Environmental Virucidal Nanomaterials: An Overview of Efficacy and Mechanisms of Action

Bryan J. Hlavinka [2,3,4], Alan A. Robles Perez [2,3,4], Christopher Taylor [2,4], Alex Wang[2], Princess Nwaege[3], Surendra Maharjan[1,2], Kenneth E. Russell[1,2,4,5], Becky Scott[5], Jerry Gates[6], Seamus A. Curran[1,2,4]

[1]Advanced Manufacturing Institute, University of Houston, 5000 Gulf Freeway, Houston, TX 77023, USA

[2]Department of Physics, University of Houston, Science & Research Building 1, 3507 Cullen Blvd., Houston, TX 77204, USA

[3]Department of Biology & Biochemistry, University of Houston, Science & Research Building 2, 3455 Cullen Blvd., Houston, TX 77004, USA

[4]Curran's Nanophysics Research Group, University of Houston, Science & Research Building 1, 3507 Cullen Blvd., Houston, TX 77204, USA

[5]Barton College, School of Business and Innovation, Hines Hall, Wilson, NC 27893, USA

[6]Gates Lubricants, E Industrial Pkwy New Caney, TX 77357

Abstract

Emerging and re-emerging communicable infectious diseases (CIDs) annually contribute toward global mortality by as much as 20%. CIDs impose an increasingly formidable threat against growing and densifying interconnected population centers. CIDs caused by viral pathogens are particularly concerning as their potential for interhost transmission and contagion are averse to preemptive mitigation. Compounding their toll on human health and life, viral contagion can also severely disrupt and/or cripple a society economically, resulting in catastrophic global fiscal and financial loss, as evidenced by the SARS-CoV-2 pandemic. Contemporary best hygiene practices, social distancing, vaccinations, and controlled herd immunity are critical to thwarting viral transmission and contagion of CIDs. This is particularly important as virally-infected individuals are limited in treatment options to roughly 90 virus-specific US FDA-approved

antiviral drugs, many of which are demonstrably ineffective. While considerable research attention has been focused on the development of antimicrobial materials, the overwhelming majority target prokaryotic pathogens. This critical review aims to provide a comprehensive overview of established and state-of-the-art environmental virucidal nanomaterials (EVNs), with a particular emphasis on rational design, synthesis, developmental challenges, and advancement. EVNs are conformable, biocompatible nanomaterials designed to inactivate, lyse, or disrupt the replication cycle of infectious virions upon contact. EVNs range broadly in their implementation, including application to high touch surfaces, sterilely functional surfaces, filtration media, textiles, personal protective equipment, and biomedical devices in healthcare settings to prevent nosocomial spread. With the expansion of globalization and increasing urban population densities, the need for human-safe preventive measures to manage transmissible infectious pathogens in the environment is imperative. Development, advancement, and implementation of EVNs are anticipated to augment best hygiene practices, social distancing, vaccines, and existing antiviral pharmaceuticals. This was amply shown during the COVID 19 and SARS-CoV-2 outbreak and the use of mask filtration with tight weaves of 300nm [95] to the potential use of combined physical/chemical methodologies used in filtration, particularly HEPA filters [96].

Introduction and Background

Communicable infectious diseases (CIDs) are caused by transmissible pathogenic organisms or agents, which include viruses, bacteria, parasites, protozoa, and fungi. Such CIDs resulted in an estimated 9.2 million deaths worldwide in 2013 and perennially account for about 20% of global mortality [1, 2]. Lower respiratory infections from CIDs result in approximately 3 million fatalities annually, consistently ranking among the top 5 causes of death globally [3-5]. Whereas mortalities due to infectious diseases have seen a downward trend in recent years, stemming

largely from advancements in genomic sequencing, rapid diagnostics, and novel vaccine platforms as well as systemic improvements in hygiene and healthcare, they remain high in low-income and socioeconomically challenged regions [6-11]. While all infectious diseases are dangerous to varying extents. They should be regarded with due caution, emerging zoonotic viruses are particularly concerning for researchers and organizations tasked with anticipating, monitoring, containing, and mitigating such contagions [12,13]. This has been substantiated by several recent high-profile outbreaks, including SARS-CoV-1 (2002-2003) Influenza A (H1N1) (2009-2010), MERS-CoV (2012), Ebola (2013-2016), Zika virus (2015-2016), Measles morbillivirus (2019), and most demonstrably in covid-19 and SARS-CoV-2 (2019-2024), which shut down world trade, devastated populations globally by deaths of at least 7 million people with over 777 million infected [97], some of which continue to persist in circulation today [10, 14-19]. Interestingly, all of the aforementioned pathogens are enveloped single-stranded RNA (ssRNA) viruses of either positive- or negative-sense. Infectious diseases caused by ssRNA viruses and their detrimental toll on global health, business, and economics are adversely compounded by an assortment of other ubiquitous viral contagions, venereal and tropical disease-causing pathogens. Such viral contagions include human coronaviruses (e.g., HCoV-OC43, HCoV-229E, HCov-NL63) and non-enveloped human viruses (e.g., adenoviruses, noroviruses, rotaviruses). An estimated 75% of all emerging infectious diseases are manifestations of RNA viruses that are principally transmitted via mucosal or respiratory routes [20]. As of 2018, there were 158 identified human RNA viruses, where 122 species spanning 11 virus families are enveloped and 36 species spanning 6 virus families are nonenveloped [21]. As the overall rate of global infections and outbreaks continue to rise, the likelihood of an infectious pathogen emerging capable of lethal contagion proportionally increases [22]. It should be noted that while the overall rate of infectious outbreaks has increased globally between 1980-2009 [11], the number of infectious outbreaks per unit population has actually decreased.

