

Pre-Exposure Prophylaxis for COVID-19 Infection: Current Concepts and Strategies

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ABSTRACT

The current pandemic of COVID-19 disease has spread, in a matter of a few months to nearly 200 countries, and the absence of a treatment has put the world in jeopardy. To date, more than 42 million people worldwide have been infected with severe acute respiratory distress syndrome coronavirus 2 (SARS CoV-2) and nearly 1.25 million have died from COVID-19 Pandemic. Many countries moved toward resuming work activities and social interaction to rescue economy. This makes population continue suffering severe losses in the absence of strict prophylaxis strategy against this pandemic. It is well known that prevention is better than cure, therefore, we plan to display the current strategies that should be implemented prior to exposure to infection and underlines its effectiveness in containing the infection. Repurposed vaccines and SARS-CoV-2 specific vaccines are also mentioned, to keep up with the most recent updates that are being carried out.

Keywords: COVID-19, Acute respiratory distress syndrome, Social interaction, Prophylaxis, Vaccines

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INTRODUCTION

The novel coronavirus has become a familiar idiom to the world at large, due to its catastrophic influence on multiple systems, healthcare and economy alike, causing panic and extensive collapse. The virus SARS-CoV-2 first emerged in Wuhan, China as a regional epidemic, to expand within a matter of few months to nearly 200 countries, becoming one of the marked pandemics ever known to mankind ¹. COVID-19 disease lethality lie in its prompt spread, where an infected individual transmits the infection to 2.3 people ², creating an exponential increase in cases as each carrier contracts it to the others simultaneously. What's more, is that COVID-19 incubation period was found to be 6.4 days ³, with symptoms similar to that of the common cold ⁴, making the differential diagnosis a tremendous challenge for health care workers. Individual's susceptibility to the infection is dependent on multiple variables, including age-related co-morbidities, evidently seen in the elderly, as they are most susceptible to the disease owing to their exposure to systemic illnesses (cardiovascular diseases, diabetes, hypertension, COPD) ⁵ that weaken their immunity, ultimately leading to severe cases of SARS-CoV-2 infections ⁶. For that reason, prophylactic measures become indispensable, and the next topic in que to explore.

Prophylactic protocol

Prophylaxis are the action steps taken to prevent the occurrence of a disease, and when the disease is classified as a world pandemic, knowledge on prophylactic measures is a must for all. Below are some of the essential prophylactic practices that can secure individuals from contracting the infection.

Quarantine

Quarantine is defined as a restriction of movement of persons suspected of exposure to a communicable disease, and social distancing ⁷. As it limits the contact of people even if they are not infected which helps in reducing the probability of getting infected. On the other hand, Isolation is defined as isolating and avoiding contact with the infected cases.

Both isolation and quarantine were used before in the SARS, and recently in COVID-19 outbreak. Isolation of cases and tracing contacts has long been a strategy in the fight against infectious diseases. However, its effectiveness has varied. As in Wuhan isolation of infected cases was only used at the beginning of the outbreak, it caused the outbreak size to be doubled in every 7.4 days on average ⁸, which shows that the mere case isolation and contact tracing is insufficient for the outbreak control holds. The reason behind the failure of isolation is, unlike the SARS virus where the transmissions occur after symptom onset, with COVID-19, signs of transmission occurred before the onset of disease symptoms ⁹, transmitting freely even during the incubation period. Transmission by people with no or mild symptoms can reduce the effectiveness of the isolation strategy because of low likelihood of isolating all cases and tracing all contacts. Tracing the contacted cases was shown effective in helping reduce the incidence of the disease and control the outbreak. However, isolation and tracing alone are not enough. That's why quarantine along with isolation and tracing is required. Quarantine helps by limiting the contact with infected cases and carriers (patients with the disease but without symptoms) which reduces the incidence rate. It allows the incubation period of carriers to pass to the onset of the disease occurrence where the

symptoms are shown (For easier screening). It also gives time for medical care and the government to trace the contacted cases during the incubation period which makes tracing easier.

