International Journal of Engineering Applied Sciences and Technology, 2021
Vol. 6, Issue 6, ISSN No. 2455-2143, Pages 197-206
Published Online October 2021 in IJEAST (http://www.ijeast.com)

MOLECULAR TECHNIQUES ADOPTED AGAINST SARS-COV-2 IN VACCINE DEVELOPMENT

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Abstract - In this review, we attempted to highlight the uniqueness and difference among vaccines. Vaccine is a biological preparation that improves immunity to diseases and protect us from Covid 19. The term vaccine applies to all biological preparations produced by the living organisms, that enhance immunity against disease and the techniques used for the development of vaccines were reverse vaccinology, structural vaccinology, synthetic biology, and vaccine adjuvants. Besides these mRNA vaccines, we will also highlight the Protein subunit vaccines, which include separated proteins from viral or bacterial diseases, vaccines improve the immune system's "memorization" of the pathogen by imitating a milder form of disease, might provide a viable alternative to the mRNA-based coronavirus vaccines and discuss their advantages and disadvantages over the mRNA-based vaccines.

Keywords: COVID-19, mRNA Vaccines, Protein-based Vaccines, Reverse Vaccinology

I. INTRODUCTION

Vaccine is a biological substance that offers active acquired immunity against a specific infectious illness. A vaccination usually comprises an agent that looks like a disease-causing bacterium and is produced from weakened or dead microbes, their toxins, or one of their surface proteins. On average the process of development of a vaccine takes about 10-15 years, and then another two years to get it approved. Vaccines have made a huge difference in the world's health. It's only because of these vaccines that we were able to eradicate the smallpox virus and now have a chance to prevent ourselves from other diseases like polio, tetanus, influenza, hepatitis, chickenpox and diphtheria etc.

Before the COVID19 pandemic, there existed a well-established body of information on the structure and function of coronaviruses that cause illnesses like SARS and MERS, allowing for the rapid development of several vaccine technologies. [1] Previously to COVID19, no vaccine for any infectious illness had ever been developed in less than a few years, and there was no vaccination available to protect people from coronavirus infection. [2] Vaccines have been developed, however, for several animal illnesses caused by coronaviruses, including infectious bronchitis virus in birds, canine coronavirus, and feline coronavirus. [3] Because of the urgency to develop a vaccine for the COVID19 virus, the dangers and failures rate of delivering a safe, effective vaccine was high. Also, the vaccines must go through multiple stages of clinical trials to determine their safety, immunogenicity, efficacy, dosage levels, and side effects. When the virus has shown to be a "moving target" with shifting transmission rates between and within nations.

In India, Covishield (a variant of the Oxford–AstraZeneca vaccine made by the Serum Institute of India) has 74.6% efficacy certified by the government in January 2021and Covaxin (developed by Bharat Biotech) which has 78%efficacy were approved for use from January 2021 . Sputnik V was certified by the government as a third vaccination in April 2021 which has 91.6% efficacy. Pfizer-BioNTech and Moderna claim that their products have a high success rate of up to 95%, depending on the age group, sex, ethnicity, infection status, and dose schedule. and the Johnson & Johnson vaccine efficacy of 72%.

II. VACCINE DEVELOPMENT TECHNOLOGIES

Techniques used for the development of vaccines were reverse vaccinology, structural vaccinology, synthetic biology, and vaccine adjuvants.

Reverse vaccinology is a new approach to design vaccines from genomic information with the help of bioinformatics. This top down, computer data-based approach to vaccine design contrasts with the classical, bottom-up laboratory-based, hypothesis driven analysis of microbes to identify components that could elicit protective.[4] In 2013, remarkable progress was achieved in genome-based vaccinations when an RNA vaccine against a potentially pandemic H7N9 influenza virus was generated in 1 week without cultivating the virus and utilizing genome sequences accessible in public sources.[5] Advantages of the reverse

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vaccinology is that it reduces the total time taken to produce a vaccine, refines the number of proteins to be studied, facilitate the selection process of antigen identification, does not require cultivation of risky microorganism and thus enabling researchers to start developing vaccines just from the genomic sequence.