Outside of the host, human viral pathogens typically transmit and propagate either directly via contact with static/airborne infectious respiratory droplets, bodily fluids, or excrement as well as indirectly via contact with fomites, vectors, or contaminated commonly-touched objects/surfaces in the environment [23-25]. While exact transmission mechanisms for many virionic species are vaguely understood, transmission of communicable viral respiratory infections are generally believed to involve host inoculation *via* contact/inhalation with sub-5-mm diameter virion-containing respiratory fluid droplets from an infected host [26-29]. Virions are typically a minority component of respiratory fluid droplets from an infected individual, which also include a small percent by weight of proteins, enzymes, commensal prokaryotes colonized in the respiratory tract, biomacromolecules shed from the respiratory tract lining, lung surfactants (e.g., phospholipoproteins), cholesterol, salts, and lactate in an environmentally sensitive aqueous suspension [30-33]. However, because the minimum infective dose (MID) for most viruses responsible for prevalent respiratory or enteric CIDs are considerably low, the concentrations of infectious virions in a respiratory fluid droplet from a virally infected individual are sufficient to infect a suitable host.[34] For instance, doses <1 Median Tissue Culture Infectious Dose ($TCID_{50}$) of Influenza A virus (Type A2), rhinovirus (RV15), adenovirus (Type 4), norovirus (8FIIa), and echovirus (Type 11) have been reported that infected at least 50% of a tested sample population [34-39].

Respiratory fluid droplets emitted by virally infected individuals from sneezing, coughing, and/or talking exist as a distribution of droplet sizes ranging broadly in diameter from 100 nm to 2000 mm [30-31, 40] (COVID 19 to SARS CoV2 50 nm to between 140). Once in the environment, heat and mass exchange immediately occur at the droplet-air interface concomitantly, resulting in rapid change in partial pressure distribution across each droplet or droplet nuclei [30]. Aerosolized sub-1-mm respiratory droplets can remain suspended in air for

up to 8 h, with their motion largely governed by diffusive Brownian motion, Basset forces, Saffman's lift forces, and electrostatic forces [30, 41]. More recently, aerosolized respiratory droplets containing infectious SARS-CoV-2 virions were shown to remain suspended in air for approximately 3 hours [26, 32]. The projectile motion of larger respiratory fluid droplets and aerosols larger than a few micrometers in diameter are principally governed by ballistic forces, gravity, thermophoresis, and other frictional drag forces [11]. Larger respiratory fluid droplets travel shorter distances before depositing on a nearby environmental surface, where virions can potentially remain infectious long after deposition [31]. For example, virions of SARS-CoV-1 and SARS-CoV-2 have been shown to remain infectious for days on non-porous environmental surfaces/fomites like glass, plastics, and stainless steel, which are commonly found in ordinary environmental settings [26, 42]. Dispersion dynamics of respiratory fluid droplets/nuclei from a modeled cough jet are highlighted as particularly dependent on relative humidity [31].

Apart from standard hygiene practices and vaccinations against viruses, rationally-engineered preventative countermeasures designed to mitigate contagion transmission are virtually non-existent in most public settings. Individuals in a designed study touched their face on average 23 times per hour while awake, where 44% of all face touches involved direct contact with a mucosal area/membrane [43]. Inter-host contagion transmission in the environment resulting from contact with infectiously contaminated surfaces/objects could be reduced through implementation of permanent, biocompatible, environmental countermeasures designed to inactivate infectious virions in the environment. These measures are particularly important when dealing with viral pathogens like Influenza A that demonstrate a propensity for genomic recombination (e.g., antigenic shift) and mutagenic shift (e.g., antigenic drift), which are problematic with regards to timely and strain-specific vaccine and antiviral development [44]. Treatment options for the virally infected are notably limited to approved antiviral drugs that

target one or more stages of the viral replication cycle, some of which are notably limited in efficacy [44-46]. The advent of mRNA vaccines in response to SARS-CoV-2, have revolutionized how immunologists have approached the prevention of some CIDs [93]. These mRNA vaccines work through the stimulation of ribosomal translation of a piece of harmless viral mRNA into a polypeptide sequence, usually identical to a membrane protein of the virus, to be recognized as an antigen, stimulating an adaptive immune response [93]. Outside of the use of mRNA vaccines which are highly specific to particular strains of a virus, existing approved antivirals are restricted in variety to a handful of nucleoside analogues, peptidomimetics, other immune response-stimulating proteins, and oligonucleotides that are all also virus-specific and therefore suffer the same lack of efficacy for broad-spectrum application [47-48]. There are currently over 90 virus-specific antiviral drugs approved by the U.S. Food and Drug Administration (FDA) for treating CIDs caused by human immunodeficiency virus type-1 (HIV-1), influenza viruses, herpes simplex viruses (HSV-1/HSV-2), hepatitis B and C, varicella-zoster viruses (VZVs), cytomegalovirus (CMV), human papilloma viruses (HPVs), and respiratory syncytial viruses (RSVs) [49-51]. Despite active research and increasing necessity, no effective human-safe broad-spectrum antiviral currently exists [47, 52].

Microbial infections and their associated CIDs remain a global challenge. In the U.S. alone, approximately 23,000 individuals succumb to antibiotic-resistant bacterial infections out of about 2 million yearly reported cases [53]. The bulk of these antibiotic-resistant bacterial infections occur in a healthcare facility/setting. Accordingly, a large segment of existing research and literature on antipathogenic/microbicidal materials disproportionately focus on broad-spectrum bactericides for antimicrobial surfaces [54-56], disinfectants [57-58], antiseptics [59], bacteriostatic/virustatic agents [60], and antiviral pharmaceuticals [47,52]. While the work is necessary and valid, the literature is devoid of a comprehensive critical review on the state-of-

the-art, rational-design, synthesis, applications, and advancement of environmental virucidal nanomaterials (EVNs) from a materials science perspective. EVNs are human-safe (i.e., non-cytotoxic/biocompatible) virucidal nanomaterials permanently immobilized on commonly touched/handled surfaces, objects, and devices in designated public or healthcare settings. Without disrupting functionality, EVNs are molecularly engineered to inactivate infectious pathogens upon contact via one or more possible mechanisms, including virion immobilization and concomitant fluidization of the phospholipid membranes of enveloped viruses [61-62]. By mitigating environmental transmission of infectious virions/pathogens, EVNs are a complementary countermeasure to existing best hygiene practices, vaccinations, and antiviral pharmaceuticals.

