


An Update on the Status of Vaccine Development for SARS-CoV-2 Including Variants. Practical Considerations for COVID-19 Special Populations

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Abstract

The progress in the development of various vaccine platforms against SARS-CoV-2 have been rather remarkable owing to advancement in molecular and biologic sciences. Most of the current vaccines and those in development focus on targeting the viral spike proteins by generating antibodies of varying spectrum. These vaccines represent a variety of platforms including whole virus vaccines, viral vector vaccines, nucleic acid vaccines representing RNA, DNA, and their hybrid forms.

The therapeutic efficacy of these vaccines varies owing to their pharmacodynamic individualities. COVID-19 variants are capable of inducing different pathologic responses and some of which may be resistant to antibodies generated by current vaccines. The current clinical use of these vaccines has been through emergency use authorization until recently. Moreover, the efficacy and safety of these vaccines have been tested in substantial numbers of individuals but studies in special populations that better reflect the global population are pending results. These specialized populations include young children, immunocompromised patients, pregnant individuals, and other specialized groups. Combination approaches, molecularly modified vaccination approaches, and vaccines conferring longer periods of immunity are being currently being investigated, as well as pharmacovigilance studies.

The continual transformation of SARS-CoV-2 and its variants are of concern along with the breakthrough infections. These considerations pose new challenges for the development of vaccination platforms. For this purpose, booster doses, combination vaccine approaches, and other modalities are being discussed. This review provides an updated account of currently available vaccines and those in advanced development with reference to their composition and mechanisms of action.

A discussion on the use of vaccines in special populations including immunocompromised patients, pregnant women and other specialized populations are also included.

Keywords

COVID-19 vaccines, COVID-19 variants, children and adolescents, pregnancy and lactation, immunocompromised patients

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been detected in more than 206 million people and has caused more than 4.3 million deaths worldwide and the coronavirus disease 2019 (COVID-19) pandemic has become a significant global health problem.¹ After its first appearance in late December of 2019, it was first reported as

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a new type of pneumonia of unknown etiology.^{2,3} However, the situation is far more complex. Although the target organ for the virus was initially thought to be the lungs, it has been recognized that binding to the endothelial lining, through angiotensin-converting-enzyme 2 (ACE 2) receptors expressed on target cells, COVID-19 can affect almost all of the organ systems.⁴⁻⁶ Most of the patients present with mild symptoms, however, a considerable subset of patients develop a more severe condition, varying from pneumonia and acute respiratory distress syndrome (ARDS) to multi-organ failure (MOF).⁷⁻⁹ The coagulation abnormalities and immunological syndromes that occur during the course of the disease can cause life threatening events, leading to significant morbidity and mortality.¹⁰⁻¹³ After more than a year of living with COVID-19, many features of the disease have been revealed, but there are still many unknowns such as lack of a curative treatment of the disease or the importance of new emerging variants over the course of the COVID-19 pandemic.¹⁴ While simple prevention measures such as using masks, physical distancing or hygiene can only slow down the pandemic, vaccines are the most powerful tools to fight against COVID-19.¹⁵ Currently there are some 19 clinically used vaccines which have been used to control COVID-19 infections and over 100 in various phases of development. Thus, global vaccination will be of paramount importance in the management of this pandemic.

The discovery of the vaccination is one of the greatest achievements of modern medicine. The eradication of smallpox is one of the best examples of how vaccination stopped a deadly disease and saved millions of lives. The vaccinations against tetanus and rabies are similar examples. Many childhood infections such as polio and measles also became preventable. Millions of lives have been saved by annual influenza vaccinations.^{16,17} Vaccines are complex biological products that need to be applied in large populations of healthy people. Due to this, the development of vaccines takes a long period of time. Generally, development of any vaccine often takes 15 years or more from the initial design stage to the clinical studies.¹⁸ Vaccine clinical trials are often expensive and require recruitment of large numbers of volunteers with different ethnicities, ages, and health conditions. Long-term monitoring is also necessary to establish vaccine efficacy and to rule out or identify rare safety issues.

The development of the vaccines against COVID-19 started as soon as the virus genome was published in early January 2020.^{19,20} Immense resources have been deployed to support vaccine development by thousands of researchers, using highly sophisticated technology, and spending huge amounts of financial resources. Eventually, several different vaccines were deployed by late December 2020, under emergency use authorization, and mass vaccination campaigns have commenced all around the world. The fact that several COVID-19 vaccine candidates entered into clinical trials in less than 6 months and were approved for emergency use in less than 10 months since the beginning of the COVID-19 pandemic, development of COVID-19 vaccines demonstrates a groundbreaking speed in vaccine development history. Despite this

high speed, safety standards for the development and approval process of these vaccines were consistent with those of previously developed vaccines, with rigorous review of their clinical data by higher health authorities such as the World Health Organization (WHO) or United States Center for Disease Control and Prevention (US-CDC). Beside the availability of vaccines, the control of this epidemic will require greater than 80% vaccination of the global population. Additionally, uniformity in the vaccination programs in various parts of the world is equally important. Most of the currently used vaccines have been approved in a fast-tracked emergency process and authorized for emergency use. Only the Pfizer vaccine has full approval as of August 24, 2021 by the US-FDA. Other widely used vaccines are likely to receive similar approvals from the US-FDA and European Medicine Agency in the near future.

Currently used vaccines provide immunity against SARS-CoV-2 by generating neutralizing antibodies through molecularly defined mechanisms. All vaccines are capable of triggering the endogenous generation of spike protein which in turn result in the formation of neutralizing antibodies and T cell responses to COVID-19. The generation of these neutralizing antibodies provide protection against viral infection by readily complexing with the COVID-19 virus and arresting its propagation and subsequent pathophysiologic manifestation. The spike proteins generated by different approaches result in the formation of COVID-19 neutralizing antibodies with differential duration of fraction and antiviral spectrum.

Figure 1 shows a comparison of whole virion COVID-19 vaccines and viral vector vaccines. Whole virion vaccines are usually derived from chemically or molecularly modified SARS-CoV-2. The viral vector vaccines are derived by recombination of genomic sequence encoding trimeric form of spike protein. Figure 2 shows an illustration of the nucleic acid vaccines with recombinant protein based vaccines. Nucleic acid vaccines are based on mRNA and DNA vaccines. mRNA vaccines represent the genetic sequence of S protein. The DNA vaccines use the plasmids as vectors to transcript S protein. The recombinant protein based vaccines employ prokaryotic cells to produce recombinant spike protein or viral particles. Additional vaccines which are currently under development will have broader targets beside the generation of spike protein which include nucleocapsid protein and other viral antigens.

It is important to note that vaccination of at least 60-80% of the world population is required to achieve herd immunity against COVID-19.²¹⁻²³ According to WHO, more than 4 billion doses of COVID-19 vaccines have been administered globally.²⁴ However, vaccination rates are far less than would be necessary to control the pandemic, especially in Africa and Southeast Asian countries. Vaccination programs widely differ due to financial and logistics constraints throughout the world with a direct impact on the prevalence of COVID-19 infections.²⁵ Additionally, public acceptance of vaccines and vaccine hesitancy have become growing concerns for the success of vaccination programs.²⁶⁻²⁹ The duration of protection of COVID-19 vaccines or requirement of a booster dose

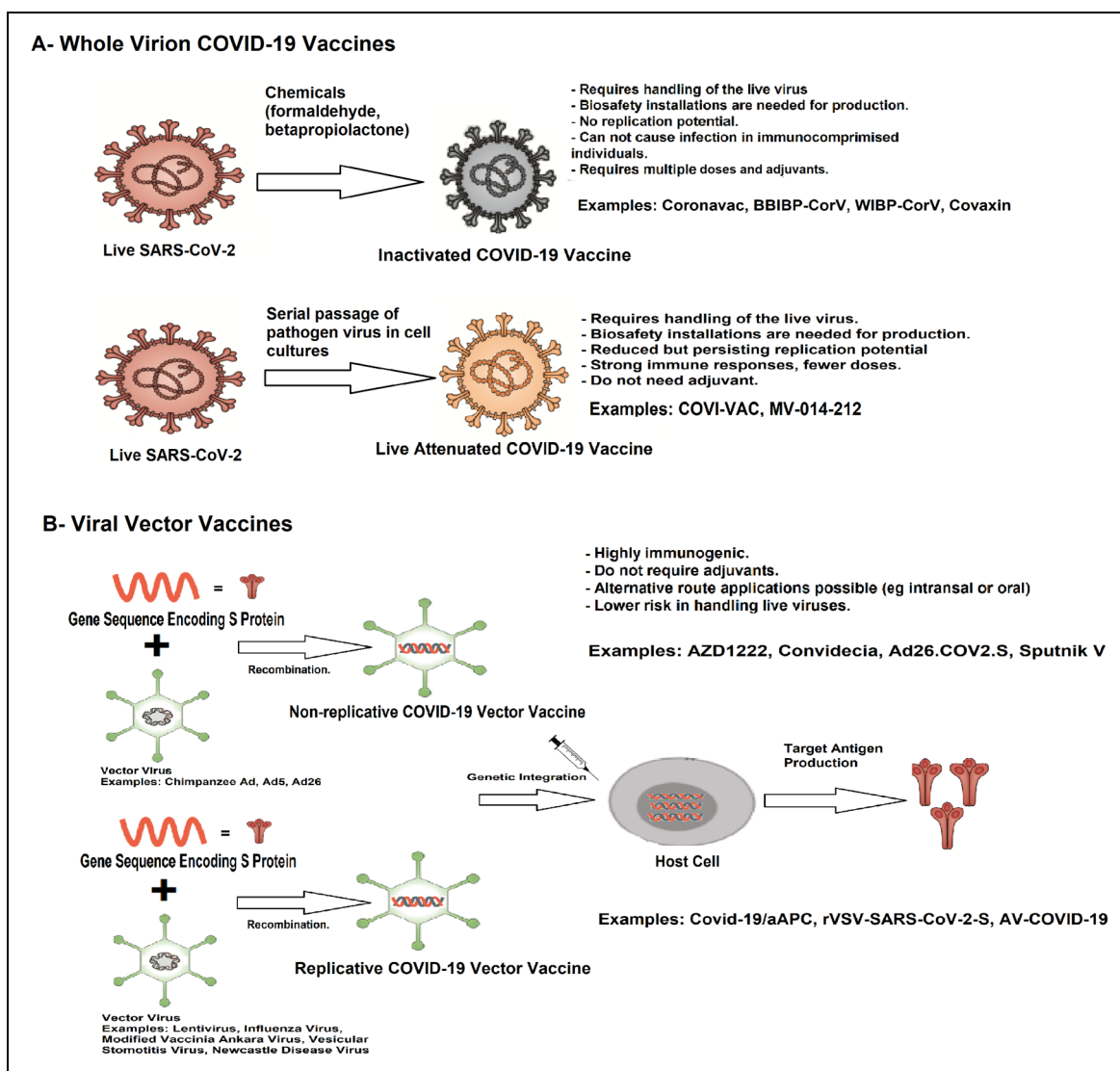


Figure 1. A comparison of whole virion COVID-19 vaccines and viral vector vaccines. Whole virion vaccines are usually derived from chemically or molecularly modified SARS-CoV-2 (Panel A). The viral vector vaccines are derived by recombination of genomic sequence encoding trimeric form of spike protein (Panel B)

are also areas of uncertainty affecting vaccine hesitancy. Emergence of variant viruses and the efficacy of current vaccines against them have also become important for the success of vaccinations.³⁰ With everything considered, the flow of newer information is rapid, requiring periodic updates and objective assessments. For this reason, in this manuscript, we tried to update and summarize the current status of COVID-19 vaccinations in the light of current literature.

Vaccine Development for COVID-19

Most of the vaccine candidates for COVID-19 were designed to induce neutralizing antibodies against the viral spike (S) protein to prevent its binding to the human angiotensin 2 converting enzyme (ACE2) receptor which mediates entrance of the virus into the human cells. The S protein is a fusion

glycoprotein that is divided into two functionally distinct parts (S1 and S2). S1 is located on the virus surface and contains the receptor-binding domain (RBD) that specifically binds to the host cell receptor. The transmembrane S2 domain contains the fusion peptide, which mediates the fusion of viral and cellular membranes. Besides the S protein, SARS-CoV-2 has other structural proteins such as membrane (M), envelope (E) and nucleocapsid (N) proteins. Antibodies that target M and E proteins have failed to neutralize the COVID-19 infection. For this reason, these 2 proteins are currently not considered as target antigen for COVID-19 vaccines. On the other hand, N protein is also highly immunogenic and can induce robust humoral and cellular immune responses.³¹⁻³³

Following the beginning of the COVID-19 pandemic, there has been a worldwide race to develop vaccines against this

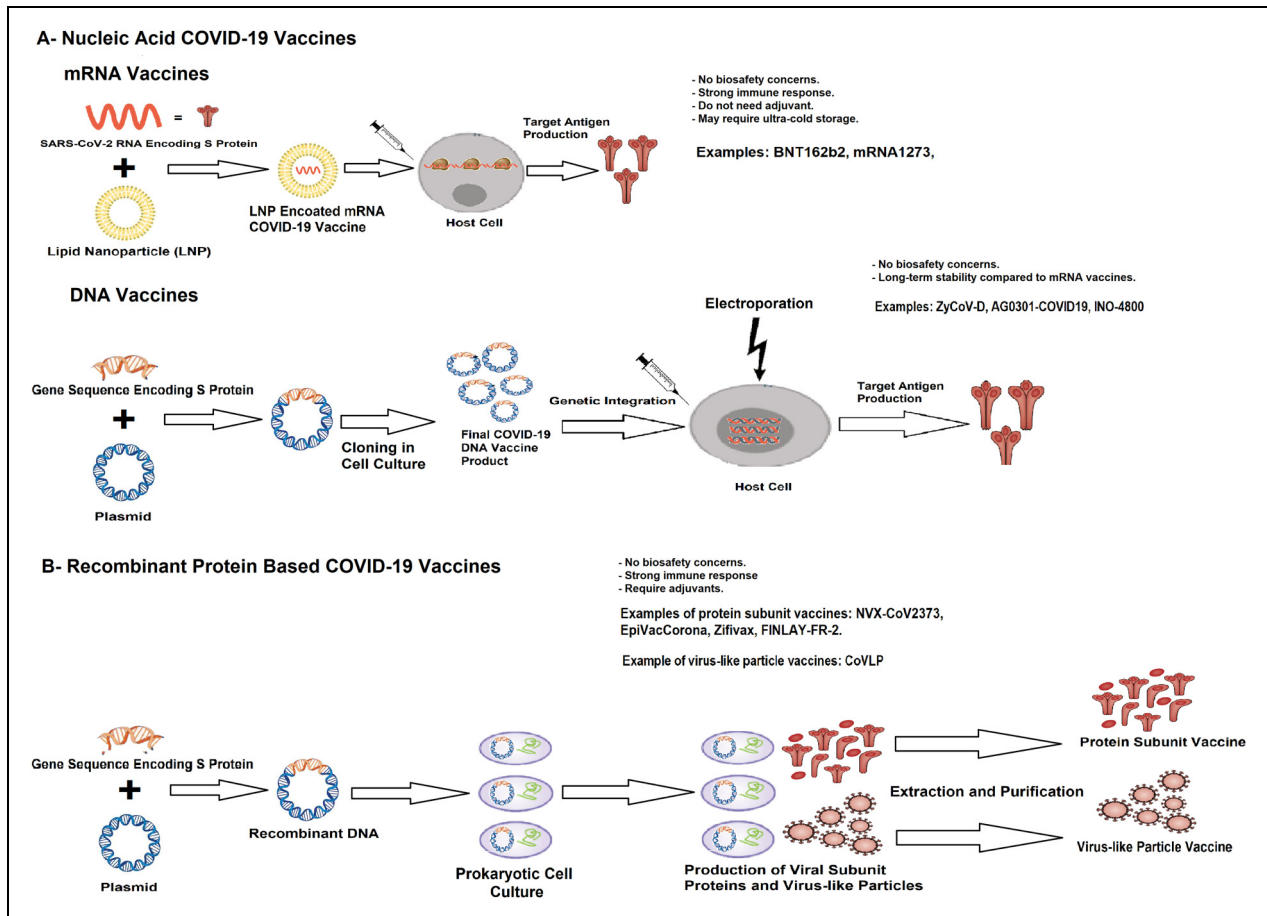


Figure 2. Illustration of the nucleic acid vaccines with recombinant protein based vaccines. Nucleic acid vaccines are based on mRNA and DNA vaccines. mRNA vaccines represent the genetic sequence of S protein (Panel A). The DNA vaccines use the plasmids as vectors to transcribe S protein. The recombinant protein based vaccines employ prokaryotic cells to produce recombinant spike protein or viral particles (Panel B).

