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Pathogenicity of CORONA Virus and Mechanism of Various Vaccines Against COVID-19

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Abstract

The Corona Virus Disease is a pandemic that originated from Wuhan, China in late 2019 and spread throughout the world. It caused major disruptions and unprecedented problems throughout the world, particularly in the healthcare systems. The severe coronavirus acute syndrome 2 (SARS-CoV-2) infected 120 million people around the world by March 2021. The replication of the freshly produced virus' RNA genome occurs with the assistance of RNA polymerase. This dangerous virus can be prevented only by the means of vaccination. For several decades, vaccinations have been the most effective method of preventing the rapid spread of infectious diseases. Vaccines give protection in a variety of ways, which vary depending on the type of vaccine administered. After receiving any type of vaccination, the body produces T-lymphocytes and B-lymphocytes which produce antibodies against pathogenic antigens and remember how to fight the virus in the future if it is exposed. Antigen subunit vaccines, viral vector vaccines, mRNA vaccinations, DNA vaccinations, and live attenuated vaccinations are some of the different forms of vaccines available against COVID-19. This study concluded that a safe and effective COVID-19 vaccine that can elicit a significant immune response to bring this pandemic to a close is an urgent priority. Identifying international finance methods to assist in the development, production, and stockpiling of coronavirus vaccines is considered a top priority by all parties. This pandemic may serve as a model for future coronavirus transmission into mammals, which has prompted international experts to not only investigate the outbreak but also predict future transmission in the future.

Keywords: *COVID-19, RNA genome, Vaccine, Working mechanism*

1.Introduction:

The Coronavirus Disease (COVID-19) is a pandemic that outbreak from Wuhan China in late 2019 (Yu et al., 2020). It has produced serious disturbances and unprecedented problems around the whole world including in worldwide healthcare systems (S. Chen et al., 2020). Severe corona viral acute syndrome 2 (SARS-CoV-2) caused severe viral pneumonia which began in December 2019 in Wuhan, China, infected over 120 million individuals and caused 2,66 million deaths on 16 March 2021 (Dong et al., 2020).

COVID-19 mainly affects the respiratory system with several symptoms, ranging from moderate rhino rhea to severe dysfunctions in breathing (Huang et al., 2020). Commonly, the coronavirus is more lethal

to elderly people living with co-morbidities such as high blood pressure, obesity, diabetes and renal disease (Bhatraju et al., 2020; Bornstein et al., 2020; Elhadi et al., 2021).

Pakistan needs ventilators, hospital clothing and personal protective equipment for the fight against the current disease with a limited budget (Dailytimes.com.pk., 2020). Despite the strict measures, 260,000 major occurrences with over 5,000 deaths were reported nationally as of 17 July 2020. In early March, provincial administrations enacted a national lockdown, unhappily opposed by hard-line clergy and religious activists who called on people to pray in congregation in Mosque. There have been countless mass meetings at the national level with little information about the epidemic during this epidemic (Ladiwala et al., 2021; Salman, 2020).

1.1. Structure of CORONA VIRUS

Coronaviruses are pleomorphic, encapsulated viruses differentiated from other viruses by a distinctive fringe of S projections on their surface. The virus's positive single-stranded RNA genome forms a complex structure with the nucleocapsid (N) protein when the N protein is present, resulting in helical nucleocapsids. The genome was polyadenylated, and the capsid protein was introduced (Carter et al., 2007). Genomic comparison of SARS-Corona virus and SARS-Corona virus-2 discovered that the two viruses shared 79 percent of their amino acid sequences, with 380 amino acid alterations primarily identified in the NSP genes. These alterations were found in the immune-dominant S protein (27 amino acid changes), as well as the NSP3 and NSP2 proteins (102 and 61 amino acid substitutions, respectively). E protein, NSP 7, NSP 13, and a few auxiliary proteins' amino acid concentrations were altered, on the other hand, had a minimal effect (Wu et al., 2020). Both SARS-Corona virus and SARS-Corona virus-2 must initially connect to a common host receptor known as hACE2, even though SARS-CoV-2 binds to the receptor with higher affinity than SARS-CoV. According to sequencing studies of the two viruses, MERS-CoV employs a completely different receptor, Dipeptidyl Peptidase 4 (DPP4), then SARS-CoV-2, and the virus is only remotely linked to SARS-CoV-2, with around 50% sequence similarity (Lu, 2020).

1.2. Mechanism of pathogenicity and life cycle of COVID-19 Virus

The transcribing and translation operations get started. (For an example, see Fig. 1.) This is accomplished with the help of an enzyme known as RNA-dependent RNA polymerase, which uses a negative stand template to replicate the newly created virus's RNA genome (see Figure 1) (Mittal et al., 2020; Sanders et al., 2020). SARS-CoV-2 has a higher binding affinity for the angiotensin-converting enzyme 2 (ACE2) receptor than previous SARS strains, allowing it to spread faster throughout the body (Gussow et al., 2020; Mittal et al., 2020; Sanders et al., 2020). The M protein is by far the most abundant

structural glycoprotein in virus particle structure (Schoeman & Fielding, 2019). It is essential for both nutrition transport through the cell membrane and viral particle shape development. The spike protein, also known as the S protein, is a type I membrane glycoprotein that is responsible for the production of virus peplomers. It's also known as the S protein in some quarters. The N protein's role is to make the viral RNA genome more easily bindable while simultaneously maintaining its stability (E. Kim et al., 2020). According to (Chen et al., 2020), the E protein is necessary for both virus release and viral assembly during pathogenesis, as demonstrated in Figures 1 and 2. SARS-entire CoV-2's genome sequence was examined, and it was identified that the virus had a significant degree of sequence similarity to SARS-CoV-1. (S. Chen et al., 2020). This demonstrates that SARS-CoV-2 is more compatible with the original virus than SARS-CoV.

