


The Race for COVID-19 Vaccines: The Various Types and Their Strengths and Weaknesses

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Abstract

SARS-CoV-2 causes the highly contagious coronavirus disease (COVID-19), first discovered in Wuhan, China, in December of 2019. As of August 21, 2021, over 211 million people have been diagnosed with COVID-19 and 4.42 million people have died from the disease worldwide. The COVID-19 pandemic has adversely affected world economies, global public health infrastructure, and social behaviors. Despite physical distancing and the advent of symptomatic and monoclonal antibody therapies, perhaps the most effective method to combat COVID-19 remains the creation of immunity through vaccines. Scientific communities globally have been diligently working to develop vaccines since the start of the pandemic. Though a few have been authorized for use, the Pfizer vaccine was the first to be given full approval in the United States in August 2021 – being the quickest vaccine to ever be developed. Although several vaccines produced via different approaches are in use, no mortality has been reported thus far from vaccine use. Here, we highlight the latest advances in the development of the COVID-19 vaccines, specifically the lead candidates that are in late-stage clinical trials or authorized for emergency use. As SARS-CoV-2 uses its spike protein to enter a host cell and cause infection, most vaccine candidates target this protein. This review describes the various COVID-19 vaccines - authorized and/or under development - and their composition, advantages, and potential limitations as the world continues to fight this devastating pandemic.

Keywords

Pfizer-BioNTech, moderna, Johnson & Johnson, pandemic, virus infection

SARS-CoV-2 and Covid-19: An Introduction *Molecular Biology*

Coronaviruses are a diverse group of viruses that infect different animals and can cause mild to severe respiratory infections in humans. There are 7 types of coronaviruses that can infect humans: 229E, NL63, OC43, HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2.¹ Though coronaviruses were first identified in the mid-1960s, they did not engender interest until the 2002 severe acute respiratory syndrome (SARS) epidemic caused by the SARS-CoV and 2012 middle eastern respiratory syndrome (MERS) outbreak caused by MERS-CoV.^{2,3} The first human infection caused by a novel type of coronavirus, SARS-CoV-2, was reported in Wuhan, China in December 2019. The disease spread to several other countries and infected many people and subsequently was declared a pandemic by the World Health Organization (WHO) in March 2020. The infectious disease caused by SARS-CoV-2 is known as the coronavirus disease 2019 (COVID-19). SARS-CoV-2 causes an outbreak of an unusual viral pneumonia. COVID-19 is highly transmissible and surpasses SARS and MERS in terms of the number of people it infects and its geographical spread.⁴

Coronaviruses are a family of enveloped positive-sense single-stranded ribonucleic acid (RNA) viruses (Coronaviridae) and their genome size is larger than that of other viruses, ranging between 27 and 34 kilobases.⁵ The SARS-CoV-2 genome has 82% overall sequence identity and >90% sequence identity for essential enzymes and structural proteins with SARS-CoV and MERS-CoV, suggesting similarities in pathogenesis mechanisms.⁶ SARS-CoV-2 has 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Table 1 and Figure 1).⁶ The virus carries the name “coronavirus” due to a distinct appearance of spikes in electron microscopy (Figure 2).

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Table 1. Components and their Functions of Coronaviruses.

Positive sense single stranded RNA	Enables Production of Proteins Needed for Other Elements of the Virus
Envelope	Protects the virus outside of the host
Nucleocapsid (N) protein	Gives the virus its structure and allows for viral replication
Envelope (E) protein	Assists with the assembly of new virus particles once the virus has infected a cell
Membrane (M) protein	Type of E protein that determines the shape of the viral envelope and binds to other structural components
Spike (S) protein	Binds to the host cell surface receptor therefore allowing for virus-cell membrane fusion and virus invasion

The main structural components of coronaviruses with a visual representation provided in [Figure 1](#).

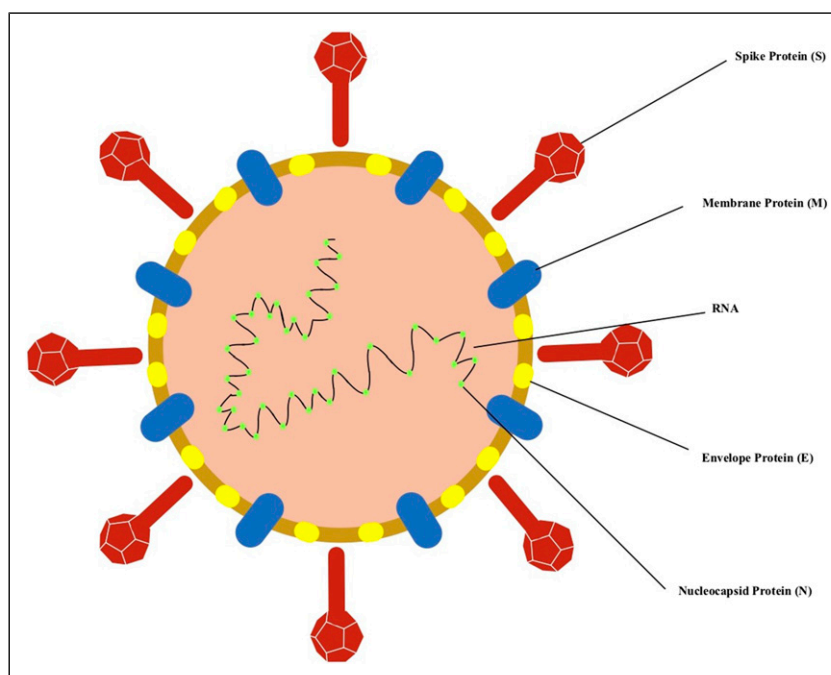


Figure 1. The Structure of SARS-CoV-2. The genome of SARS-CoV-2 is made up of positive sense single stranded RNA and is surrounded by a lipoprotein envelope. Nucleocapsid (N) proteins anchor the viral RNA. Envelope (E) proteins are on the envelope and assist with assembly of new viral particles. Membrane (M) proteins span the envelope and contribute to virus integrity. The spike (S) protein is indicated on the outer membrane and binds to the host cell surface receptor allowing for virus fusion. For full protein descriptions, refer to [Table 1](#).

