Review Article

# Review of current vaccine development platform to prevent coronavirus disease


## ABSTRACT

On January 30, 2020, the World Health Organization (WHO) declared a severe respiratory disorder syndrome which originated in Wuhan city as a global public health emergency, and the pandemic declaration by the WHO was made on March 11, 2020. Persons infected with SARS-CoV-2 are frequently asymptomatic, yet they have high respiratory viral loads, and they are major purveyors of viral spread. These factors have led to the current explosion of COVID-19 hospitalizations and deaths. Vaccines could play an important role by preventing severe diseases and increasing population immunity and reducing the ongoing health crisis. There is wealth of information for the review available since it is a current topic of interest. Initially, Google Scholar was utilized to take an initial sample of what types of articles are available. We searched other databases such as PubMed, EMBASE, and COCHRANE LIBRARY for research articles published up to March 2021, with no language restrictions. We found seven peer-reviewed publications available on the efficacy of SARS-CoV-2 vaccines: AZD1222 (AstraZeneca/University of Oxford), a ChAdOx1-based vaccine with a reported efficacy of 70.4% and two mRNA-based vaccines: BNT162b2 (Pfizer/BioNTech) with a reported efficacy of 95% and mRNA-1273 (Moderna/NIAID) with a reported efficacy of 94.1%. Internet was used as a source because of its limitless networking of resources. Sources used from the internet were written by professionals in their fields and published on reliable sites, in referred publications, or on professional organization sites. The cited references were within the last 2 years.


**Keywords:** Clinical trials, COVID-19, SARS-CoV-2, vaccine efficacy, vaccines

## INTRODUCTION

On January 30, 2020, the World Health Organization (WHO) declared a severe respiratory disorder syndrome which originated in Wuhan city as a global public health emergency, and the pandemic declaration by the WHO was made on March 11, 2020.[1] Since its emergence in November 2019, it has spread to 188 countries and 25 territories around the globe, despite elaborate efforts by the WHO and governments to contain the infection, primarily owing to the highly infectious nature of this virus.[2] Structurally, coronaviruses are pleomorphic, enveloped viruses with a characteristic fringe of projections composed of S-protein on their surface equipped with a positive-sense single-stranded RNA genome.[2]

SARS-CoV-2 enters host cell via the angiotensin-converting enzyme 2 receptor (ACE2). The S-protein of CoV, especially the receptor binding domain (RBD), is able to induce neutralizing antibodies (NAbs) and T-cell immune responses.[3] SARS-CoV-2 attacks host immune system, leading to an uncontrolled inflammatory response, lymphocytopenia, high cytokine levels, and increased antibodies.[2] Persons infected with


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SARS-CoV-2 are frequently asymptomatic, yet they have high respiratory viral loads, and they are major purveyors of viral spread. These factors have led to the current explosion of COVID-19 hospitalizations and deaths. Our only hope is safe and effective vaccines that can be widely deployed to provide herd immunity that can control viral spread.[4]

Vaccines could play an important role by preventing severe diseases and increasing population immunity and reducing the ongoing health crisis.[5] Vaccines stimulate the immune system of an individual to prepare it against a future pathogen. To address the COVID-19 public health emergency, the United States Food and Drug Administration has issued a guidance in June 2020 to assist sponsors in clinical development and licensure of vaccines for the prevention of COVID-19.[6] The WHO has implemented an access to COVID-19 tools accelerator for coordinating global vaccine development program in collaboration with The Global Alliance for Vaccines and The Coalition for Epidemic Preparedness Innovations.[7]

There are multiple methods and platforms being tried for the development of COVID-19 vaccines, such as inactivated or weakened, protein subunit, viral vector, RNA and DNA vaccines, and virus-like particles (VLPs) with each exhibiting advantages and disadvantages.

## Inactivated vaccines

They are produced by completely inactivating or killing the pathogen, on injecting it to the host they primarily induce protective antibody against epitopes on hemagglutinin glycoprotein on surface of the virus.[2]

### *BBIBP-CorV*

The candidate vaccine is an inactivated whole SARS-CoV-2 virus vaccine developed by Wuhan Institute of Biological Products and Sinopharm. The Phase I trial was conducted using three doses with 2.5 μg, 5 μg, and 10 μg antigen protein content per dose, and the results showed inactivated vaccine candidate to have better safety profiles.[2] Phase II trial was conducted using 5 μg antigen protein, and the results showed that vaccine candidate effectively produces antibody titers. No serious adverse effects and only mild-to-moderate self-limiting reactions were reported. It is administered intramuscular and can be stored at a temperature of 2°C–8°C.

