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An Overview of Leading SARS-CoV-2 Vaccine Pipeline

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 is the causative virus for the highly infectious coronavirus disease 2019. In less than 4 weeks following the first reported case of the disease, the number of cases has increased 13-folds with several countries reporting severe disease. As a result, on March 11, 2020, the WHO declared coronavirus disease 2019 a pandemic. This declaration ushered in a remarkable collaboration of the international research community to develop potential therapies and Covid-19 vaccines. Currently, there are several vaccine candidates in different stages of clinical trials. In this article, we review the vaccine candidates in their late stages of development. Results from these studies albeit preliminary, reported significant immunogenicity, efficacy, and safety at preventing Covid-19 infection, including severe disease in patients 18 years and older. Overall, reported side effects are mild and transient; there were no significant safety concerns. Subsequently, a few vaccine candidates such as the mRNA1273, BNT162b2, AZD1222, Ad26.COV2.S and Sputnik-V have either been approved or granted emergency use authorization by the various regulatory authorities.

Keywords: Coronavirus; Covid-19 vaccines; Genome

Introduction

Since the first reported case of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) the causative agent of coronavirus disease 2019 (COVID-19), there have been over 110 million cases and over 2 million deaths globally [1]. SARS-CoV-2 is highly transmissible with an estimated reproductive number (R_0) of [2,3]. Furthermore, SARS-CoV-2 is transmitted from infected individuals without symptoms [4]; thus, resulting in the current pandemic. Therefore, controlling this viral disease will depend on employing effective vaccines and therapeutics. Immunization is considered to be one of the most effective forms of infectious disease control and prevention [5]. Active immunization, or the induction of effective response of a host's immune system to a specific pathogen, involves the administration of either inactivated or attenuated whole pathogens [6]. Whereas a typical vaccine development timeline takes approximately 5 to 10 years, and sometimes longer, advances in medical technologies including the newly developed concept of messenger ribonucleic acid (mRNA) have ushered in the development of various types of vaccines to activate the immune responses in a shorter timeline. In this article, we provide a brief review of the leading vaccine candidates in the fight against SARS-CoV-2 infection.

The full sequence of the coronavirus genome was made widely available by the World Health Organization (WHO) in January 2020 [3]. Thus, making it possible to develop specific diagnostics, potential drugs, and vaccines. The genome of the coronavirus is surrounded by an envelope. The proteins that are associated with the viral envelope are the membrane protein, the envelope protein, and the spike (S) protein. The S protein promotes viral entry into the host cell by piercing through the host's cell plasma-bound membrane, while the envelope and membrane proteins function to assemble the virus. The S protein also acts as a stimulant of host immune responses. Upon entry into host cells, the S1 portion of the spike protein binds to receptors located on the surface of host cells. The S2 subunit of the spike protein fuses the host cell and viral cell membranes; thus, allowing the viral genome to enter the host. Drug development has focused on altering key steps in the infectious process, including receptor-mediated binding and fusion of the viral and host membranes [7]. The spike protein of Covid-19 is considered the best target for vaccines in part due to its high immunogenic response. The S protein can exist in two different states, pre-fusion, and post-fusion. To provoke

a sufficient quality antibody response, the S protein must stay in its pre-fusion formation to prevent binding to the host human angiotensin-converting enzyme 2 (hACE2) receptor [8]. However, the S protein also contains some non-neutralizing epitopes in the immuno-predominant domain [9]. These epitopes may induce harmful immune responses [10]. Therefore, it is essential to exclude the non-neutralizing epitopes of the S protein that may induce adverse outcomes from S protein-based vaccines.

Vaccine Platforms

Live Attenuated Vaccine

Live attenuated vaccines utilize attenuated microorganisms that can replicate within the host, but usually do not cause active disease. Live attenuated vaccines, through replication, produce an extensive array of native viral antigens with long-lasting effects resembling a natural immune response [11]. The vaccine stimulates toll-like receptors of the innate immune system, B cells, as well as CD4 and CD8 T cells [8]. Live attenuated vaccines have a long history of high immunogenicity compared to the other vaccine methods, such as the subunit or the DNA-based vaccines. Similar to whole inactivated vaccines, live attenuated vaccines may possess a biosafety risk because they contain infectious microorganisms and antibodies which can disrupt the vaccine replication. Another concern of both the live-attenuated and inactivated vaccines is the risk of recovering virulence. Patients with compromised immune systems would not be appropriate candidates for these types of vaccines. As a result of the aforementioned risks, many of the leading vaccines in development for SARS-CoV-2 have been directed toward more innovative and specific technology [11].

Inactivated Vaccine

Inactivated vaccines, also known as killed vaccines, include the whole or specific fragments of the inactivated microorganisms [12]. Formaldehyde is often used to inactivate the microorganism [13]. Physical, chemical, and biological techniques are used to isolate specific components, such as a protein, polysaccharide, or capsid from the virus or bacterium. Toxoids are developed by chemically modifying the protein toxins of the pathogen to lower their pathogenicity. Polysaccharide vaccines are developed directly from the polysaccharides of bacterial capsules. Manipulation of the pathogenic components can be performed to improve immunogenicity or change the course of the immune response. For example, conjugated vaccines join polysaccharide molecules with protein carriers resulting in a change from independent to dependent T cell response and immunologic memory. This change expands the protective capabilities of the vaccine to children under the age of two, to whom polysaccharide vaccines do not produce an adequate immune response. Overall, inactivated vaccines are more stable and safer than live attenuated vaccines. Unfortunately, the immunity obtained wanes with time; therefore, supplemental doses are required to boost immunity. There is also the possibility of administering these vaccines with an adjuvant to increase their immunogenicity. The development of inactivated vaccines against SARS-CoV-2 has the benefit of pre-existing technology and prior efficacy testing for other diseases such as Severe Acute Respiratory Syndrome-associated Coronavirus (SARS-CoV) which shares many similar amino acid substitutions [8].