The S protein of SARS-CoV and SARS-CoV-2 binds to the human angiotensin-converting enzyme 2 (ACE2) receptor. However, the MERS-CoV receptor binds to the dipeptidyl peptidase 4 receptor.^{8,9} ACE2 mRNA is known to be present in all organs while its protein expression has been shown to be abundantly localized in the epithelia of the lung.⁸ The S protein has 2 subunits: S1 or receptor binding domain (RBD), which binds to the host cell-surface receptor, and S2 which mediates viral cell membrane fusion ([Figure 3](#)).¹⁰

Infection

Viruses invade living, normal cells and use host cells to replicate and spread to kill, damage, or change the cells and make a person sick. In the present case, SARS-CoV-2 causes disease which can be asymptomatic or symptomatic where interstitial pneumonia is

a common primary manifestation.¹² Outside of host cells, viruses exist as capsids and are metabolically inert.¹³ While the replication cycle of viruses can vary between different viruses, there are common steps: attachment, viral entry, synthesis, assembly, and release. SARS-CoV-2 binds to host ACE2 receptors with its S proteins and enters the cell. The virus then undergoes uncoating and synthesis of viral proteins and nucleic acid copies are made using the host cell's transcriptional and translational machinery (ribosomes). Since the genetic material of SARS-CoV-2 is positive-sense single stranded RNA, no transcription is needed. Afterward, more viruses are produced from the viral components, assembled, reoated and released from the host cell to infect other cells ([Figure 4](#)).¹³

About 80% of patients with COVID-19 infection experience mild symptoms.¹⁴ Patients may experience lymphopenia and interstitial pneumonia with high levels of pro-inflammatory

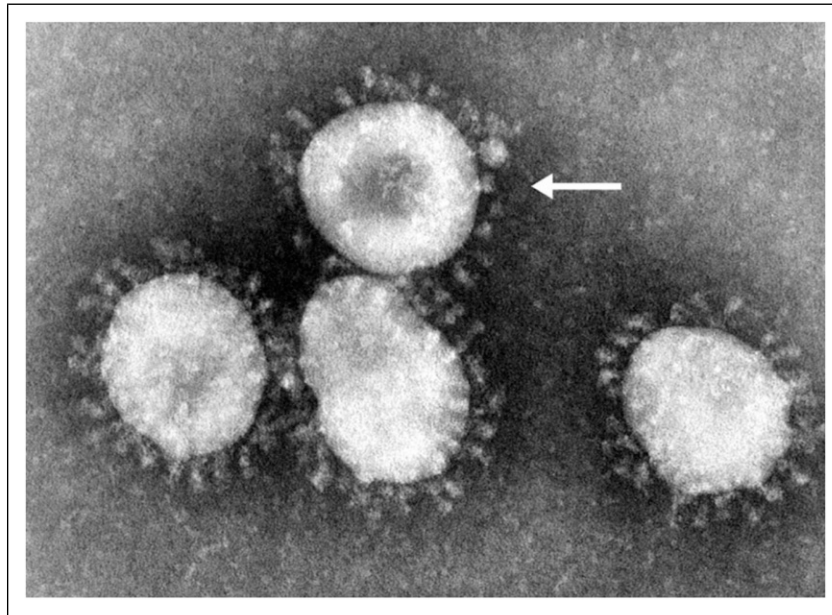


Figure 2. SARS-CoV-2 Microscopic Image. In Latin, corona means crown and the white arrow on this electron microscopy indicates the S protein that surrounds the coronavirus thereby giving the virus its unique name. Courtesy of: Centers for Disease Control and Prevention (CDC) Public Health Image Library (PHIL), identification number 4814.⁷

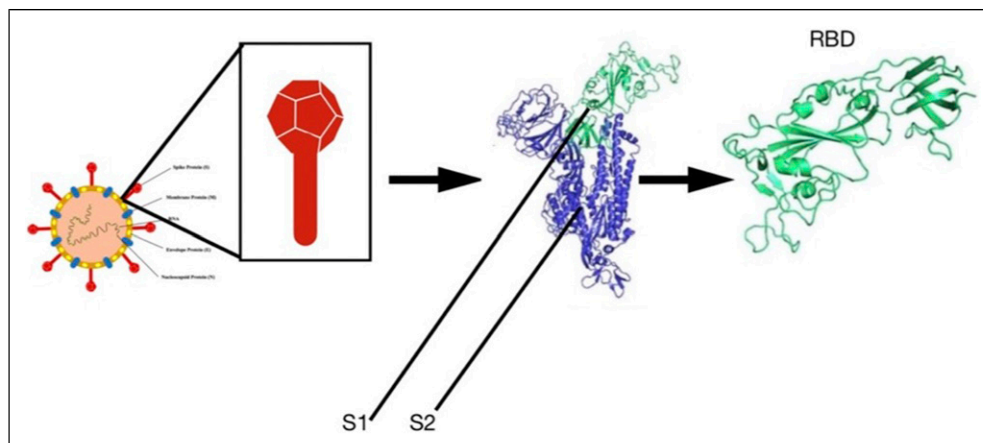


Figure 3. S protein subunits. A 3D picture of the secondary structure of the S protein depicts the S protein's I subunit, green, and S2 subunit, purple.¹¹

cytokines in severe cases of COVID-19.¹⁴ An excessive release of cytokines as a result of COVID-19 may precipitate acute respiratory distress syndrome (ARDS) and exacerbate into respiratory failure, organ failure, and potentially, death.¹⁴

An Introduction to Covid-19 Vaccinees

A vaccine is a biologic that exposes and trains the body's immune system so that it may fight a disease it has not encountered before. Vaccines also contribute to herd immunity - it becomes harder for the disease to spread if enough people are vaccinated. This paper will describe different types of vaccines including nucleic acid vaccines, viral-vectored vaccines, subunit

vaccines, and weakened and inactivated virus vaccines, provide examples of current COVID-19 vaccines under development for each type, and highlight data that allows for expedited vaccine authorization in a pandemic setting.

