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Review

SARS-CoV-2 Targets and COVID-19 Vaccines

Arthur W. Currier [1], Madeline C. Jeshurin [2] and Valerie B. Sampson [3,*]

[1] College of Medicine, Howard University, Washington, DC 20059, USA; acurrier@udel.edu
[2] Department of Biological Sciences, University of Delaware, Newark, DE 19716, USA; mjesh@udel.edu
[3] Nemours Children's Health, Nemours Biomedical Research, Wilmington, DE 19803, USA
* Correspondence: vsampson@nemours.org

Abstract: Coronavirus disease-2019 (COVID-19) vaccines are being used across the globe to reduce the risk of developing COVID-19, stop the transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and end the pandemic. To address this, a massive global effort is underway for development of COVID-19 vaccines. As of September 2021, the World Health Organization (WHO) has documented 331 COVID-19 vaccine candidates, and 107 are in clinical evaluation, with 8 in Phase IV and 30 in Phase III clinical trials (WHO; COVID-19 vaccine tracker). At least 13 different vaccines are being issued for emergency use authorization. Specifically, the goal is to produce protective immunity to SARS-CoV-2 infection by stimulating an immune response to either the whole virus, viral protein, or nucleic acid products. The spike (S) proteins of SARS-CoV-2 that give the characteristic "corona" appearance of this family of viruses has emerged as an effective target for vaccines. Other viral candidates that are being developed also aim to produce immunity for COVID-19. In this review, we describe the different vaccine platforms, target candidates for vaccines, and their progress in COVID-19 vaccine development. This is critical since newly discovered SARS-CoV-2 variants of interest require understanding of how vaccines may provide the most effective long-term protection against infection.

Keywords: inactivated virus; viral vectors; genetic variants; mRNA vaccine

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1. Introduction

The new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus is a RNA virus belonging to the *Coronaviridae* family [1]. Infection with SARS-CoV-2 causes Coronavirus disease-2019 (COVID-19). COVID-19 is a contagious disease, and the first case was identified in Wuhan, China, in December 2019 [2]. By 16 September 2021, the rapid, global spread of COVID-19 has been reported in 220 countries and territories, with 227,471,677 confirmed cases and 4,677,080 deaths (https://www.worldometers.info/coronavirus/ accessed on 9 September 2021). Although some areas are reporting reductions in infection and deaths at this time, others are experiencing spikes that require lockdowns and strict restrictions, leading to widespread social and economic disruption. The development of safe and efficacious vaccines is a critical defense strategy against SARS-CoV-2 to help end this pandemic. The first mass experimental vaccination program began in early December 2020, and by 16 September 2021, a total of 7,845,261,000 vaccine doses have been administered worldwide (WHO; COVID-19 vaccine tracker (shinyapps.io) [3]).

Vaccines trigger the immune system to produce protective antibodies, just as with natural infection. In the case of SARS-CoV-2, there is great urgency for the development of a vaccine against this newly emergent strain of CoV. At present, there are 331 COVID-19 vaccine candidates in clinical evaluation, with 8 of these in phase IV and 30 in phase III trials, Table 1. (WHO, COVID-19 vaccine tracker (shinyapps.io)). At least 13 different vaccines have now been issued for emergency use authorization (EUA) in many regions worldwide. COVID-19 vaccines have been created using existing technologies that are applied for developing vaccines against other infectious diseases. Vaccine types include

whole SARS-CoV-2 virus and SARS-CoV-2 protein subunit vaccines. Two other platforms, viral vector-based and mRNA vaccines, have been gaining attention owing to the high efficacies of response following administration. The key to combatting the current COVID-19 pandemic is to develop a variety of vaccines that are efficacious and safe to administer, elicit long-term immunity, and cover a range of SARS-CoV-2 variants. This review describes the available types of COVID-19 vaccines and brings to light the current benefits as well as risks due to the rapid advancement of new methodologies.

Table 1. COVID-19 vaccines in Phase III and Phase IV evaluation.

Vaccine	Phase	Platform	No. of Participants	No. of Doses	Location	Trial Number
Ad5-nCoV/ZF2001 prime-boost	IV	Inactivated	27,711	2	Brazil	NCT04747821
AZLB ZF2001	IV	RNA/Vector (non-replicating)	10,000	≥1	Denmark	NCT04760132
Bharat Covaxin	IV	Inactivated	4400	2 or 3	China	NCT04863638
BIBP BBIBP-CorV	IV	Inactivated	2067	2	Brazil	NCT04754698
BIBP BBIBP-CorV	IV	RNA	540	2	Sweden	NCT04780659
BioNTech BNT162 (b1/b2)	IV	Vector (non-replicating)/Protein subunit	120	2	China	NCT04833101
BNT162/mRNA-1273/ChAdOx1-S	IV	RNA	120	1 (boost)	Canada	NCT04885907
CAMS vaccine	III	Vector (non-replicating)	500,000	1	South Africa	NCT04838795
Cansino Ad5-nCoV	III	Protein subunit	48,000	3	Cuba	IG/CIGB-66I/CVD19/2103
CIGB CIGB-66/Abdala	III	Inactivated	45,000	2	Bahrain, Jordan, Egypt, UAE	NCT04510207
CureVac CVnCoV	III	Protein subunit	44,010	2 or 3	Cuba	IFV/COR/09
Gamaleya Gam-COVID-Vac/Sputnik V	III	Vector (non-replicating)	40,000	1	Argentina, Chile, Mexico, others	NCT04526990
Instituto Finlay de Vacunas FINLAY-FR-2	III	Protein subunit	40,000	3	Pending	NCT04887207
Janssen Ad26.COV2.S	III	Inactivated	34,020	2	Brazil, Malaysia	NCT04659239
Janssen Ad26.COV2.S	III	Vector (non-replicating)	33,758	2	Russia	NCT04530396
Moderna mRNA-1273	III	Protein subunit	33,000	2	USA, Mexico, Puerto Rico	NCT04611802
Novavax NVX-CoV2373	III	Vector (non-replicating)	30,000	2	USA, Belgium, Brazil, others	NCT04614948
Novavax NVX-CoV2373	III	Protein subunit	29,000	Unclear	China, Ecuador, Indonesia, others	NCT04646590
PLA-AMS ARCoV	III	RNA	28,000	2	Pending	NCT04847102
RIBSP QazCOVID-in	III	Inactivated	28,000	2	Pending	NCT04852705
Shenzhen Kangtai KCONVAC	III	Inactivated	25,800	2	India	NCT04641481

