ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Review Article

The Application of UV Light in the Treatment and Prevention of COVID-19

Mark H Chen[1] and Nicholas A Kerna[2,3]*

[1]*Clinic Director, For Your Health, LLC, USA*

[2]*Director, SMC–Medical Research, Thailand*

[3]*Director of Research, First InterHealth Group, Thailand*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com.

Received: April 24, 2021; **Published:** May 31, 2021

DOI: 10.31080/eccmc.2021.04.00409

Abstract

Low-dose x-ray therapy has been previously applied to treat pneumonia. Also, UVC light is used to disinfect N95 masks and other personal protective equipment. Thus, low-dose radiation is being considered and tested as a promising treatment and prevention method against SARS-CoV-2 infections. The combination of UVC light and riboflavin has been shown to deactivate SARS-CoV-2 particles in specific situations and applications.

UVC light is being employed indoors to control the spread of SARS-CoV-2. UVB light and UVA light demonstrate germicidal effects when applied at a greater intensity than UVC light. Nevertheless, UVC light can be harmful to superficial skin layers and correlates. Thus, it is recommended to apply UVC light at the low to lowest wavelengths. Also, the application of UVC light in buildings during unoccupied hours could control the spread of SARS-CoV-2.

A typical mercury lamp emits radiation-induced RNA damage similar to UVC light. Excimer lamps and LEDs also demonstrate germicidal effects against SARS-CoV-2. The recently developed Healight delivers UVA-level light directly when intubated into the lungs.

RNA, DNA, and recombinant proteins as viral vector-based are considered more traditional vaccines against SARS-CoV-2. Novel modes of vaccine, such as UV radiation, may be more economical than traditional vaccines. However, to date, the research on such application is in its infancy and, thus, undetermined. Although effective treatments and vaccines against SARS-CoV-2 appear eminent, there remains the likely occurrence of virus variants further complicating the containment of SARS-CoV-2.

Keyword: *Coronavirus; UV Radiation; Coagulation; Vaccination; Variant*

Abbreviations

ARDS: Acute Respiratory Distress Syndrome; DMEM: Dulbecco's Modified Eagle Medium; ECM: Extracellular Matrix; HCQ: Hydroxychloroquine; IES: Illuminating Engineering Society; IL-10: Interleukin-10; MMP-9: Matrix Metalloproteinase 9; PPE: Personal Protective Equipment; TLR: Toll-like Receptor; UV: Ultraviolet

Introduction

Treatment of viral infections with various forms of radiation

Low-dose radiation therapy is being considered and investigated as an alternative treatment against SARS-CoV-2 infections, especially in cases that have progressed, expressing severe or critical symptoms [1]. The underlying principle of using low-dose radiation therapy is the inhibition of the inflammatory response as reported in a recent study [2].

Macrophages, white blood cells that mediate and promote crucial parts of the body's inflammation response, take on an M1 phenotype when exposed to low radiation. They express anti-inflammatory cytokines, such as IL-10, and chemokines, such as CCL5 and CCL18. Also, they produce factors, such as matrix metalloproteinase 9 (MMP-9), that help with extracellular matrix (ECM) remodeling and angiogenesis [1].

Low-dose x-ray therapy has been successfully applied in the past to treat pneumonia, which is at the core of the acute respiratory distress syndrome (ARDS) phenotype during the progression of SARS-CoV-2 infection [3]. Thus, inhibiting inflammatory responses could mitigate cytokine storms and prevent ARDS from developing—allowing the immune system sufficient time to fight the viral infection. This principle plays an important role—similar to how hydroxychloroquine (HCQ) and Zn^{2+} work against SARS-CoV-2.

UVC light is used to disinfect N95 masks that are part of personal protective equipment (PPE) worn to defend against SARS-CoV-2 infection [4]. Thus, it may be possible to use the same radiation to deactivate or kill the virus inside infected body tissues.

Discussion

A recent experiment by Keil., *et al.* (2020) demonstrated that a combination of UVC radiation and riboflavin effectively deactivated SARS-CoV-2 particles in blood plasma inoculated with SARS-CoV-2 from Vero E6 cell culture [5]. Although this study was performed *in vitro* and did not use blood plasma from SARS-CoV-2-infected patients, it is reasonable to consider the combination of UVC light and riboflavin may destroy the virus in a clinical setting.