Structural vaccinology is a technique in which immunogens are rationally engineered using available structural information. Structure-based vaccine design was used for the first time to develop a vaccine that had previously been impossible to develop using other technologies.[6] In 2019, it was shown that the prefusion stabilized F protein induces extraordinary levels of neutralizing antibodies and is suitable for phase III clinical trials. The spike protein of the Middle East respiratory syndrome-related coronavirus (MERS-CoV) was stabilized in the prefusion conformation using structural vaccinology. Advantages of structural vaccinology is that atomic level resolution information can be used to rationally engineer the antigens.

Synthetic biology is a branch of bioengineering that focuses on information biological system design which blends molecular biology and lab automation with biological data-driven in silico design approaches. COVID-19 synthetic biology methods seek to drastically reduce the time it takes to create vaccines, medicines, and diagnostics. The development and clinical testing of RNA vaccines and viral vectors skyrocketed, and both technologies were poised to combat the SARS-CoV-2 epidemic.

Adjuvants are chemicals that are added to vaccinations to boost their effectiveness. Since the 1920s, aluminum phosphate or aluminum hydroxide has been utilized because they assist the body in developing better immunity to the germ in the vaccination. .[7] In 1997, the first modern adjuvant, MF59, was approved for use in influenza vaccines. Several innovative adjuvants have been licensed and used by millions of people ever since. For COVID-19 vaccines, alum, AS03 and MF59 used for inactivated whole virion vaccines.[8] CpG used in subunit vaccine and Matrix-M are being employed in clinical trials. Reverse vaccinology, structural vaccinology, synthetic biology and adjuvants are the technologies merged to develop covid 19 vaccine as show in Figure 1.

III. TYPES OF VACCINES

Vaccines come in a variety with its own set of advantages and efficacy. Sort the vaccines into the categories listed below.

(1) Live Attenuated Vaccine

(2) Whole Virion Inactivated Vero Cell

(3) Toxoid Vaccine

(4) Nucleic Acid Vaccines

(a)DNA Vaccines

(b) mRNA Vaccines

(5) Adenovirus/Viral Vector Vaccines

(6) Protein Subunit Vaccines

1. Live attenuated vaccine is closet to natural infection, they contained a weakened version of a living virus or bacteria, these types of vaccines teach your immune systems. Inactivated vaccines contain an inactivated or dead version of a virus or bacteria. Subunit vaccines contain only a part of virus or bacteria instead of whole pathogen and there is more vaccine like toxoid vaccine, nucleic acid vaccines and adenovirus vaccine.

1. Live Attenuated Vaccine

Live attenuated vaccine is a weakened form of virus or another invader. It contains a version of living microbe that has been weakened in the lab so it can't cause disease, The infectious agent is alive, so cause an infection allowing the immune system to mount a complete defence, however the agent is attenuated and doesn't cause the host to become sick. Live vaccines can usually immunize a person after a single dose, and regular boosters are not required. Examples of live attenuated vaccines are vaccines against measles, mumps and chickenpox. The BCG TB vaccination has non-specific immune system effects, however there is no evidence that it is beneficial against COVID19.

2. Whole-Virion Inactivated Vero Cell

An inactivated vaccination (also known as a killed vaccination) is made up of viral particles, bacteria, or other pathogens which have been cultivated in culture and then destroyed to remove their ability to cause illness.[9] Bharat Biotech produced COVAXIN, India's indigenous COVID-19 vaccine, in conjunction with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). Covaxin works by instructing the immune system to produce antibodies against the coronavirus SARS-CoV-2. Antibodies bind to viral proteins like the spike proteins that pepper the virus's surface. After mass-producing coronaviruses, the researchers utilised a chemical called beta-propiolactone to kill them. By binding to the coronaviruses' genes, the chemical rendered them inactive. Coronaviruses that had been inactivated could no longer multiply. However, their