Table 1. *Cont.*

Vaccine	Phase	Platform	No. of Participants	No. of Doses	Location	Trial Number
Sinovac CoronaVac	III	Protein subunit	15,000	2	UK	NCT04583995
Sinovac CoronaVac	III	Inactivated	13,000	2	Turkey	NCT04582344
Sinovac CoronaVac	III	Inactivated	12,000	2	Peru	NCT04612972
Vector Institute EpiVacCorona	III	Inactivated/Vector (non-replicating)	4000	2	UK	NCT04864561
VLA2001/ChAdOx1-S	III	Inactivated	3000	2	Argentina	NCT04560881
West China Hospital protein subunit vaccine	III	Inactivated	3000	2	Kazakhstan	NCT04691908
WIBP vaccine	III	Protein subunit	3000	2	Russia	NCT04780035
WIBP/BIBP vaccines	III	RNA	2520	2	Germany	NCT04674189
WIBP/BIBP vaccines	III	Inactivated	600	2	Morocco	ChiCTR2000039000

1.1. Whole SARS-CoV-2 Virus Vaccines

Description: This traditional method uses whole virus particles created by modifying the SARS-CoV-2 to a live attenuated virus or inactivated virus that can generate an immune response without the virus causing COVID-19 disease. For inactivated vaccines, the virus is cultivated in a qualified cell line for propagation (e.g., Vero kidney epithelial cells), and the cell culture supernatant of the infected cells is treated using heat or chemicals, for example, formalin or β-propiolactone treatment, at 2 to 8 °C for 48 h [4,5]. This kills or inactivates the virus, and it is rendered replication-incompetent. In these non-replicating viruses, the SARS-CoV-2 viral pathogen remains intact and can be recognized by the human immune system to elicit desired immune responses. When the inactivated virus is introduced into the host, neutralizing antibodies (nAbs) and T-cells typically bind to the spike transmembrane glycoproteins (S) that are present on the surface of the SAR-CoV-2, thereby making the S-genomic sequence or protein subunit a key component of COVID-19 vaccine candidates [6]. Immunological memory is thus created by the host after an initial exposure. Next, specialized memory T- and B-cells that make up the cellular component of the immunological memory, cells recognize the specific antigen and prime the immune system to produce memory cells and antibodies that will target this protein [7]. In the event of the future exposure of an individual to the virus, the immune system is primed to respond and to eliminate the SARS-CoV-2 virus.

Clinical and Preclinical Testing: The current COVID-19 vaccines in clinical testing use inactivated viral vaccines that have a complete loss of replication ability. There are 24 inactivated candidate vaccines, accounting for 15% of vaccines in preclinical and clinical development. An inactivated vaccine, the CoronaVac (inactivated SARS-CoV-2 vaccine, Vero cell), which is derived from the CN2 strain of SARS-CoV-2 containing alum (aluminum hydroxide) adjuvant, showed broad neutralization ability against SARS-CoV-2 in preclinical studies and is undergoing clinical evaluation [8]. Genneru et al. [9] also developed an inactivated whole virion using a genetically stable virus strain and induced high nAb titers in animal models. Adjuvant-induced T helper type 1 (Th1)-biased antibody responses with an elevated IgG2a/IgG1 ratio, and increased levels of SARS-CoV-2-specific IFN-γ+ CD4+ T lymphocyte response were attained [9]. At present, two of the inactivated vaccines are currently in phase IV clinical trials, the BIBP BBIBP-CorV vaccine (Sinopharm, Beijing, China, NCT04790851) and the CoronaVac vaccine (Sinovac Biotech Ltd., China, NCT04911790); seven are in phase III clinical trials, and several more are under preclinical and clinical development, Table 1. These have been authorized as a 2-dose vaccine, given at 0 and 21 days (with flexibility up to an additional 7 days) for the prevention of COVID-19 disease. A recent study reported that a single dose of the whole virus vaccine was protective

in previously infected recipients and could elicit higher titers of nAbs, suggesting efficacy as a booster dose in individuals who have already been infected by the SARS-CoV-2 [10].

