

## Review Article



# Ongoing Clinical Trials of Vaccines to Fight against COVID-19 Pandemic

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) has developed as a pandemic, and it created an outrageous effect on the current healthcare and economic system throughout the globe. To date, there is no appropriate therapeutics or vaccines against the disease. The entire human race is eagerly waiting for the development of new therapeutics or vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Efforts are being taken to develop vaccines at a rapid rate for fighting against the ongoing pandemic situation. Amongst the various vaccines under consideration, some are either in the preclinical stage or in the clinical stages of development (phase-I, -II, and -III). Even, phase-III trials are being conducted for some repurposed vaccines like Bacillus Calmette–Guérin, polio vaccine, and measles-mumps-rubella. We have highlighted the ongoing clinical trial landscape of the COVID-19 as well as repurposed vaccines. An insight into the current status of the available antigenic epitopes for SARS-CoV-2 and different types of vaccine platforms of COVID-19 vaccines has been discussed. These vaccines are highlighted throughout the world by different news agencies. Moreover, ongoing clinical trials for repurposed vaccines for COVID-19 and critical factors associated with the development of COVID-19 vaccines have also been described.

**Keywords:** Vaccines; Clinical trial; COVID-19; Repurposed vaccines; SARS-CoV-2

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has developed as a pandemic in no time and has challenged and also burdened the world's entire health care system. The mortality rate of COVID-19 has been predicted to be around 3%–4% (1). It has been observed that the risk of COVID-19 mortality is higher in the aged population and those having comorbidities (2-4). The current burden for the disease is estimated to be more than 1 trillion US\$ in the world economy and is continually rising with each passing day (5). Therefore, there is an urgent and unusual health challenge for the entire human race. Presently, there is no suitable therapeutic or vaccine available to counter this disease. A successful vaccine can help to reduce infection as well as it can significantly diminish the morbidity and mortality of this killer disease. Conversely, an effective vaccination regime for the population will help restrain the economic burden of a country.

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**Conflict of Interest**

The authors declare no potential conflicts of interest.

**Abbreviations**

3D, 3-dimensional; aAPC, artificial Ag-presenting cells; ACE2, angiotensin-converting enzyme 2; Ad5, adenovirus type-5; BCG, Bacillus Calmette–Guérin; CEPI, Coalition for Epidemic Preparedness Innovations; COVID-19, coronavirus disease 2019; DC, dendritic cell; GSK, GlaxoSmithKline; IM, intramuscular; LNP, lipid nanoparticle; MERS-CoV, Middle East respiratory syndrome-related coronavirus; MMR, measles-mumps-rubella; nAbs, neutralizing Abs; RBD, receptor-binding domain; SARS-CoV-1, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; VLP, virus-like particle.

**Author Contributions**

Conceptualization: Chakraborty C; Funding acquisition: Lee SS, Sharma AR; Supervision: Chakraborty C, Lee SS, Sharma AR; Writing - original draft: Chakraborty C, Sharma AR; Writing - review & editing: Bhattacharya M, Sharma G, Saha RP.

It is well accepted that the vaccination is the most effective and significant therapeutic approach to prevent and control any infectious diseases (6). However, in general, it has been noted that several years are required to develop a new vaccine. For instance, 5 years have been taken for the development of the Ebola vaccine. Nevertheless, till date there is no vaccine against severe acute respiratory syndrome coronavirus (SARS-CoV-1) or Middle East respiratory syndrome-related coronavirus (MERS-CoV) (6). From the previous experience in the past decade, we have understood that the researchers and the vaccine industry should act immediately in an integrated manner to develop new vaccines to fight against any epidemic or pandemic situation. However, in most cases like the development of Zika, H1N1 influenza, Ebola, etc., vaccines took a long time to address the urgency of treatment or containment. We are required to develop the vaccine on an exigent basis to encounter sudden arising epidemic or pandemic situations. One such exceptional case is the H1N1 influenza vaccine, which was developed more quickly than other vaccines (7). Now in the current COVID-19 pandemic situation, scientists and biotechnological companies have been asked to develop the vaccines rapidly to combat the spread of COVID-19.

In this extensive review, we have tried to update the current information available for the antigenic epitopes for the SARS-CoV-2 vaccine development and the various types of platforms utilized for COVID-19 vaccine development like an inactivated vaccine, live-attenuated vaccine or whole virus vaccines, nucleic acid vaccines, subunit vaccines, and recombinant vaccines. Further, an illustration of the clinical trial landscape for COVID-19 vaccine development as well as for the repurposed vaccines has been provided. Moreover, in this article, we have comprehensively discussed some noteworthy vaccine candidates and their developers, such as mRNA-1273 from ModernaTX, Inc, adenovirus type-5 (Ad5)-nCoV from CanSino Biologics Inc., INO-4800 from Inovio Pharmaceuticals, LV-SMENP-DC from Shenzhen Geno-Immune Medical Institute, artificial Ag-presenting cells (aAPC) from Shenzhen Geno-Immune Medical Institute, LUNAR-COV19 from Arcturus Therapeutics, Adjuvanted Protein Vaccine from GlaxoSmithKline (GSK) and Sanofi, mRNA Vaccine (BNT162) from BioNTech SE, Synthetic mRNA Vaccine from Curevac, COVAX19 from Vaxine, AdVac and PER.C6 technology-based vaccine from Johnson & Johnson. Finally, we have discussed some factors that are associated with the COVID-19 vaccine designing and development, such as the timeline of COVID-19 vaccine development, strategic collaboration for this vaccine development, and the scale-up probabilities.

**VACCINE AND COVID-19**

There is an urgent need for the COVID-19 vaccine to fight against the pandemic in the current situation. The entire world is eagerly waiting for the vaccine to be available in the market. Every section of the human population is being affected drastically. Moreover, a financial burden has been imposed due to the current crisis in every nation of this world.

A vaccine is designed and developed to boost the natural immune response against invading pathogens, especially viruses. In fact, vaccination produces long-lasting immunity to individuals exposed to inactivated Ags (8). It also helps to develop immunological memory to combat against the live pathogens. It can function either by providing immunity through the humoral Ab production or trigger the cellular T cells to mediate acquired immunity.

Scientists and the biotech industry are trying to develop the COVID-19 vaccine at a very astonishing speed to diminish the pandemic situation. Scientists have entitled this speedy vaccine development process as “vaccine development through pandemic speed” (7,9). Various past researches have contributed effectively to the rapid progress of the development of the COVID-19 vaccine. For instance, previous studies and diverse knowledge on the characteristic features of various coronavirus spike (S) proteins and its role in pathogenesis (specially SARS-CoV-1 spike protein), the antigenicity of the virus glycoprotein, and the knowledge about immunity and neutralizing Ab to spike proteins contributed immensely to the cause of COVID-19 vaccine (10,11). The previous knowledge about the nucleic acid vaccine technology also helped in the prompt manufacture of the mRNA vaccine against SARS-CoV-2 (12,13).