The Illuminating Engineering Society (IES) has recently released a report on electromagnetic radiation to kill germs (bacteria, parasites, and viruses) [6]. The shorter the wavelength, the more effectively UV radiation combats viruses and bacteria. UVC light, with a spectrum between 200–280 nm, has been found quite effective against viruses. However, the longer wavelengths of UVB and UVA have germicidal effects as well, but would need to be applied at higher intensities than UVC light [6].

Researchers de Abajo., *et al. (*2020) advocated for the use of UVC light indoors as a medium- to long-term solution [7] as sustained social distancing and maintaining the lockdown of businesses and social gatherings may be both economically, socially, and psychologically untenable. Moreover, according to Zheng., *et al.* (2020), various societies conduct lockdowns and social distancing differently, depending on the region affected [8]. It will likely prove beneficial in decontaminate and disinfect via light exposure as an additional weapon in the arsenal against the spread of the virus.

Indoor areas have the added disadvantage of offering many surfaces, such as elevator buttons, pens and pencils, light switches, keyboards, and other surfaces not easily reached by cleaning utensils and disinfectants [7]. Air-conditioners, central heaters, and indoor fans may spread the virus particles through the air and circulate them multiple times through buildings. Light or electromagnetic radiation might aid in destroying the virus on surfaces.

To effectively eliminate virus particles from buildings and combat their spread, UVC light emitters could be placed inside air conditioner shafts, on top of doorways, aisles, elevators, in office spaces, and other locations to diminish the area-wide spread of the virus. Significantly, UVC light—its wavelengths being between 200 and 280 nm—is not absorbed by surfaces, unlike visible light, and will be reflected multiple times on most surfaces, increasing the efficiency of UVC light exposure [9,10].

However, UVC light is harmful to humans and can cause skin burns. Thus, exposing the interior of buildings during evenings and nights when no one works in those spaces should be relatively easy to accomplish [11]**.** Viral particles adhering to a surface could be exposed to UVC light for select periods; thus, testing how well these particles survive within cell cultures and assessing the usefulness of UVC radiation in suppressing viral transmission and infectivity.

Heßling., *et al.* (2020) found that UVC radiation can be an effective antiviral treatment against numerous viruses, including coronaviruses. The authors performed a meta-analysis of available viral activation studies [12]. They assumed that UVC light would destroy viruses that belong to a common family and found that the variability in those studies was more likely due to experimental conditions, not due to electromagnetic radiation's varying efficacies against viral particles.

The upper limit of efficacy for a 90% reduction— this number was chosen as it represents a unit reduction in terms of decadic logarithm—is between 3.7 to 10.6 mJ/cm^2 [12]. UVC light damages RNA by dimerizing two uracil bases, rendering the resulting nucleic acid molecule inoperative.

A typical mercury lamp emits radiation at 254 nm, which approximates the RNA-absorption peak at which UVC radiation induces RNA damage. Moreover, when testing virus particles treated with light around that wavelength, the lowest infection rate in cell culture with *Dulbecco's Modified Eagle Medium* (DMEM) resulted. RNA damage will occur applying a radiation range from 220 to 280 nm, suggesting that other sources besides mercury arc lights can be used for disinfecting surfaces or an entire room [12].

Excimer lamps or LEDs at 222 nm or 270 nm, respectively, showed log-reduction doses with intensities that are practically feasible to attain. However, it should be noted that the authors in that study did not include any SARS-CoV-2 studies, as no peer-reviewed studies of the antiviral properties of UVC light yet existed for that specific virus (at the time the manuscript was published). However, due to their similar RNA content, comparable structures, and the notion that the researchers found numerous studies showing UVC light was effective against MERS-CoV and SARS-CoV-1, it is conceivable that UVC light will be similarly effective against SARS-CoV-2 [12].