proteins, including spike, were unaffected. The scientists then took the inactivated viruses and blended them with a little amount of an adjuvant, which is an aluminium-based chemical. Adjuvants improve the immune system's reaction to a vaccination by stimulating it. Covaxin can be injected into the arm without developing Covid-19 since the coronaviruses in it are dead. A few of the inactivated viruses are eaten by an immune cell called an antigen-presenting cell inside of the body. The coronavirus is torn apart by the antigen-presenting cell, which then displays some of the pieces on its surface. The fragment might be detected by a kind of T cell known as a helper T cell. The T cell becomes activated and can help recruit additional immune cells to respond to the vaccination if the fragment fits into one of its surface proteins. A kind of immune cell known as a B cell may potentially come into contact with the inactivated coronavirus. Surface proteins on B cells come in a wide range of forms, and a few of them could be the proper form to hook onto the coronavirus. When a B cell binds to a virus, it can drag some or all of the virus inside, resulting in coronavirus particles on its surfaces. A coronavirus-activated helper T cell can latch on to the same fragment. The B cell is also stimulated when this happens. It multiplies and produces antibodies that are identical in form to their surface proteins. The immune system can respond to a live coronavirus infection after being vaccinated with Covaxin. Antibodies produced by B cells bind to invaders. Antibodies against the spike protein can stop the virus from infecting cells. Antibodies of different types may be able to stop the virus in different ways.

Toxoid Vaccines

A Toxoid vaccine is a chemically or physically modified toxin that is no longer harmful but retains immunogenicity certain pathogens cause disease by secreting an exotoxin includes tetanus, diphtheria, botulism and cholera. Specific physical or chemical modifications of the toxins produces a toxoid, which is vaccine. Benefits of toxoid vaccines are they are safe they cannot cause the disease they prevent and there is no possibility of reversion to virulence, they cannot spread to immunized individuals and they are stable. Toxoid vaccine is not used for COVID-19, because coronavirus does not make any toxins.

Nucleic Acid Vaccines

DNA Vaccines

The development of a DNA vaccine that encodes for the antigen and an adjuvant that triggers the adaptive immune response is the most innovative method to immunisation. Transfected cells express the transgene, which produces a consistent supply of transgene-specific proteins that are very similar to those produced by a living virus.

INO-4800 (Inovio Pharmaceuticals) is a DNA vaccination that protects against SARS-CoV-2 .It employs a SARS-CoV-2 codon optimised S protein sequence with an IgE leader sequence attached. BamHI and XhoI were used to create and digest the SARS-CoV-2 IgE-spike sequence. Under the control of IE CMV and the BGH polyadenylation signal, the digested DNA was integrated into the expression plasmid pGX0001.[10]

mRNA vaccines

Moderna and Pfizer-BioNTech were two of the first organizations to disclose effective vaccines, both of which use lipid nanoparticles to contain an mRNA payload. The mRNA codes for the creation of a SARS-CoV-2-specific antigen, permitting the cell's machinery to manufacture the antigen against which the body will acquire immunity. These vaccines contain 30 g and 100 g RNA, respectively, and require storage at 70 °C (Biontech [Biontech, Mainz, Germany]/Pfizer [Pfizer, New York, NY, USA]) or 20 °C (Moderna [Moderna, Cambridge, MA, USA]) due to their fragility, protection rates against disease were as high as 95 percent and 94.1 percent, respectively, after two vaccinations.[11]Schematic representation of the vaccine MRNA acting on SARS-Cov2 as shown in Figure 2.

The Moderna vaccine, mRNA-1273, codes for the pre-fusion version of the protein and is essentially intact, with the exception of two amino-acid changes at positions 986 and 987, which serve to maintain the protein stable in this pre-fusion state. Four lipids make up the surrounding lipid nanoparticle, the specific structure of which has yet to be revealed. Moderna has already created lipid-nanoparticle-based vaccinations that include 1,2-distearoyl-sn-glycero-3-phosphocholine, cholesterol, and polyethylene glycol-lipid, which might be the case here as well.