disease. By August 2021, a total of 296 COVID-19 vaccine candidates have been developed, with 112 in clinical trials and 184 in preclinical studies.³⁴ Many different vaccine technology platforms have been used to develop a safe and effective vaccine, including conventional whole virus vaccines (live attenuated or inactivated vaccines), viral vector vaccines (non-replicating and replicating), nucleic acid vaccines (DNA- and mRNA-based vaccines) and recombinant protein-based vaccines [protein subunit vaccines, virus-like particles (VLP)].^{31–33}

Vaccine Platforms and Currently Available Vaccines

Whole Virus Vaccines

Whole virus vaccines are classified as inactivated and live-attenuated vaccines. They are the oldest and most well-established types of vaccine, used in smallpox, BCG, and measles vaccines. The technology used in this platform is decades old and is proven. Due to the presence of the whole virus with a variety of viral surface antigens, these vaccines cause a diverse immunologic response. The manufacturing

process of these vaccines requires handling live virus preparations. For this reason, a high level of bio-safety installations is needed for their production.^{35–41}

Live-attenuated vaccines are produced by serial passage of the pathogen virus in cell cultures for selection of a reduced replication potential and thus reduced virulence. The virulence of these viruses in live-attenuated vaccines is reduced, but they can still replicate. These vaccines usually produce strong and long-lasting humoral and cell-mediated immune responses by mimicking natural infection, but strict safety evaluation is required. Normally, live-attenuated viral vaccines do not cause disease, however they can be the source of infection when they are used in immunocompromised patients due to the presence of live viruses in the vaccine. Inactivated vaccines contain inactivated SARS-CoV-2 virus. They are usually inactivated by chemicals such as formaldehyde and beta-propiolactone, so that the antigenicity of the viral surface components is retained. Because they cannot replicate, they cannot cause infections even in the immunocompromised individuals. They are safer and more stable than live attenuated vaccines. These vaccines generally require multiple doses or adjuvants to achieve immunity.^{35–41}

Table 1. Current Whole Virion COVID-19 Vaccines in Clinical Trials

Vaccine	Developer	Country	Doses & Schedule	Route	Clinical Evaluation	Status of Approval
A) Inactivated Vaccines						
CoronaVac	Sinovac Research and Development Co., Ltd	China	Day 0 + 14	IM	Phase 4	Approved
BBIBP-CorV	Sinopharm + China National Biotech Group Co + Beijing Institute of Biological Products	China	Day 0 + 21	IM	Phase 4	Approved
WIBP-CorV	Sinopharm + China National Biotech Group Co + Wuhan Institute of Biological Products	China	Day 0 + 21	IM	Phase 3	Approved
Covaxin	Bharat Biotech International Limited	India	Day 0 + 14	IM	Phase 3	Approved
Minhai or KCONVAC	Shenzhen Kangtai Biological Products Co., Ltd	China	Day 0 + 28	IM	Phase 3	Approved
Name not provided yet.	Institute of Medical Biology + Chinese Academy of Medical Sciences (IMBCAMS)	China	Day 0 + 28	IM	Phase 3	Approved
CoviVac	Russian Academy of Sciences	Russia	Day 0 + 14	IM	Phase 3	Approved
QazCovid-in®	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Kazakhstan	Day 0 + 21	IM	Phase 3	Approved
COVIran	Shifa Pharmed Industrial Co	Iran	Day 0 + 14	IM	Phase 2/3	Approved
VLA2001	Valneva, National Institute for Health Research, United Kingdom	France—USA	Day 0 + 21	IM	Phase 3	Not approved yet.
ERUCOV-VAC	Erciyes University, Turkey	Turkey	Day 0 + 21	IM	Phase 3	Not approved yet.
Name not provided yet.	The Government Pharmaceutical Organization (GPO); PATH; Dynavax	USA	Day 0 + 28	IM	Phase 1/2	Not approved yet.
Name not provided yet.	KM Biologics Co., Ltd	China	Day 0 + 28	IM	Phase 1/2	Not approved yet.
FAKHRVAVAC (MIVAC)	Organization of Defensive Innovation and Research	Iran	Day 0 + 14 + /- 21	IM	Phase 1	Not approved yet.
Koçak-19	Kocak Farma, Turkey	Turkey	Day 0 + 21	IM	Phase 1	Not approved yet.
Name not provided yet.	The Scientific and Technological Research Council of Turkey (TUBITAK)	Turkey	Day 0 + 21	IM	Phase 1	Not approved yet.
Name not provided yet.	Laboratorio Avi-Mex	Mexico	Day 0 + 21	IM or IN	Phase 1	Not approved yet.
B) Live Attenuated Vaccines						
COVI-VAC	Codagenix/Serum Institute of India	India	Day 0 or Day 0 + 28	IN	Phase 1	Not approved yet.
MV-014-212	Meissa Vaccines, Inc.	USA	Day 0	IN	Phase 1	Not approved yet.

As depicted on Table 1, there are at least 19 whole virus COVID-19 vaccines or vaccine candidates that are registered in clinical trials.³⁴ While nine of these inactivated vaccines are approved for general or emergency use in several countries, the development process of remaining vaccines are continuing in different stages of clinical trials.

Coronovac is a propiolactone inactivated SARS-CoV-2 vaccine. The inactivated virus was isolated from a patient in the Jinyintan Hospital in Wuhan. (CN02 strain) The virus was cultivated in a qualified Vero cell line for propagation.^{31–33} In the Phase 1 and 2 clinical trials, the vaccine-induced neutralizing antibodies in 100% of vaccine recipients.^{42,43} There were no severe adverse reactions reported in any of the groups. Phase 3 clinical trials started in July 2020. The interim results of Phase 3 clinical trial in Turkey have been published showing an efficacy of 83.5%. Sinovac announced that the vaccine has an efficacy rate of 50.65% for all cases (83.70% for cases requiring medical treatment, and 100.00% for hospitalized, severe, and fatal cases). There were no serious adverse events related to vaccination.^{44,45} China approved the vaccine for general use in February 2021. More recent reports have alluded to lower efficacy of this vaccine.

BBIBP-CorV and *WIBP-CorV* are propiolactone inactivated SARS-CoV-2 vaccines. The inactivated virus was isolated from a patient in the Jinyintan Hospital in Wuhan. (HB02 and WIV04 Strains). The vaccine viruses were cultivated in qualified Vero cell lines for propagation. In the Phase 1 and 2 clinical trials, a robust humoral immune response was observed in 100% of vaccine recipients.^{46,47} All adverse reactions were mild or moderate in severity. No serious adverse events were reported within 28 days post vaccination for all cohorts. The Phase 3 clinical trials have been launched with these results. The interim results of the Phase 3 clinical trial in the United Arab Emirates and Bahrain, have been published showing an efficacy of 78.1% for *BBIBP-CorV* and 72.8% for *WIBP-CorV*.⁴⁸ Sinopharm CNGB announced that the vaccine has an efficacy rate of 79.34%.³⁹ China approved the vaccine for general use in December 2020.

BBV152 or *Covaxin* is a whole-virion inactivated SARSCoV-2 vaccine designed by Bharat Biotech International Limited. It has been designed with 2 adjuvant forms, using aluminum (Algel) or an imidazoquinoline molecule, which is a toll-like receptor (TLR) 7/8 agonist absorbed to aluminum (Algel-IMDG). In the Phase 1 clinical trial, 375 participants have been enrolled. *BBV152-Covaxin* elicited efficient SARS-CoV-2 neutralizing antibody titers and T cell responses.⁴⁹ Local and systemic side effects were mild or moderate and were more frequent after the first dose. Only 1 serious adverse event (Viral Pneumonitis) has been reported, which was not related to the vaccine. In the Phase 2 clinical trial, 380 participants were enrolled.⁵⁰ This study showed that *BBV152-Covaxin* has elicited high levels of neutralizing antibodies that remained elevated in all participants 3 months after the second vaccination. No serious adverse events were reported in this study. Phase 3 clinical trials started in December 2020 with these results. The results of this trial have not been published yet. The Indian Government granted

emergency use authorization in January 2021. Bharat Biotech International Limited announced interim Phase 3 clinical trial results of 25,800 participants that showed that *BBV152-Covaxin* demonstrated 81% efficacy and severe, serious and medically attended adverse events occurred in low levels and were similar between vaccine and placebo groups.

Minhai (KCONVAC), *Institute of Medical Biology Chinese Academy of Medical Sciences (IMBCAMS) COVID-19 vaccine*, *QazCovid-in®* and *COVIran Barakat* are inactivated virus vaccines that are developed by China, Kazakhstan and Iran respectively. China approved *Minhai* in May 2021 and *IMBCAMS* vaccine in June 2021 for emergency use. *QazCovid-in®* has been approved by Kazakhstan for emergency use in April 2021. Iran approved the *COVIran Barakat* for emergency use in June 2021. Although these vaccines are registered in WHO vaccine tracker and *clinicaltrials.gov*, the results of these clinical trials for individual vaccines have not been published. *CoviVac* is another inactivated virus vaccine produced by the Chumakov Centre at the Russian Academy of Sciences. There is no mention of it at *clinicaltrials.gov*, the US Centers for Disease Control and Prevention, or the WHO's vaccine tracker for *CoviVac*, but Russia approved *CoviVac* for emergency use in February 2021.^{51–57}

Viral Vector Vaccines

Viral vector vaccines are based on live recombinant virus vectors that are either replicating or non-replicating. The non-replicating vector virus cannot replicate because the key genes of the vector virus have been disabled. Although, many different viral vectors are under investigation, non-replicating adenovirus (Ad) vectors are the most commonly employed viral vectors. Following the entry of the vector virus into the host cells, the viral vector integrates its genomic code into the host cell nucleus. Upon integration, the S protein antigen is produced by the host cell itself. These expressed antigens generate strong humoral and cellular immune responses without the need of an adjuvant. Since viral vectors are common pathogens in nature, pre-existing immunity against the vector can reduce the effectiveness of these vaccines. For this reason, the vector strains that exhibit lower seroprevalence in humans (eg chimpanzee Ad, Ad5 and Ad26) are generally selected for vaccine development. In replicating vector virus vaccines, the vector virus has been attenuated to lose its pathogenic capacity and modified to carry SARS-CoV-2 genes, but it remains able to replicate in infected cells. Example of viruses that are used for replicating vector virus vaccines are lentivirus (LV), influenza virus (IFV), measles virus (MV), modified vaccinia Ankara virus (MVA), vesicular stomatitis virus (VSV) and Newcastle disease virus (NDV). Due to the replicative potential of these vaccine viruses, they are highly immunogenic and generate robust humoral and cellular-specific immunity. Their use in intranasal formulations may produce better IgA formation and prevention of asymptomatic carriage. Given that they contain live viruses, there is a risk of disease in immunocompromised individuals with their use. The production of viral

Table 2. Current Viral Vector COVID-19 Vaccines in Clinical Trials

Vaccine	Developer	Country	Schedule	Route	Clinical Evaluation	Status of Approval
A) Non-Replicating Viral Vector Vaccines						
AZD1222 (ChAdOx1-S)	AstraZeneca + University of Oxford	United Kingdom	Day 0 + 28	IM	Phase 4	Approved
Convidecia	CanSino Biological Inc./Beijing Institute of Biotechnology	China	Day 0	IM	Phase 4	Approved
Ad26.COVS.2.S	Janssen Pharmaceutical	USA	Day 0 or Day 0 + 56	IM	Phase 4	Approved
Sputnik V	Gamaleya Research Institute ; Health Ministry of the Russian Federation	Russia	Day 0 + 21	IM	Phase 3	Approved
GRAd-COV2	ReiThera + Leukocare + Univercells	Italy	Day 0	IM	Phase 2/3	Not approved yet.
AZD2816	AstraZeneca + University of Oxford	UK	Day 0 + 28	IM	Phase 2/3	Not approved yet.
DeINSI-2019-nCoV-RBD-OPT1	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	China	Day 0 + 28	IN	Phase 2	Not approved yet.
LV-SMENP-DC	Shenzhen Geno-Immune Medical Institute	China	Day 0	SC & IV	Phase 1/2	Not approved yet.
Human Adenovirus Type 5	ImmunityBio, Inc	USA	Day 0 + 21	SC or Oral or SL	Phase 1/2	Not approved yet.
AdCLD-CoV19	Cellid Co., Ltd	South Korea	Day 0	IM	Phase 1/2	Not approved yet.
NDV-HXP-S	Institute of Vaccines and Medical Biologicals, Vietnam	Vietnam	Day 0 + 28	IM	Phase 1/2	Not approved yet.
MVA-SARS-2-ST	German Center for Infection Research	Germany	Day 0 + 28	IM	Phase 1	Not approved yet.
VXA-CoV2-1	Vaxart	USA	Day 0 + 28	Oral	Phase 1	Not approved yet.
MVA-SARS-2-S	University of Munich	Germany	Day 0 + 28	IM	Phase 1	Not approved yet.
COH045I (MVA-SARS-2-S)	City of Hope Medical Center + National Cancer Institute	USA	Day 0 + 28	IM	Phase 1	Not approved yet.
BBV154	Bharat Biotech International Limited	India	Day 0	IN	Phase 1	Not approved yet.
Chad-68 and SAM	Gritstone Oncology	USA	Day 0 + 14 + 28 or Day 0 + 28 + 56 or Day 0 + 112	IM	Phase 1	Not approved yet.
SC-Ad6-1	Tetherex Pharmaceuticals Corporation	USA	Day 0 + /- 21	IM	Phase 1	Not approved yet.
CVXGA1-001	CyanVac LLC	USA	Day 0	IN	Phase 1	Not approved yet.
B) Replicating Viral Vector Vaccines						
Covid-19/aAPC	Shenzhen Geno-Immune Medical Institute	China	Day 0 + 14 + 28	SC	Phase 1	Not approved yet.
rVSV-SARS-CoV-2-S	Israel Institute for Biological Research	Israel	Day 0	IM	Phase 1/2	Not approved yet.
AV-COVID-19	Avita Biomedical, Inc. National Institute of Health Research and Development, Ministry of Health Republic of Indonesia	Indonesia	Day 0	IM	Phase 1/2	Not approved yet.

vector vaccines requires different cellular systems for high yield propagation. Great care must be taken to keep cell cultures free of any contaminating material during their production.^{35–41}

As illustrated on Table 2, there are at least 22 viral vector COVID-19 vaccines or vaccine candidates that are registered in clinical trials.³⁴ While four of these inactivated vaccines are approved for general or emergency use in several countries, the development process of the remaining vaccines is continuing in different stages of clinical trials.

Non-replicating viral vector vaccines. *ChAdOx1-S*, currently named as *AZD1222*, employs an Adenovirus derived from the chimpanzee. The use of a chimpanzee vector minimizes the possibility of interaction with preformed antibodies against adenoviruses. While the E1 deletion blocks the viral replication, the E3 deletion enables incorporation of larger genetic cargo into the viral vector. The added sequence encodes for the full-length S protein with a tissue plasminogen activator signal sequence. The S protein sequence is codon-optimized.^{31–33} In the Phase I clinical trial, the results showed no severe side effects with efficient humoral and cellular immune responses.^{58,59} On the basis of these results, they launched Phase 2-3 trials. In a recent interim analysis of Phase 2-3 trials, the outcomes of 11,636 from 23,848 enrolled participants have been published.^{60,61} Overall vaccine efficacy has been reported as 70.4%. Interestingly, while the efficacy in participants who received two standard doses was 62.1%, the efficacy in participants who received a low dose followed by a standard dose was 90.0%. In a 74,341 person/months of safety follow-up, 175 severe adverse events have been observed in 168 participants, 84 events in the AZD1222 group and 91 in the control group. However, only 3 events were initially considered to be vaccine related. These events were: a case of transverse myelitis in vaccine group that the independent neurological committee considered the most likely diagnosis to be idiopathic, a case of hemolytic anemia in the control group, and an individual who recorded fever higher than 40 °C, but who recovered rapidly without an alternative diagnosis and was not admitted to hospital and remains masked to group allocation. There were four non-COVID-19 deaths reported across the studies (three in the control arm and one in the AZD1222 arm) that were all considered unrelated to the vaccine.

