The Pharmaceutical and Chemical Journal, 2021, 8(4):33-41

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

COVID-19: Vaccines and Vaccinations

Mohammad Javad Nazari[1], Yasser Arefzadeh[2], Mehrdad Modaresi*[3]

[1]Department of Biology, Shahid Rajaii Campus, Farhangian University, Urmia, Iran
[2]Department of Biology, Shahid Bahonar Campus Farhangian University, Arak, Iran
[3]Department of Physiology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran
*Corresponding Author Email: mehrdad_modaresi@hotmail.com

Abstract Access to safe and effective vaccines is critical to controlling the Covid-19 pandemic. A large number of vaccines are being developed. Researchers are constantly working to produce safe vaccines. The vaccines produced against COVID-19 are designed to promote acquired immunity. Prior to the COVID-19 epidemic, there was a wealth of knowledge about the structure and function of corona viruses that cause diseases such as Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Numerous platforms are used in vaccine production technology. Most vaccines in clinical trials have focused on the corona virus spike protein and its variants as the primary antigen for COVID-19 infection. The RNA vaccine contains RNA that acts as a messenger RNA (mRNA) when it enters the tissue, causing cells to make foreign proteins and teaching the body an immune response. Adenovirus vector vaccines are examples of non-replicating viral vector vaccines, using an adenovirus shell containing DNA that encodes a SARS‑CoV‑2 protein. Inactivated vaccines consist of virus particles that have been grown in culture and then are killed using a method such as heat or formaldehyde to lose disease producing capacity, while still stimulating an immune response. Vaccines may have side effects, which are normal signs of the body's reaction. These side effects go away within a few days.

Keywords COVID-19, Vaccines, Side effects, Immune system

Introduction

Corona viruses are commonly found in vertebrates and humans. Corona viruses belong to the family Corona viridae and the subfamily Coro-navirinae. The virus that has recently spread to communities is known as 2019-nCoV or COVID-19. The virus is based on phylogenetic and genetic criteria of the genus Betacoronavirus, which is highly similar to SARSr-CoV (acute respiratory syndrome). Examination of the structure of COVID-19 shows that the virus consists of a pleomorphic or spherical particle that contains a single-strand (positive-sense) RNA with a nucleoprotein enclosed in a capsid consisting of a protein matrix [1].

Corona viruses have a length of 26 to 32 kb (kb) and a diameter of 60-140 nm. In addition to SARS-CoV-2, there are six other types of corona viruses: HCoV-229E, HCoV-OC43, SARS- CoV, HCoV-NL63, HCoV-HKU1 and MERS-CoV [2].

The most common symptoms of the onset of the disease are cough, fever, and fatigue, which are similar to the symptoms of the flu and may be confused with other symptoms, such as headache, hemoptysis, diarrhea, shortness of breath, and lymphopenia. COVID-19 disease can be observed [3,4,5,6]. In patients with COVID-19, the number

of leukocytes is usually higher than normal and a significant increase in the level of proinflammatory cytokines in plasma is observed [6].

Examination of the genomic sequence of COVID-19 shows 88% similarity to the acute respiratory syndrome (SARS) virus, indicating that mammals are the primary target of COVID-19 [6]. The first stage of viral infection is the binding of expressed receptor to the host cell and the subsequent fusion with the cell membrane. Epithelial cells are the main target of the virus and on the other hand, it has been reported that the virus enters the host cells through the angiotensin 2 converting enzyme receptor (ACE2) [7 and 8].

After the diagnosis of COVID-19, prevention and quarantine is the best way to prevent the spread of the disease. Although the vaccine is now available, it does not provide 100% immunity or some people refuse to be vaccinated. Oxygen therapy or antiviral drugs such as remdesivir, oseltamivir, Chloroquine, and Interferon and other antiviral drugs are used to help patients [2].

Vaccine is one of the most urgent requirements for COVID-19. One of the reasons for this urgency is that people with an underlying disease such as diabetes are twice as likely to have the disease as people without an underlying disease. Pregnant women are susceptible to viral pathogens because they undergo physiological changes in the respiratory, cardiac and immune systems during pregnancy.