Benefits and Risks: Whole pathogen vaccines can stimulate strong protective immune responses with low rates of adverse reactions in both animal models and in humans. Since current COVID-19 vaccines in clinical evaluation use inactivated SARS-CoV-2 that has a complete loss of replication ability, these may be safer than live attenuated vaccines. These are often a preferred product class for special populations, such as pregnant women, organ transplant patients, and immunocompromised individuals.

The BIBP and CoronaVac vaccines are two inactivated COVID-19 vaccine candidates that have been used for mass vaccination in China and in other selected countries (including Bahrain, Bolivia, the Seychelles, and the United Arab Emirates). VLA2001 (Valneva SE) is currently the only inactivated vaccine candidate in clinical trials against COVID-19 in Europe. Data from animal experiments and Phase I and II clinical trials have consistently demonstrated low rates of adverse events and notable immunogenicity with substantial protection mainly consisting of S- and RBD-specific immunoglobulin G (Ig G) in the serum of vaccinated mice [8,11]. Phase III clinical trials for CoronaVac suggest that the vaccine effectively prevented severe disease and death due to COVID-19 although the point estimates of efficacy against symptomatic illness are variable: 50.65% in Brazil, 65.30% in Indonesia, and 83.50% in Turkey—with a median observation time of 2 months [12]. Data for a Chilean cohort from 2 February–1 May 2021 show that the effectiveness of CoronaVac is estimated to be 65.9% for the prevention of COVID-19 and 87.5% for the prevention of hospitalization, 90.3% for the prevention of intensive care unit (ICU) admission, and 86.3% for the prevention of COVID-19–related deaths [13].

Injection site pain, fatigue, headache, muscle pain, chills, fever, and nausea are the main side effects following vaccination. Certain risk factors such as blood clotting are being monitored as a risk factor after receiving whole virus vaccines. One thrombotic event was identified among the subjects in the Phase III clinical trial for the BIBP vaccine. These clinical trials continue to evaluate how often this occurs, how severe their illness is, whether the benefits outweigh the risks, and how likely a vaccinated person is to spread COVID-19 to others. Furthermore, these early trials were conducted when variants of concern had not yet been studied. Concerns about waning neutralizing antibody titers for vaccines within 6–8 months post-introduction are emerging that support the implementation of a layered approach centered on the administration of several booster shots for long-term immunity. Although memory T- and B-cells have a long life and can last up to several decades in the body, the actual duration of this immune response for SARS-CoV-2 is still being determined. Since each vaccine has different attributes, advantages, and disadvantages, the long-term immunity data may vary among vaccine candidates and continues to evolve.

1.2. SARS-CoV-2 Protein Subunit Vaccines

Description: In place of whole viral particles, protein subunits contain a specific product of the SARS-CoV-2 virus that is used to induce immune responses. Pathogen products that are used in subunit vaccines include purified or recombinant proteins or the polysaccharides present on the surface layer. SARS-CoV-2 contains structural, non-structural, and accessory proteins [14]. Four of the major structural proteins are S, membrane (M), and envelope (E) proteins, which are all located in the viral phospholipid bilayer, and the nucleocapsid (N) protein, which is in the ribonucleoprotein core. The S-proteins bind ACE2 (angiotensin-converting enzyme-2), a specific host cell receptor that facilitates host cell attachment and viral entry [15]. The S-protein contains the S1 subunit that is a C-terminal receptor-binding domain (RBD) that determines receptor recognition, and the S2 subunit for membrane fusion, which is required for host cell entry (Figure 1). M proteins confer the shape of the virion envelope [16]. Antibodies that neutralize the virus typically bind to the S-protein, thus making the spike gene sequence or protein a major component of COVID-19 vaccines [14]. E proteins are small polypeptides that are crucial for SARS-CoV-2 infectivity. The nucleic acid-associated N-protein binds the viral RNA genome and forms the helical

nucleocapsid. SARS-CoV-2 also encodes 16 non-structural proteins and 9 accessory proteins (Orf3a, Orf3b, Orf6, Orf7a, Orf7b, Orf8, Orf9b, Orf9c, Orf10) [14].