The reduction in the incidence rate contributes to flattening the curve, which allows the cases to be within the threshold capacity of the health care system. This also provides a better health care to the infected cases. Furthermore, quarantine allows time for disinfection of general facilities to limit disease spread from contaminated areas. The control of the disease will provide time until a tested treatment or vaccine is developed, as vaccines will reduce the spread of the disease by herd immunity.

Face masks

Evidence suggests that masks are a crucial part of the Personal Protective Equipment (PPE), yet shouldn't be considered as an isolated intervention¹⁰. Masks delay the spread of the virus and offer some type of protection to exposure; for instance, countries with a known face mask culture such as Hong Kong, Singapore, Japan, and South Korea showed a higher control of the spread.

A debate arises on whether standard surgical masks have the same efficacy in preventing the COVID-19 virus spread when compared to the N95 masks. A meta-analysis that compared the efficacy of several types of masks has shown that surgical masks and N95 masks are the most reliable measures in reducing the risk of infection by respiratory illness, as they show an 80% reduction in contracting the illness amongst compliant personnel¹¹.

UV irradiation

The mechanism of UV disinfection is by the destruction of the microbial genomic materials, viral, bacterial, or fungal alike, via photo-dimers. Whether or not this method proves effective against the novel coronavirus, is the current concern and argument of this segment. And despite the fact COVID-19 has not been explicitly tested for UV decontamination, similar tests have been conducted on members of the corona viruses, such as SARS and MERS, with successful efficiency to kill > 99% of the infection in 10 minutes duration^{12,13} making the UV irradiation a worthy topic to unravel.

Welch *et al.*¹⁴ concluded that far-UVC light (207–222 nm) does not harm the outer dead layers of the skin or the eyes and cannot penetrate them due to its absorbance in biological materials, yet the small size of viruses makes it competent to inactivate them. This study also revealed that with a dose as low as 2 mJ/cm² of 222 nm of far UV-C light, successfully inactivated airborne aerosolized viruses such as the H1N1. Thus, it can be a promising agent against the new SARS-CoV-2 virus with more safety¹⁴.

The potential use of UV irradiation can be divided into: 1) far-UVC for a range of sterilization procedures, 2) far-UVC for public places, and 3) far-UVC as a selective therapy in high risk patients¹⁵.

1) far-UVC for a range of sterilization procedures

The UV germicidal irradiation use was suggested to follow the chemical disinfection methods, for the purpose of terminating any residual contamination, considering the long survival rates of the virus on surfaces for up to 9 days¹⁶.

UVGI uses UV-C that can cross-link thymidine in DNA and uracil in RNA, and thus damaging them to hinder the replication of microbes and potentially the new SARS-CoV-2 virus.

Biosafety cabinets (BSCs), being a common element in hospitals and public health laboratories using UV-C are implemented to disinfect PPE and mostly the N95 respirators, where the dose of ultraviolet radiation is specified by the amount of time these cabinets are set.

2) far-UVC for public places

Having a consistent level of a low level far-UVC overhead in public places, like hospitals, schools, airports and offices may offer an effective, non-toxic technique to control the airborne microbial infections, and thus, contribute to a safer world. Introducing an infrastructure of such will not only be effective against SARS-CoV-2, but also to limit all multi-drug resistant bacteria¹⁵.

3) far-UVC as a selective therapy in high risk patients

The functions of far-UVC extend to contain COVID-19 patients, being an accessible, cost effective treatment option, it can become a survival benefit to disinfect wounds in selective patients with a high fatality risk. However, since the human skin is unpenetrated by the far-UVC alone, pairing the far-UVC with fiber optics could assist in maneuvering the light to various regions around infection areas, covering a greater target site that wouldn't have been accessible by far-UVC light alone.

Vitamin C

The immune system is obligated to fight off the coronavirus. Therefore, the better our immunity is, the better the chances of recovery. One thing that can help improve immunity is a diet that is nutritious with the necessary minerals and vitamins. Vitamin C, has proven to be a helpful tool in fighting off infections, many of viral etiologies, enhancing the functions of innate immunity^{17,18}. It also assists the immune system by increasing the production of certain WBCs, namely phagocytes and T-lymphocytes, which collect vitamin C and utilize it to carry out their duties¹⁹.