EVNs are generally classifiable by active nanomaterial composition, which include polyionic compounds/macromolecules [23, 44, 51, 56, 63-69], N-halamines [70], metal complexes [71, 94], metal nanoparticles [52, 72, 81], metal-oxide nanoparticles [82-83], biomacromolecules [84], reactive oxygen species (ROSs) [85-86], and phytochemical compounds [87]. Preventative antimicrobial applications of EVNs have been used in facemasks, surgical facemasks [88], biomedical devices [54], personal protective equipment (PPE), fabrics/textiles [89-91], filtration media, air filters, and a variety of frequently-touched contact surfaces in domestic, healthcare, and high-traffic public settings (e.g., metals, plastics, fabrics, composites, or natural materials). This critical review considers rational design, synthesis, and application aspects of existing and emerging EVNs, with emphasis on materials science and developmental challenges, concluding with a detailed discussion on the advancement and outlook of EVNs.

Rational Design, Synthesis, and Virucidal Activity

Polyionic Compounds

Quaternary Ammonium Compounds

Quaternary ammonium compounds (QACs or quats) are well-researched and comprise the bulk of existing antimicrobial detergents/surfactants, disinfectants, and surface-sanitizing compounds. These molecules exist as permanently positively charged ions independent of the pH of their environment with a general formula of R_4N^+ and tetrahedral geometry around the nitrogen atom. These molecules are often ionically paired with halogen anions to form a salt—however, these are differentiated from N-Halamines structurally and mechanistically for their antimicrobial functionality.

The QAC cation's positive charge is definitive to its antimicrobial efficacy. Microbial cell membranes of most bacteria and enveloped viruses are negatively charged due to the presence of phospholipids, lipoteichoic acids (gram-positive bacteria), and lipopolysaccharides (gram-negative bacteria). The electrostatic attraction of the cation to the surfaces of these membranes causes adhesion and adsorption. Once adsorbed, the hydrophobic organic chains attached to the nitrogen then insert into the lipid bilayer of the microbe. The ionic interaction between the cationic QAC and the anionic membrane stabilize the interaction while the organic chains insert and disturb the packing of the membrane lipids, disrupting the electrochemical gradients and creating pores, allowing the spilling of the contents of the microbial membrane, including nucleic acids, effectively killing the microbe. Anti-microbial efficacy can also be correlated to the length of the R-chains with short chains (8-10 carbon length) having moderate anti-microbial effectiveness/low cytotoxicity, and longer chains (greater than 18 carbons) having very high anti-microbial effectiveness/high cytotoxicity.

This interaction occurs in gram-positive bacteria, some gram-negative bacteria, as well as enveloped viruses. In the case of enveloped viruses, the binding of the lipid bilayer of the envelope prevents attachment and fusion with host cells. There is limited cationic activity with non-enveloped viruses or bacterial spores as neither has a lipid surface membrane with which to interact, however, if these microbes are airborne and aerosolized in polar water-based media for their transmission, they will electrostatically adhere to the QAC, and be held and desiccated over the lifespan of the virus (several hours to days).

QACs are not microbe-specific in their function and pose risk to other living cells due to interactions with their phospholipid bilayer, however, these risks can be mitigated by working within different safe use scenarios--using low concentrations of the compounds, limiting exposure time, and specifically engineering these compounds to be used safely with biomedical or environmental applications. One means of improving the biocompatibility of QACs is by immobilizing the active compound into polymeric structures. Quaternary Ammonium Macromolecules (QAMs) are structures of QACs linked together covalently through their sidechains or an appropriate backbone structure. The advantages of QAMs as compared to QACs lies in their structural stability. Their immobilization limits QAC diffusion into the environment, even when coming into direct contact with cells and tissues, QAMs also tend to last longer than small molecule QACs, as they are more resistant to solubilization and deactivation.

Quaternary Phosphonium Macromolecules

Similar in functionality and structure to QAMs, Quaternary Phosphonium Macromolecules (QPMs) replace the central nitrogen atom with phosphorous and have a general structure of R_4P^+. Advantages of QPMs over QAMs include their lipophilicity, chemical/thermal stability and antibacterial potential due to their enhanced electrostatic and hydrophobic interactions,

especially against gram-negative bacteria which have more robust outer membranes. However, they can be less biocompatible if not properly optimized.

Metallic Complexes

Copper salts (CuX_2) are agents that demonstrate inactivation, and virucidal properties against Herpes viruses. These effects are achieved by the formation of Copper (II) ions that can attack DNA and are likely to attack RNA as well. These salts are placed in solution with different compounds like ascorbic acid, peroxides, and dimethyl sulfoxide which allow these copper ions to target the viruses.

Metal Oxides containing Aluminum and Titanium prove to be very efficient virucidal agents- these properties can be enhanced through a halogen adduct of the metal oxides in question. Similar to other metallic nanoparticles, the exact mechanism by which these compounds work is not entirely understood, however there are two main hypotheses. One possible mechanism can be attributed to these molecules' physical trauma to the virus, killing it by breaking its outer layer. Overall, these compounds show promise as virucides as they directly attack viruses, however, there is more insight needed on their exact mechanism, along with research into specificity.

ROS-Evolving Compounds

Reactive Oxide species function through photosensitization, where an irradiated compound excites Triplet O_2 into Singlet O_2. This excited state oxygen is more reactive than its ground state making it prone to oxidizing the outer proteins of both enveloped and non-enveloped viruses. After the protein outer layer is oxidized, the outer layer of the virus' inner RNA and other functional proteins leak out, leaving it inert and incapable of infection and/or propagation. The mechanism is notably difference from QACs, QAMs, and QPMs that directly attack the

phospholipid bilayer as the ROSs attack the proteins attached to the bilayer which then rupture the entire virus.

