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Future antiviral surfaces: Lessons from COVID-19 pandemic

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ABSTRACT

It is an urgent priority for advanced materials researchers to help find solutions to eliminate the COVID-19 pandemic. The transmission of the SARS-CoV-2 coronavirus is majorly through touching the contaminated surfaces and then the vulnerable mouth and eyes besides the direct contact with the infected person. This lesson inspired us to propose a strategy from the view of materials scientists on designing effective antiviral surfaces to prevent the transmission of infectious coronaviruses by disrupting their survival on various surfaces. In this perspective, based on current progress in antiviral and antibacterial coatings, we put forward some general principles for designing effective antiviral surfaces by applying natural viral inhibitors, physical/chemical modifications, and bioinspired patterns, with the mechanisms of direct disinfection, indirect disinfection, and receptor inactivation. This work maps possible solutions to inactivate the receptors of the coronavirus spikes and resist the transmission of the COVID-19 and other infectious diseases, and contribute to the prevention of future outbreaks and control of epidemics.

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1. Introduction

The currently escalating COVID-19 respiratory pneumonia-like pandemic has originated a few months ago and has already severely affected all aspects of human life worldwide [1,2]. The pandemic is caused by a novel coronavirus SARS-CoV-2, which has naturally evolved compared to its earlier SARS-CoV-1 counterpart accounted for a smaller scale SARS epidemic in 2002–2003 [3]. The rapidly mounting amount of data suggest that the new coronavirus spreads from human to human a lot more effectively than SARS-CoV-1. The human nose and mouth, a common incubator for pneumonia causing viruses, is a very vulnerable

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environment for the SARS-CoV-2 entry, largely due to the relatively higher abundance of the virus binding receptor ACE2 expressed by the epithelial cells of the nose and throat cavity and mouth, compared to most other cell types [4]. Moreover, the latest analyses suggest that the binding of the new, evolved coronavirus SARS-CoV-2 to the ACE2 receptor, is substantially stronger than for his less evolutionary advanced counterpart SARS-CoV-1 [5,6]. Recently, two groups reported that human protein neuropilin-1 (NRP1) also aids viral invasion [7,8]. It is thus very clear that SARS-CoV-2 has evolutionary advantage over SARS-CoV in at least three aspects, namely in i) stronger binding to the host receptor; ii) longer lasting ability to retain activity on diverse surfaces; and iii) more active receptor sites on the virus to bind and entry human cells. Importantly, it took less than two decades for this particular viral evolution, which is notably faster than for other known viruses. In other words, the coronavirus has likely undergone an accelerated evolution. Our speculation – antiviral materials should also undergo similarly or even faster development. Specific and non-specific actions should be developed. Specific action is for specific virus. Non-specific is for a broader range of viruses. For example, rational antiviral surfaces can be designed through studying the common features or common mechanisms of viral infectivity and entry into cells [9]. This approach can be applied to the most common and recent viruses to decrease their ability for long-term survival upon surface attachment.

The ongoing pandemic has already taught us several crucial lessons, which we consider from the perspective of development of future antiviral materials. Perhaps the most relevant lesson is in the ever-increasing role of materials surfaces in virus transmission. Indeed, one of the most accepted mechanisms of the coronavirus transmission is through surfaces of various materials that humans are exposed in everyday life [10]. The viruses contained in droplets and aerosols released during coughing or sneezing of an infected person are deposited on the surfaces, where the coronavirus can survive for a substantially longer periods of time compared to other viruses [11]. It has been surprisingly discovered that the SARS-CoV-2 remains active on soft plastic materials up to 72 h [11]. Touching the virus contaminated surfaces by hands and then the vulnerable mouth or eyes has now been widely accepted as one of the most probable mechanisms of viral infection. Chin et al. have also reported that human corona viruses can survive on the surfaces of metals, plastics, cottons, or surgical masks for tens of hours to even 7 days [12].