COVID-19 Vaccine Development

Vaccine development, on average, takes ten to 15 years.¹⁵ However, COVID-19 vaccines authorized for use in the U.S. are covered under an accelerated approval pathway which reduces the timeline to ten to 18 months (Figure 5).¹⁶ It was theorized that the most likely candidates for vaccine would be the structural components of SARS-CoV-2. S protein-based

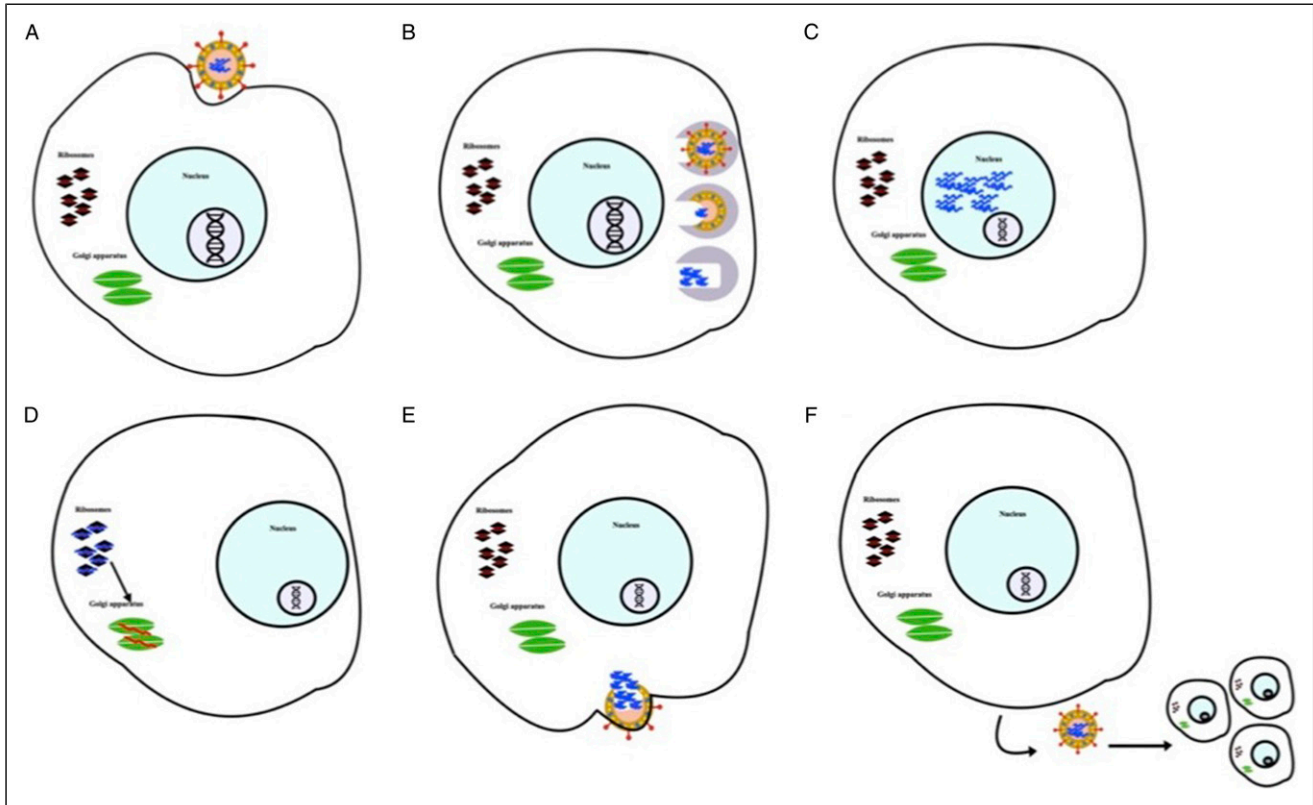


Figure 4. Virus invasion mechanism. The virus attaches to cell receptors and enters the cell (A). Then, it undergoes uncoating to remove S proteins and release its genetic material. In the case of SARS-CoV-2, this is positive-sense single stranded RNA (B). This material then goes into the cell and undergoes transcription (C) and translation (D). Note that in the case of SARS-CoV-2, no transcription takes place because of the genetic material composition. If the genetic material was DNA or negative sense RNA, then transcription would occur. The virus then undergoes genome replication afterwards and is then finally assembled, re-coated (E) and released (F) from the host cell so that it may go on to infect other cells.

Pre-Clinical	Phase I	Phase II	Phase III	Phase IV
Formulation In vitro and In vivo	Safety	Dosing and Safety	Efficacy and Safety	Post Marketing Surveillance
Normal Vaccine Developmental Process				
3-6 years	1-10 years	2-3 years	2-4 years	6 months - 2 years
COVID-19 Vaccine Developmental Process				
0-18 months	2-3 months	3-4 months Shorter if combined with Phase I	6-9 months + 2 year follow up	6 months - 2 years

Figure 5. The vaccine developmental process.

vaccines against SARS and MERS demonstrated potent immune responses and protective effects in pre-clinical and phase I trials; therefore most of the vaccines discussed in this paper focus on eliciting an immune response using the S protein.¹⁷

Clinical Trials. Prior to regulatory approval, a vaccine candidate usually undergoes trials in 3 phases. There are several differences between drug and vaccine developmental phases. In clinical trials for drugs, most participants are those with the disease but for vaccine trials, the participants are

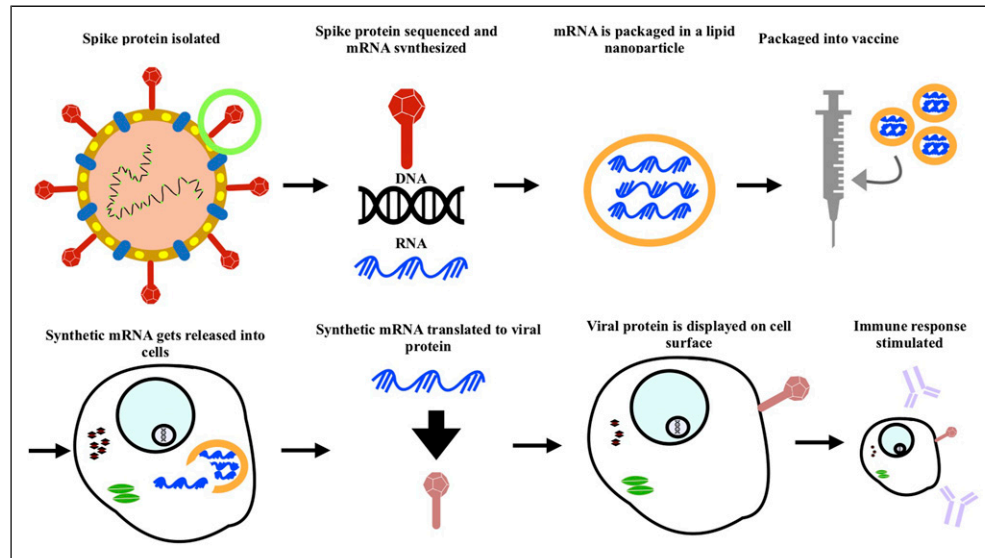


Figure 6. mRNA nucleic acid vaccine development and mechanism.

predominantly healthy subjects. As of August 2021, there are ninety-two COVID-19 vaccines under development and twenty-one vaccines authorized for use globally.¹⁸ Additionally, as of February 2021, 3 vaccines have received emergency use authorization (EUA) in the U.S. for SARS CoV-2; however these vaccines are still in their phase III trials.¹⁹ After the successful completion of phase III, and following the licensure of the product, phase IV, also referred to as post-marketing surveillance studies (PMS) is used to continue to monitor the vaccine for safety and effectiveness in the larger population (Figure 5).