As an antioxidant, this electron donor helps eliminate the free radicals produced by neutrophils and macrophages during inflammation, consequently, restricting inflammation and tissue damage related to immune responses²⁰.

A recent RCT on 167 USA patients with sepsis-related ARDS provided that the administration of ~15 g/day vitamin C intravenously for 4 days, may aid in decreasing patients mortality²¹.

More recently, a trial was registered on clinicaltrials.gov (Identifier: NCT04264533) to investigate the effect of vitamin C infusion to treat severe COVID-19 patients in Wuhan, China. It is one of the pioneer's trials to document direct influences of vitamin C and its impact on the SARS-CoV-2 virus. One hundred and forty patients will either be treated with a placebo, or vitamin C infusion at a dose of 24g/day for 1-week duration. The trial is expected to be complete by end of September²².

Vitamin D

The mechanisms by which vitamin D reduces infection risk includes cathelicidins and defensins, both lower viral replication and lowers pro-inflammatory cytokines and increases anti-inflammatory cytokines to prevent lung injury and pneumonia due to inflammation. It was reported that vitamin D supplements reduce the risk of COVID-19 infection. Vitamin D deficiency was found to contribute to ARDS, increasing the case-fatality rates. For prevention, it is recommended that people consume 10,000 IU/d of vitamin D3 for a few weeks, followed by 5000 IU/d to achieve a goal of 40-60 ng/mL. For treatment of infected individuals, higher doses might be useful²³.

The anti-viral, anti-inflammatory, and immunomodulatory effects are key methods by which vitamin D presents its benefits. It was reported that patients having pneumonia, cytokine overproduction, and ARDS experienced protective effects with the use of

vitamin D. Its role was presented in findings of receptor gene (VDR) alleles that are linked to increased susceptibility to respiratory conditions.²⁴ A combination of vitamin D with melatonin will not only present an immunomodulatory effect, but a synergistic oxidative response against COVID-19 infection, as well as down regulating renin-angiotensin system, halting its role in COVID-19 physiopathology²⁵.

Zinc

Zinc supplement administration has the potential ability to enhance the antiviral activity of both innate and adaptive immunity. The mechanism by which Zinc functions is realized through viral attachment, infection, and uncoating. Zinc can prevent viral entry via stabilizing the cell membrane, it can also inhibit the RNA synthesis of nidoviruses, to which SARS-CoV-2 belongs to²⁶. In a systematic review with a moderate quality evidence suggested that Zinc supplements reduce the duration of common cold by 1.65 days. This could indirectly support the potential prophylactic benefit of Zinc in the current pandemic, but more data is required to confirm such use.

Vinegar

Nikhat and Fazil discussed the applications of Unani medicine, a traditional system implicated during middle ages to employ natural drugs of different animal, herbal, and mineral origins for treatments. For instance, during pandemics, homes were sprayed with diluted vinegar, for its antimicrobial activity, being a safe alternative to chemicals and a cost-effective option to maintain clean air. Vinegar could also be taken orally, added to the diet or as salads topping. Sufficient evidence advocated the air-purifying activity of vinegar, and its relaxing aroma was also said to have a clearing activity on microbes²⁷. Another study by Pianta and colleagues evaluated the effects of acetic acid (vinegar) on a small number of early-stage COVID-19 patients, as a disinfectant for upper airway infections.

Acetic acid works by inactivating and disaggregating haemagglutinin glycoproteins that are found on the surface of influenza viruses. The low pH-dependent conformational change of glycoproteins and the destruction of the viral envelope inhibits its transmission. These properties and the site of infection reassemble SARS-CoV-2 entry and replication.

The antibacterial and the antiviral activity of acetic acid along its abundant availability makes it a potential adjunctive therapy for non-severe COVID-19 cases²⁸.

Mouthwash

Povidone-iodine (PVP-I) disinfectant has a more potent bactericidal and viricidal activity compared to other antiseptics. Its bactericidal activity intraorally was shown to reduce the microbial load for more than 3 hours, and although there were no in vivo documentations on its viricidal activity, in vitro studies demonstrated its efficacy against both SARS and MERS-CoVs.

