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The viability of SARS-CoV-2 on solid surfaces

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Abstract

The COVID-19 pandemic had a major impact on life in 2020 and 2021. One method of transmission occurs when the causative virus, SARS-CoV-2, contaminates solids. Understanding and controlling the interaction with solids is thus potentially important for limiting the spread of the disease. We review work that describes the prevalence of the virus on common objects, the longevity of the virus on solids, and surface coatings that are designed to inactivate the virus. Engineered coatings have already succeeded in producing a large reduction in viral infectivity from surfaces. We also review work describing inactivation on facemasks and clothing and discuss probable mechanisms of inactivation of the virus at surfaces.

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COVID-19, SARS-CoV-2, Surface, Coating, Solid, Coronavirus.

Introduction

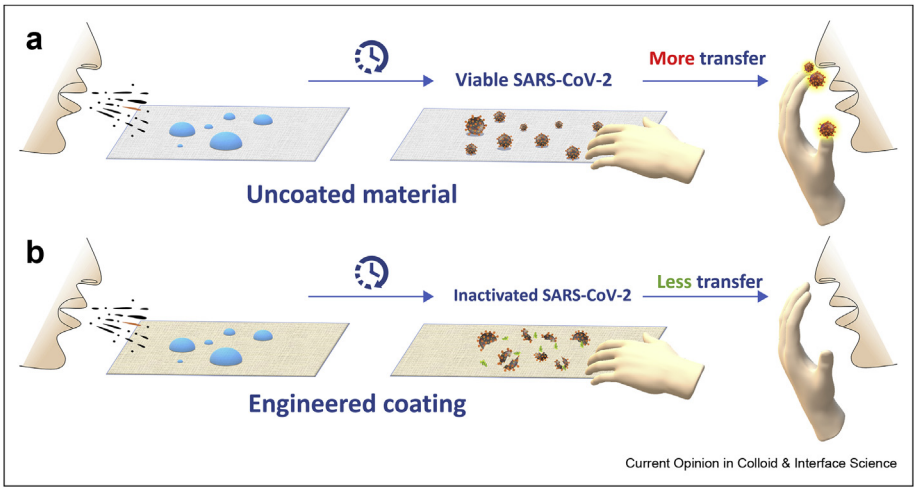
Severe acute respiratory coronavirus-2 (SARS-CoV-2) is the virus that causes COVID-19 and has been responsible for more than 100 million cases and 2 million deaths as of February 2021 (COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University, https://coronavirus.jhu.edu/map.html). SARS-CoV-2 is transmitted through infected respiratory droplets and aerosols generated by a diseased person [1,2]. Respiratory droplets and aerosols can be generated when a person sneezes, coughs, speaks, or breathes [3]. An individual is infected by the virus through nasal or oral inhalation of the infected droplets or aerosols and then attachment of the virus to the epithelial membrane [2]. The pathway to infection is not fully understood but is thought to be via inhalation of either respiratory droplets or aerosolized virus (WHO Transmission of SARS-CoV-2: implications for infection prevention precautions, https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions). For this reason, health officials have advised that individuals should avoid poorly ventilated public places [4], wear a mask in public places, and increase distance between other individuals [3,5].

The possibility of infection via solid surfaces has also been considered. In this scenario, a droplet that contains virus lands on and contaminates an inanimate object. The contaminated object is called a fomite. The next user touches the fomite, and the virus is transferred from the fomite to the user's hand. Infection can occur if the person then touches their nose, mouth, eyes, or ears (Figure 1). A preprint (Behzadinasab et al., medRxiv doi: 10.1101/2021.04.24.21256044) confirmed that SARS-CoV-2 can be transferred from fomites to artificial skin.

A study on Golden Hamsters showed that the virus can be indirectly transmitted through fomites [6], but we are unaware of a study directly showing fomite transmission in humans. The WHO not only states that "fomite transmission is considered a likely mode of transmission for SARS-CoV-2" (WHO Transmission of SARS-CoV-2: implications for infection prevention precautions. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions), but also notes that "People who come into contact with potentially infectious surfaces often also have close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern" (WHO Transmission of SARS-CoV-2: implications for infection prevention precautions. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions). Modeling of outbreaks suggests that transmission via fomites may contribute up to 25% of deaths during periods of lockdown [7].

Infection via fomites depends on the longevity of SARS-CoV-2 on a solid because an infectious dose clearly must survive until following users contact the solid. The longevity of SARS-CoV-2 depends on the solid material,

Figure 1



Infection via a fomite. (a) Uncoated material. **(b)** Engineered coating to reduce infection.

but the virus can remain viable on some solids for up to seven days [8,9]. According to the US Center for Disease Control (CDC), one method of reducing fomite transmission is washing of hands (CDC Cleaning and Disinfection for Household, https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cleaning-disinfection.html). Another method is the disinfection of common-touch objects such as door handles, railings, restaurant tables, and keypads, using disinfectants such as 70% ethanol, bleach, or peroxide (CDC Cleaning and Disinfection for Household, https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cleaning-disinfection.html). However, these disinfectants do not provide ongoing protection from SARS-CoV-2. A thin film of ethanol evaporates rapidly at room temperature therefore, the solid can be contaminated again within minutes of disinfection. Thus, conventional disinfection does not provide much protection on objects such as a subway handhold where cleaning may only be once per day whereas passengers may touch the handhold within minutes of each other. The labor cost of conventional disinfection is also high. Other methods can also be used to inactivate viable viruses on surfaces, including UV [10], sunlight [11] irradiation, cold plasma [12], and heat [13].

An alternative approach to disinfecting common-touch surfaces, and the main subject of this review, is surfaces that provide a continuous inactivation of the virus. By continuous, we mean that after application, the surface remains capable of inactivating the virus for at least a few weeks. There are two timescales for such an approach: (1) the time to inactivate the virus, which should be as short as possible, preferably minutes, and (2) the longevity of the coating, which should be as long as possible, preferably months or even years. Such a surface can provide protection to users in heavily trafficked areas and preferably at a lower cost because of the lower labor cost.