Protein Subunit Vaccine

Subunit vaccines are composed of protein or glycoprotein components of a pathogen that can induce a protective immune response and may be produced by conventional biochemical or recombinant DNA technologies. Recombinant subunit vaccines have distinct advantages over live attenuated and inactivated vaccines since they are efficient in inducing humoral and cell-mediated immunological responses, without the risks that come with handling the pathogen. Unfortunately, subunit vaccines are generally more expensive and require specific additives to enhance the immune response [14]. The antigenic properties of the isolated component must be examined extensively to determine the combination that will create the most effective immune response. Not only is this process expensive, but there is also no guarantee that the immune response will result in immunological memory. Subunit vaccines require an adjuvant to heighten the host's immune response and increase the half-life of the antigenic portion of the vaccine [8]. The vaccine mechanism of action is considered when selecting and developing an adjuvant. The specificity of an adjuvant can provide a vaccine with low immunogenicity and enduring immune response. Aluminum salt-based adjuvants, usually called 'Alum,' can induce antigen-specific humoral and Cytotoxic T Lymphocyte (CTL) responses. Adjuvants with distinct and complementary mechanisms of action may be used in combination to further improve the immunogenic effect of the protein subunit vaccine [15].

Deoxyribonucleic acid (DNA) Vaccine

Another method of producing vaccines is through recombinant Deoxyribonucleic Acid (DNA) technology. Through this technology, the DNA sequence for the desired component is isolated from the pathogen and inserted into the gene of another cell to be cultured. The developed component is separated and purified into a recombinant vaccine. This type of technique is economical and efficient [12].

Messenger Ribonucleic Acid (mRNA) Vaccine

Messenger Ribonucleic Acid (mRNA) is a single strand of RNA that is used to relay genetic information to ribosomes to create various proteins [16]. Unlike traditional vaccines, RNA-based vaccines do not introduce antigens into the body. However, the benefits of mRNA vaccines include increased stability and safety [17]. Additionally, mRNA vaccines can be manufactured within weeks and are extremely flexible, as any protein can be expressed on mRNA. The vaccines can also be manufactured to target multiple diseases [18,19]. mRNA-based vaccines can either solely encode the antigen of interest or they can encode the antigen of interest as well as the viral replication machinery to enable additional intracellular RNA duplication. mRNA is extremely immune-stimulatory, which can be either beneficial or detrimental, depending on the desired endpoint. The level of immunogenicity can be altered through purification. Decreasing immunogenicity can increase the safety profile [17].

Viral Vector vaccine

Viral vector vaccines express the pathogenic gene desired from another microorganism. The advantages of viral vector vaccines include precision and efficiency in the transduction of genes into target cells, high immunogenicity, and cellular immunity. The vaccines can induce a strong Cytotoxic T Lymphocytes (CTL) response without an adjuvant to boost the immune response. Disadvantages of viral vector vaccines include the possible development of cancer from integration into the host genome and the risk of previous immunity to the vector resulting in the attack of the vector before the induction of genetic material into host cells [20].

Adenovirus is a double-stranded DNA virus encased in a capsid with no envelope. There are more than 50 human adenoviral serotypes. Bovine and simian isolates also exist [21]. The adenovirus normally produces mild cold-like symptoms in humans. Symptoms associated with adenovirus infections include acute respiratory disease, pharyngoconjunctival fever, and gastroenteritis [20].

Adenoviruses activate the innate immune system by expressing pathogen-associated molecular patterns that bind to the host cells' pathogen recognition receptors. This initiates the production of proinflammatory cytokines and the transformation of dendritic cells into antigen-presenting cells. The adaptive immunity induced produces antibodies that primarily target the viral hexons. It should be noted that CD4+ and CD8+ T cells cross-react with different adenovirus serotypes. For many human adenovirus serotypes, as well as chimpanzee serotypes, the fiber knob of the adenovirus attaches to the coxsackie adenovirus receptor to initiate endocytosis of the viral genetic material [22].

Adenoviral vectors are currently only used in one commercially available vaccine, the rabies vaccine approved for use in wild animals [23]. Adenovirus vectors are attractive candidates for vaccine development because they are easily genetically modified and can express a wide range of antigens. Careful manipulation of the genome and deletion of certain regions (early genes E1-E3) can alter the replication abilities of the adenovirus, therefore minimizing side effects and increasing the predictability of their actions. The space remaining from the deleted genes allows for the incorporation of foreign genetic material into the vector [22].