N-Halamines

N-Halamines, with a general structure of R-N-X, are nitrogen containing compounds that differ in their chemical structure from QACs and QAMs in that their central nitrogen atom is covalently rather than ionically bonded to a halogen. N-Halamines can exist in amine, amide or imide form, which informs their virucidal mechanism. While QACs and QAMs remain permanently positively charged even after activated removal of the ionic halide as described above, N-Halamines work through oxidative halogen transfer. When N-Halamines encounter viral envelope, capsid, or nucleic acid protein components which contain nucleophilic functional groups, the bonded halogen is transferred to the reactive site via electrophilic halogenation causing oxidative damage to these viral proteins, rendering the virus inactive. The non-specific oxidation makes N-Halamines effective against enveloped and non-enveloped viruses as well as other antibiotic-resistant microbes. These nanoparticles can be engineered to retain high surface area through surface tethering in coatings and application to fibers and filtration systems and are regenerable by reforming their N-X bonds by reintroducing halogens to the spent material, i.e. using a dilute bleach wash.

Biomacromolecules

Biomacromolecules, a broad category of biosynthetic organic compounds composed of proteins, polysaccharides, lipids and nucleic acid-based materials, can be used as components of EVNs due to their high levels of biocompatibility, biodegradability, and tunable functionality. Biomacromolecules have several mechanistic strategies of antiviral action including virus binding inhibition, disruption of viral envelopes or capsids, ROS generation when coupled with metals, and medicinal use as drug delivery vehicles for encapsulated antivirals.

Phytochemicals

Phytochemicals are secondary metabolite compounds derived from plants with broad-spectrum antiviral activity, high levels of biodegradability and low cytotoxicity. Phytochemicals, when used in nanoparticle systems have similar mechanisms of virucidal action to other EVN species—blocking viral attachment and entry by interfering with surface proteins, prevention of binding to host receptors, disruption of viral envelopes and ROS generation. Phytochemical nanoparticles have generally low cytotoxicity but can be toxic to cell membranes at high concentrations and can induce oxidative damage due to ROS activity. Phytochemicals are highly biocompatible as they can be derived from dietary sources, are biodegradable into nontoxic metabolites, and exhibit low immunogenicity; however, carrier selection affects compatibility.

Future Outlook and Advancement

Prokaryotic microbes are markedly susceptible to even modest concentrations of active cationic compounds/substances provided sufficient interfacial contact [84]. While in certain cases, bactericidal efficacy may be interpolated to virucidal efficacy, they are generally not one-to-one [67, 92]. This stems from factors including dimensional disparity, variations in surface charge density, steric hindrance, desiccation and mechanisms of action [56, 61, 66, 92]. As a corollary, efficacious and rationally designed broad-spectrum virucides are anticipated to exhibit excellent bactericidal properties. However, in consideration of the vast repertoire of existing bactericidal and antimicrobial materials, promising candidates should certainly be explored for virucidal efficacy. Similarly, in developing novel ENVs, virucidal mechanisms-of-action can be extrapolated from existing antiviral pharmaceuticals designed to work in vivo to more permanent virucidal nanomaterials in the environment. Criteria for governmental approval of ENVs varies and is largely determined by country-specific regulatory bodies like the FDA and U.S.

Environmental Protection Agency (EPA) that impose necessary developmental hurdles towards safe, effective, environmentally conscious materials for human contact.

Acknowledgements

A very special thank you to Integricote LLC and the Advanced Manufacturing Institute at the University of Houston.

References

[1] Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet (**2015**), 385 (9963), 117-171, DOI: 10.1016/S0140-6736(14)61682-2.

[2] Lozano, R.; Naghavi, M.; Foreman, K.; Lim, S.; Shibuya, K.; Aboyans, V.; Abraham, J.; Adair, T.; Aggarwal, R.; Ahn, S. Y. (**2012**) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet, 380 (9859), 2095-2128.

[3] Heron, M. P. (**2017**). Deaths: leading causes for 2015.

[4] Heron, M. P. (**2016**). Deaths: leading causes for 2013.

[5] Naghavi, M.; Abajobir, A. A.; Abbafati, C.; Abbas, K. M.; Abd-Allah, F.; Abera, S. F.; Aboyans, V.; Adetokunboh, O.; Afshin, A.; Agrawal, A. (**2017**).Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet, 390 (10100), 1151-1210.

[6] Adams, N. L.; Rose, T. C.; Hawker, J.; Violato, M.; O'Brien, S. J.; Barr, B.; Howard, V. J.; Whitehead, M.; Harris, R.; Taylor-Robinson, D. C. (**2018**). Relationship between socioeconomic status and gastrointestinal infections in developed countries: A systematic review and meta-analysis. PLoS One, 13 (1).

[7] Coffey, P. M.; Ralph, A. P.; Krause, V. L. (**2018**). The role of social determinants of health in the risk and prevention of group A streptococcal infection, acute rheumatic fever and rheumatic heart disease: a systematic review. PLoS neglected tropical diseases, 12 (6), e0006577.

[8] Houweling, T. A.; Karim-Kos, H. E.; Kulik, M. C.; Stolk, W. A.; Haagsma, J. A.; Lenk, E. J.; Richardus, J. H.; de Vlas, S. J. (**2016**). Socioeconomic inequalities in neglected tropical diseases: a systematic review. PLoS neglected tropical diseases, 10 (5).

[9] Plotkin, S. A. (**2005**). Vaccines: past, present and future. Nature medicine, 11 (4), S5-S11.

[10] Morens, D. M.; Fauci, A. S. (**2013**). Emerging infectious diseases: threats to human health and global stability. PLoS Pathog, 9 (7), e1003467.

[11] Christiansen, J. (**2018**). Global Infections by the Numbers. *Scientific American*, pp. 48-49.

[12] Luo, G., & Gao, S.-J. (**2020**). Global health concerns stirred by emerging viral infections. *Journal of Medical Virology*, *92*(4), 399-400. https://doi.org/10.1002/jmv.25683.

[13] Marston, H. D., Folkers, G. K., Morens, D. M., & Fauci, A. S. (**2014**). Emerging Viral Diseases: Confronting Threats with New Technologies. *Science Translational Medicine*, *6*(253), 253ps10. https://doi.org/10.1126/scitranslmed.3009872

[14] Ghernaout, D., & Elboughdiri, N. (**2020**). Environmental Engineering for Stopping Viruses Pandemics. *Open Access Library Journal*, *7*(4), 1-17.