An important distinction between viruses and bacteria is that viruses do not have a metabolism and cannot reproduce on their own. For this reason, many do not consider viruses to be alive. This is why one does not refer to killing viruses, but rather to inactivating them. An important consequence is that, even when there is no disinfection procedure, the virus loses activity over time; therefore, any effort to inactivate the virus must be viewed against the natural decay of the viral population on the same surface. In this review, we compare the decay of the virus in some control situation without a deliberate disinfection of the surface to the decay on an engineered surface using the following metric:

$$\log \text{reduction} = \text{mean}\left[\log_{10}\left(\frac{\text{Control titer}}{\text{units}}\right)\right] - \text{mean}\left[\log_{10}\left(\frac{\text{Sample titer}}{\text{units}}\right)\right] \quad (1)$$

$$\% \text{ Reduction} = \left(1 - 10^{-\log \text{ reduction}}\right) \times 100\% \qquad (2)$$

where the same units are used for the control and sample titers. For example, the control could be an uncoated solid, and the sample would be a coated solid. The ability of the virus to infect is most commonly quantified by $TCID_{50}$, which is a measure of the dilution required before a sample no longer infects cells. The most commonly used cell is a Vero cell [14,15]. A greater value of $TCID_{50}$ (larger dilution) means that the sample of virus is more potent at infecting the cells.

A logical metric would be the ability to decrease the time required for the virus to reach some threshold level where it cannot infect mammalian cells or has some low probability of infecting cells. To date, however, the infective dose is not known, but less virus is obviously better. In the absence of a known infective dose, scientists either use their limit of detection of the virus, or a metric such as a 99.9% reduction in ability to infect. Because the range of concentrations of virus is so large, biologists usually consider the log reduction (Eqn. (1)) where a 3-log reduction is the same as a 99.9% reduction.

The selection of active ingredient is an important step in preparation of surfaces that provide ongoing inactivation of SARS-CoV-2 [16]. Research to date has been guided by the reservoir of research on antiviral and other antimicrobial materials. In this connection, although the quaternary ammonium polymeric compounds [17,18] and polyamine polymers [19] have previously shown antimicrobial activity, published work does not demonstrate a reduction in infection of SARS-CoV-2 [16,20]. To date, copper, its compounds, and silver have shown promising antiviral activity against SARS-CoV-2 [16,21–23] and were identified as potentially active elements.

The morphology of the surface can potentially play a role in inactivation of SARS-CoV-2 [24]. Surface roughness or porosity can provide a greater surfaces area and affect wettability.

In this review article, we describe the effect of different surfaces and conditions in lowering the infectivity of SARS-CoV-2. First, we review the viability of the virus on common material surfaces, and then the effect of environment conditions on the virus is assessed. A major section is devoted to the introduction of current anti–SARS-CoV-2 surfaces and coatings. Next, the current knowledge in antiviral face masks is reviewed. Finally, other methods of inactivating SARS-CoV-2 on surfaces are discussed. There are two prior reviews of the surface stability of SARS-CoV-2 by Bueckert et al. [25] and Hasan et al. [26].

SARS-CoV-2 RNA on public surfaces

RNA from SARS-CoV-2 has been found on surfaces in hospitals [27–32], laboratories [33], and public places [32,34]. Here we summarize some of the results of sampling for viral RNA by the polymerase chain reaction (PCR) technique. The result of this test does not discriminate virus that is able to infect cells from virus that has been inactivated, but simply gives the total RNA that is present. This compares to $TCID_{50}$ measurements (described above), which assay the ability of a sample to infect primate cells. Thus, the results of this section indicate that a viral component was present, not that it was able to infect humans.

Chia et al. [27] detected the SARS-CoV-2 RNA in hospital rooms where COVID-19 patients were kept (average temperature = 23 °C, relative humidity = 53–59%). Hospital surfaces were tested for SARS-CoV-2 RNA using PCR techniques. The researchers tested 245 surfaces in 30 rooms. The most likely places to be contaminated were the floor (65%), followed by the air exhaust vent (60%), bed rail (59%), bedside locker (47%), cardiac table (~40%), electrical switch (~34%), chair (~34%), and toilet seat and flush (~28%). Chia et al. found higher rates of contamination in the first week of illness compared to subsequent weeks [27].

Ong et al. [31] tested high-touch surfaces in the hospital rooms of three COVID-19 patients. The researchers tested 28 surfaces (from 26 solid types) for the SARS-CoV-2 RNA using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Prior to cleaning, RNA was detected on 61% of the surfaces. Subsequent to cleaning with sodium dichloroisocyanurate, RNA was not detected on any surface. This showed the effectiveness of common disinfection methods. However, it is costly and time-consuming to routinely clean numerous objects. As explained in detail below, an alternative or supplemental process is to use surface coatings that can be applied to continuously inactivate SARS-CoV-2 without expensive and time-consuming cleaning routines.

Harvey et al. [34] explored the presence of virus in public places over 2 months (from April to June 2020). They checked door handles, gas pump handles, ATM keypads, garbage cans, crosswalk buttons in essential businesses (i.e. grocery stores, banks, gas stations, restaurants, laundromats, and a few more). Surfaces were sampled using flocked polypropylene swabs to detect SARS-CoV-2 RNA with quantitative RT-PCR (RT-qPCR). They found that 8.3% of 348 tested objects had positive results, which is a large percentage for objects accessible to the public. The most contaminated surfaces were a trash can handle and a liquor store door handle. The percent of contaminated surfaces

decreased when temperature increased (it has been shown that SARS-CoV-2 virus half-life shortens with increasing temperature [35,36]).

Fernández-de-Mera et al. [32] also reported the detection of viral RNA on high-touch items in public spaces. They investigated 14 surfaces in public sites, including pharmacies, post offices, supermarkets, a police station, a city hall, and a few more. The researchers [32] used Dry-Sponges (pre-hydrated with an isotonic surfactant and a virus-inactivating liquid) and RT-PCR to detect SARS-CoV-2 virus RNA. They reported that 21.4% (3 out of 14) of the tested surfaces had positive results.

In summary, the studies showed that there is evidence of widespread distribution of SARS-CoV-2 (where active or not) on public surfaces during the pandemic.

Pioneering studies of the longevity of SARS-CoV-2 on solids

Two early and seminal papers by van Doremalen et al. [8] and by Chin et al. [9] started our understanding of the stability on solids. Each of these papers showed that the infective titer depended on the material type and that the titer decayed approximately exponentially with time. Van Doremalen et al. [8] examined the stability on copper, cardboard, stainless steel, and plastic. From our perspective, the most important findings were that (a) the half-life of SARS-CoV-2 was strongly dependent on the material, 1 h for copper and 7 h on plastic, which was our basis for thinking that a material or coating could be developed to minimize the longevity of the virus and (b) that the half-life was shortest on copper, which provided a starting point for choosing an active material. From the public perspective, the idea that the virus could last for days on surfaces led to increased fear of contracting COVID-19 from surfaces and led to widespread decontamination of surfaces.