The Pfizer-BioNTech vaccine, like the Moderna vaccine, is built on the virus's gene sequence for producing the spike protein. The vaccine works by using messenger RNA, which is genetic material that our cells read in order to produce proteins. If injected straight into the body, the molecule — known as mRNA for short — is fragile and would be ripped apart by our natural enzymes. Pfizer and BioNTech preserve their vaccination by wrapping the mRNA in oily bubbles comprised of lipid nanoparticles. Following injection, the vaccine particles collide with cells and fuse, releasing mRNA. Spike proteins are created once the cell's components read the code. The vaccine's mRNA is eventually eliminated by the cell, leaving no trace behind. Spike proteins generate spikes that migrate to the cell's surface and protrude from their tips. Some of the proteins are also broken down into pieces by the vaccinated cells, which they exhibit on their surface. The immune system can then identify these protruding spikes and spike protein fragments. When a

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vaccinated cell dies, the debris contains numerous spike proteins and protein fragments, which can be picked up by an antigen-presenting cell, a kind of immune cell. The cell's surface is covered with spike protein fragments. When other cells known as helper T cells recognise these pieces, they can raise an alert and assist other immune cells in fighting the infection.

2. Adenovirus Vaccine /Viral vector vaccines

Unlike most traditional vaccinations, viral vector-based vaccinations do not include antigens and instead rely on the body's own cells to manufacture them. They accomplish this by delivering genetic code for antigen, in this instance COVID-19 spike proteins present on the virus's surface, into human cells via a modified virus (the vector). The vaccine simulates what happens during natural infection with some pathogens, mainly viruses, by infecting cells and commanding them to produce huge amounts of antigen, which subsequently triggers an immune response. This has the benefit of inducing a significant cellular immunological response in T cells as well as antibody production in B cells give a long-term and high degree of antigenic protein expression, and so have a lot of promise for preventive usage since these vaccines activate and stimulate cytotoxic T lymphocytes (CTL), which then kill virus-infected cells.[12]The Gamaleya Institute in Moscow (Sputnik V) [4 University of Oxford/AstraZeneca (AstraZeneca, Cambridge, UK) (ChAdOx1 The Serum Institute of India, the world's largest vaccine maker, is producing the Oxford-AstraZeneca vaccine domestically, in the name of COVISHIELD alongside Janssen Pharmaceutica (Janssen Pharmaceutica [pharmaceutical company of Johnson & Johnson].

Chadox1 /COVISHIELD/Oxford AstraZeneca Vaccine

The Oxford-AstraZeneca vaccine (ChAdOx1) uses a chimpanzee-derived adenovirus vector with genetic sequences instructing cellular processes to manufacture the full-length SARS-CoV-2 spike protein. By removing E1 and E3 and inserting a tissue plasminogen activator leader sequence, several alterations to the genetic sequence were made to limit replication and promote translation. Coronavirus genome is integrated with the genome of the adenovirus, allowing these spike proteins to be created in the body itself if the adenovirus enters human cells. So, once this adenovirus is injected into the body in the form of a vaccine, it hooks to the cells and the cells accepts the virus inside, so it goes inside the cell, travels out, and inserts its genome into the nucleus of our cells. These cells' proteins now begin to mature and proliferate, resulting in the creation of plasma cells, which release antibodies against these spikes of protein.

