than through use of infectivity assays, so there are only limited data available on infectious viral shedding.

As displayed in Fig. 1, transmission of respiratory infections commonly involves the intermediacy of the hand. The same can be said about gastrointestinal infections (i.e., through the fecal-oral route). The SARS-CoV, MERS-CoV, and SARS-CoV-2 have been reported[18,19] to be shed from patients both within respiratory and gastrointestinal secretions/excretions, therefore it is likely that contaminated HITES and respiratory droplets/aerosols also play an important role in dissemination of the SARS-CoV-2 through the intermediacy of hands.

Viral Survival on Environmental Surfaces and in Air

Knowledge of the transmissibility and infectivity of emerging/re-emerging viruses enables one to assess the risk of spread of a viral disease in the case that infectious virus is shed from an infected individual and is deposited on environmental surfaces/fomites or in droplets/aerosols. Another important factor to consider when assessing risk is the survival (i.e., the continued infectivity) of these viruses on the environmental surfaces/fomites or in air in the form of droplets/aerosols.

There is much more information addressing survival of infectious viruses on environmental surfaces than in aerosols. The data that are available address a number of environmental factors of relevance[18], including the types and porosities of the surfaces, the matrices in which the viruses have been suspended prior to being deposited onto the surfaces the temperature and relative humidity (RH), and methods used for measuring survival (e.g., $\log_{10}$ reduction in

infectivity per unit time, infectivity half-life, etc., infectious titer after a measured duration, etc.). For Table 3, the results that have been displayed focus on room temperature (ambient) conditions at relatively low and medium RH. Table 3 should not, therefore, be considered to represent a comprehensive review of literature for survival of these viruses. For a more systematic review of coronaviruses survival on environmental surfaces under various conditions, see the reviews by Otter et al.[18] and Kampf et al.[29]. For certain viruses (e.g., SFTSV), survival data are not yet available, so data for surrogate viruses from the same or similar families are shown. Persistence of SARS-CoV-2 on surfaces and in air has recently been reported by van Doremalen et al.[30] SARS-CoV-2 was found to remain viable in aerosols for at least 3 hours, and for up to 24 hours on cardboard and 2 to 3 days on plastic and stainless steel surfaces[30].

Table 3. Environmental survival of emerging/re-emerging viruses at room temperature

Virus	Survival on surfaces	Survival in aerosols	Reference
Lassa virus	0.41 $\log_{10}$/d (glass)	t½ = 0.62 h	76,77
SFTSV	t½ = 0.75 h (aluminum)†	No data	78
Hantaan virus	t½ = 1.0 h (aluminum)	No data	78
MERS-CoV	t½ = 0.94 h (steel)	t½ = 27 h*	31,71
SARS-CoV	t½ = 10 h (steel), 18 h (plastic)	At least 3 h¶	30,72
SARS-CoV-2	t½ = 13 h (steel), 16 h (plastic)	At least 3 h¶	30
Ebola virus	0.68 $\log_{10}$/d (glass) 0.88 $\log_{10}$/d (steel)	t½ = 0.25 h	39,73,76,79,80
Influenza H5N1	<1 d (glass, metal)	No data	65
Nipah virus	1 h (plastic)	No data	79
EV-D68	t½ = 0.17 to 0.25 h (steel)‡	No data	81

†No data for SFTSV are available, the result displayed is for Crimean-Congo virus.
*Aerosol data for coronavirus 229E[31]. Survival half-life depended on humidity. The values ranged from 3.3 h (~80% RH), 67 h (50% RH), to 27 h (30% RH).
‡No data for EV-D68 are available; the result displayed is for human rhinovirus type 14 at 15-55% RH[65].
¶The authors only evaluated times up to 3 h.

Hierarchy of Microbicidal Efficacy for Inactivating Pathogens

Infectious virus survival in aerosols or on HITES represents a source for dissemination of emerging /re-emerging viruses, including SARS-CoV-2. The enveloped viruses listed in Tables 1 and 2 should be relatively susceptible to the inactivating activity of a variety of microbicides, as discussed below. Sattar[32] previously has advanced the concept of utilizing the known knowledge of the susceptibility human viral pathogens to chemical disinfecting agents (microbicides)[33,34] to predict the efficacy of such agents for inactivating emerging /re-emerging viral pathogens. This concept, referred to as a hierarchy of susceptibility to microbicides[32,33], is portrayed in Fig. 2. As shown, pathogenic agents can be viewed as displaying a continuum of susceptibilities to microbicides, with enveloped viruses at the bottom of this hierarchy, highlighting their relatively high susceptibilities to formulated microbicides[32,33].

