



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.intl.elsevierhealth.com/journals/dema](http://www.intl.elsevierhealth.com/journals/dema)

# Fighting viruses with materials science: Prospects for antivirus surfaces, drug delivery systems and artificial intelligence

Vinicius Rosa<sup>a,b,\*</sup>, Dean Ho<sup>c</sup>, Robinson Sabino-Silva<sup>d</sup>, Walter L. Siqueira<sup>e</sup>, Nikolaos Silikas<sup>f</sup>

<sup>a</sup> Faculty of Dentistry, National University of Singapore, Singapore

<sup>b</sup> Craniofacial Research and Innovation Center, National University of Singapore, Singapore

<sup>c</sup> The N.1 Institute for Health (N.1), Institute for Digital Medicine (WisDM), Department of Biomedical Engineering, and Department of Pharmacology, National University of Singapore, Singapore

<sup>d</sup> Department of Physiology, Institute of Biomedical Sciences, Federal University of Uberlandia, Brazil

<sup>e</sup> College of Dentistry, University of Saskatchewan, Canada

<sup>f</sup> Division of Dentistry, School of Medical Sciences, University of Manchester, United Kingdom

## ARTICLE INFO

### Article history:

Received 9 July 2020

Received in revised form

30 November 2020

Accepted 14 December 2020

### Keywords:

Saliva

Infection

Nanomaterial

Vaccine

Diagnostic

COVID-19

Coronavirus

Pandemic

Nanotechnology

Coating

## ABSTRACT

**Objective.** Viruses on environmental surfaces, in saliva and other body fluids represent risk of contamination for general population and healthcare professionals. The development of vaccines and medicines is costly and time consuming. Thus, the development of novel materials and technologies to decrease viral availability, viability, infectivity, and to improve therapeutic outcomes can positively impact the prevention and treatment of viral diseases. **Methods.** Herein, we discuss (a) interaction mechanisms between viruses and materials, (b) novel strategies to develop materials with antiviral properties and oral antiviral delivery systems, and (c) the potential of artificial intelligence to design and optimize preventive measures and therapeutic regimen.

**Results.** The mechanisms of viral adsorption on surfaces are well characterized but no major breakthrough has become clinically available. Materials with fine-tuned physical and chemical properties have the potential to compromise viral availability and stability. Emerging strategies using oral antiviral delivery systems and artificial intelligence can decrease infectivity and improve antiviral therapies.

**Significance.** Emerging viral infections are concerning due to risk of mortality, as well as psychological and economic impacts. Materials science emerges for the development of novel materials and technologies to diminish viral availability, infectivity, and to enable enhanced preventive and therapeutic strategies, for the safety and well-being of humankind.

© 2020 The Academy of Dental Materials. Published by Elsevier Inc. All rights reserved.

\* Corresponding author at: Faculty of Dentistry, National University of Singapore, 9 Lower Kent Ridge Road, 119085, Singapore.

E-mail addresses: [denvr@nus.sg](mailto:denvr@nus.sg), [denvr@nus.edu.sg](mailto:denvr@nus.edu.sg) (V. Rosa), [biehead@nus.edu.sg](mailto:biehead@nus.edu.sg) (D. Ho), [robinsonsabino@gmail.com](mailto:robinsonsabino@gmail.com) (R. Sabino-Silva), [walter.siqueira@usask.ca](mailto:walter.siqueira@usask.ca) (W.L. Siqueira), [nikolaos.silikas@manchester.ac.uk](mailto:nikolaos.silikas@manchester.ac.uk) (N. Silikas).  
<https://doi.org/10.1016/j.dental.2020.12.004>

0109-5641/© 2020 The Academy of Dental Materials. Published by Elsevier Inc. All rights reserved.

## Contents

1. Emerging viral infections .....	497
2. Properties affecting adhesion and survivability of viruses on materials .....	498
3. Materials science to reduce viability and infectivity of viruses common to clinical settings.....	500
4. New approaches to oral antiviral delivery materials .....	501
5. Optimizing antiviral delivery with artificial intelligence .....	502
6. Challenges and opportunities .....	502
Acknowledgments .....	503
References .....	504

### 1. Emerging viral infections

In the past few decades, viral infection outbreaks such as Middle East respiratory syndrome coronavirus (MERS-CoV), H1N1 influenza virus, Ebola virus disease, Zika virus infection and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have imposed substantial morbidity and mortality. The socioeconomic impact is worrisome as the infections could require hospitalization with high direct medical costs as well as absenteeism from work or school.

Healthcare professionals are at risk of infection as viral diseases are disseminated from person-to-person in hospital and family settings [1]. Dentists have been suggested to be within the class of workers with high risk of Coronavirus disease 2019 (COVID-19) contamination due to both high proximity to individuals and exposure to disease [2]. Several scenarios for transmission of COVID-19 and other viruses are predictable and include transmission by droplets from talking, coughing, sneezing, and potentially from aerosols produced during clinical procedures [3,4]. The droplets can spread viruses to nearby subjects but long-distance airborne spread is also predicted [4,5].

Several viruses can be isolated from saliva such as cytomegalovirus, Ebola virus, human herpesvirus, herpes simplex virus 2, Influenza virus A, rabies, and tobacco mosaic virus (more information in Ref. [6]). More recently, Zika peptides and SARS-CoV-2 have been identified in saliva [7,8]. The presence of viruses in saliva is especially concerning for dentists since treatments are performed from a short distance from the patient and often related to generation of aerosols and handling of oral fluids and blood [9].

The risk of acquiring infectious diseases in the dental office is yet to be fully determined but it cannot be neglected [10,11]. In addition to the exposure to infectious agents within the clinics, dentist may become spreaders due to the close proximity with patients and assistants during treatments [12]. The personal protective equipment (PPE) is the first layer of protection for healthcare workers [13]. Adjunctive protection namely face shield can further protect the face from direct splashing and spraying of contaminated fluids. However, the face shield does not present a tight seal around the face and cannot fully protect against aerosols invading its lateral edges [14,15]. Unfortunately, there is no strong evidence regarding the effectiveness of face shields against the transmission of viral respiratory diseases [14]. Although the PPE performs reasonably well in normal situations, the COVID-19 pandemic has exposed very concerning issues like the critical disruption

on supply chains leading to shortage of PPE at affected regions [16,17]. While most of the focus has been put on the development of new therapeutics and vaccines, further development in PPE and engineering controls can positively impact the safety of clinicians and patients.

Air contamination increases significantly following dental treatments [18,19] and may contaminate the skin and mucous membranes of the mouth, respiratory passage and eyes [12,20,21]. Previously, *Mycobacterium tuberculosis* has been found in aerosol particles generated by dental hand piece used on patients with active tuberculosis [22]. Notably, the air contamination increases significantly during dental aerosol generating procedures (from 12–75 and 216 CFU/m<sup>3</sup>, respectively). This is even more concerning in multichair dental clinics as the aerosols can contaminate inactive treatment areas (42 CFU/m<sup>3</sup>) [23]. The aerosols can remain suspended in air for 20–30 min and spread for 60 and 100 cm [12,24,25]. Hence, the clinical setting is frequently disinfected with compounds chlorine compounds or diluted isopropyl alcohol. A systematic review has suggested that the disinfection of semi-critical health care products with “alcohol 70%” allows the persistence of microorganisms (bacteria and viruses) on instrument surface even after the disinfection procedure [26]. Other chemical disinfectants like chlorine compounds can induce corrosiveness to metals or release of toxic gas when mixed with household cleaning agents containing ammonia or acids [27]. Of note, the effectiveness of these solutions seems to be associated with the mode of application, time of contact and substantivity [26]. Unfortunately, these substances only exert the biocidal effect on surfaces where they have been spread upon and this may not fully eradicate the risk of subsequent fomite transmission.

Saliva is abundant with nucleases that destabilize microbial membranes and promote fast degradation of RNA [28]. There are several salivary proteins such as alpha-2-macroglobulin, mucin MUC5B, gp340, histatins 1 and 3 that present antiviral activity based on viral disruption, neutralizing activity and/or salivary proteins aggregation before swallowing [29,30]. Nevertheless, the interactions between saliva and viruses vary considerably and although some viruses have short survival time in saliva [31,32], others are not readily affected and their presence in saliva can be even used to estimate viral systemic load [33]. The high complexity of viral/saliva interactions can be further illustrated by the controversial roles salivary gp-340 that inhibits neuraminidase activity of Influenza virus A Phil82 strain but not of the PR-8 strain [29].