Clinical Endpoints. Phase I trial parameters include evaluating vaccine safety and immunogenicity. Additionally, different dosage regimens and vaccination schedules are studied as secondary variables. Phase II consists of the same limits as Phase I in a larger population and under the accelerated approval pathway, phases I and II may be combined. Phase III endpoints include any 1 or combination of the following: COVID-19 infection, moderate COVID-19 infection, severe COVID-19 infection, symptomatic or asymptomatic COVID-19 infection. Guidance from the U.S. Food and Drug Administration (FDA) recommends minimal phase III success criteria for vaccine approval to be an estimated reduction of at least 50% in the primary endpoint when comparing the vaccine group vs the placebo group, with a 95% confidence interval — a benchmark consistent with the WHO's Solidarity Vaccines Trial design.²⁰

Nucleic Acid Vaccines

Nucleic acid-based viral vaccines may be DNA or RNA vaccines that function by employing the host's cellular transcriptional and translational machinery to produce viral

proteins which may subsequently be recognized by the human immune system (Figure 6).²¹ Nucleic acid vaccines are superior to other types of vaccines because they are relatively simple to generate.²² Nucleic acid-based vaccines are appealing as their production does not require the growth of live viruses.²³ Making a gene construct coding for the antigen instead of inactivating or attenuating the pathogen or making recombinant proteins is easier and faster than other vaccine production methods and avoids the potential risks and pitfalls of working with live pathogens.²¹ From the standpoint of vaccine storage and shelf-life, DNA-based vaccines are highly stable and have less need for refrigeration.²³

mRNA vaccines are more unstable than DNA-based vaccines, suggesting a need for special storage or delivery methods. SARS CoV-2 mRNA vaccines require 2 doses for maximal efficacy and need to be stored at ultracold temperatures. On the other hand, the half-life of DNA in cells is greater than mRNA and there is a theoretical possibility that DNA mutations may have a long-lasting impact, especially if the viral or vector DNA were to integrate with the host.²⁴ While some DNA-based vaccines were approved by the FDA for veterinary use, there are no DNA-based vaccines approved for human use in the U.S. as of March 2021.²⁵ Similarly, no mRNA vaccines have been approved for human use in the U.S. but mRNA vaccines have been previously tested in cancer clinical trials and shown promising results leading to antigen-specific T cell responses.²⁶ Therefore, the use of mRNA-based nucleic acid vaccines quickly gained popularity during the COVID-19 pandemic.

mRNA-Based SARS CoV-2 Viral Vaccines

BNT162b2. Pfizer-BioNTech developed an mRNA vaccine against SARS CoV-2 called BNT162b2, which became the

first vaccine to be authorized under the EUA (December 2020) and approved (August 2021) in the U.S. for use in humans. Early studies included 4 mRNA candidates of which 2, BNT162b1 and BNT162b2 underwent phase I and II trials.²⁷ The BNT162b1 vaccine candidate included a modified mRNA encoding the RBD of the S protein, while the BNT162b2 vaccine candidate included a modified mRNA encoding the full-length spike protein.²⁷ The BNT162b2 candidate entered phase III trials because although both candidates engendered similar antibody titers in phases I and II, the BNT162b2 vaccine induced a more pronounced T cell response, suggesting a longer lasting immune response.²⁸

BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion, stabilized, membrane-anchored COVID-19 full-length S protein.²⁹ The term “prefusion stabilized” refers to holding the viral spike protein in its prefusion conformation by preventing structural rearrangement and thereby inhibiting the externalization of antigenically preferable surfaces.³⁰ This was accomplished by designing the mRNA vaccine candidate so that the BNT162b2 mRNA included 2 proline amino acids through site-specific mutagenesis which was shown to stabilize the S protein in a prefusion conformation.³¹ Since the BNT162b2 vaccine mRNA is encapsulated in lipid nanoparticles (LNPs), the mRNA is protected from degradation by RNAases. Furthermore, the LNPs enable entry into host cells due to their phasic solubility with the cellular phospholipid bilayer.

The LNP delivery vehicles carrying the BNT162b2 mRNA are composed of 4 different lipids mixed in a defined ratio. After injection, LNPs are absorbed by the cells and the viral mRNA is released into the cytosol where it is translated by the host ribosomal machinery to produce the SARS CoV-2 viral S protein in the prefusion confirmation. Research has demonstrated that the proline-modified S antigen incorporates into cellular membranes and induces an adaptive immune response.³¹ Additionally, antigen presenting cells and somatic cells may display S protein fragments on their cell surfaces, triggering T cell-mediated immune responses, which in turn will lead to the activation of the Th2-B cell antibody production pathway.³¹ Eventually, the viral S protein will engender the production of neutralizing antibodies and memory cells, thereby providing immunity against SARS CoV-2.³¹

The BNT162b2 phase III clinical trial was a multinational, placebo-controlled, observer-blinded study including 43,448 participants. 21,720 individuals were included in the BNT162b2 test cohort group while 21,728 individuals were placed in a placebo group. Each vaccine dose was administered into the deltoid muscle at a dose of 30 µg mRNA in .3 mL. The second dose of BNT162b2 is administered 21 days after the first dose. Full immunity is assumed to be reached 7 to 10 days after the administration of the second dose.³² Recent studies have demonstrated significant efficacy even after a single dose of the BNT162b2 vaccine, though this requires further analysis.³³