### *PiCoVacc/Sinovac/CoronaVac*

It is a purified formalin-inactivated alum-adjuvanted SARS-CoV-2 virus vaccine candidate developed by China-based biotechnology company Sinovac Biotech.[6] CoronaVac is currently in Phase 3 clinical trials in a two-dose injection regimen with a 14-day interval, both dosages induced a seroconversion on more than 90% of the individuals immunized, however, no T-cell responses were reported.[8] It can be given intramuscular and can be refrigerated. The vaccine appears to be safe and did not cause any severe side effects. China has approved CoronaVac as a part of an emergency use program in the country for high-risk individuals, such as healthcare workers and essential personnel.[9]

### *Bharat Biotech's Covaxin*

It is India's first inactivated vaccine against SARS-CoV-2 making it safe to be injected into the body developed by Bharat Biotech, Indian Council of Medical Research, National Institute of Virology, Pune, by the name of Covaxin.[2] When administered, immune cells can still recognize the dead virus, prompting the immune system to make antibodies against the pandemic virus. No adverse side effects were reported and vaccine was found to generate robust immune response.[2] The vaccine is also reportedly effective against B.1.1.7 variant of SARS-CoV-2. No life-threatening events were reported in trial. The most common adverse event was pain at the injection site, followed by headache, fatigue, and fever.[10] It is administered intramuscular and can be stored at least a week at room temperature.

## Live-attenuated vaccine

### *DelNS1-SARS-CoV-2 receptor binding domain (University of Hong Kong)*

This live-attenuated vaccine is influenza-based vaccine strain with a deletion in the NS1 gene; it is reorganized to express the RBD of SARS-CoV-2 spike protein on its surface and is cultivated in the chick embryos and/or Madin–Darby Canine kidney cells. It is potentially more immunogenic than the wild-type influenza virus and can be administered as a nasal spray.[2]

## Nucleic acid vaccines

### *DNA vaccines*

They are noninfectious and nonreplicating. They are easy to produce within a short duration, cost-effective, and stable.[2] DNA vaccines have a great therapeutic potential due to their ability to enhance T-cell induction and antibody production.

### *Cadila ZyCoV-D*

It is India's second vaccine, a type of DNA plasmid vaccine expressing SARS-CoV-2 S-protein developed by Zydus Cadila Healthcare. The candidate has been approved with Phase 3 trials, according to the Drugs Controller General of India.[9] No adverse side effects were reported; it is administered intradermally and can be stored at room temperature for 3 months [Table 1].

**Table 1: Landscape of rapidly progressing anti-COVID-19 vaccines and its clinical trial stage with its efficacy and dosage: The list of all the vaccine candidates in the pipeline can be assessed from: World Health Organization, Research and Development blueprint team**