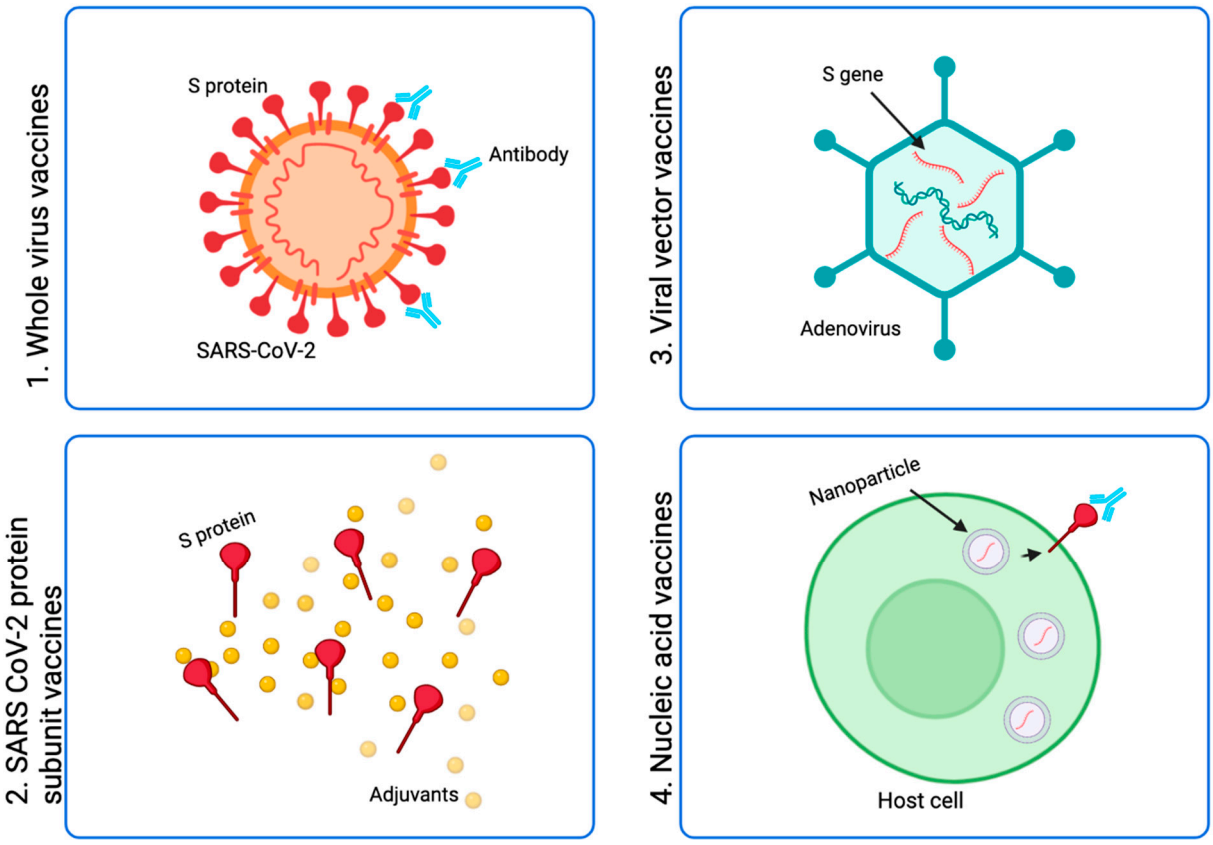

Figure 1. Strategies for SARS-CoV-2 vaccines. (**1**) Whole virus vaccines—virus is rendered non-pathogenically but retains immunogenicity by mimicking live virus infection. (**2**) SARS-CoV-2 protein subunit vaccines. Key viral proteins or peptides are manufactured in vitro in bacteria, yeast, insect, or mammalian cells and are introduced with adjuvants in whole cells. (**3**) Viral vector vaccines. Gene(s) encoding pathogen antigen(s) are cloned into non-replicating or replicating virus vectors (such as adenovirus) that generate the antigen(s) by virus-transduced host cells after immunization. (**4**) Nucleic acid vaccines. mRNA vaccines are synthesized by in vitro transcription, and they produce viral antigen(s) in the cytoplasm through direct protein translation in vivo. Created with BioRender (BioRender.com Accessed on 20 May 2021).

Clinical and Preclinical testing: The S-protein is the most efficacious candidate for vaccine development. There are 35 protein subunit vaccines in clinical development. One protein subunit vaccine, ZF2001 (Anhui Zhifei Longcom Biopharmaceutical, Hefei, China), a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine, is currently in Phase IV clinical trials as a heterologous platform (Ad5-nCoV/ZF2001, China, NCT04833101), 12 are in Phase III clinical trials, and others are under development, Table 1. ZF2001 was developed using technology like other protein-based vaccines in Phase III trials from Novavax, Vector Institute, and Medicago. Although the synthetic peptides obtained from immunodominant epitopes were immunogenic against the SARS-CoV M-protein in immunized rabbits [17], M- and E- SARS-CoV-2 proteins demonstrated less immunogenicity for humoral responses [18]. This may be due to their small ectodomains for immune cell recognition and small molecular sizes [19]. Hence, these have not yet been actively developed as candidate targets against SARS-CoV-2. However, these proteins have high sequence identity among SARS-CoV, MERS-CoV, and SARS-CoV-2 in comparison to the S-protein and RBD, suggesting that the M- and E-proteins are potential targets for cross-reactive T-cells and may be explored to expand the T-cell response of current SARS-CoV-2 vaccines. The N-protein is the most abundant viral protein and plays a role in virus neutralization during CoV infection [20]. Although this has the potential to recruit

additional effector mechanisms, the inclusion of the N-protein subunit in CoV vaccines has viral clearance and immunopathogenesis concerns. Multiple peptide fragments targeting (S, M, N) and (NSPs) SARS-CoV-2 proteins to induce T-cell responses (CD8) are under preclinical development as subunit vaccines for COVID-19. In a recent study, researchers describe new monoclonal antibodies that target the S2 subunit with broad neutralization activity against several beta-coronaviruses, including SARS-CoV-2, that may be promising for future vaccine development [21], and to a lower extent, also target the 3a protein [22].

SARS-CoV-2 candidate vaccines that use empty virus shells that lack genetic material are also classified as protein-based vaccines. These mimic the CoV structure but are not infectious and are referred to as virus-like particles [23]. Five virus-like particle vaccines are currently in Phase I, Phase II, and Phase II/III clinical development (WHO).