PVP-I disinfection on both the mouth and nasal cavities were found to be safe, and protective to patients as well as HCWs. It reduces the viral load in the upper and lower tract, being the main sites for spread and expectoration. This intervention is safe, inexpensive, and easy to deploy at scale globally, making it a fundamental tool in preventing cross infections²⁹. Passarelli *et al.*, also pointed on the importance of using PVP-I mouthwash, particularly in preoperative dental work. Patients should be administered 7-10%, applicable to both low and high risk procedures³⁰.

VACCINES REPURPOSING

Ever since the beginning of the pandemic, treatment essentially remains supportive and symptomatic³¹. However, a frequent question is asked: do pneumonia vaccines protect you against COVID-19?

It is understood why this is a frequently asked question, since pneumonia is one of the manifestations of the disease. According to science, a vaccine is a pharmacological compound that is given to protect against a particular disease. They contain the weakened form of the microorganism itself. This weakened microorganism is introduced to the immune system and allows it to create antibodies against it³².

Therefore, due to the alarming rate of spread of COVID-19, medical professionals are adopting multiple strategies in the development of the appropriate vaccine. They are aiming to target surface-exposed spike (S) glycoprotein or S protein, which is the major stimulator of neutralizing antibodies³³. This further explains why pneumonia or influenza vaccines are unable to protect against the coronavirus, since each virus has its own unique structure.

Whether it is the pneumococcal vaccine or the influenza vaccine, they are only able to protect against *Streptococcus pneumoniae* and the influenza virus respectively. They are not able to protect against the new coronavirus.

Meanwhile, researchers and healthcare exploration attempts to utilize old drugs and vaccines as a way to protect people against the novel virus has revealed a ray of hope towards BCG (*Bacille Calmette-Guerin*) vaccine for Tuberculosis³⁴.

BCG vaccination has been shown to have positive non-specific immune effects, in which it can significantly increase the secretion of pro-inflammatory cytokines, specifically IL-1B, which indicates that it can play a vital role in antiviral immunity³⁵. Additionally, studies have illustrated the vaccine's effect on reducing respiratory infections and sepsis. So, does BCG vaccine actually protect people from COVID-19? Recently, some studies, although not numerous, suggest that BCG vaccine can protect people from COVID-19; indeed, decreased morbidity and mortality rates as well as reduced total number of cases were noticed in countries that conduct BCG vaccination policies³⁶.

An epidemiological study was conducted to investigate a possible correlation between the universal BCG vaccine policies and the morbidity and mortality due to COVID-19 infections all over the world. The study compared countries that never had universal BCG vaccination policy, like Italy, USA, Lebanon, Netherland, and Belgium, with countries that have a current universal BCG vaccination policy. Moreover, middle high and high-income countries that have a current universal BCG policy (55 countries) had 0.78 ± 0.40 (mean \pm s.e.m) deaths per million people. On the other hand, middle high and high-income countries that never had a universal BCG policy (5 countries) had a larger mortality rate, with 16.39 ± 7.33 deaths per million people. This difference between countries was highly significant ($p=8.64e-04$, Wilcoxon rank sum test) (6). The study also reported that there is a correlation between the number of cases of COVID-19 in countries with BCG vaccine policy and those with none. For example, middle high and high-income countries that have a current universal BCG policy (55 countries) had 59.54 ± 23.29 (mean \pm s.e.m) cases per million inhabitants. On contrary, middle high- and high-income countries that never had a universal BCG policy

(5 countries) had about 4 times the number of cases per million inhabitants, with 264.90 ± 134.88 . This difference between countries was noteworthy ($p=0.0064$, Wilcoxon rank sum test), suggesting that broad BCG vaccination along with other measures could slow the spread of COVID-19³⁶.

