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REVIEW ARTICLE

The Immune Response, Safety, and Efficacy of Emergency Use Authorization-Granted COVID-19 Vaccines: A Review

Tafere M. Belete[1,*]

[1]*Department of Pharmacology, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia*

Abstract:

COVID-19 has affected millions of people, causing a burden on healthcare systems as well as economies throughout the world. Antiviral drugs do not work well enough for everyone. The mortality rate in the world is still significant. Developing safe, effective, affordable, and fast-acting vaccines for COVID-19 is critical for reducing new viral strains in this pandemic and re-establishing normality in the future. Therefore, several pharmaceutical companies are racing to develop effective vaccines for COVID-19. Scientists have developed different kinds of candidate vaccines with various platforms. By March 2021, thirteen vaccines were approved for emergency use in several countries across the world, whilst over 90 vaccine candidates were under clinical trials. There are also several vaccine candidates in Phase 3 trials awaiting results and approval for their use. These candidate vaccines revealed positive results in the previous phase trials, whereby they can induce an immune response with less adverse reaction in the participants. This review focuses on the development of COVID-19 vaccines and highlights the efficacy and adverse reactions of vaccines authorized for emergency use.

Keywords: COVID-19, Coronavirus, Vaccines, Clinical trials, Immunity, Population.

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1. INTRODUCTION

The pandemic of SARS-CoV-2, the cause of COVID-19, poses an unprecedented challenge to world economies and public health. Moreover, the pandemic brought the whole world to a stop due to the global crisis in the economy, health, and psychology [1]. Developing safe, effective, affordable, and fast-acting vaccines for COVID-19 remains critical for reducing new viral strains in this pandemic and re-establishing normality in the future [2]. By November 03, 2021, more than 247,472,724 confirmed cases and 5,012,337 deaths were reported. As of 31 October 2021, a total of 6,893,866,617 vaccine doses were administered [3]. The SARS-CoV-2 genome is about 30 kb in length, and the first 20 kb encode two large open reading frames (ORFs) that encode 16 replicase proteins and four important structural proteins, including envelope (E), spike protein (S), membrane (M), and nucleocapsid (N) proteins. The S protein mediates the entry of the virus into the host cells by attaching the ACE2 receptor and is the major antigenic target for vaccine development [4]. The immune system is a complex network of cells that can protect against SARS-CoV-2 infection. The immune response initiates immediately after the viral infection and lasts for months, even years. The immediate immune responses exist for ~72 hours and are acted by the "innate immune system" comprising cells, including macrophages, dendritic cells, and natural killer cells, which inhibit viral replication within the host. Besides, the host cell has receptors that help identify the virus and activate innate immune responses such as interferons (IFNs) and inflammatory mediators that send signals and bring the immune cells to the infection site. After an immediate immune response, the adaptive immune response is primarily initiated in memory B cells and T cells [5]. The adaptive immune response is slow, specific, targets new viruses that have never been encountered, and is responsible for "memory" of the immune system that helps the hosts defend rapidly during re-infections. Vaccines use memory response by exposing the host to weakened viruses or viral parts that help the host in defending against the infectious virus [4, 5].

The adaptive immune responses comprise T lymphocytes that support antibody production and killing of virus-infected host cells directly or indirectly and B lymphocytes that produce different classes of antibodies that neutralize the virus or infected cells. Information concerning the immune response for SARS-CoV-2 infection facilitates the development of new vaccines. This review presents the current data relevant to humoral and cellular immunity to SARS-CoV-2 in humans and its application to vaccine development. Moreover, this review

* Address corresponding to this author at the Department of Pharmacology, College of Medicine and Health Sciences, University of Gondar, P.O. box 196, Gondar, Ethiopia; Tel +251 918045943; E-mail: mutafere@yahoo.com

discusses the safety and efficacy of COVID-19 vaccines that are granted for emergency use [5, 6].

2. HUMORAL IMMUNITY TO SARS-CoV-2

Humoral responses involve antibodies that are produced by plasma cells. B cells secrete five different classes of antibodies based on the type of protein chains they possess. These are IgM, IgG, and IgA, along with lesser amounts of IgD and IgE. Antibodies have different characteristics, structures, and activities [7]. IgG, IgA, and IgM have an anti-viral effect, but IgG has existed for a long period. SARS-CoV-2 induces humoral S- and N-specific immune responses. The 180 kDa S proteins have two parts (*i.e*., S1 and S2) and the essential antigenic subunit that induces our immunity. The S1 subunit part has a receptor-binding domain that mediates viral binding to ACE2 receptors on susceptible tissues. S1 subunit is the major target for SARS-CoV-2 neutralizing antibodies [7, 8]. The major role of antibodies is to attach antigen and interact with cells that possess Fc γ-receptors to induce immunity. Antibodies have a significant effect on removing viruses and defending the host from viral infection. A robust B-cell identified early SARS-CoV-2 infection with the secretion of virus-specific serum antibodies against S, M, and N proteins [8].