Benefits and Risks: Protein subunit vaccines have the advantage of being relatively rapid and low-cost to produce. This approach is independent of whole SARS-CoV-2 pathogen cultivation and is favored to reduce disease burden effectively and quickly in outbreak situations. These vaccines are incapable of causing disease because protein fragments are not infectious in host cells. However, there is an overall lower possibility for protein subunits to be recognized by immune cells that are aimed at recognizing infected cells; therefore, these types of vaccines typically induce a weaker host immune response [24,25]. Because of this, subunit vaccines often include adjuvants that are designed to stimulate the immune response to obtain the desired protection for a prolonged period, Figure 1. The Novavax NVX-CoV2372 trimeric nanoparticle that is made from the full-length S-protein and contains one mutation (682-QQAQ-685) at the S1/S2 junction to increase protease resistance and two other mutations, K986P and V987P, for the increased stability of the recombinant vaccine antigen [26]. Booster doses of inactivated vaccines may be also required. Better nAb activity was observed for ZF2001 in an extended gap between the third and second doses of ZF2001 [27]. Certain at-risk populations with compromised immune systems, such as cancer patients and organ transplant patients as well as the elderly and the very young, particularly benefit from vaccines with adjuvants because their immune systems may require an extra boost to enhance protection.

Reduced effectiveness to the immunity generated by the current vaccines is being monitored, as breakthrough infections are reported for some variants of concern post-vaccination, although these are generally associated with mild disease [28]. Early reports suggest that the lambda variant may be more resistant to COVID-19 vaccines compared to other strains and may potentially be more infectious than the alpha or gamma variant [29]. Encouragingly, SARS-CoV-2 protein subunit vaccination of mice and rhesus macaques generated robust antigen-specific memory B-cell responses against the wild-type vaccine strain and a variant harboring a D614G mutation in the S-protein [30,31], and a humoral immune response to circulating SARS-CoV-2 variants was elicited by inactivated and RBD-subunit vaccines [27].

1.3. Viral Vector Vaccines

Description: There are other types of vaccines that do not directly introduce antigens into the body. Newer vaccine production platforms allow the cells in an individual's body to endogenously synthesize the SARS-CoV-2 antigens and trigger an immune response. Examples include viral vector vaccines and mRNA vaccines. In both cases, the goal is to insert a genetically engineered transgene coding for a SARS-CoV-2 antigen product, typically the S-gene, into the host cells. The DNA template is derived from SARS-CoV-2 viruses, which were isolated in Wuhan, China, at the emergence of the pandemic [32]. The genetic codes for specific antigens are extracted from the whole genome sequence. Non-replicating viral vector vaccines are based on recombinant viral vectors that are made replication non-competent and are sufficient to induce host immune responses but that cannot replicate inside host cells. The fragment of genetic code from the SARS-CoV-2 virus can be inserted into a non-infectious virus (e.g., adenovirus, adeno-associated virus, measles virus, and human parainfluenza virus) that is used as a delivery system to transfer the

antigen code into the host cell. These types of vaccines hijack the host cellular mechanism and mimic normal viral reproduction during natural infection, but rather than creating copies of the virus, the cells only produce large amounts of antigen and stimulate SARS-CoV-2-specific immune responses without causing disease. This has the advantage of triggering a strong cellular immune response by the T-cells as well as the production of antibodies by the B-cells. In the case of replication-competent vector vaccines, new viral particles are produced in the cells that they infect, which are capable of infecting new cells that will also create the vaccine antigen.

Clinical and Preclinical testing: At present, three of the non-replicating viral vector vaccines are currently in Phase IV clinical trials for single use and combination platforms (Oxford ChAdOx1-S, Swaziland, NCT04914832; BNT162/mRNA-1273/ChAdOx1-S, Denmark, NCT04760132; BNT162/CoronaVac/ChAdOx1-S, Hong Kong, NCT04775069), 2two are in Phase III clinical trials, and seven others are under clinical development, Table 1. Replicating viral vectors include replication-competent measles, horsepox, influenza, vesicular stomatitis, and Newcastle disease virus technology delivering the SARS-CoV-2 S-glycoprotein. Protein subunit vaccines can elicit both high titers of nAbs beyond the levels observed in convalescent patients and substantial T-cell responses. The S-protein in protein-based vaccines can be modified to contain additional mutations to increase resistance against proteases, which helps to further stabilize the conformation of the S-protein [33].

Benefits and Risks: Most COVID-19 viral vector vaccines under clinical development use non-replicating viral vectors. In humans, 57 adenovirus serotypes have been identified, which can be further divided into 7 subgroups (A–G). The majority of adenovirus-based vaccines are prepared using adenovirus serotype 5 (Ad5), Table 2. Adenovirus-based vaccines can induce both antibody-mediated and T cell-mediated immune responses; however, the intensity of the response depends on the virus serotype used to produce the vaccine. Of note, previous exposure to the vector could reduce effectiveness. Vector based vaccines can be complex to develop, but they can trigger strong immune responses without the need for adjuvants. The components of viral based vector vaccines include items of human or animal origin, such as cell substrates, porcine trypsin, or bovine serum. This requires extensive testing to ensure that contaminants are not introduced during various steps of the manufacturing process. Indeed, several examples for contaminants in viral vaccines, such as porcine circovirus contaminations in rotavirus vaccines [34], have highlighted this risk. In addition, one type of vector can be used to deliver the genetic codes for a range of different antigens, which can accelerate vaccine development.