Salivary markers for viral infections involve direct detection of specific viral antigens, such as proteins and nucleic acids or host antibodies to viral infections. Thus, the use of saliva for the detection of viral antigens and antibodies may provide a high accuracy point-of-care platform for detection of viral infections. Remarkably, rapid tests using oral fluids can diagnose HIV infection with very high sensitivity and accuracy [34,35]. Nevertheless, early diagnosis of viral diseases is difficult due to the need for seroconversion and this challenges the detection of asymptomatic carriers that could prevent further contaminations and assure timely treatment. Fortunately, combined antibody platforms can be promising alternatives to detect asymptomatic infected populations as some virus non-structural and structural components (e.g. RNA, proteins and peptides) could be detected in saliva in early stage of the infection [8,36,37].

Diagnostic platforms based on subject self-collecting saliva, can be pivotal to protect healthcare workers and population during outbreaks that are highly contagious. Although the presence of viable SARS-CoV-2 in saliva is known, the potential contributions of clinicians for rapid diagnostics have been largely neglected due to the current needs for specialized equipment, consumables, and skillsets. Unfortunately, the development of ready-to-use diagnostic tools is very challenging and strategies like the detection of specific antibodies to the SARS-CoV-2 virus can be limited by cross-reactivity against other coronaviruses [4]. As a result, rare (if any) ready-to-use saliva tests for COVID-19 have been made available for the public in the first eight months from the declaration of the pandemic. Nonetheless, technological developments over time have already allowed dentistry to play an important role in the development of tests for hepatitis B [38], hepatitis C [39], Epstein-Barr [40], herpes [41], and cytomegalovirus [42].

Indeed, there is a global concern on the rise and spread of viral diseases. It is common sense that the fight against viruses is a task mainly taken by virologists, geneticists, pharmaceutical researchers, and professionals from public health sector. However, materials science is receiving growing traction in this fight with several opportunities for breakthroughs to address these critical health crises. The objective of this work is to present some of the main mechanisms for interactions between viruses and materials and how properties can be tuned to negatively affect viral adhesion and survivability, decreasing their viability in environmental surfaces and infectivity in clinical settings. This paper also discusses new approaches to oral antiviral delivery materials and the potential of artificial intelligence for improved therapies.

---

## 2. Properties affecting adhesion and survivability of viruses on materials

The potential presence of viruses in saliva, throat fluids and sputum render the oropharyngeal system relevant in the dissemination of viral infections. There is growing concern that aerosols generated by dental procedures performed with high-speed handpiece or ultrasonic instruments can be a source of interpersonal transmissions. A recent study that evaluated the stability of SARS-CoV-2 and SARS-CoV-1 in aerosols and on various surfaces suggested that SARS-CoV-2 was stable and

viable on stainless steel and plastic up to 72 h [43]. Despite the inherent limitations of this study, like the apparatus design used to generate the aerosol and limited translation potential of those findings to clinical settings, this work sheds a light on the role of aerosol and surfaces on virus viability. Likewise, previous studies have shown that SARS-CoV, MERS-CoV and Influenza A virus have the ability to survive on dry surfaces for a duration suitable to facilitate further transmission [44–46]. Recently, a group of researchers confirmed the presence of SARS-CoV-2 in air outlet fans, sink, door handle, and other sites from the environment around an infected patient [47]. As several of these materials are routinely found in dental clinics and hospitals, there are concerns that transmission can occur from human contact with infected surfaces or fomite transmission due to prolonged environmental presence of viruses.

Understanding the mechanism of viral adsorption and adhesion is crucial for the development of materials and coatings with antiviral properties. It is known that the availability of viruses on surfaces depends on the nature of the materials they are spread upon. For instance, the adhesion forces of Aichi virus with polyvinyl chloride is five times greater than those measured on glass [48]. In this regard, characteristics (isoelectric point, electrical charge, roughness) from the virus and materials are critical for their interactions. Virus particles dispersed in medium present colloidal nature and the surface charge depends on the environmental pH. A review in the results published for 104 viruses has found that the isoelectric points occur in the pH range from 1.9 to 8.4 whereas the most frequent values are in the interval between 3.7 to 7.0. These results indicate that viruses with a very basic isoelectric point (<3.0) are uncommon [49]. Notably, there is a significant negative relationship between the level of viral adsorption and the isoelectric point [50], while several viruses in near-isoelectric state can be adsorbed to material bearing surface functional groups like carboxyl, primary amine or quaternary amine [51]. In fact, the high isoelectric point of cuprous oxide nanoparticles (11.0) has been suggested as a contributing factor for the high interaction capability with viruses [52]. Notably, the incorporation of copper-based nanoparticles to respiratory protective face masks has provided strong biocidal properties against Influenza A virus [53]. Hence, it may be feasible to modulate adsorption and survival of viruses on surfaces by knowing their isoelectric point and modulating material surface charge.

Viral adsorption on surfaces is generally considered to be governed by electrostatic interactions and oppositely charged surfaces and viruses usually present extensive adsorption [54,55]. The attraction of viruses dispersed in medium to surfaces can be explained by the classical theories that describe colloidal behaviour including the effects of surface charge in ionic solution and the presence of surrounding counterions. Previous work that evaluated the applicability of the Derjaguin–Landau–Verwey–Overbeek (DLVO) theory to adsorption of poliovirus to metal surfaces has suggested that the double-layer and van der Waals contributions are significant to the total free energy of adsorption [56]. However, the interactions between virus and surfaces are likely to be governed mainly by long-range electrostatics and shorter-range van der Waals interactions may be less important [57].

Viral adsorption kinetics onto surfaces need to be taken in consideration when designing materials with antiviral properties. The process of adsorption depends on the rate of virus movement through suspending medium, based upon Brownian motion. Hence, the adsorption is diffusion limited, not affected by mechanical agitation and the amount of virus adsorbed follows a linear function of the square root of time [58]. Notably, the kinetics of virus absorption are related to the charged state of sorbent surfaces. This can be taken into consideration while designing materials with antiviral properties, since the electrostatic attraction increases when the virion is oppositely charged to the adsorbent surfaces; this predictably results in fast and extensive adsorption [51,59]. Although the viral proteins in an isoelectric state would not strongly repel or attract surfaces, changes in pH can alter such behaviour. In fact, increasing the pH above the virus isoelectric point provides a net negative surface charge to the virions and can significantly enhance their adsorption onto the positively charged material. For instance, MS-2 virions with low isoelectric point of 3.9 have shown almost no adsorption onto negatively charged carboxylated silica with increasing pH. Likewise, poliovirus I has an isoelectric point of 6.6 and does not get adsorbed by negatively charged silica as the environmental pH increases [51]. This trend has been further confirmed on polymers coated with  $\text{NH}_2$  that presented higher virucidal effects compared with  $\text{COOH}$  groups against bacteriophage PRD1, which presents an acidic isoelectric point and a net negative charge at pH 7.4 [60].

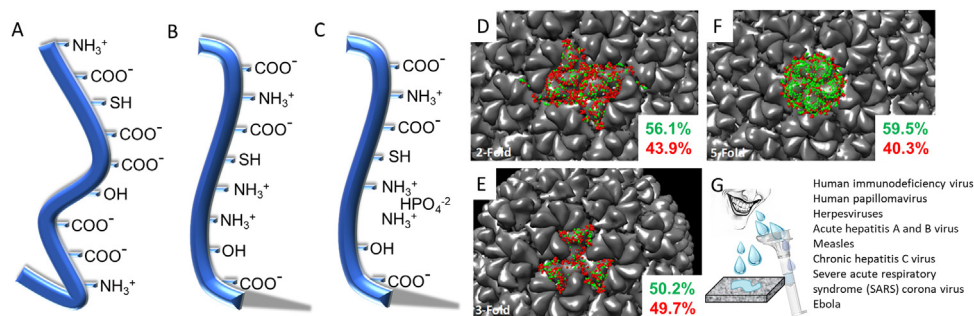
In addition, the structure of the viruses also affects adsorption. Enveloped viruses are surrounded by an outer lipid membrane which can strongly adsorb polycations. This interaction has been exploited to create polyethyleneimine coatings containing hydrophobic polycationic chains that after being absorbed can promote envelope disorganization and leakage of the viral genome resulting the viral deactivation [61,62]. Notably, viruses can bind to carbonaceous materials (“universal sorbents”) irrespective of antigenic structure of surface proteins. Nevertheless, the adsorption efficiency to these “universal sorbents” is low and governed through weak van der Waals interactions [63,64]. Finally, steric effects can hinder viral adsorption. These nonbonding interactions can be related to surface irregularities on the sorbent or asymmetries on the virus like protruding protein loops extending from the capsid surfaces which can create unfavourable steric forces hindering close contact of viruses with sorbents weakening the short-ranged van der Waals interactions as shown for MS-2, fr, and GA bacteriophages [57,65].