Even though the human coronavirus attached on the surfaces can be efficiently inactivated through cleaning with solutions containing 62–71% ethanol, 0.5% hydrogen peroxide, or 0.1 sodium hypochlorite temporarily [10], the potential of long-term durability and the low toxicity of the antiviral coatings are also the key points which we should take into considerations. Nevertheless, direct physical or chemical sanitization by spraying or wiping with disinfectants is effective to terminate the fomite transmissions through surface touching, the sanitization is labour-intensive and materials-consuming, difficult to apply for all areas, and needs periodical repetition [13]. The aspects of both materials and mechanisms of actions are critical for the development of antiviral surfaces, which ideally should capture the viruses and retain them sufficiently long for the simultaneous inactivation through the custom-designed physico-chemical mechanisms to take effect. While diverse anti-viral surfaces exist both in nature and commercially [14], there are currently no commercially available materials customised to instantly kill SARS-CoV-2 or another deadly virus, before a still active virus can shed off the surface. SARS-CoV-2 maintains active to several hours even on copper, one of the most common toxic materials to pathogens. Surgical face masks have been demonstrated to be effectively block the spread of SARS-CoV-2 virus [15], while the virus may survive over a day on textile used to fabricate N95 or similar surgical masks, commonly used for anti-viral personal protection worldwide [12]. In terms of chemical composition and nanoscale morphology the novel SARS-CoV-2 coronavirus is quite similar to SARS-CoV-1, yet features a few important distinctive features, such as a binding

glucoprotein at the foot of the viral spike [16]. These facts cause us to use the lessons learned during the COVID-19 pandemic, briefly review the state-of-the-art, and foresee the needs for future research and technology development:

- 1) What are the examples and mechanisms of action of the existing anti-viral materials in natural and technological environments?
- 2) What are the most effective structural and morphological targets of the SARS-CoV-2 coronavirus that the available modes of action of antiviral materials could utilize?
- 3) What are the likely limitations in the ability of existing anti-viral materials to impact on the selected targets of SARS-CoV-2 coronavirus?
- 4) What specific features and mechanisms of action should be taken into account in the development of future anti-viral materials that could target even more sophisticated and dangerous viruses?

These questions define the structure of our discussion, as shown in Fig. 1. We first summarize the state-of-the-art in the types and mechanisms of action of the most common anti-viral materials, in both socio-technological and natural settings. Herein, we provide a perspective on developing long-term durable and low-toxic antiviral coatings for promising large-scale applications, in terms of the class of (i) natural antiviral coatings, (ii) physical/chemical modified antiviral coatings, and (iii) bioinspired antiviral surfaces. We then examine the possible effects of the existing mechanisms on the selected structural and morphological targets of the SARS-CoV-2 coronavirus, and discuss the current limitations. Finally, we envisage the possibility of evolutionary development of the next generation, even more infectious and deadly viruses in the future and discuss the research needs to develop highly effective, potentially universal anti-viral materials of the future.

2. Antiviral surfaces and coatings

Owing to much smaller size of viruses, whose diameters are usually between 20 and 300 nm except for few filoviruses with lengths up to 1400 nm, some design principles for antibacterial surfaces cannot be directly applied for antiviral surfaces and coatings [16]. In this perspective, we intend to propose the design principles of antiviral coatings or surfaces in terms of the materials types and surface nanostructures, particularly, the artificial surfaces will be further classified based on their antiviral action mechanisms. Fig. 2 presents the major antiviral coatings based on the classification of materials types and action mechanisms.

2.1. Natural antiviral coatings

Plenty of natural species, including herbs and honey, as shown in Fig. 2a, have been demonstrated to be capable of antiviral properties against some notable pathogens, including coronavirus, HIV virus,

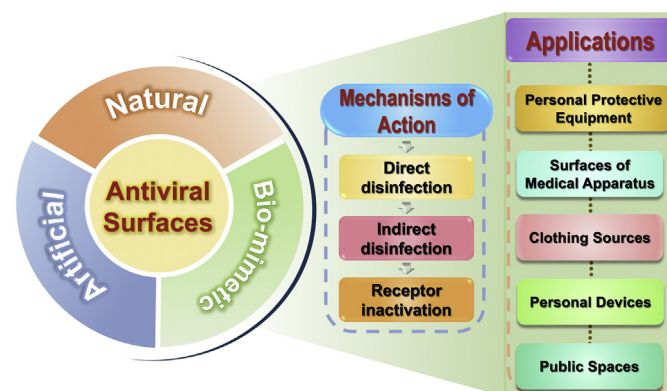


Fig. 1. Concept of antiviral surfaces, their action mechanisms, and the potential applications.