However, it is essential to understand the target population for immediate vaccination. On priority, the target population for vaccination includes school children, frontline healthcare workers, people with more than 60 years of age, and people with comorbidities including hypertension, diabetes, cardiovascular diseases, and renal disease (14,15).

## ANTIGENIC EPITOPES AND COVID-19 VACCINE DEVELOPMENT

Previously, it has been reported that the SARS-CoV recovered patients have specific Abs against SARS-CoV. In this case, human Abs were directed primarily to the SARS-CoV S glycoprotein and its receptor-binding domain (RBD). SARS-CoV requires RBD to bind to the angiotensin-converting enzyme 2 (ACE2) for entering into the host cell (16). Similarly, for SARS-CoV-2 vaccine development, researchers are analyzing whether the S glycoprotein and its RBD show a similar type of function or not (17). However, some potential epitopes might be present in the S protein other than in RBD alone. Hence, apart from epitopes present in RBD, other S proteins' epitopic sequences should be considered for developing effective vaccine candidates (17,18).

To determine conserved epitopes is a proposed strategy for vaccine development (19). A similar approach is being applied against SARS-CoV-2 as well (20,21). It has been observed that only 77% of the amino acid sequence are in the similarity between the S protein of SARS-CoV and SARS-CoV-2. Therefore, a significant variation might be expected in the RBD of these two viruses (22,23). Moreover, it has been reported that several Abs against the S protein of SARS-CoV-2 are not showing a similar type of binding and neutralizing capacity as SARS-CoV (24-26). However, using epitopes in the S1B RBD core domain of SARS-CoV-2, Abs have been identified (23,24,27). They might be a promising vaccine candidate for the pandemic virus. However, developing a multi-epitopic viable vaccine utilizing various proteins such as N-protein, S-protein, and M-protein against this virus is still an unfinished task (28).

## PROTECTIVE IMMUNITY AGAINST SARS-CoV-2 INFECTIONS

Scientists are trying to understand the protective immunity against SARS-CoV-2 infections. It is currently a significant challenge to how protective immunity against this virus can be generated (29,30). COVID-19 infection ranges from silent infection to lethal disease and largely depends on the inter-individual clinical variability. There may be a role of human

genetics in determining the inter-individual clinical variability and protective immunity against this virus (31). It has been observed that successful vaccines have a protective role against this virus (32). However, the selection of Ags is crucial for effective vaccine development and protective immunity against this virus. One such recent example is the COVID-19 vaccine candidate developed by Yang et al. (33). The vaccine candidate shows a protective immunity against SARS-CoV-2 and uses RBD of the S-protein as an Ag. The researchers have noted that CD4 T lymphocytes and quite a few immune pathways are involved in initiating the vaccine Ab response (33). Similarly, several vaccine candidates are in the developmental stages, showing a high titer of neutralizing Abs (nAbs) induced by the vaccines. However, it is presumed that the safe and effective vaccine candidates will create protective immunity against the virus and fight against the pandemic situation.

## DIFFERENT TYPES OF VACCINES PLATFORM OF COVID-19 VACCINES

Various types of vaccine platforms have been used for vaccine development from time to time. Vaccines traditionally licensed for human beings are either lively-attenuated virus (majority) or protein-conjugated subunits or virus-like particulate substances, polysaccharides, or inactivated viruses. During the last decade, advanced technological platforms have been introduced for vaccine development, such as nucleic acid vaccine (DNA or RNA vaccine) and the recombinant viral vaccine. **Supplementary Table 1** summarizes the major vaccine platforms which are under consideration for the development of the COVID-19 vaccine.

### Inactivated vaccine

This type of vaccine consists of pathogens that are inactivated for pathogenicity. These pathogens are usually grown in culture and are inactivated by various means. The inactivated virus vaccine has been in use for a long time. An example of such a vaccine is the inactivated polio vaccine (34). Gao et al. (35) recently developed a purified inactivated vaccine candidate for the SARS-CoV-2 virus. The name of the inactivated vaccine candidate is PiCoVacc and was shown to possess the ability to generate neutralizing Abs against this deadly virus in rats, mice, as well as in primates other than humans. It was reported that the vaccine generated Abs were able to neutralize 10 different strains of SARS-CoV-2. Researchers have analyzed two different doses for vaccination for protection: 3 µg and 6 µg per dose. The lower dose (3 µg) provided partial protection, while the higher dose (6 µg) gave complete protection. Presently, this inactivated vaccine (PiCoVacc) is under clinical trial (35,36). However, the vaccine requires a booster dose to maintain stable immunity, which is a disadvantage of this vaccine. For this case, a large quantity of virus needs to be handled, making another disadvantage of the vaccine.

### Live-attenuated vaccine or whole virus vaccines

The live-attenuated vaccine is another type of vaccine that has been in use for a long time. The typical example of a live-attenuated vaccine is measles-mumps-rubella (MMR) vaccine (37). Recently, Grenga et al. (38) tried to develop a whole virus vaccine against SARS-CoV-2 and tried to characterize the host cell protein dynamics through proteomics.

It was reported that scientists in Hong Kong developed a live influenza vaccine. This vaccine also expressed the proteins of SARS-CoV-2 (15). However, live attenuated virus vaccines or whole virus vaccines require extensive additional safety and need strict efficacy trials (39). It is the drawback of this vaccine.

### Subunit vaccines

Subunit vaccine contains the antigenic fragments of a pathogen, especially the surface protein, and can elicit the immune response against the pathogen (40). One such example is the influenza subunit vaccine, a thermo-stable and freeze-dried vaccine (41).

Several scientists are trying to develop the subunit vaccine for SARS-CoV-2. Kalita et al. (42) has attempted to design a subunit vaccine for COVID-19. Researchers are trying to target the S1 subunit of this virus to produce Abs (43). Another subunit vaccine developed by Qi et al. (44) comprises a recombinant fusion protein of the RBD subunit of SARS-CoV-2 and mouse IgG1 Fc domain. They reported that the subunit vaccine produced potent neutralizing Abs and stimulated cellular and humoral immunity in mice (44). Recently, a subunit vaccine was developed by Clover Biopharmaceuticals, containing a trimerized S protein. The company has used patented Trimer-Tag® technology for this subunit vaccine production (15). However, it has been noted that subunit vaccines require multiple booster shots to boost complete immunity from the pathogens (43), and it is one of the disadvantages of this vaccine. In this case, memory for future immune response is highly undoubtful.

### Nucleic acid vaccines

The nucleic acid vaccine can be regarded as a modern era vaccine. The vaccine has several advantages over other types of vaccines. Firstly, this vaccine can be quickly constructed. Secondly, it can induce strong cell-mediated and humoral immune responses, even in the absence of an adjuvant (45,46).

### DNA vaccines

Recently, DNA vaccines are being developed against SARS-CoV-2 virus by different research groups. The developed DNA vaccines mainly encode different S proteins of the SARS-CoV-2 virus. This DNA vaccine has been shown to stimulate both cellular and humoral immune responses in different animals, such as guinea pigs, mice, and rhesus macaques (47,48). Recently, a synthetic DNA-based vaccine candidate was developed for targeting SARS-CoV-2 S protein (INO-4800) (49). Similarly, another DNA vaccine showed protection against this virus in nonhuman primate animal model. The vaccine elicited the production of nAbs and generated protective immunity (48). The limitation of this vaccine is that it elicits both humoral as well as cytotoxic immunity. Therefore, titers sometimes remain low. It may induce Ab production against itself, which is another disadvantage of this vaccine (50).