[15] Gatherer, D. (**2009**). The 2009 H1N1 influenza outbreak in its historical context. *Journal of Clinical Virology*, *45*(3), 174-178.

[16] Musso, D., & Gubler, D. J. (**2016**). Zika virus. *Clinical Microbiology Reviews*, *29*(3), 487-524.

[17] Li, S.-L., Bjørnstad, O. N., Ferrari, M. J., Mummah, R., Runge, M. C., Fonnesbeck, C. J., Tildesley, M. J., Probert, W. J., & Shea, K. (**2017**). Essential information: Uncertainty and optimal control of Ebola outbreaks. *Proceedings of the National Academy of Sciences*, *114*(22), 5659-5664.

[18] Sundaram, M. E., Guterman, L. B., & Omer, S. B. (**2019**). The true cost of measles outbreaks during the postelimination era. *JAMA*, *321*(12), 1155-1156.

[19] Cauchemez, S., Nouvellet, P., Cori, A., Jombart, T., Garske, T., Clapham, H., Moore, S., Mills, H. L., Salje, H., & Collins, C. (**2016**). Unraveling the drivers of MERS-CoV transmission. *Proceedings of the National Academy of Sciences*, *113*(32), 9081-9086.

[20] Zambon, M. (**2014**). Influenza and other emerging respiratory viruses. *Medicine*, *42*(1), 45-51.

[21] Woolhouse, M. E., & Adair, K. (**2013**). The diversity of human RNA viruses. *Future Virology*, *8*(2), 159-171.

[22] Smith, K. F., Goldberg, M., Rosenthal, S., Carlson, L., Chen, J., Chen, C., & Ramachandran, S. (**2014**). Global rise in human infectious disease outbreaks. *Journal of The Royal Society Interface*, *11*(101), 20140950. https://doi.org/10.1098/rsif.2014.0950.

[23] Wong, S. Y., Li, Q., Veselinovic, J., Kim, B.-S., Klibanov, A. M., & Hammond, P. T. (**2010**). Bactericidal and virucidal ultrathin films assembled layer by layer from polycationic N-alkylated polyethylenimines and polyanions. *Biomaterials*, *31*(14), 4079-4087. https://doi.org/10.1016/j.biomaterials.2010.01.119.

[24] Wigginton, K. R., & Boehm, A. B. (**2020**). Environmental engineers and scientists have important roles to play in stemming outbreaks and pandemics caused by enveloped viruses. ACS Publications.

[25] Yan, J., Grantham, M., Pantelic, J., de Mesquita, P. J. B., Albert, B., Liu, F., Ehrman, S., Milton, D. K., & Consortium, E. (**2018**). Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. *Proceedings of the National Academy of Sciences*, *115*(5), 1081-1086.

[26] Van Doremalen, N., Bushmaker, T., Morris, D. H., Holbrook, M. G., Gamble, A., Williamson, B. N., Tamin, A., Harcourt, J. L., Thornburg, N. J., & Gerber, S. I. (**2020**). Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *New England Journal of Medicine*, *382*(16), 1564-1567.

[27] Wang, J., & Du, G. (**2020**). COVID-19 may transmit through aerosol. *Irish Journal of Medical Science (1971-)*, 1-2.

[28] Wells, W. F. (**1955**). Airborne Contagion and Air Hygiene. An Ecological Study of Droplet Infections.

[29] Udugama, B., Kadhiresan, P., Kozlowski, H. N., Malekjahani, A., Osborne, M., Li, V. Y. C., Chen, H., Mubareka, S., Gubbay, J. B., & Chan, W. C. W. (**2020**). Diagnosing COVID-19: The Disease and Tools for Detection. *ACS Nano*, *14*(4), 3822-3835. https://doi.org/10.1021/acsnano.0c02624.

[30] Liu, L., Wei, J., Li, Y., & Ooi, A. (**2017**). Evaporation and dispersion of respiratory droplets from coughing. *Indoor Air*, *27*(1), 179-190. https://doi.org/10.1111/ina.12297.

[31] Vejerano, E. P., & Marr, L. C. (**2018**). Physico-chemical characteristics of evaporating respiratory fluid droplets. *Journal of The Royal Society Interface*, *15*(139), 20170939.

[32] Huang, H., Fan, C., Li, M., Nie, H.-L., Wang, F.-B., Wang, H., Wang, R., Xia, J., Zheng, X., & Zuo, X. (**2020**). Covid-19: A call for physical scientists and engineers. *ACS Nano*, *14*(4), 3747-3754.

[33] Lin, K., & Marr, L. C. (**2019**). Humidity-dependent decay of viruses, but not bacteria, in aerosols and droplets follows disinfection kinetics. *Environmental Science & Technology*, *54*(2), 1024-1032.

[34] Yezli, S., & Otter, J. A. (**2011**). Minimum Infective Dose of the Major Human Respiratory and Enteric Viruses Transmitted Through Food and the Environment. *Food and Environmental Virology*, *3*(1), 1-30. https://doi.org/10.1007/s12560-011-9056-7.

[35] Alford, R. H., Kasel, J. A., Gerone, P. J., & Knight, V. (**1966**). Human influenza resulting from aerosol inhalation. *Proceedings of the Society for Experimental Biology and Medicine*, *122*(3), 800-804.

[36] Couch, R. B., Cate, T. R., Douglas, R. G., Jr., Gerone, P. J., & Knight, V. (**1966**). Effect of route of inoculation on experimental respiratory viral disease in volunteers and evidence for airborne transmission. *Bacteriological Reviews*, *30*(3), 517.

[37] Couch, R., Knight, V., Douglas, R. G., Jr., Black, S., & Hamory, B. (**1969**). The minimal infectious dose of adenovirus type 4; the case for natural transmission by viral aerosol. *Transactions of the American Clinical and Climatological Association*, *80*, 205.

