Review

Emerging COVID-19 vaccines: safety, efficacy and universality

Khadija EL AZHARY†, Kenza MIYARA†, Saadia AIT SSI†, Sanaa SOUAT† and Abdallah BADOU†*

†Cellular and Molecular Pathology Laboratory, Faculty of Medicine and Pharmacy, Hassan II University of Casablanca, Morocco

*Corresponding author. Email: abdallah.badou@univh2c.ma
† Contributed equally

SUMMARY

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused more than 3,807,276 deaths globally and 9,213 deaths in Morocco as of June 15 2021, in addition to a huge economic and social upheaval internationally. Developing an efficacious vaccine was essential to prevent further morbidity and mortality. Several vaccines of various platforms were approved. Their safety and efficacy was critical to their success. In this review, we will report main vaccine development approaches. We will then examine the efficacy of eight vaccines in preventing COVID-19 disease, including Pfizer-BioNTech, Moderna, Sputnik V and Novavax vaccines, which exhibited an efficiency greater than 85% (95%, 94%, 91% and 89% respectively). Finally, we will discuss the universality of these vaccines: their efficacy on distinct emerging SARS-CoV-2 virus variants.

Introduction

In late December 2019, cases of pneumonia of unknown etiology were reported in the city of Wuhan, China (Jin et al., 2020). The Coronavirus Research Group (CSG) of the International Committee for the Classification of Viruses, by analyzing the sequence of this unidentified virus, found that it is linked to the SARS virus (SARS-CoV 1) which spread in China in 2003 (Monajjemi et al., 2020; Wang et al., 2020). After analysis of the sequences and the evolutionary tree, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was identified. It belongs to the family of Coronaviridae, subfamily of Orthocoronavirinae and genera of β-CoV (Monajjemi et al., 2020; Wang et al., 2020). SARS-CoV-2 is an enveloped RNA virus with a positive-single-stranded genome that belongs to the
Betacoronavirus genus (Liu et al., 2020; Lu et al., 2020; Wong and Saier, 2021). SARS-CoV-2 binds the host cell entry receptor hACE2; human angiotensin-converting enzyme 2 through the S1 subunit of the Spike protein (S) to initiate the infection (Hoffmann et al., 2020; Y. Li et al., 2020; Perrotta et al., 2020). The attachment of the Spike protein and the co-receptor TMPRSS2 to the host surface protein results in endocytosis or immediate fusion of the viral and host cell membranes to release viral genomic RNA into the cell (Wong and Saier, 2021). The viral RNA uses the cellular machinery to synthesize co-terminal polyproteins (pp1a and pp1ab). Once synthesized, a viral protease cleaves these polyproteins into non-structural proteins (Nsps). These Nsps interact with the RNA-dependent RNA polymerase (RdRp) to form the replicase-transcriptase complex, which is responsible for the replication of the complete viral genome and the transcription of sub-genomic RNAs. The viral structural proteins (membrane protein (M), envelope protein (E) and nucleocapsid protein (N)), and encapsidated genomic RNA are translocated to the ER-Golgi intermediate compartment (ERGIC) for virion assembly. The virion bud exits through the cell membrane by exocytosis (Jeong et al., 2020; Wong and Saier, 2021).

COVID-19 has emerged as a global pandemic. It has caused significant morbidity and mortality all over the world. Development of a safe and effective vaccine appeared to be the most promising tool to limit disease transmission and to develop effective immunity against the virus. Research of promising severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines has progressed at an unprecedented pace. Various COVID-19 vaccine Platforms have emerged. These include RNA, DNA, non-replicating viral vectors and inactivated vaccines (Figure 1)(Sharma et al., 2020). RNA and DNA based vaccines can be made more rapidly in the laboratory. These approaches allow for the development process to be fast-tracked in the event of a pandemic and are able to generate a robust immune response, but these have not been developed for human use in the past (Conforti et al., 2020). In contrast, non-replicating viral vector vaccines can be safe and effective immunologically, and can be manufactured on a large scale (Sharpe et al., 2020). Viral vector vaccines have been extensively tested in completed 174 and ongoing clinical studies from multiple clinical programs. Many vaccine candidates have been evaluated, such as Ad26.ZEOBV (Ebola), Ad26.Mos.HIV (HIV) and Ad26.CS.01 (Malaria)(Custers et al., 2020). However, this method has a disadvantage due to the presence of anti-vector immunity against Ad5 in the human population, which can potentially affect the vaccine immunogenicity (Grigoryan and Pulendran, 2020). Inactivated or live attenuated viruses and recombinant protein-based vaccines are classical platforms that have successfully been used for vaccines against various infectious diseases, such as influenza, Yellow fever virus (YFV), and tick-borne encephalitis virus (TBEV) (Ilyushina et al., 2015; “Inactivated Virus Vaccine - an overview | ScienceDirect Topics,” n.d.). For many years, various recombinant proteins produced using microbes and higher organisms are used as therapeutic agents and vaccine candidates due to their proven safety record (Pollard and Bijker, 2021; Pollet et al., 2021; Tripathi and Shrivastava, 2018). Vaccinations that are live attenuated or inactivated can be generated more easily and quickly than vaccines that are not, and the body develops a powerful immune response, with immunity that can last for years. On the other hand, they have one major disadvantage: they increase the risk of infection by allowing viruses
with low virulence to become more virulent. And in order to acquire substantial and long-lasting protection, inactivated vaccines require numerous administrations (Pollard and Bijker, 2021). Whole inactivated vaccines are safer than live attenuated vaccines; however, the immunogenic epitopes of inactivated viruses may be structurally deformed during the inactivation process, which can undermine the protection they may provide. Moreover, both SARS-CoV and MERS-CoV whole inactivated vaccines have been reported to induce eosinophil-related lung pathology (Y.-D. Li et al., 2020). In this pandemic, over 200 vaccine candidates are in various stages of development, with over 50 vaccine candidates have reached human clinical trial stages (Kim et al., 2021). In this review, we will report main vaccine development approaches. We will then examine their efficacy in preventing COVID-19 disease (table 1). Finally, we will discuss the efficacy of such vaccines on distinct SARS-CoV-2 virus variants.