Post N *et al*. reviewed 150 studies that describe virus-specific antibody responses to SARS-CoV-2 infection. This review revealed that IgM detected before IgG reaches a peak between 2-5 weeks and decreases the next 3-5 weeks after post-symptom onset. IgG reaches a peak between 3-7 weeks post-symptom onset and persists for 2 months. Neutralizing antibodies are detected within 7-15 days of disease onset and increase until days 14-22 and then decrease. Low antibody titers are detected in individuals with asymptomatic or mild disease [9]. IgM and IgA titers decrease after 28 days, IgG titers reach a peak at 49 days, and immunological memory persists for greater than 6 months [10].

Generally, antibody persistence depends mainly on the antibody class and disease severity. IgA and IgM antibodies drop rapidly, but IgG antibodies against the virus persist for several months in patients with moderate to severe COVID-19 [11]. IgA is the major antibody found in mucosal cells to prevent viral infection in the respiratory tract. IgA promotes the entrapment of antigens in the mucus, preventing the attachment of the virus to the mucosal cell. The amount of RBD-specific IgA in the respiratory mucosa cell may serve as an indicator of host immune response that can be measured in the saliva and tears [12]. In mild COVID-19 patients, a rapid decrease of RBD-specific IgG within 2-4 months occurred, suggesting that SARS-CoV-2-induced humoral immunity may not be long-lasting in mild disease [13].

Understanding the duration and kinetics of SARS-CoV-2-specific humoral responses after exposure or vaccination is crucial for the long-term prevention of the disease, and it has the potential for effective vaccine intervention strategies. Several studies revealed that greater than 10% of people who develop severe COVID-19 have misguided antibodies and autoantibodies, which target the cells, tissues, and the immune system instead of the invading virus. COVID-19 patients have greater antibodies that attack themselves compared to patients with lupus, an autoimmune disorder [14, 15]. Another 3.5% of people have a genetic mutation that does not produce type I interferons in response to SARS-CoV-2. Consequently, these patients have no effective immune responses that depend on type I interferon for protecting cells from viruses. Based on these studies, the innate immune response has a key role in the prevention of SARS-CoV-2 infection [16]. Studies on rhesus macaques infected with SARS-CoV-2 have shown the protective role of neutralizing antibodies against viral challenges. In humans, anti-SARS-CoV-2 antibodies were detected in 95% of convalescents individuals up to 8 months post-infection; an antibody-decay was observed in most blood donors [17]. The development and evaluation of vaccines against SARS-CoV-2 would be facilitated by the identification of a correlate of vaccine-induced protection [17, 18].

3. CELLULAR IMMUNITY TO SARS-CoV-2

The cellular immune response is an adaptive immunity that occurs inside the infected cell with the help of the three components of the adaptive immune system, including B cells, $CD4^+$ T cells, and $CD8^+$ T cells. Helper T cells direct adaptive immune response while cytotoxic T cells remove virally infected cells [19]. For vaccine development, cellular immunity provided by T cells is essential, as shown by the animal model study on SARS-CoV [16]. Several studies suggested that the lack of T cells causes failure of viral clearance in infected mice. SARS-CoV-2- specific T cells express perforin 1 and granzymes upon in vitro restimulation with viral antigens. Serious illness relates to the reduction in CD4+ and CD8+ T cell counts compared with non-serious illness [20]. Previous infection with human coronaviruses may contribute to the presence of T cells reactive with SARS-CoV-2 in COVID-19 patients. The CD4+ T-cell response consists of T-helper-1 cells characterized by IFNγ secretion. CD8+ T-cell responses specific to SARS-CoV-2 produced IFNγ and tumor necrosis factor (TNF) α. The development of humoral and cell-mediated immune responses specific to SARS-CoV-2 includes the upregulation of IL-6, IL-8, IL-10, and C-X-C motif chemokine 10, rapidly cycling T cells expressing exhaustion markers (PD-1 and HAVcr-2), decreased natural effector and CD5+ B cells, and increased neutrophil numbers [21, 22].

Targeted treatment to reverse these changes (*e.g*., suppression of inflammatory cytokine synthesis) provides clinical benefits. Generally, several studies showed that both CD4+ T-cell and CD8+ T-cell responses occur in most COVID-19 patients within 1-2 weeks after symptom onset, synthesizing Th1 cytokines. The frequency of CD4+ T cells targeted to the spike glycoprotein correlates with neutralizing antibody titers, suggesting that the T-cell response may vary among individuals with different disease severities [22, 23]. Coronaviruses induce different amounts of persistent immunity to other coronaviruses. For example, an infected person with MERS is immune for 3 years, but immunity from seasonal Coronaviruses is short. Although cellular immunity plays a key role in COVID-19, little is known about the persistence of pre-existing memory T cells that can recognize SARS-CoV-2. This is an essential issue when considering an individual's resistance during a second time re-exposure to the virus. Pre-

existing memory helper T cells help in boosting the induction of IgG in the serum of newly infected individuals and could also increase antibody protection at mucosal surfaces by IgA in saliva, tears, or nasal secretions [24 - 26].