Among pathogens, prions are considered to be the least sensitive to microbicides, requiring highly caustic solutions for inactivation. Bacterial spores and protozoan cysts/oocysts are next on the microbicidal susceptibility spectrum. Small, non-enveloped viruses are considered to be less susceptible to microbicides, although have increased susceptibility to high pH, oxidizers such as sodium hypochlorite, formulated hydrogen peroxide, alcohols, and a variety of microbicidal actives, relative to spores and protozoan cysts/oocysts. Mycobacteria, fungi, vegetative bacteria and enveloped viruses appear to be less resistant to certain formulated microbicides, such as alcohols, oxidizers, quaternary ammonium compounds (QAC), and phenolics (e.g., p-chloro-m-xylenol)[29,32-45].

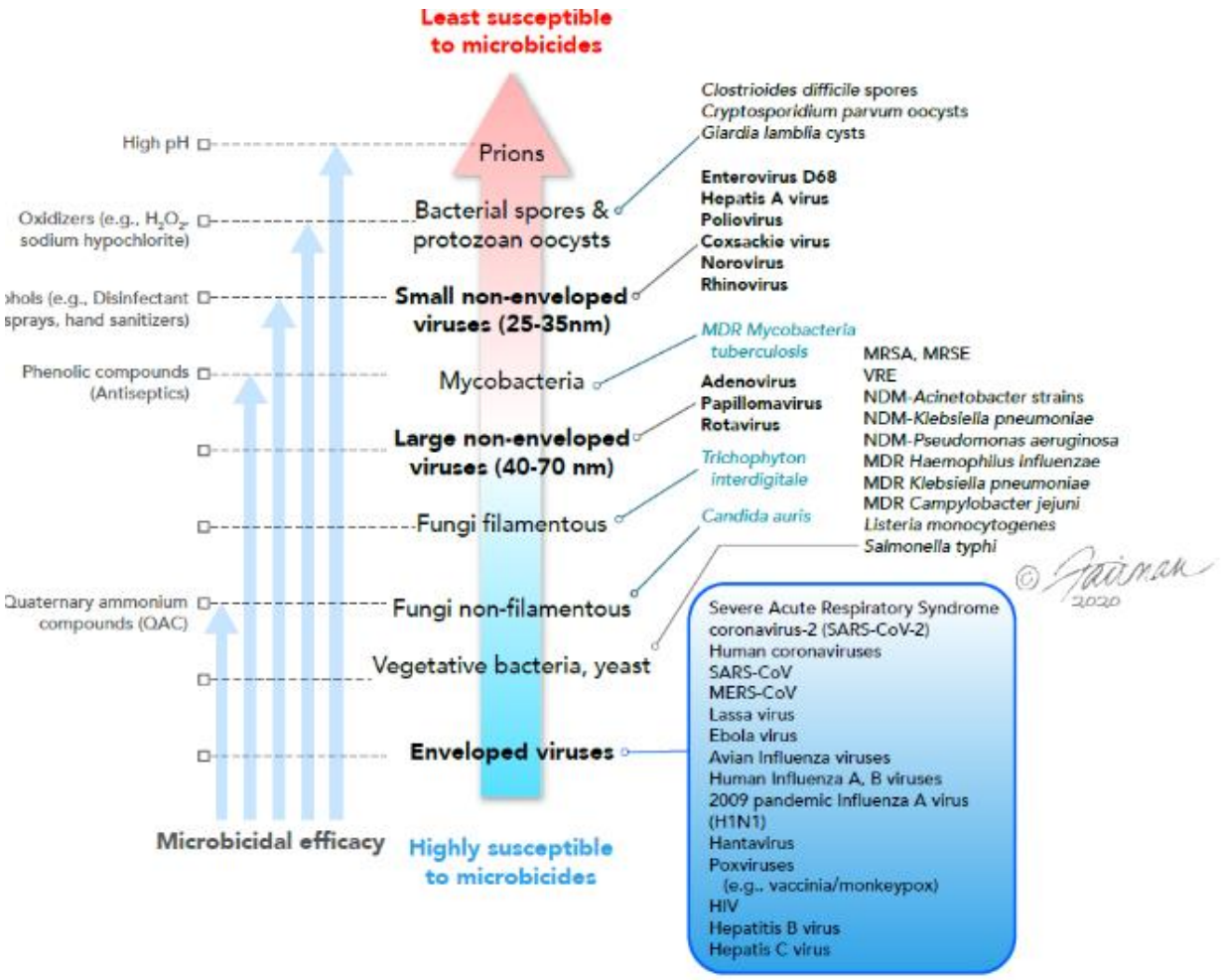

Figure 2. Hierarchy of sensitivity of pathogens to formulated chemical microbicides (adapted from Sattar[32]). Data are from a variety of sources[29,32-45].

It is of interest that the enveloped viruses are considered to be the most susceptible to a variety of formulated microbicidal actives, even more so than fungi and vegetative bacteria, yeast, and mycobacteria (Fig. 2). Viral envelopes are typically derived from portions of the host

cell membrane and therefore comprise host cell phospholipids and proteins (Fig. 3), as well as some virally inserted glycoproteins. Since the envelopes contain lipid material, they are readily destroyed by phenolics such as p-chloro-m-xylenol (PCMX), oxidizing agents such as sodium hypochlorite and activated hydrogen peroxide, quaternary ammonium compounds, alcohols, and detergents. Even mild detergents such as soap may inactivate enveloped viruses by denaturing the lipoproteins in the envelope. This makes them more susceptible to most of the formulated virucidal microbicides commonly used for IPAC.