Methodology
We identified several relevant articles on the different Covid-19 vaccine candidates based on experiments that tested the efficacy and safety of these vaccines. Our research was based on databases such as "ScienceDirect, PubMed, Scopus" as well as search engines like Google Scholar. Search strategies were adopted using key words: "Efficacy of Covid-19 vaccines", "Covid-19 vaccines","AZD1222 and SARS-CoV-2", "AZD1222 and Covid-19","AZD1222 vaccine", "BNT162b1 and SARS-CoV-2", “BNT162b1 and Covid-19", "BNT162b1 vaccine ",

Figure 1: Different approaches used in the development of COVID-19 vaccines
Table 1: Details of the Various vaccine platforms and efficacy of COVID-19 vaccines included in the review

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Vaccine type</th>
<th>Antigen</th>
<th>Dosage</th>
<th>Efficacy</th>
<th>Current approval</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b1</td>
<td>Pfizer–BioNTech</td>
<td>mRNA</td>
<td>Full-length S protein with praline substitutions</td>
<td>2 Doses 21 d apart</td>
<td>95%</td>
<td>EUA: the US, EU, Canada and UK</td>
<td>(Mulligan et al., 2020; Polack et al., 2020; Walsh et al., 2020)</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>Moderna</td>
<td>mRNA</td>
<td>Full-length S protein with praline substitutions</td>
<td>2 Doses 28 d apart</td>
<td>94%</td>
<td>EUA: Europe, the US, Canada and UK</td>
<td>(Baden et al., 2021; Corbett et al., 2020; Jackson et al., 2020)</td>
</tr>
<tr>
<td>AZD1222</td>
<td>Oxford–AstraZeneca</td>
<td>Viral Vector</td>
<td>Replication-deficient chimpanzee adenoviral vector with the SARS-CoV-2 S protein</td>
<td>2 Doses 28 d apart</td>
<td>70%</td>
<td>EUA: EU, UK, India, Morocco and Mexico</td>
<td>(Felegatti et al., 2020; Sanderskov et al., 2021; Voysey et al., 2021b)</td>
</tr>
<tr>
<td>Ad26.COV2.S</td>
<td>Johnson &amp; Johnson</td>
<td>Viral Vector</td>
<td>Recombinant replication-incompetent adenovirus 26 vector, encodes for the Sars-Cov2 S protein</td>
<td>1 Dose</td>
<td>66%</td>
<td>EUA: the US, Europe and Canada</td>
<td>(Loo et al., 2021; Sadoff et al., 2021, 2020)</td>
</tr>
<tr>
<td>rAd26 and rAd5</td>
<td>Sputnik V</td>
<td>Viral Vector</td>
<td>Heterologous adenoviral vectors, (rAd26 vector, and rAd5 vector)</td>
<td>2 Doses (first rAd26; second rAd5) 21 d apart</td>
<td>91.6%</td>
<td>EUA: Russia, Argentina, Serbia, UAE, Algeria, Palestine and Egypt</td>
<td>(Jones and Roy, 2021; Logunov et al., 2021)</td>
</tr>
<tr>
<td>NVX-CoV2373</td>
<td>Novavax</td>
<td>Protein subunit</td>
<td>Recombinant full-length, prefusion S protein</td>
<td>2 Doses</td>
<td>89.3%</td>
<td>EUA application planned</td>
<td>(Inc, 2021; Keech et al., 2020a)</td>
</tr>
<tr>
<td>BBIBP-CorV</td>
<td>Sinopharm</td>
<td>Inactivate d Virus</td>
<td>Inactivated H802 strain of SARS-CoV-2 created from Verocells</td>
<td>2 Doses 21 d apart</td>
<td>79%</td>
<td>EUA: China, Morocco, UAE, Bahrain, Serbia, Peru, and Zimbabwe</td>
<td>(Kim et al., 2021; Xia et al., 2021, 2020)</td>
</tr>
<tr>
<td>CoronaVac</td>
<td>Sinovac</td>
<td>Inactivate d Virus</td>
<td>Inactivated CN202 strain of SARS-CoV-2 created from Verocells</td>
<td>2 Doses</td>
<td>50 to 91%</td>
<td>EUA: China, Brazil, Colombia, Boli via, Chile, Uruguay, Turkey, Indonesia</td>
<td>(Kim et al., 2021; Z. Wu et al., 2021; Zhang et al., 2021)</td>
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1. The Reliability and efficiency of COVID-19 vaccines:

1.1. mRNA Vaccines

BNT162b2 or Pfizer-BioNTech COVID-19 vaccine:
Pfizer-BioNTech COVID-19 vaccine is a vaccine that is based on lipid nanoparticle–formulated BNT162b2. It is made up of a nucleoside-modified RNA molecule that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein (Walsh et al., 2020). Several studies have reported the efficacy and safety of this vaccine. Mulligan and colleagues, were the first to put the Pfizer – BioNTech vaccine to the test in a small group of people. They enlisted the help of 45 healthy adults ranging from 18 to 55 years old. The participants were given two doses of BNT162b1 at a 21-day interval: 10 g, 30 g, or 100 g (Mulligan et al., 2020). The authors decided not to proceed with the second dose due to an increase in reactogenicity and the lack of immunogenicity in the recipients after the first dose of 30 g. Local and systemic reactions were dose-dependent, ranging from mild to moderate. Walsh et al., conducted a more in-depth study by recruiting 195 participants. They were initially divided into 13 groups, each with 15 members. The vaccine was given to twelve people, while the placebo was given to three. The most vulnerable group was the older adults, with the two vaccine candidates having similar geometric mean titers (GMT) depending on the dose. However, when compared to the 18–55 year old population, the incidence and systemic reactions in BNT162b2 (encodes for full-length transmembrane S glycoprotein) were lower than in BNT162b1 (encodes for RBD-foldon) (Walsh et al., 2020). The report on the safety and efficacy of BNT162b2 was officially released at the end of 2020. The largest cohort (n = 43,548) was reunited by Polack et al., 43,448 received injections, with 21,270 receiving BNT162b2 and 21,728 receiving placebo. Despite the high efficiency of BNT162b2, there were situations in which participants developed COVID-19 after one week following the administration of the second dose (8 in the BNT162b2 and 162 in the placebo group). After the first dose, nine of the ten cases of extreme COVID-19 occurred in the placebo group and one in BNT162b2. There were no deaths and only mild to moderate side effects, which was remarkable (Polack et al., 2020). The phase 3 data demonstrated a vaccine efficacy rate of 95% in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose. The Data Monitoring Committee (DMC) for the study has not reported safety concerns related to the vaccine. Efficacy was consistent across age, gender, race and ethnicity demographics. All trial participants were continuously monitored (for an additional two years after their second dose) to assess the duration of protection and safety (“Pfizer and BioNTech Receive Authorization in the European Union for COVID-19 Vaccine | pfizeruscom,” n.d.). After completing a phase III trial, Pfizer and BioNTech sent their Covid-19 candidate vaccine to the US Food and Drug Administration (FDA) for an emergency use authorization. The FDA granted the first emergency use authorization (EUA) for a vaccine to prevent coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 16 and up on December 11, 2020. The Pfizer-BioNTech COVID-19 Vaccine is allowed to be administered in the USA under the emergency use permit (Commissioner, 2021). BNT162b2 is still widely used in Europe, USA, Canada, and many more countries and it is included in many current vaccine programs. It is given to people aged 16 and up by intramuscular injection into the deltoid muscle in a series of two doses (0.33 ml each) separated by three weeks ("Présentation de l’administration du vaccin Pfizer-BioNTech..."

**mRNA-1273 or Moderna vaccine:**

Moderna COVID-19 vaccine is an mRNA vaccine (mRNA1273) that encodes the SARS-COV-2 spike protein (Jackson et al., 2020; Oliver, 2021). Once the mRNA-1273 vaccine inside the host cells, the translation and protein production are initiated to boost the immune response (Soiza et al., 2021). To assess mRNA-1273 vaccine effectiveness, the vaccine went through different clinical trials. A preclinical trial was conducted on mice by immunizing them with different doses (0.01, 0.1, or 1 µg) of the Moderna vaccine. The results showed an increased level of pseudo-virus neutralizing antibodies responses as well as in mice expressing the muted form of the spike protein. Moreover, the 1µg dose provides a strong cytotoxic T cell response (Corbett et al., 2020). Phase I trials were performed on 45 healthy human participants from 18-55 years old by injecting them with three different shots of the Moderna vaccine (25, 100, or 250 µg) 28 days apart. The study showed that the specific antibody response was detected in a dose-dependent manner and reached a steady-state at day 15 following the first prime. Specific antibodies were apparent in less than half of the participants after the first dose but were detected in all participants following the second booster dose. Furthermore, the greatest response was associated with 100 and 250 µg doses which marked a higher CD4 T cell response (Jackson et al., 2020). The efficacy of the Moderna vaccine in people aged 58 or over was reported by the New England Journal of Medicine, which demonstrated that the antibody responses detected in older people were similar to those seen in younger people (Anderson et al., 2020). Moderna’s phase III trial was randomized including a quadruple blinding trial that required a cohort of 30,000 healthy adults aged 18 and above to test in large-scale trials vaccine safety, observe adverse reactions, and monitoring the reactogenicity and immunogenicity of the Moderna vaccine (CureVac AG 2021). The study showed that 11 participants who belong to the vaccine group were covid-19 positive after receiving the first prime dose, while, 185 participants were noted as infected by covid-19 in the placebo group. These results suggested the Moderna vaccine averaged 94% efficacy overall (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-COV-2 infection as compared with placebo(Baden et al., 2021). Similar findings were observed between days 1 and 42, seven participants were positive to COVID-19 in the mRNA1273 group, as compared with 65 cases in the placebo group. Furthermore, 0.3% of participants in the placebo group manifested asymptomatic Covid-19, however, 0.1% of cases in Moderna vaccine group had nasopharyngeal swabs that were positive for Covid-19 without any detectable symptoms following the booster dose (Baden et al., 2021). Surprisingly, the Moderna vaccine efficacy to prevent infection by Covid-19 was consistent across subgroups stratified by sex, ethnic group, race and age group (18 to <65 years of age and ≥ 65 years) (Mahase, 2020).