At about the same time Chin et al. [9], examined the stability of SARS-CoV-2 on paper, tissue paper, wood, cloth, glass, a Hong Kong banknote, stainless steel, plastic, and the inner and outer layer of a facemask (as well as several disinfectants). They also found a strong dependence of the viral titer on the material type. In particular, they found that the titer was low on fibrous materials, which we shall discuss later. One particularly interesting result, which has not been widely discussed, is that the stability in suspension at 60 min was independent of the suspension pH in the range 3−10, a range which spans the protonation of isolated carboxylates and the deprotonation of amines. The infectivity of the virus is not sensitive to temporary changes in the charged state of the proteins on the exterior, showing a strong resilience to denaturation.

Chin et al. [9] also showed that the virus was less stable at greater temperature, with the viral titer barely decaying over 14 days at 4 °C and yet becoming undetectable within 5 min at 70 °C. Clearly temperature has a much stronger influence than pH. The dependence on temperature not only points to a means of disinfection, but also signals the need to consider environmental conditions when comparing results on different solids.

The early studies focused on viral stability on everyday objects, presumably with a view to providing immediate public health information, and not on well-characterized surfaces. Subsequently, there has been a move to study well-characterized solids to elucidate chemistry relationships between activity and chemistry or structure.

Effect of environmental conditions

Later work by Biryukov et al. [35], Matson et al. [37], and Riddell et al. [36] confirmed Chin et al.'s result showing the loss of stability at high temperature. Biryukov et al. and Matson et al. demonstrated that the virus was less stable on solids that were kept at higher humidity. The effect of humidity is a curious result. Higher humidity should hasten evaporation of the droplet and therefore hasten the large change in viral environment that occurs when the virus is dehydrated. We would have expected a higher humidity to preserve the virus; however, this is clearly not observed.

Matson et al. [37] showed that other chemical components in the droplet affected the longevity. The virus was more stable in nasal mucous than in sputum at 21 °C and 27 °C. Pastorino et al. [38] evaluated the stability of the virus on addition of 10 g/L bovine serum albumin (BSA). They added BSA to change the culture medium in order to mimic the protein present in the human mucus and other respiratory fluids. Although the virus was inactivated on glass and aluminum after 44 h and 4 h, respectively, its stability was prolonged when moderate BSA concentration was added to the medium, to the point that the virus remained viable on all the surfaces even after 100 h [38]. The medium was not found to be important [37] in an unpublished study by Szpiro et al. (Szpiro et al., medRxiv doi: 10.1101/2020.08.22.20180042).

Stability on common solids

In this section, we focus on the stability of SARS-CoV-2 on common solids. Riddell et al. [36] investigated brushed stainless steel, an Australian polymer banknote, paper banknotes, glass, vinyl, and cotton cloth in the dark to eliminate the potential effect of UV inactivation. Their experiments showed that although infectivity from cotton was poor, the virus remained detectable for 28 days on other surfaces at 20 °C. Conversely, this duration declined to 1 day at 40 °C. Another study [39]

also verified the effect of temperature by evaluating the stability of SARS-CoV-2 on swine skin, cloth (35% cotton and 65% polyester), and 1 USD and 20 USD bank notes at 4 °C, 22 °C, and 37 °C. Harbourt et al. [39] illustrated that at 4 °C, the virus remain viable on swine skin and bank notes more than 336 h and 96 h, respectively, while this duration is reduced to 72 h for cloth. Moreover, the virus was detected on swine skin, bank notes, and clothing after 24 h, 8 h, and 4 h respectively at 22 C. In contrast, the stability of SARS-CoV-2 was reduced when the samples were incubated at 37 °C, reducing the stability to 4 h for skin and bank notes and less than 4 h for clothing. Pastorino et al. [38] evaluated the stability of the virus on poly styrene, glass, and aluminum with and without the addition of 10 g/L bovine serum albumin (BSA). Biryukov et al. [35] did not find a significant difference in the longevity of the virus on stainless steel, acrylonitrile butadiene styrene (ABS) plastic, or a nitrile glove (NG).

Kasloff et al. [40] examined the viability of SARS-CoV-2 on various porous and nonporous personal protective equipment (PPE) and found that the virus loses its infectivity (more than 3-log viral tier reduction) on stainless steel, PVC face shield, nitrile gloves, Tyvek, the N95 mask, and the N-100 mask after 4−7 days while cotton and reinforced nitrile gloves were able to rapidly inactivate the virus, where the infectivity on them diminished after 1 h and 4 h, respectively. However, the virus remained detectable on stainless steel, PVC face shield, N95 and N100 masks and Tyvek for 14−21 days, on nitrile gloves for 7−14 days, on reinforced nitrile gloves for 7 days and on cotton for only 24 h. Kasloff et al. [40] believed that the rapid loss of the virus viability on cotton is related to its porous nature, providing a large surface area to evaporate the infected droplet and causing a decrease in viable virus accordingly while maintaining the RNA level over the test period. This is in agreement with Kratzel et al. findings [41]. They observed that the infectivity of the virus is greatly reduced up to 100-fold upon drying. Riddell et al. [36] also demonstrated a rapid loss of viable virus on cotton.

Our overall summary of the work on common materials is that (1) the virus can last for a long time, as much as several weeks, (2) the recovery of virus depends on the type of material, (3) there is low recovery from porous materials, and (4) recovery from metallic copper is particularly poor, suggesting that it is an active material.

Stability on antimicrobial coatings

The long persistence of SARS-CoV-2 on surfaces and the need for frequent disinfection of common touch surfaces have given rise to the development and fabrication of anti-SARS-CoV-2 materials. The implementation of such surfaces could greatly reduce the risk of indirect transmission of the virus through surfaces. Given the recent discovery and impact of SARS-CoV-2, there are only a few studies showing the design and fabrication of coatings that are active against SARS-CoV-2 to date. All of the work on coatings are based on copper materials; however, we also describe work on the effect of other particles in suspension.