They may be at risk for preterm birth, reduced fetal growth, or increased prenatal mortality rates after the disease. Among them, the group with the highest risk is the group of pregnant women with diabetes. This group should be vaccinated immediately due to their greater vulnerability than other groups [9]. One of the most effective ways to fight infectious diseases is to produce vaccines that can be very economical for us to control the disease in society.

Meanwhile, the production of COVID-19 vaccine is a top priority for us today. In this way, there is a need for a comprehensive study and detailed studies on S glycoproteins and SARS-CoV-2 epitopes, which are the main cause of COVID-19 pathogenesis [10 and 11].

Functional mechanism of some vaccines:

1. **Clinical MERS-CoV vaccines based on protein S:** The function of this protein is to identify receptors and further the entry of the virus into the host cell. Antibodies to the S protein target play an important role in controlling the disease, although this type of response alone is not sufficient to prevent MERS-CoV infection [12, 13]. A number of vaccines that target the S protein produce based on MERS-CoV DNA, viral vectors, proteins, virus-like particles (VLPs), bacterial particles (BLPs), and nanoparticles are produced [14-18].
2. **Protein-based vaccines:** These vaccines have been evaluated at different stages based on RBD (CTD), S1 and S proteins. Among these, the vaccine for RBD has been extensively studied [19].

   Antibodies were extracted to neutralize MERS-CoV infection [20]. These vaccines have strong immunogenicity and stimulate the immune system well, and although they are relatively easy to produce, a strong response is required for a strong response. Although they are relatively easy to produce, they require a number of additives and adjuvants for a strong response. These vaccines also lack live components and are usually not particularly dangerous, but their problem is that it is unclear how long they can provide immunity and persistence in the future, and that denaturation of protein isolates can cause binding to other antibodies. Become non-target.

   Protein-based vaccines are classified into three groups: protein subunits, polysaccharide vaccines, and conjugated vaccines [21, 22]

In general, we see the use of various technologies to make vaccines, including DNA and RNA-based vaccines, cell culture-based vaccines, and recombinant protein vaccines [23]. In the meantime, DNA and RNA-based vaccines produced by entering human cells can kill the virus protein copy and create immunity [24].

Major vaccines in the world:

Several vaccine candidates developed against COVID-19 use different technologies.

- **Pfizer:** One of the most important vaccines in this country is Pfizer vaccine, which has taken the first place with 95% effectiveness. The vaccine was also highly effective in clinical trials at preventing COVID-19 among people of diverse age, sex, race, and ethnicity categories and among people with underlying medical conditions.
- **Moderna:** After Pfizer, the vaccine is Moderna, which contains mRNA, encoded spike, and lipid nanoparticles. The vaccine can survive at -20 $^{\circ C}$ for 30 days. The Moderna vaccine has been shown to have an efficacy of approximately 94.1 per cent in protecting against COVID-19, starting 14 days after the first dose.
- **Astrazeneca:** Another vaccine is the Astrazeneca vaccine, which contains chimpanzee adenovirus and wild-type spike, which should also be refrigerated at 2-8$^{\circ C}$ [25]. The AstraZeneca vaccine is effective at protecting people from the extremely serious risks of COVID-19, including death, hospitalization and severe disease.
- **Janssen–Johnson**: This vaccine uses a human adenovirus 26 that has also been modified to be nonreplicating.
- **Novavax**: This vaccine is on the list of effective vaccines, which consists of a protein subunit with capsule nanoparticles, after which the protein is injected into the person with a number of additives to show its effect [26].
- **GSK–Sanofi**: is protein subunit vaccines in which a baculovirus is used to produce the recombinant protein in insect cells. In the partnership between the two Companies, Sanofi provides its recombinant antigen and GSK contributes its pandemic adjuvant, both established vaccine platforms that have proven successful against influenza.
- **Sputnik V**: Sputnik V is a vaccine that acts as a viral vector against COVID_19, which contains two human adenovirus serotypes that are administered in two doses, each containing the SARS-CoV-2 S antigen that enters cells. A heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V), showed a good safety profile and induced strong humoral and cellular immune responses in participants in phase 1/2 clinical trials. To make this vaccine, the methods used to make the Ebola vaccine have been used. One of the new technologies for making the vaccine is the use of virus carriers, for example, this type of technology has been used to make the Ebola vaccine.
- **Sinopharm:** The Sinopharm vaccine is produced by Beijing Bio-Institute of Biological Products Co Ltd, subsidiary of China National Biotec Group (CNBG). After a thorough review by SAGE, WHO assessed the vaccine efficacy for Sinopharm is up to 75 percent. The COVID-19 Sinopharm vaccine triggers the immune system to produce a response to the inactivated version of the COVID-19 virus.