Sputnik

Sputnik is a viral two-vector vaccine that employs two human adenoviruses — a common cold virus – to trigger an immune response by incorporating the gene that encodes the full-length spike protein (S) of SARS-CoV-2.[13-15] The vaccination uses both recombinant adenovirus types 26 and 5 as vectors. The SARS-CoV-2 S protein cDNA was obtained using biotechnology. Both are given into the deltoid muscle, with the Ad26-based vaccination being given on the first day and the Ad5 vaccine being given on the 21st day to increase immune response.[16-18] To hinder replication, the E1 gene was removed from both Ad26 and Ad5. HEK 293 cells with the E1 gene, which is required for viral replication, then generate large amounts of both adenoviruses. Ad5 can occasionally acquire the E1 gene from HEK 293 cells, restoring its replication capabilities.[19] The vaccine may be done in two ways: as a ready-to-use water solution which is frozen at 18 °C or 0 °F or lower at the typical home-freezer storage temperature; and as a freeze-dried powder called "Gam-COVID-Vac-Lyo" that is stored at 2–8 °C or 36–46 °F at the typical home-refrigerator temperature. Before used, the freeze-dried powder must be reconstituted with water.[20] The body begins to create antibodies that are specifically adapted to the coronavirus after being vaccinated. This implies that when the immune response comes into contact with coronavirus for the first time, it will be ready to combat it. The Sputnik vaccine, unlike some other comparable vaccinations, employs two slightly different forms of the vaccine for the first and second doses, which are given 21 days apart. They both aim for the coronavirus's unique "spike," but they employ different vectors - neutralised viruses that carry the spike to the body. The theory is that utilising two distinct formulae strengthens the immune response more than using the same one twice and may provide longer-term protection.[21]

Janssen Ad26.COV2.S

COVID-19 vaccine by Johnson & Johnson.[22] created at janseen vaccine in Netherlands.[23] It's a viral vector vaccine developed on a human adenovirus that's been engineered to include the gene for the SARS-CoV-2 virus's spike protein, which produces COVID-19. Antibodies produced by the body's response of the immune system to this spike protein.[24] This vaccine is developed on the same technology as the Oxford–AstraZeneca COVID-19 vaccine as well as the Sputnik V COVID-19 vaccine.[25]The replication-incompetent recombinant adenovirus type 26 (Ad26) vector encoding t (SARS-CoV-2) spike (S) protein in a stable conformation makes up the Johnson & Johnson COVID-19 vaccine.[26]

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Protein Subunit Vaccines

A subunit vaccine is one that introduces one or more antigens to the immune system without injecting whole or fragmented pathogen particles. Any molecule, such as proteins, peptides, or polysaccharides, might be implicated.[27] Recombinant protein vaccines are regarded a safer method than vaccines produced from live viruses since they are non-replicating and lacking any of the pathogenic elements of an, although attenuated, viral particle.[28] Examples of Protein subunit vaccines are Novovax and in India it is names as Covovax and Corbevax.

Novovax

Novovax is a vaccine nanoparticle specially designed with the only key components of target pathogens are highly purified stable and highly immunogenic offering a cutting edge approach to vaccine development. Novovax is a protein subunit vaccine ,[29] as well as virus like particle vaccine.[30] An engineered baculovirus with a gene for a modified SARS-CoV-2 spike protein is used to make the vaccine. Two proline amino acids were added to the spike protein to stabilize the pre-fusion version of the protein. [31] Once the DNA or RNA sequence of new pathogen has been identified novovax can determine the genes required for vaccine development these genes are genetically synthesized for expression and novovax is proven, baculovirus then infects Sf9 moths cell, which produce and display the spike protein onto their cell membranes. The spike proteins then are extracted and reassembled onto a synthetic lipid nanoparticle with a diameter of fifty nanometers and up to 14 spike proteins on each side. A saponin-based adjuvant is included in the formulation.It is given in 2 doses, 21 days intervals.[32] The objective of vaccine is to elicit long-term antigen-specific antibody responses from plasma cells, as well as to build antigen memory in T-cells and B-cells (ie, humoral and cellular immune response. The vaccine contains a part of the viral antigen from the spike (S) protein; after vaccination, an immunological response to the protein component is induced.[33]