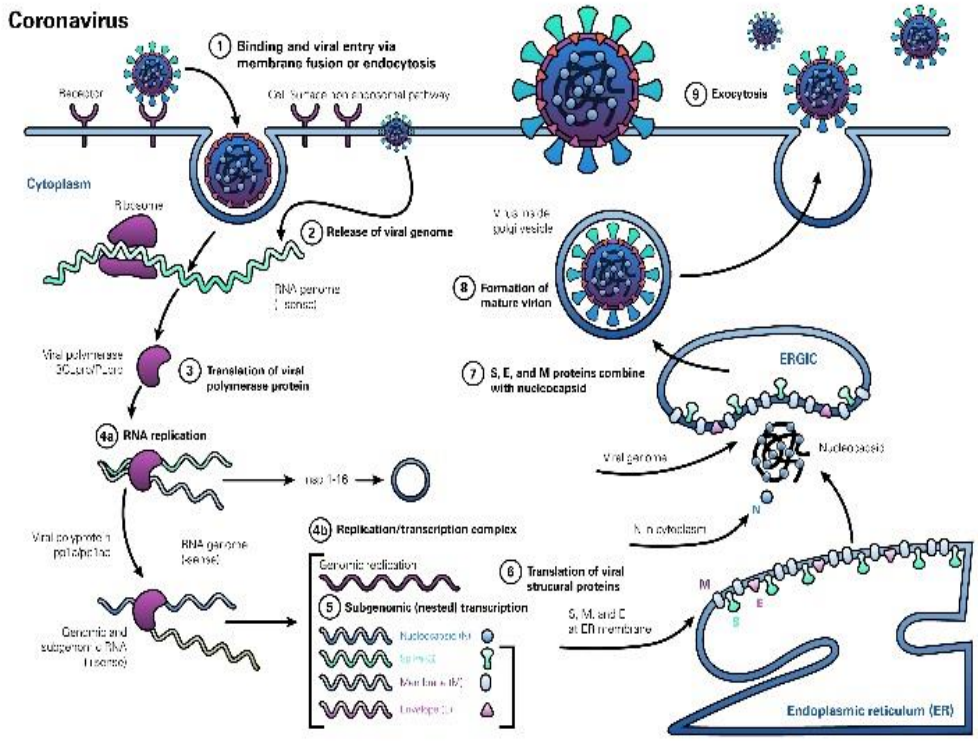

Figure 1: Life cycle of Sar-cov-2 (Chilamakuri & Agarwal, 2021)

1.3. COVID-19 vaccine

Vaccination is the most efficient technique of preventing the rapid spread of infectious diseases for several decades. Several organizations and unaware people have recently begun to spread vaccine misconceptions and conspiracy theories, putting further strain on healthcare officials and personnel (Paterson et al., 2016). The development and distribution of the COVID-19 vaccine is a continuous process. Across Europe and North America, a considerable number of applicants for healthcare

personnel and high-risk groups, such as the elderly and those with chronic diseases, have been made available for recruitment (Voysey et al., 2021). Developing and third world countries are at risk of postponing vaccination due to a variety of factors, including a lack of public awareness, trust, resource constraints, and a scarcity of vaccine supplies, as developed countries receive vast amounts of vaccinations and ignore the needs of other countries (Wouters et al., 2021). As a consequence of this difference, poor nations may be at a high risk of disadvantages as a result of their limited ability to resist COVID-19 in conjunction with their current healthcare system status (Elhadi et al., 2020). The new alliance, which was initiated in September 2020 by several firms with their efforts, 2021 it was able to believe that about 100 million COVID-19 vaccine doses will be distributed to poor countries (Knoll & Wonodi, 2021).

Much effort has been invested in developing vaccines against COVID-19 in the hope of averting a virus outbreak, and the S-protein from SARS-CoV-2 has been used in the majority of vaccine candidates now being developed (Dhama et al., 2020). According to the WHO, there are 158 SARS-CoV-2 vaccine candidates in preclinical or exploratory stages of development (World Health Organization, 2020). ChAdOx1 (University of Oxford), Pathogen-specific aAPC (ShinzenGeno-Immune Medical Institute), INO-4800 (Inovio, Inc.), Ad5-nCoV (CanSino Biologicals), and the drugs mRNA-1273 (Moderna) and LV-SMENP-DC are all being investigated in phase I/II clinical trials (World Health Organization, 2020). Several vaccines are developed around the world, each type of vaccine has its own set of benefits and drawbacks.

Each kind of vaccine is now being evaluated by the FDA for licensure (Wang et al., 2020). Researchers now have access to a range of adjuvant technologies, including MF-59 (Novartis), CpG 1018 (Dynavax), AS03 (GSK), and others, that can be utilized to boost the immunogenicity of a vaccine during development (Andreadakis et al., 2020). This technique is also being used to identify epitopes for SARS-CoV-2 vaccine candidates, which is an additional application of the technique. Using this method, the key B cell epitopes and cytotoxic T cells present in viral proteins recognized by the immune system can be identified. (Gupta et al., 2006).