**1.2. Viral vector vaccines:**

**AZD1222 or Oxford–AstraZeneca vaccine:**

The ChAdOx1 nCoV-19 vaccine (AZD1222) is a vaccine against SARS-CoV-2 virus, which was developed by Oxford University and AstraZeneca (Soiza et al., 2021). AZD1222 consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2 (Folegatti et al., 2020; Soiza et al., 2021). Preclinical trials were carried out on pig models, the results demonstrated that two doses of ChAdox1 vaccine bring out a significant increase in neutralizing antibodies, which bind to the SARS-
Cov-2 virus and suppress infection (Sharma et al., 2020). A phase I and II trials were then designed to establish whether the two doses might elicit a high immune response. A randomized single-blinded trial had been conducted on 1077 healthy volunteers, aged between 18-55, in the UK. Following the second shot of the vaccine at 28 days, the ChAdOx1 nCOV-19 group showed a high and sustained level of specific antibodies until day 56. High neutralizing antibodies response was noted among 91% of participants after the first dose, while 100% of participants gave rise to a high specific antibody response following the second dose, across all age groups. On day 14, specific T cell responses peaked in the ChAdOx1 nCOV-19 group, however, anti-spike IgG responses rose by day 28 and were increased after a booster dose (Folegatti et al., 2020). Following initiation of a phase 1 clinical trial in the UK (COV001, phase 1/2) on April 23, 2020, three further trials of the candidate vaccine were initiated across the UK (COV002, phase 2/3), Brazil (COV003, phase 3), and South Africa (COV005, phase 1/2). The immunogenicity results from the phase 2 cohort in COV002 in older adults (≥56 years) have been published and showed an acceptable safety profile for the vaccine with induction of binding and neutralizing antibodies as well as generation of interferon-γ enzyme-linked immunospot responses, with higher antibody titers after a second dose of vaccine (Voysey et al., 2021a). Early results of phase III trials which were conducted among 32 449 participants have found that the AstraZeneca vaccine was 80% efficacy on people over 65 years, 60% among them had comorbidities related to a high risk of severe covid-19 disease. Interim results of 21 583 participants who took at least one prime of vaccine illustrated that this group of people did not manifest any risk or event associated with thrombosis. ChAdOx1 nCOV-19 vaccine was also 79% effective at preventing symptomatic Covid-19 and 100% effective at preventing severe disease and admission to hospital, and consistent across ethnic groups: 79% of participants were white, 22% Hispanic, 8% black or African American, 4% Native American, and 4% Asian (Voysey et al., 2021a).

The combined findings from clinical trials in the United Kingdom, Brazil, and South Africa demonstrated that AZD1222 vaccine was safe and effective at preventing Covid-19 in the adult population from 18 years old. This led the European Medicines Agency to recommend the Covid-19 AstraZeneca vaccine for authorization in the European Union. However, weeks after starting AstraZeneca vaccine, a number of European countries suspended vaccination or limit it to subjects over 60 years, due to blood clots in vaccinated people. Following extensive analysis of these thromboembolic events, the European Medicines Agency declared that the advantages greatly outweigh the side effects of ChAdOx1 vaccine, especially that infected subjects by Covid-19 undergo thrombotic complications, which reassured several countries to restart vaccination (Sønderskov et al., 2021).

**Ad26.COV2.S or Jonhson & Jonhson vaccine:**

Johnson & Johnson has developed their vaccine candidate using Ad26 to fight COVID-19. It’s a recombinant, replication-incompetent adenovirus serotype 26 vector that encodes for the SARS-CoV-2 spike protein. Phase I/II trials that began in July in healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3), at a dose of 5×10^{10} or 1×10^{11} viral particles per milliliter or placebo in a single or two doses. The most frequent solicited adverse events were fever, fatigue, headache, myalgia, and injection-site pain. They were less common in
cohort 3 than in cohort 1 and in those who received the low vaccine dose than in those who received the high dose. Neutralizing-antibody titers against wild-type virus were detected in 90% or more of all participants on day 29 after the first vaccine dose, regardless of vaccine dose or age group, and reached 96% by day 57 with a further increase in titers in cohort 1. A second dose provided an increase in the titer by a factor of 2.6 to 2.9. On day 15, CD4+ T-cell responses were detected in 76 to 83% of the participants in cohort 1 and in 60 to 67% of those in cohort 3, with a clear skewing toward type 1 helper T cells. CD8+ T-cell responses were robust overall but lower in cohort 3.

