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Mechanism and design of vaccines against SARS-CoV-2, narrative review

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Abstract: The infection produced by the SARS-CoV-2 virus, known as COVID-19, has caused high morbidity and mortality across the world. After having deciphered the virus's genome and carried out investigative endeavors that led to the creation of a variety of vaccines with different mechanisms of action, it has been possible to decrease the morbidity and mortality associated with the virus. It was necessary to accelerate the vaccine production process, which was facilitated by advanced scientific knowledge within the disciplines of genetics and virology, in order to provide the human species with a safe and effective form of protection against the aggressive and progressive infection. Vaccines are classified differently depending on their action mechanisms: there are some based on non-replicating viral vectors, recombinant vaccines, ones that are based on attenuated or inactivated viruses, and (the greatest novelty of current scientific developments) vaccines based on DNA and messenger RNA. The latter has demonstrated significant efficacy and safety in the prevention of the SARS-CoV-2 infection as observed in preliminary studies, and they have meaningfully impacted the population by reducing the rates of infection and mortality. As a result, decreased levels of spread of and mortality from COVID-19 have been evidenced across the globe following the beginning of the vaccine distribution period.

Key words: COVID-19; vaccines; mRNA; immunization; SARS-CoV-2; spike protein

1 Introduction

During the second week of December 2019, some patients in Wuhan, Hubei Province, China, were diagnosed with a rare atypical pneumonia, which was later recognized as a symptom of infection by a viral agent identified as SARS-CoV-2. The genome of this virus was sequenced in mid-January 2020, and on March 11, 2020, the World Health Organization (WHO) declared a global pandemic [1]. From the onset of these events through July 5, 2023, approximately 6,948,764 people worldwide have died from SARS-CoV-2 infection out of a total of 767,726,861 confirmed cases. As of June 27, 2023, 13,461,751,619 vaccine doses have been administered (data obtained from https://covid19.who.int).

The exponential increase in global mortality led some governments to enact laws allowing clinical research protocols to be adapted to current needs and modified in line with the latest scientific and technological developments. After the WHO declared a pandemic, vaccines were considered the most effective way to prevent SARS-CoV-2 disease. Despite the approval of vaccines for emergency use, with novel mechanisms that were explored, these vaccines have demonstrated overall efficacy and safety. However, there remains concern regarding vaccine effectiveness due to the replication of

mutant viruses that confer new characteristics to SARS-CoV-2. Additionally, there is the issue of safety, as some new, previously unknown side effects could emerge over time.

This narrative review will evaluate the mechanism of action of SARS-CoV-2 vaccines, their efficacy, and reported adverse events. Additionally, it will provide a brief overview of the scientific process required to develop a drug or vaccine, the timelines involved, and the importance of these factors.

2 Core topic

2.1 Virology

SARS-CoV-2 is a virus genetically composed of a single-stranded RNA chain containing 29,903 nucleotides. The virus's genome encodes, among many others, three surface glycoproteins: Spike (S), Matrix (M), and Envelope (E); one nucleoprotein; and 16 non-structural proteins [2] (Figure 1).

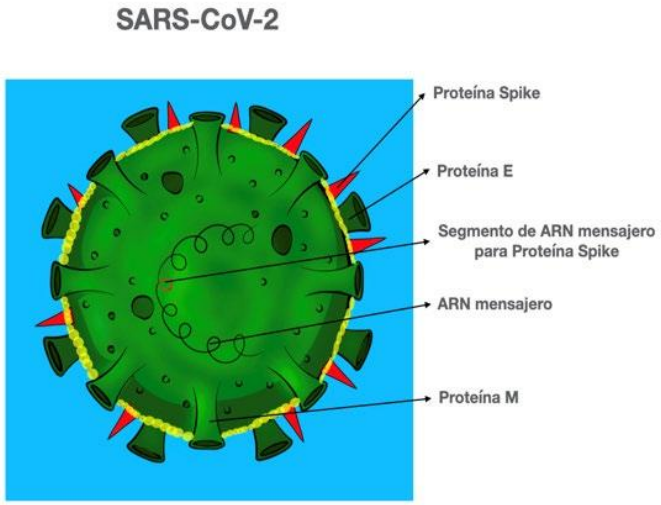

Figure 1. Representation of SARS-CoV-2 with its main proteins: Spike (S), Envelope (E), Matrix (M), messenger RNA, and the segment of the messenger RNA that encodes the Spike protein

The Spike protein plays a crucial role in the process of invading the host cell; it is responsible for binding to the host cell's receptor, known as Angiotensin-Converting Enzyme 2 (ACE2); in fact, this protein has a high affinity for the receptor. This protein complex introduces the virus into the host cell's cytoplasm, where the viral RNA is released via endocytosis to undergo translation at the ribosomes and complete viral replication with the assistance of the endoplasmic reticulum and Golgi apparatus of the invaded cell [2] (Figure 2).