Behzadinasab et al. [16] evaluated the anti-SARS-CoV-2 properties of cuprous oxide coated glass and stainless steel. They applied a thin layer of polyurethane (PU) as the adhesive layer and then applied a 10 wt.% Cu_2O suspension in ethanol followed by a 2-h drying at 120 °C; then argon plasma treatment. The viral tests were done with 5 μL droplets of SARS-CoV-2 culture with a TCID of 7.8 log unit ($TCID_{50}$/mL). This coating inactivated more than 99.9% of the virus within 1 h. The half-life of the virus was 3−4min. The coating remained as potent after five cycles of exposure to the virus and the following disinfection with 70% ethanol. Additionally, the coating still showed identical ability to inactivate SARS-CoV-2 after being kept under water for 2 weeks, which showed that this coating can endure any level of humidity in all climates. The ASTM D3359B adhesion test showed a high degree of peel resistance. This was the first published coating to specifically target SARS-CoV-2. This group also assessed the anti−SARS-CoV-2 activity of polyallylamine and poly-diallyldimethylammonium chloride coated on glass [16]. Although these polymers have previously shown to have potential antimicrobial activity [19,42,43], they were unable [16] to inactivate the novel coronavirus.

Hutasoit et al. [22] assessed the activity of cold-sprayed copper coatings. They coated 5−60 μm copper particles on two stainless steel plates using a Lightspee3D spray system, where a stationary nozzle deposited particles on a moving substrate at 500 °C and air pressure of 3 MPa. A post-fabrication heat treatment annealing was applied to one of the plates, and then both plates were polished by a motor-driven steel brush to yield a uniform surface with 0.45 mm thickness. They applied 50 μL of SARS-CoV-2 in culture medium containing $10^{5.5}$ $TCID_{50}$/mL on each surface and studied the reduction of viral titer versus time and found that the annealed and as-deposited samples are able to reduce the infectivity by 96% and 92%, respectively. When the virus was left on the surface for 5 h, the reduction increased to 99.2% and 97.9%, respectively. Hutasoit et al. [22] hypothesized that the release of Cu(I) from the surface and contact killing caused inactivation through their coatings. Manto et al., in a preprint paper (Mantlo et al., medRxiv doi: 10.1101/2020.07.05.20146043), write that there is a plateau of 99% inactivation on a copper alloy between 2 and 8 h.

Hosseini et al. [44] fabricated a porous coating of CuO. The idea was to create a hydrophilic, porous surface so that suspensions of SARS-CoV-2 would be rapidly drawn

into the porous interior where diffusion distances are short, there is a large surface area of active material, and the active material can be protected from abrasion. The CuO coating was produced by heat treatment of cuprous oxide particles at 700 °C, which oxidized the particles to CuO and caused early-stage sintering to produce a robust coating without the use of a polymer. They examined this coating's potential against SARS-CoV-2 by incubating a 5 µL of viral culture containing 7.8 log unit $TCID_{50}$/mL. Their experiments showed that a 30 µm coating of cupric oxide is able to reduce the virus infectivity by 99.8% in 30 min and below the detection limit after 1 h. When a droplet was placed on a thicker layer (about 50 µm), the droplet was completely imbibed and infectivity was reduced by 99.7% in less than 1 min. At half an hour, the infectivity was below the detection limit (about 99.99%). The coating resisted peeling (ASTM D3359B test) and was unaffected by 70% ethanol or 3% bleach. Their experiments revealed that the infectivity of the virus is reduced by contact with this surface and that the leachate (ions) does not have any antiviral activity. This group also discussed that the drying time on this coating is reduced compared to a flat surface, which probably aids in the reduction of infection of SARS-CoV-2 on this CuO coating.

Hasan et al. [24] studied the anti—SARS-CoV-2 property of nanostructured aluminum (Al 6063) and found that the surface roughness is another factor in the viability of the virus on surfaces. The aluminum was etched by 2 M NaOH to produce ridges that were about 23 nm wide. The etching increased the root mean squared roughness from 0.6 nm to 995 nm, and the static contact angle from 96.3° to 17.7°. Although not a coating, we have included it here as a surface modification. Nanoscale surface texturing has previously shown to improve the antimicrobial activity of surfaces [45]. The longevity of SARS-CoV-2 in culture medium (10^5 $TCID_{50}$/mL) from a 10 µL droplet was compared on the roughened and the smooth surface. Their experiments demonstrated that the etched sample is able to produce a 5-log (99.999%) reduction in SARS-CoV-2 on the surface in 6 h and more than 2-log (99%) reduction in 3 h, while this duration on control flat aluminum took 48 h. This could be due to the adsorption or trapping the virions within the nanostructure texture [24]. They also reported that not only the roughness increased from 0.6 nm to 995 nm, but the wettability of aluminum changed when it was etched, reducing the static contact angle from 96.3° to 17.7°.

Mechanism of action against SARS-CoV-2

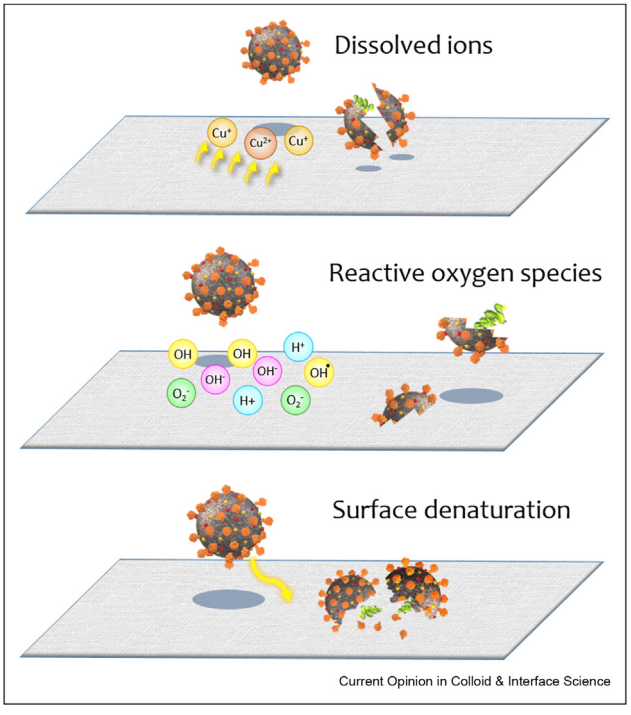
The literature currently lacks studies that explore mechanism of actions specifically against the SARS-CoV-2 virus. In this section, we summarize mechanisms of active ingredients against other viruses. Of course, the mechanism of action depends on both the specific microbe and the active ingredient; therefore, the results are only a guideline for the mechanism for SARS-CoV-2. Most of the surface coatings that inactivate the SARS-CoV-2 virus are made from copper or its oxide states; therefore, we focus on the mechanisms of copper species .