Phase I/II trials yielded results that stated the vaccine had a good safety profile and immunogenicity after only a single dose. The vaccine induced an immune response in the participants with a high seroconversion rate, and only mild to moderate side effects were reported (Sadoff et al., 2021, 2020). This led to Phase III trials in September 2020 with 60,000 participants. Towards the end of January 2021, Johnson & Johnson announced that their Ad26.COV2.S vaccine was 66% effective in preventing moderate to severe COVID-19, 28 days after vaccination. The first onset of protection was observed on day 14 post immunization (Loo et al., 2021).

rAd26/rAd5 or the Sputnik V vaccine:
Sputnik Vis a Human Adenovirus Vector-based Covid-19 vaccine, it was developed by Gamaleya National Research Centre for Epidemiology and Microbiology in Russia. Also known as Gam-COVID-Vac. The vaccine was designed on a platform of heterologous adenoviral vectors, a recombinant adenovirus type 26 (rAd26) vector, and a recombinant adenovirus type 5 (rAd5) vector, both of which carry the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (rAd26-S and rAd5-S) (Logunov et al., 2020). The aim of using two different vectors for the first and second injections is to enhance the effect of the vaccine and to provide long-lasting immunity compared to vaccines using the same components for both injections (Jones and Roy, 2021). The vaccine was manufactured in two formulations, frozen (Gam-COVID-Vac) and lyophilized (Gam-COVID-Vac-Lyo) (Logunov et al., 2020). So, to evaluate the safety and immunogenicity of these two formulations, Logunovetal, conducted two open, phase 1/2 non-randomized trials in 76 healthy adult volunteers (men and women), aged between 18 and 60 years. In phase 1 of both studies, eighteen volunteers (nine per group) received on day 0 one dose of rAd26-S or rAd5-S and investigated any beneficial activities for 28 days. In phase 2 of both studies, vaccination began not earlier than 5 days after the first shot, twenty volunteers received one dose of rAD26-S on day 0 and one dose of rAD5-S on day 21 as a prime-boost vaccination. Pain at the injection site (44 [58%]), hyperthermia (38 [50%]), headache (32 [42%]), asthenia (21 [28%]), and muscle and joint pain (18 [24%]) were the most common adverse reactions. The heterologous vaccine was well-tolerated and produced humoral and cellular immune responses in healthy adults. The efficacy of the vaccine was confirmed by IgG titres that are significantly higher than those reported in people who have recovered from COVID-19. An analysis for antibodies that neutralize the SARS-CoV-2 showed a significant increase at day 14 and continued to increase over the observation period. The spike protein-specific T cell response were detected at day 28 after vaccination, with 2.5% CD4+ and 1.3% CD8+ for the frozen formulation, and 1.3% CD4+ and 1.1% CD8+ for that lyophilized, respectively (Logunov et al., 2020). Subsequently, Logunov et al. conducted another study with the main objective of
evaluating the same parameters but on a larger scale. A randomized, double-blind placebo-controlled multicentre phase 3 trial was conducted in Moscow, Russia, to assess the efficacy, immunogenicity, and safety of Gam-COVID-Vac. In this study, 21,977 adults aged 18 to 60 years, were randomly assigned to receive vaccine or placebo (n=16,501 / 5476 respectively) in frozen liquid form, with a 21-day interval between doses. In the interim efficacy analysis report (0.1%) from the vaccine group and (1.3%) from placebo, were confirmed as SARS-CoV-2-positive patients. In both groups, the incidence rate showed that the immunity necessary to prevent disease occurred within 18 days after receiving the first dose. Thus, Sputnik V was 91.6% (95% CI 85.6–95.2) effective in preventing severe cases of COVID-19. The protection applied to all age groups, including those older than 60 years. Four fatalities occurred in the vaccine (n=3) and placebo (n=1) group, that has been concluded to not be associated with the vaccine. No serious adverse events considered to be vaccine-related were recorded, but non-vaccine-related serious adverse events were reported in 45 participants in the vaccine group and 23 participants in the placebo group (Logunov et al., 2021). Another study was performed to compare the efficacy of candidate vaccines in inducing neutralizing antibodies against SARS-CoV-2. The network meta-analysis showed that Sputnik V, AZD1222, BNT162b2, New Crown COVID-19, and BBIBP-CorV induced a very large effect on the level of neutralizing antibodies (SMD > 1.3) and that Sputnik V and BNT162b2 were more effective (p < 0.05) than Ad26.COV2. on this outcome (Rogliani et al., 2021). The overall results showed that Sputnik V was 91.6% effective, providing full protection against COVID-19, and it is one of only three vaccines in the world with an efficiency of over 90% (Mishra and Tripathi, 2021).