### RNA vaccines

Similarly, RNA vaccines are also being developed for this killer virus (12,51). It has been noted that the RNA is generally delivered via lipid nanoparticles (LNPs). Some mRNA vaccines that are being developed against this virus have shown high potency. These are promising vaccine candidates compared to conventional vaccines. The mRNA-1273 appears to be a promising vaccine candidate against this virus in nonhuman primates and have showed induced Ab production levels (52). This vaccine candidate shows safety and immunogenicity, even in older populations (53). Another mRNA vaccine candidate is BNT162b1, which is a lipid-nanoparticle formulated vaccine. It showed safety and tolerability among 18–55 years healthy adults in phase-I/II clinical trial (54). However, the technology of mRNA vaccine is new; however, one of this technology's advantages is that the vaccine is produced absolutely *in vitro* method (55). Unfortunately, this vaccine candidate is very unstable, making it a non-significant vaccine candidate.

### Recombinant vaccines

Scientists use the recombinant vaccine platform to avoid the need to work with live infectious viruses. In this case, adjuvants can be applied to increase immunogenicity (51). A recombinant MERS-CoV vaccine was developed by expressing the S protein of MERS-CoV. It has been successfully evaluated through the phase-I trial (56). Lei et al. (57) have made an attempt to develop a recombinant vaccine using ACE2-Ig against the SARS-CoV-2 virus. Kim et al. (58) have developed another recombinant vaccine by utilizing the SARS-CoV-2 S1 subunit sequence. Interestingly, this vaccine can be delivered through microneedle arrays technology to develop IgG Abs (59). However, there are some limitations to recombinant vaccines. It uses a subunit sequence that may not induce the proper Ab production. Therefore, effective Ag and adjuvant selection are essential for this type of vaccine development (60).

### Peptide and protein vaccine

Peptide vaccines are synthetic vaccines composed of a chemically synthesized chain of 20-30 amino acids of specific antigenic B cells and/or T cells epitope (20,21). These peptides are associated with the infectious virus and are able to induce specific immune responses. The advantages of peptide and protein vaccines are low cost, easy synthesis, increased relative safety, and stability (61). Various peptide vaccine candidates are currently studied and are in different stages of vaccine development. In this case, the selection of Ags, delivery system, and adjuvants is a critical process. Selection decides the efficacy of the vaccine as well as the inducibility of immune response. Moreover, the safety of the delivery strategy is another significant concern (62).

### Virus-like particles (VLPs)

VLPs are self-assembled structures composed of the viral envelope and/or capsid proteins. In most cases, these VLPs represent a similar structure and antigenicity as the parent virus. In addition, VLPs can serve as platforms for the possible modification, i.e., insertion or fusion of foreign proteins, *via* chemical conjugation to develop chimerically VLPs. VLPs possess more potent immunogenic properties than recombinant or subunit vaccines (61,63). Therefore, VLPs are recognized as the best suitable candidate for vaccine development. However, in case of VLPs, highly efficient delivery vehicles selection is a critical process and it is one of the disadvantages of this vaccine (64).

## PRECLINICAL STUDIES FOR COVID-19 VACCINE DEVELOPMENT

According to World Health Organization, various vaccine candidates for COVID-19 are currently in preclinical development (65). Some of the vaccine candidates for COVID-19 that are in preclinical stages are shown in **Supplementary Table 2**. In a vaccine developmental process, preclinical testing in animals is one of the prerequisites for the approval of any vaccine candidate before clinical trials. It has been observed that most of the suggested vaccine or therapeutic candidates fail to confirm their efficacy in animals (66), though they show efficacy *in vitro* conditions. It might be due to the simplified and outdated *in vitro* conditions that are unable to mimic the complex *in vivo* environment.

Presently, it is essential to enhance the speed of studies owing to the faster spread of COVID-19. Therefore, there is an urgent need to update preclinical studies' standards to

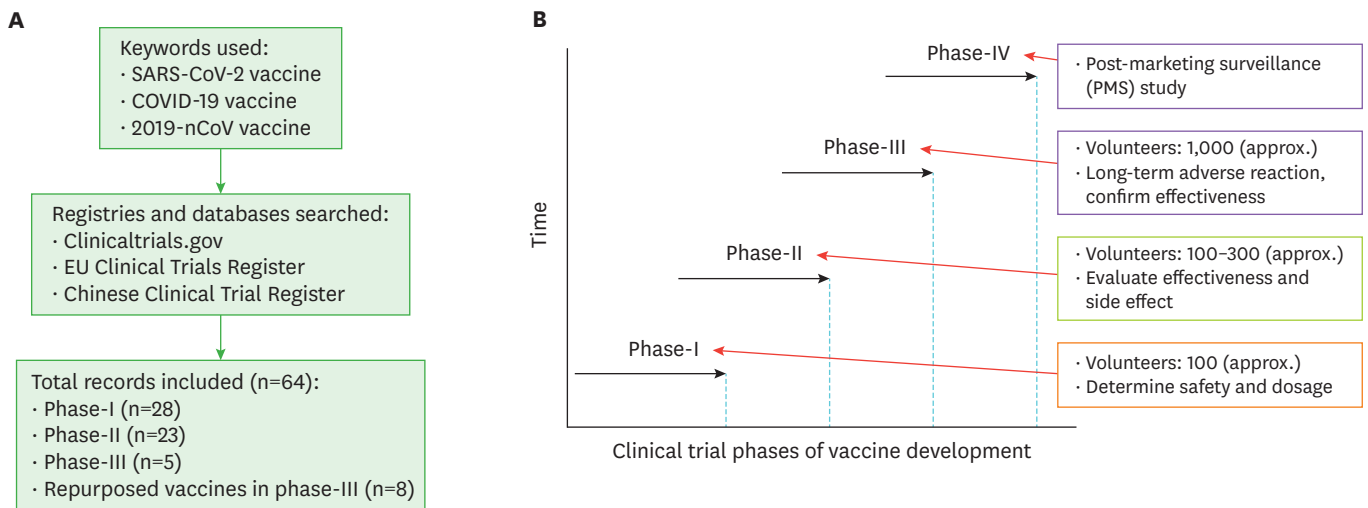
ensure the efficacy and safety of vaccine candidates before entering clinical trials for human use. Recently, various bioengineering tools have been developed to speed up the vaccine development process for COVID-19, such as 3-dimensional (3D) culture models, microfluidic chambers, and intravital imaging (67). The 3D and organoid models can represent *in vivo*-like dynamics, compared to 2D cell monoculture models. Moreover, organoids and 3D models are more permissive for viral infections and show more realistic expression markers to confirm the maximum extent of vaccine efficacy.