A distinct advantage of using UVC light at the lowest wavelengths, e.g., 222 nm wavelength, is the destruction of the virus without harming human skin, eyes, and other sensitive and exposed areas of the body. The radiation at such wavelengths only penetrates a few millimeters into the skin, stratum corneum, and comparable tissues.

UVC light at 222 nm destroys airborne influenza viruses. Moreover, the same wavelength can kill SARS-CoV-1 particles and, likely, SARS-CoV-2. However, no tests have been performed on SARS-CoV-2 [13].

Nevertheless, a wavelength of 222 nm can be produced relatively cheaply as the corresponding excimer lamps are not costly. At 0.5 mJ/cm^2, the radiation can eliminate 90% of all virus infectiousness—as measured by irradiated viruses' ability to generate plaque-forming units in cell culture [13]. These results could be confirmed by studying an irradiated virus's ability to infect cells in culture, using immunofluorescence and fluorescent or confocal microscopy. Moreover, using such low doses of 222 nm, the formation of cyclobutane pyrimidine dimers (CPDs) or 6-4 photoproducts of pyrimidine-pyrimidone (6-4PP), the development of skin cancer is highly improbable, compared to 254 nm [13].

The presence versus absence of lesions using 254 nm versus 222 nm UVB irradiation on mice was investigated: mouse skin remains without blemish only when the lower wavelength was applied. These results suggest that excimer lamps that emit UVB radiation are not only cheaper and more cost-effective to use, they are also safer to human tissue.

Sunlight consists of a spectrum of wavelengths, including UVC radiation at 254 nm. As previously noted, in the study by Heßling., *et al.* (2020), the sensitivity of COVID-19 to exposure from artificial UVC light or sunlight is comparable to other viruses harboring single-stranded RNA, such as the common influenza [12].

According to Sagripanti and Lyle (2020), in cities located in temperate zones during the winter months, SARS-CoV-2 deposited on surfaces could remain active for an extended period, while the activity may be significantly reduced during the summer months and in cities that are located in warmer, tropical climates [14]. Moreover, the researchers estimated that the virus could survive on surfaces for greater than one day in most cities and regions within the United States during the winter months. From human contact with SARS-CoV-2-contaminated surfaces, virus particles can cause direct infection or coalesce into an aerosol form, infecting nearby people [14].

However, during midday in the warmer summer months, the virus would only survive for up to thirty minutes [14]. The Sagripanti and Lytle (2020) study used a model framework for their calculations based on the sunlight's angle that reaches the Earth. The researchers did not test their calculations. Also, it was not clear how much UVC light will reach the Earth after traversing through the atmosphere. Besides, most cities during summer months have an active nightlife with people congregating and in large groups with no sunlight. Despite these potential shortcomings, the study provided fundamental concepts and hypotheses that could be further tested.

Since UV light can be used on the external surfaces of objects, it is conceivable that it could be applied on surfaces (external and internal) of the body that are prone to viral infection, such as the bronchial tubes. The US-based company Aytu Biosciences Inc. has recently developed an apparatus called Healight, consisting of a tube with a frontal lens that can be intubated into the body and used to emit ultraviolet light directly into the lung [15].

However, in contrast to surface disinfection, the Healight platform uses UVA radiation, which emits light of a much longer wavelength (about 364 nm) [15]. The technology is entering expedited clinical studies in intubated patients who are connected to a ventilator. Since most ventilated patients are critically ill, the risk-reward profile is inapposite: without Healight, the majority of those patients will likely die. Thus, if UVA irradiation can kill viruses, this innovative application seems relevant. Nevertheless, ICU-admitted COVID-19 patients tend to suffer more from an overall inflammatory reaction within the lungs than from the viral load [16].

The Healight technology may be most efficacious for early-stage rather than late-stage patients. The technology employs radiation at 364 nm, not 222 nm (which is effective while causing little harm to human tissues). It is posited that 222 nm light may penetrate lung tissues further than skin or eye tissues, making it dangerous to use directly on the lungs [15]. As yet, there are no preliminary results regarding the application of the Healight technology for SARS-CoV-2. However, it is theorized that the technology will destroy viruses and hopefully does not damage healthy cells within the infected tissues [17].