Biological E

Corbevax is a recombinant subunit vaccine produced by Biological-E, which implies it is made up of a particular component of the new coronavirus, spike protein. It uses the same technology as the hepatitis vaccination. As a result, unlike the mRNA vaccines developed by Pfizer and Moderna, which are the first of their type to be brought out against any infection, this two-dose vaccination has been tried and tested, according to the company. Corbevax only injects this spike protein from the virus into the human body to produce an immunological response. Because just the spike protein is used in this vaccine, it is unlikely to be dangerous because the rest of the virus is missing.[34]. Overview of all vaccines with their development technology, type, doses required, method of administration and efficacy is show below in Table 1.

Protein Based Vaccines against SARS-Cov2 may provide advantages over mRNA Based vaccines

Most of the vaccinations that have been authorized thus far are based on mRNA, vectors, or DNA. Because they transmit the coding sequence for the spike antigen rather than just the immunogen itself, vector- and RNA-based vaccines may be created quickly.[35] In terms of price, convenience, production capabilities, transportation, and administering, subunit vaccines outperform nucleic-acid-based vaccines. Protein based vaccine work by simulating a milder type of illness and aiding the immune system's "memorization" of the pathogen. As a result, they include some component of an infected individual capable of eliciting an immune response, like viral genetic material, RNA or DNA, or virus proteins that interact with human cells. Protein based vaccine relatively mild side effect and protein-based vaccine are logistic because it can be refrigerated up to six months. They are simple to make and may be placed into a variety of carriers. In addition, there is room for additional genetic engineering. In addition, when compared to other types of vaccinations, they pose less dangers. Furthermore, they are simple to manufacture on a big scale. These advantages enable them to outperform other forms of vaccines, resulting in increased growth in the worldwide recombinant vaccines market.

IV. DISCUSSION

Covid 19 is a dangerous and contagious illness that causes significant health problems. There is no stopping this deadly disease, which has resulted in the deaths of many people around the world. I am very curious to know how this deadly disease will be ended, so scientists all over the world have developed various vaccines to combat the disease in order to protect people from it due to the efficacy of vaccines. Vaccination is the best option for resuming normal life and contributing to the global economy. This has resulted in a rush to develop vaccinations. The vaccine is believed to be the cheapest COVID-19 vaccine available in India, with the two doses costing less than Rs 400 in total. Currently, India's medicines authority has granted emergency permission to three COVID-19 vaccines: Covishield from the Serum Institute of India (SII), Covaxin from Bharat Biotech, and Sputnik V from Russia. According to the article, all three vaccinations cost between Rs 300 and Rs 1,000. Recombinant protein vaccines missed out on the initial wave of government and commercial financing while having several cases in the clinic for many years. Recombinant vaccines may give an advantage to nucleic acid vaccines, viral vector vaccines and mRNA vaccines because Novovax

is a vaccine nanoparticle specially designed with the only key components of target pathogens are highly purified stable and highly immunogenic offering a cutting-edge approach to vaccine development. Subunit vaccines beat nucleic-acid-based vaccinations in terms of affordability, convenience, production capacity, transportation, and administration. Vaccines operate by mimicking a less severe form of disease and assisting the immune system in "memorizing" the pathogen. As a result, they include some component of an infected person that might provoke an immune response, such as viral genetic material, RNA or DNA, or virus proteins that interact with human cells. Corbevax is recombinant protein vaccine.