Vaccines must eventually make antigens to create the immunity that these antigens originate from memory T cells. These cells are also the main target of vaccines, so that diseases such as HIV, tuberculosis and malaria also require the activity of T cells in order to produce immunity by producing antigens [11, 29]. These cells store their information when they first come in contact with the pathogen, and after the next contact with the pathogen, they respond appropriately to suppress the infection. Memory T cells accumulate and function mostly in lymphatic tissues [30].

One of the criticisms of DNA vaccines is that by injecting these types of vaccines into the cell, there is a risk of mutation in the host cell [31]. On the other hand, there are concerns such as the effect of DNA vaccines on inflammation and allergies, so that the SPIKE protein of Corona virus may have areas prone to allergies and its processing in the cell leads to allergic reactions and antigenic responses [32]. But the production of nucleic acid-based vaccines no longer requires cell culture or fermentation, and their production costs are lower than other vaccines. These characteristics make these vaccines have the greatest potential for development and production. [33].

Since the outbreak of the coronavirus pandemic worldwide, various mutations have been observed around the world, for example the B117 virus, which has spread to the United Kingdom. Other mutations in the coronavirus in South Africa, the United States and Brazil have raised concerns about the effectiveness of current vaccines against these mutants.

In order to find out whether the current vaccines are effective, laboratory and animal studies should be performed to address these concerns [34].

Advantages and disadvantages of a number of vaccines

Although a safe and effective vaccine holds the greatest promise for resolving the COVID-19 pandemic, hesitancy to accept vaccines remains common. Even though safe and effective vaccines are now being administered, vaccination programs still face significant obstacles. One study suggested that 35.8% of adults refuse to take flu vaccines. Recent estimates from the Centers for Disease Control and Prevention (CDC) show that only about 63% of children under the age of 18 and 45% of adults received a flu vaccination during the 2018–2019 flu season.

Inactivated vaccines, like most influenza vaccines, are now very effective and are mainly produced, but they also have drawbacks, including harmful immunity or inflammatory responses, so use this. Vaccines should be used with caution [37]. On the other hand, live attenuated vaccines have a good history in producing vaccines for chickenpox, yellow fever, polio, mumps and measles. However, although these vaccines have a good history, they have a serious risk of recurrence of the recombinant or mutant type, which in turn causes a new dangerous and unknown outbreak in unvaccinated populations, especially animals [38, 39].

Protein-based vaccine production is another type of vaccine-making technology that can effectively suppress disease by neutralizing antibodies to the virus. There have also been reports of active infection of B cells or other immune cells exposed to SARS-CoV [40, 41, 42].

Vaccines can vary in the type and severity of side effects. For example, some people who have received the Astrazeneca vaccine have experienced mild side effects such as fever or chills and swelling at the injection site [43]. About 3.7% of Pfizer vaccine volunteers reported fatigue side effects after the first dose, and 2% experienced symptoms such as headache after the second dose. Studies have also shown that ethnicity, age and race are effective in the efficacy and effectiveness of the vaccine [44].

Currently, the best way to fight the coronavirus is to use a vaccine, but there are barriers to this, such as side effects, persistent mutations in the virus, or people being pessimistic about the vaccine due to the ineffectiveness of previous vaccines such as the flu vaccine. In the meantime, the efficacy and effectiveness of the vaccine can restore public confidence and be considered the most important factor in deciding to vaccinate [45, 46].