Convidecia is another non-replicating adenoviral (Ad5) vector vaccine encoding for the full-length S protein. The vaccine gene was derived from the Wuhan-Hu-1 sequence for SARS-CoV2. Similar to the AZD1222 vaccine, the gene of the vaccine contains E1 and E3 deletions with a tissue plasminogen activator signal sequence.^{31–33} In the Phase 1 dose-escalation trial, 108 participants have reported high levels of neutralizing antibody titers with specific T cell responses. No serious adverse events have been reported.⁶² In the Phase 2 trial, 508 participants were included. In this trial *Convidecia* induced significant immune responses and no serious adverse events reported.⁶³ The Phase 3 clinical trials have been launched with these results. The results of this trial have not been published yet. CanSino Biologics announced

that the vaccine has an efficacy rate of 65.28%. China approved the vaccine for general use in February 2021.

Ad26.COV2.S is a recombinant non-replicating viral vector vaccine that uses adenovirus serotype 26 (Ad26). The vector encodes a full length and stabilized SARS-CoV-2 S protein. The vaccine gene was derived from the first clinical isolate of Wuhan strain.^{31–33} The safety and efficacy have been studied in 805 participants in Phase 1 and 2 clinical trials.⁶⁴ In these trials, regardless of vaccine dose or age group, neutralizing antibody titers against the wild-type virus were detected in 90% or more of all participants with accompanying T cell responses.

The results of Phase 3 clinical trials have been published.⁶⁵ In January 2021, Johnson & Johnson announced that the efficacy of their vaccine is 72% in the USA, 64% in South Africa and 61% in Latin America. The local and systemic adverse events were mostly mild or moderate. Severe adverse events have been reported in 83 of vaccine recipients (N = 21,895) and 96 of placebo recipients (N = 21,888). A numerical imbalance for venous thromboembolic events (11 in the vaccine group vs 3 in the placebo group) were observed. Deep venous thrombosis has been reported in 6 of the vaccine recipients and 2 of the placebo recipients. Pulmonary embolism has been reported in 4 of the vaccine recipients and 1 of the placebo recipients. Transverse sinus thrombosis has been reported in 1 of the vaccine recipients and none of the placebo recipients. Seizures have been reported in 4 of the vaccine recipients and 1 of the placebo recipients. Tinnitus has been reported in 6 of the vaccine recipients and none of the placebo recipients. For these imbalances, no causal relationship can be determined. Three deaths were reported in the vaccine group and 16 in the placebo group, all of which were considered by the investigators to be unrelated to the trial intervention. No deaths related to COVID-19 were reported in the vaccine group, whereas 5 deaths related to COVID-19 were reported in the placebo group. Transverse sinus thrombosis with cerebral hemorrhage and a case of Guillain-Barré syndrome were each seen in 1 vaccine recipient. In the light of these findings, the United States Food and Drug Administration (FDA) issued an emergency use authorization in February 2021.

Sputnik V is an adenovirus-based vaccine combining two adenoviruses, rAd5 and rAd26 designed by the collaboration of the Gamaleya Research Institute with the Health Ministry of the Russian Federation.^{31–33} Both have been developed as frozen and lyophilized formulations. In the Phase 1 clinical trial, the vaccine showed high efficacy with a low side effect profile. The most common side effects were pain at the injection site, hyperthermia, headache, fatigue and muscle/joint pain. These adverse events were mostly mild, and no serious adverse events reported.⁶⁶ The Phase 3 clinical trial involved 21,977 participants, showing a vaccine efficacy of 91.6%.⁶⁷ While most reported adverse events were grade 1, 45 of 16,427 participants in the vaccine group and 23 of 5435 participants in the placebo group had serious adverse events. None of these were considered to be associated with vaccination by the independent data monitoring committee. Four deaths were

reported during the study period. Three participants (1 death is due to thoracic vertebral fracture, 2 deaths are due to COVID-19 infection) were in the vaccine group, 1 participant (due to hemorrhagic stroke) in the placebo group. None of the deaths are considered to be vaccine related. Russia approved Sputnik V in August 2020.

GRAd-COV2 is a replication defective Simian Adenovirus (GRAd) vaccine candidate from Italy, that is derived from a gorilla, encoding full length profusion stabilized S protein for SARS-CoV-2. It has a genome deleted of the entire E1 and E3 regions and the native E4 region replaced with the E4 orf6 of human Ad5 (hAd5).⁶⁸ The clinical trial results have not been published yet, but ReiThera Srl announced that its vaccine candidate is well tolerated and induced a clear immune response in Phase 1 clinical trial. The Phase 2/3 clinical trials are ongoing for this vaccine candidate.⁶⁹

AZD2816 is a viral vector vaccine that is developed by AstraZeneca company in the UK. It is designed using the same adenoviral vector platform as *AZD1222*, with minor genetic alterations to the spike protein based on the Beta (B.1.351, South African) variant. The vaccine candidate is currently being evaluated in Phase 2/3 clinical trials.⁷⁰

DelNS1-2019-nCoV-RBD-OPT1 is a non-replicative viral vector vaccine candidate from China, that uses influenza virus as the vaccine platform. It is applied through an intranasal route. The NS1 gene segment of the virus is knocked out so that the virus can only multiply one round inside the cell at the upper airway and will not disseminate inside the body. In the empty space of the NS1 gene, the surface S protein receptor binding domain (RBD) of COVID-19 applied which makes it a safe mucosal vaccine platform.^{71–73} The clinical trial results have not been published yet. The vaccine candidate is under investigation in Phase 2 clinical trials.⁷⁴

LV-SMENP-DC is developed by Shenzhen Geno Immune Medical Institute in China. It is made by modifying dendritic cells (DCs) with LV vectors expressing COVID-19 minigene (SMENP) and immune modulatory genes. The antigen-specific cytotoxic T lymphocytes (CTLs) will be activated by LV-DC presenting COVID-19 specific antigens. Currently, Phase 1/2 clinical trials are ongoing for this vaccine candidate.⁷⁵

Human Adenovirus Type 5 vaccine candidate (hAd5 S+N bivalent vaccine) is a second-generation viral-vector vaccine that is developed by ImmunityBio, Inc in USA. It is targeting both S and N SARS-CoV-2 proteins to generate B and T cell memory to these antigens and, potentially, long-term immunity to the virus.⁷⁶ The hAd5 vaccine platform was developed to elicit anti-SARS-CoV-2 immune responses even in Ad-immune individuals, meaning subjects can receive the vaccine multiple times. The stimulation of anti-hAd5 immune responses is attenuated with the second-generation platform in comparison with the first-generation platforms due to additional genetic deletions. Phase 1 studies of subcutaneous dosing in the US have demonstrated no serious adverse events and potent T-cell responses after a single prime dose. In addition, a single prime subcutaneous vaccination with this vaccine candidate induced a 10-fold increase in T cell response—equivalent

to T cell responses from patients previously infected with SARS-CoV-2. The Phase 1/2/3 trial is planned to study the efficacy, safety, and immunogenicity of this vaccine as a booster in participants who have already received a S-only antibody-based vaccine. Finally, hAd5 vaccine candidate has been developed in four formulations for different routes of administration: SC injection, (sublingual) SL drops, intranasal spray, and a room-temperature-stable oral capsule that could potentially overcome the cold-chain distribution hurdles affecting many current COVID-19 vaccines. The vaccine candidate is currently being evaluated in Phase 1/2 clinical trials.⁷⁷

AdCLD-CoV19 is a replication-defective human adenovirus type 5/35 vector based vaccine developed by Cellid Co., Ltd in South Korea. The vaccine candidate is under investigation in Phase 1/2 clinical trials.⁷⁸

NDV-HXP-S (known as ButanVac in Brazil, COVIVAC in Vietnam, HXP-GPOVac in Thailand, Patrial in Mexico) is a NDV vector expressing membrane-anchored pre-fusion-stabilized trimeric S protein of SARS-CoV-2, with or without the adjuvant CpG 1018. CpG 1018 is a TLR 9 agonist adjuvant.^{79,80} Unlike the vaccines that are already in use, NDV-HXP-S can be produced using chicken eggs similar to flu vaccine production, making it simpler to manufacture, especially for middle-and-low-income countries. The vaccine candidate is under investigation in Phase 1/2 clinical trials.⁸¹

MVA-SARS-2-ST is developed by the German Center for Infection Research in Hamburg, is a vector vaccine candidate based on MVA virus. The vector expresses a stabilized SARS-CoV-2 S protein. The results of the Phase I clinical trial showed that the vaccines are safe and well tolerated—however, the immune responses were below expectations. For this reason, the Phase 2 trial planned for early 2021 was postponed. With an optimized vaccine, the vaccine candidate is under evaluation in Phase 1 trial.⁸²

VXA-CoV2-1 is an oral COVID-19 vaccine that is developed by Vaxart company in USA. It is formulated as tablets that are enteric coated for efficient delivery to the small bowel. The enteric coating protects the active ingredient from the stomach's acidic environment. While traditional injectable vaccines work by inducing a strong IgG response in the blood, oral vaccines induce an IgA response in the GI and respiratory tracts with some IgG responses in the blood as well. This is important in reducing viral shedding and preventing transmission. Vaxart's vaccine platform uses a non-replicating adenovirus type 5 (Ad5) vector that delivers the antigen. The antigen in VXA-CoV2 is composed of the genes coding for both the SARS-CoV-2 S protein and the N protein. VXA-CoV2-1 is one of the first COVID-19 vaccine candidates that contains genes for both proteins. This is important because the mutations that occur in S protein may decrease the efficacy of vaccines. The N protein is largely conserved between emerging strains of the SARS-CoV2 and may provide long-term immunity through vaccinations. Vaxart also announced that they are working on a S-only vaccine which targets specifically variant strains. VXA-CoV2-1 also uses a TLR-3 agonist, as an adjuvant that activates the innate immune system. The results of clinical

studies have not been published yet, but Vaxart announced that their vaccine candidate was safe and effective.^{83,84} The vaccine candidate is currently being evaluated in Phase 1 clinical trials.⁸⁵

MVA-SARS-2-S, is a vaccine candidate that uses a MVA virus as a vector. It is developed by the University of Munich in Germany. MVA is a highly attenuated strain of vaccinia virus originating from growth selection on chicken embryo tissue cultures, showing a characteristic replication defect in mammalian cells, and allows unimpaired production of heterologous proteins. MVA is a weakened poxvirus approved by the U.S. Food and Drug Administration for the prevention of smallpox and monkeypox.⁸⁶ The vaccine candidate is under investigation in Phase 1 clinical trials.⁸⁷

COH04S1 (MVA-SARS-2-S) is based on a synthetic MVA (sMVA) platform. It is developed by the City of Hope Medical Center in California. The vaccine candidate contains the SARS-CoV-2 S and N proteins inserted into the MVA platform. MVA can replicate DNA within cells, leading to the expression of SARS-CoV-2 proteins in order to trigger host immunity against the virus. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.⁸⁸

BBV154 is an intranasal vaccine candidate that is developed by Bharat Biotech in India. It uses a non-replicating Ad5 vector platform to present S protein antigen to the immune system. Similar with other mucosal vaccines, it stimulates a broad immune response including neutralizing IgG, mucosal IgA, and T cell responses.⁸⁹ Currently, the vaccine candidate is under investigation in Phase 1 clinical trials.⁹⁰

Chimpanzee Adenovirus serotype 68 (ChAd) and self-amplifying mRNA (SAM); Gritstone Oncology is working on a different vaccine platform. In this platform, Chimpanzee Adenovirus serotype 68 (ChAd) and SAM vectors are used, which express either S alone or S plus additional SARS-CoV-2 T cell epitopes. This vaccine candidate is under investigation in Phase 1 clinical trials.⁹¹

SC-Ad6-1 is developed by Tetherex Pharmaceuticals Corporation in Oklahoma, USA. It is a novel single-cycle adenovirus vector (SC-Ad) expressing the SARS-CoV-2 S protein. The SC-Ad6-1 vector undergoes replication in the initial cells that it enters but lacks the genetic information to form infectious particles. Therefore, SC-Ad6-1 utilizes the potency of a replication competent adenovirus vector but does not have the capacity to cause adenovirus infections in patients and/or personnel through the formation of infectious particles. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.⁹²

CVXGAI-001 is developed by CyanVac LLC company in USA. It is a viral vector vaccine that uses Parainfluenza Virus Type 5 (PIV5) as the vector which encodes the SARS-CoV-2 S protein. It is administered intra-nasally. The vaccine candidate is under investigation in Phase 1 clinical trials.⁹³

Replicating viral vector vaccines. *Covid-19/aAPC* vaccine is developed by Shenzhen Geno-Immune Medical Institute in China. The COVID-19/aAPC vaccine is prepared by applying LV modification with immune modulatory genes and the viral

mini-genes to the artificial antigen presenting cells (aAPCs). The COVID-19/aAPCs are then inactivated for proliferation and safety is extensively tested. The vaccine candidate is under investigation in Phase 1 clinical trials.⁹⁴

rVSV-SARS-CoV-2-S vaccine is developed by Israel Institute for Biological Research in Ness Ziona. The replication competent recombinant VSV- Δ G-spike vaccine, in which the glycoprotein of VSV is replaced by the S protein of SARS-CoV-2.^{95,96} The VSV can be easily propagated and reaches high titers and most of the general population is seronegative for VSV. Currently the vaccine candidate is under investigation in Phase 1/2 clinical trials.⁹⁷

AV-COVID-19, developed by Aivita Biomedical, Inc, is a dendritic cell (DC) vaccine. It is created by using AIVITA's autologous cell therapy platform. In this vaccine platform, autologous DCs are extracted and loaded with multiple recombinant SARS-CoV-2 S antigens to create a vaccine that is specific to each individual. These cells are re-administered to the individual, with or without GM-CSF, to create fast immune protection against the coronavirus. A kit containing all materials is provided to local sites, which can carry out steps with minimal equipment, to de-centralize manufacturing even in a third party GLP setting. The vaccine candidate is under investigation in Phase 1/2 clinical trials.⁹⁸

Nucleic Acid Vaccines

Similar to viral vector vaccines, nucleic acid vaccines introduce genetic instructions (mRNA or DNA encoding the target antigen) to host cells for production of disease specific antigens. Once these instructions have been taken by the host cell, the S protein antigen is produced by the host cell itself. The production of these antigens by the host cells effectively elicits both antibody production and T-cell induction, which are important parameters of vaccine protection. The mRNA vaccine technology consists of artificial synthesis of the mRNA sequence of the SARS-CoV-2 that encodes the S protein. Incorporation of lipid nanoparticles (LNP) into mRNA vaccines protects them from enzymatic degradation and ensures efficient cellular uptake. Following the cellular uptake, mRNA vaccines induce a prompt antigen expression, and the expressed antigens generate both humoral and cellular immune responses. When it is compared to other vaccine platforms, the production of mRNA vaccines has less biosafety concerns, making them faster to produce. However, they require ultra-cold conditions for long-term storage.³⁵⁻⁴¹

DNA vaccines use plasmids for this purpose. They generally depend on cloning the SARS-CoV-2 S gene into bacterial plasmids that contain a strong mammalian promoter, such as CMV and/or SV40, followed by large plasmid production in a competent bacterium. The advantages of plasmid DNA vaccines are that they can target and stimulate both humoral and cellular immune responses, they allow for flexible and simple large-scale production and formulation processes over short periods of time, and they offer flexibility for multivalency and room-temperature storage of the final vaccine. However, because of