| Vaccine type | Vaccine | Developed by | Number of doses | Timing of doses (days) | Efficacy | Clinical trial stage |
|---|---|---|---|---|---|---|
| Inactivated vaccine | | | | | | |
| 1.1 | BBIBP-CorV/Sinopham | Wuhan Institute of Biological products/ Sinopham | X2 | 0-21 | 73% | Phase 3 NCT04456595669/UN6. KEP/EC/2020 NCT04582344 |
| 1.2 | PiCoVacc/Sinovac/ CoronaVac | Sinovac Biotech | X2 | 0-14 | 50.65% Brazil trial, 91.25% in Turkey trial | Phase 3 NCT04560881 |
| 1.3 | Covaxin/BBV152 | Bharat Biotech, ICMR and NIV (Pune) | X2 | 0-28 | 78% | Phase 3 NCT04471519 |
| Live-attenuated vaccine | | | | | | |
| 2.1 | DelNS1-SARS-CoV-2 RBD (Intranasal flu-based RBD) | University of Hong Kong | - | - | - | Phase 1 ChiCTR2000037782 |
| Nucleic acid vaccines | | | | | | |
| DNA vaccines | | | | | | |
| 3.1 | Cadila ZYCoV-D | Zydus Cadila Healthcare | X3 | 0-28-56 | Unknown | Phase 1/2 CTRI/2020/07/026352 |
| 3.2 | INO-4800 | iNOVIO Pharmaceuticals | X2 | 0-28 | Unknown | Phase 1/2 NCT04447781 NCT04336410 |
| RNA vaccines | | | | | | |
| 3.1 | BNT162b1/Comirnaty | Pfizer/Fosum/BioNTech | X2 | 0-21 | 91% | Phase 3 NCT04368728 |
| 3.2 | m-RNA 1273 | Moderna | X2 | 0-28 | 94% | Phase 3 NCT04470427 |
| 3.3 | CvnCoV | CureVac | X2 | 0-28 | Unknown | Phase 2 NCT04515147 |
| Nonreplicating viral-vectored vaccines | | | | | | |
| 4.1 | Ad5nCoV/Convidicea | Cansino Biologics | X1 | - | 65.28% | Phase 3 NCT04526990 NCT04540419 |
| 4.2 | Ad26CoV2.S/JNJ 78436735 | Janssen Pharmaceuticals | X1 | - | 72% | Phase 3 NCT0505722 |
| 4.3 | CoroFlu | University of Wincosin-Madison/Flugen/ Bharat Biotech | X1 | - | | Preclinical |
| 4.4 | LV-SMENP-DC | Shenzen Geno-Immune Medical Institute | - | - | - | Phase ½ NCT04276896 |
| 4.5 | ImmunityBio | ImmunityBio Pharmaceuticals | X2 | 0-21 | | Phase 1 NCT04591717 |
| 4.6 | ChAdoX1n CoV19/ AZD122/Covishield/ AstraZeneca/Vaxzevria | University of Oxford in collaboration with Serum Institute of Pune (India)/ AstraZeneca | X2 | 0-28 | 62%-90% | Phase 3 NCT04674651 ISRCTN89951424 |
| 4.7 | Sputnik V | Gamaleya Research Institute of Epidemiology and Microbiology | X2 | 0-21 | 92% | Phase 3 NCT 04530396 NCT 04564716 |
| Protein subunit vaccines | | | | | | |
| 5.1 | Molecular clamp-stabilized spike protein V | University of Queensland/ GSK/Dynavax | X2 | 0-28 | - | Phase 1 ACTRN12620000674932p |

*Contd...*

**Table 1: Contd...**

| Vaccine type | Vaccine | Developed by | Number of doses | Timing of doses (days) | Efficacy | Clinical trial stage |
|---|---|---|---|---|---|---|
| 5.2 | EpiVacCorona | Federal Budgetary Research Institution State Research Centre of Virology and Biotechnology | X2 | 0-21 | Unknown | Phase 1 NCT04527575 |
| 5.3 | Novavax/ NVX-CoV2373 | Emergent Biosolutions/ Novavax | X2 | 0-21 | 96% against original coronavirus, 86% against B.1.1.7, 49% against B.1.351 | Phase 3 NCT04368988 |
| 5.4 | PittCoVac | University of Pittsburgh | - | - | - | Preclinical |
| 5.5 | Triple Antigen vaccine | Premas BioTech, India | - | - | - | Preclinical |
| 5.6 | ZF-2001 | China's Anhui Zhifei Longlon Biopharmaceutical and Institute of Chinese Academy of Sciences | X2 | 0-28 | Unknown | Phase 1 NCT04445194 Phase 2 NCT04466085 |
| Plant-based vaccine | | | | | | |
| 6.1 | CoVLP | Medicago Inc. | X2 | 0-21 | Unknown | Phase 2/3 ACTRN 1262000008179 |

NCT: Mandatory reporting of national clinical trial, ChiCTR: Chinese clinical trial registry, ACTRN: Australian clinical trial registration number, ISCTR: International standard for clinical trial registration, mRNA: Messenger RNA, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RBD: Receptor binding domain, ICMR: Indian Council of Medical Research, NIV: National Institute of Virology, GSK: Glaxo Smith Kline

### *Ino-4800 (iNOVIO pharmaceuticals)*

It is a prophylactic DNA vaccine against SARS-CoV-2 developed by iNOVIO. It uses codon-optimized S-protein sequence of SARS-CoV-2 to which an IgE leader sequence is affixed.[2] The vaccine is injected intradermally at a dose of 1.0 mg to 40 healthy volunteers in Phase 1 trial at baseline and at 4 weeks, followed by electroporation. No adverse side effects were reported and can be stored at room temperature.