Et al. reviewed 61 studies and showed that symptomatic COVID-19 patients consistently show peripheral T cell lymphopenia that positively correlates with disease severity, duration of RNA positivity, and non-survival. However, asymptomatic and pediatric patients preserved T cell counts. An individual with severe disease mostly induces robust virus-specific T cell responses. T cells act against many viral epitopes, and cross-reactive T cell responses are displayed in an uninfected person, but the significance for protection remains unclear [27].

4. VACCINES AGAINST SARS-CoV-2

Vaccination is the best medical achievement in modern civilization. The eradication of smallpox is an example of how vaccines are effective in defending us against deadly infectious diseases. Currently, vaccines prevent about 2.5 million deaths per year. Vaccines that protect us from SARS-CoV-2 induce immune responses that are important for the prevention of mortality [28]. Several studies proposed that a balanced humoral and Th1-directed immune response may be important in preventing death from COVID-19 disease [29].

By 02 November, 2021, over 194 vaccine candidates were in pre-clinical trial, and over 128 vaccine candidates were in the clinical trial with different vaccine platforms, including live attenuated vaccines, nucleic acid vaccines, inactivated virus vaccines, protein or peptide subunit vaccines, and viral-vectored vaccines. Among these, 10 vaccine candidates were in Phase 4, 28 vaccine candidates were in Phase 3, 54 in Phase 1/2, 2, 2/3, and 34 in Phase I trials. WHO issued guidance vaccines success benchmark for COVID-19 with the highest at 70% efficacy for one year, and the minimum threshold being 50% efficacy for six months [30]. The developed vaccines have to be effective without raising safety concerns in people receiving the vaccination. The vaccines must fulfill all regulatory requirements in terms of quality, efficacy, and safety before a market authorization is granted [30, 31]. Many mutations of SARS-CoV-2 have been identified; so, vaccine development could be obstructed if the virus later evades immunity to the spike glycoprotein used to construct the vaccine — the so-called Achilles heel of COVID-19 vaccines [32, 33]. This review presents the safety and efficacy of the COVID-19 vaccine approved for emergence use [33].

4.1. Adenovirus Vector-Based Vaccines

Adenoviruses are the most important viral vectors used for SARS-CoV-2 vaccine development. Adenoviruses are non-enveloped double-stranded DNA viruses with a packaging ability of 7.5 kb of foreign genes. The gene for the SARS-CoV-2 S protein is synthesized and added into the adenovirus genome by replacing an adenovirus gene (E1) that is crucial for virion assembly and replication [34]. Due to this manipulation, the adenovirus cannot replicate and infect but can enter the cells and express the inserted foreign gene to produce the coronavirus S protein. Typically, adenovirus can be propagated in human embryonic kidney 293 (HEK293 cells) in bioreactors. Nonreplicating viral vector vaccines are a new strategy, and no vaccine was approved before this pandemic [35]. Adenoviral vector-delivered antigens induce both cellular and humoral immunity. Adenoviral vectors may induce unwanted responses from the innate immune system. Adenoviral vectors trapped in the spleen and liver by macrophages induce inflammation by Toll-like receptor (TLR) 2 and 9 dependent induction of cytokines. Adenoviral vectors also enhance CD4+ Th1 and humoral immune responses. Currently, more than several Adenoviral vector vaccine candidates are under clinical trials against COVID-19 [36, 37].

4.1.1. AstraZeneca

The ChAdOx1-S, ChAdOx1 nCoV-19, or AZD1222 is a nonreplicating chimpanzee viral (ChAdOx1) vector-based vaccine for COVID-19 designed by the University of Oxford in collaboration with AstraZeneca. ChAdOx1 is an isolated Y25-derived replication-deficient simian adenoviral vector, and our body has no pre-existing immunity against the virus [38]. It is one of the most promising vaccine candidates for MERS-CoV, and ChAdOx1 MERS is repurposed for SARS-CoV-2. AZD1222 encode full-length S protein with tissue plasminogen activator (tPA) human leader sequence at the 5′ end, flanked by the cytomegalovirus (CMV) promoter and a bovine growth hormone (BGH) poly-A signal sequence. Leader tPA sequences enhance immunogenicity and the induction of recombinant proteins [39]. AdV particles target innate immune cells like DCs and macrophages and stimulate innate immune responses by engaging multiple pattern-recognition receptors, including those that bind dsDNA — in particular TLR9 — to induce type I interferon secretion. Unlike AdV vectors, mRNA vaccines do not engage TLR9, but both vaccine formulations converge on the production of type I interferon [40].

Several studies have revealed that AZD1222 induces humoral responses characterized by anti-spike glycoprotein IgG and IFNγ T-cell responses in most recipients after the first dose and enhanced humoral immune response after the second dose. The humoral immune responses were similar to those displayed in convalescent plasma from the COVID-19 recovered patient. AZD1222 also induces a cellular response and significantly suppresses viral load in the lower respiratory tract tissue as compared to control [41]. According to European Medicines Agency (EMA) indications, protection from COVID-19 starts from 3 weeks after the first dose of AZD1222 and may not be fully protected until 15 days after the second dose is administered. AZD1222 was authorized by the EMA for use after endorsement by the European Commission on 29 January, 2021 [42].