Table 3. Current Nucleic Acid COVID-19 Vaccines in Clinical Trials

Vaccine	Developer	Country	Schedule	Route	Clinical Evaluation	Status of Approval
A) RNA Vaccines						
BNT162b2	Pfizer/BioNTech + Fosun Pharma	USA—Germany	Day 0 + 21	IM	Phase 4	Approved
mRNA-1273	Moderna + National Institute of Allergy and Infectious Diseases	USA	Day 0 + 28	IM	Phase 4	Approved
mRNA-1273.351	Moderna + National Institute of Allergy and Infectious Diseases	USA	Day 0 or Day 0 + 28 or Day 56	IM	Phase 4	Not approved yet.
CVnCoV	CureVac AG	Germany	Day 0 + 28	IM	Phase 3	Not approved yet.
ARCoV	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	China	Day 0 + 14 or Day 0 + 28	IM	Phase 3	Not approved yet.
mRNA-1273.211	Moderna TX, Inc.	USA	Day 0	IM	Phase 2/3	Not approved yet.
ARCT-021	Arcturus Therapeutics	USA—Singapore	ND	IM	Phase 2	Not approved yet.
MRT5500	Sanofi Pasteur and Translate Bio	France—USA	Day 0 + 21	IM	Phase 2	Not approved yet.
DS-5670a	Daiichi Sankyo Co., Ltd	Japan	Day 0 + 21	IM	Phase 1/2	Not approved yet.
EXG-5003	Elixigen Therapeutics, Inc	USA	Day 0	ID	Phase 1/2	Not approved yet.
LNP-nCoVsaRNA	Imperial College London	United Kingdom	ND	IM	Phase 1	Not approved yet.
ChulaCov19 mRNA vaccine	Chulalongkorn University	Thailand	Day 0 + 21	IM	Phase 1	Not approved yet.
PTX-COVID19-B	Providence Therapeutics	Canada	Day 0 + 28	IM	Phase 1	Not approved yet.
CoV2 SAM	GlaxoSmithKline	United Kingdom	Day 0 + 30	IM	Phase 1	Not approved yet.
HDT-301	SENAI CIMATEC	Brasil	Day 0 + 28	IM	Phase 1	Not approved yet.
mRNA-1283	Moderna TX, Inc.	USA	Day 0 + 28	IM	Phase 1	Not approved yet.
mRNA COVID-19 vaccine	Shanghai East Hospital and Stemirna Therapeutics	China	TBD	IM	Phase 1	Not approved yet.
LNP-nCOVsaRNA-02	MRC/UVRI and LSHTM Uganda Research Unit	United Kingdom	Day 0 + 28	IM	Phase 1	Not approved yet.
B) DNA Vaccines						
ZyCoV-D	Zyodus Cadila	Israel	Day 0 + 28 + 56	ID	Phase 3	Not approved yet.
AG0301-COVID19	AnGes + Takara Bio + Osaka University	Japan	Day 0 + 14	IM	Phase 2/3	Not approved yet.
INO-4800	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	USA	Day 0 + 28	ID	Phase 2/3	Not approved yet.
GX-19N	Genexine Consortium	South Korea	Day 0 + 28	IM	Phase 1/2	Not approved yet.
GLS-5310	GeneOne Life Science, Inc.	South Korea	Day 0 + 56 or Day 0 + 84	ID	Phase 1/2	Not approved yet.
AG0302-COVID19	AnGes, Inc	Japan	Day 0 + 14 + 28	IM	Phase 1/2	Not approved yet.
COVID-eVax	Takis + Rottapharm Biotech	Italy	Day 0 + 28	IM or	Phase 1/2	Not approved yet.
Covigenix VAX-001	Entos Pharmaceuticals Inc.	Canada	Day 0 + 14	IM	Phase 1	Not approved yet.
CORVax	Providence Health & Services	USA	Day 0 + 14	ID	Phase 1	Not approved yet.
bacTRL-Spike	Symvivo Corporation	Canada	Day 0	Oral	Phase 1	Not approved yet.
COVIGEN	University of Sydney, Bionet Co., Ltd Technovalia	Australia	Day 0 + 28	ID or IM	Phase 1	Not approved yet.

their low immunogenicity in humans, they require several doses for optimum protection. Long-term risk of carcinogenesis is another concern for DNA vaccines due to integration of plasmid DNA to the host cell.^{35–41}

As shown on Table 3, there are at least 29 nucleic acid COVID-19 vaccines or vaccine candidates that are registered in clinical trials.³⁴ While two of these vaccines are approved for general or emergency use in several countries, the developmental processes of remaining vaccines are continuing in different stages of clinical trials.

mRNA vaccines. *BNT162b2* is a LNP formulated, nucleoside-modified messenger RNA (mRNA) vaccine, which encodes the RBD of the S1 protein. The RBD is constructed on a T4-fibrin derived fold on trimerization base, which helps to guide antigen folding into the native trimeric state. The N-methyl pseudo-uridine (m1Ψ) nucleoside modification protects it from innate immunity. It is encapsulated with an LNP that protects it from enzymatic degradation and ensures efficient cellular uptake.^{31–33} In the Phase 1 clinical trial, BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers with robust T cell responses. In addition, side effects were also acceptable, which were mainly composed of short-term local (ie, injection site) and systemic responses.⁹⁹

In the Phase 3 clinical trial, a total of 43,448 participants were enrolled: 21,720 receiving BNT162b2 and 21,728 receiving the placebo.¹⁰⁰ A two-dose regimen of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older. Local reactions were common and included pain, erythema and swelling at injection sites. Transient systemic reactions such as fever, fatigue, headache, and muscle and joint pain were also noted. The number of serious adverse events that were reported were similar, showing 126 (0.6%) serious adverse events reported in the vaccine group and 111 (0.5%) serious adverse events in the placebo group. Only four serious adverse events (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia) can be related with BNT162b2. During follow-up, two BNT162b2 recipients (one from arteriosclerosis, one from cardiac arrest), and four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction) have died. No deaths were considered to be related to the vaccine or placebo.

The mRNA-1273 is another mRNA vaccine approved for use. It is developed by Moderna Company in USA. It encodes the pre-fusion form of the S antigen that includes a transmembrane anchor and an intact S1–S2 cleavage site. Two proline substitutions in the vaccine mRNA keep the protein stable in its perfusion conformation. It is also encapsulated with an LNP. In the Phase 1 dose escalation clinical trial, mRNA-1273 showed encouraging results in safety and immunogenicity.¹⁰¹

In the Phase 3 trials, 30,420 volunteers were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). The efficacy has been reported as 94.1% for the prevention of symptomatic

SARS-CoV-2 infection and 100% for preventing severe COVID-19 as compared with placebo. Although transient local and systemic reactions were higher in the vaccine recipients, the frequency of unsolicited adverse events, unsolicited severe adverse events, and serious adverse events reported during the study period were generally similar among participants in the two groups. Three deaths occurred in the placebo group: (one from intra-abdominal perforation, one from cardiopulmonary arrest, and one from severe systemic inflammatory syndrome in a participant with chronic lymphocytic leukemia and diffuse bullous rash) and two in the vaccine group (one from cardiopulmonary arrest and one by suicide).¹⁰²

The mRNA-1273.351 is another mRNA vaccine that is developed by Moderna company. It is an LNP-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2 B.1.351 variant. The vaccine candidate is currently being evaluated in Phase 2 clinical trials.¹⁰³

The mRNA-1273.211 is a multivalent booster vaccine candidate developed by Moderna company. The mRNA-1273.211, which combines mRNA-1273 and mRNA-1273.351 in a single vaccine. The vaccine candidate is currently being evaluated in Phase 2/3 clinical trials.¹⁰⁴

mRNA-1283 is another vaccine candidate that is developed by Moderna company in Massachusetts, USA. It is designed as a refrigerator-stable mRNA vaccine to ease the distribution, handling, and administration of vaccination programs, especially in developing countries. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.¹⁰⁵

CVnCoV is an mRNA vaccine candidate developed by CureVacs in Tübingen, Germany. It is composed of mRNA nucleotides which expresses the full-length S protein and formulated with LNPs. CureVacs has announced that CVnCoV remains stable for at least three months when stored at a standard refrigerator temperature and for up to 24 hours as ready-to-use vaccine when stored at room temperature.¹⁰⁶ CureVacs announced the final data from the Phase 2b/3 clinical trial showed an overall vaccine efficacy of 48% against COVID-19 of any severity across all age groups and 15 variants. The efficacy was 53% against disease of any severity, 77% against moderate and severe disease and 100% against hospitalization or mortality. The vaccine candidate is currently under investigation in Phase 3 clinical trials.¹⁰⁷

ARCoV is a LNP-encapsulated mRNA vaccine candidate from China that encodes the RBD of SARS-CoV-2. In preclinical studies with mice and primates, it has been shown that immunization with ARCoV triggers potent T cell mediated immune response and neutralizing antibodies against COVID-19. It is manufactured as a liquid formulation and can be stored at room temperature for at least 1 week.¹⁰⁸ ARCoV is currently being evaluated in Phase 3 clinical trials.¹⁰⁹

ARCT-021 is a mRNA vaccine candidate developed by Arcturus Therapeutics in California. It combines self-transcribing and replicating mRNA (STARR™) with LUNAR® lipid-mediated delivery technology, which is

designed to enhance and extend antigen expression, enabling vaccination at lower doses. Arcturus Therapeutics announced that their vaccine candidate requires up to a 40-fold smaller dose than other mRNA vaccines. Due to this, ARCT-021 is expected to require less manufacturing capacity than other mRNA vaccines. Additionally, it is designed as a single shot, lyophilized, non-viral vector vaccine that may potentially provide an extended variant coverage and can also be used for periodic booster doses. The vaccine candidate is currently being evaluated in Phase 2 clinical trials.¹¹⁰

MRT5500 is developed by Sanofi Pasteur company in Lyon, France and Translate Bio company in Massachusetts, USA. It is an mRNA vaccine candidate with 2P/GSAS, S protein modifications of S protein. In MRT5500's preclinical design, this modification was selected among several mRNA constructs of S protein because it is more effective for immunogenicity and protection from COVID-19.¹¹¹ MRT5500 is currently being evaluated in Phase 2 clinical trials.¹¹²

DS-5670a, is developed by Daiichi Sankyo Co., Ltd in Japan. It is an mRNA vaccine candidate that targets SARS-CoV-2 S protein. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹¹³

EXG-5003 is a temperature-sensitive self-replicating RNA vaccine expressing the RBD of the SARS-CoV-2 S protein. It is optimized for intradermal injection with potential dose-sparing and safety benefits. The vaccine candidate is currently being evaluated in phase 1/2 clinical trials.¹¹⁴

LNP-nCoVsaRNA is developed by Imperial College London in the UK. It is a purified, synthetic mRNA vaccine candidate encoding the S glycoprotein of SARS-CoV-2 virus. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹¹⁵

ChulaCov19 is an mRNA vaccine candidate that is developed by Chulalongkorn University in Thailand. Chulalongkorn University announced that ChulaCov19 can be stored in refrigerators for 3 months and at room temperature for 2 weeks. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.¹¹⁶

PTX-COVID19-B, is an mRNA vaccine candidate that is designed by Providence Therapeutics in Canada. The vaccine candidate encodes a full-length membrane-anchored S protein taken from the Wuhan-Hu-1 isolate with a D614G mutation to match predominant SARS-CoV-2 variant strains in circulation. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹¹⁷

CoV2 SAM is developed by GlaxoSmithKline company in the UK. It is a self-amplifying mRNA (SAM) vaccine candidate that targets the S protein of SARS-CoV2 virus. Similar to other mRNA vaccines, it is coated with an LNP. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.¹¹⁸

HDT-301 is a self-replicating mRNA vaccine candidate from Brazil, formulated with a novel Lipid-Inorganic Nanoparticle (LION™) that encodes for a full-length S protein of the SARS-CoV-2 virus. As a self-replicating mRNA vaccine, it is considered to allow dose sparing and possibly a single dose vaccine in comparison with current mRNA platforms. The

vaccine candidate is currently under investigation in Phase 1 clinical trials.¹¹⁹

COVID-19 mRNA is a vaccine candidate that is developed by Stemirna Therapeutics and Shanghai East Hospital in China. It is a mRNA vaccine that targets the S protein. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹²⁰

LNP-nCOV saRNA-02 is a vaccine candidate that is developed by Imperial College London in the UK. It is a self-amplifying RNA encapsulated in LNPs. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.¹²¹

DNA vaccines. *ZyCoV-D* is a DNA plasmid vector vaccine candidate from Israel, that encodes the S protein of SARS-CoV-2 virus. The vaccine is given as an intra-dermal injection using a spring-powered jet injector. The vaccine candidate is currently being evaluated in Phase 3 clinical trials.^{122,123}

The AG0301—COVID-19 is developed by AnGes Inc. and Osaka University in Japan. It is a plasmid DNA vaccine candidate that targets S protein of COVID-19 virus. The vaccine candidate is currently under investigation in Phase 2/3 clinical trials.¹²⁴

INO-4800 is developed by Inovio Pharmaceuticals in Pennsylvania, USA. It is a nucleic-acid-based vaccine candidate that contains the plasmid pGX9501, which encodes for the entire length of the S glycoprotein of SARS-CoV-2 virus. It is stable at room temperature for more than a year and does not require freezing for transport or storage. Inovio introduced a proprietary hand-held smart device called CELLECTRA®, which uses a brief electrical pulse to open small pores in the cell reversibly to allow the plasmids to enter. This allows an optimal entry of plasmids with DNA into cells and provides a better immune response. The vaccine candidate is currently being evaluated in Phase 2/3 clinical trials.^{125–127}

GX-19N is developed by the Korean biotech company Genexine. It is a DNA vaccine candidate that encodes both S and N proteins of SARS-CoV-2 virus. The vaccine candidate is currently being evaluated in Phase 1/2 clinical trials.¹²⁸

GLS-5310 is a DNA vaccine candidate encoding the S protein and a second antigenic target of SARS-CoV-2. It is developed by GeneOne Life Science, Inc. in South Korea. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹²⁹

AG0302-COVID19 is another DNA vaccine candidate developed by AnGes, Inc in Japan. It encodes the S protein of SARS-CoV-2. The vaccine candidate is currently being evaluated in Phase 1/2 clinical trials.¹³⁰

COVID-eVax, is a plasmid DNA vaccine candidate from Italy. It targets the RBD of S protein. It is administered as an intramuscular injection followed by a short, low voltage, electrical pulse application. The procedure is called Electro-Gene-Transfer (EGT) which allows efficient DNA transfer into the host cells. The vaccine candidate's EGT system is based on a special Cliniporator™ technology which is already available for use in cancer patients in Europe. The

vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹³¹

Covigenix VAX-001 is developed by Entos Pharmaceuticals Inc in Canada. It is a DNA vaccine candidate that uses a proteo-lipid vehicle (PLV) formulation. The vaccine candidate is currently being evaluated in Phase 1 clinical trial.¹³²

CORVax is a S protein plasmid DNA vaccine candidate that is developed by Providence Health & Services in USA. It uses immune stimulant plasmid IL-12 to promote a better immune response against the SARS-CoV-2 virus. *CORVax* is currently under investigation in a Phase 1 clinical trial.¹³³

bacTRL-Spike is an oral DNA vaccine candidate that is developed by Symvivo Corporation in Canada. It is composed of a bacterial medium with colony-forming-units of live *Bifidobacterium longum* which is engineered to deliver synthetic DNA encoding S protein by plasmids. Bacterially mediated delivery of plasmid DNA *bacTRL* product produces, secretes and delivers plasmid DNA to human cells. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.¹³⁴

COVIGEN is a DNA vaccine candidate developed by Technovalia company in Australia. The delivery of the vaccine is via a needle-free device which penetrates the skin with a jet spray. The vaccine candidate is under investigation in Phase 1 clinical trial.¹³⁵

Recombinant Protein Based Vaccines

Subunit vaccines are based on targeting viral protein subunits. Besides the S protein, SARS-CoV-2 has other structural proteins such as membrane (M), envelope (E) and N proteins. Antibodies that target M and E proteins have failed to neutralize the COVID-19 infection. For this reason, these 2 proteins are currently not considered as target antigen for COVID-19 vaccines. On the other hand, N protein is highly immunogenic and induces robust humoral and cellular immune responses. To produce these recombinant protein vaccines, bacterial expression systems represent the most commonly used technique. These vaccines often require multiple doses and effective adjuvants to obtain a robust immune response. As live virus handling is not required, the subunit vaccine manufacturing process is safer and simpler, although manufacturing these vaccines can be difficult for mass vaccinations.³⁵⁻⁴¹ To date, four subunit vaccines are available for use. These are NVX-CoV2373, EpiVacCorona, ZifiVax and FINLAY-FR-2 vaccines.