## CLINICAL TRIAL LANDSCAPE FOR COVID-19 VACCINE DEVELOPMENT

Currently, more than 135 vaccines are being developed for COVID-19. Several vaccines are in their preclinical trial stages, while few of them have entered the different phases of clinical trials (46). International Committee entitled “International Committee of Medical Journal Editors” has advocated in 2005 that all clinical trials can be registered in the public domain and can be considered for publication (59). The relevant publicly available domains are ClinicalTrials.gov, European clinical registry, and the International Clinical Trials Registry Platform. These domains can be accessed for different facts and figures of the clinical trials, such as patient group, methodology, inference, and the outcome of the clinical trial (Fig. 1A).

To date, more than 64 novel vaccines have been registered and are in various development stages of clinical trials. Near about 28 registries have been documented for phase-I clinical trials (Table 1). About 23 registries have been noted for the phase-II clinical trial (Table 2), and about 5 registries were reported for the phase-III clinical trial (Table 3).

Moderna developed an mRNA encapsulated LNPs based vaccine, and this was a collaborative effort of the company with the Research Center at NIH. Currently, it is in phase-I clinical trial (NCT04283461, ClinicalTrials.gov). It was the first vaccine to begin clinical trials outside of China and was highlighted in the news (68).



**Figure 1.** Different information about SARS-CoV-2 vaccine development and clinical trial. (A) Flow diagram that describes the clinical selection process of different vaccines during our study, which is in different phases of the clinical trial. (B) Different clinical trial phases of vaccine deployment and their salient features.

## Ongoing Clinical Trials of COVID-19 Vaccines

**Table 1.** Ongoing/completed phase-I clinical trial for COVID-19 vaccines

Sl. No.	Clinical trial ID	Study start date and end date (probable)	No. of patients enrolled in this clinical trial	Randomized	Developer	Country of origin	Vaccine type	Current status	Remark
1	NCT04283461	March 16, 2020 and November 22, 2021	120	No	National Institute of Allergy and Infectious Diseases	United States	mRNA	Not recruiting	Study understand the immunogenicity and safety of mRNA-1273 vaccine
2	NCT04299724	February 15, 2020 and December 31, 2024	100	No	Shenzhen Geno-Immune Medical Institute	China	Artificial antigen presenting cells	Recruiting	Study uses aAPC vaccine for 100 human which received subcutaneous injection to understand immunogenicity
3	NCT04428073	July 2020 and December 2021	32	No	GeneCure Biotechnologies	USA	Therapeutic vaccine (Covax-19™)	Not yet recruiting	Measuring the severity of local and systemic adverse events
4	NCT03348670	July 20, 2020 and November 10, 2020	20	No	Medicine Invention Design, Inc.	USA	Multiple gene mutation COVID-19 virus strains	Not recruiting	Assess for therapeutic vaccine activity and suggests the potential benefit of this vaccine
5	NCT04313127	March 16, 2020 and December 20, 2022	108	No	CanSino Biologics Inc.	China	Ad5 vector (Ad5-nCoV)	Not recruiting	This recombinant vaccine (Ad5-nCoV) understands safety and immunogenicity
6	NCT04405908	June 19, 2020 and March 30, 2021	150	Yes	Clover Biopharmaceuticals AUS Pty Ltd	Australia	Subunit type vaccine of recombinant trimeric S protein	Recruiting	Alum adjuvant linked multiple dosage level study
7	NCT04450004	July 10, 2020 and April 30, 2021	180	Yes	Medicago Inc.	Canada	Recombinant coronavirus-like particle (VLP)	Recruiting	Assessment the safety and immunogenicity using this vaccine containing VLP
8	NCT04453852	June 30, 2020 and July 1, 2021	40	Yes	Vaxine Pty Ltd	Australia	Monovalent recombinant S protein vaccine	Recruiting	To understand the safety and immunogenicity of this recombinant vaccine
9	NCT04449276	June 18, 2020 and August 2021	168	Yes	CureVac AG	Germany	mRNA vaccine	Recruiting	Evaluate the safety and reactogenicity of mRNA based vaccine (CVnCoV) through IM injection
10	NCT04336410	April 3, 2020 and July 2021	120	No	Inovio Pharmaceuticals	United States	DNA vaccine (INO-4800)	Not recruiting	INO-4800 vaccine was used to evaluate the safety, tolerability
11	NCT04276896	March 24, 2020 and December 31, 2024	100	No	Shenzhen Geno-Immune Medical Institute	China	Protein vaccine	Recruiting	This protein vaccine modulate T cell response
12	ChiCTR2000030906	March 16, 2020 and December 31, 2020	36	No	Jiangsu Provincial Center for Disease Control and Prevention	China	mRNA	Recruiting	Recombinant type adenoviral vector based vaccine targeted to COVID-19
13	NCT04324606	April 23, 2020 and October 2021	1,090	Yes	University of Oxford	United Kingdom	Adenovirus-vectored vaccine (COV001)	Not recruiting	This vaccine (COV001) was used among contain 1090 volunteers to understand the immunogenicity
14	NCT04470609	July 10, 2020 and November 2021	471	Yes	Chinese Academy of Medical Sciences	China	Inactivated type of vaccine	Enrolling by invitation	This trial evaluate the immunogenicity and doses
15	NCT04412538	May 15, 2020 and September 2021	942	Yes	Chinese Academy of Medical Sciences	China	Inactivated type of vaccine	Recruiting	In this study healthy volunteers (18 to 59 years) was chosen to understand the immunogenicity
16	NCT04276896	March 24, 2020 and December 31, 2024	100	No	Shenzhen Geno-Immune Medical Institute	China	Synthetic Minigene vaccine	Recruiting	This vaccine contains viral structural proteins etc.

(continued to the next page)