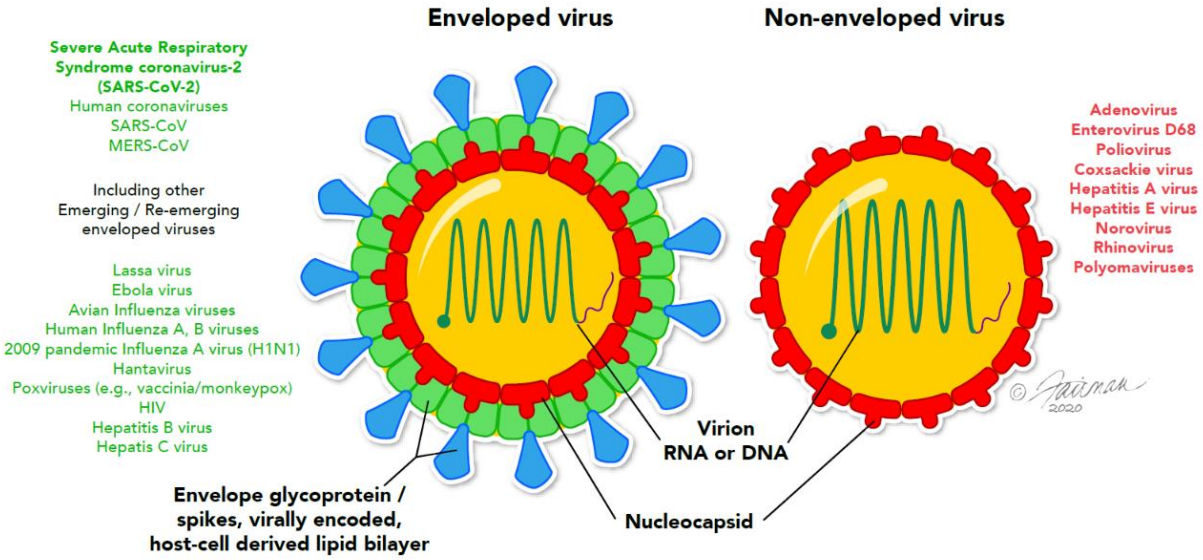

Figure 3. Ultrastructural differences between enveloped and non-enveloped viruses. Genotypically, these viral genomes may be single-or double-stranded, and segmented or non-segmented (examples are not shown in the figure).

It can be assumed as a starting point, therefore, that the enveloped emerging/re-emerging viruses listed in Table 1 should be readily inactivated by a variety of formulated microbicidal actives. This assumption has, in fact, been verified by extensive empirical data[29,32-40,42-44], and has been embraced by the U.S. Environmental Protection Agency[46]. The data for various members of the *Coronaviridae* family have recently been reviewed by Kampf et al.[29], and these data support the expectation that SARS-CoV-2 and other coronaviruses of concern (e.g., MERS-CoV, SARS-CoV, mouse hepatitis virus, porcine epidemic diarrhea virus, etc.) should be readily inactivated by commonly employed and commercially available microbicides, including QAC. In addition, a European guidance document[47] recently has been issued that lists a variety of microbicidal agents that have demonstrated efficacy against a variety of human and animal coronaviruses, and that, therefore, could be applied for decontamination of surfaces in non-healthcare facilities.

Aqueous solutions of the phenolic, PCMX, at concentrations of 0.12 -0.48% by weight were shown to inactivate >4 $\log_{10}$ of infectious Ebola virus - Makona variant (EBOV/Mak) suspended in an organic load and evaluated in liquid inactivation studies[43,48] or dried on a steel surface in a carrier inactivation study[48]. In each case, complete inactivation of ≥6.8 $\log_{10}$ of EBOV/Mak was observed after contact times ≥5 min. In addition, EBOV/Mak dried on prototypic steel carriers was completely inactivated (≥6.5 $\log_{10}$) by aqueous solutions of 70% ethanol or 0.5% or 1% NaOCl (≥0.5%) after contact times ≥2.5 min[39].

Microbicidal formulations based on oxidizing agents, QAC, alcohols, phenolics, and aldehydes displaying virucidal efficacy for enveloped viruses and relatively less susceptible non-enveloped viruses (such as human norovirus surrogates) have been recommended for decontaminating environmental surfaces or materials used for food preparation[49,50]. The efficacy of ethanol and QAC actives for inactivating the norovirus surrogate feline calicivirus depends on how the microbicides are formulated. Factors such as the addition of an alkaline agent were found to increase their efficacy[51]. Microbicides satisfying these requirements can be regarded as effective against emerging/re-emerging viruses such as SARS-CoV-2. Following this logic, the U.S. EPA has invoked an Emerging Viral Pathogen Policy in the past for the 2009 pandemic influenza, for the Ebola virus, and most recently for SARS-CoV-2[52].