During the process of producing new viral components, particularly the new genome, genotypic errors occur (insertion, substitution, or deletion). These errors lead to changes in the behavior of the new viruses in the environment and in the host (phenotypic changes). Furthermore, these mutations can cause alterations in how the new viruses are transmitted, changes in signs and symptoms, and, of course, modifications in viral behavior. SARS-CoV-2 changes by approximately 1 or 2 nucleotides per month, per lineage, across its nearly 30,000 base pairs. Although any organelle or part of the virus may be altered by a mutation, mutations originating in the Spike protein have a significant impact, as this has been the target in vaccine development and, consequently, for neutralizing antibodies [3]. In summary, due to the scientific importance of the Spike protein, viral variants have been classified according to the mutations observed in it.

Some new viruses resulting from mutations include the B.1.1.7 (Alpha) variant, first detected in the United Kingdom; the B.1.351 (Beta) variant, first detected in South Africa; and the B.1.617.2 (Delta) variant, first detected in India. Unlike the first two, the Delta variant has been associated with a higher probability of causing pneumonia than the wild-type or

original variant (OR: 1.88 {95% CI 0.95–3.76}) and may be more transmissible. However, vaccination has been associated with a reduction in disease severity [4]. A variant was also detected in Brazil, P1 (Gamma); the first two cases were reported in February 2021 [5,6]. In November 2021, the B.1.1.529 (Omicron) variant was reported in South Africa, which became the most common variant worldwide [7].

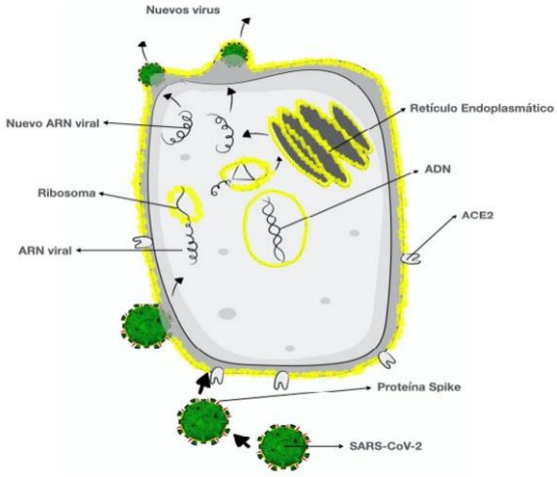

Figure 2. Schematic representation of a cell infected by SARS-CoV-2. The virus enters the cell after the viral spike protein binds to the cell's ACE2 receptors. The cellular ribosome translates the viral messenger RNA. The endoplasmic reticulum and Golgi apparatus then synthesize the viral structures. Finally, assembly and release of new viruses, and possible destruction of the host cell

When SARS-CoV-2 infects a host, it triggers an inflammatory response that can lead to lymphopenia, high levels of cytokines, and high levels of antibodies. In the virus's complex replication mechanism, antigen-presenting cells also expose antigens to T and B cells to generate immunoglobulin M, which acts in the viral clearance process for a short time (around 12 weeks), and immunoglobulin G, which has a much longer-lasting effect [8].

The virus affects the respiratory system, liver, brain, kidneys, and intestines. It has an incubation period of four to five days on average, with symptoms lasting between 11 and 12 days. Although some people are asymptomatic, they retain the ability to spread the virus; a small percentage of severely infected patients develop acute respiratory distress syndrome (ARDS) [9].

2.2 The scientific process for vaccines in general

Historically, the scientific process for developing a vaccine has taken between 10 and 15 years. It begins with the first stage (exploratory phase), where basic laboratory studies are conducted and the target antigen is selected. The second scientific stage consists of demonstrating immunogenicity, efficacy, and safety; first in the laboratory, then in animals, and finally in humans (a stage that lasts between two and three years). The scientific method must follow three phases [10].

Phase I: This is the initial trial in a small group of humans. The safety, side effects, dosage, and immunogenicity of the vaccine under study are evaluated. This phase takes between two and three years.

Phase II: The vaccine is tested on a larger group of humans (hundreds) and across different demographic groups to re-evaluate safety, appropriate dosage, side effects, and immunogenicity. This phase takes between two and three years.