The safety and efficacy of the AZD1222 vaccine were tested in South Africa, Brazil, and United Kingdom with 23,745 participants aged 18 years and older. The overall efficacy of the vaccine provides 70.4% prevention against symptomatic COVID-19 (131 confirmed COVID-19 cases among over 11,000 participants, 30 in the vaccine group, and 101 in the control group). Starting from the 21st day after the first dose, 10 patients were hospitalized for COVID-19, all in the control arm. COVID-19 was severe in two of these patients,

and one patient died. Similar results were obtained in the multicentre phase III clinical trial [43, 44].

The study with 17,177 individuals in the UK, Brazil, and South Africa showed that a single dose of vaccine provided 76% efficacy against symptomatic COVID-19. These data showed that the dosing interval, and not the dose level, has a significant effect on the efficacy of the vaccine. The vaccine achieved 82.4% protection after a second dose with a dosing interval of 12 weeks. If two doses are given less than 6 weeks apart, the efficacy decreases to 54.9%. The new data on the Oxford AstraZeneca vaccine backs a 12-week dosing interval [45].

The most common side effects from the first dose included injection site tenderness and pain, fatigue, headache, malaise, myalgia, pyrexia, and fever, which were resolved within a short period. Side effects during second vaccinations were similar but "milder and less frequent." The trial protocol included paracetamol to reduce local and systemic reactions to the vaccine [45]. Although the average efficacy is lower than Moderna and Pfizer/BioNTech, its recommended storage conditions are worth consideration. AZD1222 nCoV-19 can be transported, stored, and distributed at refrigerated conditions (2-8 ◦C) for a minimum of six months [46].

Since 11 March 2021, several countries have suspended the use of the AZD1222 nCoV-19 vaccine amid reports of the death of a vaccinated person due to a blood clot. This precaution measure was undertaken, despite the EMA and WHO's assurance that there was no strong evidence that the vaccine caused the thromboembolic disorder [47]. AstraZeneca announced that the safety of the vaccine in the blood clot prevalence was "much lower than that proposed to occur naturally in a population of this size." There were 169 cases of cerebral venous sinus thrombosis and 53 cases of splanchnic vein thrombosis among 34 million individuals who used the vaccine. Vaccination with AZD1222 nCoV-19 causes a rare immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PFf4 that mimics heparin-induced thrombocytopenia [47, 48].

Results from Phase IV studies correlate with the clinical trial result. AZD1222 effectiveness after single-dose administration was 48.7-64% against Alpha, 48% against Beta/gamma, and 30-67% against Delta. After full immunization, the effectiveness of AZD1222 was 90-92% against unspecified strains. AZD1222 also showed 74.5% effectiveness against Alpha and 67% against Delta in the UK [49 - 51].

4.1.2. Johnson & Johnson

The Janssen Pharmaceutical Companies released Johnson & Johnson (J&J) vaccine in the U.S. for emergency use. The J&J vaccine is replication-defective Ad26 due to deletion of the

E1 gene and replaced with the spike gene that encodes spike glycoprotein. The first single-dose vaccine induces strong neutralizing antibody responses that defend SARS-CoV-2 virus infection, similar to the two-dose mRNA vaccines [52]. The J&J vaccine induces antibodies against the COVID-19 causing virus in 90% of participants after the first dose. Several studies showed that 1 dose of the J&J vaccine was 66% effective in protecting moderate to severe COVID-19 and 100% effective in protecting COVID-19-caused hospitalization and death [53]. The J&J vaccine also protects from the B.1.351 variant infection of South Africa. The two doses of the J&J vaccine may defend our body from the virus infection equivalent to the mRNA vaccines and better prevent against B.1.351 variant. J&J vaccine is effective against the UK variant but may not induce protection against the B.1.351 variant, limiting its use in Africa. The J&J vaccine needs to be stored at 2-8°C [54].

The safety data after 7.98 million doses of administration of the J&J vaccine found that the most common side effects were similar to those displayed during clinical trials. Among these side effects, 97% were not serious. However, 17 thrombotic events with thrombocytopenia were reported, including three non-cerebral venous sinus thrombosis events with thrombocytopenia among women aged <60 years during the pause in the J&J vaccine usage. Among 88 deaths after J&J vaccine administration, three deaths occurred in patients with CVST, and no other deaths were associated with vaccination [55, 56].

4.1.3. Gamaleya

The Gamaleya National Research Centre for Epidemiology and Microbiology (Russian Federation) developed a candidate vaccine for COVID-19. The vaccine consists of a recombinant adenovirus serotype 26 (rAd26) vectors and a recombinant adenovirus serotype 5 (rAd5) vector. Both vectors possess the gene for the SARS-CoV-2 spike glycoprotein [57]. Recombinant adenoviruses are widely used as vectors because adenoviruses can accommodate large genetic material and, even if adenoviruses cannot replicate, they can induce innate immunity sufficiently. Consequently, they do not require an adjuvant and can induce enough immune response after a single dose delivery. The administrations of two different serotypes that are given 21 days apart help prevent pre-existing immunity and community raised against the viral vector after the first immunization [57, 58].