As to whether or not children have been vaccinated, a population of 12-16year old has been vaccinated with Pfizer, but fortunately no serious side effects have been reported. Also, no decision has been made yet about vaccinating children under 5 years old, and we do not know exactly what side effects can be expected if the vaccine is given to this age group. Although the pathogenicity of the virus is lower in children than in adults, children can transmit the disease latently and infect other adults [47].

The side effects of the vaccines are universally common and there is nothing to worry about, so headaches or fever are common side effects of these vaccines, so it takes time for the body to produce after the vaccine has stimulated the immune system. Antibodies and after that these symptoms will disappear [48]. Another thing that people should consider before vaccination is whether they are allergic or not. If a person is allergic to any of the substances in the COVID-19 vaccine, they should not get the vaccine. To access the materials used in coronavirus vaccines, we can visit the CDC website and learn about the materials used in each vaccine.

Another question that arises is what are the long-term side effects of the vaccine? This is a question that has occupied the minds of many people around the world. Vaccines that are produced are subjected to clinical trials for up to 8 weeks for long-term side effects, and it is very unlikely that the vaccine will have any specific side effects after 8 weeks [49].

Although today it has been proven that vaccines are the most effective way to fight epidemics [50], but problems such as the anti-vaccination movement have recently emerged in the United States and Europe over the past decade.

However, the main problem with people's reluctance to get vaccinated is concerns about vaccine safety. The World Health Organization has identified non-vaccination as one of the top ten threats to global health [51]. The effectiveness of the vaccine is another important component of the vaccine, as scientists have stated that there is still no 100% certainty about the effectiveness of vaccines, and more observations and longer time are needed to further evaluate the effectiveness of vaccines [52-53].

There have been reports of anaphylaxis after the Pfizer vaccine, which is 11.1 per million during the census, which is a small number. The cause of anaphylaxis in these people is polyethylene glycol (PEG) and PEG derivatives, such as polysorbates [54, 55]. Another thing to keep in mind is that due to the lack of evidence for COVID-19 vaccines, we should avoid this vaccine as much as possible at the same time as other vaccines such as influenza.

Thus, as recommended by the United States, it is best to inject other vaccines after at least 14 days [56]. In general, COVID-19 vaccines can in rare cases have side effects such as anaphylaxis, swelling of the face or swelling of the lips or tongue, and a number of other symptoms, some of which are due to allergies to a specific substance in the vaccine [57].

One way to produce a vaccine is to produce it based on biomimetic nanoparticles that contain viral antigen molecules, protein scaffolds, and a number of additives. This type of vaccine is safer and has side effects such as fever, diarrhea, and nausea. Vaccines are much lower [58 and 59].

Biochemical nanoparticles such as VLPs, virosomes, self-assembled protein nanoparticles, and synthetic nanoparticles are used to produce these vaccines [60]. Obviously, vaccine production is a time-consuming process due to the risk of genetic mutations in humans, so that in the United States, for example, the vaccine was tested on 30,000 to 60,000 human volunteers to produce the vaccine and ensure its side effects [61]. Freedom of health is a topic that was first discussed in the United States and people wanted freedom of use of the vaccine, but this discussion was not just about vaccines, and before that these people wanted the freedom to use the mask and social distance [62].

There have been many rumors about vaccines, one of which is that GMOs, or genetically modified organisms, have been linked to the vaccine, so far no medical report has been recorded to prove this statement [63]. One of the side effects of vaccines that can manifest itself in the long run is that autoimmune diseases in individuals (especially genetically predisposed individuals) increase the risk of side effects [64]. For example, interferon-blocking autoimmune diseases can cause thrombosis [65]. However, there have been no reports of severe side effects in people with autoimmune diseases, although we need further studies on the effect of COVID-19 vaccines on people with autoimmune diseases such as myasthenia gravis [66].

It should be noted that we do not have anything like the best vaccine, which means that although the effectiveness of the vaccine is higher, its effectiveness is higher, but the term "best vaccine" can not be used due to differences in immune response in different people[67].One of the major concerns of people, especially those with underlying diseases, is that they believe that the vaccine production process has accelerated and that the long-term effects of vaccines have not been fully and definitively identified.