Vaccines specific for COVID-19

The swift development of vaccines against COVID-19 infection permitted taking the next step into the clinical trials for evaluation. There is a large diversity in vaccine platforms, including nucleic acid mRNA, DNA, viral vectors whether they're replicating or non-replicating, subunits, and nanoparticles. Each platform has its pros and cons, however, the most important characteristics that need to be met include reactogenicity and safety, cellular and humoral immunogenicity, immune durability, speed, flexibility, scale, and cost of manufacture, stability, and cold chain requirements, which are unlikely to be met by a single vaccine alone, urging a multi-pronged strategic approach.

mRNA and DNA vaccines can have a rapid potential to reach the clinics, due to their dependence on the viral sequence through their generation. DNA vaccines require injector delivery device or electroporation to allow its entry into cells, while mRNA viruses can be delivered via lipid nanoparticles.

The recombinant protein technology can be employed to express spike proteins, and unlike nucleic vaccines, this technology has a robust commercial experience, despite requiring longer times to establish cell lines for manufacturing.

Viral vectors vaccines deliver the gene of interest through deactivated viruses, such as adenovirus (Ad) and vesicular stomatitis virus (VSV). This platform has a good potential for large-scale manufacturing³⁷.

There is a large variety of vaccines, in different stages of research, preclinical, and early clinical phases³⁸, 23 of which are in clinical trials, and only three has entered phase III clinical trials, gaining a renowned reputation, and will be the center of the discussion in the following segment.

Oxford Vaccine

On April, in a phase 1/2 single-blind randomized controlled trial on a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) held in five sites in the UK, involving over a thousand adult healthy volunteers, developed by the University of Oxford collaborating with AstraZeneca biopharmaceutical company. Safety, immunogenicity and reactogenicity were assessed of the vaccine expressing SARS-CoV-2 spike protein in comparison to the control meningococcal conjugate vaccine (MenACWY). Results displayed proper safety profile, while inducing both cellular (T cells) and humoral immunity (antibodies). No serious adverse events were reported, encouraging scientists to go for phase III program³⁹.

Phase III final trial was held in Brazil with 5000 volunteers, divided to receive ChAdOx1 vaccine verses quadrivalent meningitis ACWY vaccine as control, in a randomized double blind trial, eventually, to be also conducted in the USA, UK, and South Africa in hopes to recruit up to 50,000 volunteers. Early results from all trials is expected to be collected in November, followed by submission for initial registration once the vaccine is proven effective. The body's immune response was developed in 8-10 days post vaccination, and researchers would collect blood samples after 28 days to guarantee the establishment of proper defense-cell protection.

Partial preliminary results from the combination of the aforementioned trials is expected to be ready by November⁴⁰.

Moderna vaccine

A different vaccine candidate in the U.S. was founded by Moderna biotech company, and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, identifier: NCT04470427.

Phase I trial was an open label, dose escalating trial involving 45 healthy adults to receive two vaccinations 28 days-apart, having 15 participants divided onto 3 groups to receive a dose of mRNA-1273 of 25 µg, 100 µg, or 250 µg. Results displayed patients tolerance, and successful anti-SARS-CoV-2 immune responses in all the volunteers, with no limiting safety concerns, supporting further progress with the vaccine⁴¹.

Phase III random double-blinded trial intends to recruit 30,000 healthy volunteers from 89 different sites in the U.S. to test the efficacy of the mRNA vaccine. The vaccine encodes the SARS-CoV-2 spike protein (S-2P immunogen) to directs the body's cells into expressing the spike protein to evoke a broad immune response. Two IM injections are to be given 28 days apart from each other. Participants will receive either two 100 mcg of mRNA injections, or saline placebo. The trial's objective is to confirm the safety of the vaccine, to see if it can prevent positive symptomatic COVID-19 patients after being given two doses, it also aims to study its prevention capabilities of severe COVID-19 patients with or without presented symptoms. The trial also searches if the mRNA vaccine can prevent death, and whether or not one dose is enough to prevent symptomatic COVID-19 infection⁴².