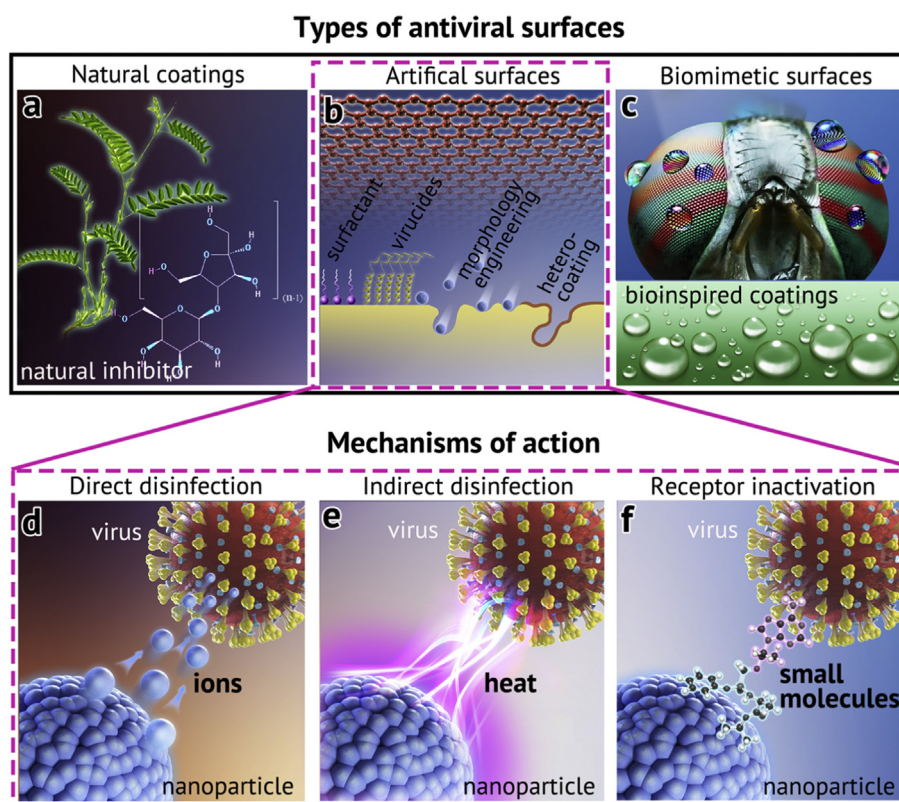


Fig. 2. Promising antiviral coatings based on selection of materials and engineering of surface nanostructures and the antiviral action mechanisms.

Hepatitis B Virus, measles virus, monkey pox virus, etc. [17,18]. Some of the natural herbs can work as immunity enhancer and some can improve the respiratory health by taking into the human digestive and circulatory systems, while some natural species contain active antiviral compounds which can directly destroy viruses upon contact. For example, natural inhibitors, including myricetin, scutellarein, flavonoids, and phenolic compounds, have been identified to be effectively against the SARS- and MERS-CoV enzymes, such as the nsP13 helicase and 3CL protease [17,18]. These efficient natural inhibitors can be extracted from natural herbs of *Isatis indigotica* and *Torreya nucifera* [18–20]. It is worth noting that the water extract from *Houttuynia cordata* is capable to against SARS- CoV-1 by inhibiting the 3CL protease and blocking the activity of the RNA-dependent RNA polymerase of the viruses [18,21]. These natural antiviral agents existing in traditional herbs are very promising virucide reagent for antiviral coatings.

Besides the promising potential of natural herbs, some natural extracts have also excellent antiviral properties. Pyankov et al. have demonstrated that biologically active tea tree oil and eucalyptus oils, two natural disinfectants from the most common plants of Australia, presented plausible antiviral performance [22]. The extracted essential oils presented antiviral activity against broad range of microbial, fungal, and viral species, and particularly were effective in inactivation of airborne influenza virus when applied onto the filter surfaces as the pre-coating of the filter fibers. Very recently, Jones et al. have successfully engineered novel broad-spectrum non-toxic antiviral materials by modified sugar molecules, cyclodextrins, which are naturally occurring glucose derivatives [23]. These molecules exhibited the capability to attract viruses before breaking them down on contact, and then destroy the viruses. The antiviral mechanism of the modified cyclodextrins is virucidal.