The antiviral mechanism of copper surfaces can have three potential routes: via ion release from copper solids, via generation of reactive oxygen species (ROS), and contact killing (See Figure 2).

Attack of the virus by dissolved Cu(I) or Cu(II) species

The speciation of copper in aqueous solutions that have salts and other chemicals is complex [46]. The dissolved species include the bare ions (Cu^+ and Cu^{2+}) and potentially oxides and/or hydroxides of the copper ions. These ions can affect the virus in two ways. First, the dissolved ions affect the range of electrostatic interactions through the Debye-length or bind to charged groups and by either action alter the self-assembly of viral structures. At present, it is unknown whether the copper species can permeate through SARS-CoV-2 viral envelope; however, if that is possible, binding to the (anionic) phosphate groups of the viral RNA is a possibility and would affect the availability of RNA. If not, the binding will only affect the viral envelope proteins. A second effect is that the ions can participate in redox reactions, which is particularly important for copper

Figure 2



Possible mechanisms of inactivation of SARS-CoV-2 on solids.

species. Cu^{2+} is somewhat unusual for a bare metal ion in that it has a positive standard electrode potential ($Cu^{2+}_{(aq)} + 2e^- \rightarrow Cu_s$, E = 0.34 V and $Cu^{2+}_{(aq)} + e^- \rightarrow Cu^{+}_{(aq)}$, E = 0.15 V) and therefore is a mild oxidizing agent. It may be able to reduce some components in a virus. The converse is that Cu and Cu^+ are mild reducing agents. Warnes et al. [47] explored the inactivation of murine norovirus on copper, and they found release of copper ions, particularly cuprous ion (Cu^+), is an important factor for the virus inactivation.

Generation of ROS at the solid–liquid interface or by dissolved species

ROS, which include the radicals, superoxide ($O_2^{-\bullet}$) and hydroxyl radicals ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2), are extremely active species. They can interact with and oxidize different biomolecules of a virus, such as different proteins of SARS-CoV-2, its envelope, or the RNA. Starting with reactions between copper ions and superoxide/hydrogen peroxide, the species undergo a series of redox reactions that lead to generation of hydroxyl radicals. Superoxide and hydrogen peroxide are produced by bacteria, but viruses do not have active metabolism to generate these. Thus, existing literature suggests that generation of ROS is not important for the inactivation of viruses. For example, Warnes et al. [47] found generation of ROS does not seem to play a role in the inactivation of norovirus by copper. Additionally, a study by Sunada et al. [48] concluded that ROS generation does not contribute to inactivation of bacteriophage viruses by Cu_2O particles.

Contact-killing

This mechanism is distinct from the other two in that it is dependent on the virus coming into direct contact with the solid. Here, we include interaction with the electrostatic double-layer as contact killing. When the virus engages with the surface potential and also with short-range intermolecular forces arising from the solid, the conditions for self-assembly change. It is well known that proteins can denature when they adsorb [49,50] and that lipid vesicles can deposit as bilayer or monolayer structures depending on the solid interface [51]; therefore, it is reasonable that the native self-assembly of the virus could be undone by surface contact. This interaction would also depend on the surface roughness. The electrostatic interaction depends on the charges on both the solid and SARS-CoV-2. The spike protein has 10 cationic amino acids, seven anionic amino acids, and one histidine [52], giving a net charge of about +3.5 at pH 7.4; the M protein has eight cationic and two anionic amino acids, giving a net charge of +6. The envelope (E) protein has three of each charge [53]. Because there is a variety of both charges, the proteins could be attracted to charges of either sign on the surface; however, the preponderance of cationic groups suggests that adsorption will best on anionic solids [44].

The virus may also be disrupted by hydrophobic surfaces. Hydrophobic domains of proteins and lipid tails may assemble on hydrophobic surfaces (as is observed for vesicles) leading to loss of viral integrity.

Sunada et al. [48] concluded that direct contact between the cuprous oxide particles and the virus was the primary method for viral inactivation. This was based on experiments where the activity of suspended Cu_2O particles against bacteriophage viruses was reduced by blocking the surface with a passivating agent. This experiment is difficult to interpret because surface passivation also reduces the dissolution of Cu species. Pezzotti et al. [54] have recently described work where suspensions of both silicon nitrite (Si_3N_4) and aluminum nitride (AlN) were shown to inactivate SARS-CoV-2. They hypothesize a similar method for inactivation via the reactive nitrogen species (RNS), ammonia, generated as the surface of the particles. The mechanism of contact killing is yet to be fully understood [55].

In addition to inactivation, there are other effects which may lead to reduced infectivity of a sample:

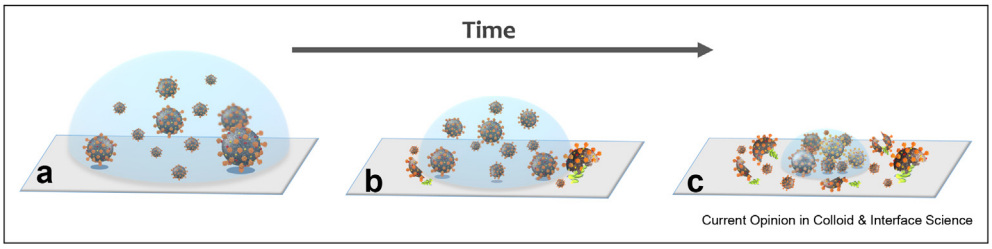
Adsorption

The assays that assess viral inactivation by solids have two stages: recovery of the virus from the solid and an assay of the activity of the virus on cells. If the virus is not recovered from the solid, whether or not it is active, then the assay will not register viral activity. Irreversible adsorption (trapping) will therefore reduce the infectivity of a viral suspension, whether or not the virion is still intact. Trapping of virus not only affects the assays, but also has an effect of the ability of a surface to infect individuals. In contrast to bacteria, which can live and reproduce on solids, viruses cannot reproduce on their own and undergo a natural decay of activity with time. It is enough to trap them, even if they are intact. This adsorption will be affected by intermolecular and surface forces that were described in Contact-killing.