One of the main challenges of developing an adenovirus vaccine for SARS-CoV-2 is the risk of the patients having pre-existing immunity to the viral vector. Therefore, some of the current vaccines in production are utilizing adenoviruses that infect non-human primates. In 2012, the University of Oxford developed an adenovirus derived from chimpanzees known as ChAdOx1 to combat many diseases including the Middle East Respiratory Syndrome (MERS). With this prior technology, pathogenic SARS-CoV-2 wild-type S protein genetic material was incorporated into the vector, creating the vaccine ChAdOx1 nCov-19 or AZD1222 [23]. The University of Oxford developed this vaccine using a coding sequence for S glycoprotein amino acids (2-1273) synthesized with tissue plasminogen activator which is incorporated into a shuttle plasmid.[8] The past research on developing a MERS vaccine showed T cell protection lasting 12 months, elevated antibodies a year later, but only about half developed antibodies [23].

Clinical Trials

BNT162b1 and BNT162b2

Pfizer and BioNtech began the development of the Covid-19 vaccine on July 27, 2020. (NCT04368728) It is an mRNA-based vaccine that is delivered via intramuscular injection as a lipid nanoparticle [24]. When exposed to host cells, the spike protein of the SARS-CoV-2 rearranges to shift the virus into the cells via membrane fusion [25]. Targeting the spike structural protein on the surface of the virus is essential in inhibiting viral replication [24]. Prevention of membrane fusion can occur by mutating the spike protein into its perfusion formation [25].

In the early phase, 1 trial, the safety, and immunogenicity of BNT162b1 and BNT162b2 were assessed in healthy adults ages 18 to 85. Both vaccines elicited similar levels of immunogenicity; however, BNT162b2 elicited milder systemic reactions such as chills, headaches, and fevers. No serious adverse events were recorded in either group. The reason for the lower reactogenicity of BNT162b2 over BNT162b1 was not reported; however, BNT162b2 encodes for the full-length spike protein, whereas BNT162b1 encoded for the receptor-binding domain. Due to the milder reactions, Pfizer decided to advance the development of BNT162b2 [26].

In a Phase I/II study of the COVID-19 mRNA vaccine, 45 healthy male and female participants with a mean age of 35.4 years were randomized to receive the following dosing regimens. For each dosing regimen of 10 μg or 30 μg, 12 participants were vaccinated with BNT162b1 on days 1 and 21; 12 and 9 participants received a the100-μg dose or placebo respectively on the first day [27]. The Receptor-Binding Domain (RBD) binding IgG concentrations and SARS-CoV-2-neutralizing titers were assessed at baseline, at 7 and 21 days after the first dose, at 7 days (day 28), and 14 days (day 35) after the second dose of BNT162b1. By the 21 days after the first dose for all three doses, RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers in serum increased with dose-dependent level and after the second dose. Geometric mean neutralizing titers reached 1.9-4.6-fold of COVID-19 convalescent patient serum which was obtained at least 14 days after a positive SARS-CoV-2. A second inoculation with 100 μg was suspended because of the increased reactogenicity and a lack of meaningfully increased immunogenicity after a single dose compared with the 30-μg dose [27]. Adverse Events (AEs) were reported by 50.0% (6/12) of participants who received either the 10 μg or 30 μg of BNT162b1 vaccine candidate; 58.3% (7/12) of those who received 100 μg of BNT162b1, and 11.1% (1/9) of placebo recipients. Two participants reported a severe AE: Grade 3 fever two days after vaccination in the 30-μg group, and sleep disturbance 1 day after

vaccination in the 100-µg group. Related AEs were reported by 25% (3/12 in the 10-µg groups) to 50% (6/12 each in 30-µg and 100-µg groups) of BNT162b1 recipients and by 11.1% (1/9) of placebo recipients. There were no reported serious adverse events or any significant changes in routine clinical laboratory values for most study participants [27].

A phase III multinational, placebo-controlled, partially blinded, the pivotal study evaluated the safety and efficacy of the BNT162b2 vaccine candidate [28]. 43,448 patients ages 16 or older were randomly assigned in a 1:1 ratio to receive two doses of either BNT162b2 30 µg or placebo 21 days apart. The first primary endpoint was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose. The second primary endpoint was efficacy in participants with or without any evidence of prior infection and vaccine safety. Of the 21,720 patients who received the BNT162b2 candidate, there were 8 cases of Covid-19 with onset at least 7 days after the second dose. Among the 21,728 placebo recipients, 162 Covid-19 cases were reported. BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6) [28]. Similar vaccine efficacy (generally 90 to 100%) was observed across the stratified groups of age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 cases occurred in the placebo group and 1case in a BNT162b2 vaccine recipient. The side effect profile of BNT162b2 was categorized as short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively) [28]. BNT-162b2 is the first vaccine candidate to be approved in the United Kingdom. On December 11, 2020, the FDA granted Emergency Use Authorization (EUA) for the BNT-162b2 vaccine in patients 16 years and older.

mRNA-1273

The mRNA-1273 vaccine candidate was developed alongside investigators from the National Institute of Allergy and Infectious Diseases' Vaccine Research Center. In animal studies, vaccination with mRNA-1273 induced a high level of antibodies. Viral replication was not detectable in bronchoalveolar lavage fluid in the vaccinated animal groups, nor was viral replication noted in the nose or lungs of the vaccinated animals. Overall, animal studies showed that mRNA-1273 had substantial neutralizing activity and evoked potent antibody response, similar to those of humans who had recovered from Covid-19 infection [18].

mRNA-1273 was also evaluated in phase III multicenter, stratified, placebo-controlled, observer-blinded, efficacy and safety trial. 30,420 volunteers at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two doses intramuscularly of either mRNA-1273 100 µg (n=15,210) or placebo (n=15,210) 28 days apart. The primary endpoint was the prevention of Covid-19 illness onset at least 14 days after the second injection in the per-protocol participants who had not previously been infected with SARS-CoV-2. The secondary endpoints were the prevention of severe Covid-19 as defined by prespecified criteria, the prevention of Covid-19 after a single dose, or the prevention of Covid-19 according to a secondary Center for Disease Control and Prevention case definition [29]. Over 96% of study participants completed the course of vaccination.