1.3. Nanoparticle Vaccine

NVX-CoV2373 or Novavax vaccine: NVX-CoV2373 is a Recombinant Spike Protein Nanoparticle Vaccine, developed by Novavax and manufactured at Emergent Bio-solutions. It was developed using recombinant nanoparticle technology to generate an antigen derived from the coronavirus spike (S) protein with Matrix-M™ adjuvant to enhance the immune response (Tian et al., 2021). A Phase 1/2 randomized, observer-blinded, placebo-controlled trial was conducted at two sites in Australia in healthy adults aged between 18 to 59 years. In this study, 131 participants were randomly assigned to receive the vaccine with adjuvant (n=83), without adjuvant (n=25), or a placebo (n=23), with two-dose regimens of 5μg and 25 μg. The vaccination consisted of two intramuscular injections, with a 21-day interval between doses. Overall reactogenicity was absent or mild and no serious adverse events were reported. The safety and immunogenicity analyses results indicate that the adjuvanted, recombinant, full-length spike protein nanoparticle vaccine NVX-CoV2373 had acceptable tolerance and induced high immune responses, with neutralizing antibody levels correlating closely with anti-spike IgG. Also, after the second injection with the adjuvanted vaccine, neutralizing antibody responses exceeded the values observed in symptomatic Covid-19 outpatients (5 times greater than without adjuvant) and approximated the magnitude of the levels observed in convalescent serum of hospitalized patients with COVID-19 (4 times greater than those in symptomatic outpatients with Covid-19). Besides, the adjuvanted vaccine-induced polyfunctional antigen-specific CD4+ T-cell responses were reflected by the production of IFN-γ, IL-2, and TNF-α upon stimulation with spike protein, with a strong bias toward Th1 phenotype.
NVX-CoV2373 is currently being evaluated in two pivotal Phase 3 trials: a trial in the U.K that completed enrolment in November 2020 and the PREVENT-19 trial in the U.S. and Mexico that began in December 2020. It is also being tested in two ongoing Phase 2 studies that began in August: a Phase 2b trial in South Africa, and a Phase 1/2 continuation in the U.S. and Australia. A study of the efficacy of the NVX-CoV2373 vaccine was conducted during a period of high transmission and with the emergence of a new, widely circulating British variant strain of the virus. The phase 3 clinical trial was conducted in the United Kingdom, enrolling more than 15,000 participants aged between 18-84 years. Participants were randomized to receive NVX-CoV2373 with Matrix-M™ adjuvant or placebo. Serious, severe adverse events occurred at low levels and were balanced between the vaccine and placebo groups. Analyses of 62 cases revealed 56 cases (90%) of COVID-19 in the placebo group versus 6 cases (10%) in the NVX-CoV2373 group, resulting in a vaccine efficacy estimate of 89.3% (95% CI: 75.2 - 95.4)(Inc, 2021; “Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial | Novavax Inc. - IR Site,” n.d.). This study was conducted during the emergence of a new, widespread British variant strain of the virus. Preliminary analysis indicates that the UK variant strain was detected in more than 50% of symptomatic PCR-confirmed cases. Based on PCR performed on strains from 56 cases, the efficacy per strain was calculated to be 95.6% against the original COVID-19 strain and 85.6% against the UK variant strain(Inc, 2021; “Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial | Novavax Inc. - IR Site,” n.d.; Shinde et al., 2021; Yan et al., 2021).

1.4. Conventional Inactivated Vaccines

BBIBP-CorV or the Sinopharm COVID-19 vaccine:

BBIBP-CorV, also known as the Sinopharm COVID-19 vaccine, is an inactivated vaccine developed from the strain 19nCoV-CDC-Tan-HB02 (HB02). It is developed by the Beijing Institute of Biological Products (Xia et al., 2021). Xia and colleagues conducted an interim analysis of phase 1 and 2 clinical trials that were randomized, double-blind, and placebo-controlled. The trials were conducted in the Chinese province of Henan, with 320 participants, 96 (phase 1) and 224 (phase 2) healthy adults, ranging in age from 18 to 59 years old. Within the first phase, the participants were assigned to 3 dose groups (2.5, 5, and 10 μg/dose) and an aluminum hydroxide (alum) adjuvant-only group (n = 24 per group) and received, at three distinct intervals—day 0, 28, and 56, 3 intramuscular injections. The 7-day adverse reactions occurred in 3 (12.5%), 5 (20.8%), 4 (16.7%), and 6 (25.0%) patients in the alum only, low-dose, medium-dose, and high-dose groups, respectively. In the phase 2 trial, all 224 were randomized to 5 μg/dose in 2 schedule groups—day 0 and 14 (n = 84) versus alum only (n = 28), and days 0 and 21 (n = 84) versus alum only (n = 28). The adverse reactions occurred in 5 (6.0%) and 4 (14.3%) patients who received injections on days 0 and 14 for vaccine and alum only, and 16 (19.0%) and 5 (17.9%) patients who received injections on days 0 and 21 for vaccine and alum only, respectively. The most common adverse reaction was injection site pain, followed by fever, which were mild and self-limiting; no serious adverse reactions were noted. The geometric mean titers of neutralizing antibodies in the low-, medium-, and high-dose groups at day 14 after 3 injections were 316 (95% CI, 218-457), 206 (95% CI, 123-343), and 297 (95% CI, 208-424),
respectively, in the phase 1 trial, and were 121 (95% CI, 95-154) and 247 (95% CI, 176-345) at
day 14 after 2 injections in participants receiving
vaccine on days 0 and 14 and on days 0 and 21,
respectively, in the phase 2 trial. Two-dose
immunization with 4 μg vaccine on days 0 and 21
or days 0 and 28 achieved higher neutralizing
antibody titers than the single 8 μg dose or 4 μg
dose on days 0 and 14 (Xia et al., 2020). Xia et al.
took further this research and performed a
randomized, double-blind, placebo-controlled,
phase 1/2 trial at Shangqiu City Liangyuan District
Center for Disease Control and Prevention in
Henan Province, China. The participants were
separated into two age groups (18–59 years and
≥60 years) and randomly assigned to receive
vaccine or placebo. They reported that BBIBP-
CorV, was safe and well tolerated at all tested
doses in the two age groups. Humoral responses
against SARS-CoV-2 were induced in all vaccine
recipients on day 42. Two-dose immunization with
4 μg vaccine on days 0 and 21 or days 0 and 28
achieved higher neutralizing antibody titers than
the single 8 μg dose or 4 μg dose on days 0 and 14
(Xia et al., 2021). Sinopharm has announced
efficacy of 79% (Kim et al., 2021).