Material wetting properties may affect virus adsorption and survival. For instance, hydrophobic octadecyltrichlorosilane film had promoted extensively viral disassembly by disrupting the packing of virus coat proteins [66]. Viruses capsids often present ionizing residues (*e.g.*,  $\text{NH}_3^+$  and  $\text{COO}^-$ , Fig. 1) and hydrophobic moieties (*e.g.*, propyl group) that can interact with chemical groups from the surfaces of materials and promote physisorption [56]. Hydrophobic interactions promoting virus particles absorption can be observed on highly oriented pyrolytic graphite (HOPG), which presents nonpolar surface [57]. For instance, P22 viruses presented higher adsorption on perfluorodecyltriethoxysilane surface, compared with two other sorbents namely triethoxysilane

(APTS) and (3-glycidyloxypropyl) trimethoxysilane (GPTS), suggesting that the hydrophobic interactions regulate the virus adsorption at pH of 7.0 [67]. A previous study has shown negative correlations between viral number and total wax content, and concentrations of fatty acids and alkanes found in vegetables and tomatoes. Notably, the contact angles have been correlated with alkane concentrations, fatty acids and total wax but not with viral adsorption which was more influenced by the three-dimensional arrangement of the superficial wax crystals than by the hydrophobic character of the substrates. This study has also shown that the concurrent analysis of several physiochemical properties (*e.g.*, chemical composition, roughness and contact angle) accounts for only 60% of the variations in viral adsorption [68]. Hence, wetting properties cannot be used in isolation to predict the susceptibility to virus adsorption on materials but shall be considered in combination with other properties to enhance materials antiviral potential.

Material roughness may also affect the adsorption and adhesion of viruses but has been mostly neglected, possibly due to the difficulty of producing surface features controlled at a nanometric scale, a spatial resolution required considering the small diameter of viruses like F-specific RNA bacteriophages (20–30 nm) and SARS-CoV-2 (60–140 nm) [69]. The roughness of materials can influence the virus adsorption since surface features (peaks or depressions) can affect the electric double layer surface structure and the electrostatic interaction energy profile between the colloidal particle and the adsorbent. On nanometric scale, the size of the particles have little effect on adhesion when they are smaller than the dominant surface feature as the adhesion will be mostly governed by the geometrical effects of the surface/particle interactions [70]. Previous work has shown that the phage adhesion on glass with a mean square average of the surface profile (RMS) of 5 nm is weaker than on polypropylene and stainless steel substrates with RMS of 25 and 250 nm, respectively. Interestingly, the surface concentration of adhered Q $\beta$ , GA or MS2 phages was lower on glass compared with stainless steel regardless of both materials presenting similar hydrophobicity (5% and 20% equivalent  $-\text{CH}_3$  surface fraction). However, the increase in adhesion forces does not follow a linear trend with surface area [71]. Previous study has shown that surface roughness combined with contact angle and alkanes/ketones/fatty acids/alcohols concentration, can explain 60% of the variation in viral adsorption on organic surfaces [68]. Hence, it seems that surface roughness can be a contributing factor to viral adsorption but the exact mechanism still needs to be fully determined, especially bearing in mind that the role of roughness on adhesion of other microorganisms is still surrounded by many controversial findings.

Porosity is one of the most relevant parameters involved in the manufacturing of membranes for the filtration processes involved in the purification of biopharmaceuticals products derived from human or animal origin. Although other methods can be used to remove virus from solutions (*e.g.*, heat, radiation, solvent detergents), they can change the original state of the product or promote extensive degradation of proteins. Thus, filtration by membranes has become a popular method to reject virus particles without changing the chemical composition and characteristics through size exclu-



**Fig. 1 – A to C.** Arrangement of functional groups on coat protein segments of different viruses in neutral pH. The coat protein from virion with an IEP in the acid regime present more deprotonated carboxyl groups (A) whereas a virion with IEP at neutral pH will have the negatively charged groups balanced out by a relative higher number of protonated amino groups (B). The binding of hydrogen phosphate to the oxygen atoms on the coat protein shown in B, causes a water chemistry-dependent IEP alteration. This surface complexation neutralizes the positive charge and decreases the IEP of the virion (C). D to F. Protein residue maps at the different symmetries of the P22 virus facets (D) edges (E) and pentons (F). The of percentages of hydrophobic and polar features exposed are shown in green and red. (G) The human saliva can be the source of spread or a diagnostic tool of several viruses (panels A to G were adapted with permission from Refs. [49,67]).

sion [72,73]. The commercial virus filters were firstly designed to reject retroviruses with diameters higher than 50 nm but nanofiltration systems are effective in removing viruses with diameters between 18 and 24 nm [74]. The membranes can be modified to add functionalities and enhance performance and durability. One strategy relies on the functionalization of polymeric membranes with polycationic chains which can damage lipid membranes of viruses [61,75]. This has been shown on polycationic glass slide coated with *N,N*-dodecyl methyl-polyethylenimine, which has shown potent virucidal effects killing the totality of Influenza A virus after 5 min [61]. Likewise, polycations (polyethylenimine and generation 4.0 dendrimer) decreased the titer of bacteriophage PRD1 by at least 75% [60].

As seen, several properties like wetting characteristics, surface features, and electrostatic interaction forces affect the interaction between materials and viruses and shall be mutually considered when designing novel materials with virucidal and antiadhesive properties.

### 3. Materials science to reduce viability and infectivity of viruses common to clinical settings

Transmission of viral diseases from contaminated dry surfaces is possible through self-inoculation of mucous membranes [76,77]. This is especially important for dental and hospital settings where viral particles can remain in the air and become available on surfaces potentially contributing to infection of nearby subjects [4]. Therefore, designing novel materials with the potential to decrease virus availability, survivability, and infectivity is of utmost importance to minimize viral diseases in the public and in healthcare settings.

To prevent fomite transmission, researchers often focus on surface modifications that inhibit viral adhesion or promote protein destabilization). Designing smart materials with self-

adjusting surface mechanisms could be a promising way to decrease virus availability on contaminated materials.

Surface modifications that change the docking orientation of viruses can potentially decrease their adsorption and retention onto materials. This concept has been shown with P22 virus-like particles cultured on substrates coated with different organosilanes namely 2H-Perfluorodecyltriethoxysilane (PFDS), (3-aminopropyl) triethoxysilane (APTS), and GPTS. The P22 virus-like particles present with an icosahedral structure and can be adsorbed in fivefold (S5), threefold (S3), and twofold (S2) symmetry axes. Notably, PFDS favoured adsorption by S5 symmetry, and adsorption on the other organosilanes occurred via S3 and S2 symmetries. Interestingly, APTS tends to deform the virus as it is adsorbed through the facets or the ridges (S2/S3). This orientation lower virus adsorption on APTS and GPTS by 66% and 32% relative to PFDS and can be explained by the repulsive forces acting on the hydrophobic domains of the P22 virus-like particles promoting adhesion by S3 and S2 symmetries (Fig. 1, [67]).

Fine-tuning material surface charge and pH could also be promising alternatives to decrease viral availability. This has been shown with reovirus types 1 and 3, which were adsorbed by negatively charged silica when the environmental pH was lower than the virions isoelectric point [51]. Indeed, the role of environmental pH on viral adsorption to adsorbent materials is well established. Hence, novel materials that can self-adjust the pH upon environmental changes could be promising in preventing the spread of viruses. It is possible to fabricate pH-responsive smart devices that change their wetting character by surface modification with a mixed thiol containing carboxylic groups and methyl groups [78]. Another pH-responsive mechanism has been achieved in poly(acrylic acid) hydrogel modified with upconverting nanoparticle-assisted photocleavage of a ruthenium complex photobase. The pH of the materials has been manipulated with the use of near-infrared light in a process called photon upconversion pH manipulation where the upconverting nanoparticles change near infra-red light into blue light,

triggering the release of n-butylamine from the ruthenium complex photobase, resulting in the deprotonation of the poly(acrylic acid) hydrogel [79]. These and other strategies could be used to design re-applicable pH-responsive surface coatings. Manipulating surface charges with self-adjusting and pH-responsive materials may be interesting strategies to decrease adhesion and survivability of viruses on materials.