Phase III: The vaccine's efficacy is evaluated in a larger group of humans (thousands). Statistical calculations determine the incidence rate of the disease in the vaccinated group and the placebo group, and the magnitude of the reduction in disease incidence among the vaccinated population is analyzed. This phase takes between two and three years.

Following the research phases, based on clinical studies, the vaccine must be approved by regulatory agencies such as

the FDA (Food and Drug Administration) in the United States or the EMA (European Medicines Agency) in Europe. This process takes between one and two years. However, vaccines may be approved more quickly in the event of a pandemic (due to high morbidity and mortality).

After this, the approved vaccine will be made available for sale (this period can take between two and three years), but studies for the ongoing evaluation of the vaccine's safety and effectiveness must continue for a period during and after its administration to the population [10].

The estimated timelines in the vaccine development process are based on needs, the technology used, scientific knowledge regarding the subject matter, budget, and other factors. Therefore, these timelines may change and be adjusted according to the times and needs.

2.3 Types of vaccines (see Table 1 and Table 2)

2.3.1 Non-replicating viral vectors

The non-replicating viral vectors most commonly used to generate immunity against COVID-19 are adenoviruses. These are double-stranded DNA viruses from which the E1 strand is removed to render them non-replicating. Although replication is ineffective, these viruses retain the ability to generate humoral and cellular immunogenicity. Given that SARS-CoV-2 uses the Spike protein to enter the host cell, vaccines developed using engineered adenoviruses have the genetic code encoding the S subunit inserted [8,11]. There are currently 19 prototypes of this class of vaccines under study [8].

The University of Oxford, in collaboration with the pharmaceutical company AstraZeneca, has used a chimpanzee adenovirus. This is to eliminate the possibility that prior immunity to human adenoviruses might reduce the generation of immunity against SARS-CoV-2, particularly against the Spike protein. This vaccine is known as AZD-1222 or ChAdOx1-nCoV-19. Following the first dose, a second dose administered 28 days later ensures the development of long-lasting immunity [11].

In December 2020, a clinical trial was published demonstrating the efficacy and safety of the ChAdOx1-nCoV-19 vaccine, with better tolerability in older adults than in younger adults, but with similar immunogenicity between these age groups [12]. Another publication, based on an interim analysis of four randomized controlled clinical trials involving 11,636 participants in Brazil, South Africa, and England, shows an overall efficacy of 70.4% for the ChAdOx1-nCoV-19 vaccine [13]. As is well known, vaccines can cause side effects. The most common side effects of the ChAdOx1-nCoV-19 vaccine are mild: pain and swelling at the injection site, headaches, muscle aches, and nausea. These disappear a few days after vaccination.

Table 1. Types of vaccines

Types of vaccines classified by viral state and immunization technique	Name or identifier	Developing research institution
Non-replicating viral vectors	AZD-1222 or ChAdOx1-nCoV-19	University of Oxford in collaboration with AstraZeneca
	JNJ-78436735	Johnson & Johnson
	Sputnik, or Gam-COVID-Vac	Gamaleya Research Institute
Recombinant or protein subunit vaccines	NVX-CoV2373	Novavax
mRNA (messenger RNA) vaccines	BNT 162b2	BioNTech and Pfizer
	mRNA1273	National Institute of Allergy and Infectious Diseases (NIAID) in collaboration with Moderna
DNA-based vaccines	INO-4800	INOVIO Pharmaceuticals
Inactivated whole virus vaccines	CoronoVac	Sinovac Life Sciences (Beijing, China)

Table 2. Vaccine efficacy

COVID-19 Vaccines	Efficacy	Initial Study Population
AZD-1222 or ChAdOx1-nCoV-19	70.40%	11,636 people
JNJ-78436735	66.90%	43,783 people
Sputnik, or Gam-COVID-Vac	91.60%	21,977 people
NVX-CoV2373	89.70%	14,039 people
BNT 162b2	95%	43,448 people
mRNA1273	94.10%	30,420 people
INO-4800	--	--
CoronaVac	83.50%	11,303 people

However, a case report has recently been published in which 23 patients with a mean age of 46 years developed thrombosis and thrombocytopenia between 6 and 24 days after receiving the first dose of the ChAdOx1-nCoV-19 vaccine. These patients had no history of prothrombotic diseases, and 22 patients tested positive for the presence of antibodies against platelet factor 4 [14]. It is possible that vaccination with ChAdOx1-nCoV-19 triggers the production of these antibodies and leads to the thrombotic and thrombocytopenic response.