For the primary endpoints in the interim primary analysis in the per-protocol participants, Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% Confidence Interval [CI], 48.7 to 65.3) and 11 participants in the mRNA1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection compared with placebo [29]. Similar findings were reported in the key secondary analysis including assessment starting 14 days after dose 1 (225 cases with placebo, vs. 11 with mRNA-1273, indicating a vaccine efficacy of 95.2% [95% CI, 91.2 to 97.4]). In the assessment of participants who were SARS-CoV-2 seropositive at baseline in the per-protocol analysis; there were 187 and 12 cases in the placebo and mRNA-1273 group, respectively. 7 cases of Covid-19 were identified in the mRNA-1273 group compared with 65 cases in the placebo group between days 1 and 42 [29]. The frequency of solicited adverse events was more in the mRNA-1273 group than in the placebo group after both the first dose (84.2%, vs. 19.8%) and the second dose (88.6%, vs. 18.8%). Solicited systemic adverse events were reported more often in the mRNA-1273 group than in the placebo group after both the first dose (54.9%, vs. 42.2%) and the second dose (79.4%, vs. 36.5%). The severity of these events increased after the second dose in the mRNA-1273 group, with increasing proportions of grade 2 events (from 16.5% after the first dose to 38.1% after the second dose) and grade 3 events (from 2.9% to 15.8%). Other reported adverse events include fever, chills, headache, fatigue, myalgia, arthralgia, nausea, and vomiting [29].

INO-4800

The tolerability, safety, and immunogenicity of INO-4800 against SARS-CoV2 were evaluated in the phase I clinical trial [30]. In this open-label study, INO-4800 was evaluated in two groups of 20 healthy volunteers. Participants in each group received INO-4800 vaccine candidate either 1mg or 2mg intradermally followed by a CELLECTRA™ electroporation delivery device at 0- and 4-week intervals. Thirty-nine subjects completed both doses; one subject in the 2mg group discontinued trial participation before receiving the second dose [30]. Safety and immunogenicity endpoints comprised of systemic and local administration site reactions for up to 8 weeks post first dose;

antigen-specific binding antibody titers, neutralization titers, and antigen-specific interferon-gamma (IFN-g) cellular immune responses were monitored after the 2 doses of the vaccine candidate. Live virus neutralization responder defined as Week 6 Plaque Reduction Neutralization Test (PRNT) at the concentration required to inhibit 50% of infection IC50 ≥10, or ≥4 if a subject is a responder in ELISA were also assessed.

In this preliminary report, 39 of 40 subjects completed the visit 8 weeks following the first vaccine dose. A total of 6 vaccine-related local and systemic AEs were reported by 8 weeks. Grade 1 or mild AEs accounted for 15% (3/20 subjects) and 10% (2/20 subjects) of the participants in 1 mg and 2 mg doses, respectively. All AEs were mild in severity. Five of the six related AEs were injection site reactions including mild erythema and severe pain at the injection site. One mild (grade 1) systemic AE related to the vaccine was nausea. All related AEs occurred on the day that subjects received the first or second vaccination. There were no reported febrile reactions. No subject discontinued the trial due to an AE. No serious adverse events nor adverse events of special interest were reported. There were no abnormal laboratory values that were deemed clinically significant by the investigators throughout the initial 8-week follow-up period. There was no increase in the number of participants who experienced AEs related to the vaccine in the 2 mg group (10%, 2/20), compared to that in the 1 mg group (15%, 3/20). Also, there were no increases in frequencies of AEs with the second dose over the first dose in both dose groups [30]. The INO-4800 vaccine candidate generated humoral and cellular immune responses in all 38 participants who were evaluated. The participants' T-cells and antibody responses were displayed following two doses of the INO-4800 vaccine candidate. Humoral responses measured by binding or neutralizing antibodies were observed in 95% (18/19) of the participants in both the 1 mg and 2 mg dose groups. The neutralizing antibodies, measured by live virus neutralization assay, were seen in 78% (14/18) and 84% (16/19) of participants, and the corresponding geometric mean titers (GMTs) were 102.3 [95% CI (37.4, 280.3)] and 63.5 [95% CI (39.6, 101.8)] for the 1 mg and 2 mg dose groups, respectively. Cellular immune responses were observed in 74% (14/19) and 100% (19/19) of the 1 mg and 2 mg dose groups, respectively. The magnitude of T cell responses in the 2 mg dose group was higher than the Covid-19 convalescent samples tested [30].

A Phase II/III, randomized, placebo-controlled, multi-center trial evaluating the safety, immunogenicity, and efficacy of INO-4800 to prevent COVID-19 disease in participants at high risk of exposure to SARS-CoV-2 is ongoing. (INNOVATE; NCT04642638)

The Phase II segment of this trial will access the immunogenicity and safety in approximately 400 participants, who will receive either (1) or (2) mg of INO-4800 on day 0 and 28-day intervals across three age groups (18-50 years, 51-64 years, and 65 years and older) for the subsequent phase III efficacy evaluation. The safety and immunogenicity outcomes from the phase II segment will be used to determine the dose level for the phase III efficacy trial which will involve approximately 6178 participants. For the phase III segment, the primary endpoint will evaluate the percentage of participants with virologically confirmed COVID-19 infection from 14 days after completion of the second dose regimen up to 12 months following the dose.