Surface wettability

Serval studies have suggested that a hydrophilic surface facilitates the inactivation by providing a higher contact area between the infected droplet and the active surface and maximize the use of antiviral surface [16,24,44]. In this connection, porous hydrophilic surfaces can act as the extreme for maximizing the contact between the surface and the droplet. Several studies have shown the correlation between porosity and efficacy for inactivating SARS-CoV-2 inactivation time [36,40,41,44], which might be either through the contact killing or capturing the virus within the porosity. Hosseini et al. [44] recently developed and tested a porous CuO that may operate partially on the trapping mechanism.

Figure 3



The effect of droplet drying on the surface. The concentration of dissolved species increases, and diffusion times get shorter. Passage of the air–liquid interface subjects adsorbed virus to a tension that may damage the virus.

Drying of the respiratory droplet in contact with the solid

The inactivation of the virus increases with time and with the temperature of the contaminated droplet on an active surface [36] (Figure 3). All of the mechanisms discussed would be enhanced if the droplet size were reduced, thereby more quickly bringing the virus into contact with the active ingredient; therefore, the drying of the droplet is likely to be important and beneficial. An increase in wettability through roughening a surface may also help to spread the droplet on the surface to a higher extent. This will accelerate the evaporation and reduce transport distances and hasten virus inactivation accordingly.

An extreme version of roughening is to create a porous coating to accelerate the drying time by infiltrating the liquid and spreading it on the surface to have a more area for evaporation [44,56]. The phenomenon by which a droplet spreads into a porous medium through capillary forces is called imbibition [57]. This phenomenon depends on the size, contact angle, geometry, tortuosity, and thickness of the pores [58–60], and drying is faster when the porous media has a broad pore size distribution [61].

Therefore, porous surfaces have a number of advantages: more surface area for an active ingredient, shorter diffusion times, greater adsorption area, and faster drying time [44]. It may not even be necessary to have an active ingredient on a porous surface; if the virus is trapped in the pores, and preferably dried on to the interior space, it will become inactivated with time and is not in a position to infect another person.

An additional action of the drying action is that drying will lead to the air–water interface passing over adsorbed virions. At this time, the interfacial tension may damage adsorbed virus.

Inactivation of the SARS-CoV-2 virus in suspensions

In addition to the inactivation of SARS-CoV-2 on surface coatings, there has been interest in inactivation of virus in suspensions. Jeremiah et al. [23] examined the effect of silver nanoparticles (AgNPs) on inactivation of SARS-CoV-2. The authors noted that silver cytotoxicity (i.e. toxic effects on cells rather than virus) only occurred if the nanoparticle concentration was above a threshold of 20 ppm; thus, their experiments were conducted at 2 ppm. They performed three experiments: (a) mixing virus suspension with AgNPs (for 1 h at 37 °C), (b) infecting cells with the virus and later incubation with 10 nm polyvinylpyrrolidone (PVP)-coated AgNPs (48 h at 37 °C), or (c) incubation of 10 nm PVP-coated AgNPs in cells (3 h at 37 °C) and later infection with SARS-CoV-2. The first two experiments showed complete inhibition of virus while the third showed less inactivation of the virus. Thus, the researchers note that silver has very strong anti–SARS-CoV-2 properties.

In a preprint, Ornstein et al. (Ornstein et al., medRxiv doi: 10.1101/2020.10.01.20204214) provided a preliminary study of the anti–SARS-CoV-2 effect of metal organic frameworks (MOFs). They tested microporous crystalline titanium dicarboxylate MIL-125(Ti)–NH_2 MOF nanoparticles with 100 µL of 1×10^5 TCID50/mL SARS-CoV-2 culture. Based on the details of their method, we calculated the concentration of MOF nanoparticles to be ~50 w/w% in the viral culture. After mixing the nanoparticles with the virus liquid, the researchers exposed UV-C light on the liquid for 30 min. Additionally, they tested a MIL-127(Fe) MOF with the same method and found that both MOFs have anti–SARS-CoV-2 activities. The authors did not provide statistical evaluation and noted that the results cannot be separated from the effect of UV-C alone. UV-C can be harmful to humans; thus the researchers tested two MOFs (MIL-125(Ti)–NH_2 and MIL-177-HT) with the virus and exposed them to room light for 30 min. They reported MIL-177-HT inactivated 50% of the SARS-CoV-2, while MIL-125(Ti)–NH_2 did not show anti–SARS-CoV-2 effect.

Pezzotti et al. [54] measured the activity of silicon nitride (Si_3N_4), copper (Cu), and aluminum nitride

(AlN) microparticles (average size = ~0.5–2 μm) *in vivo*. They added 15 w/w% of each powder to PBS, in addition to adding SARS-CoV-2 suspension that contained 2×10^5 $TCID_{50}$. After slow rotation of the two suspensions for 1 or 10 min, the microparticles were separated by centrifugation and filtration with 0.2 μL filter. Subsequently, the supernatant was used to determine the inactivation of the virus by the $TCID_{50}$ method. The authors reported 100% viral reduction with only 1 min of virus exposure to either Si_3N_4, Cu, or AlN.

A related pre-print by Lehman et al. (Lehman et al., bioRxiv: 10.1101/2020.08.29.271015) also reported that in vivo Si_3N_4 can inactivate the virus. The researchers incubated similar-size particles of Si_3N_4 to Pezzotti et al.'s study [54] with a viral culture that contained 2×10^4 PFU/mL. They employed Si_3N_4 concentration from 5 up to 20 w/v%. To provide contact between the virus and active particles, the suspension was vortexed for 30 s, followed by slow rotation using a tube revolver from 1 to 10 min. The results depended on both concentration and incubation duration, as one might expect: with 1 min incubation, the virus was reduced 85% and 98% when using 5% Si_3N_4 and 20% Si_3N_4, respectively. Longer incubation periods led to increased inactivation of the virus. The authors showed that ~91% and 99.6% reduction of SARA-CoV-2 can be achieved when 5% Si_3N_4 and 20% Si_3N_4 are utilized, respectively.

Other methods for inactivating SARS-CoV-2 at surfaces

SARS-CoV-2 can be inactivated by other methods, such as light-activated coatings [62], ultraviolet (UV) light [63–65], atmospheric cold plasma [12], heat treatment [66], and ozone [67].