Alternative solution may be the development of materials with intrinsic virucidal properties. Perhaps the most explored chemical elements in this category are silver and copper, which have been deemed as an antimicrobial materials in countless publications. Silver-containing technologies, like the incorporation of silver-zeolite compounds into metals and polymers, had germicidal effects on air conducts in real healthcare settings [80]. This effect may be related to the release of silver ions in the presence of moisture that interfere with microbial enzymatic and respiratory activities and ion binding to the genetic material [80,81]. Despite these promising findings, coating door handles with Agion silver zeolite technology have been shown to be effective against only a portion of the bacterial populations and there are concerns about the emergence of resistant strains [82]. Notably, copper-containing surfaces present *contact killing* property in both moist and dry conditions [83]. Previously, the placement of copper alloy-surfaced objects in intensive care units have reduced the rates of colonization with vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus* (MRSA) and decreased the risk of healthcare-acquired infections in patients by more than half [84]. Similarly, copper-made door handles installed in hospital presented high antibacterial activity against methicillin-resistant *S. aureus* even after being routinely used for 3 years [85]. Previous work has shown Influenza A virus remained infectious on stainless steel ( $5 \times 10^5$  viable virus particles at 24 h) but not on copper surfaces ( $5 \times 10^2$  viable virus particles at 6 h [86]). The virucidal effect of copper can be further enhanced by the addition of peroxide and this combination inactivates several DNA or RNA viruses, such as phi X174, T7, phi 6, Junin, and herpes simplex viruses which have been found in contaminated medical devices [87]. One of the potential mechanisms related to the *killing by contact* potential is the binding of copper to the double-helical structure of DNA promoting their disorder or the formation of crosslinks between bases on opposite DNA strands [88,89]. It is possible that such potential can also decrease virus survivability and spread in clinic and hospital settings. There is evidence that HuCoV-229E particles are severely damaged with evidence of detrimental morphological changes when genomic RNA from virus is exposed to copper surfaces [90].

The antimicrobial potential of metal nanoparticles has been extensively reported and there are raising interests in using them for antiviral applications. For instance, silver nanoparticles have promising inhibitory potential against the formation of intracellular HepBV RNA and extracellular virions [91]. Also, the addition of silver nanoparticles to chitosan results in a composite with antiviral activity against H1N1 Influenza A virus. The antiviral potential is dose-dependent with complete eradication of the virus at a concentration of 300 silver nanoparticles per  $\mu\text{g}$  of chitosan [92]. Likewise,

porous gold nanoparticles can attenuate the infectivity of Influenza A virus strains (H1N1, H3N2, and H9N2). Notably, MDCK cells had a viability of 96% when treated with viruses exposed to the gold nanoparticles whereas only 33% of the cells were viable when non-treated viruses were used [93]. The antiviral activity of silver nanoparticles has also been confirmed against hepatitis B virus, with promising antiviral potential and low cytotoxicity with silver particles with sizes of 10 and 50 nm [91]. Likewise, silver nanoparticles interact with HIV-1 in a size-dependent manner where only nanoparticles with sizes ranging from 1 to 10 nm have attached to virus surface [94]. The mechanisms behind the antiviral potential of gold, silver, and copper are diverse. For instance, gold nanoparticles could interact with virus surface proteins promoting the cleavage of their disulphide bonds decreasing the infectivity potential [93]. Silver and copper can form complexes with sulphur-containing functionalities and induce protein destabilization through the breakage of disulphide bonds [95]. Also, silver nanoparticles bind preferentially to viral sulphur-bearing residues of gp120 glycoprotein knobs and this can prevent viral binding to host cells by blocking other proteins inhibiting post-entry stages of infection, or by binding directly to nucleic acids reducing proviral transcription processes [94,96,97]. In addition, copper and silver compounds such as  $\text{Ag}_2\text{O}$  and  $\text{CuCl}_2$  can promote virus inactivation by the inhibition of neuraminidase activity whereas  $\text{Cu}_2\text{O}$  cause the structural denaturation of hemagglutinin, impairing host cell recognition through ligand-receptor interactions [95].

Other strategies make use of novel materials to eradicate viruses with destruction mechanisms. Recently, a graphene derivative has been shown to inactivate both DNA and RNA viruses by structural destruction at a non-cytotoxic concentration. The antiviral mechanism was attributed to the negative charge and nanosheet structure [98]. Likewise, graphene-like materials have inhibited HSV-1 infection through cell attachment inhibition at low concentrations [99]. Similar potential has been observed with the Ebola virus matrix protein VP40, which has been disrupted by graphene nanosheets at the C-terminal domain interface that is crucial in forming the Ebola viral matrix [100]. Also, graphene oxide has been shown to capture viruses and to destroy their surface proteins. Interestingly, the superficial bioreduction provided by graphene oxide allows the extraction of higher quantities of viral RNA [101].

---

#### 4. New approaches to oral antiviral delivery materials

The challenges in developing oral antiviral delivery materials are considerable, but not insurmountable. Bearing in mind the advantages of oral delivery, including easy administration, cost-effectiveness, and flexibility in dosage, it is understandable that oral drug delivery is acknowledged as one of the most preferred and convenient routes [102,103]. Frequently, this route has been used with a therapeutic focus; however, an emerging and less explored strategy is the development of sophisticated oral antiviral delivery materials to reduce the spread of viral infections transmitted orally. For instance, the oral epithelial cells have high ACE-2 expression hence it is a critical point in COVID-19 infection susceptibility [104,105].

Therefore, we envisage that health care workers and the general population, who are under high exposure risk from COVID-19 infection, are good candidates to use pre-exposure prophylaxis antivirals or inhibitors of post-entry replication via adapted antiviral-based oral drug delivery systems. The Glycyrrizin, dapivirine, and Griffithsin are powerful inhibitors of viral entry and were successfully coupled to drug delivery materials [106–108]. For instance, poly(lactic-co-glycolic acid) (PLGA) nanoparticles have been designed to co-deliver Griffithsin and dapivirine and this strategy has been shown to prevent viral infection *in vitro* [108].

Another potential strategy to inhibit the virus infection in oral mucosa is to develop oral drug delivery materials coupled with natural occurring salivary protein/peptides with antiviral activity. Some examples of natural occurring proteins that were coupled with nanocarriers system are alpha-2-macroglobulin, mucin MUC5B, histatins 1, histatin 3 and its related peptides [109–111]. Previously, chitosan-glycopolymers mucoadhesive gel has been shown to deliver antiretroviral Efavirenz through mucosa *in vitro* [112]. Furthermore, several compounds that are capable of inhibiting post-entry replication of coronaviruses, such as broad-spectrum antiviral agent as Nitazoxanide [113] or papain-like and chymotrypsin-like protease [114] can be attached in microcarriers system. For instance, copolyester poly(glycol adipate-co- $\omega$ -pentadecalactone) microparticles have been shown to effectively release  $\alpha$ -Chymotrypsin but only for 7 h [115]. The fundamentals of these studies suggest that preventing and treating viral infections with oral delivery systems may be feasible if material properties are tailored to promote controlled and sustained release of antiviral agents in the oral cavity.

---

## 5. Optimizing antiviral delivery with artificial intelligence

A broad range of materials can be leveraged for potential innate antiviral properties, as well as the delivery of a broad spectrum of candidate therapies. This represents an opportunity to novel materials design and combination therapy (e.g., drug pair-based synergy prediction, to traditional target-based drug selection [116,117]). Co-delivering multiple therapies through nanoparticles emerges as a potential platform for enhanced drug synergy. However, achieving optimal drug combination design depends on the simultaneous optimization of drug and dose selection. This can be insurmountably challenging when considering the fact that a small pool of 12 drugs with each drug studied at 10 dosing levels results in 1 trillion possible drug combinations. To overcome this testing challenge, we have previously harnessed an artificial intelligence (AI)-driven quadratic relationship between drug/dose inputs and efficacy/safety outputs to markedly reduce the number of prospective assays needed to pinpoint the right drugs and doses with potential to improve treatment outcomes [118–123]. To this end, the patient's clinical/laboratorial data (baseline and follow-ups) and therapeutic regime (initial and adjusted doses) are constantly analyzed using computational power like quadratic phenotypic optimization platform. This analytical system keeps adjusting

the therapeutic scheme based on new inputs till an optimal combination of drugs, dosage and administration scheme is achieved at the individual level (Fig. 2). This strategy has been successfully used to customize the treatment for metastatic prostate cancer resulting in controlled PSA levels without disease progression and reduced lesion size [122]. Likewise, AI has been used in a pilot study to optimize the dose of antiretroviral drugs for treating HIV infection. The AI platform identified that the tenofovir dose could be reduced for the long-term maintenance regimen with no relapse for 33 months [121].