Clinical trial data from the UK, Brazil, and South Africa show that after full vaccination, although the Oxford-AstraZeneca chimpanzee adenovirus-vectored ChAdOx1 nCoV-19 vaccine (AZD1222) has an acceptable safety profile, lower neutralizing antibody responses were induced [41] in comparison to other types of vaccines, which may underlie its reduced protection, with an overall efficacy of 62.1% [42]. No serious adverse events or deaths that were treatment associated have occurred in ChAdOx1 nCoV-19 recipients. The Ad26.COV2.S (Janssen/Johnson & Johnson, Beerse, Belgium) COVID-19 single-dose adenovirus vaccine is reported to be 72% effective at preventing moderate to severe COVID-19 [38], but was less effective in South Africa at 57% (where 95% of cases with sequence data were the B.1.351 variant) [43] and was 85% effective at preventing severe disease with the COVID-19 virus caused by the Delta variant. The Ad26.COV2.S vaccine has been associated with the rare but increased risk of thrombosis with thrombocytopenia syndrome [44]. Analyses of these data have determined that the rate of adverse events with vaccination with Ad26.COV2.S is low, and thromboembolic events have mainly occurred in persons who have risk factors for thromboembolism. As a precaution, vaccine agencies in EU countries and in the UK have issued age-based restrictions on the use of Ad26.COV2.S.

Table 2. Efficacy of selected vaccines with Approval and Emergency Use Authorization.

Vaccine	Efficacy	Source
Anhui Zhifei Longcom Biopharmaceutical ZF2001	76%	Primary efficacy analysis [35]
Bharat Covaxin/BBV152	81%	Press release: 3 March 2021
BioNTech/Pfizer BNT162b2	95%	Primary efficacy analysis [36]
Beijing/Sinopharm BBIBP-CorV	79%	Press release: 30 December 2020
Cansino Ad5-nCoV	65.28%	Press release: 24 February 2021
CIGB CIGB-66/Abdala	92.28%	Press release: 22 June 2021
Chumakov Center CoviVac	Pending	WHO; COVID-19 tracker
Gamaleya Gam-COVID-Vac/Sputnik V	92%	Primary efficacy analysis [37]
Janssen Ad26.COV2.S	67%	Primary efficacy analysis [38]
Moderna mRNA-1273	94%	Primary efficacy analysis [39]
Oxford/AstraZeneca ChAdOx1-S	62–90%	Interim data [40]
Research Institute for Biological Safety Problems QazCOVID-in	Pending	WHO; COVID-19 tracker
Sinovac CoronaVac	50%	Press release: 3 April 2021
Vector Institute EpiVacCorona	Pending	WHO; COVID-19 tracker
CoronaVac/Sinopharm vaccine	Pending	WHO; COVID-19 tracker [12]

1.4. Nucleic Acid Vaccines

Description: These are RNA and DNA vaccines that use mRNA and plasmid DNA, respectively, or viral replicons as a template to endogenously produce antigens. To create RNA vaccines, using RNA polymerase, candidate RNA molecules can be generated using a template plasmid. Such vaccines do not include additional protein sequences to induce self-amplification of the inserted mRNA sequence. These sequences require additional key components to make them recognizable to human cells and safe from degradation. Non-replicating mRNA vaccines contain the 5′ cap, the 5′ untranslated region (UTR), the target antigen coding sequence (CDS), the 3′ UTR, and a poly-adenosine (poly-A) tail. Nucleic acid-encoded antigens offer the advantage of mimicking protein synthesis during an infection, i.e., protein localization to the plasma membrane, and modifications such as glycosylation patterns can be formed. The production of antigens in the target cells can stimulate humoral as well as cell-mediated immune responses. Nucleic acid vaccines use delivery systems such as lipo-nanoparticles. Nanoparticle walls are specifically modeled to fuse with the host cell membranes for uptake and delivery into cells. For example, cholesterol may be used to adjust the fluidity or rigidity of a lipid membrane, depending on temperature.

Clinical and Preclinical testing: Two 2-dose mRNA vaccines, the mRNA-1273 vaccine from Moderna and the BNT162b2 vaccine from Pfizer-BioNTech, received EUA by the US Food and Drug Administration (FDA) in December 2020 for persons aged $\geq$18 years and aged $\geq$16 years, respectively [36,39]. Clinical testing for the two mRNA vaccines encouragingly show that both these vaccines elicit high titers of nAbs beyond the levels observed in convalescent patients and substantial T-cell responses. While studies are ongoing, current reports that the mRNA vaccines elicit antibodies to emerging SARS-CoV-2 variants [45]. Early research findings suggest that after full vaccination, the Pfizer-BioNTech COVID-19 vaccine is 88% effective at preventing symptomatic COVID-19 virus caused by the delta (B.1.617.2) variant and is 93% effective at preventing symptomatic COVID-19 virus caused by the alpha variant [46].