The phase ½ sputnik V candidate vaccine data showed promising safety results. The vaccine generated robust antibody responses to the S protein that included neutralizing antibodies that block the virus from binding to its receptor. The vaccine also triggered T-cell responses that should not quickly wane. The Institute of Biology at the Academy of Military Medical Sciences announced the approval of their adenovirus-vectored vaccine (Sputnik V, Gam- COVID-Vac) on August 12, 2020, before phase 3 clinical studies had started [30, 59].

Phase 3 study was undertaken with 22 000 participants aged 18 years or older, 75% of whom were grouped to receive two doses of the vaccine that were given 21 days apart. Results showed that the vaccine was 91.4% effective in preventing symptomatic infection. The vaccine prevented moderate or severe COVID-19 cases. In the vaccine group, several cutaneous adverse reactions such as extremity abscess [1], allergic skin reactions [6], skin dermatitis [12], petechial eruptions [1], itch [4], acneiform dermatitis [1], eczema [2], and alopecia [2] were reported. The deaths of four people (3 in

the vaccine group and 1 in the placebo group) reported during the study period were not related to the vaccine. Phase 1/2 and phase 3 studies do not provide detailed information on mild and moderate adverse events, making it difficult to evaluate the possible cutaneous side effects [60]. Greater than 29 countries approved Sputnik V for emergency use, including Hungary, an European Union state, although the European Medicines Agency is reviewing the vaccine [61].

4.1.4. CanSino Biologics

China-based CanSino Biologics has developed a recombinant adenovirus serotype 5-vectored COVID-19 vaccine that expresses the SARS-CoV-2 full-length spike glycoprotein from the Wuhan-Hu-1 virus strain. Researchers reported a safe phase 1 study and strong immune response phase 2 trials [62]. A phase II trial of a single dose of the CanSino vaccine showed seroconversion rates of 96%-97% for antibodies against RBD and T cell responses in 88%-90%. The phase 3 clinical trials involving 30,000 individuals show the efficacy of 65.7% in preventing symptoms and 91% in preventing severe disease [63]. The Chinese company CanSinoBIO reported a phase 1 trial with 195 participants, of which 108 participants received the vaccine. The trial showed only mild injection-site reactions such as pain, indurations, redness, and swelling. Phase 2 trials with 508 individuals showed a similar safety profile as the phase 1 trial. Apart from the mild injection-site reactions, some cutaneous and mucosal reactions were reported, such as noninfective gingivitis, buccal ulcerations, lymphadenopathy, and oral hypoesthesia [64]. Casino Biologics Inc released data from 40,000 participants in the phase III trial, showing that the efficacy of the vaccine was 65.28% and 90.07% at preventing symptomatic and severe COVID-19, respectively, 28 days after a single dose [65].

4.2. Nucleic Acid Vaccines

Nucleic acid vaccines introduce genetic instructions (DNA or mRNA) to host cells and utilize the host cells' protein-making machinery to generate immunogens that induce an immune response. In addition, nucleic acid vaccines can easily be manufactured on a large scale. DNA vaccines use plasmid DNA containing a mammalian expression promoter and a transgene encoding the protein antigen, such as S protein in the case of COVID-19 vaccines. No DNA vaccine has yet been approved, but 11 candidates against COVID-19 are in clinical trials [66].

4.3. mRNA Vaccines

The mRNA vaccines possess the genetic code of the protein antigens with the mRNA encapsulated in lipid nanoparticles (LNPs). During vaccination, LNP-mRNA is released into the cytoplasm of the host cells and subsequently used as a template for protein synthesis. In several COVID-19 mRNA vaccines, the genetic instruction of S protein is released and translated into S protein using the host cells' machinery without genome integration in the cytoplasm [2].

Analogous to other vaccine platforms, the mRNA vaccines also can induce both antibody production and T-cell responses because the protein antigen is synthesized in the vaccinated person cells. Compared to other vaccine platforms, mRNA vaccines possess unique advantages, including versatility, efficient delivery, use of the protein translational machinery of the host, and short developmental time [4, 67]. Besides, antigen synthesis after mRNA vaccination is transient, limiting its persistence in the body. These properties proposed that mRNA can be a fast, safe, and efficient platform for vaccine development. Optimizations of (non-coding) part of the mRNA, including CAP structure, poly (A) tail, and untranslated regions (UTRs), improve mRNA stability, protein synthesis capacity, and ribosome dwell time. However, recent data of rare cases of moderate to severe reactions of mRNA vaccines raised significant concerns regarding safety and immunogenicity. Therefore, it is important to assess the risks of RNA vaccine, including the local and systemic inflammatory responses, induction of auto-reactive antibodies, the persistence of induced antigen, and toxic effects due to delivery components [68 - 70].