Micochova et al. [62] evaluated the efficacy of TiO_2 and TiO_2–Ag coatings on lowering the infectivity of SARS-CoV-2 while a surface is illuminated with light. They described that radicals are initiated by photons on the TiO_2 surface and that these radicals inactivate the virus. A spray gun was used to coat TiO_2 or TiO_2–Ag on ceramic tiles. Micochova et al. showed that the percentage of the infected SARS-CoV-2 after 1 h was only 15% on the illuminated coating compared to 80% on polystyrene. They also reported that the introduction of silver into their coatings did not improve the antiviral activity.

Inagaki et al. [64] reported a dramatic reduction in SARS-CoV-2 viability by utilizing a deep UV-emitting diode (DUV-LED) with a wavelength of 280 ± 5 nm. They placed 150 μL of 2×10^4 PFU/mL virus stock on a petri dish (the material was not described) and irradiated it for various times (intensity of 3.75 mW/cm^2 from a 2 cm height). This resulted in 87.4% (1s), 99.9% (10s), and >99.9% (20 s) reduction in infection titer of SARS-CoV-2 compared to control (i.e., no UV irradiation). These results are impressive; however, the UV wavelength that the researchers used is on the boundary of the UV-C region (UV–C wavelength = 100–280 nm), and UV-C light is known to be harmful to humans. This may limit application to situations where humans are not present or protected by shielding. Additionally, Inagaki et al. used a low concentration of virus (only 2×10^4 PFU/mL); however, in the publication by Heilingloh et al. [63] a 5×10^6 TCID50/mL viral stock was employed.

Heilingloh et al. [63] compared the ability of UV-A versus UV-C lights for the inactivation of SARS-CoV-2. UV-A has a wavelength of 320–400 nm while UV-C wavelength is between 100 and 280 nm. The researchers added 600 μL of 5×10^6 TCID50/mL virus stock (i.e. much more concentration than Inagaki et al.) in well plates and fixed the UV lamp at a distance of 3 cm (UV–C and UV-A intensities of 1940 and 540 mW/cm^2, respectively). UV-C irradiation resulted in complete inactivation of virus in 9 min, while UV-A light was much less impactful. The authors noted that the required UV dose for complete inactivation of virus is 1048 mJ/cm^2. Additionally, they investigated the effect of combined UV-A and UV-C light combined, and, as one might expect, by this method SARS-CoV-2 was inactivated the fastest. This resulted in 100% reduction in virus viability within 3 min.

Chen et al. [12] reported that cold atmospheric plasma can rapidly inactivate SARS-CoV-2 on solids. They used argon plasma (flow rate: 6.4 L/min, distance from surface: 15 mm, discharge voltage of 16.8–16.6 kV [peak–peak] at 12.9 kHz frequency) and achieved complete inactivation of virus in less than 180 s. The surfaces they tested were plastic, metal, cardboard, a football, a basketball, and a baseball. The researchers did not specify which type of plastic, metal, cardboard, and so on they used. Chen et al. also investigated similar goal using helium-fed argon with a flow rate of 16.5 L/min (distance from surface: 15 mm, discharge voltage of 16.8–16.6 kV [peak–peak] at 12.7 kHz frequency) and found that it is much less effective for inactivation of SARS-CoV-2. They were not able to reach complete inactivation of the virus in 5 min on plastic or metal. The researchers noted the surface that was Ar-plasma–treated reached a high of 32 °C, while that treated with He-plasma reached 29 °C. The results by Chen et al. [12] are significant.

Thermal treatment is also highly effective. For example, Daeschler et al. [66] used heat to disinfect personal protective equipment (PPE). They used high temperature to inactivate SARS-CoV-2 virus on four models of commercial N95 masks. The researchers incubated 5 μL of 7.8 log units $TCID_{50}$/mL virus stock on both unprocessed and 10 times heat processed N95 masks and

found that thermal treatment at 70C and 0% relative humidity for 60 min disinfects the masks from SARS-CoV-2. Daeschler et al. [66] also tested the properties of the mask after the disinfection treatments and reported no impact of the heat treatment on the mask. Thus, heat treatment is a low cost and simple method for disinfecting surfaces; however, compared to a coating, it requires active intervention and power.

Facemasks and clothing

Facemasks are another area where ingredients have been added to inactivate SARS-CoV-2. This research has much in common with antiviral surface coatings; however, in this case, the active ingredient is incorporated into a fabric. A normal facemask has two main tasks: to reduce the density of respiratory droplets transmitted from the person wearing the mask and to reduce the density of other people's respiratory droplets that are inhaled by the wearer. The former is the main goal of hand-made and basic surgical masks that are being worn during the COVID-19 pandemic. Masks worn to protect others should mainly contain microbes that already infect the user and can be handled by the user but not others. Masks that are worn to protect the user are more problematic because they may infect the user during handling. Particularly in this case, it would be useful to have mask materials with an active material that continuously inactivates SARS-CoV-2. An additional hazard for mask wearers is that bacteria, unlike viruses, can colonize and reproduce on masks, and therefore bacterial numbers from the environment and the user can increase with time.

There exist two broad methods of designing self-cleaning textiles. One is by hydrophobizing a surface so that droplets have weak adhesion and roll off at a low tilt angle. This is aided by the fact that many surfaces are worn in near vertical orientation. The other approach is to modify the fabric to incorporate biocidal properties. Both approaches will be discussed. A key element of textiles is that they usually consist of fibers, which are essentially porous materials. If hydrophilic, the textiles can imbibe droplets of viral suspension.

Examples of poorly wetting fabrics were in existence before the COVID-19 pandemic and include the work of Chauhan et al. [68] who designed a superhydrophobic cotton textile that displayed antibacterial properties. Galante et al. [69] designed a hydrophobic coating on nonwoven polypropylene textile that displayed reduced infection by two nonenveloped virions. This technology could be applied to the exterior of masks or other PPE to reduce the imbibition of droplets containing viral suspension.