The secondary endpoints of Phase III clinical trial will include the percentage of participants with local and systemic adverse events and death from all causes and death from Covid-19 disease from 14 days after completion of the second dose regimen up to 12 months post-dose. This study is expected to be completed in September 2022.

Sputnik V

Gam-COVID-Vac (Sputnik V) is a heterogenous recombinant adenovirus (rAd)-based vaccine. It consists of rAd26 and rAd5, both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein S.

The efficacy, immunogenicity, and safety of the Gam-COVID-Vac combined vector vaccine against the SARS-CoV-2-induced COVID-19 were evaluated in healthy subjects 18 years and older in a phase III trial [31]. In this randomized, double-blind, placebo-controlled study at multiple sites in Moscow, eligible participants with negative SARS-CoV-2 tests, without infectious diseases in the past 14 days, and no other vaccinations in the 30 days before the trial were enrolled. The study's major outcome was the proportion of participants without COVID-19 from day 21 after receiving the first dose. The primary outcome was assessed in participants who had received two doses of vaccine or placebo, serious adverse events were assessed in all participants who had received at least one dose at the time of database lock, and rare adverse events were assessed in all participants who had received two doses and for whom all available data were verified in the case report form at the time of database lock [31].

21977 adults were randomly assigned in 3:1 to the vaccine (n=16501) or the placebo (n=5476). Study participants received two doses of the vaccine candidate (0·5 mL/dose) intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5) or placebo. 14964 in the vaccine group and 4902 in the placebo group had received two doses per study protocol and were included in the primary outcome analysis. 16 (0·1%) of 14964 participants in the vaccine group and 62 (1·3%) of 4902 in the placebo group were confirmed to have COVID-19 following the second vaccine dose; vaccine efficacy was 91·6% (95% CI 85·6–95·2). Most reported adverse events were grade 1 (7485 [94·0%] of 7966 total events). 45 (0·3%) of 16427 participants in the vaccine group and 23 (0·4%) of 5435

participants in the placebo group had serious adverse events; none were considered associated with vaccination. Four deaths were reported during the study (three [<0·1%] in the vaccine group and one [<0·1%] in the placebo group), none of which were considered related to the vaccine [31].

ADZ1222 (Val)

AZD1222 coronavirus vaccine candidate, formerly known as ChAdOx1 nCoV-19 is a chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein.

In phase I-II single-blind, multicenter, randomized controlled trial in the United Kingdom (UK), ChAdOx1 nCoV-19 was assessed for safety and immunogenicity against the SARS-CoV-2 virus. The trial included 1077 healthy participants aged 18-55 years who were assigned (1:1) to receive either ChAdOx1 nCoV-19 at a dose of 5 x 10^{10} viral particles (n=543) or the control, meningococcal group A, C, W-135, and Y (MenACWY) conjugate vaccine (n=534). Of the participants, ten were assigned to a non-randomized, unblinded ChAdOx1 nCoV-19 prime-boost group and received a booster 28 days after the first dose. The co-primary outcomes were to evaluate safety and efficacy measured by the occurrence of serious adverse events and symptomatic virologically confirmed COVID-19 cases, respectively. Adverse reactions, such as feeling feverish, pain, chills, headache, muscle ache, and malaise were significantly more common in the ChAdOx1 nCoV-19 group (all $p<0.05$) and often reduced by the prophylactic use of paracetamol [32]. Although a small number of participants in the prime-boost group, the reactogenicity profile following the second dose were less severe. No serious adverse events were associated with ChAdOx1 nCoV-19, all events were self-limiting with mild to moderate severity. Spike-specific T-cell responses peaked at 14 days in the ChAdOx1 nCoV-19 group. In participants who received one dose, responses of anti-spike IgG rose by day 28 [median 157 ELISA units (EU), 96-317; n=127] and remained elevated up to day 56 (119 EU, 70-203; n=43). In the prime-boost group, anti-spike IgG increased at day 56 (639 EU, 360 - 792: n=10). Using a 50% plaque reduction neutralization assay ($PRNT_{50}$), 100% of participants achieved neutralizing titers at day 28 [median titer 218 (IQR 122-395)]. Similarly, with a microneutralization assay (MNA_{80}), neutralization was achieved in 91% of participants after one dose (median titer 51, 32-103) and 100% of participants after the second dose (median titer 136, 115-241). In the Marburg VN assay, neutralizing antibodies were detected in 62% of participants by day 56 after one dose and 100% of participants who received the booster dose [32]. Thus, the preliminary results of this trial promote the safety, tolerability, and immunogenicity of ChAdOx1 nCoV-19 and support the progression of ChAdOx1 nCoV-19's clinical development.