**Table 1.** (Continued) Ongoing/completed phase-I clinical trial for COVID-19 vaccines

Sl. No.	Clinical trial ID	Study start date and end date (probable)	No. of patients enrolled in this clinical trial	Randomized	Developer	Country of origin	Vaccine type	Current status	Remark
17	NCT04473690	December 20, 2020 and March 23, 2024	180	Yes	Kentucky BioProcessing, Inc.	United States	KBP vaccine	Not yet recruiting	Adult subjects of different age group was accessed and evaluated immunogenicity and safety
18	NCT04445389	June 17, 2020 and June 17, 2022	210	Yes	Genexine, Inc.	Korea, Republic of	DNA vaccine	Recruiting	This DNA vaccine was used to understand the immunogenicity and tolerability among 60 healthy volunteers
19	NCT04380532	May 15, 2020 and June 15, 2021	20	No	Immunitor LLC	Canada	Tableted thermostable vaccine	Not recruiting	Tableted vaccine developed from pooled plasma of COVID-19 patients
20	NCT04386252	February 2021 and February 2022	175	Yes	Aivita Biomedical, Inc.	United States	DC vaccine	Not yet recruiting	Antigens combined with autologous DCs is the combination of this vaccine
21	NCT04334980	October 2020 and February 28, 2021	12	Yes	Symvivo Corporation	United States	bacTRL-spike vaccine	Not yet recruiting	This is orally delivered vaccine
22	NCT04398147	August 1, 2020 and December 30, 2021	696	Yes	CanSino Biologics Inc.	Canada	Recombinant nCoV (Ad5 vector) vaccine	Not yet recruiting	To understand the safety, tolerability of Ad5-nCoV
23	NCT04471519	July 13, 2020 and June 30, 2021	755	Yes	Bharat Biotech International Limited	India	Whole-Virion inactivated type vaccine	Recruiting	BBV152 vaccine formulations was access in 3 investigational subgroups
24	NCT04463472	June 29, 2020 and July 31, 2021	30	No	AnGes, Inc.	Japan	DNA vaccine	Recruiting	Study to assess safety and immunogenicity of 2 doses of IM AG0301-COVID-19
25	NCT04444674	June 24, 2020 and December 2021	2,130	Yes	University of Witwatersrand	South Africa	ChAdOx1 nCoV-19	Recruiting	This study accessed the immunogenicity and safety of adults aged 18-65 years living with and without HIV
26	NCT04380701	April 23, 2020 and November 2020	456	No	BioNTech RNA Pharmaceuticals GmbH	Germany	RNA vaccine	Recruiting	This RNA vaccine evaluate the immunogenicity and safety
27	NCT04480957	August 4, 2020 and January 2021	92	Yes	Arcturus Therapeutics, Inc.	Singapore	Self-replicating (replicon) mRNA formulated in a LNP	Not yet recruiting	Safety and tolerability and immunogenicity of investigational vaccine ARCT-021

Information has been taken from: <https://ClinicalTrials.gov>, EU Clinical Trials Register, Chinese Clinical Trial Register. All information about the table was accessed on 30 November 2020.

The significant vaccines registered for phase-I clinical trials are assessed for safety, dosage, and immunogenicity. In this stage, the vaccine is applied to 80 to 100 healthy human subjects. Some dominant vaccine candidates that are in phase-I clinical trial are artificial Ag-presenting cells or aAPC based vaccine (NCT04299724), adenoviral vector 5 based vaccine (NCT04313127), mRNA based vaccine (NCT04283461), DNA based vaccine (NCT04336410), chimpanzee adenoviral vector ChAdOx1 based vaccine (NCT04324606), and a lentiviral vector-based vaccine (NCT04276896) (69) (Table 1).

The vaccines that are registered for the phase-II clinical trials are assessed for the effectiveness and associated side effects if any. In this stage, the vaccine is applied to 100 to

## Ongoing Clinical Trials of COVID-19 Vaccines

**Table 2.** Ongoing/completed phase-II clinical trial for COVID-19 vaccines

Sl. No.	Clinical trial ID	Study start date and end date (probable)	No. of patients enrolled in this clinical trial	Randomized	Developer	Country of origin	Vaccine type	Current status	Remark
1	NCT04405076	May 29, 2020 and August 2021	600	Yes	ModernaTX, Inc	United States	mRNA	Not recruiting	Study was performed for dose-confirmation and accessed the safety
2	NCT04470609	July 10, 2020 and November 2021	471	Yes	Chinese Academy of Medical Sciences	China	Inactivated type of vaccine	Enrolling by invitation	This trial evaluate the immunogenicity and doses
3	NCT04412538	May 15, 2020 and September 2021	942	Yes	Chinese Academy of Medical Sciences	China	Inactivated type of vaccine	Recruiting	In this study healthy volunteers (18 to 59 years) was chosen to understand the immunogenicity
4	NCT04276896	March 24, 2020 and December 31, 2024	100	No	Shenzhen Geno-Immune Medical Institute	China	Synthetic Minigene vaccine	Recruiting	This vaccine contains viral structural proteins etc.
5	NCT04437875	June 17, 2020 and August 10, 2020	38	No	Gamaleya Research Institute of Epidemiology and Microbiology	Russian Federation	Lyophilisate solution	Completed	Gam-COVID-vaccine lyophilisate to open study of safety, tolerability and immunogenicity
6	NCT04473690	December 20, 2020 and March 23, 2024	180	Yes	Kentucky BioProcessing, Inc.	United States	KBP vaccine	Not yet recruiting	Adult subjects of different age group was accessed and evaluated immunogenicity and safety
7	NCT04445389	June 17, 2020 and June 17, 2022	210	Yes	Genexine, Inc.	Korea, Republic of	DNA vaccine	Recruiting	This DNA vaccine was used to understand the immunogenicity and tolerability among 150 healthy volunteers
8	NCT04380532	May 15, 2020 and June 15, 2021	20	No	Immunitor LLC	Canada	Tableted thermostable vaccine	Not recruiting	Tableted vaccine developed from pooled plasma of COVID-19 patients
9	NCT04341389	April 12, 2020 and January 31, 2021	508	Yes	Institute of Biotechnology, Academy of Military Medical Sciences	China	Ad5 vector (Ad5-nCoV)	Not recruiting	In this study Ad5-nCoV was accessed among 508 healthy volunteers
10	NCT04386252	February 2021 and February 2022	175	Yes	Aivita Biomedical, Inc.	United States	DC vaccine	Not yet recruiting	Antigens combined with autologous DCs is the combination of this vaccine
11	NCT04324606	April 23, 2020 and October 2021	1,090	Yes	University of Oxford	United Kingdom	ChAdOx1 nCoV-19	Not recruiting	This study accessed the immunogenicity and safety
12	NCT04398147	August 1, 2020 and December 30, 2021	696	Yes	CanSino Biologics Inc.	Canada	Recombinant nCoV (Ad5 vector) vaccine	Not yet recruiting	To understand the safety, tolerability of Ad5-nCoV
13	NCT04471519	July 13, 2020 and June 30, 2021	755	Yes	Bharat Biotech International Limited	India	Whole-Virion inactivated type vaccine	Recruiting	BBV152 vaccine formulations was access in 3 investigational subgroups
14	NCT04463472	June 29, 2020 and July 31, 2021	30	No	AnGes, Inc.	Japan	DNA vaccine	Recruiting	Study to assess safety and immunogenicity of 2 doses of IM AG0301-COVID-19

(continued to the next page)