4.3.1. Moderna

Moderna, in collaboration with the U.S. National Institute for Allergy and Infectious Diseases (NIAID), developed an mRNA-based vaccine (mRNA-1273) that possesses a sequence-optimized mRNA-inducing spike protein encapsulated in lipid nanoparticles. Codon optimization of mRNA and the uses of SM-102 lipid improve stability against cleavage by endonucleases. mRNA-1273 has biodegradable ionizable lipid that introduces ester-linkages in the lipid tails [71]. In phase 1 study, this vaccine induces both spike glycoprotein binding and virus-neutralizing antibody responses. The humoral immune responses were similar to those observed in convalescent plasma from patients who recovered from COVID-19. Vaccine recipients also developed cellular responses, mostly biased towards CD4+ Th1 cells. CD8+ T-cell responses were marginal, except for those in recipients of two vaccinations with the higher dose. The mRNA-1273 vaccine showed 94.1% efficacy in preventing severe COVID-19 illness [72, 73].

Safety monitoring of mRNA-1273 vaccine recorded 10 cases (2.5 cases per million) of anaphylaxis after 4 041 396 first doses of mRNA-1273 vaccine delivery. Anaphylaxis is a life-threatening condition that occurs within minutes and needs rapid management. Among 43 cases of non-anaphylaxis, allergic reaction that occurs within 0-1 day are not serious. The most prevalent mild reactions are pain at the injection site, chills, fatigue, myalgia, and fever occurring within a few days of vaccination [74]. One potential issue for vaccine deployment is that a storage temperature of –20°C is required. On December 18, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) of mRNA-1273 vaccine delivery as 2 doses, 1 month apart [75].

4.3.2. Pfizer and BioNTech

Pfizer/BioNTech has developed a lipid nanoparticle (LNP)-formulated, nucleoside-modified mRNA-based vaccine termed BNT162b2 that encodes the S protein captured in its prefusion conformation. BNT162b2 is approved for emergency use in the U.S. and provides excellent protection up to 95% in preventing symptomatic COVID-19 in the phase 3 trial.

BNT162b1, a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine, elicited RBD-binding IgG and neutralizing antibodies [76]. Cellular and humoral immune responses of BNT162b1 and BNT162b2 induced similar dose-dependent neutralizing antibodies. However, BNT162b2-vaccinated participants showed higher CD4+ and CD8+ T-cell responses against the S protein and RBD than the BNT162b1-vaccinated participants. Because BNT162b2 induced higher T-cell responses and showed a better safety profile, BNT162b2 was the candidate vaccine selected in phase 3 trials. In the phase 3 trial, the BNT162b2 vaccine was well tolerated. BNT162b2 requires storage at –80°C, and once delivered, it can then be kept in a fridge for five days [76, 77].

On December 11, 2020, US FDA issued EUA for the Pfizer BNT162b2, delivered as 2 doses separated by 21 days. After delivery of 1, 893, 360 first doses of BNT162b2 vaccine, CDC recorded 4,393 (0.2%) adverse events; of these, 21 cases (11.1 cases per million doses) were anaphylaxis [78]. As of May 12, 2021, 141.6 million doses of the BNT162b2 vaccine were given to persons aged ≥16 years. On May 10, 2021, FDA expanded the EUA for the BNT162b2 vaccine to include adolescents aged 12-15 years. Leaked documents show that some batches of Pfizer-BioNTech vaccine had a lower than expected amount of mRNA, prompting questions about assessing this novel vaccine platform [79]. A national surveillance data in Israel showed that two doses of BNT162b2 after 7 days were 91.5% effective in preventing asymptomatic infection and 97.0% against symptomatic infection, COVID-19 hospitalizations, severe disease, and death, during a period in which the variant of concern, a (B.1.1.7), was predominant in Israel [80, 81].

Single-dose administration of mRNA vaccines was 38.2-88% effective against Alpha, 0-83% against Beta/Gamma, 35.6-517 72% against Delta, and 57-90% against unspecified strain in a study undertaken several countries. After full dose immunization, mRNA vaccines revealed 88-100% efficacy against Alpha strain, 76-100% against Beta/Gamma, 87-88% against Delta, and 89-100% against unspecified strains. Generally, mRNA vaccines induce a strong immune response after full vaccination. However, a small number of fully vaccinated participants develop asymptomatic or symptomatic infections [49].

4.3.3. CureVac

CVnCoV is an mRNA vaccine candidate against COVID-19 developed by CureVac using mRNA technology. The vaccine is a non-chemically modified mRNA encoding S protein with two proline mutations (S-2P), which helps stabilize protein conformation. CVnCoV is formulated within Lipid Nano Particles (LNPs) [82]. Pre-clinical studies in mice and hamsters showed neutralizing titers against the virus and balanced humoral and cellular immune responses. The phase I study showed that the CVnCoV vaccine candidate was immunogenic, safe, and well-tolerated. The immune response was comparable to recovered COVID-19 patients, mimicking the immune response after natural COVID-19 infection [83, 84]. In December 2020, CureVac started phase 2b/3clinical trial with a 12μg dose of CVnCoV. In February 2021, CureVac initiated a rolling submission with the EMA for CVnCoV [85].