[38] Teunis, P. F., Moe, C. L., Liu, P., Miller, S. E., Lindesmith, L., Baric, R. S., Le Pendu, J., & Calderon, R. L. (**2008**). Norwalk virus: how infectious is it? *Journal of Medical Virology*, *80*(8), 1468-1476.

[39] Saliba, G. S., Franklin, S. L., & Jackson, G. G. (**1968**). ECHO-11 as a respiratory virus: quantitation of infection in man. *The Journal of Clinical Investigation*, *47*(6), 1303-1313.

[40] Konda, A., Prakash, A., Moss, G. A., Schmoldt, M., Grant, G. D., & Guha, S. (**2020**). Aerosol filtration efficiency of common fabrics used in respiratory cloth masks. *ACS Nano*, *14*(5), 6339-6347.

[41] Morawska, L. (**2005**). Droplet fate in indoor environments, or can we prevent the spread of infection? In *Proceedings of Indoor Air 2005: The 10th International Conference on Indoor Air Quality and Climate* (pp. 9-23). Springer.

[42] Siyang, L. J. B. Z. L., Wenfu, Z. D. L. Y. Z., & Li, J. (**2003**). Survival study of SARS virus in vitro. *Chinese Journal of Disinfection*, *2*.

[43] Kwok, Y. L. A., Gralton, J., & McLaws, M.-L. (**2015**). Face touching: A frequent habit that has implications for hand hygiene. *American Journal of Infection Control*, *43*(2), 112-114. https://doi.org/10.1016/j.ajic.2014.10.015.

[44] Hsu, B. B., Wong, S. Y., Hammond, P. T., Chen, J., & Klibanov, A. M. (**2011**). Mechanism of inactivation of influenza viruses by immobilized hydrophobic polycations. *Proceedings of the National Academy of Sciences*, *108*(1), 61-66.

[45] Weinstock, D. M., & Zuccotti, G. (**2009**). The evolution of influenza resistance and treatment. *JAMA*, *301*(10), 1066-1069.

[46] Boone, S. A., & Gerba, C. P. (**2007**). Significance of Fomites in the Spread of Respiratory and Enteric Viral Disease. *Applied and Environmental Microbiology*, *73*(6), 1687-1696. https://doi.org/10.1128/aem.02051-06.

[47] Cagno, V., Andreozzi, P., D'Alicarnasso, M., Jacob Silva, P., Mueller, M., Galloux, M., Le Goffic, R., Jones, S. T., Vallino, M., Hodek, J., Weber, J., Sen, S., Janeček, E.-R., Bekdemir, A., Sanavio, B., Martinelli, C., Donalisio, M., Rameix Welti, M.-A., Eleouet, J.-F., Han, Y., Kaiser, L., Vukovic, L., Tapparel, C., Král, P., Krol, S., Lembo, D., & Stellacci, F. (**2018**). Broad-spectrum non-toxic antiviral nanoparticles with a virucidal inhibition mechanism. *Nature Materials*, *17*(2), 195-203. https://doi.org/10.1038/nmat5053.

[48] De Clercq, E., & Li, G. (**2016**). Approved antiviral drugs over the past 50 years. *Clinical Microbiology Reviews*, *29*(3), 695-747.

[49] Afdhal, N., Zeuzem, S., Kwo, P., Chojkier, M., Gitlin, N., Puoti, M., Romero-Gomez, M., Zarski, J.-P., Agarwal, K., Buggisch, P., Foster, G. R., Bräu, N., Buti, M., Jacobson, I. M., Subramanian, G. M., Ding, X., Mo, H., Yang, J. C., Pang, P. S., Symonds, W. T., McHutchison, J. G., Muir, A. J., Mangia, A., & Marcellin, P. (**2014**). Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. *New England Journal of Medicine*, *370*(20), 1889-1898. https://doi.org/10.1056/NEJMoa1402454.

[50] Feld, J. J., Jacobson, I. M., Hézode, C., Asselah, T., Ruane, P. J., Gruener, N., Abergel, A., Mangia, A., Lai, C.-L., Chan, H. L. Y., Mazzotta, F., Moreno, C., Yoshida, E., Shafran, S. D., Towner, W. J., Tran, T. T., McNally, J., Osinusi, A., Svarovskaia, E., Zhu, Y., Brainard, D. M., McHutchison, J. G., Agarwal, K., & Zeuzem, S. (**2015**). Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *New England Journal of Medicine*, *373*(27), 2599-2607. https://doi.org/10.1056/NEJMoa1512610.

[51] Schandock, F., Riber, C. F., Röcker, A., Müller, J. A., Harms, M., Gajda, P., Zuwala, K., Andersen, A. H. F., Løvschall, K. B., Tolstrup, M., Kreppel, F., Münch, J., & Zelikin, A. N. (**2017**). Macromolecular Antiviral Agents against Zika, Ebola, SARS, and Other Pathogenic Viruses. *Advanced Healthcare Materials*, *6*(23), 1700748. https://doi.org/10.1002/adhm.201700748.

[52] Chen, L., & Liang, J. (**2020**). An overview of functional nanoparticles as novel emerging antiviral therapeutic agents. *Materials Science and Engineering: C*, 110924.

[53] Talbot, G. H., Bradley, J., Edwards, J. E., Jr., Gilbert, D., Scheld, M., & Bartlett, J. G. (**2006**). Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *42*(5), 657-668.

[54] Jiao, Y., Niu, L.-n., Ma, S., Li, J., Tay, F. R., & Chen, J.-h. (**2017**). Quaternary ammonium-based biomedical materials: State-of-the-art, toxicological aspects and antimicrobial resistance. *Progress in Polymer Science*, *71*, 53-90. https://doi.org/10.1016/j.progpolymsci.2017.03.001.

[55] Arora, A., & Mishra, A. (**2018**). Antibacterial Polymers—A Mini Review. *Materials Today: Proceedings*, *5*(9, Part 1), 17156-17161. https://doi.org/10.1016/j.matpr.2018.04.124.

[56] Timofeeva, L., & Kleshcheva, N. (**2011**). Antimicrobial polymers: mechanism of action, factors of activity, and applications. *Applied Microbiology and Biotechnology*, *89*(3), 475-492.