As depicted on Table 4, there are at least 40 recombinant protein based COVID-19 vaccines or vaccine candidates that are registered in clinical trials.³⁴ To date, four subunit vaccines are approved for general or emergency use in several countries. These are NVX-CoV2373, EpiVacCorona, ZifiVax and FINLAY-FR-2 vaccines. The developmental processes of remaining vaccines are continuing in different stages of clinical trials.

Protein subunit vaccines. *NVX-CoV2373* is a recombinant SARS-CoV-2 (rSARS-CoV-2) nanoparticle vaccine

constructed from the full-length (including the transmembrane domain) and wild-type SARS-CoV-2 S glycoprotein. The vaccine was designed with a special adjuvant called Matrix-M™. Matrix-M™, an adjuvant based on saponin extracted from the *Quillaja saponaria* Molina tree induces high and long-lasting levels of broadly reacting antibodies supported by a balanced TH1 and TH2 type of response. Although the mode-of-action of Matrix-M adjuvant has not been elucidated in detail; the adjuvant promotes rapid and profound effects on cellular drainage to local lymph nodes creating a milieu of activated cells including T cells, B cells, Natural Killer cells, neutrophils, monocytes and DCs. From the previous vaccine studies, it has shown a significant dose-sparing effect and an acceptable safety profile.³¹⁻³³ In the Phase 1-2 clinical trial, participants were enrolled to receive the vaccine or placebo.¹³⁶ At 35 days, NVX-CoV2373 elicited immune responses that exceeded levels in COVID-19 convalescent serum. No serious adverse events were reported. After these results, Phase 3 clinical trials have been launched in many different countries around the world. The results of these trials have been published.¹³⁷ Novavax announced interim Phase 3 clinical trial results in the UK and South Africa in March 2021. The results of these studies showed 100% efficacy in preventing severe disease. The overall efficacy was 96.4%. In both the UK and South Africa trials, the vaccine was well-tolerated, with low levels of severe, serious and medically attended adverse events at day 35, balanced between vaccine and placebo groups. Novavax announced that their vaccine might get authorization by the US FDA in May 2021.

EpiVacCorona is a subunit vaccine containing chemically synthesized peptide immunogens corresponding to selected protective epitopes of SARS-CoV-2 coronavirus S protein, conjugated to recombinant SARS-CoV-2 protein N, as a carrier, adjuvanted with aluminum hydroxide.³¹⁻³³ The Phase 1-2 trials were published in March 2021. In this study, the two-dose vaccination scheme induced the production of antibodies specific to the antigens that make up the vaccine in 100% of the volunteers.¹³⁸ No serious adverse events have been reported. Phase 3 clinical trials were registered in March 2021 and have not been published yet.¹³⁹ Russia approved EpiVacCorona in October 2020. Turkmenistan approved EpiVacCorona in January 2021.

ZifiVax also known as *ZF2001* is a recombinant protein subunit vaccine from China manufactured in the Chinese Hamster Ovary (CHO) cell lines, encoding a dimeric form of the receptor-binding domain of S protein. The vaccine was jointly developed by the Institute of Microbiology, the Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutical. In the Phase 1 and 2 clinical trials, the vaccine showed high efficacy with a low side effect profile.¹⁴⁰ China authorized the emergency use of the vaccine on March 10, 2021. Currently the vaccine candidate is currently being evaluated in Phase 3 clinical trials.¹⁴¹

FINLAY-FR-2 or *Soberana 02* is a COVID-19 vaccine produced by the Finlay Institute, a Cuban epidemiological research institute. It is a conjugate vaccine. It consists of the RBD of the

Table 4. Current Recombinant Protein Based COVID-19 Vaccines in Clinical Trials

Vaccine	Developer	Country	Schedule	Route	Clinical Evaluation	Status of Approval
A) Protein Subunit Vaccines						
NVX-CoV2373	Novavax	USA	Day 0 + 21	IM	Phase 3	Approved
EpiVacCorona	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	Russia	Day 0 + 21	IM	Phase 3	Approved
Zifivax (ZF2001)	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	China	Day 0 + 28 or Day 0 + 28 + 56	IM	Phase 3	Approved
FINLAY-FR-2	Instituto Finlay de Vacunas	Cuba	Day 0 + 28	IM	Phase 3	Approved
VAT00002	Sanofi Pasteur + GSK	France—UK	Day 0 + 21	IM	Phase 3	Not approved yet.
West China Hospital COVID-19 vaccine	West China Hospital + Sichuan University	China	Day 0 + 28	IM	Phase 3	Not approved yet.
CIGB-66	Center for Genetic Engineering and Biotechnology (CIGB)	Cuba	Day 0 + 14 + 28 or Day 0 + 28 + 56	IM	Phase 3	Not approved yet.
Nanocovax	Nanogen Pharmaceutical Biotechnology	Vietnam	Day 0 + 21	IM	Phase 3	Not approved yet.
SCB-2019	Clover Biopharmaceuticals Inc./GSK/Dynavax	Australia—United Kingdom—USA	Day 0 + 21	IM	Phase 2/3	Not approved yet.
UB-612	Vaxxinity	USA	Day 0 + 28	IM	Phase 2/3	Not approved yet.
COVAX-19	Vaxine Pty Ltd/CinnaGen Co.	Australia—Iran	Day 0 + 21	IM	Phase 2	Not approved yet.
MVC-COV1901	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)	China—USA	Day 0 + 28	IM	Phase 2	Not approved yet.
FINLAY-FR1	Instituto Finlay de Vacunas	Cuba	Day 0 + 28	IM	Phase 2	Not approved yet.
Razi Cov Pars	Razi Vaccine and Serum Research Institute	Iran	Day 0 + 21 + 51	IM and IN	Phase 2	Not approved yet.
V-01	Guangdong Provincial Center for Disease Control and Prevention/Gaozhou Center for Disease Control and Prevention	China	Day 0 + 21	IM	Phase 2	Not approved yet.
SCB-2020S	Clover Biopharmaceuticals AUS Pty Ltd	Australia	Day 0 + 21	IM	Phase 2	Not approved yet.
202-CoV; SARS-CoV-2	Shanghai Zerun Biotechnology + Walvax Biotechnology + CEPI	China	Day 0 + 28	IM	Phase 2	Not approved yet.
KBP-COVID-19	Kentucky Bioprocessing Inc.	USA	Day 0 + 21	IM	Phase 1/2	Not approved yet.
CIGB-669	Center for Genetic Engineering and Biotechnology (CIGB)	Cuba	Day 0 + 14 + 28 or Day 0 + 28 + 56	IN	Phase 1/2	Not approved yet.
BECOV2	Biological E. Limited	India	Day 0 + 28	IM	Phase 1/2	Not approved yet.
S-268019	Shionogi	China	Day 0 + 21	IM	Phase 1/2	Not approved yet.
AKS-452	University Medical Center Groningen + Akston Biosciences Inc.	Netherlands—USA	Day 0 + 28	SC or IM	Phase 1/2	Not approved yet.
COVAC-2	University of Saskatchewan	Canada	Day 0 + 28	IM	Phase 1/2	Not approved yet.
GBP510	SK Bioscience Co., Ltd and CEPI	South Korea	Day 0 + 28	IM	Phase 1/2	Not approved yet.
EuCorVac-19	POP Biotechnologies and EuBiologics Co., Ltd	South Korea	Day 0 + 21	IM	Phase 1/2	Not approved yet.
CoVePit	OSE Immunotherapeutics	France	Day 0	IM	Phase 1/2	Not approved yet.
QazCoVac-P	Baghfeiat-allah University of Medical Sciences	Iran	Day 0 + 21	IM	Phase 1/2	Not approved yet.
IMP CoVac-I	University Hospital Tübingen	Germany	Day 0	SC	Phase 1	Not approved yet.
AdimrSC-2f	Adimmune Corporation	Taiwan	ND	ND	Phase 1	Not approved yet.
	The University of Queensland	Australia	Day 0 + 28	IM	Phase 1	Not approved yet.

(continued)

Table 4. (continued)

Vaccine	Developer	Country	Schedule	Route	Clinical Evaluation	Status of Approval
SARS-CoV-2 Sclamp vaccine						
SK SARS-CoV-2 (NBP2001)	SK Bioscience Co., Ltd	South Korea	Day 0 + 28	IM	Phase I	Not approved yet.
Name not provided yet.	Walter Reed Army Institute of Research (WRAIR)					
ReCOV	Jiangsu Rec-Biotechnology	USA	Day 0 + 28 + 180	IM	Phase I	Not approved yet.
CoV2-OGENI	Research Institute for Biological Safety Problems	China	Day 0 + 21	IM	Phase I	Not approved yet.
Baiya SARS-CoV-2 VAX1	Baiya Phytopharm Co., Ltd	Russia	Day 0 + /- 14	Oral	Phase I	Not approved yet.
B) Virus like particle Vaccines						
CoVLP	Medicago Inc.	Thailand	Day 0 + 21	IM	Phase I	Not approved yet.
RBD SARS-CoV-2 HBsAg VLP vaccine	Serum Institute of India + Accelagen Pty + SpyBiotech	Canada	Day 0 + 21	IM	Phase 2/3	Not approved yet.
VBI-2902a		India	Day 0 + 28	IM	Phase 1/2	Not approved yet.
SARS-CoV-2 VLP Vaccine	VBI Vaccines Inc.	Canada	Day 0 + 28	IM	Phase 1/2	Not approved yet.
	The Scientific and Technological Research Council of Turkey	Turkey	Day 0	SC	Phase I	Not approved yet.
ABNCoV2	Radboud University	Netherlands	Day 0 + 28	IM	Phase I	Not approved yet.

SARS-CoV-2 S protein which is conjugated chemically to tetanus toxoid. Iran authorized the emergency use of the FINLAY-FR-2 in June 2021.¹⁴² The vaccine candidate is under investigation in Phase 3 clinical trials.¹⁴³

VAT00002 is a recombinant protein subunit vaccine candidate from France and the UK that is formulated in three forms. While two monovalent forms of the vaccine target either D614 or B.1.351 mutations, the bivalent form targets both mutations. It is developed by Sanofi Pasteur and GSK companies. The vaccine candidate is currently being evaluated in Phase 3 clinical trials.¹⁴⁴

West China Hospital COVID-19 vaccine is a vaccine candidate that is developed by West China Hospital and Sichuan University in China. This vaccine is made by using baculovirus as a vector and expressing SARS-CoV-2 S-RBD in Sf9 cells, which is purified by antigen isolation and added with aluminum hydroxide adjuvant. Insect cell line Sf9 has been shown as an efficient protein expression system with eukaryotic protein folding and modifications.¹⁴⁵ The vaccine candidate is under investigation in Phase 3 clinical trials.¹⁴⁶

CIGB-66 is a recombinant protein-based vaccine from Cuba that targets the RBD of SARS-CoV-2 virus. The vaccine candidate contains aluminum hydroxide as an adjuvant. The vaccine candidate is currently being evaluated in Phase 3 clinical trials.¹⁴⁷

Nanocovax is a subunit vaccine candidate that is developed and manufactured at Nanogen Pharmaceutical Biotechnology in Vietnam. It contains the full-length pre-fusion stabilized recombinant S glycoprotein of SARS-CoV-2 virus and aluminum hydroxide adjuvant.¹⁴⁸ The vaccine candidate is under investigation in Phase 3 clinical trials.¹⁴⁹

SCB-2019 is a recombinant protein-based vaccine from Australia, UK and USA which consists of a trimeric form of the S protein (S-Trimer) formulated with either CpG 1018 with Alum adjuvant or AS03 preparations. CpG 1018 is a TLR9 agonist that increases vaccine efficacy. AS03 is an oil-in-water emulsion adjuvant which is composed of α -tocopherol, squalene and polysorbate 80.¹⁵⁰ The vaccine candidate is currently being evaluated in Phase 2/3 clinical trials.

UB-612 is developed by Vaxxinity company in USA. It targets the S protein of SARS-CoV-2. It can be stored at temperatures between 2 °C-8 °C. The vaccine candidate is under investigation in Phase 2/3 clinical trials.¹⁵¹

COVAX-19 or Spikogen is developed by Vaxine Pty Ltd/ CinnaGen Co from Australia and Iran. It is a monovalent recombinant protein subunit vaccine candidate that targets S protein of the SARS-CoV-2 virus. Currently, this COVID-19 candidate vaccine is being evaluated in Phase 2 clinical trial.^{152,153}

MVC-COV1901 is another protein subunit vaccine candidate from China and USA. It is based on a prefusion SARS-CoV-2 S immunogen with CpG 1018 and aluminum hydroxide serving as adjuvants.^{154,155} The vaccine candidate is currently being evaluated in Phase 2 clinical trials.¹⁵⁶

FINLAY-FR1 is a COVID-19 vaccine produced by the Finlay Institute in Cuba. It is a vaccine candidate that targets the RBD of S protein.¹⁵⁷ This vaccine candidate is currently under investigation in Phase 2 clinical trials.¹⁵⁸

Razi Cov Pars is developed under the leadership of Iran's Health Ministry and Food and Drug Organization expertise. It is an injected-inhaled recombinant corona protein vaccine which is currently being evaluated in Phase 2 clinical trial.¹⁵⁹

V-01 is a recombinant protein vaccine from China that targets RBD of S protein. However RBD is armed with an interferon- α at the N-terminus and dimerized by human IgG1 Fc at the C-terminus (named I-R-F) to target and activate DCs to migrate toward the local draining lymph nodes, thus enhancing antigen processing and presentation.¹⁶⁰ This vaccine candidate is currently under investigation in Phase 2 clinical trials.¹⁶¹

SCB-2020S is developed by Clover Biopharmaceuticals AUS Pty Ltd in China. It targets the SARS-CoV-2 trimeric S-protein from B.1.351 variant. The vaccine candidate is currently being evaluated in phase 2 clinical trials.¹⁶²

202-CoV is developed by Shanghai Zerun Biotechnology Co. Ltd in China. It is a protein subunit vaccine targeting S protein of SARS-CoV-2. The vaccine candidate is currently being evaluated in Phase 2 clinical trials.¹⁶³

KBP-COVID-19 is a plant-based subunit vaccine from USA candidate that targets S protein. Kentucky BioProcessing Inc. (KBP) is primarily known for utilizing tobacco plants for the production of vaccines along with other biopharmaceutical products. KBP has utilized *N. benthamiana* as a bioreactor for the production of the target S protein. The widely used agro-infiltration technique is also employed by KBP to infiltrate the tobacco leaves with the genetically modified *A. tumefaciens* to enable the production of the target protein. This indirect gene transfer technique increases the rate of transgene expression. The vaccine candidate is under investigation in Phase 1/2 clinical trials.¹⁶⁴

CIGB-669 (Mambisa) is a conjugate subunit vaccine from Cuba that uses the hepatitis B protein as an antigen. It will be applied nasally, with the ability to stimulate the immune response at the mucosal level, the first barrier against a pathogen. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁶⁵

BECOV2 is developed by Indian company Biological E. The vaccine candidate has an antigen developed by the Texas Children's Hospital Center for Vaccine Development and in-licensed from BCM Ventures, Baylor College of Medicine's integrated commercialisation team, and Dynavax Technologies' advanced adjuvant, CpG 1018. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁶⁶

S-268019 is a recombinant protein vaccine candidate from China that contains a purified S antigen protein. The vaccine candidate was developed by a special platform called Baculovirus Expression Vector System (BEVS) for production. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁶⁷

AKS-452 is a biologically engineered SARS-CoV-2-RBD-Fc fusion protein vaccine candidate from Netherlands. In this vaccine candidate full RBD of SARS-CoV-2 is fused with Fc portion of an immunoglobulin molecule, providing better

presentation of the S antigen to the immune system. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁶⁸

COVAC-2 is developed by the University of Saskatchewan in Canada. The vaccine candidate contains a portion of the SARS-CoV-2 S protein, called S1. COVAC-2 contains a SWE adjuvant. This adjuvant belongs to a family of oil-based adjuvants that have been previously used in influenza vaccines. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁶⁹

GBP510 is a recombinant protein vaccine candidate from South Korea, that targets RBD of S protein. The nanoparticle technology applied to this vaccine candidate provides significant dose-sparing effect. The vaccine candidate can be stored at refrigerator conditions.¹⁷⁰ The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁷¹

EuCorVac-19 is a recombinant protein vaccine from South Korea, that targets the S protein. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁷²

CoVepit is another recombinant protein vaccine that is developed by OSE Immunotherapeutics in France. The vaccine candidate incorporates 11 neoepitope targets chosen following bioinformatic analysis of more than 167,000 different SARS-CoV-2 sequences collected globally. Selection and generation of this SARS-CoV-2 multi-target peptide vaccine (targeting S, M, N, and several non-structural proteins), cover for already observed up to 46,000 SARS-CoV-2 sequences with recurrent mutations isolated worldwide and is ready to use for future virus evolution. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁷³

QazCoVac-P is a recombinant protein vaccine from Iran, that targets RBD and N-proteins of the SARS-CoV-2 coronavirus. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁷⁴

IMP CoVac-1 is a SARS-CoV-2-derived multi-peptide vaccine in combination with the TLR 1/2 ligand XS15 from Germany. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁷⁵

AdimrSC-2f is developed by Adimmune Corporation in Taiwan. It is based on recombinant protein technology. According to the amino acid sequence of the S-protein SARS-CoV-2, a candidate vaccine fragment was designed and fused with the Fc fragment gene of human IgG1 antibody for this vaccine. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁷⁶

SARS-CoV-2 Sclamp vaccine is an adjuvanted protein subunit vaccine from Australia, that comprises a recombinant SARS-CoV-2 S glycoprotein and squalene-oil-in-water adjuvant MF59. A molecular clamp is used to stabilize the S protein in the authentic pre-fusion conformation that preserves neutralising epitopes present on the virion surface. This mimics the response induced by natural infection and minimises the induction of potentially confounding non-neutralising antibodies. MF59 is a commercially approved adjuvant with a well-established safety record in children, adults, and older people and that elicits strong antibody responses, along with a balanced

T-helper 1 (Th1) and T-helper 2 (Th2) cell response. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁷⁷

SK SARS-CoV-2 (NBP2001) is a recombinant surface antigen protein subunit vaccine from South Korea, which is adjuvanted with aluminum. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁷⁸

Walter Reed Army Institute of Research in USA developed another recombinant protein vaccine. The researchers in WRAIR designed and characterized four categories of engineered nanoparticle immunogens that recapitulate the structural and antigenic properties of pre-fusion S, S1 and RBD. Additionally, a liposomal formulation of QS21 (ALFQ) adjuvant has also been used in this vaccine candidate. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁷⁹

ReCOV is a recombinant protein vaccine candidate from China, that is developed by Jiangsu Rec-Biotechnology. It is a two-component vaccine that targets both S and RBD protein of SARS-CoV-2. The vaccine candidate is manufactured in the Chinese Hamster Ovary (CHO) cell lines. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁸⁰

CoV2-OGENI is a recombinant protein based vaccine candidate from Russia, that targets the S protein. The vaccine candidate incorporates a novel oral-delivery platform, allowing individuals to obtain immune response orally without injection. It is currently under investigation in Phase 1 clinical trials.¹⁸¹

Baiya SARS-CoV-2 VAXI is developed by Baiya Phytopharm Co., Ltd in Thailand. It is a RBD-Fc based protein subunit vaccine. The vaccine candidate is currently being evaluated in Phase 1 clinical trials.¹⁸²

Virus like particle vaccines. *CoVLP* is a COVID-19 vaccine candidate developed by Medicago company in Canada and GlaxoSmithKline company in the UK. The virus-like particles are produced by creating a bacterium engineered with genes of the virus, then introducing the bacteria into *Nicotiana benthamiana* plants. The plants take up the bacteria virus-derived generic material, producing in its leaves the virus-like particles, which are then harvested and extracted. The method of using a plant like *N. benthamiana* has been called “molecular farming” or a “plant-based factory”, having vaccine manufacturing advantages of rapid, low-cost production of proteins, large scalability for production, and safety of using plants for pharmaceutical production.¹⁸³ The vaccine candidate is currently under investigation in Phase 2/3 clinical trials.¹⁸⁴

RBD SARS-CoV-2 HBsAg VLP is a vaccine candidate that is developed by Serum Institute of India and SpyBiotech company in India. It is a virus-like particle vaccine candidate where the RBD antigen is conjugated to the hepatitis B surface antigen. Virus-like particles (VLPs) are protein-based vaccines that stimulate high immune responses because of their repetitive structures. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁸⁵

VBI-2902a is an enveloped virus-like particle (eVLP) vaccine candidate from Canada, that expresses the SARS-CoV-2 S protein and contains an aluminum phosphate adjuvant. The vaccine candidate is currently under investigation in Phase 1/2 clinical trials.¹⁸⁶

SARS-CoV-2 VLP is developed by The Scientific and Technological Research Council of Turkey. It is a vaccine candidate that harbors M, N, E, and hexapropyl modified S proteins of SARS-CoV-2 virus. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁸⁷

ABNCoV2 is developed by Radboud University in Netherlands. It is a capsid virus-like particle (cVLP) vaccine candidate. The vaccine is made in insect cells and is linked to a nanoparticle. It uses an adjuvant called MF59. The vaccine candidate is currently under investigation in Phase 1 clinical trials.¹⁸⁸

COVID-19 Variants and Vaccine Efficacy

All viruses mutate over time, and this includes SARS-CoV-2. Since the beginning of the COVID-19 pandemic, several mutations have risen in the viral genome of SARS-CoV-2, leading to many new variants in different countries. In the analysis of an international database covering the infections between February and May 2020, 5775 new variants have been reported.¹⁸⁹ A consistent nomenclature has not been established for SARS-CoV-2 variants. Three mainly used nomenclature systems are GISAID (Global Initiative on Sharing Avian Influenza Database), Nextstrain Platform and PANGOLIN (Phylogenetic Assignment of Named Global Outbreak Lineages) systems. Currently, eight global clades (S, O, L, V, G, GH, GR, and GV) have been identified in GISAID; thirteen major clades (19A, 19B, 20A–20J and 21A) have been identified in Nextstrain Platform and six major lineages (A, B, B.1, B.1.1, B.1.177, B.1.1.7) have been identified in PANGOLIN system.^{190–193}

An emerging variant that carries one or more of these mutations and becomes the responsible agent for the increasing proportion of the cases is considered as variant of interest (VOI). Further expansion of VOIs, causing public health risks at national or global levels, are considered as variants of concerns (VOCs).^{194,195} In fact, the surveillance of new SARS-CoV-2 variants is very important and is carried out by identification of new viral sequences. However, genome sequencing capabilities are limited in most parts of the world. More efforts are needed for the necessary surveillance of these variants in an international level of attention. As national authorities, institutions and researchers continue to monitor SARS-CoV-2 mutations, the WHO has assigned simple, easy to say and remember labels for key variants of SARS-CoV-2 using letters of the Greek alphabet in May 2021. According to these labels four VOCs (Alpha, Beta, Gamma and Delta) and four VOIs (Eta, Iota, Kappa and Lambda) have been designated for emerging variants (Table 5).

A major focus of current research is whether any of these mutations have any potential to significantly alter important

viral properties, such as the mode or rate of transmission, or the ability to cause disease. However, the observation that a new mutation is increasing in prevalence or geographic range is not sufficient to prove its selective advantage because such increases can also be generated by other causes such as non-compliance to the preventive measures.¹⁹⁶ Variant mutations can occur in any part of the viral genome such as in structural protein genes or non-structural protein coding regions. The mutations that occur in the S protein genes, particularly the RBD coding regions are of the greatest importance because they are the main cause of SARS-CoV-2 variants with increased transmission rates, increased disease severity-mortality rates and less susceptibility to monoclonal or polyclonal antibodies produced in response to infection or vaccination. These mutations can also negatively impact diagnostics or drug therapies that are used for COVID-19 disease.¹⁹⁷ (Table 6)

Vaccine efficacy is the reduction of the risk or odds of disease or infection among vaccinated persons. While new variants continue to emerge, evaluation of the efficacy of COVID-19 vaccines in different settings and populations has become more difficult.^{199,200} The necessity of additional vaccine doses for declining protection over time and decreased efficacy for different variants of COVID-19 are unresolved issues for vaccine efficacy. Real world vaccine efficacy may differ from the results of randomized controlled trials because of the different target populations or different vaccine schedules that are applied in different countries. While many vaccine efficacy studies are continually published, the majority of these came from three countries with early introduction of vaccination campaigns: Israel, the UK and the USA. Additionally, most of these reports on vaccine efficacy were carried out on only two vaccines—BNT162b2 (Pfizer) and AZD1222 (AstraZeneca). To improve vaccine efficacy studies, WHO has produced best practice guidance on how to undertake vaccine efficacy studies.²⁰¹

In general, symptomatic disease efficacy results of these studies, for fully vaccinated individuals, have been similar to the results of the randomized controlled studies of individual vaccines. Overall, vaccine efficacy against severe disease, hospitalization and death is higher than efficacy against non-severe disease, with the overall efficacy of above 80% for AZD1222, mRNA-1273, BNT162b2, and Coronavac vaccines. Although, the vaccine efficacy against infection and asymptomatic infection are slightly lower for AZD1222, mRNA-1273, and BNT162b2 vaccines, the vaccine efficacy rates for these outcomes are almost uniformly >60%. Additionally, several studies have shown that the transmission to household members is reduced by approximately 50% when the infected household member was vaccinated with at least one dose as compared to unvaccinated. Importantly, vaccine efficacy appears to be consistently higher for all outcomes after full vaccination, defined as at least 7-14 days after the final dose.¹⁹⁸ (Table 7)

There is widespread concern that existing COVID-19 vaccines may have reduced vaccine efficacy against the four VOCs designated by WHO. Neutralization studies have

shown that there is a several-fold reduction in neutralization of the VOCs, specifically Beta, Gamma and Delta. However, a reduction in neutralization does not directly correlate with reduced vaccine efficacy. This can be explained by several reasons: 1) there is currently no known threshold of neutralization below which vaccines no longer protect; 2) some vaccines produce higher neutralizing antibody concentrations so reductions in neutralization will likely have a lesser effect on the efficacy for these vaccines; 3) and other factors besides neutralizing antibody levels, such as cellular immunity, may maintain protection. More vaccine efficacy studies of additional vaccines against the Delta variant and other VOCs are needed to better understand vaccine efficacy against VOCs.¹⁹⁸

COVID-19 Vaccination in Pregnant or Breastfeeding Women

Although, much progress has been achieved since the beginning of the COVID-19 pandemic, the issue of vaccinations in special populations remains unclear. One of these populations is pregnant or breastfeeding women. Vaccination during pregnancy and lactation is common to prevent maternal and infant morbidity from other infectious diseases. Although live vaccinations, such as measles, mumps, and rubella and varicella are contraindicated in pregnancy, influenza and Tdap vaccinations are specifically recommended to prevent infections during pregnancy.²⁰² All currently approved COVID-19 vaccines are not live virus vaccines.

According to available information in the literature, pregnant women do not appear to get infected by COVID-19 more frequently than the general population and when they are infected, most experience mild to moderate disease.^{203,204} However, approximately 8–11% of pregnant women require hospital admission for COVID-19 related morbidity, and between 2% and 4% of pregnant women require intensive care unit admission during the course of the disease.^{205–211} Risk factors for severe COVID-19 in pregnant women include race/ethnicity, older maternal age, pre-pregnancy obesity, asthma, cardiovascular disease, pre-gestational diabetes mellitus, chronic hypertension, chronic lung disease and healthcare personnel.^{212–214} Pregnant women with COVID-19 may also have an increased risk of preterm birth.^{215–218} The risk for preterm delivery has ranged from 10% to 25% in the literature with rates as high as 60% among women with critical illness. Additionally, the Centers for Disease Control and Prevention (CDC) has included pregnancy as a risk factor that can lead to increased risk for severe COVID-19.²¹⁹

It is important to note that pregnant and lactating women were not included in COVID-19 vaccine trials.^{220–225} For this reason, the evidence for efficacy and safety of COVID-19 vaccinations during pregnancy and lactation is scarce, which makes the decision making more difficult. In this regard, most of the information comes from animal studies and the inadvertent vaccination of pregnant women during clinical trials or observational studies. The safety and efficacy of COVID-19 vaccines

have been tested in animal models, including mice, ferrets, sheep, and nonhuman primates. Developmental and reproductive toxicology (DART) studies on the BNT162b2, mRNA 1273, AdCoV2S, AZD122, Coronavac and BBIBP-CorV vaccines have not shown any harmful effects in pregnancy.^{226–231} Inadvertent pregnancies in low number of recipients occurred in women having received a COVID-19 vaccine during BNT162b2, mRNA 1273, AdCoV2S and AZD1222 COVID-19 vaccine trials, revealing no difference in miscarriage rates between COVID-19 vaccinated and placebo-vaccinated women.^{232–235} The results of observational studies have shown that vaccinations in pregnant and lactating women generated robust humoral immunity with immunogenicity and reactogenicity similar to that observed in non-pregnant women.²³⁶ Immune transfer of neutralizing antibodies from mother to neonates was observed via placenta and breast-milk in these studies.^{237,238} However, the vast majority of these studies were performed on mRNA vaccines and information on the effect of inactivated, viral vector and subunit vaccines on pregnancy or lactation is scant.^{239–242} Furthermore, although a causative relationship has not been fully established, a very rare syndrome, called vaccine induced thrombotic thrombocytopenia (VITT) has been described and only seems to occur after adenovirus viral vector vaccines.²⁴³ However, similar kinds of viral vector vaccines have been given to pregnant women in previous Ebola and Zika virus vaccination programs without adverse pregnancy-related outcomes.^{244–246} Any intervention in pregnancy, including vaccinations, especially new ones, requires special careful attention to ensure safety of the pregnant women and their children. After several vaccines became available for use, a large amount of guidance was published by governmental public health agencies, drug regulatory

agencies, and health care organizations regarding administration of the COVID-19 vaccines in pregnant or lactating women. With the flow of new information, these guidance documents have been substantially changed over time, between December 2020 until today.^{247–253} Overall further decisions on the use of COVID-19 vaccines in pregnancy and lactation period should include a risk–benefit analysis based on availability of the vaccine, the best available data and the exposure risk in the epidemiological background. It is important to highlight that the benefits of vaccinations in pregnant or breastfeeding women far outweigh the risks.