1.4. Working Mechanism of COVID-19 Vaccine

Vaccines give protection in a variety of ways, which vary depending on the type of vaccine administered. After receiving any type of vaccination, the body produces T-lymphocytes and B-lymphocytes which produce antibodies against pathogenic antigens and remember how to fight the virus in the future if it is exposed (Shah, 2021). After receiving a vaccination, the body begins to produce immune cells i.e. T-lymphocytes and B-lymphocytes (Alberts et al., 2002). A person can get the virus that causes COVID-19 before or after the immunizations and later becomes ill as a result of the vaccine failing to provide adequate protection against the virus. After vaccination, symptoms such as fever may arise as a result

of the immune system's attempt to strengthen its defense. These signs and symptoms are usual and signal that the body is putting together an immunological response to an infection (CDC, 2021).

1.5. Types of COVID-19 Vaccine and their working Mechanism

1.5.1. Protein Sub-unit vaccine

Subunit vaccination is utilized to elicit a long-term protective or therapeutic immune response in the patient via the use of recombinant antigenic proteins or else synthetic peptides (Wang et al., 2020). On the other hand, the sub-unit vaccine has low immunogenicity and the addition of an adjuvant is needed to boost the immune responses enhance by immunization. It is possible to enhance the immunomodulatory cytokine response or raise the antigenic material biological half-life. Adjuvants are used to assist compensate for some of the drawbacks of protein subunit vaccinations (Cao et al., 2018). The most efficient antigen for producing neutralizing antibodies is the S protein (SARS-CoV-2 virus). S Protein is made up of two subunits. This collection of domains can be found in both S1 and S2, with S2 including domains FP, HR 1, and 2, as well as other domains (Ou et al., 2020). The virus invades the cell through endocytosis and makes contact with the hACE2 receptor via the S-Protein. The subunit vaccine's targets are the S-Protein and its antigenic components (Wang et al., 2020). The S glycoprotein can be recognized from the other glycoproteins during the pre-fusion and post-fusion phases. As a result, to protect the epitopes and elicit effective antibody responses, the antigen needs to retain the surface chemistry along with the shape of pre-fusion spike protein (Graham, 2020). As previously indicated, using RBM antigen will boost the counterbalancing antibody response as well as the entire efficacy of vaccination.

Novavax (NVX-CoV2373):

NvxCoV2373 is an immunizing vaccine based on recombinant coronavirus S-Protein expression. It is a pre-fusion, stable protein that is utilized to block the transmission of disease-causing coronaviruses (Coleman et al., 2014). It was possible to express the protein in a stable manner using Baculovirus technology (Tu et al., 2020). According to the business, the Matrix-M adjuvant will be employed by increasing the production of neutralizing antibodies to stimulate the immune response versus the SARS-CoV-2 spike protein. After solo immunization, animal models developed a statistically significant number of anti-spike in nature protein antibodies that inhibit the hACE2 receptor binding region and were capable of triggering SARS-CoV-2 wild-type virus nullifying antibodies (Novavax covid 19 vaccine trial, 2020).

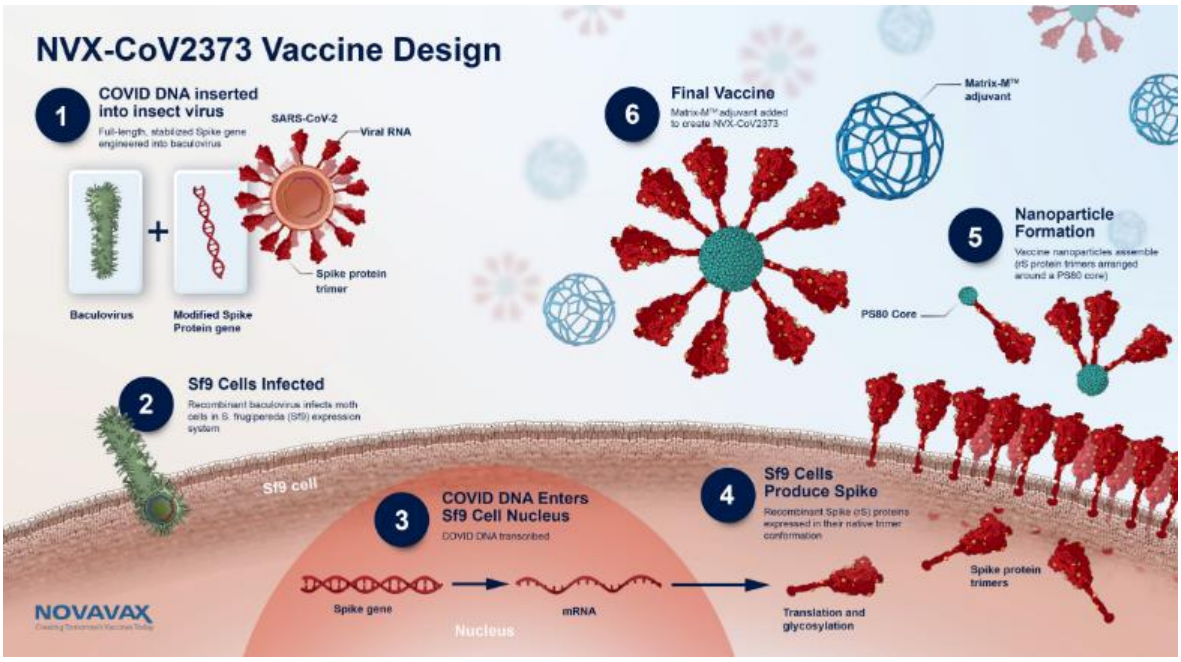

Figure 2: Working mechanism of NOVAVAX (Irfan, 2021)

PittCoVacc: There is now an investigational vaccine for rSARS-CoV-2 being developed using microneedle arrays (MNAs). rSARS-CoV-2 S1 and rSARS-CoV-2-S1fRS09 virus strains are delivered by microneedle arrays (MNAs) to infected people who have rSARS (recombinant immunogens). Two weeks after the start of the preclinical trials, a statistically significant accrue was observed in antigen-specific antibodies in the models of mice which is used in the preclinical trial base studies, indicating that the treatment was effective. The results of the preclinical trials were published in the journal Clinical Immunology. Even though the vaccine had been sterilized via gamma radiation, the immunogenicity of the vaccine was retained, which was a significant achievement in and of itself. When statistically significant antibody titers are detected early in the disease, as well as before boosting, this provides further evidence that the MNA-SARS-CoV-2 vaccine is feasible in clinical practice (Kim et al., 2020).