Apart from the above-mentioned natural active antiviral agents, some other extracts from natural resources are also promising to be applied as antiviral coating materials. The oleuropein containing in olive

leaves have been identified as powerful inhibitor to a wide range of viruses by blocking the production of enzymes for virus replication [24]. Pau d'arco (*Tabebuia impetiginosa*) is the common name for several species of trees grow in Central and South American and its inner bark has been marketed as a supplement to reduce inflammation and promote weight loss. It supposed that quinoids in Pau d'arco can be extracted to inhibit virus replications by damage the DNA and RNA inside the viral proteins [25]. These interesting natural extractions, however, have rarely been studied as direct on-contact antiviral reagents but should be very promising to be antiviral coating candidates.

There are some distinct advantages in utilizing natural antiviral reagents for coatings. First, most of natural extractions from herbs or plants are environmentally friendly through natural self-biodegradation and pose no significant risk for contamination of the environment. Second, most of the natural extractions are non-toxic or mild to human skin, which can be applied on the surfaces in public areas but avoid possible allergy or health risks aroused by the contact or evaporation of the reagent. Third, the resources of most natural viral inhibitors have been well documented with easy extraction processes. Moreover, the coating of natural antiviral extractions is easy for large-scale operation. The disadvantage is that some natural extracts have high price owing to the low content in the natural plants.

2.2. Artificial antiviral surface and coatings

In contrast to the surfaces modified with “natural” antiviral reagents, artificial surfaces or coatings made from “man-made” reagents or techniques, as shown in Fig. 2b, are another major type of surfaces to achieve antiviral performances. Based on the action mechanisms towards the attached virus, we further classify the artificial surfaces with direct (direct disinfection, Fig. 2d) or indirect mechanisms (indirect disinfection, Fig. 2e) of antiviral action, and chemically modified materials surfaces for a specific action (e.g., targeting binding with the specific receptor, Fig. 2f).

2.2.1. Nanomaterials with direct antiviral properties

There is a class of metal nanoparticles that have been found to possess direct antiviral properties, such as silver nanoparticles [26]. Silver and its nanoparticles have known for centuries as effective and wide spectrum antibacterial, antifungal, and antiviral agents in preventing infections and resisting putrefaction of food, owing to that the fact that Ag^+ ions strongly restrain the growth of bacterial and the proliferation of virus by inhibiting the activity of respiratory enzymes and interfering the functions of RNA/DNA in the virus [27,28]. Galdiero et al. summarized the application of silver nanoparticles against a wide range of viruses, including retroviridae viruses (i.e. HIV virus), herpesvirus, paramyxoviridae viruses (such as Respiratory Syncytial Virus), Hepatitis B virus, influenza virus, by interfering with cellular receptor binding or inhibiting viral replication [28].

The SARS-CoV-2 virus is a typical respiratory syncytial virus, which should be also inhabited by silver ions released from silver-containing nanoparticles (Fig. 2d). Moreover, silver-containing nanoparticles can provide continuous Ag^+ ions for a long-term duration. The silver ions have been demonstrated to be non-toxic to humans and the silver-ion containing nanoparticles can be easily dispersed or coated on a variety of surfaces, such as wound dressings, mask filtering layers, life keyboards, elevator handrail, chairs and cargos of trains, coaches, subways, etc. Therefore, the active metal-ion containing nanoparticles which have direct antiviral properties should be very promising to be applied at a large-scale as antiviral coating materials. Recent research reveals that surgical face masks is an effective way to avert the transmission of influenza viruses and SARS-CoV-2 coronaviruses from symptomatic individuals [15], while the viruses can survive for up to 7 days on the surfaces of the layers of face masks, which brings risks during use and disposal. The application of a silver-ion containing nanoparticle treatment on the surface of the filtering layer should be a good solution towards this challenge.

For the metal ions with direct viricidal properties, there are some clear advantages, such as matured preparation technologies, long-term stability, controllable coating/substrate interface, and usually low health risks. The cons of this type of coatings include limited resources or precursors, high cost of both the raw materials and the preparation procedures, etc.