Electromagnetic radiation could become a direct and effective weapon in the fight against the spread of viral pandemics. Instead of using drugs to assist the immune response or inhibit specific biological functions within the virus or the cells that the virus infects, UV light could kill viral particles directly within infected tissues or on their surfaces, effectively eliminating viral spread.

Table 1 depicts various methods of SARS-CoV-2 treatment, respective effects, and reference sources.

Treatment	Effect	Reference
HCQ vs. no drug	HCQ group: 70% (14/20) PCR negative at day-6 after symptom onset; Control group: 12.5% (2/16) PCR negative at day-6 after symptom onset	Gautret., *et al*. (2020) [18]
HCQ and HCQ + AZI	81.2% (65/80) patients discharged after 4 days of treatment	Gautret., *et al*. (2029)b [19]
REM	Recovery time reduced from 15 to 11 days	Ledford (2020) [20]
222 nm UVC	Log reduction dose 0.56 J/cm^2 of SARS-CoV in aerosols	Heßling., *et al*. (2020) [12]
254 nm UVC	Successful inactivation of murine coronavirus on surfaces	Heßling., *et al*. (2020) [12]

Table 1: *Available methods for SARS-CoV-2 reduction.*

UV radiation as a proposed vaccine against SARS-CoV-2 infection

UV radiation can be employed to deactivate the virus when used as a vaccine. However, despite the seeming advantage of exposing the immune system to an impaired version of the virus, it still retains its structure and complete set of isotopes, resulting in persistent challenges. For example, mice that were vaccinated with a UV-inactivated version of SARS-CoV-1 showed a robust immune reaction after being inoculated with a live virus. However, in those mice, eosinophils infiltrated lung tissue, which significantly increased lethality as the organ cannot function properly [21]. One factor in this immunopathologic reaction was the virus' nucleocapsid protein, which seemed to be the central cause of immune cell infiltration into the respiratory system [21,22]. Iwata-Yoshikawa., *et al.* (2014) found that the eosinophilic immune pathology after UV-inactivated SARS-CoV-1 vaccination can be mitigated by supplementing the vaccine with toll-like receptor (TLR) antagonists, such as polysaccharides and ribonucleic acids [23].

Toll-like receptor antagonists in proposed vaccines against SARS-CoV-2 infection

These additives also managed to reduce typical genes, upregulated and activated, that mediate chemotaxis, cell polarity, and cell migration in eosinophils and related immune cells. These finding suggest that TLR antagonists, given as adjuvants during the vaccination, can help protect the respiratory system from mass invasion by immune cells [23]. It is unclear whether this design of a vaccination therapy would work with CoV-2, although both coronaviruses' relative structural similarity suggests that it would work similarly. Nevertheless, these early experiments in mice need to be repeated in human cell culture and clinical trials to determine whether they are helpful in the long term.

TLR antagonists are currently approved for human use [23]. Lin., *et al.* (2007) found that injecting individuals with UV-inactivated SARS-CoV-1 results in the generation of a corresponding antibody titer. Thus, inactivated virions do not create an immediate threat to the body [24]. Based on mouse studies, such vaccinations may subsequently induce an excessive immune reaction.

RNA, DNA, and recombinant proteins as viral vector-based vaccines against SARS-CoV-2 infection

Economic factors sometimes limit the development of a vaccine. For example, several vaccines for SARS-CoV-1 were already in phase I clinical trials. However, these trials were discontinued as the virus was more or less eliminated from the population. Thus, the priority for the development of a vaccine was reduced. As there is at least one monoclonal antibody that cross-reacts with antigens on the surface of SARS-CoV-1 and SARS-Cov-2. A SARS-CoV-1 vaccine may also protect against SARS-CoV-2. As the SARS-CoV-1 vaccine has progressed to phase I trials, it may be relatively easy to resume the corresponding trials to expedite vaccine development [25].

In general, vaccines can be based on either the complete virus or parts of it [26]. RNA vaccines inject mRNA for a specific part of the virus into the body. Once the nucleic acid is taken up by cells, they start making the protein product for which the RNA codes and extravasate a viral antigen—which the individual's immune system recognizes as foreign and subsequently produces antibodies against it [27]. RNA can be generated easily in the lab, albeit its storage may be challenging since RNA can eventually be degraded by RNases, which are abundantly present in many lab environments [27,28].