1.5.2. Viral Vectored vaccines

It is possible to build a vaccine that gives preventive protection against a disease-causing virus through the use of viral vectors. The fact that they are exceedingly precise in terms of carrying genes to their specific target cells, so they were extremely response effective in terms of gene transduction, also they are quite successful in terms of eliciting an immune response are all other characteristics of these vaccines (Ura et al., 2014). Their ability to maintain a high level of antigenic protein expression for a protracted length of time makes them excellent candidates for use in preventative medicine. Vaccines

like these activate and boost cytotoxic T lymphocytes (CTL), which results in the elimination of virus-infected cells as a result of vaccination delivery (Le et al., 2020).

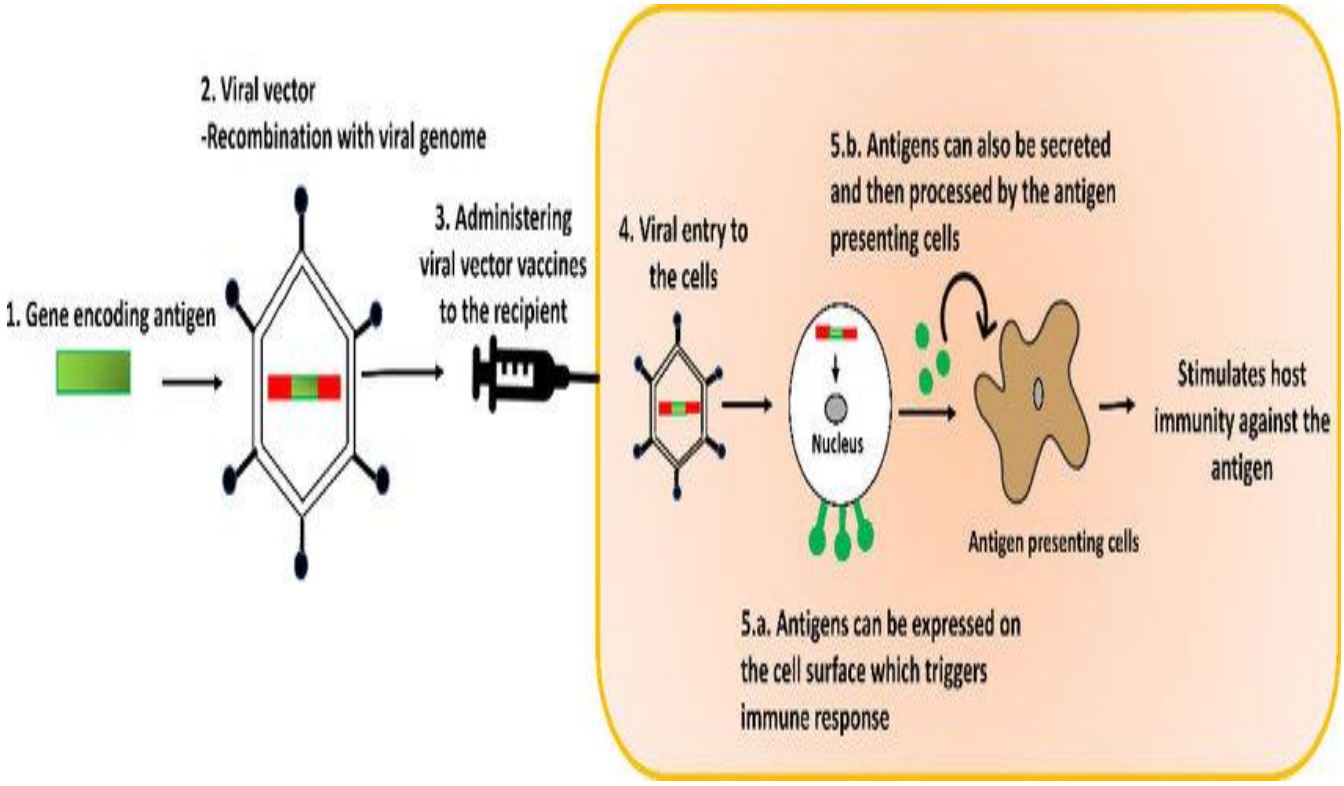

Figure 3: Working mechanism (Shrestha & Iqbal, 2019)

CanSino Biologics (Ad5-nCoV)

Adenovirus type-5 vector encrypts the SARS-CoV-2 recombinant protein (spike protein) (Ad5). The S Protein and plasminogen activator (signal peptide gene) genes were cloned into the Ad5 vector without the E1 and E3 genes. A vaccine was developed using Microbix Biosystems' Admax vaccine development technology. Clinical trials in phase I indicated an effective antibody response. This is the first time. The peak in neutralizing antibodies specific for the RBD and S proteins occurred 28 days following vaccination. The CD4+ and CD8+ T cell responses peaked 14 days after vaccination and then declined. In comparison, preexisting anti-Ad5 immunity had little effect on T cell and antibody responses (Le et al., 2020; Thames et al., 2020; Zhu et al., 2020). A second phase of the trial will examine antibody response in people aged 18 to 60 who have received one of three study dosages. The protocol requires three and six-month follow-up (Thames et al., 2020).