Nanoparticle-based vaccines also offer a new approach to COVID-19 immunity. Joyce M. et al. [47] designed engineered ferritin nanoparticle immunogens that recapit-

ulate the structural and antigenic properties of prefusion spike, S1, and RBD that elicit protective immunity. They demonstrated that these immunogens induced robust S-binding, ACE2 (angiotensin-converting enzyme)-inhibition, and authentic and pseudovirus nAbs against SARS-CoV-2 in mice.

Benefits and Risks: These vaccines can be quick and cheap to develop, but they are a relatively new technology. Proper mRNA capping is critical to the production of the most biologically active and immunogenic mRNA. Nucleic acid-based technologies support fast and flexible vaccine development and production. Since all vaccines can be produced using the same basic components, the manufacturing of several vaccines can take place in one established facility, reducing both the costs and time of vaccine production dramatically. Their synthesis mostly relies on chemically synthesized material, supporting large-scale production with relative ease.

mRNA COVID-19 vaccines have not been associated with significantly higher rates of 23 serious adverse events 1 to 21 days after receiving one or two doses than after 22 to 42 days [48]. In a recently conducted study examining whether natural infection-induced or vaccine-induced neutralizing antibodies are capable of eliminating the risk of the recently emerged Indian variant (B.1.617.1) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was reported that mRNA-based COVID-19 vaccines are effective against the Indian SARS-CoV-2 variant [49].

Confirmed COVID-19 cases in children and adolescents have been increasing in number but not severity since the Delta variant became predominant. On 23 August 2021, the US Food and Drug Administration granted full approval of the Pfizer-BioNTech COVID-19 vaccine for persons aged $\geq$16 years. The Pfizer/BNT162b2 clinical trial involving children < 12 years established that 10 µg of the COVID-19 vaccine is safe, tolerable, and elicits an immune response. Clinical trial participants aged 6 months to 5 years will receive a 3 µg dose.

2. Efficacy of COVID-19 Vaccines

COVID-19 clinical trials are ongoing, multinational, placebo-controlled, observer-blinded, and age-specific. The primary end points of clinical trials are the efficacy of the vaccine against laboratory-confirmed COVID-19 and safety. Table 2 lists the data for at least 13 different vaccines that are now issued for EUA. Participants received the vaccine or a placebo by intramuscular injection and were followed for the development of COVID-19 for approximately 2–3 months. The Pfizer/BNT162b2 COVID-19 vaccine reports the highest efficacy (95%) and shows immunity 7 days after the second dose [36].

The correlations between efficacy and neutralizing and binding antibody titers in vitro across various vaccine platforms are being established. Overall, higher antibody responses to the mRNA vaccines and to the Novavax protein subunit vaccine are reported than they are to the inactivated virus and viral vector vaccines [50]. The highest efficacy is reported for a two-dose regimen of BNT162b2, which confers 95% protection against COVID-19 in persons $\geq$ 16 years of age. Limited interim data from the USA suggests that full vaccination lowers the chances of an individual becoming infected with COVID-19 by 3 1/2-fold and reduces the chances of having symptoms by 8-fold [51].

3. SARS-CoV-2 Variants

Another concern is that new SARS-CoV-2 variants may escape the immunity elicited by natural infection or subunit vaccination efforts. Currently, variants of concern have been detected, including the alpha variant, also known as lineage B.1.1.7, which originated in the United Kingdom; the beta variants of lineage B.1.351.1, B.1.351.2, and B.1.351.3 are of South African origin; and the gamma variants (lineage P.1, P.1.1, and P.1.2) are reported from Brazil (WHO). There are six delta variants, the B.1.427 and B.1.429, both originating from California (Center of Disease Control and Prevention, CDC, Atlanta, Georgia, U.S.A.) and B.1.617.1, AY.1, AY.2, and AY.3, which are reported from India (WHO). The SARS-CoV-2 lambda BS variant, also known as lineage C.37, was recently detected in Peru

(WHO). Each variant has multiple mutations, some of which occur in critical regions of the viral genome. Both the Brazilian and South African variants contain one key mutation (N501Y) in the S-protein [52]. Antibodies from individuals who recovered after infection or who have received a targeted vaccine may not bind as efficiently to a genetic-variant antigen, resulting in the reduced neutralization of the mutated virus. This could lead to an increase in transmissibility or detrimental changes in COVID-19 epidemiology and clinical presentation as well as the lowered effectiveness of current vaccines.

4. Discussion

Vaccine development is a long and extensive process than can last 10–15 years. The current pandemic has seen the accelerated development of COVID-19 vaccines to receive rapid approval or authorization for large-scale immunizations. Many features of the pandemic allow accelerated timelines for each clinical trial phase, including the accumulation of cases in humans to assess vaccine efficacy, the application of recent advances in technologies, and scaled-up manufacturing capacity after Phase III trials and regulatory approval. Preclinical testing of vaccine candidates typically starts in animal models: first in small mammals such as mice, rats, or rabbits and then non-human primates such as monkeys and are important for eliminating potential vaccines that are either toxic or that do not induce protective immune responses. For COVID-19, cases accumulate rapidly to assess vaccine efficacy because of the pandemic, allowing vaccine candidates that are very promising in preclinical testing to advance quickly into Phase I/II clinical trials to assess safety and immune responses. Currently, some of the major concerns concerning the impact of vaccination are the durability of SARS-CoV-2 vaccine-mediated immunity, appropriate dosing concentrations for different age groups to achieve high immunity, and efficacy against new variants of the virus that cause COVID-19.