In the case of highly pathogenic emerging/re-emerging viruses such as SARS-CoV-2, effective and frequent targeted hygiene using appropriate microbicides is essential for prevention of dissemination. Practicing hygiene inappropriately and only once daily may not be sufficient. For instance, infectious coronavirus 229E was detected on HITES (e.g., door knobs) in a university classroom in which samples were collected daily over a one-week period[53]. Vigilant decontamination of HITES becomes of paramount importance when dealing with highly pathogenic viruses with relatively low human infectious doses, as is the case with many of the emerging/re-emerging viruses, including SARS-CoV-2, being discussed in this review.

The enveloped emerging/re-emerging viruses listed in Table 1 display high susceptibility to inactivation by ultraviolet light at 254 nm, an inactivation approach amendable to inactivation of aerosolized viruses[31]. For instance, empirical data[54] for Lassa virus, Hantavirus, and Ebola virus, and for the virus families (*Coronaviridae, Orthomxyoviridae, Paramyxoviridae, Phenuiviridae*) indicate that UV fluencies of 3 to 14 mJ/cm^2 should inactivate 4 $\log_{10}$ of the enveloped viruses in Table 1. These fluency values are relatively low, compared to those needed to inactivate 4 $\log_{10}$ of the least susceptible viruses, such as those of the *Adenoviridae* (98-222 mJ/cm^2) and *Polyomaviridae* (235-364 mJ/cm^2) families of non-enveloped viruses[55].

Personal Hygiene Practices for Preventing Infectious Virus Acquisition

A 2005 study on SARS-CoV indicated the presence of genomic material for that virus in air and on HITES within a SARS patient's room[56], indicating the likelihood of airborne droplet transmission for this coronavirus. This suggests that appropriate respiratory protection, as well as targeted HITES decontamination and hand hygiene, represent important interventional practices for limiting virus dissemination during outbreaks such as that occurring now with SARS-CoV-2.

The WHO has posted on their website a webpage entitled Coronavirus Disease (COVID-19) advice for the public[57]. Basic protective measures against SARS-CoV-2 recommended by the WHO[57] include: frequent hand washing with soap and water or an alcohol-based rub, and maintenance of social distancing (at least 1m, see Fig 1) especially in the presence of people who

are coughing, sneezing, or have a fever. The latter recommendation is applicable to any of the viruses listed in Table 2 for which transmission by respiratory aerosols is expected. Avoidance of touching eyes, nose, mouth, or other mucus membranes with hands post-contact with HITES is also recommended[57]. As displayed in Fig 1, the hands play an important role in transfer of infectious virus from contaminated HITES to susceptible host's mucus membranes, enabling virus-host interactions initiating infection. Following the appropriate hygiene practices described above can potentially help in prevention and control of emerging and re-emerging viruses, including the currently circulating SARS-CoV-2.

Discussion

As Dr. Anthony Fauci eloquently stated in 2005[58] "Public health officials once suggested that it might someday be possible to 'close the book' on the study and treatment of infectious diseases. However, it is now clear that endemic diseases as well as newly emerging ones (e.g., severe acute respiratory syndrome [SARS]), reemerging ones (e.g., West Nile virus), and even deliberately disseminated infectious diseases (e.g., anthrax from bioterrorism) continue to pose a substantial threat throughout the world." Recent experience certainly verifies these predictions. Weber et al.[41] have correctly emphasized that "Preventing disease acquisition via person-to-person transmission or contact with the contaminated environment depends on rapid and appropriate institution of isolation precautions, appropriate hand hygiene, and appropriate disinfection of medical equipment, devices, and the environmental surfaces. Importantly, once the nature of the emerging infectious agent is known (i.e., enveloped virus, bacteria, fungi, nonenveloped virus, mycobacteria, or non-enveloped virus), it is possible to determine the appropriate hygienic interventions. For example, an enveloped virus (e.g., Ebola, MERS-CoV) or vegetative bacterium (e.g., CRE, MRSA) would be inactivated by any formulated microbicidal active(s) known to be effective against vegetative bacteria, filamentous fungi, mycobacteria, or non-enveloped viruses."[41].