An interim analysis of four ongoing blinded, multinational, randomized controlled trials assessed the safety and efficacy of ChAdOx1 nCoV-19 vaccine. A prespecified global pooled analysis combined data from COV002 Phase II/III in the UK and COV003 Phase III in Brazil to assess the interim efficacy. All four studies [COV001 Phase I/II in the UK, COV002, COV003, and COV005 (Phase I/II in South Africa)] are used to assess the safety of the vaccine. Of the four studies, only one is double-blind (COV005), the others are single-blind. Across the four studies, 23,848 participants were enrolled. Of the participants enrolled, 11,636 participants in COV002 and COV003 were included in the primary analysis, 5,807 received two doses of ChAdOx1 nCoV-19 and 5,829 received two doses of the control (MenACWY or saline). In COV002, a subset received a half dose (low dose) first, followed by 5 x 10 x 10^{10} viral particles (standard dose) of ChAdOx1 nCoV-19. The timing of the second administration varied between studies. The primary outcome was to assess the efficacy of ChAdOx1 nCoV-19, measured by symptomatic virologically confirmed COVID-19 cases. There were 30 (0.5%) cases of symptomatic COVID-19 in the vaccine arm and 101 (1.7%) cases in the control group, which results in an overall vaccine efficacy of 70.4% (95.8% CI 54.8-80.6). The vaccine efficacy in those who received two standard doses was 62.1% (95% CI 41.0-75.7) compared to those who initially received a low dose, efficacy was 90.0% (67.4-97.0; $p_{interaction}=0.010$). In the control arm, ten participants were hospitalized for COVID-19 after 21 days following the first dose: two were classified as severe, including one death. There were 175 serious adverse events (84 in the vaccine group and 91 in the control group), of which three were considered possibly related to the vaccine or control [33]. As displayed in this interim analysis, ChAdOx1 nCoV-19 has an acceptable safety profile and is efficacious; thus, it was approved in the UK on December 29, 2020, for individuals 18 years or older. Currently, there is an ongoing Phase III trial in the United States.

Ad26.COV2.S

The vaccine candidate, Ad26.COV2.S, is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein [34].

In the interim results of the phase I-IIa, multicenter, double-blind, randomized controlled trial, Ad26.COV2.S was evaluated in two age cohorts (Cohort 1 adults 18-55 years & Cohort 3 adults 65 years or older) for its safety, reactogenicity, and immunogenicity. The participants of cohort 1a and 3 were randomly assigned (1:1:1:1:1) to one of five groups: low dose (5 x 10^{10} viral particles) followed by low dose, low dose followed by placebo, high dose (1 x 10^{11} viral particles) followed by high dose, high dose followed by placebo, and placebo followed by placebo [34]. Data provided was following the administration of the second dose in cohort 1a and following the first dose in cohort 3. The primary endpoints were safety and reactogenicity assessed on days 7, 28, and 71 after vaccination in each cohort. The secondary endpoint was immunity to the spike protein of SARS-CoV-2 assessed on days 29, 57, and 71. Among the two cohorts, solicited local and systemic events were mostly of grade (1) or (2), most frequent events being injection site pain, fatigue, headache, myalgia, and fever, with a trend of higher incidences in the younger population and higher vaccine dose. Following the second administration of low or high dose among the younger participants, grade (3) solicited systemic events were lower than following the first administration. On day

29, neutralizing-antibody titers were detected in 88-96% of cohort 1a participants (Geometric Mean Titer [GMT], 224 to 354). By day 57, neutralizing-antibody titers were detected in 100% of cohort 1a low dose/placebo group and 96% in other groups with a further increase in titers (GMT, 288 to 488). On day 71 (after the first dose), neutralizing antibodies were detected in 100% of cohort 1a and titers were stable (GMT, 321 to 388). In those who received a second dose, neutralizing antibodies were detected in 100% of participants after 14 days and titers increased by a factor of 2.6 to 2.9 (GMT, 827 to 1266). Fifteen days after the first dose, a type 1 helper t-cells (Th1) response to S peptides was detected in 76% of low dose participants and 83% of high dose participants in cohort 1a; and in cohort 3 detected in 60% and 67%, respectively. On day 15, S-specific CD8+ T-cell responses were detected in 51% of low dose participants and 64% of high dose participants in cohort 1a; the corresponding values in cohort 3 were 36% and 24%, respectively [34]. The results of this interim analysis display the safety and immunogenicity of Ad26.COV2.S in younger and older adults and supports the progression to phase III trials of single-dose or two-dose regimens.

Investigators are currently awaiting the results of a randomized, double-blind, placebo-controlled phase IIa trial that began on August 28, 2020, and is expected to be completed on December 15, 2021, with an estimated enrollment of 1,210 participants (clinicaltrials.gov NCT04535453,). This trial will evaluate a range of dose levels and vaccination intervals in healthy adolescents and adults. Also, a randomized, double-blind, placebo-controlled phase III trial (ENSEMBLE) started on September 7, 2020, will assess the efficacy and safety of a single dose of Ad26.COV2.S for the prevention of SARS-CoV-2 in 44,325 adults (clinicaltrials.gov NCT04505722). On November 15, 2020, Johnson & Johnson announced the initiation of a second phase 3 trial (ENSEMBLE 2) which will study the safety and efficacy of a two-dose regimen (clinicaltrials.gov NCT04614948). As of December 1, 2020, the biologic license application was submitted in Canada and Europe.