[57] Bridier, A., Briandet, R., Thomas, V., & Dubois-Brissonnet, F. (**2011**). Resistance of bacterial biofilms to disinfectants: a review. *Biofouling*, *27*(9), 1017-1032.

[58] Kim, B., Anderson, J., Mueller, S., Gaines, W., & Kendall, A. (**2002**). Literature review—efficacy of various disinfectants against Legionella in water systems. *Water Research*, *36*(18), 4433-4444.

[59] McDonnell, G., & Russell, A. D. (**1999**). Antiseptics and disinfectants: activity, action, and resistance. *Clinical Microbiology Reviews*, *12*(1), 147-179.

[60] Gulve, N., Kimmerling, K., Johnston, A. D., Krueger, G. R., Ablashi, D. V., & Prusty, B. K. (**2016**). Anti-herpesviral effects of a novel broad range anti-microbial quaternary ammonium silane, K21. *Antiviral Research*, *131*, 166-173.

[61] Kabanov, V., & Yaroslavov, A. (**2002**). What happens to negatively charged lipid vesicles upon interacting with polycation species? *Journal of Controlled Release*, *78*(1-3), 267-271.

[62] Ikeda, T., Lee, B., Yamaguchi, H., & Tazuke, S. (**1990**). Time-resolved fluorescence anisotropy studies on the interaction of biologically active polycations with phospholipid membranes. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1021*(1), 56-62.

[63] Botequim, D., Maia, J., Lino, M., Lopes, L., Simoes, P., Ilharco, L., & Ferreira, L. (**2012**). Nanoparticles and surfaces presenting antifungal, antibacterial and antiviral properties. *Langmuir*, *28*(20), 7646-7656.

[64] Haldar, J., An, D., de Cienfuegos, L. A., Chen, J., & Klibanov, A. M. (**2006**). Polymeric coatings that inactivate both influenza virus and pathogenic bacteria. *Proceedings of the National Academy of Sciences*, *103*(47), 17667-17671.

[65] Haldar, J., Chen, J., Tumpey, T. M., Gubareva, L. V., & Klibanov, A. M. (**2008**). Hydrophobic polycationic coatings inactivate wild-type and zanamivir- and/or oseltamivir-resistant human and avian influenza viruses. *Biotechnology Letters*, *30*(3), 475-479. https://doi.org/10.1007/s10529-007-9565-5.

[66] Haldar, J., Weight, A. K., & Klibanov, A. M. (**2007**). Preparation, application and testing of permanent antibacterial and antiviral coatings. *Nature Protocols*, *2*(10), 2412-2417. https://doi.org/10.1038/nprot.2007.353.

[67] Liu, H., Elkin, I., Chen, J., & Klibanov, A. M. (**2015**). Why do Some Immobilized N-Alkylated Polyethylenimines Far Surpass Others in Inactivating Influenza Viruses? *Biomacromolecules*, *16*(1), 351-356. https://doi.org/10.1021/bm5015427.

[68] Sinclair, T. R., Patil, A., Raza, B. G., Reurink, D., van den Hengel, S. K., Rutjes, S. A., de Roda Husman, A. M., Roesink, H. D. W., & de Vos, W. M. (**2019**). Cationically modified membranes using covalent layer-by-layer assembly for antiviral applications in drinking water. *Journal of Membrane Science*, *570-571*, 494-503. https://doi.org/10.1016/j.memsci.2018.10.081.

[69] Weber, T. P., & Stilianakis, N. I. (**2008**). Inactivation of influenza A viruses in the environment and modes of transmission: a critical review. *Journal of Infection*, *57*(5), 361-373.

[70] Hui, F., & Debiemme-Chouvy, C. (**2013**). Antimicrobial N-Halamine Polymers and Coatings: A Review of Their Synthesis, Characterization, and Applications. *Biomacromolecules*, *14*(3), 585-601. https://doi.org/10.1021/bm301980q.

[71] Sagripanti, J.-L., Routson, L. B., Bonifacino, A. C., & Lytle, C. D. (**1997**). Mechanism of copper-mediated inactivation of herpes simplex virus. *Antimicrobial Agents and Chemotherapy*, *41*(4), 812-817.

[72] Broglie, J. J., Alston, B., Yang, C., Ma, L., Adcock, A. F., Chen, W., & Yang, L. (**2015**). Antiviral Activity of Gold/Copper Sulfide Core/Shell Nanoparticles against Human Norovirus Virus-Like Particles. *PLoS One*, *10*(10), e0141050. https://doi.org/10.1371/journal.pone.0141050.

[73] Castro-Mayorga, J. L., Randazzo, W., Fabra, M. J., Lagaron, J. M., Aznar, R., & Sánchez, G. (**2017**). Antiviral properties of silver nanoparticles against norovirus surrogates and their efficacy in coated polyhydroxyalkanoates systems. *LWT - Food Science and Technology*, *79*, 503-510. https://doi.org/10.1016/j.lwt.2017.01.065.

[74] Hajipour, M. J., Fromm, K. M., Ashkarran, A. A., de Aberasturi, D. J., de Larramendi, I. R., Rojo, T., Serpooshan, V., Parak, W. J., & Mahmoudi, M. (**2012**). Antibacterial properties of nanoparticles. *Trends in Biotechnology*, *30*(10), 499-511.

[75] Lara, H. H., Ayala-Nuñez, N. V., Ixtepan-Turrent, L., & Rodriguez-Padilla, C. (**2010**). Mode of antiviral action of silver nanoparticles against HIV-1. *Journal of Nanobiotechnology*, *8*(1), 1. https://doi.org/10.1186/1477-3155-8-1.

[76] Lara, H. H., Garza-Treviño, E. N., Ixtepan-Turrent, L., & Singh, D. K. (**2011**). Silver nanoparticles are broad-spectrum bactericidal and virucidal compounds. *Journal of Nanobiotechnology*, *9*(1), 30. https://doi.org/10.1186/1477-3155-9-30.