It is fortunate, though perhaps a little perplexing, that so many of the emerging/re-emerging viruses (examples listed in Table 1 and below) are enveloped viruses. It is not clear why there are not more small, non-enveloped viruses mentioned in the WHO list of viral diseases of concern[10]. The small non-enveloped viruses are much less susceptible to commonly employed cleaning agents (antiseptics, detergents, non-formulated microbicidal actives) and, in general, display relatively longer survival on environmental surfaces. According to theoretical modeling of sustained person-to-person transmissibility[12-14], small non-enveloped viruses are predicted to be more likely to lead to sustained infections within the community. The reality is that the emerging/re-emerging viruses of concern, both in humans and in economically important animals, have more typically included enveloped viruses. Recent examples include porcine epidemic diarrhea virus, MERS-CoV, SARS-CoV and SARS-CoV-2 (*Coronaviridae*), African swine fever virus (*Asfarviridae*), Schmallenberg virus (*Peribunyaviridae*), Crimean-Congo hemorrhagic fever virus (*Nairoviridae*), Rift Valley fever virus (*Phenuiviridae*), and West Nile virus and Zika virus (*Flaviviridae*), Hantaviruses (*Hantaviridae*), and Lassa viruses (*Bunyaviridae*).

The fact that the emerging/re-emerging viruses are predominantly RNA viruses might be explained in part by the notion[59] that RNA viruses can more readily adapt to the rapidly changing global and local environment due to the high error rate of the polymerases that replicate their

genomes. The RNA viruses are thought therefore to display higher evolution rates through mutation, gnomonic reassortment, or recombination.

The likelihood of experiencing future emergent zoonotic viruses is high[60], and therefore defining in advance appropriate approaches for limiting spread of such viruses through IPAC is essential. We now have the sequencing tools necessary for rapidly identifying a novel virus such as SARS-CoV-2, the genetic sequence of which was determined within just over one week[4]. Provided that a novel emerging virus is found to be a member of a viral family for which we have sufficient microbicidal data available, including IPAC expertise, it should be possible to make accurate predictions as to viral transmission, survival on surfaces, and microbicidal efficacy. SARS-CoV-2 is no exception in this regard.

References

1. World Health Organization. Novel Coronavirus (2019-nCoV). https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Gorbalenya, A. E. *et al.* Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the Coronavirus Study Group. *bioRxiv* https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1
3. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 88; https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200417-sitrep-88-covid-191b6cccd94f8b4f219377bff55719a6ed.pdf?sfvrsn=ebe78315_6 (2020).
4. Zhu, N. *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med*. **382**, 727-733 (2020).
5. Ang, B. S. P., Lim, T. C. C. & Wang, L. Nipah virus infection. *J. Clin. Microbiol*. **56**:e01875-17. doi.org/10.1128/JCM.01875-17 (2018).
6. Viral Hemorrhagic Fever Consortium. Lassa https://vhfc.org/diseases/lassa/
7. Laenen, L. *et al*. *Hantaviridae*: current classification and future perspectives. *Viruses* doi: 10.3390/v11090788 (2019).
8. Brocato, R. L. & Hooper, J. W. Progress on the prevention and treatment of hantavirus disease. *Viruses* **11**, 610; doi:10.3390/v11070610 (2019).
9. Zhan, J. *et al*. Current status of severe fever with thrombocytopenia syndrome virus in China. *Virol. Sin*. **32**, 51-62 (2017).
10. World Health Organization. WHO publishes list of top emerging diseases likely to cause major epidemics. Https://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/
11. Bailey, E. S., Fieldhouse, J. K., Choi, J. Y. & Gray, G. C. A mini review of the zoonotic threat potential of influenza viruses, coronaviruses, adenoviruses, and enteroviruses. *Front. Pub. Health*. **6**:104. doi: 10.3389/fpubh.2018.00104 (2018).
12. Fieldhouse, J. K., Wang, X., Mallinson, K. A., Tsao, R. W. & Gray, G. C. A systematic review of evidence that enteroviruses may be zoonotic. *Emerg. Microb. Infect*. **7** doi.org/10.1038/s41426-018-0159-1 (2018).
13. Geoghegan, J. L., Senior, A. M., Di Giallonardo, F. & Holmes, E. C. Virological factors that increase transmissibility of emerging human viruses. *Proc. Natl. Acad. Sci. USA* **113**, 4170-4175 (2016).