NVXCoV2373

In phase I-II randomized, placebo-controlled trial, NVXCoV2373 (also known as recombinant severe acute respiratory syndrome coronavirus 2 [rSARS-CoV-2]) nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant was evaluated for the safety and immunogenicity of two doses with or without Matrix-M1 adjuvant in 131 healthy adults aged 18-59 years [35]. Participants were randomly assigned to one of the five groups with doses given 21 days apart: placebo (group A, n=23), 25-µg doses of rSARS-CoV-2 (group B, n=25), 5-µg doses of rSARS-CoV-2 plus Matrix-M1 (group C, n=29), 25-µg doses of rSARS-CoV-2 plus Matrix-M1 (group D, n=28), and a single 25-µg dose of rSARS-CoV-2 plus Matrix-M1 followed by a single dose of placebo (group E, n=26). The primary outcomes were the amount of solicited local and systemic reactogenicity, laboratory values, and anti-spike protein response measured on days 0, 7, 21, 28, and 35. The secondary outcomes were unsolicited adverse events, wild-type virus neutralization, and T-cell responses. The majority of participants had absent or mild reactogenicity following administration of both doses. One participant in group D reported a fever of 38.1°C after the second administration lasting only for a day. The duration of reactogenicity was typically short with a mean of 2 days or less. Abnormal laboratory values did not lead to any clinical manifestations and did not worsen after the second vaccination. The two-dose regimens of 5 µg and 25 µg of rSARS-CoV-2 plus adjuvant-induced high immune responses, with closely correlated levels of neutralizing antibodies and anti-spike IgG. Also, after the second vaccinations of rSARS-CoV-2 plus adjuvant, neutralizing antibodies exceeded values seen in symptomatic COVID-19 outpatients and were similar to levels seen in convalescent serum from COVID-19 hospitalized patients. Participants who received regimens including Matrix-M1 adjuvant displayed induced CD4+ T-cell responses and minimal Th2 responses. The addition of Matrix-M1 to rSARS-CoV-2 displayed benefits such as antigen-dose sparing, high neutralizing antibody, and Th1 responses [35]. The results of this trial endorse the advancement of efficacy trials.

There is currently an ongoing phase IIa/b trial to evaluate the efficacy, immunogenicity, and safety of rSARS-CoV-2 plus Matrix-M1 adjuvant in South African adults living with or without HIV (clinicaltrials.gov NCT04533399). Similarly, a phase III trial began on December 27, 2020, assessing the efficacy, immunogenicity, and safety of rSARS-CoV-2 with Matrix-M1 adjuvant in adults in the United States and Mexico. (clinicaltrials.gov NCT04611802) (Tables 1 and 2).

Table 1. Vaccine Platforms and Technologies for SARS-CoV-2.[3]

VACCINE PLATFORM	TARGET PROTEIN	EXISTING APPROVED HUMAN VACCINE	ADVANTAGES	DISADVANTAGES
RNA	S Protein	No	Vaccines are typically immunogenic, rapid production	Questionable reactogenicity safety concerns.
DNA	S Protein	No	Heat stable; tested in human for SARS-CoV-1, rapid production, relatively low cost	Requires specific delivery devices to ensure adequate immunogenicity
Protein Subunit	S Protein	Yes, for baculovirus (influenza, HPV) and yeast expression (HBV, HPV)	No infectious virus handling, adjuvants can be added to increase immunogenicity.	Mass production could be limited. High yields are required.
Viral vector-based	S Protein	Yes, for VSV (Ervebol only)	Well-documented preclinical and clinical data for many emerging viruses, including MERS-CoV.	Vaccine efficacy is vector immunity dependent.
Live attenuated	Entire virion	Yes	Proven documented process used for several licensed human Vaccines.	Establishing infectious clones for attenuated coronavirus vaccine seeds is time-consuming.
Inactivated	Entire virion	Yes	Proven documented process used for several licensed human vaccines, tested in humans for SARS-CoV-1, adjuvants can be used to increase immunogenicity.	Requires large amounts of infectious virus.