1.5.2. mRNA Vaccine

As a result of the discovery of microRNA (mRNA), a new non-integrating and non-infectious platform with a minimal threat of insertional mutagenesis have developed, enabling the development of novel treatments. Researchers are now looking into non-replicating RNAs, as well as virus-derived self-replicating RNAs, as prospective research areas for the near future. While it is hard to eliminate the immunogenicity of the mRNA, it is conceivable to make modifications to the vaccines to extend their shelf life significantly. Because the mRNA genetic vector is the least immunogenic genetic vector available, anti-vector immunity is avoided, allowing the immunization to be administered several times without creating an adverse reaction to the patient (Zhang et al., 2019). Using this platform, which is highly adaptable and capable of reproducing both the antigen expression and structure observed during the natural infection, vaccines have been developed more quickly than any other platform available (Mulligan et al., 2020).

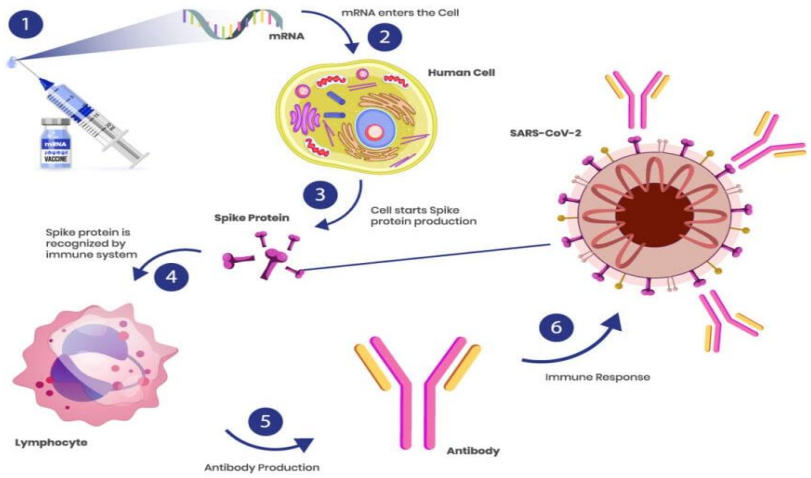

Figure 4: mRNA vaccine working mechanism (oligotherapeutics.org, 2020)

Pfizer (BNT162b1)

With the use of codon optimization, researchers have created a vaccine (mRNA) that encrypts for the trimerized SARS-CoV-2 RBD, which serves as a substantial target for the virus's neutralizing antibodies (nAb). The RBD antigen has been modified to include a T4 fibritin-derived fold on the trimerization domain, which is thought to have resulted in a higher level of immunogenicity in the final vaccine product, according to the researchers. For the most efficient delivery feasible, mRNA has been encapsulated in ionizable cationic lipid nanoparticles with an 80-nm diameter to ensure that it is given

as quickly as possible. It was reported that RBD-specific IgG antibody levels were elevated in the Phase 1/2 clinical trial, with geometric mean concentrations ranging from 8 to 46.3 times higher than those found in convalescent serum. Those discovered in the serum panel, on the other hand, had geometric mean titers of SARS-CoV-2 offset antibodies that were 1.8-2.8 times higher than those found in the convalescent serum panel. This is by prior research findings. No adverse effects were observed or reported as a result of the minor and brief local reactions that occurred, as well as the systemic events that happened as a result of these events. In contrast, no investigation was carried out to determine the participants' safety or immunological reactions after the second dose had been administered for more than 2 weeks and they had been exposed to the second dose (Mulligan et al., 2020).

1.6. DNA Vaccines

The overview of the DNA vaccine, which codes for an adjuvant and antigens that brings an adaptive immune response, was one of the most ground-breaking developments in the field of vaccination. Specifically, it is the transgenic gene that is expressed in the transfected cells, and it is this transgene that is responsible for delivering a consistent supply of transgene-specific proteins that are comparable to those produced by live viruses in the laboratory. It has been shown by researchers in a recent paper that was published in The Journal of Immunology that the antigenic material is also taken up by immature Dendritic Cells, were then also presented to CD8+ and CD4+ T cells on the cell surface, where it stimulates effectual humoral and cellular immune retorts (Hobernik & Bros, 2018).