As a result, large numbers of people have refused to be vaccinated. There are also people who believe that if they strengthen their immune system, there is no need to get vaccinated and fear the risk of side effects [68]. Reasons for hesitation in getting vaccinated are similar among different ethnic groups. For example, some believe that the vaccine should not be trusted, and on the other hand, several groups of people were more concerned about the side effects of the vaccine [69]. Guillain-Barré syndrome (GBS) is a neuroimmune disease that includes an inflammatory polyradiculonuropathy associated with viral infections [70 and 71]. People with this disease in some cases suffer from respiratory failure, which should be considered in the vaccination of these people [72].

Short-term side effects of some indicator vaccines:

- Pfizer: fever, cough, chills, diarrhea or vomiting, sore throat and ....
- Moderna: fever (usually below 38 $^{\circ}C$), sore throat, olfactory and taste disorders, myalgia, etc.
- AstraZeneca: fever (usually below 38 $^{\circ}C$), shortness of breath, cough, anosmia, etc. [73].

The biggest current vaccination problem in the world is the fear of long-term side effects of existing vaccines. Although, as mentioned earlier, this possibility is very low, but vaccination can still have long-term side effects, which may be observed in some vaccines over time, but as mentioned, this possibility is very low and better. Ignore it because the side effects of vaccines are normal and refusing to get vaccinated increases the risk of death.

References

[1]. Mousavizadeh, L., & Ghasemi, S. (2021). Genotype and phenotype of COVID-19: Their roles in pathogenesis. Journal of Microbiology, Immunology and Infection. 54(2):159-163.

[2]. Ouassou, H., Kharchoufa, L., Bouhrim, M., Daoudi, N. E., Imtara, H., Bencheikh, N., ... & Bnouham, M. (2020). The Pathogenesis of coronavirus disease 2019 (COVID-19): Evaluation and prevention. Journal of immunology research, 10:1357983.

[3]. Ren, L. L., Wang, Y. M., Wu, Z. Q., Xiang, Z. C., Guo, L., Xu, T., ... & Wang, J. W. (2020). Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chinese medical journal. 133(9): 1015-1024.

[4]. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 395(10223): 497-506.

[5]. Wang, W., Tang, J., & Wei, F. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. Journal of medical virology, 92(4): 441-447.

[6]. Carlos, W. G., Dela Cruz, C. S., Cao, B., Pasnick, S., & Jamil, S. (2020). Novel Wuhan (2019-nCoV) Coronavirus. Am J Respir Crit Care Med, 7: 8.

[7]. Rothan, H. A., & Byrareddy, S. N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity, 109: 102433.

[8]. Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of virology, 94(7): e00127-20.

[9]. Jamwal, S., Gautam, A., Elsworth, J., Kumar, M., Chawla, R., & Kumar, P. (2020). An updated insight into the molecular pathogenesis, secondary complications and potential therapeutics of COVID-19 pandemic. Life sciences, 25: 118105.

[10]. Toumi M, and Ricciardi W. (2015). The economic value of vaccination: why prevention is wealth. J Market Access Health Policy.3:29204.

[11]. Sumirtanurdin, R., & Barliana, M. I. (2021). Coronavirus disease 2019 vaccine development: an overview. Viral Immunology, 34(3): 134-144.

[12]. Du L, Yang Y, Zhou Y, et al. MERS-CoV spike protein: a key target for antivirals. Expert Opin Ther Targets. 21(2):131–143.

[13]. Wang C, Zheng X, Gai W, et al. (2017). Novel chimeric virus-like particles vaccine displaying MERS-CoV receptor-binding domain induce specific humoral and cellular immune response in mice. Antiviral Res. 140:55–61.

[14]. Li E, Chi H, Huang P, et al. (2019). A novel bacterium-like particle vaccine displaying the MERS-CoV receptor-binding domain induces specific mucosal and systemic immune responses in mice. Viruses11 (9):E799.

[15]. Muthumani K, Falzarano D, Reuschel EL, et al. (2015). A synthetic consensus anti-spike protein DNA vaccine induces protective immunity against Middle East respiratory syndrome coronavirus in nonhuman primates. Sci Transl Med. 7(301):301ra132.