The primary endpoint of the BNT162b2 phase III clinical trial was vaccine efficacy and patient safety over the course of 2 months. Secondary endpoint of this same trial included efficacy of BNT162b2 in severe COVID-19 cases. Vaccine efficacy was consistent across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions.³² Local and systemic reactogenicity was more common in the treatment group and specifically, systemic reactogenicity was significantly prominent in the younger generation (ages 16-55). Among the 36,523 participants who had no evidence of existing or prior COVID-19 infection, 8 cases of COVID-19 occurred within the 7-day period following the second vaccine dose compared to 162 COVID-19 positive cases in the same period in the placebo group attributing to a 95% efficacy profile following the administration of both doses.³²

mRNA-1273. Moderna developed a different mRNA vaccine called mRNA-1273 that also encodes the stabilized prefusion SARS-CoV-2 S protein.³⁴ The vaccine is delivered at a concentration of 100 µg mRNA in .5 mL solvent in 2 doses, with the second dose being administered 28 days after the first dose. Full immunity is achieved 7 days after the second dose.³⁴ The mRNA-1273 phase III clinical trial was a randomized, observer-blinded, placebo-controlled trial that enrolled 30,420 participants and divided them in a 1:1 ratio for the treatment and placebo groups respectively. Like the BNT162b2 vaccine, the primary endpoint of the mRNA-1273 study was patient safety and efficacy and a secondary endpoint included efficacy in severe COVID-19 infections. mRNA-1273 vaccine efficacy was consistent across most subgroups. The overall efficacy of the mRNA-1273 vaccine was 94.1% and aside from transient local and systemic reactions, no safety concerns were identified.³⁴

A Comparison of the Pfizer-BioNTech and Moderna Vaccines. The Pfizer-BioNTech and Moderna vaccines contain the same mRNA sequence, but they differ in excipient composition (Table 2). BNT162b2 and mRNA-1273 are both anticipated to have lasting effects for at least 90 days and are highly reactogenic meaning they may cause fever or aches during antibody development. Although the BNT162b2 vaccine found efficacy to be similar across all subgroups, the mRNA-1273 vaccine found efficacy to be similar across all subgroups except for older groups (>65 years old).^{32,34} Under their respective initial EUAs, the BNT162b2 vaccine was approved for administration in persons 16 years of age or older but the mRNA-1273 vaccine was approved for administration to those above the age of 18 years. The BNT162b2 vaccine study was multinational and has been authorized for emergency use in many countries whereas the mRNA-1273 vaccine study was limited to the U.S. and has been granted EUA in the U.S. only.

Importantly, clinical trials of the Pfizer-BioNTech and Moderna vaccines differ in asymptomatic transmission

Table 2. The Composition of the mRNA Vaccine Formulations: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna).

	BNT162b2 (Pfizer-BioNTech) original formulation	BNT162b2 (Pfizer-BioNTech) updated formulation ^a	mRNA-1273 (moderna)	Composition
mRNA	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Active ingredient: The mRNA contains the genetic material that codes for SARS-CoV-2 S protein
Lipids	2 [(polyethylene glycol)-2000]-N, N-ditetradecylacetamide 1,2-distearoyl- <i>sn</i> -glycero-3-phosphocholine Cholesterol (4-hydroxybutyl) azanediyl) bis(hexane-6,1-diyl) bis(2-hexyldecanoate)	2 [(polyethylene glycol)-2000]-N, N-ditetradecylacetamide 1,2-distearoyl- <i>sn</i> -glycero-3-phosphocholine Cholesterol (4-hydroxybutyl) azanediyl) bis(hexane-6,1-diyl) bis(2-hexyldecanoate)	Polyethylene glycol (PEG) 2000 dimyristoyl glycerol (DMG): 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol 1,2-distearoyl- <i>sn</i> -glycero-3-phosphocholine Cholesterol SM-102: heptadecane-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy)hexyl) amino) octanoate	The delivery vehicle: 1) protects the mRNA cargo from degradation upon injection 2) provides a hydrophobic exterior that encapsulates the mRNA thereby assisting with its entry into host cell
Excipients	Potassium chloride Monobasic potassium phosphate Sodium chloride Dibasic sodium phosphate dihydrate Sucrose	Tromethamine Tromethamine hydrochloride – – Sucrose	Tromethamine Tromethamine hydrochloride Acetic acid Sodium acetate Sucrose	These formulation excipients: 1) balance the vaccine pH to resemble physiological pH 2) maintain vaccine integrity and stability after production Assists the molecules to maintain their shape during freezing

The active ingredient, mRNA, in the BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines is identical but the excipients differ as listed.

^aThe updated formulation is for all Pfizer vaccines ages 12+. It has the same active ingredients as the previous formulation but uses different stabilizers, ingredients that help keep the vaccine molecules stable while the vaccine is manufactured, frozen, shipped, and stored.

analysis post-vaccine administration. For instance, in the mRNA-1273 phase III clinical trial, there were 3 times as many asymptomatic COVID-19 cases in the placebo group compared to the vaccine group – however the sample size used to find this significance is very small and thus needs further investigation.^{34,35} Though the same may be true for the BNT162b2 vaccine, additional data is needed.³⁶ Pfizer-BioNTech declared that a serologic endpoint capable of detecting history of infection regardless of symptomatic infection will be reported later.³⁶

Both mRNA vaccines may have a more pronounced adverse effect profile following administration of the second dose. Side effects may include injection-site pain, fatigue, headache, muscle pain, joint pain, chills, and fever.^{34,35} BNT162b2 appears to be slightly less reactogenic than the mRNA1273 vaccine suggesting that the mRNA1273 vaccine engenders a more robust antibody response and may be better at preventing severe COVID-19. However, clinical significance is unknown and more follow up research is needed.¹⁶

During vaccine shortages earlier in the pandemic, the mRNA-1273 vaccine was found to have superior storage and did not require dilution. In comparison, the BNT162b2 vaccine required ultracold temperatures (-80°C to -60°C) for

transportation and storage as well as dilution prior to use. However, extended stability studies and subsequent product reformulation of the BNT162b2 vaccine has resulted in improved stability (including 12 hours at room temperature upon vial opening) and no dilution prior to use.^{32,34} The BNT162b2 vaccine still has more stringent storage requirements comparatively since the mRNA-1273 vaccine can be stored under normal refrigeration conditions (2°C to 8°C).