## RNA vaccines

### *mRNA-1273/Moderna*

The messenger RNA (m-RNA)-1273 vaccine is a lipid nanoparticle-encapsulated nucleoside modified m-RNA–based vaccine developed by Moderna and National Institute of Allergy and Infectious Diseases.[2] It encodes the spike glycoprotein (S-protein) present on the surface of SARS-CoV-2. The safety and efficacy results from the Phase 3 trial of mRNA-1273 were published in the *New England Journal of Medicine*, confirming the vaccine candidate's 94.1% efficacy and safety profile.[8] Binding antibody responses increased rapidly after the first immunization.[11] The local reactions to vaccination were mild; however, moderate-to-severe systemic side effects, such as fatigue, myalgia, arthralgia, and headache, were noted in about 50% of participants in the mRNA-1273 group after the second dose. These side effects were transient, starting about 15 h after vaccination and resolving in most participants by day 2, without sequelae.[12] It is administered intramuscularly and can be stored till 30 days with refrigeration and for 6 months at −4°F (−20°C).

### *Comirnaty/BNT162b1*

It is a codon-optimized, lipid nanoparticle-encapsulated mRNA vaccine that encodes for the trimerized SARS-CoV-2 RBD, a critical target of the virus NAb developed by BioNTech, Fosun Pharma, and Pfizer, available in the name of Comirnaty. Researchers have administered the BNT162b1 vaccine candidate intramuscularly at three different doses 10 µg, 30 µg, and 100 µg and found that it exhibits acceptable safety profile and elicits adequate antibody titer.[2] A two-dose regimen of BNT162b1 30 µg per dose, given 21 days apart, was found to be safe and 95% effective against COVID-19.[13] In the interval between the first and second doses, the observed vaccine efficacy against COVID-19 was 52%, and in the first 7 days after dose two, it was 91% reaching full efficacy against disease with onset at least 7 days after dose.[14] Most of the reported adverse reactions were mild or moderate in severity and resolved in the first 7 days after each BNT162b1 dose for the prime and boost vaccinations.[15] It showed acceptable safety profile, and long-term assessment of vaccine candidate for efficacy and tolerability is ongoing in Phase 3 trials. It can be stored at −25°C to −15°C [Table 2].

### *CVnCoV*

CureVac is developing an m-RNA–based vaccine, CVnCoV. It works by using nonchemically modified nucleotides within mRNA to provide a strong and balanced activation of the immune system. No life-threatening side effects were reported. It is administered intramuscularly and can be stored for at least for 3 months at 36°F–46°F (2°C–8°C) [Table 2].

**Table 2: List of COVID-19 vaccine along with its clinical trial remarks, signs and symptoms, storage temperature, and route of administration: The list of all the vaccine candidates in the pipeline can be assessed from: World Health Organization, Research and Development blueprint team**