**Table 2.** (Continued) Ongoing/completed phase-II clinical trial for COVID-19 vaccines

Sl. No.	Clinical trial ID	Study start date and end date (probable)	No. of patients enrolled in this clinical trial	Randomized	Developer	Country of origin	Vaccine type	Current status	Remark
15	NCT04444674	June 24, 2020 and December 2021	2,130	Yes	University of Witwatersrand	South Africa	ChAdOx1 nCoV-19	Recruiting	This study accessed the immunogenicity and safety of adults aged 18–65 years living with and without HIV
16	NCT04380701	April 23, 2020 and November 2020	456	No	BioNTech RNA Pharmaceuticals GmbH	Germany	RNA vaccine	Recruiting	This RNA vaccine evaluate the immunogenicity and safety
17	NCT04480957	August 4, 2020 and January 2021	92	Yes	Arcturus Therapeutics, Inc.	Singapore	Self-replicating (replicon) mRNA formulated in a LNP	Not yet recruiting	Safety and tolerability and immunogenicity of investigational vaccine ARCT-021
18	NCT04400838	May 28, 2020 and September 2021	12,390	Yes	University of Oxford	United Kingdom	ChAdOx1 nCoV-19	Recruiting	Phase-II/phase-III study to evaluate the immunogenicity of 12,330 volunteers
19	NCT04368728	April 29, 2020 and January 29, 2023	43,998	Yes	BioNTech SE	United States	RNA vaccine (BNT162)	Recruiting	Evaluate the safety and immunogenicity of this vaccine (BNT162)
20	NCT04324606	April 23, 2020 and October 2021	1,090	Yes	University of Oxford	United Kingdom	Adenovirus-vectored vaccine (COV001)	Not recruiting	This vaccine (COV001) was used among contain 1,090 volunteers to understand the immunogenicity
21	NCT04368988	May 25, 2020 and November 18, 2021	1,419	Yes	Novavax, Inc.	Australia	Nanoparticle based vaccine contains recombinant S protein	Recruiting	Evaluate the immunogenicity of this vaccine with/without matrix-M adjuvant
22	NCT04447781	July 15, 2020 and February 22, 2022	160	Yes	Inovio Pharmaceuticals	United States	DNA based	Recruiting	Vaccine (plasmid pGX9501), which encodes for the full length of the Spike glycoprotein of SARS-CoV-2 to determine the immunogenicity
23	NCT04515147	September 28, 2020 and November 9, 2021	660	Yes	CureVac AG	Germany	mRNA vaccine	Recruiting	mRNA vaccine (CVnCoV) at different dose levels and to evaluate the humoral immune response

Information has been taken from: <https://ClinicalTrials.gov>, EU Clinical Trials Register, Chinese Clinical Trial Register. All information about the table was accessed on 30 November 2020.

300 healthy volunteers. Some important vaccines that are registered for the phase-II clinical trials are mRNA based vaccine (NCT04405076), Ad5 vector (NCT04341389), and DNA vaccine (NCT04445389) (**Table 2**).

Vaccines that are registered for the phase-III clinical trials are analyzed for the immune response and side effects. In this stage, the vaccine is applied to 1,000 to 3,000 healthy volunteers. Some vital vaccines that are registered for phase-III are mRNA vaccine (NCT04470427) and adsorbed COVID-19 (inactivated) vaccine (NCT04456595) (**Table 3**).

**Table 3.** Ongoing/completed phase-III clinical trial for COVID-19 vaccines

Sl. No.	Clinical trial ID	Study start date and end date (probable)	No. of patients enrolled in this clinical trial	Randomized	Developer	Country of origin	Vaccine type	Current status	Remark
1	NCT04470427	July 27, 2020 and October 27, 2022	30,000	Yes	ModernaTX, Inc.	United States	mRNA	Recruiting	Primarily evaluate the efficacy and immunogenic curve using this vaccine
2	NCT04456595	July 21, 2020 and October 2021	8,870	Yes	Butantan Institute	Brazil	Adsorbed COVID-19 (inactivated) vaccine	Recruiting	Assess efficacy and safety of the Adsorbed COVID-19 (inactivated) vaccine
3	NCT04400838	May 28, 2020 and September 2021	12,390	Yes	University of Oxford	United Kingdom	ChAdOx1 nCoV-19	Recruiting	Phase-II/phase-III study to evaluate the immunogenicity of 12330 volunteers
4	NCT04368728	April 29, 2020 and January 29, 2023	43,998	Yes	BioNTech SE	United States	RNA vaccine (BNT162)	Recruiting	Evaluate the safety and immunogenicity of this vaccine (BNT162)
5	NCT04526990	September 15, 2020 and January 30, 2022	40,000	Yes	CanSino Biologics Inc.	China	Adenovirus vector vaccine	Recruiting	Evaluate the efficacy, safety and immunogenicity of recombinant novel coronavirus vaccine (Ad5 vector)

Information has been taken from: <https://ClinicalTrials.gov>, EU Clinical Trials Register, Chinese Clinical Trial Register. All information about the table was accessed on 30 November 2020.

## REPURPOSED VACCINES FOR COVID-19 AND CLINICAL TRIAL

Already approved vaccines that are licensed for various infectious diseases have been shown to enhance the immune system and protect against COVID-19. Bacillus Calmette–Guérin (BCG), polio, and MMR vaccines are being repurposed for COVID-19 (**Table 4**). Near about 8 controlled trials on repurposed vaccines are currently in progress. It has been observed that the BCG vaccine has been tested in clinical trials for health workers in different countries, such as the Netherlands, Australia, and South Africa (66).

### BCG vaccine in the context of COVID-19 pandemic

BCG vaccine is a live attenuated vaccine, and the vaccine strain was derived from *Mycobacterium bovis*. The vaccine can induce nonspecific immunity. Utilizing nonspecific immunity, the vaccine shows protection against several bacterial and viral pathogens, which is called ‘off-target’ protection. Several scientists are providing the hypothesis that this vaccine may protect against severe COVID-19 (70,71). The BCG vaccines have been tested in clinical trials for health workers in different countries, such as the Netherlands, Australia, and South Africa (66). However, there is no sufficient evidence to recommend the use of BCG for the control of COVID-19.

## SOME SIGNIFICANT VACCINE CANDIDATES AND ITS DEVELOPERS

### The mRNA-1273 from ModernaTX, Inc

ModernaTX, Inc developed a novel LNP-encapsulated mRNA-based vaccine called mRNA-1273 vaccine. This vaccine encodes the complete stabilized S-protein of SARS-CoV-2. LNPs are constituted of diverse components such as ionizable lipid, 3 commercially available lipids, SM-102, DSPC, PEG2000 DMG, and cholesterol. This vaccine has completed phase-I clinical trial (NCT04283461). The phase-I clinical trial was open-label, and NIH, USA carried

**Table 4.** Ongoing/completed phase-III clinical trial for repurposed vaccines which can be used as COVID-19 vaccines

Sl. No.	Clinical trial ID	Study start date and end date (probable)	No. of patients enrolled in this clinical trial	Randomized	Developer	Country of origin	Vaccine type	Current status	Remark
1	NCT04350931	April 20, 2020 and December 1, 2020	900	Yes	Ain Shams University	Egypt	BCG vaccine	Not yet recruiting	The immunogenicity of Egyptian healthcare workers was assessed through this repurpose BCG vaccine
2	NCT04328441	March 25, 2020 and April 30, 2021	1,500	Yes	UMC Utrecht	Netherlands	BCG vaccine	Recruiting	Enhanced trained immune responses through BCG vaccination
3	NCT04475302	July 1, 2020 and May 2021	2,175	No	Tuberculosis Research Centre	India	BCG vaccine	Recruiting	Enhance innate and adaptive immune responses, IgM, IgG, and IgA antibody titers generated in a subset of individuals
4	NCT04461379	July 21, 2020 and January 1, 2021	908	Yes	Hospital Universitario	Mexico	BCG vaccine	Not yet recruiting	Vaccine offers towards the prevention and reduction of severity in cases of COVID-19
5	NCT04327206	March 30, 2020 and March 30, 2022	10,078	Yes	Murdoch Childrens Research Institute	Australia	BCG vaccine	Recruiting	This repurpose vaccine was used among the healthcare workers
6	NCT04379336	May 4, 2020 and April 28, 2021	500	Yes	TASK Applied Science	South Africa	BCG vaccine	Recruiting	Enhancing non-specific immune responses through BCG vaccination
7	NCT04384549	May 20, 2020 and February 20, 2021	1,120	Yes	Assistance Publique - Hôpitaux de Paris	France	BCG vaccine	Not yet recruiting	Controlled trial was conducted to understand the immunogenicity through BCG vaccination
8	NCT04357028	July 13, 2020 and November 1, 2020	200	Yes	Kasr El Aini Hospital	Egypt	MMR vaccine	Recruiting	Controlled trial was conducted among health care professional to understand the immunogenicity through MMR vaccination