According to the report from the European Medicines Agency's Pharmacovigilance Risk Assessment Committee, as of April 4, 2021, among 34 million people who received the ChAdOx1-nCoV-19 vaccine in Europe and the United Kingdom, 169 cases of cerebral venous sinus thrombosis and 53 cases of splenic vein thrombosis were reported. Most of these cases occurred in women and took place within the first two weeks following vaccination [15].

A systematic review, based on 12 articles, reported 36 cases of cerebral venous sinus thrombosis, four strokes, and one intracerebral hemorrhage; of the 41 patients, 18 died; of the 32 patients for whom sex was reported, 23 were women. The event occurred between four and 19 days after vaccination, and headache was the most common symptom [15]. Regarding the performance of these vaccines against new variants of the SARS-CoV-2 virus, it is expected that vaccines synthesized based on the original Spike protein will be affected when mutations occur in it. However, it has been demonstrated that vaccination with ChAdOx1-nCoV-19 maintains some efficacy against the Alpha variant, but there is a reduction in neutralizing activity against the same variant when compared to the Victoria lineage (BetaCoV/Australia/VICO1/2020) [16]. Similarly, this vaccine has been found to have limited efficacy in preventing mild and moderate disease caused by the B.1.351 (South African) variant of COVID-19, and the report on its efficacy in preventing severe disease after two doses of vaccination is inconclusive [17].

A study revealed that a second dose of the BNT162b2 vaccine, following a first dose of ChA-dOx1-s, induces a strong immune response with acceptable and manageable reactogenicity [18]. It may be acceptable to administer a first dose of a vaccine with a specific design (non-replicating viral vectors) and a second dose with a different design (messenger RNA vaccines); this is called heterologous boosting. A non-inferiority clinical trial concluded that immunogenicity was higher when using the ChAdOx1-nCoV-19/BNT162b2 sequence compared to the ChAdOx1-nCoV-19/ChAdOx1-nCoV-19 sequence [19].

The other major vaccine in this class is JNJ-78436735, developed by Johnson & Johnson. A single dose has 72% efficacy (in the United States), although it is less effective in other countries when exposed to different variants of the virus. Immune thrombotic thrombocytopenia has been reported as a side effect [9]. Also known as Ad26.COV2.S, this non-replicating viral vector-based vaccine demonstrated efficacy in protecting against severe and moderate disease of 66.9% (95% CI: 59.0–73.4) 14 days after a single dose. This was reported in a clinical trial published in the NEJM, which enrolled a total of 43,783 patients (Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States) [20]. Although non-neutralizing antibodies and the T-cell response are preserved in patients receiving this vaccine, some data indicate a reduction in neutralizing antibodies against the B.1.351 and P1 variants [21].

In the same systematic review mentioned above, two articles are reported involving 13 female patients who developed cerebral sinus venous thrombosis associated with cerebral hemorrhage and thrombotic thrombocytopenia induced by the Ad26.COV2.S vaccine; the event occurred between six and 14 days after vaccination. The most common symptom was headache; one patient was taking oral contraceptives, and six patients were obese; the mean age was 43 years [15].

Now, in another geographic region, we find the Sputnik vaccine, or Gam-COVID-Vac, developed by the Gamaleya Research Institute (Russia). This vaccine uses two different adenoviruses, Ad26 and Ad5, to reduce the likelihood of failure due to prior immunity to adenoviruses; its efficacy rate is 79.4% after one dose and 91.6% after two doses [9].

Nevertheless, controversies arose during the vaccine's research process due to failures in adhering to the scientific protocol, some confusing statistical data, numerical inconsistencies, and poor communication of the results [22,23]. Ultimately, the Phase III clinical trial was published in February 2021; out of a total of 21,977 adults evaluated, 16 people in the vaccinated group and 62 people in the placebo group developed the disease. The calculated efficacy was 91.6% (95% CI: 85.6–95.2); most adverse events were classified as Grade 1, 0.3% in the vaccinated group and 0.4% in the placebo group [24]. At this point, it is important to note that Phase II of this study was completed in August 2020 and that since then, the Russian government has approved the use of the vaccine in high-risk population groups. This information is important because vaccines are typically approved for use in the general population following Phase III trials.

With regard to variants B.1.1.7, B.1.617.3, B.1.1.141, and B.1.1.317, the virus-neutralizing activity following administration of the Sputnik vaccine remains unchanged. However, the virus-neutralizing activity in response to the vaccine for variants B.1.351, P.1, and B.1.617.2 has been found to be statistically reduced [25].