Sinovac (Sinovac Life Sciences, Beijing, China)
is an inactivated vaccine candidate against COVID-
19 that has shown good immunogenicity in mice,
rats, and non-human primates with vaccine-induced
neutralizing antibodies to SARS-CoV-2 (Gao et al.,
2020). Yanjun Zhang and al., tested the safety and
efficacy of CoronaVac in healthy adults aged from
18 to 59 years. They found that two doses of
CoronaVac at different concentrations and using
different dosing schedules were well tolerated and
moderately immunogenic. The incidence of adverse
reactions in the 3 μg and 6 μg group were similar,
indicating no dose-related safety concerns but more
long-term follow-up is needed. Furthermore, most
adverse reactions were mild, with the most
common symptom being injection-site pain (Zhang
et al., 2021). Between April 16 and April 25, 2020,
144 participants were enrolled in the phase 1 trial,
the incidence of adverse reactions for the days 0
and 14 cohort was 29% in the 3 μg group, 38% in
the 6 μg group, and 8% in the placebo group, and
for the days 0 and 28 cohort was 13% in the 3 μg
group, 17% in the 6 μg group, and 13% in the
placebo group. The seroconversion of neutralizing
antibodies on day 14 after the days 0 and 14
vaccination schedule was seen in 46% in the 3 μg
group, 50% in the 6 μg group, and 0% in the
placebo group; whereas at day 28 after the days 0
and 28 vaccination schedule, seroconversion was
seen in 83% in the 3 μg group, 79% in the 6 μg
group, and 4% in the placebo group. Between May
3 and May 5, 2020, 600 participants were enrolled
in the phase 2 trial. The incidence of adverse
reactions for the days 0 and 14 cohort was 33%
in the 3 μg group, 35% in the 6 μg group, and 22% in
the placebo group, and for the days 0 and 28 cohort
was 19% in the 3 μg group, 19% in the 6 μg group,
and 18% for the placebo group. Seroconversion of
neutralizing antibodies was seen for 92% in the 3
μg group, 98% in the 6 μg group, and 3% in the
placebo group at day 14 after the days 0 and 14
schedule; whereas at day 28 after the days 0 and 28
schedule, seroconversion was seen in 97% in the 3
μg group, 100% in the 6 μg group, and 0% in the
placebo group (Zhang et al., 2021). Zhiwei Wu and
al. tested the safety and efficacy of CoronaVac in
adults aged 60 years and older. CoronaVac was
well tolerated and induced humoral responses in
adults aged 60 years and older, which supports the
use of this vaccine in an older population. Among
the three doses evaluated, the neutralizing antibody
titers induced by the 3 μg dose were similar to
those of the 6 μg dose, and higher than those of the
1.5 μg dose. Combined with the safety and production capacity, the 3 μg dose of CoronaVac with a two-dose immunization schedule is being used in the ongoing phase 3 trials to assess protection against COVID-19 (Z. Wu et al., 2021). CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2, which supported the approval of emergency use of CoronaVac in China. Several countries participating in the Sinovac efficacy trials have announced efficacies of 50%, 65%, 78% and 91%. Sinovac has yet to comment, and these data have not been published or peer reviewed (Kim et al., 2021).


B.1.1.7 variant

Following a wide amount of genome replication (Robson et al., 2020), SARS-CoV-2 provoked the appearance of a huge number of Covid-19 variants worldwide including several variants of concern (VOC), specifically B.1.1.7 that was discovered to have emerged for the first time in the United Kingdom in September 2020 (Volz et al., 2021). B.1.1.7 variant carries a constellation of nine genetic mutations in the spike protein including N501Y, A570D, D614G, P681H, T716I, S982A, D1119H, and deletions of residues 69-70 and 144 (Muik et al., 2021). Studies have reported that B.1.1.7 variant was more infectious, it exhibited increased transmissibility and associated with a higher risk of hospitalization and mortality (Jewell, 2021). The efficacy of the Moderna (mRNA1273) or Pfizer-BioNTech (BNT162b2) vaccines, against N501Y, E484K, or K417N mutations shows that these mutations can reduce the neutralization potency of plasma from vaccinated individuals or naturally infected individuals against SARS-CoV-2 pseudo-types viruses (Muik et al., 2021; K. Wu et al., 2021). Different studies have reported that the spike protein with a full set of B.1.1.7 manifested a small reduction in monoclonal antibodies neutralizing using serum from individuals who received two doses of BNT162b2 or mRNA1273 vaccine (Muik et al., 2021; K. Wu et al., 2021). On the other hand, Janssen and Novavax showed an estimated (85.6%) efficacy against the UK B.1.1.7 (Haseltine, n.d.), ChAdOx1 nCOV-19 vaccine has recently reported (75%) efficacy against B.1.1.7, compared to (84%) against other lineages (Emary et al., 2021).