Chinese vaccine

An inactivated vaccine created by Wuhan Institute of Biological Products under the China National Pharmaceutical Group, Sinopharm, and the Wuhan Institute of Virology (WIV) entered clinical trials. Total of 96 volunteers were enrolled in the randomized, double-blind, placebo controlled first phase trials in Jiaozuo, Henan Province, and the vaccine demonstrated good safety, fostering the movement to the second phase on 12th of April to focus on the procedure of vaccination. There has been supportive evidence from animal challenge study that the vaccine protected the animals without antibody-dependent enhancement (ADE)⁴³.

The vaccine passed phase I and II trials having 100% of the participants developing antibodies after two doses in 28 days, therefore, initiating phase III trial in Abu Dhabi, accepting up to 15,000 adult volunteers in three to six months. The vaccine administration will include two strains and a placebo, and the two doses are given three weeks apart, whilst patients are to be followed for a year⁴².

CONCLUSION

Economy does not allow complete lockdown, so term of smart lock down has surfaced in some countries, schools resumed, and passive social distancing became more difficult, therefore an urgent need for active prophylaxis against COVID-19 is crucial. Until a vaccine can be found, pre exposure prophylaxis for COVID-19 seems a logical and feasible choice for resumption of work activities and social interaction on a worldwide scale.

REFERENCES

1. Madabhavi I, Sarkar M, Kadakol N. Covid-19: A review. *Monaldi Arch Chest Dis.* 2020;90(2):248-258. doi:10.4081/monaldi.2020.1298