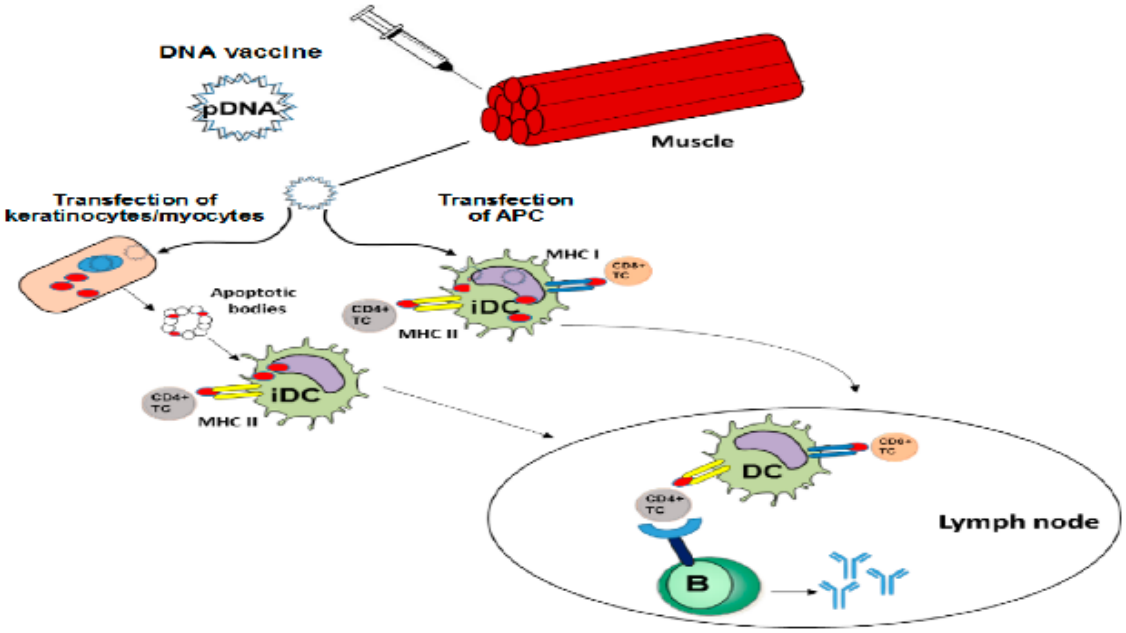

Figure 5: Adaptive immune responses are induced by DNA vaccines (Hobernik & Bros, 2018).

INO-4800

DNA vaccines have the potential to prevent infection caused by CORONA Virus (Safety, 2020). The INO-4800 vaccine also targets the major surface antigen spike protein of the SARS-CoV-2 virus and has been demonstrated to elicit a significant binding and neutralizing antibody response in guinea pigs and mice (Smith et al., 2020). Using a hand-held smart device known as CELECTRA®, the vaccine is administered to the patient. The device utilizes a brief electrical pulse to reversibly generate microscopic pores in the cells, allowing the plasmids to enter the cells (Safety, 2020).

1.7. Live Attenuated Vaccines

DelNS1-SARS-CoV2i-RBD: This vaccine is an influenza-based vaccination strain that has had the NS1 gene removed, which improves the vaccine's efficiency by increasing the vaccine's potency. It has been demonstrated that growing viruses that have been re-organized in chick embryos or Madin Darby Canine Kidney Cells (MDCK) state the RBD domain of the SARS-CoV-2 spike protein on their surfaces were efficient in inhibiting the spread of the virus. Compared influenza virus wild type, this influenza virus can have delivered through the nasal passages and has the potential to be more immunogenic (Kumari et al., 2021).

1.8. Conclusions

SARS-CoV-2 has been declared a pandemic, halting all economic activity globally. Scientists from all across the world are collaborating to repurpose drugs, produce vaccines, and create new technologies. Several COVID-19 vaccine candidates have previously been identified using various methods. Despite continued efforts, no solution has been found. Vaccine production takes time and goes through multiple stages before reaching the clinic. Some phases can be omitted if sufficient data is available now; however, other phases can be skipped to speed up regulatory review, approval, manufacturing, and quality control. Due to the discovery of this unique Coronavirus, scientists have had to design new vaccine approaches. Vaccination must be very effective, have few side effects, and cause no serious diseases, according to the WHO. The vaccine is safe for all ages, including pregnant and nursing moms. To be effective, it must provide rapid protection with a single dose and be safe for one year following therapy.

New vaccines require extensive testing to verify their safety and efficacy. To mass-produce and distribute coronavirus vaccines, scientists will need to create methods and skills. Many pandemic vaccine candidates are presently being developed globally in conjunction with the Coalition for Epidemic Preparedness Innovation (CEPI), an international non-governmental organization. Moderna and the Vaccine Research Centre have produced a virus coated in lipid nanoparticles. Moderna is a biotech company developing mRNA-based vaccinations. Companies including Novavax, Sichuan Clover

Biopharmaceuticals, iBio, and the University of Queensland are all working on S glycoprotein vaccines. The University of Oxford and CanSino Biologics are also working on viral vector-based vaccinations that target the immune system's S glycoprotein. Inovio and Applied DNA Sciences are also working on SARS-CoV-2 S glycoprotein vaccines. Some vaccine candidates will take months, if not years, to develop before being licensed for human use.

Finding a COVID-19 vaccine that is both safe and effective is critical to ending this pandemic. Finding international funding sources to help develop, produce, and stockpile coronavirus vaccines is a major goal for all stakeholders. Possible future coronavirus transmission into mammals has spurred worldwide specialists to not only analyze the outbreak but also anticipate future transmission. If the virus spreads globally, even a one-week delay in vaccine delivery might result in millions of deaths. It also appears to be a scientifically possible endeavor provided sufficient resources are made accessible.

References

1.Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). Lymphocytes and the cellular basis of adaptive immunity. In Molecular Biology of the Cell. 4th edition. Garland Science.

2.Andreadakis, Z., Kumar, A., Román, R. G., Tollefsen, S., Saville, M., & Mayhew, S. (2020). The COVID-19 vaccine development landscape. Nature reviews. Drug discovery, 19(5), 305-306.

3.Bhatraju, P. K., Ghassemieh, B. J., Nichols, M., Kim, R., Jerome, K. R., Nalla, A. K., Greninger, A. L., Pipavath, S., Wurfel, M. M., & Evans, L. (2020). Covid-19 in critically ill patients in the Seattle region—case series. New England Journal of Medicine, 382(21), 2012-2022.