14. Walker, J. W., Han, B. A., Ott, I. M. & Drake, J. M. Transmissibility of emerging viral zoonoses. *PLoS ONE* **13** (11): e0206926. doi.org/10.1371/journal.pone.0206926 (2018).
15. Munster, V. J., Koopmans, M., van Doremalen, N., van Riel, D. & de Witt, E. A novel coronavirus emerging in China – key questions for impact assessment. *N. Engl. J. Med.* **382**, 692-694 (2020).
16. Sun, J., Hu, X.-Y. & Yu, X.-F. Current understanding of human enterovirus D68. *Viruses* **11**:490; doi:10.3390/v11060490 (2019).
17. Paterson, B. J., Mackenzie, J. S., Durrheim, D. N. & Smith, D. A review of the epidemiology and surveillance of viral zoonotic encephalitis and the impact on human health in Australia. *NSW Pub. Health Bull*. **22**, 99-103 (2011).
18. Otter, J. A., Donskey, C., Yezli, S., Douthwaite, S., Goldenberg, S. D. & Weber, D. J. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. *J. Hosp. Infect*. **92**, 235-250 (2011).
19. Zhang, Y. *et al*. Isolation of 2019-nCoV from a stool specimen of a laboratory-confirmed case of the coronavirus disease 2019 (COVID-19). *Chin. Center Dis. Control Prevent. Weekly*. **2,** 11 (2020).
20. Westwood, J. C. N. & Sattar, S. A. The minimal infective dose: can it establish infection? International Conference on "Viruses in Water", Mexico City, Mexico. (June 1974).
21. Haas, C. N., Rose, J. B. & Gerba, C. P. Quantitative Microbial Risk Assessment. John Wiley, NY (2014).
22. Yezli, S. & Otter, J. A. Minimum infective dose of the major human respiratory and enteric viruses transmitted through food and the environment. *Food Environ. Microbiol.* **3**, 1-30 (2011).
23. Bibby, K., Fischer, R. J., Casson, L. W., de Carvalho, N. A., Haas, C. N. & Munster, V. J. Disinfection of Ebola virus in sterilized municipal wastewater. *PLoS Negl. Trop. Dis*. **11**:e0005299.doi:10.1371/journal/pntd.005299 (2017).
24. Franz, D. R. *et al*. Clinical recognition and management of patients exposed to biological warfare agents. *J. Am. Med. Assoc*. **278**, 399–411 (1997).
25. Cieslak, T. J., Herstein, J. J., Kortepeter, M. G., Hewlett, A. L. A methodology for determining which diseases warrant care in a high-level containment care unit. *Viruses* **11**, 773; doi:10.3390/v11090773 (2019).
26. Watanabe, T., Bartrand, T. A., Weir, M. H., Omura, T. & Haas, C. N. Development of a dose-response model for SARS coronavirus. *Risk Anal*. **30**: DOI: 10.1111/j.1539-6924.2010.01427.x (2010).
27. Hassan, M. Z. *et al*. Nipah virus contamination of hospital surfaces during outbreaks, Bangladesh, 2013-2014. *Emerg. Inf. Dis*. **24**, 15-21 (2018).
28. Killerby, M. E., Biggs, H. M., Midgley, C. M., Gerber, S. I. & Watson, J. T. Middle East Respiratory Syndrome coronavirus transmission. *Emerg. Infect. Dis*. **26**, 191-198 (2020).
29. Kampf, G., Todt, D., Pfaender, S. & Steinmann, E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. *J. Hosp. Inf.* **104**, 246-251 (2020).
30. Van Doremalen *et al*. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020;382:1564-1567

31. Ijaz, M. K., Brunner, A. H., Sattar, S. A., Nair, R. C. & Johnson-Lussenburg, C. M. Survival characteristics of airborne human coronavirus. *J. Gen. Virol*. **66**, 2743-2748 (1985).
32. Sattar, S. A. Hierarchy of susceptibility of viruses to environmental surface disinfectants: a predictor of activity against new and emerging viral pathogens. *J. AOAC Int.* **90**, 1655-1658 (2007).
33. Klein, M. & Deforest, A. Principles of viral inactivation. In: Block SS, editor. Disinfection, sterilization, and preservation, 3rd edition: Philadelphia: Lea and Febiger; 1983 p. 422-434.
34. McDonnell, G. & Russell, A. D. Antiseptics and disinfectants: activity, action, and resistance. *Clin. Microbiol. Rev.***12**, 147-179 (1999).
35. Rabenau, H. F., Cinatl, J., Morgenstern, B., Bauer, G., Preiser, W. & Doerr, H. W. Stability and inactivation of SARS coronavirus. *Med. Microbiol. Immunol*. **194**, 1-6 (2005).
36. Sattar, S. A., Springthorpe, V. S., Karim, Y. & Loro, P. Chemical disinfection of non-porous inanimate surfaces experimentally contaminated with four human pathogenic viruses. *Epidemiol. Infect.* **102**, 493-505 (1989).
37. Geller, C., Varbanov, M. & Duval, R. E. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses* **4**, 3044-3068 (2012).
38. Maillard, J.-Y., Sattar, S. A. & Pinto, F. Virucidal activity of microbicides. In Russell, Hugo & Ayliffe's: Principles and Practice of Disinfection, Preservation and Sterilization, 5th Edition, Fraise AP, Maillard J-Y, Sattar A (eds). (2013) https://doi.org/10.1002/9781118425831.ch9
39. Cook, B. W. M. *et al*. Evaluating environmental persistence and disinfection of Ebola virus Makona variant. *Viruses* **7**, 1975-1986 (2015).
40. Cook, B. W. M., Cutts, T. A., Nikiforuk, A. M., Leung, A., Kobasa, D. & Theriault, S. S. The disinfection characteristics of Ebola virus outbreak variants. *Sci. Rep.* **6**,38293 https://doi.org/10.1038/srep38293 (2016).
41. Rutala, W. A., Kanamori, H., Gergen, M. F., Sickbert-Bennett, E. E. & Weber, D. J. Susceptibility of *Candida auris* and *Candida albicans* to 21 germicides used in healthcare facilities. *Inf. Control Hosp. Epidemiol*. **40**, 380-382 (2019).
42. Weber, D. J., Sickbert-Bennett, E. E., Kanamori, H. & Rutala, W. A. New and emerging infectious diseases (Ebola, Middle Eastern respiratory syndrome coronavirus, carbapenem-resistant *Enterobacteriacae*, *Candida auris*): Focus on environmental survival and germicide susceptibility. *Am. J. Inf. Control* **47**, A29-A38 (2019).
43. Cutts, T. A., Ijaz, M. K., Nims, R. W., Rubino, J. R. & Theriault, S. S. Effectiveness of Dettol Antiseptic Liquid for inactivation of Ebola virus in suspension. *Sci. Rep.* **9**:6590 doi.org/10.1038/s41598-019-42386-5 (2019).
44. Vaughan, A. *et al*. Human-to-human transmission of monkeypox virus, United Kingdom, October 2018. *Emerg. Infect. Dis*. **26**, https://doi.org/10.3201/eid2604.191164 (2020).
45. Senghore, M. *et al*. Evolution of *Mycobacterium tuberculosis* complex lineages and their role in an emerging threat of multidrug resistant tuberculosis in Bamako, Mali. *Sci. Rep*. **10**, 327 doi: 10.1038/s41598-019-56001-0 (2020).
46. US Environmental Protection Agency. Guidance to Registrants: Process for Making Claims against Emerging Viral Pathogens not on EPA-Registered Disinfectant Labels.