DNA-Based Nucleic Acid Vaccines Against SARS CoV-2

DNA-based vaccines are composed of purified circular plasmid DNA or non-replicating viral vectors containing genes that encode viral antigens. To create a DNA-based vaccine, an antigen-encoding gene is cloned into a plasmid, which is delivered to the host by traditional vaccination routes.²⁴ The vaccine formulation is made such that the genetic material is translocated to the host's cell nucleus, where the promoter present in the vector structure is activated, triggering the transcription of the necessary gene through the host's cellular machinery.²⁴ After the translation of the translocated gene into a protein or protein fragment, it is further processed into peptides that bind to major

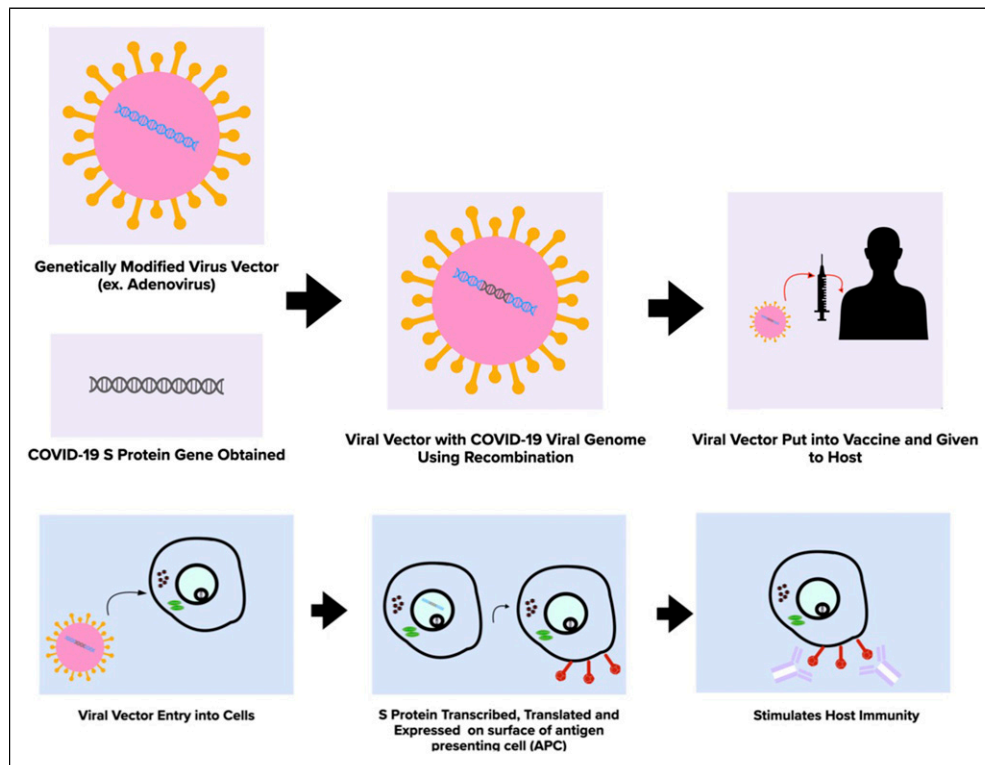


Figure 7. Viral vectored vaccine development and mechanism.

histocompatibility complex (MHC) class I or II allowing for the activation of CD8⁺ and CD4⁺ T cells, respectively.^{25,37} CD4⁺ T cells stimulate antibody or B-cell mediated immunity resulting in the production of high-affinity class-switched antibody responses, long-lived plasma cells, and memory B cells.³⁸ Since handling of infectious viral particles is not required in the preparation and manufacturing of DNA vaccines, they are considered to be theoretically safer to handle and relatively inexpensive to generate.³⁹ Furthermore synthetic DNA has greater shelf-stability than mRNA vaccines.³⁹ However, antibody and T cell titers are low with DNA vaccines and due to the potential integration with the host genome, there are chances for mutations in this vaccine type.³⁹

COVID-19 DNA Vaccine. Based on the prior successful development of a synthetic DNA vaccine targeting the MERS S protein, a synthetic DNA vaccine against COVID-19 (INO-4800) is currently being designed by Inovio Pharmaceuticals. INO-4800 has been shown to result in prominent *in vitro* production of the S protein.⁴⁰ This vaccine is currently under investigation in phase II clinical trials.

Viral Vectored Vaccines

Viral vectored vaccines use viral vectors as a medium to deliver the desired immunogen.⁴¹ The vector delivers viral

genes used to produce antigens against an infectious agent thereby allowing the body to mount an immune response (Figure 7). For example, the gene encoding the SARS-CoV-2 S protein is integrated in another viral vector genome that has been genetically engineered to not cause disease.⁴² For example, the virus in a COVID-19 viral vectored vaccine is not coronavirus but rather a different virus, such as adenovirus (Ad). The viral vector itself, however, plays an additional important role of further boosting the immune response leading to a more robust reaction than if the pathogen's genetic sequence was delivered on its own.⁴³

Viral vectored vaccines do not require adjuvants and possess distinct advantages over other vaccines because of their targeted delivery and induction of robust cellular immunity.⁴² However, viral vectored vaccines carry the risk of being mutagenic as viral vectors require viral integration into the host genome.³⁹ Additionally, if the host has already been exposed to the virus and produced neutralizing antibodies against the virus before vaccine administration, vaccine efficacy decreases.⁴⁴

Ad viruses cause common illnesses. They are non-enveloped double-stranded DNA (dsDNA) viruses with a packaging capacity of up to 7.5 kb of foreign genes and have been shown to elicit robust antibody response and protection against COVID-19 in rodents, primates, and humans in phase 1 and 2 clinical trials.⁴⁵

AZD1222

The University of Oxford and AstraZeneca developed a non-replicating chimpanzee adenovirus viral vector vaccine, AZD1222.⁴⁶ In addition to the previously discussed endpoints with the mRNA vaccines, the AZD1222 clinical trials studied acetaminophen's effect on the amelioration of vaccine induced adverse events. Furthermore, AZD1222 phase III clinical trials also investigated asymptomatic transmission and the vaccine was tested with either single or multidose regimens.⁴⁶ Clinical trials for AZD1222 have the following strengths: large sample size, randomization, inclusion of diverse vaccination sites including different races and ethnicities, standardization of key elements between the trials, balance of participant characteristics between the vaccine groups, inclusion of all participants in the safety assessment, and having similar results across study groups.⁴⁷

Phase III clinical trials of AZD1222 included 23,848 patients from the United Kingdom, Brazil, and South Africa who received 2 standard doses (5×10^{10} viral particles per dose) around 12 weeks apart; overall, the interval between doses varied between 3 to 23 weeks.^{47,48} The primary endpoint was efficacy against symptomatic COVID-19 15 days or more after the second dose among participants who were seronegative at trial entry.⁴⁸ Ultimately, a total of 14,380 participants were eligible for inclusion in the efficacy analysis (43% in the United Kingdom, 47% in Brazil, 10% in South Africa).⁴⁸ There were 271 COVID-19 cases with onset 15 days or more after the second dose, with 74 cases in the vaccinated group and 197 in the control group. Thus, overall vaccine efficacy after 2 standard doses was 63.09%.^{47,48} Based on preliminary phase III trials, participants who received a low dose (2×10^{10} viral particles) followed by a standard dose 12 weeks or greater apart exhibited a maximal vaccine efficacy of 81.2%.⁴⁷ When the interval was reduced to 6 weeks or less, the efficacy was only 55%, therefore results most likely need further investigation.