These concerns have yet to be fully answered and are being addressed in ongoing studies. Phase III/IV clinical trials are critical to understanding whether vaccines are safe and effective, and the assessment of short- and long-term safety is also a major goal of these trials. This means that although the FDA has authorized the use of 13 vaccine candidates through an EUA, comprehensive proof of the efficacy of the vaccine is predicted but is yet unknown, especially for COVID-19 that causes high mortality. The efficacy obtained in accelerated clinical trials may not accurately predict what happens for longer periods of time. Although early data suggest initial robust antibody protection, a six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers reports a marked and statistically significant antibody decrease in healthcare workers [53]. This highlights that there may be a slow decrease in the level of protection to the virus variant used in vaccines coupled with the potential for lack of cross protection against new variants. This has led to current recommendations by the CDC for a third dose of mRNA vaccine for those who are immunocompromised. Encouragingly, more recent interim data from the USA suggests that a booster shot given two months after the first dose of Ad26.COV2.S increases both the antibody responses (four-fold increase in antibodies against S-protein) and vaccine effectiveness for protection against moderate to severe disease to 94%. Further, a booster shot given at six months provides a 12-fold increase in antibodies (September 2021 press release, Johnson & Johnson, unpublished data). Notably, it is not ideal to compare the current efficacies of different vaccines, as this requires a study in the same clinical trial, with same inclusion criteria, and that is conducted during the same time. This is unlikely for COVID-19 due to the challenges presented by the pandemic, including the number of individuals who participate in trials, the pre-existing efficacy data, rates of vaccine production, and levels of pre-existing immunity in the population. The use of standardized trial protocols could be implemented for future pandemics.

Current studies indicate that acquired immunity after infection with SARS-CoV-2 offers transient protection at a population level [54]. Therefore, to attain long-term protection, SARS-CoV-2 vaccines might require greater immunogenicity and durability than natural infection. The platforms using whole virus, either attenuated or inactivated, aspire

to induce a broader, more heterologous polyclonal response against several viral antigens. The majority of the candidate vaccines for COVID-19 that employ the administration of viral antigens or viral gene sequences aim to induce neutralizing antibodies against the viral S-protein, preventing uptake through the human ACE 2 receptor, therefore blocking infection [6]. A growing body of literature highlighting the importance of cellular responses on the recovery of COVID-19 patients has promoted not only the use of vaccine strategies that favor the induction of T-cell-mediated responses but also the screening of their production in clinical trial participants. The importance of computational modeling in the prediction of the course of the ongoing COVID-19 pandemic, as well as the evaluation of multiple potential candidate leads is a field that is rapidly developing. A new study recently described a set of designer vaccine antigens that may improve vaccine stability as well as enhance the neutralizing antibody response [55]. Most of these vaccines are based on modified S-protein and are stabilized in the prefusion conformation by a couple of amino acid changes in the S2 spike domain that can enhance vaccine efficacy.

The precise mechanism of protection of COVID-19 vaccines is still not well established. Data derived from efficacy trials suggest that both binding and nAb titers correlate with protection. Binding predominantly targets the RBD within the S1 sub-domain [53]. Some fully vaccinated individuals will acquire SARS-CoV infection and will develop COVID-19. The current strategy being studied to boost immunity is a third dose of vaccine targeting the initial reference strain. Currently, immunocompromised individuals are eligible for a third-shot booster starting 28 days after the second dose of a mRNA vaccine. Mixed doses of CoV vaccines, i.e., receiving a different vaccine type as a second dose than the first dose, are being studied to determine the types of immune responses that are induced, the longevity of the response, and the safety profile. Because some vaccines are delivered into the body using a modified virus, it is possible for the immune system to attack the vaccine itself, inhibiting the vaccine. Mixing the platforms for the booster could increase immunity, reduce the risk of developing immunity against the viral vector vaccine, and protect against variants of concern and the long-term threat of other coronaviruses. However, mixing mRNA vaccines with adenovirus-based vaccines and vice versa has not been done before, as COVID-19 was the first instance of mRNA vaccine technology being approved for human use. Whether mixed-dose vaccination might help people become fully vaccinated faster or offer stronger protection against COVID-19 than using the same vaccine for all doses remains to be determined.

Overcoming the pandemic will require a coordinated effort on a global scale. A major concern is to allow more people to have access to the COVID-19 vaccine. Vaccines may be harder for people to access based on factors such as where they live or how far they live from a vaccination site. Reaching everyone will require partnerships with community-based organizations and local health centers that have on-the-ground expertise to ultimately reach everyone.

5. Conclusions

The rapid development and rollout of COVID-19 vaccines have been some of the incredible successes in the response to the COVID-19 pandemic. It provides hope for crucial questions of the future of the COVID-19 pandemic and when the pandemic will end. In part, an epidemiological endpoint will depend on the overall response of the vaccines to current and careful surveillance for the emergence of new SARS-CoV-2 variants coupled with the achievement of population immunity and the management of COVID-19 as an endemic disease worldwide. Nonetheless, a new variant that substantially evades existing immunity would remain the biggest overall risk, indicating that vaccines may need to be updated periodically to avoid a potential loss of clinical efficacy. In addition, the establishment of booster shots, the full approval of vaccines, and authorization for children will be important to maintain immunity over time.

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