Development of new drugs is costly and very time-consuming. Alternatively, drug repurposing aims to reuse existing approved drugs for new medical conditions. Since the outcomes known are limited by the parameters tested, it is feasible that potential drug candidates are discarded merely because that combination/dose/regime tested had not provided positive results, which does not mean that further adjustments could not lead to more promising outcomes [124]. For instance, an artificial intelligence platform has been used to predict drugs potentially active against animal coronavirus that are available in the market (3CL proteases inhibitors, HIV and Influenza drugs). This approach has identified 80 candidate drugs and 8 of them decreased viral proliferation *in vitro* [125]. Another study for drug repurposing using artificial intelligence has shown that the optimal combination of drugs has decreased the viral infection rate from 21% to only 1.5% *in vitro* (Fig. 2A [123]). These studies show that AI has great potential to optimize combination therapy for viral diseases.

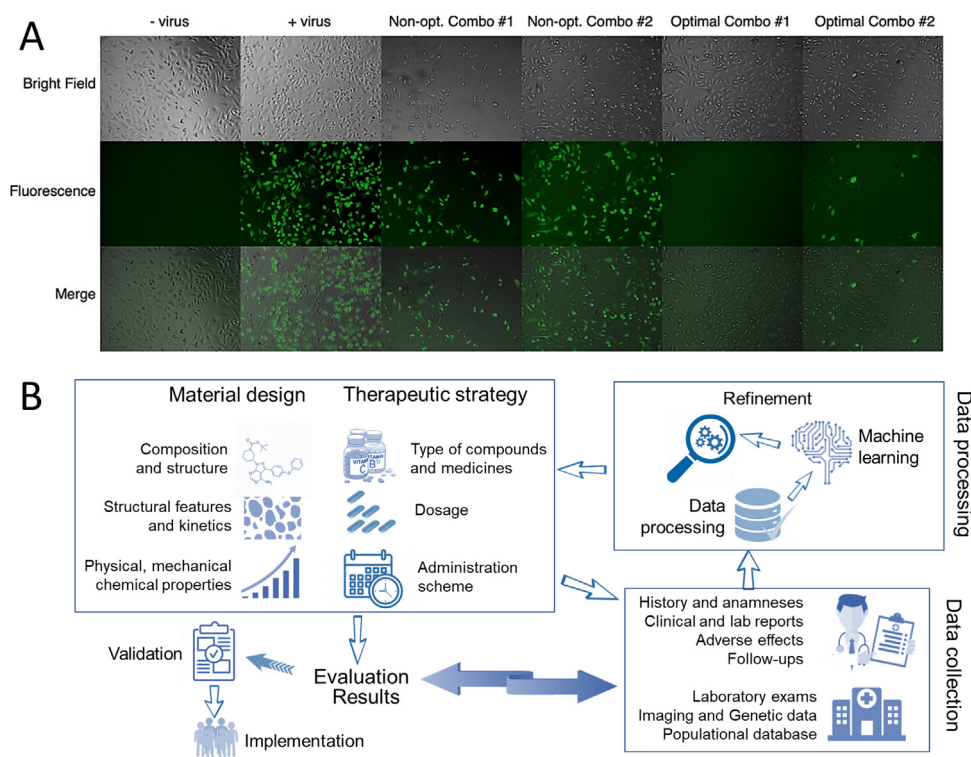
It needs to be highlighted that achieving drug synergy after designing suitable drug combinations does not guarantee favorable treatment outcomes. In addition, drug synergy has been shown to be time/dose dependent and patient-specific [118–122]. In the context of materials-driven drug therapy, this point is important since drug dosing within a combination regimen may need to be dynamically modulated to sustain treatment optimisation (Fig. 2B). This may also entail the use of different nanomaterial platforms to carry their best suited specific therapies so that drug ratios can be modified in time, since high-dose and fixed-ratio treatment may preclude the ability to individualise treatment for the full duration of care. Therefore, it is important to leverage emerging small data-based platforms to both optimise drug combination design while also sustaining treatment optimisation with dynamically dosed regimens.

---

## 6. Challenges and opportunities

Viral infections are concerning due to risk of morbidity and mortality, as well as psychological and economic impacts. In the battle against viruses, most of the focus is placed on the development of vaccines and antiviral drugs. However, materials science has attracted the spotlight since the public have become fully aware that environmental surfaces can contribute for the transmission of viruses [126]. Although the mechanisms of viral attraction to surfaces have been extensively reported, breakthroughs in “antiviral surfaces” have not come to full fruition vis a vis the great concerns surrounding the susceptibility to nosocomial and cross-infections in clinical settings during the COVID-19 out-





**Fig. 2 – (A) Microscope imaging of nonoptimal and optimal combinations of a “5-drug validation test”. Optimal drug combinations almost completely eradicate viral infection without evident signs of cell toxicity [123]. (B) Three stages of optimization of material-driven antiviral delivery with artificial intelligence. The first stage includes the design of the candidate materials and compounds/drugs/medicines and fully characterized *in vitro* and *in vivo*. In the second stage, the drug delivery system is tested in a small population and the results are periodically collected and processed by an artificial intelligence platform. The digital system will identify opportunities for improvement in material design and optimization of the therapeutic strategies and feedback to the development stage. This schedule is repeated until the design is final and validated in a larger population and implemented.**

break. It is understandable, nonetheless, that inhibiting the attraction of viruses onto surfaces is not simple and some lessons learned from studies on other microorganisms may not be directly applied for antiviral applications. For instance, it is known that bacteria and fungi often exhibit difficulties in attaching and proliferating on hydrophobic materials [127,128]; however, the adsorption of nanometric particles like viruses is also affected by chemical composition, environmental pH, net surface charge, development of electrostatic forces and other factors [54,55,57]. Hence, novel responsive materials or with self-adjusting properties or ability to change electrical character upon external stimuli could offer an advantage to decrease the viral load and survivability. Some promising strategies for the production of such materials have been reported [78,79] but their potential against viruses remain largely unknown. It is worth mentioning that the microbial inhibition potential of some (but not all) materials can be attenuated in the presence of salivary pellicle [129,130] and this needs to be taken in consideration while developing coatings with antiviral potential. Also, the incorporation of drugs to intraoral delivery systems need to be carefully considered as their presence may cause oral dysbiosis and promote the rise of other drug-resistant microorganisms. Other point that

deserves attention is the scarcity of innovative strategies that do not include necessarily copper, gold, or silver. The development of new strategies containing alternative metals that can expand the range of applications while solving the drawbacks associated with those metals traditionally studied. Of note, new coatings to protect surfaces from contamination need to be cost-effective and allow the application without much technical expertise for broad adoption by clinicians. Finally, focus on artificial intelligence for rational design can unlock and maximize antiviral potentials for preventive measures or therapeutic purposes.

In the emergence of new viral infections, the vaccines are not readily available and therapeutic strategies are developed as the outbreaks develop. Unfortunately, these developments demand high sums of money, a long time, and are likely to be virus type specific. Thus, material scientists must play an important role by unlocking materials with characteristics that negatively affect a multitude of viruses, decreasing their availability and infectivity. On the other front, merging materials science and artificial intelligence technologies can enable faster and effective preventive and therapeutic strategies, improving the safety and well-being of humankind.

## Acknowledgments

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. VR is supported by the grants from the Ministry of Education, Singapore (Academic Research Fund Tier 1, R-221-000-104-114, R-221-000-132-114). RSS acknowledges CAPES, Brazil (#23038.014934/2020-59). WLS acknowledges Canadian Institutes of Health Research (CIHR #446892). DH gratefully acknowledges support from the Office of the President, Office of the Senior Deputy President and Provost, and Office of the Deputy President for Research and Technology at the National University of Singapore. DH also gratefully acknowledges the Ministry of Education, Singapore Tier 1 FRC Grant, National Research Foundation Singapore under its AI Singapore Programme (Award Number: AISG-GC-2019-002), and Singapore Ministry of Health's National Medical Research Council under its Open Fund-Large Collaborative Grant (OF-LCG, MOH-OFLCG18May-0028).