Table 2. Leading Vaccine Candidates in Clinical Trials

VACCINE CANDIDATE	CLINICAL TRIALS	TRIAL OUTCOMES	VACCINE STATUS
mRNA1273	Phase III, multicenter, placebo-controlled, observer-blinded, 100µg x 2 doses, 28 days apart.	185 Covid-19 cases confirmed in placebo vs.11 cases in mRNA1273. 94.1% vaccine efficacy in preventing clinical disease for the primary endpoint. The severity of ADE increased after the second dose.[29]	Granted emergency use authorization by the FDA
BNT162b2	Phase III, multinational, placebo-controlled, partially blinded, 30µg x 2 doses, 21 days apart.	95% efficacy in preventing Covid-19; 8 vs.162 cases of in treatment vs. placebo groups 7 days after receiving the second dose. Well tolerated across all age groups.[28]	Granted emergency use authorization by the FDA; approved in the UK, Canada, and Bahrain
INO-4800	Phase I, open label for safety, tolerability, and immunogenicity. 1mg or 2 mg of INO-4800 followed by CELLECTRA electroporation device at 0- and 4-weeks' intervals. Phase II/III trial (INNOVATE), randomized, placebo-controlled, multicenter trial; phase II will assess safety and immunogenicity in 400 participants in 3 age groups (18-50; 51-64; ≥65 years). The outcome of this phase will be used to determine the dose for the Phase III segment.	INO-4800 generated neutralizing antibodies, cellular immune responses were 74% and 100% in 1 mg and 2 mg groups. The magnitude of T-cell responses in the 2mg arm higher than Covid-19 convalescent plasma samples. Mild ADE mostly injection sites' reaction.[30] Phase III will enroll about 6178 participants. The primary endpoint will assess changes from baseline in antigen-specific cellular immune and neutralizing antibody responses; and the percentage of participants with virologically confirmed Covid-19 infection from day 14 up to 12 following the second dose. NCT04642638)	The study is expected to be completed in September 2022
AZD1222	Phase I/II single-blind, multicenter, randomized trial in the UK for safety and immunogenicity. Participants received vaccine or placebo at 28 days intervals. An interim analysis of four different phases of ongoing blinded, multinational, randomized controlled trials assessed the safety and efficacy of ChAdOx1 nCoV-19 vaccine. A prespecified global pooled analysis combined data from (Phase II/III in the UK) (Phase III in Brazil) to assess the interim efficacy. All four studies [(Phase I/II in the UK), and (Phase I/II in South Africa)] are used to assess the safety of the vaccine.	In the prime-boost group, anti-spike IgG increased at day 56 (639 EU, 360-792: n=10). 100% of participants achieved neutralizing titers on day 28. Preliminary results of this trial suggest the safety, tolerability, and immunogenicity of ChAdOx1 nCoV-19. [32] Overall vaccine efficacy of 70.4% (95.8% CI 54.8-80.6). The vaccine efficacy in those who received two standard doses was 62.1% (95% CI 41-75.7) compared to those who initially received a low dose, efficacy was 90.0% (67.4-97; $p_{int.} = 0.010$). There were 175 serious adverse events (84 in the vaccine group and 91 in the control group), of which three were considered possibly related to the vaccine or control.[33] As displayed in this interim analysis, ChAdOx1 nCoV-19 has an acceptable efficacy and safety.	WHO Authorizes Emergency Use on February 15, 2021. Approved in the UK on December 29, 2020, for individuals ≥18 years. Phase III trial ongoing in the United States.
Sputnik V	Phase III, randomized, placebo-controlled, double-blinded, multiple sites in Moscow, Russia. Participants received 0.5 ml X 2 intramuscularly at a 21-day interval.	16 (0.1%) Covid-19 cases confirmed in vaccine group vs. 62 (1.3%) cases in placebo. 91.6% vaccine efficacy in preventing clinical disease for the primary endpoint. Grade 1 reported adverse events 45 (0.3%) in vaccine group vs. 23 (0.4%) in placebo arm. Four non-vaccine related death.[31]	Initially approved for distribution in Russia on the preliminary results of Phase I–II studies. Emergency mass-supply of the vaccine began in December 2020 in Russia, Argentina, Belarus, Hungary, Serbia, and the United Arab Emirates. As of February 2021, twenty-one countries have granted Sputnik V emergency use authorization.[37]

NVX-CoV2373	Phase I/II randomized, placebo-controlled trial evaluated the safety and immunogenicity of two doses of NVX-CoV2373 with or without Matrix M1 adjuvant given 21 days apart in 131 healthy adults aged 18-59 years. Phase III trial began on December 27, 2020, assessing the efficacy, immunogenicity, and safety of the vaccine with Matrix-M1 adjuvant in adults in the US and Mexico (clinicaltrials.gov NCT04611802 2021).	Phase I/II data reported the vaccine plus adjuvant-induced high immune responses. Second vaccinations plus adjuvant elicited neutralizing antibodies that exceeded values seen in convalescent serum from COVID-19 patients.[35]	Ongoing Phase III trial in the U.S and Mexico.
Ad26.COV2.S	Randomized, double-blind, placebo-controlled phase III trial (ENSEMBLE) started enrolment on September 7, 2020. The study will assess the efficacy and safety of a single dose of Ad26.COV2.S for the prevention of SARS-CoV-2 in 44,325 adults (clinicaltrials.gov NCT04505722) A second phase III trial (ENSEMBLE 2) will evaluate the safety and efficacy of a two-dose regimen (clinicaltrials.gov NCT04614948).	Phase I-IIa, multicenter, double-blind, randomized controlled trial evaluated for safety, reactogenicity, and immunogenicity. Antibodies to SARS-CoV-2 were observed after a single injection. On day 29, neutralizing-antibody titers were detected in 88-96% and 100% was detected after the second dose by day 57 in participants.[34]	The biologic license application was submitted in Canada and Europe on December 1, 2020. Granted emergency use authorization by the FDA on February 27, 2021)

The SARS Coronavirus 2 pandemic ushered in a remarkable collaboration of the international research community including the WHO to develop specific diagnostics, potential therapies, and Covid-19 vaccines at an unprecedented pace. The genomic sequence of the SARS Coronavirus-2 was made available by the WHO in January 2020; thus, paving the way for the rapid development of potential vaccines and other therapeutics.

Currently, there are 70 vaccine candidates, including RNA, live virus, attenuated, and recombinant protein subunit vaccines in different stages of clinical trials [36]. In this review, we focused on only those vaccine candidates in their late stages of development. Preliminary results from these trials reported significant efficacy and safety at preventing Covid-19 sickness, including severe disease in patients 18 years and older. Common adverse vaccine-related events reported were transient local and system reactions; there were no significant safety concerns.

As a result, a few vaccine candidates such as mRNA1273, BNT162b2, AZD1222, Ad26. COV2.S, and Sputnik V have either been approved or granted emergency use authorization by the various regulatory authorities.

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