4.3.4. Inactivated Viral Vaccines

Inactivated vaccines (IVV) are manufactured by multiplying SARS-CoV-2 in cell culture, usually on Vero E6 cells, followed by chemical inactivation of the virus. IVV is manufactured easily, but the productivity of the virus in cell culture and production facilities can affect the yield [86]. These vaccines are mostly delivered intramuscularly and may possess alum (aluminium hydroxide) or other adjuvants. Because the whole virus exists in the immune system, the immune responses act not only on the S protein but also the envelope, matrix, and nucleoprotein [86, 87].

In IVV, the virus cannot replicate; thus, it is safe for use in a vaccine for inducing an immune response. The IVV cannot enter into the host cells but only depends on endocytosis to enter into the cells. If the vaccine entered into dendritic cells, presentation of the antigen only stimulates some amount of cytotoxic T cells. IVV has lesser immunogenicity and a shorter duration of action than live vaccines. IVV mainly induces humoral responses that secrete antibodies. Therefore, repeat dose administration and the use of adjuvant are necessary to overcome the weak immune responses [87, 88].

4.3.5. Sinovac Biotech

CoronaVac is a β-propiolactone-inactivated, aluminum hydroxide-adjuvanted whole-virus preparation administered in a two-dose regimen (at day 0 and day 28). CoronaVac COVID-19 vaccine was developed by Sinovac Biotech, China, and the Chinese government approved its emergency use authorization [89]. Sinovac's vaccine was evaluated in phase 3 studies in several countries, including Brazil, Turkey, Chile, the Philippines, and Indonesia. The study in Brazil reported 50.4% effectiveness in protecting symptomatic infections, 78% in protecting mild cases, and 100% effectiveness against hospitalization, severe cases, and death. Phase 3 results from Turkey showed an efficacy of 83.5% against symptomatic COVID-19 after the second dose and 100% against hospitalization. There was a 65.3% efficacy rate in the Indonesian trial. CoronaVac does not need to be frozen, and both the vaccines could be transported and refrigerated at 2-8 °C [89, 90]. Phase ½ clinical trials showed CoronaVac has good safety and immunogenicity with seroconversion occurring in 92.4% of individuals after the 3 μg dose given on a 0-14 day schedule and 97.4% of individuals with the same dose on a 0-28 day interval. Preliminary results from the Instituto Butantan trial declared CoronaVac is safe with no reported serious adverse events. However, the trial in Brazil was briefly suspended due to patient death, though the trial was resumed later [85, 91]. A study undertaken in healthcare workers after single-dose administration of the CoronaVac vaccine showed 35.1% effectiveness against Gamma [92]. After the CoronaVac vaccine, full immunization effectiveness against hospitalization was 87.5%, and against mortality, it was 86.3% [93].

Table 1. List of COVID-19 vaccines approved for emergency use.

Platform	Vaccine	Developer	Doses and	Efficacy	Ref
mRNA	BNT162b2	Pfizer/BioNTech	2 (3 weeks apart)	95%	[76]
	mRNA-1273	Moderna	2 (4 weeks apart)	94	[73]
	CVnCoV	CureVAC	2 (4 weeks apart)	77%	[97]
Non-replicating viral vector (DNA Adenovirus vector)	Ad26.COV2.S	Janssen/Johnson &Johnson	1(a single dose)	67%	[53]
	ChAdOx1nCoV- 19	AstraZeneca/ University of Oxford	2 (4/8- 12 weeks)	70%	[43]
	Gam-COVID-Vac (sputnik V)	Gamaleya Institute	2 (3 weeks apart)	92%	[60]
	Convidecia ™ Ad5-nCoV	CanSino	Single dose	95.47%	[98]
inactivated whole-virus	BBIBP-CorV	Sinopharm/China National Pharmaceutical Group	2 (3 weeks apart)	79%	[95]
	CoronaVac	Sinovac Biotech	2 (4 weeks apart)	100	[99]
	Covaxin	Bharat Biotech	2 (4 weeks apart)	100	[100]
Recombinant protein based	NVX-CoV2373	Novavax	2 (3 weeks apart	89.3%	[96]

4.3.6. Sinopharm

Sinopharm has developed two inactivated alum-adjuvanted vaccines. The first vaccine candidate (New Crown COVID-19) was developed by the Wuhan Institute of Biological Products. New Crown vaccine was produced from virus particles grown in a lab culture, usually in Vero E6 cells (extracted from African green monkey kidney cells). These viruses lose the ability to cause infection and disease. The second vaccine candidate (BBIBP-CorV) being tested by Sinopharm was developed by the Beijing Institute of Biological Products [94].