DNA vaccines are similar in their primary function. They get taken up by target cells and produce antigens, which are then recognized by the adaptive immune system, producing antibodies against them [29].

Recombinant protein vaccines consist of an antigen synthesized in the lab, and injected into the person to be vaccinated. The immune system will recognize those antigens as foreign and produce antibodies against them, priming the body for a more efficient immune defense once the body is infected with the live virus. In live viral vector vaccines, the nucleic acid sequence is inserted into a viral vector which, in and of itself, is harmless to the host. The immune system can then, once again, recognize the foreign DNA or amino acid sequence as foreign and generate antibodies against it [30].

The advantage of a viral vector-based vaccine is that it is delivered to the body efficiently. The disadvantage is that the host's immune system may already show some immunogenicity against the viral delivery vector, reducing the immune response effectiveness against the antigen [31].

Total virions as a vaccine against SARS-CoV-2 infection

Besides the vaccines based on specific proteins and epitopes, some vaccines use the entire virion—either a live virus that has been attenuated or a wholly inactivated virus (still retaining the complete virus' structure) [32]. Injecting entire virions has the advantage that the immune system can form a complete response and non-response against an artificially selected part of the virus. However, the disadvantage is that the virus could cause an allergic reaction or cause the immune system to overreact by providing 'too strong' of an antigen [33]. The number of injected virions during vaccination may be vastly different from the number of live viruses to which the immune system is exposed [34]. Also, viral infections use entryways into the body that are different from direct injection into the blood. During an infection, the virus must overcome several immune system barriers that prevent the particles from getting through epithelial layers and mucus membranes. The sequence of immune responses in reactions to viral infection may be entirely different from the sequence that is employed if the virus is directly introduced into the blood [35].

To generate a vaccine against COVID-19, many companies are currently engaging in research and development using all the templates mentioned abo**ve** [25].

Conclusion

Several vectors are being proposed and investigated as potential vaccines against SARS-CoV-2 infection, including RNA, DNA, and recombinant proteins as viral vector-based vaccines. Also, novel vectors, such as UV radiation, are being tested, showing promise as effective treatments while vaccines against SARS-CoV-2 infection might be more economical to apply.

Low-dose radiation therapy is demonstrating potential as a treatment and preventive measure against SARS-CoV-2 infections. Low-dose x-ray therapy has been previously applied to treat pneumonia.

UVC light is used to disinfect N95 masks and other personal protective equipment. UVC light and riboflavin have been shown to deactivate SARS-CoV-2 particles in blood plasma inoculated with SARS-CoV-2. Thus, some researchers propose utilizing UVC light indoors as medium-term to long-term prevention in social distancing situations. Moreover, although UVC light has been found most effective against viruses, UVB light and UVA light have also demonstrated germicidal effects at a greater intensity than UVC light.

UVC light can be harmful to humans, particularly the skin. Thus, it has been suggested to use UVC-emitting lights in buildings during unoccupied hours for disinfection, which is relatively easy to enact. Moreover, there is an advantage of using UVC light at the lowest wavelengths in destroying the virus without harming human skin, eyes, and other sensitive and exposed areas of the body. This lowest-level UVC radiation only penetrates a few millimeters into the skin, stratum corneum, and comparable tissues.

Other sources of light radiation are being considered as treatments for SARS-CoV-2. Like UVC-emitting lights, a mercury lamp that emits radiation-induced RNA damage. Excimer lamps and LEDs showed log-reduction doses. The Healight can be intubated into the lungs while emitting UVA-level light directly.

As a potential vaccine, UV radiation is being studied as it deactivates specific viruses. However, it is unclear if such a vaccine would be effective against SARS-CoV-2. Effective vaccines have arrived, using either the more traditional modes of RNA, DNA, and recombinant proteins as viral vector-based vaccines against COVID-19 or the novel UV-light models. Nevertheless, evolving virus variants will remain a significant challenge in containing COVID-19.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note

This paper is based on prior doctoral research: Chen M.H. (2019). "SARS-CoV-2: Dynamic Stimulation and Control of the Immune System by Integrated Therapies" (unpublished doctoral dissertation).