Information has been taken from: <https://ClinicalTrials.gov>, EU Clinical Trials Register, Chinese Clinical Trial Register. All information about the table was accessed on 30 November 2020.

a dose-ranging trial. Phase-I study helps to understand the immunogenicity and safety of the vaccine. A total of 120 healthy human participants were enrolled in the study. Human subjects received intramuscular (IM) injection in the deltoid muscle with either 10 or 100 µg of mRNA-1273 in 1 ml of 1× PBS into the right hind leg. Orthogonal studies confirmed the role of the mRNA-1273 vaccine in the induction of S-specific CD4 T cells, followed by the production of IL-21, suggesting the generation of potent Ab response (52). Moreover, higher ACE2 binding inhibition and higher neutralizing activity were observed with the mRNA-1273 vaccine candidate (52). The patient can be vaccinated twice after a 28-day interval, which will again have a follow up for 1 year (53,72). Phase-II clinical trial (NCT04405076) for mRNA-1273 was a randomized, placebo controlled, clinical trial. Study evaluated the reactogenicity, immunogenicity and safety of mRNA-1273. In this study, 600 participants (young adults [18–54 years] and olders [65+ years]) were enrolled. In patents 2 doses were analysed (50 mcg and 100 mcg). This vaccine showed 94.5% effectiveness in phase-III trial (NCT04470427). More than 30,000 US participants were enrolled in this trial. Participants even included about 5,000 individuals under 65 years of age with high-risk chronic disease and 7,000 individuals over 65 years of age (73,74).

#### Ad5 vectored COVID-19 vaccine from CanSino Biologics Inc.

CanSino Biologics is a Chinese biopharmaceutical company that developed the Ebola vaccine (Ad5-EBOV). CanSino Biologics and Beijing Institute of Biotechnology developed Ad5 vectored COVID-19 vaccine (Ad5-nCoV) that is currently in phase-III clinical trial

(NCT04526990) in collaboration with CDC Jiangsu Province, CDC Hubei Province, Academy of Military Medical Sciences, and Tongji Hospital. It is a recombinant vaccine that was developed from Ad5 vector (75,76). The open-label phase-I clinical trial was completed with 108 healthy volunteers in-between 18 to 60 years of age. The 108 participants were divided into three groups and received single IM injection in a dose-escalating manner ( $5 \times 10^{10}$  viral particles per 0.5 ml,  $1 \times 10^{11}$  viral particles per ml or  $1.5 \times 10^{11}$  viral particles per 1.5 ml) in the deltoid muscle (77). At 28 days after vaccination, it was observed that the Ad5 vectored COVID-19 vaccine can induced humoral and T cell responses. Moreover, both CD4<sup>+</sup> and CD8<sup>+</sup> T cells were activated in vaccine recipients (77). On the other hand, they have also completed the phase-II trial to understand the immunogenicity and safety. In this study, 603 volunteers were recruited. The volunteers received 2 types of doses. Some volunteers received  $1 \times 10^{11}$  viral particles and other received  $5 \times 10^{10}$  viral particle. Although, adverse reactions were reported by 72% from first group and 74% from second group, no serious adverse reactions were observed from the study. Therefore, the study concluded that  $5 \times 10^{10}$  viral particles are safe for vaccination (78).

### **INO-4800 from Inovio Pharmaceuticals**

Inovio Pharmaceuticals is a biotechnology company that developed a DNA based INO-4800 vaccine. This vaccine completed phase-I clinical trial (NCT04336410), in collaboration with the Coalition for Epidemic Preparedness Innovations (CEPI), and is currently registered in phase-II clinical trial (NCT04447781), to evaluate the tolerability, safety, and immunological profile of this vaccine. This Clinical study has recruited 120 participants who will receive one intradermal injection from 0.5 mg to 1 mg, as per the study group, followed by EP (electroporation) using CELLECTRA® 2000. The vaccine is administered on day 0 and wk 4. Preclinical results showed that mice and guinea pigs vaccinated with INO-4800 showed induction of Ag-specific T cell responses and SARS-CoV-2 neutralizing antibodies. Moreover, inhibition of spike protein binding to the ACE2 receptor and the presence of antibodies against SARS-CoV-2 in the lungs were also observed (47).

### **LV-SMENP-DC from Shenzhen Geno-Immune Medical Institute**

Shenzhen Geno- Immune Medical Institute in collaboration with Third People's Hospital, Shenzhen and Second People's Hospital, Shenzhen developed a lentiviral vaccine (LV-SMENP-DC) that is based on the conserved domains of polyprotein protease and the viral structural proteins. They used a lentivirus vector system to modify dendritic cells (DC) and activate T cells by expressing immune-modulatory genes and viral proteins. This vaccine candidate is registered in phase-I/phase-II clinical trial (NCT04276896). This study recruited 100 participants who are receiving  $5 \times 10^6$  LV-DC vaccine and  $1 \times 10^8$  CTLs via injection (subcutaneous) and intravenous infusion, respectively.

### **The aAPC vaccine from Shenzhen Geno-Immune Medical Institute**

Shenzhen Geno- Immune Medical Institute is developing another vaccine for SARS-CoV-2, which is based on a lentiviral vector system that can modify aAPC and can activate T cells via expressing viral proteins and immune-modulatory genes. This vaccine candidate is registered in phase-I clinical trial (NCT04299724) in collaboration with Shenzhen second people's hospital and Shenzhen third people's hospital. This study recruited 100 participants who are receiving a 3 subcutaneous injection with a total of  $5 \times 10^6$  cells each time on days 0th, 14th, and 28th.

### **LUNAR-COV19 from Arcturus Therapeutics**

Arcturus Therapeutics has formed a partnership with the Duke-National University of Singapore Medical School to develop an mRNA vaccine against SARS-CoV-2. They are

developing mRNA STARR™ Technology in combination with the LUNAR® RNA medicine delivery technology based LUNAR-COV19 (ARCT-021) vaccine. This is a self-replicating low dose mRNA vaccine that encodes for the prefusion spike protein of SARS-CoV-2. This vaccine can be produced more quickly than a protein-based vaccine, and the duration of Ag expression is more, resulting in prolonged protection from COVID-19 with a single dose. It is registered for phase-I/phase-II clinical trial (NCT04480957), with 92 healthy participants (age between 21 to 55 years). This study is expected to complete in December 2020.