(2016) https://www.epa.gov/sites/production/files/2016-09/documents/emerging_viral_pathogen_program_guidance_final_8_19_16_001_0.pdf
47. European Centre for Disease Prevention and Control. Interim guidance for environmental cleaning in non-healthcare facilities exposed to SARS-CoV-2. (2020) https://www.ecdc.europa.eu/en/publications-data/interim-guidance-environmental-cleaning-non-healthcare-facilities-exposed-2019
48. Cutts, T. A., Ijaz, M. K., Nims, R. W., Rubino, J. R. & Theriault, S. S. Efficacy of Dettol Antiseptic Liquid for inactivation of Ebola-Makona virus suspended in an organic load – a targeted hygiene intervention for reducing virus spread. International Conference on Emerging Infectious Diseases (ICEID 2018) Atlanta Georgia, USA; 2018; Board LB-78. https://www.cdc.gov/iceid/docs/ICEID-2018-program-book-P.pdf
49. Zonta, W., Mauroy, A., Farnir, F. & Thiry, E. Comparative virucidal efficacy of seven disinfectants against murine norovirus and feline calicivirus, surrogates of human norovirus. *Food Environ. Virol*. **8**, 1-12 (2016).
50. Scott, E., Bruning, E. & Ijaz. M. K. Decontamination of environmental surfaces in everyday settings. In: McDonnell G, Hansen J, editors. Block's disinfection, sterilization, and preservation, 6th edition: Philadelphia: Wolters Kluwer; 2020. p. _-_.
51. Whitehead, K. & McCue, K. A. Virucidal efficacy of disinfectant actives against feline calicivirus, a surrogate for norovirus, in a short contact time. *Am. J. Infect. Control* **38**, 26-30 (2010).
52. US Environmental Protection Agency. Coronavirus Cases Trigger EPA Rapid Response. 2020. https://www.epa.gov/pesticides/coronavirus-cases-trigger-epa-rapid-response
53. Bonny, T. S., Yezli, S. & Lednicky, J. A. Isolation and identification of human coronavirus 229E from frequently touched environmental surfaces of a university classroom that is cleaned daily. *Am. J. Infect. Control* **46**, 105-107 (2018).
54. Lytle, C. D. & Sagripanti, J.-L. Predicted inactivation of viruses of relevance to biodefense by solar radiation. *J. Virol.* **79**, 14244-14252 (2005).
55. Nims, R. & Plavsic, M. Identification of worst-case model viruses for selected viral clearance steps. *Bioprocess. J.* **13**, 6-13 (2014).
56. Booth, T. F. *et al*. Detection of airborne severe acute respiratory syndrome (SARS) coronavirus and environmental contamination in SARS outbreak units. *J. Infect. Dis.* **191**, 1472-1477 (2005).
57. World Health Organization. Coronavirus disease (COVID-19) advice for the public. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public
58. Fauci, A. S. Emerging and reemerging infectious diseases: The perpetual challenge. *Acad. Med.* **80**, 1079-1085 (2005).
59. Jaijyan, D. K., Liu, J., Hai, R. & Zhu, H. Emerging and reemerging human viral diseases. *Ann. Microbiol. Res*. **2**, 31-44 (2018).
60. Morens, D. M. & Fauci, A. S. Emerging infectious diseases: threats to human health and global stability. *PLoS Pathog*. **9,** e1003467. https://doi.org/10.1371/journal.ppat.1003467 (2013).
61. St. Georgiev, V. Chapter 23. Defense against biological weapons (biodefense). (2009). Frontiers in Research. Springer
62. Jiang, H., Du, H., Wang, L. M., Wang, P. Z. & Bai, X. F. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. *Front. Cell. Inf. Microbiol*. **6**, doi: 10.3389/fcimb.2016.00001 (2016).