COVID-19 Vaccination in Immunocompromised Patients

It has been shown that patients with cancer are at significantly increased risk for COVID-19 infection. Additionally, when cancer patients are infected with COVID-19, they may have worse outcomes.^{254–258} This is caused partly by the disease itself and also by the immunosuppression caused by different treatment approaches such as chemotherapy, radiotherapy, and stem cell transplantation also make these patients more vulnerable to COVID-19. Since the beginning of the COVID-19 pandemic, cancer patients have been classified as high-risk patients for severe disease, excluding them from early vaccine trials. Infectious Diseases Society of America (IDSA) and The European Conference on Infections in Leukemia (ECIL) guidelines recommend vaccination with inactivated influenza, Hepatitis B subunit and pneumococcus vaccinations in cancer patients.^{259–261} In general, live-attenuated vaccines are not usually recommended in primary or acquired immunodeficient

Table 5. WHO defined VOCs and VOIs^a

WHO Label	PANGO Lineages	GISAID Clade	Nextstrain Clade	Additional Mutations	Earliest Documented Samples	Date of Designation
A) Variant of Concerns (VOCs)						
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom— Sep 2020	Dec 2020
Beta	B.1.351 B.1.351.2 B.1.351.3	GH/501Y.V2	20H (V2)	+S:L18F	South Africa—May 2020	Dec 2020
Gamma	P.1 P.1.1 P.1.2	GR/501Y.V3	20J (V3)	+S:681H	Brazil—Nov 2020	Jan 2021
Delta	B.1.617. AY.1 AY.2 AY.3	G/478K.V1	21A	+S:417N	India—Oct 2020	VOI: 4-Apr-2021 VOC: 11-May-2021
B) Variant of Interests (VOI)						
Eta	B.1.525	G/484K.V3	21D	+S:484K	Multiple countries – Dec 2020	Mar 2021
Iota	B.1.526	GH/ 253G.V1	21F	+S:484K	United States of America Nov-2020	Mar 2021
Kappa	B.1.617.1	G/452R.V3	21B	+S:484Q	India, Oct-2020	Apr 2021
Lambda	C.37	GR/452Q.V1	21G	+S:452Q	Peru, Dec-2020	Jun 2021

^aModified from WHO Tracking SARS-CoV-2 variants.¹⁹⁴

Table 6. Summary Of WHO defined VOCs and Their Impact on Vaccinations^a

WHO Label	Transmission	Disease Severity	Risk of Reinfection	Impacts on Diagnosis
Alpha	Increased transmission and secondary attack rate.	Increased risk of hospitalization, possible increased risk of severity and mortality.	Neutralizing activity retained, risk of reinfection remains similar.	Limited impact – S gene target failure (SGTF); no impact on overall result from multiple target RT-PCR, No impact on Ag RDTs observed.
Beta	Increased transmission.	Not confirmed, possible increased risk of in-hospital mortality.	Reduction in neutralizing activity reported; T cell response elicited by D614G virus remains effective.	No impact on RT-PCR or Ag RDTs observed.
Gamma	Increased transmission.	Not confirmed, possible increased risk of hospitalization.	Moderate reduction in neutralizing activity reported.	None reported to date.
Delta	Increased transmission and secondary attack rate.	Increased risk of hospitalization.	Reduction in neutralizing activity reported.	None reported to date

^aModified from WHO Weekly epidemiological update on COVID-19 – 6 July 2021.¹⁹⁸

patients because of the risk of infection development by the live pathogens present in the vaccine. All currently approved COVID-19 vaccines are not live virus vaccines.

Cytotoxic chemotherapies interfere with DNA replication, synthesis, and cell cycle progression. Lymphocytes are also suppressed by these therapies.²⁶² However, this suppression is not complete and immune responses can be achieved by vaccinations, although, the patients are on cytotoxic chemotherapy.^{263–268} Titers can be helpful to assess the need for revaccination. Higher doses or boosters can be employed to enhance immunogenicity. Overall, with the exception of intensive chemotherapy periods, patients undergoing chemotherapy are expected to generate protective responses with COVID-19 vaccinations.

Targeted therapies including the receptor tyrosine kinase inhibitors (TKIs) such as erlotinib, sunitinib, imatinib and ibrutinib and monoclonal antibodies such as trastuzumab, do not directly cause immunosuppression but they may have inhibitory effects on APC function, T cell activation and B cell signaling. However, cancer patients that are receiving these therapies can still produce enough immune response against vaccines.^{269–274} Thus, it is reasonable to expect that the patients being treated with targeted therapies will generate protective responses with COVID-19 vaccination.

Immune checkpoint inhibitors target immunological pathways such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that are up-regulated in tumor-reactive T cells. Checkpoint inhibitors can cause immune-related adverse events (IRAEs), depending on the specific therapy.²⁷⁵ There is a theoretical concern that vaccination could stimulate an over-reactive immune response and increase IRAEs in patients actively treated with immune checkpoint inhibitors.²⁷⁶ However, larger studies with non-vaccinated comparison groups did not show higher frequencies of IRAEs with vaccinations.^{277,278}

Plasma-cell-depleting and lymph-depleting therapies, such as anti-CD20 and anti-CD38 monoclonal antibodies or

CAR-T cells against CD19, reduce the number of peripheral B cells in patients. In practice, it is recommended that vaccines be given at least 6 months after anti-B cell therapy due to decreased efficiency.^{279–286} However patients on anti-B cell therapy are at especially high risk for severe disease and death from COVID-19 can be an exception for this because vaccines are the most powerful tools in prevention of COVID-19 infections.

Radiation therapy is commonly used for patients with malignancies as a curative or palliative treatment option. It is known that radiation involving a large part of the body can have an impact on the bone marrow, however it is rare for radiation to have a significant impact on the immune system.^{287,288} Therefore, most patients treated with radiation can generate protective immune responses to COVID-19 vaccines.

COVID-19 prognosis is poor in patients receiving hematopoietic stem cell transplantation (HSCT). In HSCT recipients who develop COVID-19, the overall survival has been found to be 68% for recipients of allogeneic HSCT and 67% for recipients of autologous HSCT.²⁸⁹ In general, vaccines can be administered 4-6 months after HSCT. Live-attenuated vaccines are not recommended and should be administered at least 24 months after HSCT in patients who do not have graft versus host disease (GVHD) and take no immunosuppressive drugs in the last three months.²⁹⁰

Overall, most cancer treatments do not impair proper immune response against vaccines. However, the immune response may be weak in some cancer patients including those who are on intensive immunosuppression or HSCT. Many oncology professional scientific societies including the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), Society for Immunotherapy of Cancer (SITC), and the American Association for Cancer Research (AACR) strongly recommend vaccinating patients with cancer.^{291–294} It seems that vaccination in all cancer patients is safe, effective, and recommended,

Table 7. Summary of Vaccine Efficacy against Variants of Concern^a

Alpha	Beta	Gamma	Delta
Protection retained against all outcomes	Protection retained against severe disease, possible reduced protection against symptomatic disease and infection	Unclear impact; very limited evidence	Protection retained against severe disease, possible reduced protection against symptomatic disease and infection
A) Vaccine Efficacy against disease or infection (full vaccination)			
Severe Disease			
↔: mRNA-1273, BNT162b2 ↓: AZD1222	↔: Ad26.COVS. S, BNT162b2	No evidence	↔: AZD1222, BNT162b2
Symptomatic disease			
↔: mRNA-1273, BNT162b2 to ↓: AZ1222 ↓: NVX-CoV2373	↔: Ad26.COVS. S ↓↓↓: AZD1222, NVX-CoV2373	↔ to ↓: CoronaVac	↔ to ↓: BNT162b2 ↓: Covaxin ↓↓: AZD1222
Infection			
↔: BNT162b2 ↔ to ↓: AZD1222	↔: mRNA-1273 ↓: BNT162b2	No evidence	↓: AZD1222, BNT162b2
B) Neutralization (full vaccination).			
↔: Zifivax, BBIBP-CorV, Covaxin, Sputnik V, NVX-CoV2373 ↔ to ↓: Ad26.COVS. S, mRNA-1273, BNT162b2, CoronaVac ↓ to ↓↓: AZD1222	↔ to ↓: Zifivax, BBIBP-CorV ↓: Covaxin ↓ to ↓↓: mRNA-1273, BNT162b2, CoronaVac ↓ to ↓↓↓: Ad26.COVS. S ↓↓: AZD1222, Sputnik V ↓↓↓: NVX-CoV2373	↔ to ↓: BNT162b2, CoronaVac ↓: AZD1222, Ad26.COVS. S, mRNA-1273	↔: Janssen-Ad.COV 2.5 (1)79 • ↓: Zifivax, AZD1222, Covaxin, mRNA-1273, AZD1222 ↓ to ↓↓: BNT162b2 ↓ to ↓↓↓: CoronaVac

↔: <10% reduction in vaccine efficacy, or vaccine efficacy >90% with no comparator, or that there was a <2-fold reduction in neutralization.

↓: 10 to <20% reduction in vaccine efficacy, or 2 to <5-fold reduction in neutralization.

↓↓: 20 to <30% reduction in vaccine efficacy, or 5 to <10-fold reduction in neutralization.

↓↓↓: ≥30% reduction in vaccine efficacy, or ≥10-fold reduction in neutralization.

When more than one neutralization study is available, the interquartile range (25th and 75th percentiles) of fold-reductions across all studies for specific vaccine/variant was used.

^aModified from WHO Weekly epidemiological update on COVID-19 – 6 July 2021.¹⁹⁸

except for those who are on anti-B cell therapies, for whom a 4–6 months interval is needed after medication. It is important to complete the vaccination schedule and vaccination of household members. All types of vaccines are safe and effective in these patients, except live-attenuated vaccines.

Due to the immunosuppression that is needed for preventing graft rejection, the solid organ transplant (SOT) recipients are susceptible to diverse infectious diseases including COVID-19.^{295,296} SOT recipients are also at increased risk of developing severe COVID-19 infections and higher mortality rates compared to the general population.^{297–300} Furthermore, due to the immunosuppressed status, these patients experience prolonged SARS-CoV-2 shedding, which has been linked to the emergence of viral mutants.^{301–304} Although, prevention of COVID-19 infections is critical in SOT recipients, they were excluded from recent SARS-CoV-2 vaccine trials, so neither efficacy, and durability, nor safety are known in this patient subpopulation. In SOT recipients the immune response to vaccinations produce lower antibody titers compared to the general populations.^{305–307} Although there have been some concerns, vaccines have not been associated with graft rejection in SOT recipients.³⁰⁸

In general, live-attenuated virus vaccines are usually not recommended in SOT recipients due to the risk of disseminated infection.³⁰⁹ The American Society of Transplantation (AST), the International Society for Heart and Lung Transplantation

(ISHLT) and the European Society for Organ Transplantation recommend that all solid organ transplant recipients should be vaccinated against SARS-CoV-2, using locally approved vaccines. All healthcare workers and household members who care for these patients should also be vaccinated against COVID-19 infection. Whenever possible, vaccinations are recommended prior to transplantation (ideally with completion of vaccine series a minimum of 2 weeks prior to transplant). The best time for COVID-19 vaccine administration in the post-transplantation period is probably a minimum of three months after transplantation when immunosuppression is diminished, and other prophylactic medications are reduced. COVID-19 vaccination should be avoided in acute cellular rejection (ACR) status until ACR episodes are resolved, and high dose corticosteroid usage is not required anymore. Administration of an additional dose (third dose) of vaccine after completion of the vaccine series has been authorized by the EUA in the US as of August 12, 2021.^{310–312}

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease affecting the central nervous system (CNS), often leads to irreversible disability.³¹³ The MS has become a concerning issue in the COVID-19 pandemic. The use of lifelong disease modifying therapies (DMTs) in MS patients, cause immunosuppression and these patients become more susceptible to infections.^{314–316} Additionally,

even with mild infections, exacerbations of the MS (relapses or progressions) can be observed. About 30–40% of MS patients experience post-upper respiratory infection relapse, although the mechanism is unknown.^{317–321} This kind of disease flares have also been observed during the course of COVID-19 disease.³²² The incidence of COVID-19 in people with MS ranges from below 1% to 11%. COVID-19-related MS mortality has been reported to be approximately 1–4%.³²³ Several studies have shown that some DMTs are associated with increased risk of COVID-19. However, patients who are not receiving DMTs have also been shown as a high risk for COVID-19 infection in some studies.^{324,325} Moreover, discontinuing the routine therapeutic regimen for vaccination may cause progression and relapse, which needs to be taken into consideration. For all of these, vaccinations against COVID-19 in MS patients are very important, because vaccinations can be an effective way to prevent COVID-19.^{326–328} It is important to highlight that there is no proven relationship between vaccination and relapse or progression in MS patients.³²⁹ But MS patients may not display the adequate immune response because of the administration of DMTs. For this reason, patients who are on DMTs, a post-vaccination checkup may be necessary to make sure that the immunization has occurred properly. If an adequate response is not seen, a booster dose of vaccine may be administered.³²⁷ Patients using β -interferons, teriflunomide, natalizumab, glatiramer acetate, or dimethyl fumarate probably have no issues regarding vaccine safety and efficacy. The vaccine could be administered at any given time. In patients using fingolimod, alemtuzumab, ocrelizumab, rituximab, or oral cladribine, there is a possibility of insufficient response to the vaccine. For instance, it was suggested to vaccinate patients starting B-cell-depleting therapies, 4–6 weeks before their first dose. If the patient has started therapy, the best vaccination time is 4–6 months after the last infusion. In the case of alemtuzumab, if the medicine has been used in the last 12–24 months, a reduction in the vaccine efficacy may happen. Thus, it is recommended to postpone the treatment until vaccination is completed. In patients on immunosuppressive treatments, such as mitoxantrone, cyclophosphamide, azathioprine, and methotrexate, vaccination is probably safe, but proper immunization might not occur. For high dose corticosteroid therapy, the best time of vaccine administration is 4–6 weeks following the last corticosteroid treatment to achieve optimal immunization. Vaccination is recommended in all MS patients without discontinuing their disease-modifying therapies, which could increase the risk of relapse and progression. Right timing is of great importance to maximize the efficacy, especially in patients using high-dose corticosteroids and B cell-depleting therapies such as rituximab and ocrelizumab.^{330–333}

Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a typical systemic immune mediated inflammatory disease that presents with chronic inflammation of the digestive tract, which is also associated with the development of extraintestinal manifestations. The impact of IBD on the risk of COVID-19 infection is controversial. Despite the above-mentioned information, there is no solid

evidence indicating that IBD patients are at a higher risk of COVID-19 infection.^{334,335} However, as with other immune-mediated inflammatory diseases, patients with IBD are treated with immunosuppressive drugs, such as high-dose corticosteroids (≥ 20 mg prednisolone or equivalent), immunomodulators (thiopurines, methotrexate, and calcineurin inhibitors), anti-cytokine therapies (including anti-TNF and anti-IL-12p40 drugs), anti-integrin therapies (vedolizumab), and small-molecule inhibitors of signaling (tofacitinib), which can leave them susceptible to infections.³³⁶ Considering the importance of vaccinations in prevention of COVID-19 infection, the safety and efficacy of vaccines in IBD have been the subject of debate. Due to the exclusion of IBD patients from the phase 3 clinical trials for approved vaccines, the data regarding vaccinations is lacking for IBD. Based on previous experiences, it is possible to conclude that immunosuppressive treatments can impair the vaccination efficacy. Live-attenuated COVID-19 vaccines are not safe in patients receiving immune-modifying treatments or those going to receive such therapies in the next eight weeks. There is no relationship between vaccination and the IBD disease onset, flares, or exacerbation of IBD. The patients that are treated with glucocorticoids and biologic agents may have impaired immune response to COVID-19 vaccines. Vaccinations against COVID-19 are strongly recommended in patients with IBD. SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving immune-modifying therapies. In patients with severe IBD flares or those who need hospitalization, a delay in vaccination is preferred. In patients receiving systemic corticosteroids, it is recommended to vaccinate IBD patients when the dose of corticosteroids is at their lowest level.^{337,338}

Patients with rheumatic diseases that are treated with corticosteroids, immunomodulators and biologics are at an increased risk of infection during COVID-19 pandemic due to their immunocompromised status.^{339,340} Moreover, a higher risk of COVID-19 morbidity and mortality might be possible due to the comorbidities present in rheumatic disease patients. Although, data regarding clinical outcomes in COVID-19 patients with an underlying rheumatic disease is very limited, the use of moderate to high doses of corticosteroids increased the chance of hospitalization. On the other hand, the use of TNF α inhibitors reduced the hospitalization rates. The use of NSAIDs (non-steroidal anti-inflammatory drugs), DMARDs (disease-modifying anti-rheumatic drugs), and JAK (Janus kinase) inhibitors did not change the rates of hospitalizations in COVID-19 infections.³⁴¹ Similar with other special populations, patients with rheumatic diseases were not included in COVID-19 vaccine trials. Only in BNT162b2 vaccine trial, 62 subjects (0.3%) with rheumatic disease included and received BNT162b2.⁹⁸ Vaccination against COVID-19 has been highly recommended by the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR) and the British Society of Rheumatology (BSR) in patients with rheumatic disease.^{342–344}