2.3.2 Recombinant or protein subunit-based vaccines

Recombinant and highly purified proteins from various viral agents are the most common in vaccine research. Viral genes encoding proteins important for immunogenicity have been cloned, expressed, and purified as immunogenic targets. An example of this type is the hepatitis B vaccine. Currently, there are about 13 COVID-19 vaccine candidates under investigation [8]. The Novavax laboratory completed the Phase III trial, called NVX-CoV2373; this vaccine consists of the full-length SARS-CoV-2 spike glycoprotein, which is capable of inducing both humoral and cellular immunity [11]. In a clinical trial involving 14,039 patients aged 18 to 84, data were collected at 33 sites in the United Kingdom; the study found an efficacy of 89.7% (95% CI: 80.2–94.6%) seven days after the second intramuscular dose (21 days between doses). A subsequent analysis of the data revealed an efficacy of 86.3% (95% CI: 71.3−93.5%) against the Alpha variant and 96.4% (95% CI: 73.8–99.5%) against other variants (the Omicron variant had not yet emerged). Likewise, adverse events were similar in the group that received the vaccine and in the placebo group [26].

2.3.3 Messenger RNA-based vaccines

The idea of introducing messenger RNA into cells to manipulate gene expression was evaluated in the late 1980s. Then, in the early 1990s, RNA vectors were used to produce vasopressin in rats, and in 1993 it was demonstrated in mice that an in vitro-synthesized vaccine, based on messenger RNA encoding an influenza virus nucleoprotein, could induce activation of cytotoxic T lymphocytes. Based on the above, during the 2012 MERS (Middle East Respiratory Syndrome) outbreak, mRNA-based anti-MERS vaccines were developed; however, because the virus did not re-emerge, the vaccine evaluation process was not continued [27].

The mechanism of these vaccines involves intramuscular injection of the messenger RNA encoding the Spike protein, encapsulated in a lipid nanoparticle layer. This complex enters muscle cells via endocytosis; after which the messenger RNA is translated in the ribosomes; the resulting Spike protein fragments are degraded by cytoplasmic endosomes and incorporated as part of the Major Histocompatibility Complex class I (MHC-I), and then presented to CD8 and CD4

lymphocytes, respectively. Similarly, dendritic cells transfected with the messenger RNA will incorporate these fragments into the Major Histocompatibility Complex class II (MHC-II) to be presented to immune cells [27] (Figure 3).

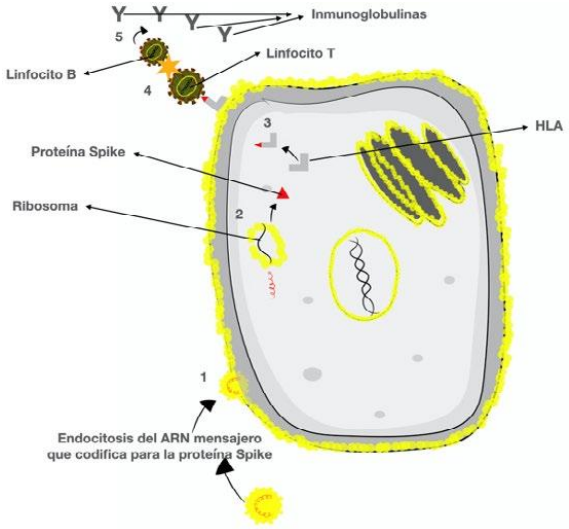

Figure 3. Schematic representation of the mechanism of RNA vaccines. 1: The vaccine encapsulated in a lipid nanoparticle layer enters the human cell. 2: The segment of messenger RNA encoding the Spike protein is translated in the ribosome. 3: Subsequently, HLA is generated. 4: The cell presents the information to the T lymphocyte, which in turn presents the information to the B lymphocyte. 5: Finally, antibodies and cellular immunity are generated

Currently, there are two types of these vaccines: non-amplified messenger RNA and self-amplifying messenger RNA. About 25 mRNA vaccine candidates are currently being studied [8]. Two prototypes of non-amplified messenger RNA vaccines are the mRNA-1273 vaccine (National Institute of Allergy and Infectious Diseases in collaboration with Moderna) and the BNT162b2 vaccine (BioNTech and Pfizer), both of which contain a segment of messenger RNA encoding the SARS-CoV-2 spike glycoprotein1 [11]. This segment of messenger RNA has been packaged in a lipid envelope that facilitates endocytosis in the host cell.

On December 11 and 18, 2020, the FDA in the United States issued emergency use authorization for the BNT 162b2 (Pfizer) and mRNA 1273 (Moderna) vaccines, respectively, for patients aged 16 and 18 and older. This authorization was based on research conducted through the end of Phase III of each vaccine.