[16]. Haagmans BL, van den Brand JM, Raj VS, et al. (2016). An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels. Science. 351 (6268):77–81.

[17]. Du L, Tai W, Yang Y, et al. (2016). Introduction of neutralizing immunogenicity index to the rational design of MERS coronavirus subunit vaccines. Nat Commun. 7:13473.

[18]. Coleman CM, Venkataraman T, Liu YV, et al. (2016). MERS-CoV spike nanoparticles protect mice from MERS-CoV infection. Vaccine. 35 (12):1586–1589.
[19]. Zhang, N., Shang, J., Li, C., Zhou, K., & Du, L. (2020). An overview of Middle East respiratory syndrome coronavirus vaccines in preclinical studies. Expert Review of Vaccines, 19(9): 817-829.
[20]. Mou H, Raj VS, van Kuppeveld FJ, et al. (2013). The receptor binding domain of the new Middle East respiratory syndrome coronavirus maps to a 231-residue region in the spike protein that efficiently elicits neutralizing antibodies. J Virol. 87(16):9379–9383.
[21]. Zhang J, Zeng H, Gu J, et al. (2020). Progress and prospects on vaccine development against SARS-CoV-2. Vaccines 8:E153.
[22]. World Health Organization. Types of vaccine and adverse reactions. 2020. https://www.who.int/vaccine_safety/initiative /tech_support/Part-2.pdf (accessed April 23, 2020).
[23]. Mao HH, Chao SJCAoPB. Advances in Vaccines. Adv Biochem Eng Biotechnol.2020; 171:155-88.
[24]. Callaway, E. (2020). Coronavirus Vaccines. Nature, 580: 577.
[25]. Rasmussen, S. A., Kelley, C. F., Horton, J. P., & Jamieson, D. J. (2021). Coronavirus disease 2019 (COVID-19) vaccines and pregnancy: what obstetricians need to know. Obstetrics and gynecology, 137(3): 408.
[26]. Onyeaka, H., Al-Sharify, Z. T., Ghadhban, M. Y., & Al-Najjar, S. Z. (2021). A review on the advancements in the development of vaccines to combat coronavirus disease 2019. Clinical and Experimental Vaccine Research, 10(1): 6.
[27]. Dolzhikova I, Tokarskaya E, Dzharullaeva A, Tukhvatulin A, Shcheblyakov D, Voronina O, et al. Virus-vectored Ebola vaccines. Acta Naturae (англоязычная версия). 2017; 9(3):4-11.
[28]. Zandi, M., Rashid, S., Nasimzadeh, S., Pourhossein, B., & Fazeli, M. (2020). A Snapshot of Different Types of Under Research Vaccines against COVID-19: A Review. Archives of Medical Laboratory Sciences, 6: 1-7.
[29]. Plotkin S. (2016). Vaccines: correlates of vaccine-induced immunity. Clin infect Dis 47:401–409.
[30]. Pulendran B, and Ahmed R. (2011). Immunological mechanisms of vaccination Nat Immunol 12:509–517
[31]. Liu MA. (2019). A comparison of plasmid DNA and mRNA as vaccine technologies. Vaccines 7:37.
[32]. Usmani, S. S., & Raghava, G. P. (2020). Potential challenges for coronavirus (SARS-CoV-2) vaccines under trial. Frontiers in immunology, 11: 2562.
[33]. Zhou, X., Jiang, X., Qu, M., Aninwene, G. E., Jucaud, V., Moon, J. J., ... & Khademhosseini, A. (2020). Engineering antiviral vaccines. ACS nano, 14(10): 12370-12389.
[34]. https://www.catie.ca/en/treatmentupdate/treatmentupdate-239/covid-19/messenger-rna-novel-approach-coronavirus-vaccines.
[35]. Amanat, F., & Krammer, F. (2020). SARS-CoV-2 vaccines: status report. Immunity, 52(4), 583-589.
[36]. Zhou, P., Li, Z., Xie, L., An, D., Fan, Y., Wang, X., ... & Li, Q. (2021). Research progress and challenges to coronavirus vaccine development. Journal of Medical Virology. 93(2):741-754.
[37]. Ma, C., Su, S., Wang, J., Wei, L., Du, L., & Jiang, S. (2020). From SARS-CoV to SARS-CoV-2: safety and broad-spectrum are important for coronavirus vaccine development. Microbes and infection, 22(6-7): 245-253.
[38]. Lauring, A. S., Jones, J. O., & Andino, R. (2010). Rationalizing the development of live attenuated virus vaccines. Nature biotechnology, 28(6): 573-579.
[39]. Vignuzzi, M., Wendt, E., & Andino, R. (2008). Engineering attenuated virus vaccines by controlling replication fidelity. Nature medicine, 14(2): 154-161.
[40]. Jaume, M., Yip, M. S., Cheung, C. Y., Leung, H. L., Li, P. H., Kien, F., ... & Peiris, J. M. (2011). Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH-and cysteine protease-independent FcγR pathway. Journal of virology, 85(20): 10582-10597.