B1.427/B.429 Variant

The SARS-CoV-2 B.1.427/B.1.429 variant originated in California in May 2020 and has been detected in more than 29 countries to date (Rambaut et al., 2020). The fast rise in the number of cases associated with the B1.427/B.429 lineages led to their classification as VOC by the US Center for Disease Control. B1.427/B.429 Variant is characterized by the S13I, W152C mutations in the NTD and by the L452R mutation in the RBD (McCallum et al., 2021).

To assess the impact of the three mutations, present in the B1.427/B.429 S glycoprotein on neutralization activity, the serum specimens were obtained from individuals who were recovered from Covid-19 and from persons who received mRNA-1273 Moderna and NVX-CoV2373 Novavax (Shen et al., 2021, p. 351). The results indicated that this variant was approximately 2 to 3 times less sensitive to neutralization by convalescent serum and by serum samples obtained from vaccinated individuals (Shen et al., 2021). Another study showed that neutralization potency of plasma obtained from peoples who received two doses of the Moderna and Pfizer/BioNTech was reduced to 2.8-fold and to 4-fold respectively for B1.427/B.429 compared to wild type (D614G) S (McCallum et al., 2021). These data suggest that B1.427/B.429 lineage induce a modest decrease of
neutralization potency from vaccine-elicited plasma due to S13I, W152C, L452R mutations that were resistant to certain therapeutic monoclonal antibodies.

**B.1.351 variant**

In December 2020, a new B.1.351 variant of SARS-CoV-2 was first detected in the Eastern Cape Province of South Africa (Mwenda, 2021). Also known as 501Y.V2, this variant strain is characterized by nine mutations that affect the spike gene (Tegally et al., 2020), three substitutions (K417N, E484K, and N501Y) in the spike receptor-binding domain (RBD), also a cluster of four mutations in the N-terminal domain (NTD) and one mutation near the furin cleavage site (A701V) (Wang et al., 2021a). These mutations are associated with increased transmissibility and resistance to antibody neutralization (Greaney et al., 2021; Wang et al., 2021b). The B.1.351 variant has spread at a rapid rate and is associated with a higher viral load after infection, which could attenuate the naturally acquired immunity or reduce vaccine efficacy (Mwenda, 2021). In a phase 2a–b trial of NVX-CoV2373 in South Africa during a period of predominant circulation of the B.1.351 variant virus, has been found that two doses of the vaccine had an efficacy of 49.4% (95% CI: 6.172.8) (Shinde et al., 2021). In another study, Shen et al evaluated the sensibility of the B.1.351 variant to neutralizing antibodies induced by the NVX-CoV2373 or mRNA-1273 vaccine compared to the prototypic D614G variant. The results showed that B.1.351 was approximately 9 to 14 times less sensitive to neutralization by convalescent serum and by serum from vaccinated individuals (Shen et al., 2021). It was reported in a press release that the mRNA-1273 vaccine produces neutralizing titers against the B.1.351 variant and with a six-fold reduction compared to previous variants (Moderna, Inc., 2021). To combat the pandemic and increase neutralizing antibody titers against emerging strains, Moderna has advanced an emerging variant booster candidate (mRNA-1273.351) against B.1.351 variant. The company is advancing mRNA-1273.351 in trials to evaluate the immunological advantage of stimulation with strain-specific spike proteins (Moderna, Inc., 2021). The multinational Phase 3 clinical trial of Janssen's vaccine (Ad26.COV2.S) was conducted in South Africa during the spread of the new B.1.351 variant. Almost 95% of cases were infected with this emerging variant. It was reported that after 28 days post-vaccination, the level of protection against moderate to severe infection with COVID-19 was 57% (Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 ENSEMBLE Trial, 2021). However, a multicenter trial of the ChAdOx1 nCoV-19 vaccine (AZD1222) in HIV-negative individuals in South Africa showed that both doses of the vaccine were ineffective (10.4%; 95% [CI], -76.8 to 54.8) to protect against moderate to severe SARS-COV2 infection caused by the emerging B.1.351 variant. And that viral neutralization by sera obtained from those vaccinated against coronavirus variant B.1.351 was significantly reduced compared with the parental coronavirus strain (Madhi et al., 2021). Furthermore, the results of a study based on the comparison of convalescent sera from patients infected with the B.1.351 variant and the Victoria strain showed that neutralization titers were reduced 7.6-fold for B.1.351 compared to the Victoria strain (Zhou et al., 2021). All these data demonstrate that the B.1.351 strain is resistant to neutralization by antibodies elicited by different vaccines compared to the parental strains, which would pose a serious challenge to the protective
efficacy of distinct SARS-CoV-2 vaccines.

**Conflicts of Interest:**

There is no conflict of interests

**References**


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