## REFERENCES

- [1] Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;395:514–23.
- [2] Gamio L. The workers who face the greatest coronavirus risk. *New York: The New York Times*; 2020.
- [3] Xie X, Li Y, Sun H, Liu L. Exhaled droplets due to talking and coughing. *J R Soc Interface* 2009;6.
- [4] Sabino-Silva R, Jardim ACG, Siqueira WL. Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis. *Clin Oral Investig* 2020;24:1619–21.
- [5] Zuo YY, Uspal WE, Wei T. Airborne transmission of COVID-19: aerosol dispersion, lung deposition, and virus-receptor interactions. *ACS Nano* 2020;14:16502–24.
- [6] Corstjens PLAM, Abrams WR, Malamud D. Saliva and viral infections. *Periodontol* 2000 2016;70:93–110.
- [7] Yuen K-Y, Chan JF-W, Cheng VC-C, Hung IF-N, Fung AY-F, Poon RW-S, et al. Consistent detection of 2019 novel Coronavirus in saliva. *Clin Infect Dis* 2020;71:841–3.
- [8] Zuanazzi D, Arts EJ, Jorge PK, Mulyar Y, Gibson R, Xiao Y, et al. Postnatal identification of Zika virus peptides from saliva. *J Dent Res* 2017;96:1078–84.
- [9] Harrel SK, Molinari J. Aerosols and splatter in dentistry. *J Am Dent Assoc* 2004;135:429–37.
- [10] Kumar PS, Subramanian K. Demystifying the mist: sources of microbial bioload in dental aerosols. *J Periodontol* 2020;91:1113–22.
- [11] Volgenant CMC, de Soet JJ. Cross-transmission in the dental office: does this make you ill? *Curr Oral Health Rep* 2018;5:221–8.
- [12] Bentley CD, Burkhart NW, Crawford JJ. Evaluating spatter and aerosol contamination during dental procedures. *J Am Dent Assoc* 1994;125:579–84.
- [13] Volgenant CMC, Persoon IF, Ruijter RAG, Soet JJ. Infection control in dental health care during and after the SARS-CoV-2 outbreak. *Oral Dis* 2020;27:1–10.
- [14] Designing and engineering effective PPE. Larson EL, Liverman CT, editors. Preventing transmission of pandemic influenza and other viral respiratory diseases. Washington, USA: National Academies Press; 2011.
- [15] Li DTS, Samaranyake LP, Leung YY, Neelakantan P. Facial protection in the era of COVID-19: a narrative review. *Oral Dis* 2020;27:1–9.
- [16] Wu H-I, Huang J, Zhang CJP, He Z, Ming W-K. Facemask shortage and the novel coronavirus disease (COVID-19) outbreak: reflections on public health measures. *EClinicalMedicine* 2020;21.
- [17] Centers for Disease Control and Prevention. Strategies for optimizing the supply of facemasks; 2020.
- [18] Larato DC, Ruskin PF, Martin A, Delanko R. Effect of a dental air turbine drill on the bacterial counts in air. *J Prosthet Dent* 1966;16:758–65.
- [19] Zhou D, Zemouri C, de Soet H, Crielaard W, Laheij A. A scoping review on bio-aerosols in healthcare and the dental environment. *PLoS One* 2017;12.
- [20] Miller RL. Generation of airborne infection. . . by high speed dental equipment. *J Am Soc Prev Dent* 1976;6:14–7.
- [21] Holbrook WP, Muir KF, Macphee IT, Ross PW. Bacteriological investigation of the aerosol from ultrasonic scalers. *Br Dent J* 1978;144:245–7.
- [22] Belting CM, Haberfelde GC, Juhl LK. Spread of organisms from dental air rotor. *J Am Dent Assoc* 1964;68:648–51.
- [23] Grenier D. Quantitative analysis of bacterial aerosols in two different dental clinic environments. *Appl Environ Microbiol* 1995;61:3165–8.
- [24] Veena HR, Mahantesha S, Joseph PA, Patil SR, Patil SH. Dissemination of aerosol and splatter during ultrasonic scaling: a pilot study. *J Infect Public Health* 2015;8:260–5.
- [25] Chuang C-Y, Cheng H-C, Yang S, Fang W, Hung P-C, Chuang C-Y. Investigation of the spreading characteristics of bacterial aerosol contamination during dental scaling treatment. *J Dent Sci* 2014;9:294–6.
- [26] Ribeiro MM, Neumann VA, Padoveze MC, Graziano KU. Efficacy and effectiveness of alcohol in the disinfection of semi-critical materials: a systematic review. *Rev Lat Am Enfermagem* 2015;23:741–52.
- [27] Mrvos R, Dean BS, Krenzelok EP. Home exposures to chlorine/chloramine gas. *South Med J* 1993;86:654–7.
- [28] Park NJ, Li Y, Yu T, Brinkman BM, Wong DT. Characterization of RNA in saliva. *Clin Chem* 2006;52:988–94.
- [29] White MR, Helmerhorst EJ, Ligtenberg A, Karpel M, Teclé T, Siqueira WL, et al. Multiple components contribute to ability of saliva to inhibit influenza viruses. *Oral Microbiol Immunol* 2009;24:18–24.
- [30] Gilbertson B, Edenborough K, McVernon J, Brown LE. Inhibition of Influenza A virus by human infant saliva. *Viruses* 2019;11:766.
- [31] Bardell D. Survival of herpes simplex virus type 1 in saliva and tap water contaminating some common objects. *Microbios* 1993;74:81–7.
- [32] Baron S, Poast J, Cloyd MW. Why is HIV rarely transmitted by oral secretions? Saliva can disrupt orally shed, infected leukocytes. *Arch Intern Med* 1999;159:303–10.
- [33] Hermida M, Ferreira MC, Barral S, Laredo R, Castro A, Diz Dios P. Detection of HCV RNA in saliva of patients with hepatitis C virus infection by using a highly sensitive test. *J Virol Methods* 2002;101:29–35.
- [34] Carvalho LH, Belete W, Deressa T, Feleke A, Menna T, Moshago T, et al. Evaluation of diagnostic performance of non-invasive HIV self-testing kit using oral fluid in Addis Ababa, Ethiopia: a facility-based cross-sectional study. *PLoS One* 2019;14.
- [35] Pascoe SJS, Langhaug LF, Mudzori J, Burke E, Hayes R, Cowan FM. Field evaluation of diagnostic accuracy of an oral fluid rapid test for HIV, tested at point-of-Service sites in Rural Zimbabwe. *AIDS Patient Care STDS* 2009;23:571–6.