[41]. Wang, S. F., Tseng, S. P., Yen, C. H., Yang, J. Y., Tsao, C. H., Shen, C. W., ... & Huang, J. C. (2014). Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochemical and biophysical research communications, 451(2), 208-214.
[42]. Jaume, M., Yip, M. S., Kam, Y. W., Cheung, C. Y., Kien, F., Roberts, A., ... & Altmeyer, R. (2012). SARS CoV subunit vaccine: Antibodymediated neutralisation and enhancement.18 Suppl 2: 31-6.
[43]. Motta, M. (2021). Can a COVID-19 vaccine live up to Americans' expectations? A conjoint analysis of how vaccine characteristics influence vaccination intentions. Social Science & Medicine, 272, 113642.
[44]. Thomas, K. (2020). New Pfizer results: Coronavirus vaccine is safe and 95% effective. The New York Times, 18.
[45]. Kaplan, R. M., & Milstein, A. (2021). Influence of a COVID-19 vaccine's effectiveness and safety profile on vaccination acceptance. Proceedings of the National Academy of Sciences, 118(10).
[46]. S. M. Wishik, Attitudes and reactions of the public to health programs. Am. J. Public Health Nations Health. 48: 139–141.
[47]. Mahase, E. (2021). Covid vaccine could be rolled out to children by autumn. BMJ: British Medical Journal (Online), 372.
[48]. Sah, R., Shrestha, S., Mehta, R., Sah, S. K., Raaban, A. R., Dharma, K., & Rodriguez-Morales, A. J. (2021). AZD1222 (Covishield) vaccination for COVID-19: Experiences, challenges and solutions in Nepal. Travel medicine and infectious disease.40: 101989.
[49]. Depar, U. S. (2021). www.cdc.gov/coronavirus/vaccines.
[50]. Wadman, M., & You, J. (2017). The vaccine wars.
[51]. Yin, F., Wu, Z., Xia, X., Ji, M., Wang, Y., & Hu, Z. (2021). Unfolding the determinants of COVID-19 vaccine acceptance in China. Journal of medical Internet research, 23(1), e26089.
[52]. de Vrieze, J. (2020). Reinfections, still rare, provide clues on immunity. 20;370(6519):895-897
[53]. Callaway, E. (2020). Oxford covid vaccine results puzzle scientists. Nature, 588: 16-18.
[54]. Cyranoski D. (2020). Why emergency COVID-vaccine approvals pose a dilemma for scientists. Nature 588(7836):18-19. [doi: 10.1038/d41586-020-03219-y] [Medline: 33230275]
[55]. Jung, J. (2021). Preparing for the coronavirus disease (COVID-19) vaccination: evidence, plans, and implications. Journal of Korean Medical Science, 36(7) 123-135.
[56]. Cabanillas B, Akdis C, Novak N. Allergic reactions to the first COVID-19 vaccine: a potential role of Polyethylene glycol? Allergy. Forthcoming. DOI: 10.1111/all.14711.
[57]. Cirillo, N. (2021). Reported orofacial adverse effects of COVID-19 vaccines: the known and the unknown. Journal of Oral Pathology & Medicine, 50(4): 424-427.
[58]. Huang, L., Rong, Y., Pan, Q., Yi, K., Tang, X., Zhang, Q., ... & Wang, F. (2020). SARS-CoV-2 vaccine research and development: conventional vaccines and biomimetic nanotechnology strategies. Asian Journal of Pharmaceutical Sciences. 16(2): 136-146.
[59]. Petrovsky N. (2015). Comparative safety of vaccine adjuvants: a summary of current evidence and future needs. Drug Saf. 38:1059–74.
[60]. López-Sagaseta, J., Malito, E., Rappuoli, R., & Bottomley, M. J. (2016). Self-assembling protein nanoparticles in the design of vaccines. Computational and structural biotechnology journal, 14: 58-68.
[61]. Pronker ES, Weenen TC, Commandeur H, Claassen EHJHM, Osterhaus ADME. (2013). Risk in vaccine research and development quantified. PLoS ONE;8(3):e57755. doi: 10.1371/journal.pone.0057755.
[62]. Hotez, P., Batista, C., Ergonul, O., Figueroa, J. P., Gilbert, S., Gursel, M., ... & Bottazzi, M. E. (2021). Correcting COVID-19 vaccine misinformation: Lancet Commission on COVID-19 vaccines and therapeutics task force members. E. ClinicalMedicine, 33: 234- 254.
[63]. Palm, R., Bolsen, T., & Kingsland, J. T. (2021). The Effect of Frames on COVID-19 Vaccine Resistance. Frontiers in Political Science, 3: 41.
[64]. Shoenfeld, Y. (2020). Corona (COVID-19) time musings: our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. Autoimmunity reviews, 19(6): 102538.