Another important aspect is whether to continue or discontinue pharmacologic therapies in rheumatic disease patients

with respect to SARS-CoV-2 vaccine administration. In this regard no modifications have been recommended for hydroxychloroquine, sulfasalazine; leflunomide, apremilast, azathioprine, cyclophosphamide (oral), intravenous immune globulin (IVIG), TNFi, IL-6R, IL-1R, IL-17, IL-12, IL-23, belimumab; oral calcineurin inhibitors and glucocorticoids. Withholding of methotrexate for 1-2 weeks after single-dose COVID-19 vaccination have been recommended for a better outcome. JAK inhibitors have been recommended to withhold for 1 week after each vaccine dose. Abatacept have been recommended to withhold 1 week prior to and 1 week after the first COVID-19 vaccine dose. Administration of abatacept can be scheduled so that the first vaccination will occur 4 weeks after abatacept infusion and postpone the subsequent abatacept infusion by 1 week (a 5-week gap in total); no medication adjustments for the second vaccine dose. Administration of cyclophosphamide (IV) have been recommended to be scheduled ~1 week after each vaccine dose, when feasible. For rituximab, vaccine series is recommended to initiate ~4 weeks prior to next scheduled rituximab cycle; and delay rituximab 2–4 weeks after final vaccine dose. Due to considerable B cell suppression alternative treatments recommended if available.^{342–344}

COVID-19 Vaccination in Children and Adolescents

As of 2020, the population under 20 years of age make up 33.3% of the world's population and 24.8% of the US population.³⁴⁵ Similar with other special populations children and adolescents, are excluded from vaccine trials. In children and adolescents the course of COVID-19 infections is mostly asymptomatic or mild. The case fatality rate of COVID-19 infection is significantly lower. Although it is rare, severe courses of COVID-19 infections are also observed in children and adolescents.^{346,347} Severe COVID-19 infections can be prevented by vaccinations in high-risk children and adolescents.³⁴⁸ Additionally, vaccines may also prevent multisystem inflammatory syndrome in children, which is associated with COVID-19. The indirect benefit of vaccinations in children and adolescents is the formation of herd immunity. If only adults are vaccinated, COVID-19 outbreaks may continue in the population of unvaccinated children and adolescents. Because infections may spread from children and adolescents to the adults, restrictions on school and limitations on social activities of pediatric population may continue. Therefore, vaccinating children and adolescents may be necessary to effectively prevent the spread of COVID-19 infections.

The results from phase 3 trials of multiple vaccines across different vaccine platforms have confirmed that the vaccines are effective in preventing SARS-CoV-2 infection in adults. The mRNA vaccine BNT162b2 has shown 100% efficacy and robust antibody responses in adolescents aged 12–15 years, leading to the FDA authorization for emergency use in adolescents 12 through 15 years of age.^{349,350} Coronavac was well tolerated and safe and induced humoral responses in children and adolescents aged 3–17 years.³⁵¹ Other vaccine companies have also

been started to assess the safety and efficacy of various vaccines among the population aged 6 months to 17 years. It is important to note that, there are currently no data on the long-term effects of these new platform vaccines. Therefore, careful approach must be taken in the decision for vaccinating children and adolescents. Therefore, it is absolutely necessary to obtain safety data prior to the decision of vaccinating children and adolescents.

Important Points Regarding COVID-19 Vaccinations

Both WHO and CDC recommend vaccination against COVID-19 in older adults.^{352,353} Adults 65 and older who received COVID-19 vaccines showed a reduced risk of COVID-19-related hospitalization. COVID-19 vaccines in older adults reduce deaths, hospital visits, and number of cases. Vaccines are the safest and most powerful way to protect them from COVID-19 infection. Particular concerns should be counseled by respected scientific authorities.³⁵⁴

The administration of a third booster dose is motivated after the emergence of the B.1.617.2 (delta) variant throughout the world. COVID-19 vaccines that are currently in use seem to be more than 90% effective against hospitalization and death from COVID-19. Although, some studies have found that vaccine-induced antibody levels wane after several months, this is typical for all vaccines and not necessarily indicative of waning protection against the coronavirus. A few trials have tested booster doses. Third doses of vaccines mRNA1273, BNT162b2, AZD1222 AND Coronavac prompted a spike in levels of neutralizing antibodies, when administered several months after the second dose. What scientists do not know is whether these decrease in vaccine-induced antibody levels reflect a decline in protection against the virus. The drop in neutralizing antibody titers is not equal to waning cellular immunity.

To look more closely for evidence of waning protection, analysis of health records may be a clue for evidence. In Israel, health records of more than 1.3 million people who were vaccinated between January and April 2021 analyzed, they found that the risk for infection was 53% higher for early vaccine recipients compared to those vaccinated later. At the end of July 2021, Pfizer–BioNTech, published data on a preprint server showing that the vaccine efficacy against symptomatic disease had dropped from 96% to 84% after 6 months. However, vaccine efficacy against severe disease have remained high at 97%. While some countries like Germany and Israel have announced their plans for booster-shot programs, countries including the United Arab Emirates, China and Russia have started administering extra doses of vaccines. The WHO has called for a moratorium on COVID-19 boosters until the end of September 2021, with the aim of ensuring that at least 10% of people in all countries are vaccinated before extra doses are handed out. Because, 58% of people in high-income countries had received at least one vaccine dose; in low-income countries this number stood at just 1.3%. Global vaccine availability is limited and will only become more limited if boosters

are commonly used. However, If vaccines were not scarce, boosters would be less controversial. It is important to remember that: “No one is safe until everyone is safe” which has become the mantra of the COVID-19 pandemic. Unmitigated transmission means rampant viral replication, which in turn means infinite opportunities for the emergence of new, more transmissible variants that could escape natural or vaccine-induced immunity. On the other side, Israel announced plans to give people aged over 60 a third dose of the BNT162b2 vaccine. The United Kingdom has drawn up the plans to offer vaccines to those over 50, as well as other high-risk groups, from September 2021. The CDC released a joint statement saying that they have developed a plan to begin offering these booster shots this fall subject to FDA conducting an independent evaluation and determination of the safety and effectiveness of a third dose of available vaccines and CDC’s Advisory Committee on Immunization Practices (ACIP) issuing booster dose recommendations based on a thorough review of the evidence.^{355–357}

Another important point about COVID-19 vaccines is mixing and matching approach in their administration. Currently, most of the current vaccination regimens include a second homologous booster dose following a priming dose with approximately a month interval. The idea of mixing vaccines has come from the aim of increased protection, simplifying immunization efforts for countries facing insufficient supplies of the vaccines. This concept is not something new but has been previously used for multiple illnesses including HIV, malaria, Ebola and influenza. “Heterologous prime-boost vaccination” involves delivery of the same or similar antigens of the disease-causing agent through two different vaccine types with the first dosage being used to prime the immune system while the subsequent dosage using different vaccine types to boost the immune response. This aims to increase the protective efficacy and rationalize the usage of the available vaccines. Mixing two different vaccines can also elicit a strong and long-lasting immune response as compared with the single vaccine regimen. This idea has been simulated in animal studies.³⁵⁸ One potential risk involved in vaccine mixing may include increased side effects. However, the clinical evidence for COVID-19 mixing is scarce and is limited to small number of studies. During the abrupt reactions to the AZD1222 vaccine, which left certain populations who had received their first dose of AZD1222 vaccine, but not the second dose, some countries urged these recipients to proceed with the second dose of AZD1222, while others, like Canada and several European countries, recommended a different vaccine for the second dose. However only a few of the potential vaccine combinations have been tested in clinical trials.^{359–361} In these studies, researchers have found that following one dose of the AZD1222 vaccine with a dose of the BNT162b2 vaccine produces strong immune response, with an acceptable safety profile.^{362–366} Several studies are now ongoing to test the combinations of BNT162b2, mRNA1273, AZD1222, NVX-CoV2373, Coronavac and Convidecia vaccines.^{367–373} (Table 8).

Future Considerations

SAR-CoV-2 and related variants will continue to emerge for years to come owing to the molecular adaptability and mutation during replication. Such variants will have a wide spectrum of pathogenic potential and will continually require optimized approaches to control their impact on public health. Until a long-lasting vaccine is developed, periodic vaccination and booster dosages will be required for specialized and compromised populations.

Currently, breakthrough infections with such variants as B.1.1.7 are occurring more frequently. Besides vaccination, other measures are recommended for the control of these mild infections. The vaccine supply has steadily increased to meet the demand and there is a need to provide vaccination globally. There is a need for more controlled vaccinations in countries where the vaccination rates are low, and the insurgence of new cases are high.

There is also growing concern regarding the vulnerability of the vaccine in the upcoming fall and winter seasons. This may result in an increase of the positivity rate in not only the non-vaccinated population but also in the vaccinated groups due to breakthrough infection. Despite this, a large percentage of people may not want to get the vaccine due to the wrongful information regarding the adverse outcomes in vaccines. Although various initiatives have been taken at different levels to promote vaccination due to the ill-founded public reluctance, reaching vaccination coverage greater than 80% is doubtful. Initial approaches such as non-vaccine antiviral drugs will soon be introduced, however, the effectiveness of such an approach is questionable.

Currently available vaccines confer time dependent immunity as evident by the breakthrough infections in some of the vaccinated individuals, however definitive information on such breakthrough infection is not available at this time on specific vaccines. There is a need for multiple dosing vaccine to maintain a desired level of immunity against this virus.

The complete elimination of SARS-CoV-2 infection may be possible in countries with high vaccination rates and appropriate booster vaccine recommendations. However, such regional diminishment in COVID-19 cases will be hindered secondary to international travel and pathogenicity of variants. Thus, potential travel restrictions and other embargo approaches may require consideration.

While the mortality rate of COVID-19 will be reduced with the use of vaccination, it will remain higher than what is observed with influenza. Moreover, the emergence of new variants will continue to impact on current approaches to provide broad-spectrum immunity. The variants forms are unpredictable and advanced approaches on molecular modelling may provide leads to developing a broad-spectrum vaccine with longer lasting effects. This will require continued pre-clinical and clinical research.

Of great concern is the potential emergence of other coronavirus pandemics with resistant viral pathologic profiles that may require focused or regional approaches for their control. It is unlikely that coronavirus mediated infection

Table 8. Current Studies on COVID-19 Vaccine Combinations

Ref #	Country	Vaccine Combination	Safety & Efficacy
Borobia et al. (2021) ³⁶²	Spain	CombiVacs Study: Study Group: first Dose AZD1222, second Dose BNT162b2 Control Group: Received only first dose and not received any second dose.	Efficacy: BNT162b2 given as a second dose induced robust immune responses. Safety: Acceptable and manageable reactogenicity profile.
Groß et al. (2021) ³⁶³	Germany	Study Group: first dose: AZD1222 second dose: BNT162b2 No control group.	Efficacy: BNT162b2 given as a second dose induced potent humoral and T cell immune responses. Variants of concern B.1.1.7, B.1.351 and B.1.617 are potentially neutralized by sera of all participants. Safety: No serious adverse events have been observed.
Shaw et al. (2021), Liu et al. (2021) ^{364,365}	UK	ComCov1 Study Study Group: Arm 1: first Dose AZD1222, second Dose BNT162b2 Arm 2: first Dose BNT162b2, second Dose AZD1222 Control Group: Arm 1: first Dose AZD1222, second Dose AZD1222 Arm 2: first Dose BNT162b2, second Dose BNT162b2	Efficacy: AZD1222/BNT162b2 was non-inferior to AZD1222/AZD1222. The non-inferiority of the BNT162b2/AZD1222 against AZD1222/AZD1222 could not be shown. Safety: Both combination vaccine schedules induced greater systemic reactogenicity following the second dose than the vaccine schedules using the same vaccine. Most common symptom was fever. No serious adverse events occurred related to vaccinations.
Hillus et al. (2021) ³⁶⁶	Germany	EICOV-COVIM Study Study Group: Arm 1: first Dose AZD1222, second Dose BNT162b2 Arm 2: first Dose BNT162b2, second Dose BNT162b2	Safety and Efficacy: AZD1222/BNT162b2 vaccine schedule is well tolerated and improved immunogenicity compared with AZD1222/AZD1222 vaccinations.
University of Oxford ³⁶⁸	UK	ComCov2 Study Study Group: Arm 1: first Dose AZD1222, second Dose AZD1222 Arm 2: first Dose AZD1222, second Dose mRNA1273 Arm 3: first Dose AZD1222, second Dose NVXCoV2373 Control Group: Arm 1: first Dose BNT162b2, second Dose BNT162b2 Arm 2: first Dose BNT162b2, second Dose mRNA1273 Arm 3: first Dose BNT162b2, second Dose NVXCoV2373	Study is ongoing.
Canadian Immunization Research Network ³⁶⁹	Canada	MOSAIC Study—Main Comparison Groups first Dose mRNA1273, second Dose mRNA1273. first Dose mRNA1273, second Dose BNT162b2 first Dose BNT162b2, second Dose BNT162b2. first Dose BNT162b2, second Dose mRNA1273. first Dose AZD1222, second Dose mRNA1273. first Dose AZD1222, second Dose BNT162b2.	Study is ongoing.

(continued)

Table 8. (continued)

Ref #	Country	Vaccine Combination	Safety & Efficacy
National Institute of Allergy and Infectious Diseases (NIAID) ³⁷⁰	USA	NIH Study—Main Comparison Groups first Dose Ad26.COVS-S, second Dose mRNA-1273.211 first Dose BNT162b2, second Dose mRNA-1273.211 first Dose Ad26.COVS.2.S, second Dose mRNA-1273 first Dose mRNA-1273, second Dose mRNA-1273 first Dose BNT162b2, second Dose mRNA-1273 first Dose Ad26.COVS-S, second Dose Ad26.COVS-S first Dose mRNA-1273, second Dose Ad26.COVS.S first Dose BNT162b2, second Dose Ad26.COVS.S first Dose Ad26.COVS.2.S, second Dose BNT162b2 first Dose mRNA-1273, second Dose BNT162b2 first Dose BNT162b2, second Dose BNT162b2	Study is ongoing.
Jiangsu Province Centers for Disease Control and Prevention ³⁷¹	China	Main Comparison Groups first Dose CoronaVac, second Dose Convidecia first Dose Convidecia, second Dose CoronaVac	Study is ongoing.
Assistance Publique—Hôpitaux de Paris ³⁷²	France	Main Comparison Groups first Dose BNT162b2, second Dose BNT162b2. first Dose BNT162b2, second Dose mRNA1273. first Dose mRNA1273, second Dose mRNA1273. first Dose mRNA1273, second Dose BNT162b2	Study is ongoing.
Medical University Innsbruck ³⁷³	Austria	Main Comparison Groups first Dose AZD1222, second Dose AZD1222 first Dose BNT162b2, second Dose BNT162b2 first Dose AZD1222, second Dose BNT162b2	Study is ongoing.

will be eradicated in the foreseeable time or may be phased out to viral mutation.

Continual research including the information generated by pharmacovigilance and drug safety programs will be of true importance in the overall management of COVID-19 and related infections.

Finally, it must be acknowledged that the supply, logistics, and monitoring of vaccine distribution and administration cannot be underestimated. These aspects of supply-chain management require an unprecedented level of strategy and proper tactical execution that spans the globe. Only through

cooperative actions across countries and regions of the world with these considerations be met.

Conclusions

In the fight against the COVID-19 pandemic, the vaccines have been our most effective weapon. Since the beginning of the pandemic, the development and distribution of the vaccines have been on an accelerated schedule like we have never seen before. In an incredibly short period of time, vaccines that are quite effective have been developed and delivered to hundreds

of millions of people throughout the world. Today, the future still holds some questions like the long-term effects of the vaccines, how to vaccinate children or other currently unvaccinated populations, or other virus variants that may develop. However, it has been incredibly uplifting to see the efforts and collaboration of the many researchers, physicians, corporations, institutions, and governments across the globe slow down the spread of a global pandemic and offer hope to eradicate it someday soon.

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