Furthermore, the study also found that inclusion of acetaminophen significantly reduced common local and systemic adverse events, most likely due to an amelioration of the cytokine storm, with no negative impact on vaccine efficacy.⁴⁹ Importantly, 1 unexpected outcome of the clinical trial was that a number of asymptomatic infections were prevented in participants who were administered a first lower dose followed by the standard vaccine dose.⁵⁰ The AZD1222 vaccine efficacy against asymptomatic infections was 59%.⁵⁰ Despite these positive outcomes, in March of 2021, AZD1222 vaccine use was suspended in thirteen European countries due to an increasing incidence of a rare thrombolytic event in patients. Nevertheless, the WHO has recommended continuation of the use of AZD1222 because its benefits outweigh its risks, especially considering the bottlenecks in the production and availability of COVID vaccines.⁵¹

JNJ-78436725

Janssen, a pharmaceutical company of Johnson & Johnson, developed JNJ-78436725, a COVID-19 viral vectored vaccine based on a recombinant, replication-incompetent, adenovirus type-26 vector skeleton encoding the SARS-CoV-2 spike gene. This vaccine is a suspension originally intended for intramuscular injection as a single dose.⁵² However, now a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine is advised 28 days after first dose for immunocompromised patients. Alongside, a booster dose of the JNJ-78436725 may be administered 2 months after primary vaccination.⁵³

The phase III clinical trial of JNJ-78436725 was a randomized, double-blinded, placebo-controlled, international, multi-center study with 43,783 participants in 8 different countries. In the trials, the vaccine was administered as a single dose with 5×10^{10} viral particles in .5 mL solvent.⁵⁴ Compared to the development phase of BNT162b2 and mRNA-1273, the endpoints of the JNJ-78436725 were different and therefore the study outcomes are not immediately comparable. In all 8 countries, the vaccine was 77% effective in preventing severe COVID-19 occurring at least 14 days after vaccination, 85% against severe COVID-19 at least 28 days after vaccination, 67% effective in preventing moderate to severe COVID-19 occurring at least 14 days after vaccination, and 66% against severe COVID-19 occurring at least 28 days after vaccination.⁵⁴ However, when looking at the U.S, South America and South Africa specifically, the JNJ-78436725 is respectively 72%, 66% and 57%, effective against moderate to severe COVID-19. Most importantly, the JNJ-78436725 vaccine was found to be 100% effective in protecting against death from the disease in each country it was tested.⁵⁴ The JNJ-78436725 vaccine received EUA in the U.S. on February 27, 2021. Around 6.8 million doses of the JNJ-78436725 have been administered in the U.S.⁵⁵ On April 13, 2021, the vaccine was suspended in the U.S. due to 6 cases of vaccine-associated blood clots but was quickly reinstated for use after a thorough safety review.⁵⁵

AZD1222 Vs JNJ-78436725 – A Comparative Analysis

Both AZD1222 and JNJ-78436725 are adenovirus vectored vaccines. The AZD1222 and JNJ-78436725 vaccines utilize Ad5 and Ad26 vector backbones respectively and encode the full-length S protein of SARS CoV-2.^{45,56} The participant size of the JNJ-78436725 vaccine clinical trial was larger when compared with AZD1222. Most individuals do not have immunity to the Ad26 virus used in the JNJ-78436725, perhaps allowing for an adequate immune response after just a single dose. On the other hand, the Ad5 viral vector used

Table 3: Price Per Dose of Vaccines in U.S.D.⁵⁷

Vaccine	U.S. Price (\$)
BNT162b2	19.50
mRNA-1273	15.00
JNJ-78436725	10.00
AZD1222	4.00

Price per dose of vaccines in U.S.D. as of April 2021. Note that AZD1222 is not authorized for use in The U.S. but price is shown.

passaging,” a process in which a virus is forced to replicate repeatedly in tissue culture and by doing so becomes incapable of causing disease, though its ability to engage the immune system remains (Figure 8).⁵⁸

The advantages of live-attenuated vaccines over inactivated vaccines include long-lasting immunity and high potency. Comparative disadvantages include that attenuated vaccines require extensive safety testing and thus are time-consuming in their developmental process.³⁹ Also, attenuated

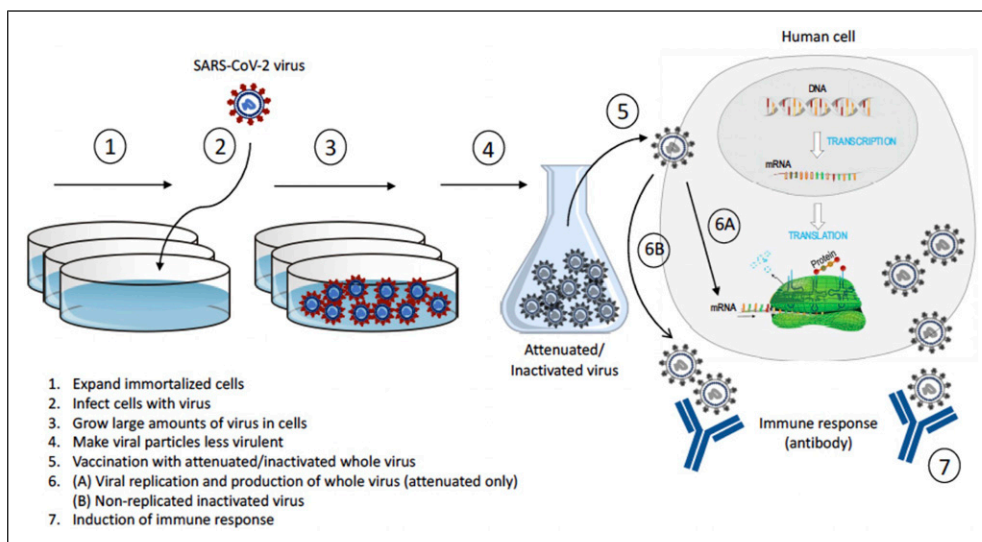


Figure 8. Live attenuated/Weakened and inactivated virus vaccine development and mechanism. Courtesy of Charlotte Lozier Institute, A Visual Aid to Viral Infection and Vaccine Production, Issue I.⁵⁸

in the AZD1222 vaccine comes from a more common type of adenovirus known to infect a greater set of the population. Therefore, it is likely that its ability to generate an immune response with high levels of pre-existing antibodies in some populations impedes efficacy, resulting in more doses or booster shots required.⁵⁶

In terms of a larger comparison between DNA and mRNA vaccines, AZD1222 and JNJ-78436725 are DNA-based, and thus more shelf-stable than the BNT162b2 and mRNA-1273 mRNA-based vaccines, and therefore require less stringent temperature storage requirements. Additionally, the production of AZD1222 has been made with non-profit intentions, offering the vaccine free of cost as long as the pandemic is ongoing, to provide the vaccine to developing countries (Table 3). In comparison, the BNT162b2, mRNA-1273 and JNJ-78436725 vaccines are 3 times more expensive.