2. Zhang S, Diao MY, Yu W, Pei L, Lin Z, Chen D. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis. *Int J Infect Dis.* 2020. doi:10.1016/j.ijid.2020.02.033
3. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20 January 2020. *Eurosurveillance.* 2020;25(5):1-6. doi:10.2807/1560-7917.ES.2020.25.5.2000062
4. Worrall G, Watch FP. Common cold. *Can Fam Physician.* 2007;53:1735-1736.
5. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with covid-19: Evidence from meta-analysis. *Aging (Albany NY).* 2020. doi:10.18632/AGING.103000
6. Chow N, Fleming-Dutra K, Gierke R, et al. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12-March 28, 2020. *Morb Mortal Wkly Rep.* 2020. doi:10.15585/MMWR.MM6913E2
7. Sundwall DN. Quarantine in the 21st Century: To be effective, public health policies must be inclusive. *Am J Public Health.* 2019. doi:10.2105/AJPH.2019.305224
8. Niud Y, Xu F. Deciphering the power of isolation in controlling COVID-19 outbreaks. *Lancet Glob Heal.* 2020. doi:10.1016/S2214-109X(20)30085-1
9. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Heal.* 2020. doi:10.1016/S2214-109X(20)30074-7
10. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of Masks and Respirators Against Respiratory Infections in Healthcare Workers: A Systematic Review and Meta-Analysis. *Clin Infect Dis.* 2017. doi:10.1093/cid/cix681
11. Smith JD, MacDougall CC, Johnstone J, Copes RA, Schwartz B, Garber GE. Effectiveness of N95 respirators versus surgical masks in protecting health care workers from acute respiratory infection: A systematic review and meta-analysis. *CMAJ.* 2016. doi:10.1503/cmaj.150835
12. Huang SH. What We Know So Far (As of March 26, 2020) About COVID-19—An MRT Point of View. *J Med Imaging Radiat Sci.* 2020. doi:10.1016/j.jmir.2020.03.004
13. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Infect.* 2020. doi:10.1016/j.jhin.2020.01.022
14. Welch D, Buonanno M, Grilj V, et al. Far-UVC light: A new tool to control the spread of airborne-mediated microbial diseases. *Sci Rep.* 2018. doi:10.1038/s41598-018-21058-w
15. Haider I, Ali A, Arifeen T, Hassan AS. Far UV-C Lights and Fiber Optics Induced Selective Far UV-C treatment against COVID-19 for Fatality-Survival tradeoff. 2017;XX.
16. Kowalski WJ. 2020 COVID-19 Coronavirus Ultraviolet Susceptibility 2020 COVID-19 Coronavirus Ultraviolet Susceptibility. *purple sun.* 2020. doi:10.13140/RG.2.2.22803.22566
17. Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in disease prevention and cure: An overview. *Indian J Clin Biochem.* 2013. doi:10.1007/s12291-013-0375-3
18. Moores J. Vitamin C: a wound healing perspective. *Br J Community Nurs.* 2013. doi:10.12968/bjcn.2013.18.sup12.s6
19. Van Gorkom GNY, Klein Wolterink RGJ, Van Elssen CHMJ, Wieten L, Germeaad WTV, Bos GMJ. Influence of Vitamin C on lymphocytes: An overview. *Antioxidants.* 2018. doi:10.3390/ANTIOX7030041
20. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients.* 2017. doi:10.3390/nu9111211
21. Fowler AA, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients with Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. In: *JAMA - Journal of the American Medical Association.* ; 2019. doi:10.1001/jama.2019.11825
22. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. *Crit Care.* 2020. doi:10.1186/s13054-020-02851-4
23. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin d supplementation could reduce risk of influenza and covid-19 infections and deaths. *Nutrients.* 2020. doi:10.3390/nu12040988
24. Jakovac H. COVID-19 and vitamin D-Is there a link and an opportunity for intervention? *Am J Physiol - Endocrinol Metab.* 2020. doi:10.1152/ajpendo.00138.2020
25. Martín Giménez VM, Inserra F, Tajer CD, et al. Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. *Life Sci.* 2020. doi:10.1016/j.lfs.2020.117808
26. Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. *Med Hypotheses.* 2020. doi:10.1016/j.mehy.2020.109848
27. Nikhat S, Fazil M. Overview of Covid-19; its prevention and management in the light of Unani medicine. *Sci Total Environ.* 2020. doi:10.1016/j.scitotenv.2020.138859
28. Pianta L, Vinciguerra A, Bertazzoni G, et al. Acetic acid disinfection as a potential adjunctive therapy for non-severe COVID-19. *Eur Arch Oto-Rhino-Laryngology.* 2020. doi:10.1007/s00405-020-06067-8
29. Kirk-Bayley J, Challacombe S, Sunkarani V, Combes J. The Use of Povidone Iodine Nasal Spray and Mouthwash During the Current COVID-19 Pandemic May Protect Healthcare Workers and Reduce Cross Infection. *SSRN Electron J.* 2020. doi:10.2139/ssrn.3563092
30. Passarelli PC, Rella E, Manicone PF, Garcia-Godoy F, D'Addona A. The impact of the COVID-19 infection in dentistry. *Exp Biol Med.* 2020. doi:10.1177/1535370220928905
31. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr.* 2020. doi:10.1007/s12098-020-03263-6
32. Ginglen JG, Doyle, MQ. Immunization. In: StatPearls Publishing; 2020.
33. Dhama K, Sharun K, Tiwari R, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Hum Vaccines Immunother.* 2020. doi:10.1080/21645515.2020.1735227
34. Luca S, Mihaescu T. History of BCG Vaccine. *Maedica (Buchar).* 2013.
35. Kleinnijenhuis J, Quintin J, Preijers F, et al. Long-

- Lasting Effects of BCG Vaccination on Both Heterologous Th1/Th17 Responses and Innate Trained Immunity. *J Innate Immun.* 2014;6(2):152-158. doi:10.1159/000355628
36. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. *medRxiv.* 2020. doi:10.1101/2020.03.24.20042937
37. Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D: A public-private partnership and platform for harmonized clinical trials aims to accelerate licensure and distribution. *Science* (80-). 2020;368(6494):948-950. doi:10.1126/science.abc5312
38. Wu SC. Progress and Concept for COVID-19 Vaccine Development. *Biotechnol J.* 2020. doi:10.1002/biot.202000147
39. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet.* 2020. doi:https://doi.org/10.1016/S0140-6736
40. DAMASIO K. Oxford vaccine enters final phase of COVID-19 trials. Here's what happens now.
41. Jackson LA, Anderson EJ, Roupheal NG, et al. An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. *N Engl J Med.* July 2020. doi:10.1056/nejmoa2022483
42. Phase 3 clinical trial of investigational vaccine for COVID-19 begins | National Institutes of Health (NIH).
43. China approves clinical trials of third Covid-19 vaccine candidate.