On December 10, 2020, the clinical trial demonstrating 95% efficacy and the safety of the BNT 162b2 vaccine was published. A total of 43,548 participants aged 16 and older were enrolled; 43,448 patients received an injection, 21,720 with BNT 162b2 and 21,728 with a placebo. Eight patients in the BNT 162b2 group and 162 patients in the placebo group were diagnosed with COVID-19. Adverse effects included mild to moderate pain at the injection site, fatigue, and headache; serious events were rare and similar in both groups [28]. Similarly, a meta-analysis based on 19 observational studies shows a vaccine efficacy of 53% (95% CI: 32–68%) 14 days after the first dose and 95% (95% CI: 96–97%) seven days after the second dose [29].

Another recent clinical trial, which sought to evaluate the non-inferiority of the vaccine in 2,264 patients aged 12 to 15 years, demonstrated that the BNT 162b2 vaccine has a favorable safety profile and a stronger immune response in patients within the analyzed age group than in young adults. It is much more effective against SARS-CoV-2 disease in these younger patients [30].

After a six-month follow-up following the vaccination date for patients in the two previous clinical trials (study of the efficacy and safety of the BNT 162b2 vaccine in adults and adolescents), it was reported that efficacy at six months

remained at 91.3% (95% CI: 89–93.2%) and that safety remained favorable. In this study, the 42,094 patients were over 12 years of age and had no prior history of SARS-CoV-2 infection [31].

As is to be expected with all new drugs, vaccines, and foods, new adverse events may emerge over time. For example, if a vaccine is studied for 10 years and its adverse effects are identified during this period, it would not be possible to know in advance what other unknown complications will arise after that time, nor what effects might occur naturally, how frequently they occur, or how they affect certain populations. Therefore, the only way to observe the adverse events that vaccines may cause, including those against SARS-CoV-2, is to continue monitoring changes over time.

In this context, some adverse reactions to the BNT 162b2 vaccine have been reported: lymphadenopathy [32], severe allergic reactions [33],and some cases of myocarditis [34-36]. Similarly, in South Korea, a self-reporting survey was conducted among healthcare workers; the most common systemic reactions were muscle pain (69.1%), fatigue (65.7%), headache (48.7%), chills (44.2%), and fever (32.1%). These reactions were more common among women and in the younger age group [37].

Regarding vaccine boosters (third doses or more), a study in Israel based on data from a population of 1,137,804 individuals aged 59 and older, who had been vaccinated with BNT 162b2 (two doses) at least five months prior, compared the group that received the third dose with the group that received only two doses. It was found that the rate of confirmed infections was lower among those who received three doses than among those who received two doses, with a ratio of 11.3 (95% CI: 10.4–12.3). Additionally, the rate of severe disease was lower, with a ratio of 19.5 (95% CI: 12.9–29.5) [38]. This indicates that a booster dose of the BNT 162b2 vaccine in people aged 59 and older reduces the likelihood of SARS-CoV-2 infection by nearly 11-fold and, in the event of infection, reduces the likelihood of severe disease by nearly 19-fold.

On the other hand, on December 30, 2020, the results of a clinical trial involving 30,420 volunteers aged 18 and older, recruited from 99 medical centers in the United States, were published. The trial demonstrated 94.1% efficacy (CI: 89.3%–96.8%; $p<0.001$) and adequate safety of the mRNA-1273 vaccine. Some adverse events were reported: pain at the injection site, erythema, edema, lymphadenopathy, fever, headache, fatigue, myalgia, arthralgia, nausea, vomiting, and chills [39]. On August 11, 2021, another clinical trial was published whose primary objective was to evaluate the safety and non-inferiority of the mRNA-1273 vaccine in adolescents aged 12 to 17 years, compared to the efficacy observed in the previous study, which included adults aged 18 to 25 years. On this occasion, it was confirmed that the vaccine was safe in adolescents and that it generated immunity in both adolescents and adults [40].

Finally, on September 22, an analysis of the follow-up of the 30,420 volunteers (study published in December 2020) was published, showing that five months after receiving the two doses of the vaccine, efficacy in preventing SARS-CoV-2 remained at 93.2% (95% CI: 91–94.8%) and at 98.2% (95% CI: 92.8–99.6%) for preventing severe cases [41].

Among the most common symptoms reported by healthcare workers after vaccination with mRNA-1273 are: localized pain, generalized weakness, headache, muscle aches, chills, fever, nausea, joint pain, sweating, swelling at the injection site, dizziness, itching, decreased appetite, muscle spasms, decreased sleep quality, and dizziness [42]. Other less frequent and more severe reactions have been reported: bullous rash [43], myocarditis [35], thrombocytopenic purpura [44,45], encephalitis [46] ,and anaphylaxis [45].