V. CONCLUSION

Vaccine technology Improvements in vaccination technology were critical for limiting and preventing infectious illnesses, which still account for around 40% of all fatalities worldwide. Scientists are attempting to address this persistent issue and save lives by changing how existing vaccinations are used, creating novel vaccine delivery methods, and inventing new vaccines. There are different types of vaccine available for COVID -19 which work accordingly to their mechanism but Protein Based Vaccines against SARS-Cov2 may provide advantages over mRNA Based vaccines . Protein-based vaccines operate by mimicking a milder form of infection and assisting the immune system in "memorising" the pathogen. As a result, they include some component of an infected person that might provoke an immune response, such as viral genetic material, RNA or DNA, or virus proteins that interact with human cells. Protein-based vaccines have a low risk of adverse effects, and they may be stored for up to six months in the refrigerator. The majority of SARS-COV-2 subtype protein vaccines primarily target the S-protein to prevent it from attaching to the host Angiotensin-converting enzyme 2 receptor.Tradional vaccines take years or even decades to develop in addition many pathogen have evolved to avoid immunity by tradional vaccines,one of the protein subunit vaccine novovax uses vaccine technology combines the power and speed of genetic engineering to efficiently produce a high class immunogenic vaccine with high efficacy once the RNA or DNA sequence of a new pathogen has been identified novovax can determine the genes required for vaccine development ,Novovax is proven Sf9 insect cell baculuvirous to construct two types of immunogenic that form to form the basis of vaccine that is recombinant protein nanoparticles and virus like particles optimizing the biological responses necessary for active immunity to construct defences superior to other vaccine.

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International Journal of Engineering Applied Sciences and Technology, 2021
Vol. 6, Issue 6, ISSN No. 2455-2143, Pages 197-206
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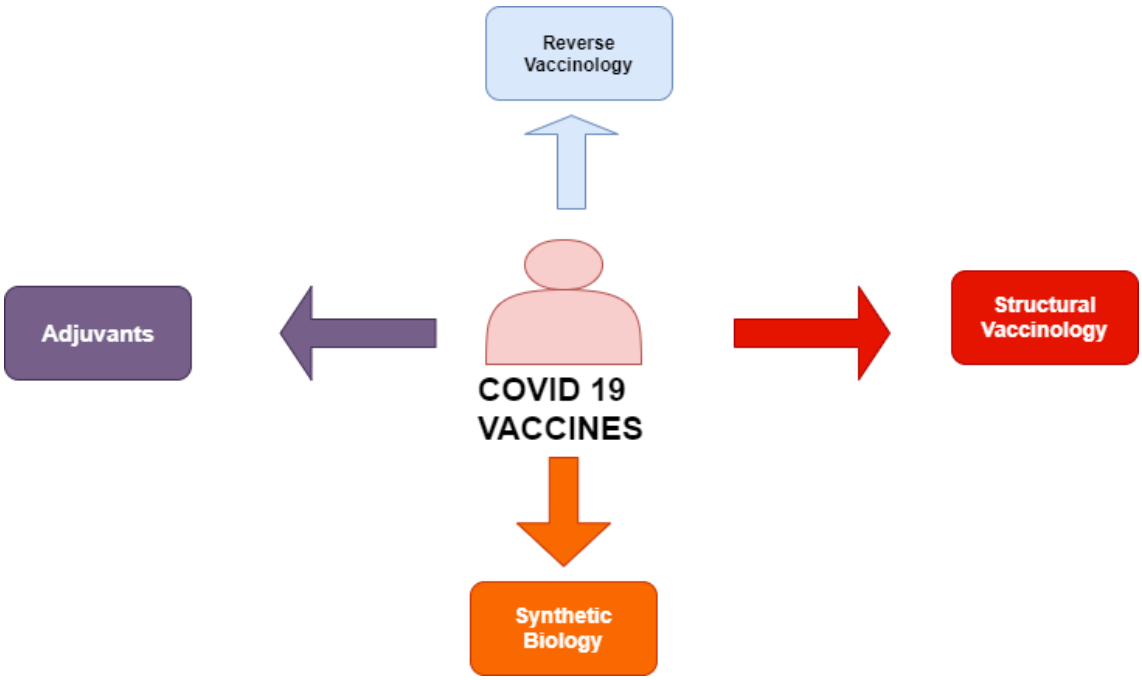
Vaccine	**Vaccine Development Technology**	**Type**	**Doses Required**	**Method for Administration**	**Efficacy**
PFIZER	MRNA technology	mRNA	2	Intramuscular injection	95%
MODERNA	MRNA technology	mRNA	2	Intramuscular injection	94.1%
Janssen Ad26.COV2.S	Tradional virus based technology	VIRAL VECTOR	1	Intramuscular injection	66%
ASTRAZENECA OR COVISHIELD	Viral Vector platform technology	VIRAL VECTOR	2	Intramuscular injection	74.6%
SPUTNIK V	Adenovirus based vector technology	VIRAL VECTOR	2	Intramuscular injection	91.6%
COVAXIN	Whole Virion inactivated Vero cell Technology	INACTIVATED VIRUS	2	Intramuscular injection	78%
NOVOVAX	Recombinant nanoparticle technology	PROTEIN BASED	2	Intramuscular injection	91%
Biological-E	Recombinant protein technology	PROTEIN BASED	2	Intramuscular injection	90%