[65]. Forni, G., & Mantovani, A. (2021). COVID-19 vaccines: where we stand and challenges ahead. Cell Death & Differentiation, 28(2); 626-639.

[66]. Novelli L, Motta F, De Santis M, Ansari AA, Gershwin ME, Selmi C. (2020). The JANUS of chronic inflammatory and autoimmune diseases onset durin COVID-19 - a systematic review of the literature. J Autoimmunity.117:102592. https://doi.org/10. 1016/j.jaut.2020.102592.

[67]. Muppidi S, Guptill JT, Jacob S, Li Y, Farrugia ME, Guidon AC, et al. (2020). COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). Lancet Neurol. 19:970–1.

[68]. Momplaisir, F., Haynes, N., Nkwihoreze, H., Nelson, M., Werner, R. M., & Jemmott, J. (2021). Understanding drivers of COVID-19 vaccine hesitancy among Blacks. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. Clin Infect Dis. 2021 Feb 9;ciab102. doi: 10.1093/cid/ciab102.

[69]. Robertson, E., Reeve, K. S., Niedzwiedz, C. L., Moore, J., Blake, M., Green, M., ... & Benzeval, M. J. (2021). Predictors of COVID-19 vaccine hesitancy in the UK household longitudinal study. Brain, behavior, and immunity, 94: 41-50.

[70]. Caress, J. B., Castoro, R. J., Simmons, Z., Scelsa, S. N., Lewis, R. A., Ahlawat, A., & Narayanaswami, P. (2020). COVID-19–associated Guillain-Barré syndrome: The early pandemic experience. Muscle & nerve, 62(4): 485-491.

[71]. Haber, P., Sejvar, J., Mikaeloff, Y., & DeStefano, F. (2009). Vaccines and guillain-barre syndrome. Drug Safety, 32(4): 309-323.

[72]. Lunn, M. P., Cornblath, D. R., Jacobs, B. C., Querol, L., van Doorn, P. A., Hughes, R. A., & Willison, H. J. (2021). COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. Brain, 144(2): 357-360.

[73]. Stafford, I. A., Parchem, J. G., & Sibai, B. M. (2021). The coronavirus disease 2019 vaccine in pregnancy: risks, benefits, and recommendations. American Journal of Obstetrics and Gynecology, 224(5): 484-495.