Phase 3 studies were undertaken in Argentina, Bahrain, Egypt, Morocco, Pakistan, Peru, and the United Arab Emirates with over 60,000 participants. The overall efficacy of the schedule 0, 14 in phase 3 trial of the emergency use was 50.65%, 83.50%, 65.30% in Brazil, Turkey, and Indonesia, respectively [94]. The two inactivated vaccines against COVID-19 generally displayed safe and significant humoral responses in adults 18 years and older in phase 1/2 trials. In the phase 3 trial, the two vaccines with 40,382 participants showed the efficacy of 72.8% and 78.1% against symptomatic COVID-19 cases. The two vaccines had a rare serious adverse reaction similar to the alum-only control, and the majority was not related to the vaccinations. The two vaccines induced significant neutralizing antibodies, similar to the results of the phase 1/2 trials [95]. BBIBP-CorV is approved in more than 53 countries for emergency use. Sinopharm has reportedly administered these vaccines to hundreds of thousands of people under an emergency use condition approved by the Chinese government [94, 95].

4.4. Particle and Protein Vaccines

Novavax's vaccine, NVX-CoV2373, is a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length S glycoprotein and saponin-based adjuvant Matrix-M1. The S protein is expressed in a baculovirus insect cell expression system, forming VLPs. In phase 1/2, clinical trials of two doses at days 0 and 21 showed that it was safe [96]. It induces the highest levels of VNAs and offers levels of protection approaching 89.3%. The Novavax particle vaccine is expected to be released for emergency use in the U.S. in a few months. Several other recombinant protein vaccines are also in development and may offer advantages in terms of low cost and easy accessibility [96].

5. IMPACT OF SARS CoV-2 VIRUS VARIANTS ON VACCINES EFFICACY

Since the appearance and the spread of SARS-CoV-2, mutations of the virus were imminent and an issue in vaccine development. Based on the location of mutations in S protein, reductions in neutralization are expected. However, several mutations were identified in the community, and most of the virus appeared to be antigenically stable. Some variants may be more transmissible, including the UK variant B.1.1.7 (N501Y.V1), the South African strain B.1.351 (N501Y.V2), and the Brazilian strain B.1.1.28.1 (P.1), which possess mutations in the S protein [101]. The UK strain has eight mutations in the S protein; one of them (N501Y) is in the RBD region. The Brazilian and South African strain contains two additional mutations [102]. Studies on the neutralization potential of the wild and the new variants after vaccination or infection are consistent. The UK variant neutralized equally as the original variant by both Moderna mRNA and Biotech/Pfizer mRNA vaccine. The Oxford/Astra Zeneca vaccine showed an equally protective effect against B.1.1.7, although the humoral response was nine times lower. The Moderna vaccine showed a reduced neutralization in South African mutants. A recent phase 3 study on the Novavax subunit vaccine showed lower efficacy in the South African strain than in the UK strain. Therefore, monitoring the emergence and spread of new variants is important not only for increased transmissibility but also because of the risk of escape from vaccine-induced immunity [103, 104].

CONCLUSION

Morbidity, mortality, and the enormous socioeconomic consequences that have resulted from the COVID-19 pandemic necessitate the urgent development of a safe and effective vaccine.

There are currently more than 230 vaccine candidates under development, with a number of them already receiving EUAs, as shown in Table **1**. mRNA-based vaccine encompasses a great proportion of COVID-19 vaccine

candidates. Its rapid development was due to key aspects of previous studies, including antigen selection, route of administration, delivery methods, and dosage. RNA vaccines may give important immunological properties. Issues due to the unstable property of RNA vaccine are overcome by using suitable dose formulations and storage approaches to prevent degradation. BNT16b2 (BioNTech/Fosun Pharma/Pfizer) and mRNA-1237 vaccine (Moderna Therapeutics/ NIAID) are RNA vaccines approved by the U.S. FDA for emergency use.

Viral vector vaccines induce a significant immune response, although pre-existing immunity may limit their effectiveness. So far, three COVID-19 viral vector vaccines have been approved. The Ad5-nCoV was approved by the Chinese government for use in their armed forces, in addition to Gam-COVID-Vac (Sputnik V) by the Russian government for emergency use authorization. Furthermore, the University of Oxford and AstraZeneca have approved the AZD1222 viral vector vaccine.

Phase 3 trials are still ongoing for the COVID-19 vaccines, and it is difficult to ascertain which vaccine is most suitable and effective against the COVID-19. Each vaccine candidate induces an immune response and shows a good safety profile. The most suitable vaccine choice depends on the efficacy and safety of the vaccine. The safety of vaccines is important and cannot be compromised for higher efficacy. Continuous follow-up of participants is essential to detect any severe adverse reactions to ensure the vaccine is safe for use. Vaccination is the best solution, but care is essential for its adverse reaction and the emergency of mutant COVID-19 strains.

LIST OF ABBREVIATIONS

LAV	=	Live-Attenuated Vaccines
EMA	=	European Medicines Agency
NmAb	=	Neutralizing Monoclonal Antibodies
SARS-CoV	=	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	=	severe Acute Respiratory Syndrome Coronavirus-2

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CONFLICT OF INTEREST

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