References

1. Dhawan G., *et al*. "Low dose radiation therapy as a potential life saving treatment for COVID-19-induced acute respiratory distress syndrome (ARDS)". *Radiotherapy and Oncology* (2020). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7206445/

2. Calabrese EJ., *et al*. "Radiotherapy treatment of human inflammatory diseases and conditions: optimal dose". *Human and Experimental Toxicology* 38.8 (2019): 888-898. https://journals.sagepub.com/doi/abs/10.1177/0960327119846925?journalCode=hetb

3. Calabrese EJ and Dhawan G. "How radiotherapy was historically used to treat pneumonia: could it be useful today?" *The Yale Journal of Biology and Medicine* 86.4 (2013): 555. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3848110/

4. Cadnum JL., *et al*. "Effectiveness of ultraviolet-C light and a high-level disinfection cabinet for decontamination of N95 respirators". *Pathogens and Immunity* 5.1 (2020): 52-66. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7192214/

5. Keil SD., *et al*. "Inactivation of severe acute respiratory syndrome coronavirus 2 in plasma and platelet products using a riboflavin and ultraviolet light-based photochemical treatment". *Vox Sanguinis* (2020). https://pubmed.ncbi.nlm.nih.gov/32311760/

6. IES. IES committee report: Germicidal ultraviolet (GUV) - frequently asked questions (2020). https://www.ies.org/standards/committee-reports/ies-committee-report-cr-2-20-faqs/

7. García de Abajo FJ., *et al*. "Back to normal: An old physics route to reduce SARS-CoV-2 transmission in indoor spaces". *ACS Nano* (2020). https://pubs.acs.org/doi/10.1021/acsnano.0c04596

8. Zheng L., *et al*. "Is lockdown bad for social anxiety in COVID-19 regions? A national study in the SOR perspective". *International Journal of Environmental Research and Public Health* 17.12 (2020): 4561. https://pubmed.ncbi.nlm.nih.gov/32599911/

9. Correia G., *et al*. "Airborne route and bad use of ventilation systems as non-negligible factors in SARS-CoV-2 transmission". *Medical Hypotheses* 141 (2020): 109781. https://pubmed.ncbi.nlm.nih.gov/32361528/

10. Lim T., *et al*. "Predictions and measurements of the stack effect on indoor airborne virus transmission in a high-rise hospital building". *Build Environ* 46.12 (2011): 2413-2424. https://www.sciencedirect.com/science/article/abs/pii/S036013231100117X

11. Dai T., *et al*. "Ultraviolet C irradiation: an alternative antimicrobial approach to localized infections?" *Expert Review of Anti-infective Therapy* 10.2 (2012): 185-195. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3292282/

12. Heßling M., *et al*. "Ultraviolet irradiation doses for coronavirus inactivation–review and analysis of coronavirus photoinactivation studies". *GMS Hygiene and Infection Control* (2020): 15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273323/.

13. Buonanno M., *et al*. "Far-UVC light (222 nm) efficiently and safely inactivates airborne human coronaviruses". *Scientific Reports* 10.1 (2020): 1-8. https://www.nature.com/articles/s41598-020-67211-2

14. Sagripanti JL and Lytle CD. "Estimated inactivation of coronaviruses by solar radiation with special reference to COVID-19". *Photochemistry and Photobiology* 96.4 (2020): 731-737. https://pubmed.ncbi.nlm.nih.gov/32502327/

15. Brusie C. "UV light therapy is being studied as COVID-19 treatment at Cedars Sinai hospital". Web (2020). https://clinicaltrials.gov/ct2/show/NCT04572399

16. Ratanarat R., *et al*. "Critical Care Management of Patients with COVID-19: Early Experience in Thailand". *The American Journal of Tropical Medicine and Hygiene* 103.1 (2020): 48-54. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7356442/

17. Yi Y., *et al*. "COVID-19: what has been learned and to be learned about the novel coronavirus disease". *International Journal of Biological Sciences* 16.10 (2020): 1753-1766. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7098028/