2.2.2. Nanomaterials with indirect antiviral properties

Another typical class of metal or inorganic nanoparticles is those that can provide antiviral ability through an excitonic effect to generate localized heat, light, free radicals, and free charges and carriers to kill or interfere the adhesion and replication of the viruses and germs (Fig. 2e).

Some noble or heavy metal nanoparticles, including gold, copper, and silver nanoparticles exhibit an interesting localized surface plasmon resonance (LSPR) effect under visible light irradiation [29]. It was reported that the generated surface plasmons are effective to provide photodynamic killing of bacteria [30]. If taking the much smaller size and vulnerability of viruses into consideration, these metal nanoparticles with the surface plasmon effect would also be effective against viral infection under normal visible light irradiations. While some noble nanoparticles like Pt, Pd, and Ir intend to strongly absorb light and generate heat, owing to the produced hot electrons are not involved in charge transfer process [31]. It has been reported that coronavirus is very sensitive to temperature [32]. Based on this effect, a class of photothermal therapy nanomaterials has been developed, which can convert light especially infrared light into localized heat to kill cancer cells [33]. Inspired by this, the nanomaterials with a significant light-heat effect, including those with LSPR and those with significant light absorption ability, can be developed as antiviral coating materials, which have the capability to generate localized hot-spots under light stimulation and to kill the viruses or inactivation the proteins of the spikes.

Some inorganic nanoparticles can interact with moisture and/or light to generate free radicals such as hydroperoxyl groups. One typical

example is TiO_2 nanoparticles. TiO_2 can react with moisture and produce hydrogen peroxide under visible light, which are very efficient to kill germs attached on its surface [34]. We emphasize that a large number of semiconductor nanoparticles, e.g. ZnO , CuO , SnO , Fe_2O_3 , etc., can be categorized into this class of antiviral coating materials.

The third type of nanomaterials has also the potential as antiviral agents through active surface redox reactions between the materials and the virus [35]. The surface redox reactions can be driven by the chemical potential difference between the surface ions and the viruses. Some highly catalytic active materials would be potential candidates, such as cerium oxide, tungsten oxide, etc., can generate redox reactions with the contact viruses with the existence of electrolyte or localized potential differences. In general, the viruses are too small to bear large environmental fluctuations and very vulnerable to light, heat, and free radicals, which provide us a lot of opportunities to develop effective coating materials that can tune the local environment surrounding the virus.

2.2.3. Small molecules with receptor inactivation capability

Antiviral coatings can also be achieved by chemical modification through some small molecules, as shown in Fig. 2f, which have high affinity towards viruses and capture the viruses, and then passivate the receptors of the spikes and resist the entry of virus into human cells [36]. Smith et al. have screened that 77 small molecules that can stick to the spike protein (S-protein) of SARS-CoV-2 coronavirus [37]. If these small molecules are applied on the surface, e.g., of face masks or other personal protective equipment (PPE), they would effectively capture the viruses, inactivate the receptors, and thus resist the further transmission either into or outwards the filtering layers of the face masks.

2.3. Bioinspired antiviral surfaces

It was reported that the novel coronavirus SARS-CoV-2 is primarily transmitted from infected person through contact routes and droplets of coughs or sneezes with sizes in an order of few micrometers to few millimeters, together with the transmission through airborne [38,39]. When the droplets attach to smooth surfaces, the SARS-CoV-2 virus can survive up to 4 days on glass and banknotes and 7 days on stainless steel and plastics [12]. Hence, self-cleaning coatings can be applied on the surfaces which can easily be contaminated and touched to avoid the attachment of infectious microdroplets. Over the past decades, significant progress has been achieved on bioinspired superhydrophobic coatings by learning from nature. Both inorganic and polymer-based nanostructured coating materials have been developed to generate superhydrophobicity through mimicking the natural structures of lotus leaves, gecko setae, water striders, fly eyes, etc. [40–42] (Fig. 2c). We expect that the bioinspired nanocoatings possessing the features of robust stability and scalable production can be applied to repel the attachment of infective droplets.