- [36] Petherick A. Developing antibody tests for SARS-CoV-2. *Lancet* 2020;395:1101–2.
- [37] Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol* 2020;92:1518–24.
- [38] van der Eijk AA, Niesters HG, Gotz HM, Janssen HL, Schalm SW, Osterhaus AD, et al. Paired measurements of quantitative hepatitis B virus DNA in saliva and serum of chronic hepatitis B patients: implications for saliva as infectious agent. *J Clin Virol* 2004;29:92–4.
- [39] van Doornum GJ, Lodder A, Buimer M, van Ameijden EJ, Bruisten S. Evaluation of hepatitis C antibody testing in saliva specimens collected by two different systems in comparison with HCV antibody and HCV RNA in serum. *J Med Virol* 2001;64:13–20.
- [40] Ikuta K, Satoh Y, Hoshikawa Y, Sairenji T. Detection of Epstein-Barr virus in salivas and throat washings in healthy adults and children. *Microbes Infect* 2000;2:115–20.
- [41] Spicher VM, Bouvier P, Schlegel-Haueter SE, Morabia A, Siegrist CA. Epidemiology of herpes simplex virus in children by detection of specific antibodies in saliva. *Pediatr Infect Dis J* 2001;20:265–72.
- [42] Lucht E, Brytting M, Bjerregaard L, Julander I, Linde A. Shedding of cytomegalovirus and herpesviruses 6, 7, and 8 in saliva of human immunodeficiency virus type 1-infected patients and healthy controls. *Clin Infect Dis* 1998;27:137–41.
- [43] van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020;382:1564–7.
- [44] van Doremalen N, Bushmaker T, Munster V. Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. *Eurosurveillance* 2013;18.
- [45] Chan KH, Peiris JSM, Lam SY, Poon LLM, Yuen KY, Seto WH. The effects of temperature and relative humidity on the viability of the SARS Coronavirus. *Adv Virol* 2011;2011:1–7.
- [46] Oxford J, Berezin EN, Courvalin P, Dwyer DE, Exner M, Jana LA, et al. The survival of influenza A(H1N1)pdm09 virus on 4 household surfaces. *Am J Infect Control* 2014;42:423–5.
- [47] Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *JAMA* 2020;323:1610–2.
- [48] Shim J, Stewart DS, Nikolov AD, Wasan DT, Wang R, Yan R, et al. Differential MS2 interaction with food contact surfaces determined by atomic force microscopy and virus recovery. *Appl Environ Microbiol* 2017;83, e01881–17.
- [49] Michen B, Graule T. Isoelectric points of viruses. *J Appl Microbiol* 2010;109:388–97.
- [50] Dowd SE, Pillai SD, Wang S, Corapcioglu MY. Delineating the specific influence of virus isoelectric point and size on virus adsorption and transport through sandy soils. *Appl Environ Microbiol* 1998;64:405–10.
- [51] Zerda KS, Gerba CP, Hou KC, Goyal SM. Adsorption of viruses to charge-modified silica. *Appl Environ Microbiol* 1985;49:91–5.
- [52] Mazurkow JM, Yüzbaşı NS, Domagala KW, Pfeiffer S, Kata D, Graule T. Nano-sized copper (oxide) on alumina granules for water filtration: effect of copper oxidation state on virus removal performance. *Environ Sci Technol* 2019;54:1214–22.
- [53] Tavis JE, Borkow G, Zhou SS, Page T, Gabbay J. A novel anti-influenza copper oxide containing respiratory face mask. *PLoS One* 2010;5:e11295.
- [54] Gutierrez L, Li X, Wang J, Nangmenyi G, Economy J, Kuhlenschmidt TB, et al. Adsorption of rotavirus and bacteriophage MS2 using glass fiber coated with hematite nanoparticles. *Water Res* 2009;43:5198–208.
- [55] da Silva AK, Kavanagh OV, Estes MK, Elimelech M. Adsorption and aggregation properties of norovirus GI and GII virus-like particles demonstrate differing responses to solution chemistry. *Environ Sci Technol* 2011;45:520–6.
- [56] Gerba CP. Applied and theoretical aspects of virus adsorption to surfaces. *Adv Appl Microbiol* 1984;30:133–68.
- [57] Armanious A, Aeppli M, Jacak R, Refardt D, Sigstam T, Kohn T, et al. Viruses at solid–water interfaces: a systematic assessment of interactions driving adsorption. *Environ Sci Technol* 2015;50:732–43.
- [58] Cookson JT, North WJ. Adsorption of viruses on activated carbon. Equilibria and kinetics of the attachment of *Escherichia coli* bacteriophage T4 on activated carbon. *Environ Sci Technol* 1967;1:46–52.
- [59] Zhuang J, Jin Y. Virus retention and transport through Al-oxide coated sand columns: effects of ionic strength and composition. *J Contam Hydrol* 2003;60:193–209.
- [60] Gelman F, Lewis K, Klibanov AM. Drastically lowering the titer of waterborne bacteriophage PRD1 by exposure to immobilized hydrophobic polycations. *Biotechnol Lett* 2004;26:1695–700.
- [61] Haldar J, An D, Alvarez de Cienfuegos L, Chen J, Klibanov AM. Polymeric coatings that inactivate both influenza virus and pathogenic bacteria. *Proc Natl Acad Sci U S A* 2006;103:17667–71.
- [62] Lucas W. Viral capsids and envelopes: structure and function. In: *Encyclopedia of life sciences*; 2010.
- [63] Ivanova MV, Burtseva EI, Ivanova VT, Trushakova SV, Isaeva EI, Shevchenko ES, et al. Adsorption of influenza A and B viruses on detonation nanodiamonds materials. *MRS Proc* 2012;1452:14–9.
- [64] Ivanova VT, Garina EO, Burtseva EI, Kirillova ES, Ivanova MV, Stejskal J, et al. Conducting polymers as sorbents of influenza viruses. *Chem Paper* 2016;71:495–503.
- [65] Kolawole AO, Li M, Xia C, Fischer AE, Giacobbi NS, Ripinger CM, et al. Flexibility in surface-exposed loops in a virus capsid mediates escape from antibody neutralization. *J Virol* 2014;88:4543–57.
- [66] Britt DW, Buijs J, Hlady V. Tobacco mosaic virus adsorption on self-assembled and Langmuir–Blodgett monolayers studied by TIRF and SFM. *Thin Solid Films* 1998;327–329:824–8.
- [67] Moreno-Cerrada D, Rodríguez C, Moreno-Madrid F, Selivanovitch E, Douglas T, de Pablo PJ, et al. Loading the dice: the orientation of virus-like particles adsorbed on titanate assisted organosilanized surfaces. *Biointerphases* 2019;14:011001.
- [68] Kirk M, Lu L, Ku K-M, Palma-Salgado SP, Storm AP, Feng H, et al. Influence of epicuticular physicochemical properties on porcine rotavirus adsorption to 24 leafy green vegetables and tomatoes. *PLoS One* 2015;10.
- [69] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD. Features, evaluation and treatment Coronavirus (COVID-19) [updated 2020 Mar 20]. *StatPearls Publishing*; 2020.
- [70] Duval JFL, Leermakers FAM, van Leeuwen HP. Electrostatic interactions between double layers: influence of surface roughness, regulation, and chemical heterogeneities. *Langmuir* 2004;20:5052–65.
- [71] Dika C, Ly-Chatain MH, Francius G, Duval JFL, Gantzer C. Non-DLVO adhesion of F-specific RNA bacteriophages to abiotic surfaces: importance of surface roughness, hydrophobic and electrostatic interactions. *Colloids Surf Physicochem Eng Aspects* 2013;435:178–87.