4.Bornstein, S. R., Rubino, F., Khunti, K., Mingrone, G., Hopkins, D., Birkenfeld, A. L., Boehm, B., Amiel, S., Holt, R. I., & Skyler, J. S. (2020). Practical recommendations for the management of diabetes in patients with COVID-19. The lancet Diabetes endocrinology.

5.Cao, Y., Zhu, X., Hossen, M. N., Kakar, P., Zhao, Y., & Chen, X. (2018). Augmentation of vaccine-induced humoral and cellular immunity by a physical radiofrequency adjuvant. Nature communications, 9(1), 1-13.

6.Carter, J., Saunders, V., & Saunders, V. A. (2007). Virology: principles and applications. John Wiley & Sons.

7.CDC. (2021, May 27, 2021). Understanding How COVID-19 Vaccines Work. Retrieved August 14 from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html

8.Chen, Liu, Q., & Guo, D. (2020). Emerging coronaviruses: genome structure, replication, and pathogenesis. Journal of medical virology, 92(4), 418-423.

9.Chen, S., Li, F., Lin, C., Han, Y., Nie, X., Portnoy, R. N., & Qiao, Z. (2020). Challenges and recommendations for mental health providers during the COVID-19 pandemic: the experience of China's First University-based mental health team. Globalization health, 16(1), 1-10.

10.Chilamakuri, R., & Agarwal, S. (2021). COVID-19: Characteristics and therapeutics. Cells, 10(2), 206.

11.Coleman, C. M., Liu, Y. V., Mu, H., Taylor, J. K., Massare, M., Flyer, D. C., Glenn, G. M., Smith, G. E., & Frieman, M. B. (2014). Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice. Vaccine, 32(26), 3169-3174.

12.Dailytimes.com.pk. (2020). Govt Warns Stern Actions Against Traders Who Raise Face Mask Price: Nausheen Hamid. Retrieved 25 June from https://dailytimes.com.pk/567976/govt-warns-stern-actions-against-traders-who-raise-face-mask-price-nausheen-hamid

13.Dhama, K., Sharun, K., Tiwari, R., Dadar, M., Malik, Y. S., Singh, K. P., & Chaicumpa, W. (2020). COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Human vaccines & immunotherapeutics, 16(6), 1232-1238.

14.Dong, E., Du, H., & Gardner, L. (2020). An interactive web-based dashboard to track COVID-19 in real time. The Lancet infectious diseases, 20(5), 533-534.

15.Elhadi, M., Alsoufi, A., Alhadi, A., Hmeida, A., Alshareea, E., Dokali, M., Abodabos, S., Alsadiq, O., Abdelkabir, M., & Ashini, A. (2021). Knowledge, attitude, and acceptance of healthcare workers and the public regarding the COVID-19 vaccine: a cross-sectional study. BMC public health, 21(1), 1-21.

16.Elhadi, M., Msherghi, A., Alkeelani, M., Alsuyihili, A., Khaled, A., Buzreg, A., Boughididah, T., Abukhashem, M., Alhashimi, A., & Khel, S. (2020). Concerns for low-resource countries, with under-prepared intensive care units, facing the COVID-19 pandemic. Infection, disease health, 25(4), 227-232.

17.Graham, B. S. (2020). Rapid COVID-19 vaccine development. Science, 368(6494), 945-946.

18.Gupta, V., Tabiin, T. M., Sun, K., Chandrasekaran, A., Anwar, A., Yang, K., Chikhlikar, P., Salmon, J., Brusic, V., & Marques, E. T. (2006). SARS coronavirus nucleocapsid immunodominant T-cell epitope

cluster is common to both exogenous recombinant and endogenous DNA-encoded immunogens. Virology, 347(1), 127-139.

19.Gussow, A. B., Auslander, N., Faure, G., Wolf, Y. I., Zhang, F., & Koonin, E. V. (2020). Genomic determinants of pathogenicity in SARS-CoV-2 and other human coronaviruses. Proceedings of the National Academy of Sciences, 117(26), 15193-15199.

20.Hobernik, D., & Bros, M. (2018). DNA vaccines—how far from clinical use? International journal of molecular sciences, 19(11), 3605.

21.Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., & Gu, X. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 395(10223), 497-506.

22.Irfan, U. (2021). What the Novavax vaccine means for the global fight against Covid-19. Retrieved August 14 from https://www.vox.com/22533090/novavax-vaccine-trial-covid-19-coronavirus-variants

23.Kim, Lee, J.-Y., Yang, J.-S., Kim, J. W., Kim, V. N., & Chang, H. (2020). The architecture of SARS-CoV-2 transcriptome. Cell, 181(4), 914-921. e910.

24.Kim, E., Erdos, G., Huang, S., Kenniston, T. W., Balmert, S. C., Carey, C. D., Raj, V. S., Epperly, M. W., Klimstra, W. B., & Haagmans, B. L. (2020). Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine, 55, 102743.

25.Knoll, M. D., & Wonodi, C. (2021). Oxford–AstraZeneca COVID-19 vaccine efficacy. The lancet, 397(10269), 72-74.

26.Kumari, D., Prasad, B. D., Dwivedi, P., & Sahni, S. (2021). COVID-19 Vaccines: A possible solution to ongoing pandemic.

27.Ladiwala, Z. F. R., Dhillon, R. A., Zahid, I., Irfan, O., Khan, M. S., Awan, S., & Khan, J. A. (2021). Knowledge, attitude and perception of Pakistanis towards COVID-19; a large cross-sectional survey. BMC public health, 21(1), 1-10.