18. Gautret P., *et al*. "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial". *International Journal of Antimicrobial Agents* (2020): 105949. https://pubmed.ncbi.nlm.nih.gov/32205204/

19. Gautret P., *et al*. "Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study". *Travel Medicine and Infectious Disease* (2020): 101663. https://pubmed.ncbi.nlm.nih.gov/32289548/

20. Ledford H. "Hopes rise for coronavirus drug remdesivir (2020a). https://www.nature.com/articles/d41586-020-01295-8

21. Sariol A and Perlman S. "Lessons for COVID-19 Immunity from Other Coronavirus Infections". *Immunity* 53.2 (2020): 248-263. https://www.sciencedirect.com/science/article/abs/pii/S1074761320303125

22. Perlman S and Dandekar AA. "Immunopathogenesis of coronavirus infections: implications for SARS". *Nature Reviews Immunology* 5.12 (2005): 917-927. https://pubmed.ncbi.nlm.nih.gov/16322745/

23. Iwata-Yoshikawa N., *et al*. "Effects of Toll-like receptor stimulation on eosinophilic infiltration in lungs of BALB/c mice immunized with UV-inactivated severe acute respiratory syndrome-related coronavirus vaccine". *Journal of Virology* 88.15 (2014): 8597-8614. https://pubmed.ncbi.nlm.nih.gov/24850731/

24. Lin J., *et al*. "Safety and immunogenicity from a phase I trial of inactivated severe acute respiratory syndrome coronavirus vaccine". *Antiviral Therapy* 12.7 (2007): 1107. https://pubmed.ncbi.nlm.nih.gov/18018769/

25. Amanat F and Krammer F. "SARS-CoV-2 vaccines: status report". *Immunity* 52 (2020): 582-589. https://www.sciencedirect.com/science/article/pii/S1074761320301205

26. Kaur SP and Gupta V. "COVID-19 Vaccine: A comprehensive status report". *Virus Research* 288 (2020): 198114. https://pubmed.ncbi.nlm.nih.gov/32800805/

27. Pardi N., *et al*. "mRNA vaccines - a new era in vaccinology". *Nature Reviews Drug Discovery* 17.4 (2018): 261-279. https://www.nature.com/articles/nrd.2017.243

28. Vincent HA and Deutscher MP. "Insights into how RNase R degrades structured RNA: analysis of the nuclease domain". *Journal of Molecular Biology* 387.3 (2009): 570-583. https://pubmed.ncbi.nlm.nih.gov/19361424/

29. Hobernik D and Bros M. "DNA Vaccines-How Far From Clinical Use?" *International Journal of Molecular Sciences* 19.11 (2018): 3605. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6274812/

30. Nascimento IP and Leite LC. "Recombinant vaccines and the development of new vaccine strategies". *Brazilian Journal of Medical and Biological Research* 45.12 (2012): 1102-1111. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3854212/

31. Ura T., *et al*. "Developments in Viral Vector-Based Vaccines". *Vaccines* 2.3 (2014): 624-641. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494222/

32. Sanders B., *et al*. "Inactivated Viral Vaccines". In: Nunnally B., Turula V., Sitrin R. (eds) Vaccine Analysis: Strategies, Principles, and Control. Springer, Berlin, Heidelberg (2015). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189890/

33. Rouse BT and Sehrawat S. "Immunity and immunopathology to viruses: what decides the outcome?" *Nature Reviews Immunology* 10.7 (2010): 514-526. https://www.researchgate.net/publication/44799269_Immunity_and_immunopathology_to_viruses_What_decides_the_outcome

34. Pulendran B., *et al*. "Immunity to viruses: learning from successful human vaccines". *Immunological Reviews* 255.1 (2013): 243-255. https://pubmed.ncbi.nlm.nih.gov/23947360/

35. Mueller SN and Rouse BT. "Immune responses to viruses". *Clinical Immunology* (2008): 421-431. https://www.immunology.org/public-information/bitesized-immunology/pathogens-and-disease/immune-responses-viruses

Volume 4 Issue 6 June 2021