- [72] Wickramasinghe SR, Stump ED, Grzenia DL, Husson SM, Pellegrino J. Understanding virus filtration membrane performance. *J Membr Sci* 2010;365:160–9.
- [73] Cameron R, Smith K. Virus clearance methods applied in bioprocessing operations: an overview of selected inactivation and removal methods. *Pharm Bioprocess* 2014;2:75–83.
- [74] Novokhatny V, Rebbeor J, Scuderi P, Petteway S. Acid-stabilized plasmin as a novel direct-acting thrombolytic. In: *Production of plasma proteins for therapeutic use*; 2012. p. 259–71.
- [75] Sinclair TR, Robles D, Raza B, van den Hengel S, Rutjes SA, de Roda Husman AM, et al. Virus reduction through microfiltration membranes modified with a cationic polymer for drinking water applications. *Colloids Surf Physicochem Eng Aspects* 2018;551:33–41.
- [76] Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. *J Hosp Infect* 2016;92:235–50.
- [77] Dowell SF, Simmerman JM, Erdman DD, Wu JS, Chaovavanich A, Javadi M, et al. Severe acute respiratory syndrome coronavirus on hospital surfaces. *Clin Infect Dis* 2004;39:652–7.
- [78] Ju G, Cheng M, Shi F. A pH-responsive smart surface for the continuous separation of oil/water/oil ternary mixtures. *NPG Asia Mater* 2014;6, e111-e.
- [79] Chen Z, Xiong Y, Etchenique R, Wu S. Manipulating pH using near-infrared light assisted by upconverting nanoparticles. *Chem Commun (Camb)* 2016;52:13959–62.
- [80] Tinteri C, Potenza M, Rizzetto R. Antimicrobial efficacy and longevity of silver+zeolite incorporating preinsulated ducts installed in real healthcare settings. *J Prev Med Hyg* 2012;53:177–80.
- [81] Schierholz J. Efficacy of silver-coated medical devices. *J Hosp Infect* 1998;40:257–62.
- [82] Potter BA, Lob M, Mercaldo R, Hetzler A, Kaistha V, Khan H, et al. A long-term study examining the antibacterial effectiveness of Agion silver zeolite technology on door handles within a college campus. *Lett Appl Microbiol* 2014;60:120–7.
- [83] Espirito Santo C, Lam EW, Elowsky CG, Quaranta D, Domaille DW, Chang CJ, et al. Bacterial killing by dry metallic copper surfaces. *Appl Environ Microbiol* 2011;77:794–802.
- [84] Salgado CD, Sepkowitz KA, John JF, Cantey JR, Attaway HH, Freeman KD, et al. Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. *Infect Control Hosp Epidemiol* 2015;34:479–86.
- [85] Colin M, Klingelschmitt F, Charpentier E, Josse J, Kanagaratnam L, De Champs C, et al. Copper alloy touch surfaces in healthcare facilities: an effective solution to prevent bacterial spreading. *Materials* 2018; 11:2479.
- [86] Noyce JO, Michels H, Keevil CW. Inactivation of influenza A virus on copper versus stainless steel surfaces. *Appl Environ Microbiol* 2007;73:2748–50.
- [87] Sagripanti JL, Routson LB, Lytle CD. Virus inactivation by copper or iron ions alone and in the presence of peroxide. *Appl Environ Microbiol* 1993;59:4374–6.
- [88] Rifkind JM, Shin YA, Heim JM, Eichhorn GL. Cooperative disordering of single-stranded polynucleotides through copper crosslinking. *Biopolymers* 1976;15:1879–902.
- [89] Eichhorn GL, Shin YA. Interaction of metal ions with polynucleotides and related compounds. XII. The relative effect of various metal ions on DNA helicity. *J Am Chem Soc* 1968;90:7323–8.
- [90] Warnes SL, Little ZR, Keevil CW, Colwell R. Human Coronavirus 229E remains infectious on common touch surface materials. *mBio* 2015;10, e01697-15.
- [91] Lu L, Sun RW, Chen R, Hui CK, Ho CM, Luk JM, et al. Silver nanoparticles inhibit hepatitis B virus replication. *Antivir Ther (Lond)* 2008;13:253–62.
- [92] Mori Y, Ono T, Miyahira Y, Nguyen VQ, Matsui T, Ishihara M. Antiviral activity of silver nanoparticle/chitosan composites against H1N1 influenza A virus. *Nanoscale Res Lett* 2013;8:93.
- [93] Kim J, Yeom M, Lee T, Kim H-O, Na W, Kang A, et al. Porous gold nanoparticles for attenuating infectivity of influenza A virus. *J Nanobiotechnol* 2020;18:54.
- [94] Elechiguerra J, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, et al. Interaction of silver nanoparticles with HIV-1. *J Nanobiotechnol* 2005;3:6.
- [95] Minoshima M, Lu Y, Kimura T, Nakano R, Ishiguro H, Kubota Y, et al. Comparison of the antiviral effect of solid-state copper and silver compounds. *J Hazard Mater* 2016;312:1–7.
- [96] Lara HH, Ayala-Nuñez NV, Ixtapan-Turrent L, Rodriguez-Padilla C. Mode of antiviral action of silver nanoparticles against HIV-1. *J Nanobiotechnol* 2010;8:1.
- [97] Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. *Molecules* 2011;16:8894–918.
- [98] Ye S, Shao K, Li Z, Guo N, Zuo Y, Li Q, et al. Antiviral activity of graphene oxide: how sharp edged structure and charge matter. *ACS Appl Mater Interfaces* 2015;7:21571–9.
- [99] Sametband M, Kalt I, Gedanken A, Sarid R. Herpes simplex virus type-1 attachment inhibition by functionalized graphene oxide. *ACS Appl Mater Interfaces* 2014;6:1228–35.
- [100] Pokhrel R, Gc J, Bhattarai N, Chapagain P, Gerstman B. Potential disruption of Ebola virus matrix by graphene nano-sheets. *Biophys J* 2018;114.
- [101] Song Z, Wang X, Zhu G, Nian Q, Zhou H, Yang D, et al. Virus capture and destruction by label-free graphene oxide for detection and disinfection applications. *Small* 2015;11:1171–6.
- [102] Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics* 2019;11:129.
- [103] Hu X, Yang G, Chen S, Luo S, Zhang J. Biomimetic and bioinspired strategies for oral drug delivery. *Biomater Sci* 2020;8:1020–44.
- [104] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci* 2020;12:8.
- [105] To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020;20:565–74.
- [106] Selyutina OY, Polyakov NE, Korneev DV, Zaitsev BN. Influence of glycyrrhizin on permeability and elasticity of cell membrane: perspectives for drugs delivery. *Drug Deliv* 2016;23:858–65.
- [107] Krajnovic T, Maksimovic-Ivanic D, Mijatovic S, Draca D, Wolf K, Edeler D, et al. Drug delivery system for emodin based on mesoporous silica Sba-15. *Nanomaterials (Basel)* 2018;8:322.
- [108] Yang H, Li J, Patel SK, Palmer KE, Devlin B, Rohan LC. Design of poly(lactic-co-glycolic acid) (plga) nanoparticles for vaginal co-delivery of griffithsin and dapivirine and their synergistic effect for HIV prophylaxis. *Pharmaceutics* 2019;11:184.
- [109] Tsai H, Bobek LA. Human salivary histatins: promising anti-fungal therapeutic agents. *Crit Rev Oral Biol Med* 1998;9:480–97.

- [110] Federici Canova D, Pavlov AM, Norling LV, Gobbetti T, Brunelleschi S, Le Fauder P, et al. Alpha-2-macroglobulin loaded microcapsules enhance human leukocyte functions and innate immune response. *J Control Release* 2015;217:284–92.
- [111] Griffiths PC, Cattoz B, Ibrahim MS, Anuonye JC. Probing the interaction of nanoparticles with mucin for drug delivery applications using dynamic light scattering. *Eur J Pharm Biopharm* 2015;97:218–22.
- [112] Raskin MM, Schlachet I, Sosnik A. Mucoadhesive nanogels by ionotropic crosslinking of chitosan-g-oligo(NiPAam) polymeric micelles as novel drug nanocarriers. *Nanomedicine* 2016;11:217–33.
- [113] Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral Res* 2014;110:94–103.
- [114] Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. *Science* 2003;300:1763–7.
- [115] Gaskell EE, Hobbs G, Rostron C, Hutcheon GA. Encapsulation and release of  $\alpha$ -chymotrypsin from poly(glycerol adipate-co- $\omega$ -pentadecalactone) microparticles. *J Microencapsul* 2008;25:187–95.
- [116] Zimmer A, Katzir I, Dekel E, Mayo AE, Alon U. Prediction of multidimensional drug dose responses based on measurements of drug pairs. *Proc Natl Acad Sci U S A* 2016;113:10442–7.
- [117] Beerenwinkel N, Lengauer T, Daumer M, Kaiser R, Walter H, Korn K, et al. Methods for optimizing antiviral combination therapies. *Bioinformatics* 2003;19 Suppl 1:i16–25.
- [118] Ho D. Artificial intelligence in cancer therapy. *Science* 2020;367:982–3.
- [119] Ding X, Chang VHS, Li Y, Li X, Xu H, Ho CM, et al. Harnessing an artificial intelligence platform to dynamically individualize combination therapy for treating colorectal carcinoma in a rat model. *Adv Ther* 2019;3:1900127.
- [120] Zarrinpar A, Lee D-K, Silva A, Datta N, Kee T, Eriksen C, et al. Individualizing liver transplant immunosuppression using a phenotypic personalized medicine platform. *Sci Transl Med* 2016;8:333ra49–ra49.
- [121] Shen Y, Liu T, Chen J, Li X, Liu L, Shen J, et al. Harnessing artificial intelligence to optimize long-term maintenance dosing for antiretroviral-naive adults with HIV-1 infection. *Adv Ther* 2019;3:1900114.
- [122] Pantuck Aj, Lee D-K, Kee T, Wang P, Lakhota S, Silverman Mh, et al. Modulating bet bromodomain inhibitor zen-3694 and enzalutamide combination dosing in a metastatic prostate cancer patient using CURATE.AI, an artificial intelligence platform. *Adv Ther* 2018;1:1800104.
- [123] Abdulla A, Wang B, Qian F, Kee T, Blasiak A, Ong YH, et al. Project iDentif.AI: harnessing artificial intelligence to rapidly optimize combination therapy development for infectious disease intervention. *Adv Ther* 2020;3.
- [124] Ho D. Addressing COVID-19 drug development with artificial intelligence. *Adv Intell Syst* 2020;2:2000070.
- [125] Ke Y-Y, Peng T-T, Yeh T-K, Huang W-Z, Chang S-E, Wu S-H, et al. Artificial intelligence approach fighting COVID-19 with repurposing drugs. *Biomed J* 2020;43:355–62.
- [126] Sattar SA. Microbicides and the environmental control of nosocomial viral infections. *J Hosp Infect* 2004;56:64–9.
- [127] Zhao Q, Wang S, Müller-Steinhagen H. Tailored surface free energy of membrane diffusers to minimize microbial adhesion. *Appl Surf Sci* 2004;230:371–8.
- [128] Agarwalla S, Ellepola K, Costa M, Fechine G, Morin J, Neto AC, et al. Graphene inhibits biofilm formation of pathogenic bacteria and fungi. *Dent Mater* 2019;35:1–11.
- [129] Ebi N, Imazato S, Noiri Y, Ebisu S. Inhibitory effects of resin composite containing bactericide-immobilized filler on plaque accumulation. *Dent Mater* 2001;17:485–91.
- [130] Li F, Weir MD, Fouad AF, Xu HHK. Effect of salivary pellicle on antibacterial activity of novel antibacterial dental adhesives using a dental plaque microcosm biofilm model. *Dent Mater* 2014;30:182–91.