Biocidal fabrics can be created by coating or impregnating fabric with a biocide such as copper, silver, or zinc particles. Again, these fabrics were studied before the COVID-19 pandemic. For example, in 2010, Borkow et al. [70] designed an antiviral face mask by impregnating N95 face masks with copper oxide particles. This mask was able to inactivate influenza A within 30 min and maintained its filtration properties even after impregnation. During 2020, researchers have specifically targeted SARS-CoV-2. Hewawaduge et al. [71] designed three-layer 70 Denier (D) nylon, 75 D polyester, and 20 D spandex facemasks impregnated with copper sulfide that inactivate SARS-CoV-2 within 30 min. Additionally, the masks were fabricated to maximize particle entrapment. Kumar et al. [72] designed a facemask that was spray-coated with copper nanoparticles and shellac — a hydrophobic biopolymer — that inactivated virus-like particles (VLPs) that were sprayed on the mask. Copper is a known biocide, but here the photocatalytic properties were examined as well, with the mask showing better antibacterial properties when exposed to sunlight. Marti et al. [73] designed coated face mask filters from nonwoven spunlace fabric filters that were dip coated with benzalkonium chloride that inactivated 99% of deposited SARS-CoV-2 particles within 1 min. As well as inactivating SARS-CoV-2, the coated masks also inactivated methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), both very contagious and hazardous. In a preprint, Zinn et al. (Zinn et al., bioRxiv doi: 10.1101/384040) designed cellulose/polyester fabrics coated with a copper-based metallic gel called "ActiveCopper" (aCu). They showed that aCu inactivated 99.9% of deposited SARS-CoV-2 virus within 30 s ActiveCopper also inactivated a wide range of microbes and was shown to be very robust, displaying no change in antimicrobial capability even after 14 days of repeated use. In a preprint, Tremiliosi et al. (Tremiliosi et al., bioRxiv doi: 10.1101/152520) designed polyester/cotton fabrics impregnated with silver nanoparticles using a pad-dry-cure method that inactivated 99.99% of deposited SARS-CoV-2 virus after 2 min. The treated fibers also showed no irritating, photoirritating, or photosensitizing responses when applied and can be considered hypoallergenic, which is very important for a textile. In another preprint, De Maio et al. (De Maio et al., medRxiv doi: 10.1101/2020.09.16.20194316) attached graphene (G) and graphene oxide (GO) into cotton and non-woven polyurethane, although the method of attachment was not described. The authors report that these functionalized materials were able to significantly increase the percentage of viable VERO cells within 2 h on incubation. They also showed that their materials cause a 0.5-log reduction in the number of *Escherichia coli* (*E. coli*) after 2 h and found that neither G nor GO demonstrate any cytotoxicity effect against A549 pulmonary tumor cells. In another preprint, Gopal et al. (Gopal et al., bioRxiv doi: 10.1101/365833) showed that polyamide 6.6 fibers embedded with zinc oxide during the polymerization process inactivated SARS-

CoV-2 within 30 min. Additionally, the biocidal ability of the fabrics remained after 50 washes using a standardized home laundry test protocol.

These modified textiles have been shown the ability to be very robust, long lasting, breathable, and capable of inactivating a wide array of microbes very quickly. Since users inhale though the mask, a key element of these active masks will be showing the lack of toxicity of the active material.

Future perspectives

Characterization of surfaces

A large fraction of stability studies of SARS-CoV-2 to date have been on common substances such as paper and steel. These previously conducted studies are undoubtedly valuable sources of information; however, we suggest that future studies should contain a thorough description and characterization of the test solids. The inclusion of such information would help to understand the mechanism. At minimum, the exact source of the test surface and the cleaning procedure should be specified.

The surface chemistry can be measured by surface-selective techniques such as X-ray photoelectron spectroscopy and energy-dispersive X-ray spectroscopy and Fourier-transform infrared spectroscopy, which are widely available in collaborative efforts or in service centers. Surface morphology studies can be carried out through scanning electron microscopy, optical microscopy, and atomic force microscope. The shape and size of particles and porous nature of the samples can be revealed by studying of surface topology. If the solid is porous, Brunauer—Emmett—Teller analysis can specify the surface area associated with the porosity.

The contact angle measurements also provide useful information on the wettability of the droplet on the surface. One complication here is that a natural viral suspension produced by an infected individual may contain many different ingredients depending on its source and that these ingredients may affect the wettability. Surface characterization in future studies will enable discovery of the correlation between surface properties and inactivation and help to determine the mechanism. It will lead the way to the design of optimal surfaces to reduce the half-life of the virus on the solid.

Porosity

In general, porosity is very important for future coatings because it (1) can trap the virus, (2) allows for a greater area of active ingredient, (3) the internal structure is protected by the overlying structure from damage by abrasion, and (4) diffusion distances between the active ingredient and the virus can be made very small with small pore sizes. Several papers have noted the correlation between effectiveness and porosity. At this point only one, by Hosseini et al. [44], has shown that an increased pore volume of CuO led to a decrease in the viral titer of SARS-CoV-2.

Active ingredients

To date, active ingredients have been based mainly on prior work on other viruses. There have been no specific active ingredients that have been targeting specifically at SARS-CoV-2. Given the efforts to find drugs that target specific portions of SARS-CoV-2, we may expect that some of these will be incorporated into future surface coatings.

Multiple organisms

The deployment of vaccines the COVID-19 pandemic will, hopefully, mean that SARS-CoV-2 will have less impact on life beyond 2021. But the lessons learned from coatings can still be applied to other organisms, such as bacteria, fungi, and other viruses. We expect that multimicrobe coatings will continue to be fruitful areas of research following public sensitivity to microbial diseases.

Transfer from surfaces to humans

To date, the focus has been on surfaces that inactivate SARS-CoV-2; however, to cause infection, the virus must be transferred to the respiratory tract. To reach the respiratory tract, there needs to be contact transfer from the solid to hands and from hands to the face. Transfer of virus through this chain of contacts is an interesting future area of research.

The mechanism of the inactivation of SARS-CoV-2

Studies of the mechanism of action of new antiviral materials should provide valuable insight into the selection of new antimicrobial agents and the design and fabrication of improved antimicrobial surfaces.

Summary

SARS-CoV-2 has been found on many public surfaces during the pandemic, and the lifetime of infective virus on solids is as long as a week under laboratory conditions. To diminish the window of opportunity for infection from surfaces, several researchers, including those from our group, have sought to prepare coatings that rapidly inactivate SARS-CoV-2. Such surfaces are already capable of causing a 99.9% reduction in 1 h [16] or cause almost immediate loss of infectivity through adsorption into porous coatings [44].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: William Ducker is a part owner of a company that plans to make surface coatings.

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