Live-Attenuated and Inactivated Vaccines

A live-attenuated vaccine is 1 that contains a weakened version of the harmful virus and is prepared by introducing the virus into a “non-host” species in which it does not replicate well. An alternative strategy is laboratory—based “cell

vaccines cannot be used in immunocompromised patients for fear of potentially causing life-threatening infections.⁵⁹ Often, this vaccine type is administered as a single dose.⁶⁰

On the other hand, inactivated vaccines are manufactured by heat, irradiation or chemical insult (Figure 8).⁵⁹ However, inactivated vaccines predominantly stimulate a humoral or antibody mediated immune response. This is because they cannot infect cells, thereby producing no cell mediated immunity.⁶⁰ Additionally, inactivated vaccines have a low production titer and therefore require booster doses.³⁹ Manufacture of inactivated vaccines can be complex as large amounts of the virus need to be handled and antigen integrity needs to be confirmed in a laboratory setting.³⁹ Inactivated vaccines are more stable and safer compared to live attenuated virus vaccines and may be used in immunocompromised patients.³⁹

SINOVAC

In the context of the SARS CoV-2 coronavirus, Beijing’s SinoVac Biotech generated an inactivated vaccine.⁶¹ The vaccine was developed by first growing large stocks of SARS CoV-2 in monkey kidney cells in culture under laboratory conditions

followed by chemical inactivation using β -propiolactone, which damages viral S proteins, disabling SARS-CoV-2 from binding host cells.⁶¹ In subsequent manufacturing steps, the inactivated virus may be mixed with an aluminum-based compound which stimulates the immune system to boost its response.

SinoVac Biotech conducted a randomized, double-blinded, placebo-controlled phase I and II clinical trial where participants were divided into treatment and placebo groups in a 1:1 ratio. A single dose of either low or high dose, 3 μ g per .5 mL and 6 μ g per .5 mL of aluminum hydroxide diluent per dose, respectively, was administered to participants in the test cohorts.⁶¹ The low dose vaccine was found to be safer. Upon completion of phase III trials, the vaccine was found to have a 78% efficacy however, this later dropped to 50.4% when including “very mild” COVID-19 cases.⁶¹ Lastly, the level of antibodies against SARS-CoV-2 was significantly reduced in those given the vaccine compared to those that recovered from the disease.⁶¹

Subunit Vaccines

Subunit vaccines contain parts of the infectious agent that are known to cause an immune response, – antigens. Subunit vaccines may be composites and could contain anywhere from 1 to twenty different antigens. It is critical to add adjuvants to these vaccine types to ensure long-term immunity.⁶² The benefit of subunit vaccines is that by employing just the essential antigens, adverse events (i.e., hypersensitivity) may be reduced.⁶³ Laboratory steps to prepare subunits vaccines include growing the virus (or infectious agent) of interest, breaking it apart and garnering the necessary antigens. Alternatively, the antigen molecules could be obtained using DNA technology (DNA sequencing, polymerase chain reaction, DNA cloning, and gel electrophoresis).⁶⁴ Outbreak scenarios, such as the COVID-19 pandemic, limits vaccine development. In a pandemic setting, a vaccine’s development is urgent, and the subunit vaccine is not ideal as it requires whole pathogen cultivation.⁶⁴ In contrast to the previously discussed vaccines against COVID-19, the subunit vaccines currently being studied not only targeted the S protein but also the N and M proteins.⁶⁴ An example of a subunit vaccine against SARS CoV-2, NVX-CoV2373, is discussed next.

NVX-CoV2373

Novavax, a vaccine development company, developed NVX-CoV2373, which is based on the S protein and matrix-M1 adjuvanted recombinant protein.⁶⁵ This vaccine contains a full-length, prefusion S protein made using recombinant technology. The purified S protein is obtained from the genetic sequence of SARS-CoV-2 and produced

in insect cells.⁶⁶ NVX-CoV2373 is administered in 2 doses of 5 μ g of protein and 50 μ g adjuvant 21 days apart in the deltoid muscle.⁶⁶ A phase III clinical trial with 30,000 participants is ongoing. However, in a United Kingdom phase III study with 16,000-participants, NVX-CoV2373 demonstrated an efficacy of 89.3% against COVID-19.⁶⁶ NVX-CoV2373 was well-tolerated and elicited higher levels of antibodies than those seen in people who had recovered from clinically significant COVID-19.⁶⁶ The addition of the matrix-M1 adjuvanted recombinant protein led to enhanced immune responses and induced a T helper 1 response. NVX-CoV2373 was shown to have fewer adverse events compared to other vaccine types and made increasing amounts of neutralizing antibodies and S protein specific IgG.⁶⁶ NVX-CoV2373 must be stored at 2°C to 8°C and thus, requires special temperature storage, similar to BNT162b2 and mRNA-1273.⁶⁷

Future Work and Conclusion

Viral variants or mutant strains originate following mutations in the viral genome.⁶⁸ Several mutations may be advantageous for a virus, allowing it to evolve to spread more easily or it could make a virus more deadly, thereby giving the virus an opportunity to spread efficiently. A preliminary study from Britain indicated that some SARS-CoV-2 variants could be associated with more severe disease.⁶⁸ A ferocious wave of infections in April 2021 were attributed to the B.1.617.2 or delta variant. This variant was shown to be more transmissible, infectious and moderately resistant to current vaccines.

Vaccines continue to reduce a person’s risk of contracting COVID-19 and its variants. Therefore, future studies should analyze the timeline of protection from current vaccines, their long-term effects and efficacy against new coronavirus variants. This information may reduce anti-vaccine sentiment and pave the way for herd immunity. Since the BNT162b2 and mRNA-1273 vaccines utilize mRNA technology, they may be the easiest, cheapest, and quickest to evolve to address the new coronavirus variants, through booster shots or new vaccine development.

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