A recent systematic review found that the in vitro neutralizing antibody sensitivity, following two doses of the BNT 162b2 and mRNA1273 vaccines, was reduced against the new Alpha, Beta, Delta, and Gamma variants. The highest sensitivity was observed against the Alpha variant, the lowest against the Beta variant, while the Delta and Gamma variants showed an intermediate reduction in sensitivity to neutralizing antibodies [47]. This suggests that mRNA vaccines provide lower protection against the aforementioned variants, although they remain effective.

2.3.4 DNA-based vaccines

The mechanism of these vaccines involves transferring genes via plasmids, adenoviruses, lentiviruses, or viral vesicles from SARS-CoV-2 into host cells to generate viral proteins that trigger an immune response [2]. There are approximately 18 prototypes currently under investigation. Since 1990, researchers have identified the potential use of this technique to generate vaccines by injecting intact nucleic acids into rat muscles; this technique produces both humoral and cellular immunity.

INOVIO Pharmaceuticals is working on the INO-4800 vaccine, based on the DNA sequence of the Spike protein with a leader IgE attached to the N-terminus, which increases its expression in the target cell and, therefore, its immunogenicity [8,11]. There is a potential problem with these DNA vaccines: the introduction of a nucleic acid sequence into the host's DNA could cause cellular abnormalities and may lead to some form of autoimmunity [48].

2.3.5 Attenuated virus-based vaccines

In this type of vaccine, viruses are weakened to the point where they are unable to cause infection but are still capable of activating the immune system to generate humoral and cellular immunity. The classic example of these vaccines is the oral polio vaccine [8].

2.3.6 Inactivated whole-virus vaccines

In this case, the viruses are completely inactivated (killed viruses). These vaccines tend to produce weak immunogenicity; therefore, an adjuvant is necessary to boost the host's immune response. Approximately 19 prototypes using this technique are currently being studied against SARS-CoV-2. An example of this type of vaccine is the injectable polio vaccine [8]. In this process, the viruses are inactivated through treatment with formalin or other chemicals or exposure to ultraviolet light [2].

In February 2021, Sinovac Life Sciences (Beijing, China) published a clinical trial demonstrating that the CoronaVac vaccine, based on an inactivated virus, was well tolerated and induced immunogenicity. During phases I and II of the study, 743 patients aged 18 to 59 were vaccinated with the investigational products (CoronaVac or placebo). The primary objective was to evaluate seroconversion and the production of neutralizing antibodies against SARS-CoV-2. CoronaVac is an inactivated vaccine created by inoculating SARS-CoV-2 into monkey kidney cells. Subsequently, the viruses were inactivated with B-propiolactone and adsorbed onto aluminum hydroxide [49]. In July 2021, the Phase III study, a clinical trial, was published. A total of 11,303 volunteers aged 18 to 59 were vaccinated with CoronaVac or a placebo at 24 sites in Turkey, and the vaccine was found to be 83.5% effective, with adverse effects that were similar between the vaccinated group and the placebo group [50]. Similarly, in February 2021, another Phase I and II clinical trial demonstrated efficacy in terms of seroconversion (generating neutralizing antibodies) and safety regarding side effects in 422 patients over the age of 69 [51]. Another publication from June 2021, involving patients aged 3 to 17 years in a Phase I and II clinical trial, revealed the efficacy of 3.0 mcg of CoronaVac in inducing seroconversion and few adverse events during the first 28 days following vaccination [52].

It should be noted that during the course of the research CoronaVac did not follow the usual sequence of evaluating the vaccine in a Phase III trial and then bringing it to market. Instead, this vaccine was used in the population before the Phase III study began.

2.4 Impact of vaccines on the population

After the vaccines are used in the general population, it is important to conduct follow-up to determine their effectiveness and safety in the real world, outside the population sample from the original study. This will allow for ongoing evaluation of the vaccines' effectiveness and adverse effects in the general population, especially when dealing

with a virus, due to its constant mutation and behavior across different geographic areas and host genetic conditions.