### **Adjuvanted protein vaccine from GSK and Sanofi**

GSK and Sanofi S.A. are multinational Biopharmaceutical companies. They are developing the adjuvanted protein vaccine for SARS-CoV-2. Sanofi has provided S protein Ag which is developed through recombinant DNA technology. On the other hand, GSK has provided adjuvant technology for the production of this vaccine. It is in preclinical trial and will enter in phase-I clinical trial (47).

### **The mRNA vaccine (BNT162) from BioNTech SE**

BioNTech is Biopharmaceutical Company, which is also called as BioNTech RNA Pharmaceuticals GmbH. In collaboration with Pfizer, BioNTech is developing mRNA vaccine candidate against SARS-CoV-2 which is under clinical trial (79). Two types of clinical trials are registered for this mRNA vaccine in ClinicalTrials.gov. The first one is NCT04380701, which consists of 4 BNT162 vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). This is a multicentric phase-I/phase-II clinical study with 456 participants. Single to escalating doses of these vaccines are IM injected in different groups of patients. Second study is NCT04368728, which consists of BNT162b1 (phase-II) and BNT162b2 (phase-III) vaccines. In this study 43,998 participants have enrolled who are taking mid dose to low dose of vaccine through IM injection. Recently it was reported that phase-III clinical trial is completed for BNT162b2 and has applied for vaccine licensing in USA (74).

### **Synthetic mRNA vaccine from Curevac**

CureVac is a biopharmaceutical company that has developed a synthetic mRNA vaccine for COVID-19. They have completed phase-I clinical trial (NCT04449276) in collaboration with the CEPI. This study recruited 168 participants who are receiving vaccine through IM injection at escalating dose on day 1 and day 29 at the dose levels of 2, 4, and 8 µg. They have also completed phase-II clinical trial (NCT04515147), and initiation of phase-III of clinical trial is in pipeline (74).

### **COVAX19 from Vaxine**

Vaxine, a biotechnology company dealing in vaccine development, have developed COVAX19 vaccine against SARS-CoV-2 in collaboration with Central Adelaide Local Health Network Incorporated. It contains SARS-CoV-2 recombinant spike Ag with Advax-SM adjuvant. This vaccine is registered in phase-I clinical trial (NCT04453852) where 40 participants are enrolled. The human volunteer will receive the 25µg vaccine Spike Ag and 15 mg Advax-2 adjuvant.

### **AdVac and PER.C6 Technology based vaccine from Johnson & Johnson**

Johnson & Johnson is a pharmaceutical company that has developed adenovirus-vector based vaccine for COVID-19 using 2 technologies, i.e. AdVac® and PER.C6® technology. For this project this company has collaborated with Biomedical Advanced Research and Development Authority. The product is in preclinical trial.

### ChAdOx1 nCoV-19 from University of Oxford

The University of Oxford (Jenner Institute) along with the Oxford Vaccine Group has developed the ChAdOx1 nCoV-19 vaccine for the pandemic virus. This vaccine showed protectiveness in vaccinated animals against pneumonia (80). This vaccine is registered for the phase-I/phase-II and phase-II/phase-III clinical trial.

We found 2 clinical trial entries for this vaccine in the ClinicalTrials.gov. First one is noted as NCT04324606 which is dealing with phase-I/phase-II as well as randomized clinical study with 1,090 participants volunteers (aged 18–55 years). They have divided the participants into 13 groups (group 1a, group 1b, group 2a, group 2b, group 2c, group 2d, group 2e, group 3, group 4a, group 4b, group 4c, group 4d). Here, the participants received a single variable dose of this vaccine via IM injection with or without paracetamol to determine the immunogenicity and efficacy. Folegatti et al., (81) has published preliminary report of this clinical trial which showed increased and boosting homologous Ab response, as well as suitable safety profile of this vaccine against this pandemic virus.

Second one is noted as NCT04400838 which is dealing with phase-II/phase-III randomized clinical study with 10,260 participants' volunteers. In this study the participants are divided in 8 different groups (groups 1 & 7 with 56–69 years age; groups 2 & 8 with 70 year of age and over; group 3 with children with 5–12 years of age; groups 4 and 6 with 18 years of age; group 5 with 18–55 years of age). Recently Ramasamy et al. (82) reported the preliminary findings of safety and immunogenicity of ChAdOx1 nCoV-19 from a single-blind, randomised, phase-II/phase-III clinical trial. The study shows that the vaccine is better tolerated in older adults compare to younger adults. After a boost dose, the vaccine has alike immunogenicity throughout all age groups (82). Serum institute of India has collaborated for the production of ChAdOx1 nCoV-19 vaccine (83).

## CHALLENGES INFLUENCING THE DEVELOPMENT OF COVID-19 VACCINE

There are several other factors which are influencing the vaccine development of COVID-19 (Fig. 1B).

The vaccine development is in itself a long process and takes near about 10 years per vaccine in general (84). However, the hour of need is to develop this vaccine at a pandemic speed. Because of the limited time span, the vaccine clinical trial phases are overlapping in this case to fight against the pandemic (71). The phase-I to phase-III timelines are very extensive, and all the regulatory authority of vaccine licensing are thinking about a new timeline for this vaccine.

Vaccine development process (up to licensing of the vaccine) requires huge money involvement. It has been estimated that the cost of development to bring a vaccine candidate to the end of phase-II trials requires US\$31–68 million (85). Collaboration is the most significant strategy for therapeutic development and new research (86). Therefore, a different representative from the academia and biopharmaceutical companies is collaborating to fulfill the growing demands (87). The collaborations between the private and public sector might help to develop this vaccine very quickly.



There is a need for billions dosages of this vaccine and it create high production requirement. Therefore, the proper bio manufacturing infrastructure should be developed in this direction, including the and up to the finish product development.

## CONCLUSION

To develop the COVID-19 vaccine, it is critical to understand the interactive modulation of viral proteins with human host receptors. Furthermore, it is essential to understand the mechanism of protective immune responses against SARS-CoV-2 infection. These understandings might facilitate the development of a potential vaccine for COVID-19 by providing us guidance for appropriate Ag selection. Till now, extensive academic and research collaborations have enabled the development of various vaccines for COVID-19 that are currently under clinical trials, mostly in phase-I/phase-II/phase-III. Some vaccine have completed phase-III and have applied for licensing. As the clinical trials and approval of vaccines is a long-term process, we need to do out-of-the-box planning for getting the fast regulatory approval, funding for the vaccine, creation of cGMP production facility, and enhanced bio manufacturing capacity for this vaccine. What we need to understand is that it is global security urgency, and we should move appropriately and promptly towards generating the vaccine against COVID-19.

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## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Different platforms of COVID-19 vaccine development with their advantages and disadvantages. List of various companies or organizations utilizing these platforms

[Click here to view](#)

### Supplementary Table 2

Vaccine in preclinical development stage for COVID-19

[Click here to view](#)

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