It is interesting that a class of natural bactericidal surfaces have been reported for antibacterial applications. *Pseudomonas aeruginosa* cells have been killed within 3 min when contact with the surface of cicada wings, which have periodic nanopillars to form unique patterns on the wings [43]. In this report, the bactericidal property of the natural cicada wings was only related to the nanostructure but not affected by the surface chemistry. This research gives us inspirations that natural antiviral structures probably also exist, even though virus has a much smaller size than bacteria and will bring extra difficulties in find the optimum structure-property relationship in designing effective antiviral coatings.

3. Outlook: what to expect, how to prepare?

The latest results have now confirmed that the proteins in the spike of the SARS-CoV-2 are the “entry keys” used by the virus to enter the human cells and replicate, which should be targeted as the potential

Achilles's heels for this type of viruses [44]. More specifically, as the emergence of SARS-CoV-2 has occurred through recombination and strong purifying selection of the receptor binding motif (RBM) on the viral spike [45], the targeted destruction could be focused onto the RBM nanoscale areas. One could envisage that direct inactivation of spikes on the virus shells could be among the most effective and relevant applications of antiviral materials. As shown in Fig. 3, the antiviral coatings could operate by using the mechanisms summarized in Fig. 2 and discussed above. These mechanisms could be enhanced by synergistic application of surface plasmas, infrared or UV irradiation, and some other mechanisms. The combined action is expected to disable the binding domain proteins of the spike and hence to the loss of the ability of the virus to enter the cells. Moreover, the use of natural extracts which can directly inhibit the viral protease and block the contact of receptors of virus with human cells is a green approach and amendable for large-scale applications. Some active small molecules which can stick to and inactivate the spike proteins of coronavirus are also highly promising antiviral agents for the design of future antiviral coatings.

There are more open questions than answers, most obvious is what to expect from the next, even more evolved, and potentially a lot more deadly virus? The dream is to identify the likely next zoonotic virus to jump from animals to humans and predict the next step of the viral evolution that makes the expected jump possible, and then prepare the next-generation antiviral materials using some of the thoughts we have presented above. We do acknowledge that it is easier for us to speculate than achieve, but the latest breakthrough [45] gives us strong optimism that the target viruses and their evolution trajectories are now a lot more realistic to identify. On the other hand, search for more universal antiviral materials should be continued with even higher intensity, along with the efforts targeting to uncover the universality of the common viral receptors. We hope that this article can help find solutions to inactivate the receptors of the coronavirus spikes and resist the transmission of the COVID-19 and other infectious diseases, and contribute to the prevention of future outbreaks and control of epidemics and prevent the highly undesirable pandemic and ultimately endemic developments.

The current COVID-19 pandemic-caused “wake-up call” made us realize how little we know, and has already generated a huge amount of new knowledge and rapidly developing (e.g., antibodies, drugs, vaccines, etc.) technologies [46–49]. It is great time for antiviral materials technologies to do their part, and evolve by differentiating more from their parent anti-bacterial technologies by bringing the unique viral

features (e.g., shown in Fig. 3) into the design of next generation effective antiviral agents.

Declaration of Competing Interest

The authors declaim that no conflict of interest.

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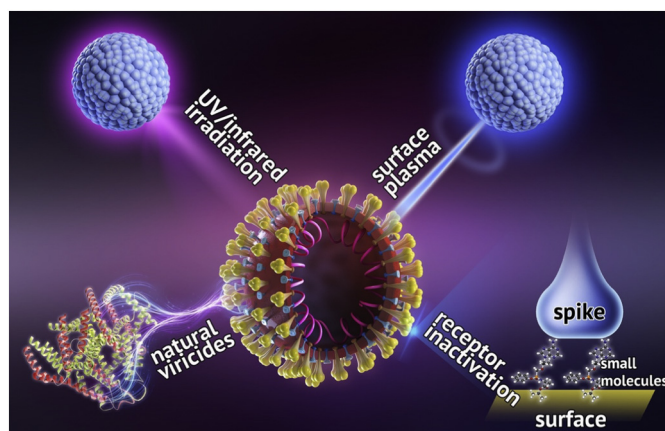


Fig. 3. Possible structural targets and effective reactive agents for coronavirus inactivation. Since the latest natural evolution leading to the novel coronavirus SARS-CoV-2 was in the specific binding domain to human cells located on its spikes, these receptor binding domains (RBDs) may be targeted as potential “Achilles's heels” of the next, more evolved and potentially even deadlier viruses to cause future outbreaks.

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