On May 5, 2021, an observational study was published that sought to evaluate the effectiveness of the BNT 162b2 vaccine seven days after the second dose in the population over 15 years of age in Israel. During the analysis period from January 24, 2021, to April 3, 2021, there were 232,268 SARS-CoV-2 infections, 7,694 hospitalizations, 4,481 severe cases, and 1,113 deaths due to SARS-CoV-2. By the end of this period, 4,714,932 people (72.1%) aged 15 and older, out of a total population of 6,538,911 in Israel, had been vaccinated with two doses of BNT 162b2. After assessing the presence of infection (via laboratory testing) and using a binomial regression analysis, the vaccine was found to be 95.3% effective (95% CI: 94.9–95.7%) in preventing SARS-CoV-2 infection, 91.5% effective (95% CI: 90.7–92.2%) for preventing asymptomatic infection, 97% (95% CI: 96.7–97.2%) for symptomatic infection, 97.2% (95% CI: 96.8–97.5%) against infection requiring hospitalization, 97.5% (95% CI:97.1–97.8%) against severe infection, and 96.7% (95% CI: 96–97.3%) against death from SARS-CoV-2 [53].

To compare clinical findings and infection severity between vaccinated patients (with BNT 162b2 or mRNA1273) and unvaccinated patients, a U.S. study conducted from December 15, 2020, to March 30, 2021, used a case-control design to identify patients with a positive PCR test for SARS-CoV-2. The results reveal that being vaccinated at the time of infection reduces the risk of severe disease and mortality compared to cases in which infection occurs without vaccination. Furthermore, the presence of anemia in infected patients is a risk factor for severe disease and mortality [54]. Another study with similar characteristics was conducted in Qatar between December 23, 2020, and March 28, 2021, in patients vaccinated with BNT 162b2, including cases and controls. The findings of the previous study confirm that vaccinated patients who contract SARS-CoV-2 infection are less likely to develop severe symptoms and die compared to unvaccinated patients. Furthermore, it was observed that advanced age is associated with greater severity and mortality [55].

From December 14, 2020, to April 10, 2021, data were collected from patients vaccinated with BNT 162b2 or mRNA-1273 in different regions of the United States (RECOVER and HEROES databases). Analysis of this data reveals that effectiveness is 91% (95% CI: 76–97%) in patients who received two doses of the vaccines and 81% (95% CI: 64–94%) in partially vaccinated patients. Furthermore, the vaccine reduces viral load, the risk of febrile symptoms, and the duration of symptoms when compared to unvaccinated patients [56]. Similarly, another case-control study using data collected from December 15, 2020, to March 4, 2021, following vaccination, reveals an efficacy of 96.2% (95% CI: 95.5–96.9%) for the BNT 162b2 vaccine and 98.2% (95% CI: 97.5–98.6%) for the mRNA1273 vaccine [57].

Data from the U.S. Department of Health and Human indicated that, following the emergence of the Delta variant of SARS-CoV-2, the effectiveness of the BNT 162b2 and mRNA1273 vaccines decreased (adjusted effectiveness from 67.5% to 53.1%) [58]. However, the homologous booster of the BNT 162b2 vaccine has demonstrated persistent efficacy against infection by the Delta and Omicron variants of 88%–93% and 76%, respectively; and 97% and 89%, respectively, against severe disease. Meanwhile, the effectiveness of the homologous booster for the BNT 162b2 and mRNA1273 vaccines remains at 93% and 67%, in that order, against the Delta and Omicron variants for infection, and effectiveness in preventing hospitalization ranges from 94% to 90%, respectively. Furthermore, when the first dose is ChAd0x1 and the booster is BNT 162b2, effectiveness against infection is 94% for Delta and 71% for Omicron. The BNT 162b2 booster is associated with a low risk of SARS-CoV-2 infection among healthcare workers, the elderly, and young people [59].

3 Conclusion

Although significant progress has been made in the understanding and development of new vaccines to prevent SARS-CoV-2 infection, many questions have arisen. However, the dynamism of science and its drive toward the cutting edge will resolve these questions, and there will always be new questions that will enable continuous scientific

advancement.

For now, it is true that being vaccinated against SARS-CoV-2 reduces the risk of becoming ill and dying. Likewise, those who do become ill after being vaccinated have a lower risk of developing severe infections and dying. On the other hand, common side effects are very mild; that is, there will always be a risk of severe side effects with vaccines, but this risk is low in relation to SARS-CoV-2 vaccines. Similarly, effectiveness and adverse events depend as much on the vaccines and their mechanisms of action as on the host's genetic response, among other factors.

In conclusion, it is worth noting that the development of new technologies and advanced knowledge has made it possible to create new types of vaccines, reduce the time required for their synthesis, and update protocols in line with current objectives and the times. Therefore, it is important to recognize that during the development of the BNT 162b2 and mRNA1273 vaccines, safety margins were maintained in the population by adhering to the scientific method throughout the research phases.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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