28.Le, T. T., Andreadakis, Z., Kumar, A., Román, R. G., Tollefsen, S., Saville, M., & Mayhew, S. (2020). The COVID-19 vaccine development landscape. Nat Rev Drug Discov, 19(5), 305-306.

29.Lu, R. (2020). Caracterización genómica y epidemiología del nuevo coronavirus 2019: implicaciones para los orígenes del virus y la unión al receptor. The lancet, 395(10224), 566-568.

30.Mittal, A., Manjunath, K., Ranjan, R. K., Kaushik, S., Kumar, S., & Verma, V. (2020). COVID-19 pandemic: Insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. PLoS pathogens, 16(8), e1008762.

31.Mulligan, M. J., Lyke, K. E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., Raabe, V., Bailey, R., & Swanson, K. (2020). Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Jul [cited 2020 Oct 14]. Google Scholar.

32.Novavax covid 19 vaccine trial. (2020). Novavax to commence human trial for Covid-19 vaccine https://www.clinicaltrialsarena.com/news/novavax-covid-19-vaccine-trial/

33.oligotherapeutics.org. (2020). Facts about mRNA Vaccines and the Decades of Research That Went into Creating Them https://www.oligotherapeutics.org/facts-about-mrna-vaccines-and-the-decades-of-research-that-went-into-creating-them/

34.Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., Guo, L., Guo, R., Chen, T., & Hu, J. (2020). Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nature communications, 11(1), 1-12.

35.Paterson, P., Meurice, F., Stanberry, L. R., Glismann, S., Rosenthal, S. L., & Larson, H. J. (2016). Vaccine hesitancy and healthcare providers. Vaccine, 34(52), 6700-6706.

36.Safety, T. (2020). Immunogenicity of INO-4800 for COVID-19 in Healthy Volunteers. ClinicalTrials. gov.

37.Salman, Y. (2020). Public management reforms in Pakistan. Public Management Review, 1-11.

38.Sanders, W., Fritch, E. J., Madden, E. A., Graham, R. L., Vincent, H. A., Heise, M. T., Baric, R. S., & Moorman, N. J. (2020). Comparative analysis of coronavirus genomic RNA structure reveals conservation in SARS-like coronaviruses. BioRxiv.

39.Schoeman, D., & Fielding, B. C. (2019). Coronavirus envelope protein: current knowledge. Virology journal, 16(1), 1-22.

40.Shah, S. (2021). Covid-19 Pandemic and Vaccine. Journal of Universal College of Medical Sciences, 9(01), 1-3.

41.Shrestha, A., & Iqbal, M. (2019). Enhancing protective efficacy of poultry vaccines through targeted delivery of antigens to antigen presenting cells. Access Microbiology, 1(1A), 66.

42.Smith, T. R., Patel, A., Ramos, S., Elwood, D., Zhu, X., Yan, J., Gary, E. N., Walker, S. N., Schultheis, K., & Purwar, M. (2020). Immunogenicity of a DNA vaccine candidate for COVID-19. Nature communications, 11(1), 1-13.

43.Thames, A. H., Wolniak, K. L., Stupp, S. I., & Jewett, M. C. (2020). Principles Learned from the International Race to Develop a Safe and Effective COVID-19 Vaccine. ACS Central Science, 6(8), 1341-1347.

44.Tu, Y.-F., Chien, C.-S., Yarmishyn, A. A., Lin, Y.-Y., Luo, Y.-H., Lin, Y.-T., Lai, W.-Y., Yang, D.-M., Chou, S.-J., & Yang, Y.-P. (2020). A review of SARS-CoV-2 and the ongoing clinical trials. International journal of molecular sciences, 21(7), 2657.

45.Ura, T., Okuda, K., & Shimada, M. (2014). Developments in viral vector-based vaccines. Vaccines, 2(3), 624-641.

46.Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., Angus, B., Baillie, V. L., Barnabas, S. L., & Bhorat, Q. E. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The lancet, 397(10269), 99-111.

47.Wang, N., Shang, J., Jiang, S., & Du, L. (2020). Subunit vaccines against emerging pathogenic human coronaviruses. Frontiers in microbiology, 11, 298.

48.World Health Organization, W. (2020). Background paper on Covid-19 disease and vaccines: prepared by the Strategic Advisory Group of Experts (SAGE) on immunization working group on COVID-19 vaccines, 22 December 2020.

49.Wouters, O. J., Shadlen, K. C., Salcher-Konrad, M., Pollard, A. J., Larson, H. J., Teerawattananon, Y., & Jit, M. (2021). Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. The lancet.

50.Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P., Meng, J., Zhu, Z., Zhang, Z., & Wang, J. (2020). Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell host & microbe, 27(3), 325-328.

51.Yu, G., Lou, Z., & Zhang, W. (2020). Several suggestion of operation for colorectal cancer under the outbreak of Corona Virus Disease 19 in China. Zhonghua wei chang wai ke za zhi= Chinese journal of gastrointestinal surgery, 23(3), 9-11.

52.Zhang, C., Maruggi, G., Shan, H., & Li, J. (2019). Advances in mRNA vaccines for infectious diseases. Frontiers in Immunology, 10, 594.

53.Zhu, F.-C., Li, Y.-H., Guan, X.-H., Hou, L.-H., Wang, W.-J., Li, J.-X., Wu, S.-P., Wang, B.-S., Wang, Z., & Wang, L. (2020). Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. The lancet, 395(10240), 1845-1854.