63. Middle East Respiratory Syndrome Coronavirus. (2013) https://www.aabb.org/tm/eid/Documents/middle-east-respiratory-syndrome-coronavirus.pdf
64. Zhou, P. *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* https://doi.org/10.1038/s41586-020-2012-7 (2020).
65. Wood, J. P., Choi, Y. W., Chappie, D. J., Rogers, J. V. & Kaye, J. Z. Environmental persistence of a highly pathogenic avian influenza (H5N1) virus. *Environ. Sci. Technol*. **44**, 7515-7520 (2010).
66. Cassidy, H., Poelman, R., Knoester, M., Van Leer-Buter, C. & Niesters, H. G. M. Enterovirus D68 – the new polio? *Front. Microbiol.* **9**, doi:10.3389/fmicb.2018.02677 (2018).
67. Xing, X. *et al.* Natural transmission model for severe fever with thrombocytopenia syndrome bunyavirus in villages in Hubei Province, China. *Medicine* **95**, doi:10.1097/MD.0000000000002533 (2016).
68. Nolte, K. B. *et al*. Hantavirus pulmonary syndrome in the United States: a pathological description of a disease caused by a new agent. *Hum. Pathol*. **26**, 110-120 (1995).
69. Krüger, D. H., Schönrich, G. & Klempa, B. Human pathogenic hantaviruses and prevention of infection. *Hum. Vaccines* **7**, 685-693 (2011).
70. Paules, C. I., Marston, H. D. & Fauci, A. S. Coronavirus infections - more than just the common cold. *J. Am. Med. Assoc*. **323**, 707-708 (2020).
71. van Doremalen, N., Bushmaker, T. & Munster, V. J. Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. *Euro. Surveill.* **18**, doi.org/10.2807/1560-7917.ES2013.18.38.20590 (2013).
72. Chan, K. H., Peiris, J. S. M., Lam, S. Y., Poon, L. L. M., Yuen, K. Y. & Seto, W. H. The effects of temperature and relative humidity on the viability of the SARS coronavirus. *Adv. Virol*. doi:10.1155/2011/734690 (2011).
73. Fischer, R., Judson, S., Miazgowicz, K., Bushmaker, T., Prescott, J. & Munster, V. J. Ebola virus stability on surfaces and in fluids in simulated outbreak environments. *Emerg Inf. Dis.* **21**, 1243-1246 (2015).
74. Centers for Disease Control and Prevention. Highly pathogenic Asian avian influenza A (H5N1) in people. https://www.cdc.gov/flu/avianflu/h5n1-people.htm (2015).
75. Oermann, C. M., Schuster, J. E., Conners, G. P., Newland, J. G., Selvarangan, R. & Jackson, M. A. Enterovirus D68: A focused review and clinical highlights from the 2014 U.S. outbreak. *Ann. Am. Thorac. Soc*. **12**, 775-781 (2015).
76. Sagripanti, J.-L., Rom, A. M. & Holland, L. E. Persistence in darkness of virulent alphaviruses, Ebola virus, and Lassa virus deposited on solid surfaces. *Arch. Virol*. **155**, 2035-2039 (2010).
77. Stephenson, E. H., Larson, E. W. & Dominik, J. W. Effect of environmental factors on aerosol-induced lassa virus infection. *J. Med. Virol*. **14**, 295-303 (1984).
78. Hardestam, J., Simon, M., Hedlund, K. O., Vaheri, A., Klingström, J. & Lundkvist, Å. Ex vivo stability of the rodent-borne Hantaan virus in comparison to that of arthropod-borne members of the Bunyaviridae family. *Appl. Environ. Microbiol*. **73**, 2547-2551 (2007).
79. United States Environmental Protection Agency. Persistence of categories A and B select agents in environmental matrices. EPA/600/R-14/074 2014

80. Piercy, T. J., Smither, S. J., Steward, J. A., Eastaugh, L. & Lever, M. S. The survival of filoviruses in liquids, on solid substrates and in a dynamic aerosol. *J. Appl. Microbiol.* **109**, 1531-1539 (2010).
81. Sattar, S. A., Karim, Y. G., Springthorpe, V. S. & Johnson-Lussenburg, C. M. Survival of human rhinovirus type 14 dried onto nonporous inanimate surfaces: effect of relative humidity and suspending medium. *Can. J. Microbiol.* **33**, 802-806 (1987).

Declarations

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