[77] Mori, Y., Ono, T., Miyahira, Y., Nguyen, V. Q., Matsui, T., & Ishihara, M. (**2013**). Antiviral activity of silver nanoparticle/chitosan composites against H1N1 influenza A virus. *Nanoscale Research Letters*, *8*(1), 93. https://doi.org/10.1186/1556-276X-8-93.

[78] Pfaff, F., Glück, B., Hoyer, T., Rohländer, D., Sauerbrei, A., & Zell, R. (**2019**). Tungsten carbide nanoparticles show a broad spectrum virucidal activity against enveloped and nonenveloped model viruses using a guideline-standardized in vitro test. *Letters in Applied Microbiology*, *69*(4), 302-309. https://doi.org/10.1111/lam.13208.

[79] Rai, M., Deshmukh, S. D., Ingle, A. P., Gupta, I. R., Galdiero, M., & Galdiero, S. (**2016**). Metal nanoparticles: The protective nanoshield against virus infection. *Critical Reviews in Microbiology*, *42*(1), 46-56. https://doi.org/10.3109/1040841X.2013.879849.

[80] Richter, A. P., Brown, J. S., Bharti, B., Wang, A., Gangwal, S., Houck, K., Hubal, E. A. C., Paunov, V. N., Stoyanov, S. D., & Velev, O. D. (**2015**). An environmentally benign antimicrobial nanoparticle based on a silver-infused lignin core. *Nature Nanotechnology*, *10*(9), 817.

[81] Yang, X. X., Li, C. M., & Huang, C. Z. (**2016**). Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. *Nanoscale*, *8*(5), 3040-3048.

[82] Häggström, J., Balyozova, D., Klabunde, K. J., & Marchin, G. (**2010**). Virucidal properties of metal oxide nanoparticles and their halogen adducts. *Nanoscale*, *2*(4), 529-534.

[83] Mazurkova, N., Spitsyna, Y. E., Shikina, N., Ismagilov, Z., Zagrebel'nyi, S., & Ryabchikova, E. (**2010**). Interaction of titanium dioxide nanoparticles with influenza virus. *Nanotechnologies in Russia*, *5*(5-6), 417-420.

[84] Ferreira, L., & Zumbuehl, A. (**2009**). Non-leaching surfaces capable of killing microorganisms on contact. *Journal of Materials Chemistry*, *19*(42), 7796-7806.

[85] Lhotáková, Y.; Plíštil, L.; Morávková, A.; Kubát, P.; Lang, K.; Forstová, J.; Mosinger, J. (**2012**). Virucidal nanofiber textiles based on photosensitized production of singlet oxygen. PLoS One, 7 (11), e49226-e49226, DOI: 10.1371/journal.pone.0049226.

[86] Li, Y.; Zhang, C.; Shuai, D.; Naraginti, S.; Wang, D.; Zhang, W. (**2016**). Visible-light-driven photocatalytic inactivation of MS2 by metal-free g-C3N4: Virucidal performance and mechanism. Water Research, 106, 249-258, DOI: https://doi.org/10.1016/j.watres.2016.10.009.

[87] Naithani, R., Mehta, R. G., Shukla, D., Chandersekera, S. N., & Moriarty, R. M. (**2010**). Antiviral Activity of Phytochemicals: A Current Perspective. In R. R. Watson, S. Zibadi, & V. R. Preedy (Eds.), *Dietary Components and Immune Function* (pp. 421-468). Humana Press.

[88] Junter, G.-A.; Lebrun, L. (**2017**). Cellulose-based virus-retentive filters: a review. Rev Environ Sci Biotechnol, 16 (3), 455-489, DOI: 10.1007/s11157-017-9434-1.

[89] Simoncic, B.; Tomsic, B. (**2010**). Structures of novel antimicrobial agents for textiles-a review. Textile Research Journal, 80 (16), 1721-1737.

[90] Varan, N. Y., & Eryuruk, S. (**2018**). The Effects of Quat-Silane Antimicrobials on the Physical and Mechanical Properties of Cotton and Cotton/Elastane Fabrics Used for Clothing. *IOP Conference Series: Materials Science and Engineering*, p. 012004. IOP Publishing.

[91] Zanoaga, M.; Tanasa, F. (**2014**). Antimicrobial reagents as functional finishing for textiles intended for biomedical applications. I. Synthetic organic compounds. Chemistry Journal of Moldova, 9 (1), 14-32.

[92] Sommer, J.; Fister, S.; Gundolf, T.; Bromberger, B.; Mester, P.-J.; Witte, A. K.; Kalb, R.; Rossmanith, P. (**2018**). Virucidal or Not Virucidal? That Is the Question-Predictability of Ionic Liquid's Virucidal Potential in Biological Test Systems. Int J Mol Sci, 19 (3), 790, DOI: 10.3390/ijms19030790.

[93] Gote, V., Bolla, P. K., Kommineni, N., Butreddy, A., Nukala, P. K., Palakurthi, S. S., & Khan, W. (**2023**). A Comprehensive Review of mRNA Vaccines. International journal of molecular sciences, 24(3), 2700. https://doi.org/10.3390/ijms24032700.

[94] Wei, Z., Burwinkel, M., Palissa, C., Ephraim, E., & Schmidt, M. F. (**2012**). Antiviral activity of zinc salts against transmissible gastroenteritis virus in vitro. *Veterinary Microbiology*, *160*(3-4), 468-472. https://doi.org/10.1016/j.vetmic.2012.06.019.

[95] Konda A., Prakash A., Moss G., Schmoldt M., Grant G., Guha S. (**2020**). Aerosol Filtration Efficiency of Common Fabrics Used in Respiratory Cloth Masks. ACS Nano. XXXX. 10.1021/acsnano.0c03252.

[96] Perry J., Agui J., Vijayakumar, R. (**2016**). Submicron and Nanoparticulate Matter Removal by HEPA-Rated Media Filters and Packed Beds of Granular Materials. https://ntrs.nasa.gov/citations/20170005166.

[97] World Health Organization Data. https://data.who.int/dashboards/covid19/cases.