International Journal of Engineering Applied Sciences and Technology, 2021
Vol. 6, Issue 6, ISSN No. 2455-2143, Pages 197-206
Published Online October 2021 in IJEAST (http://www.ijeast.com)

Summary of all Vaccines.



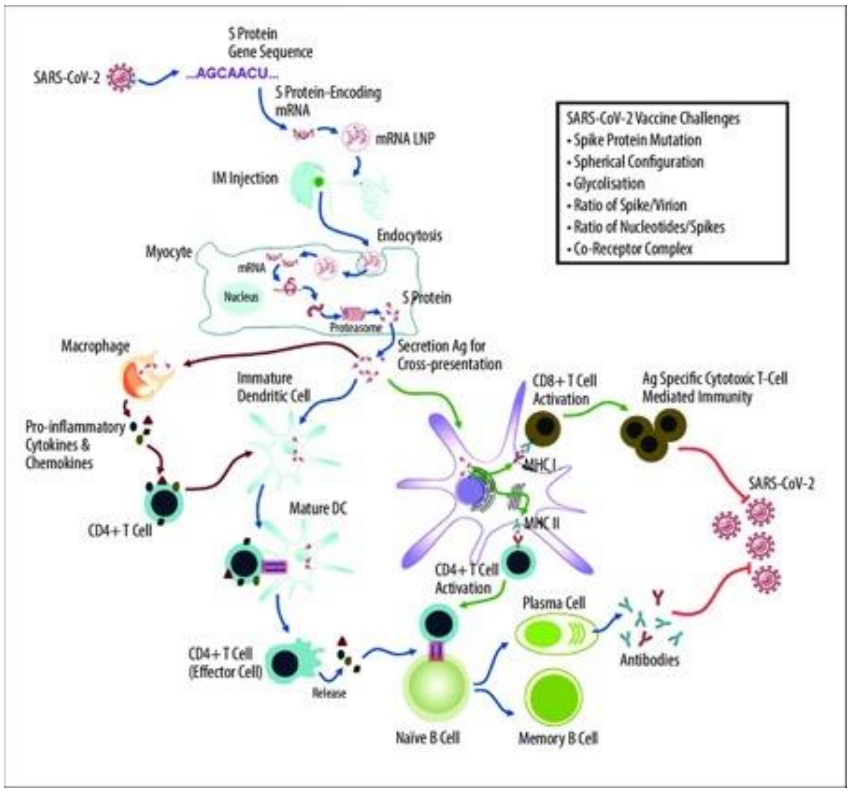


Figure 1. Technological merged to develop a COVID-19 Vaccine.

Figure 2: Schematic diagram of mrna based vaccine targeted to the spike protein (S protein of severe acute respiratory syndrome coronovirus 2(SARS-CoV-2)

(Source: 12 Wang, F., Kream, R. M., & Stefano, G. B. (2020). An evidence based perspective on mRNA-SARS-CoV-2 vaccine development. *Medical science monitor: international medical journal of experimental and clinical research*, *26*, e924700-1.)