| Name of vaccine | Clinical trial remarks | Signs and symptoms | Storage temperature | Route of administration |
|---|---|---|---|---|
| BBIBP-CorV (Sinopham) | Animal trials suggest that the vaccine protects the model animals without ADE | No serious adverse effects, only mild-to-moderate self-limiting reactions | 2°C-8°C | Intramuscular |
| PiCoVacc/Sinovac/ CoronaVac | The phase 1/2 clinical trials of the inactivated viral vaccine candidate PiCoVacc demonstrated that the vaccine induces neutralizing antibodies with a seroconversion rate of 90% in a 0-0314-day schedule. The Company has got the permission for conducting the Phase 3 clinical trials in Brazil in collaboration with Instituto Butantan. Furthermore, it is expected to get further approvals in Bangladesh for the Phase 3 clinical trials | No severe side effects | Refrigerated | Intramuscular |
| Covaxin/BBV152 | It is the whole virion-inactivated experimental vaccine under the phase 1/2 clinical trials. These trials are supposed to study the safety and reactogenicity, tolerability, and the immunogenicity in the healthy volunteers | No life-threatening events. Most common adverse events are pain at injection site followed by headache, fatigue, and fever | At least a week at room temperature | Intramuscular |
| DelNS1-SARS-CoV-2 RBD (intranasal flu-based RBD) | It is attenuated by the deletion of a key virulent element and the immune antagonist, NS1, which is potentially more immunogenic than the wild-type influenza virus | No adverse side effects were reported | - | Intranasally |
| Cadila ZYCoV-D | It is a genetically engineered DNA plasmid-based vaccine encoding for the membrane proteins of the virus. The clinical trials to study the immunogenicity, and safety of the vaccine | No adverse side effects were reported | Stable at room temperature for 3 months | Intradermal |
| INO-4800 | Preclinical trials reveal induction of the antigen specific T cell responses, and functional nAb, thus creating an obstacle for the S protein to bind to the hACE2 receptor. Phase I clinical trials will evaluate the safety, immunogenicity, and tolerability of the vaccine | No adverse side effects were reported | Over a year at room temperature | Intradermal |
| BNT162b1/ Comirnaty/ Tozinameran | BNT162b1, the mRNA based vaccine induced a high dose-dependent nAb titers along with the RBD-binding IgG concentrations after the second dose. This was accompanied by the CD4+ and CD8+ T cell responses | Mild to moderate in severity | (−25°C-−15°C) | Intramuscular |
| m-RNA 1273 | The geometric mean of RBD specific antibody titers showed a rapid increase in all the participants. Seroconversion was observed after 15 days and the median magnitude of antibody responses was similar to the magnitude in convalescent sera. However, the pseudovirus neutralizing activity was not high before the administration of the second dose, which indicates the requirement of a two-dose vaccination schedule | Local reaction to vaccination are mild, however moderate-to-severe side effects such as fatigue, myalgia, arthralgia, and headache | 30 days with refrigeration, 6 months at−4°F (−20°C) | Intramuscular |
| CVnCoV | m-RNA as a data carrier to instruct the human body to produce its own proteins capable of fighting a wide range of diseases is used | No life-threatening side effects were reported | Stable at least 3 months at 36°F-46°F (2°C-8°C) | Intramuscular |
| Ad5nCoV/ Convidicea | The randomized, double-blind, placebo-controlled Phase 2 clinical trials of the recombinant Ad5-vectored vaccine represented a positive cellular response at $5\times10^{10}$ viral particles along with seroconversion of the humoral immune response. Severe adverse reactions were reported in 9% of the individuals in the $1\times10^{11}$ viral particles dose group and 1% volunteers exhibited these adverse reactions in the $5\times10^{10}$ viral particles dose group | No serious adverse events, those reported are mild to moderate and resolved within 2 days of reaction onset | 2°C-8°C | Intramuscular |

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**Table 2: Contd...**

| Name of vaccine | Clinical trial remarks | Signs and symptoms | Storage temperature | Route of administration |
|---|---|---|---|---|
| Ad26CoV2.S/JNJ 78436735 | To accelerate the development of the vaccine the company will use the AdVac® and PER.C6® technologies | Mild side effects reported such as fatigue, headache, fever, pain at injection site which generally resolves within 1-2 days | Up to 2 years frozen at−4°F (−20°C), and up to 3 months refrigerated at 36°F–46°F (2°C-8°C) | Intramuscular |
| CoroFlu | The M2SR is self-limiting because it does not undergo viral replication because of the absence of M2 gene | No adverse events were reported | - | Intranasally |
| LV-SMENP-DC (lentiviral-based minigene DC and T-cell vaccine) | LV-SMENP-DC vaccine is designed by altering DC with lentivirus vectors to express the "SARS-CoV-2 SMENP minigene and immune modulatory genes." LV-DC that presents SARS-CoV-2 specific antigens will activate the CTLs | - | - | Subcutaneous |
| ChAdoX1n CoV19/ AZD122/Covishield/ AstraZeneca | The preliminary reports of phase 1/2, single-blind, randomized controlled trials of the ChAdOx1 nCoV-19 vaccine have showcased the spike-specific T-cell responses along with the Antispike IgG response in 91% participants as per the MNA80 while an assay PRNT50 depicted a 100% response after a single dose. Nevertheless, after the booster dose neutralizing response was seen in all the participants which had a substantial correlation with the neutralizing antibody titers as measured by ELISA | Mild side effects reported such as fatigue, headache, fever, pain at injection site which generally resolves within 1-2 days | Stable in refrigerator for at least 6 months | Intramuscular |
| Sputnik V | Two types of the vaccines - fluid based and powder based for infusions - will be tried on two batches of volunteers, 38 individuals each. The members will be isolated in two Moscow medical clinics | No adverse side effects were reported | 2°C-8°C | Intramuscular |
| Molecular clamp/ stabilized/Spike Protein V | It is a stabilized prefusion viral protein subunit vaccine which is based upon the molecular clamp technology and uses AS03 adjuvant system from GSK. In mice, vaccination with MF59C.1-adjuvanted S clamp was found to elicit a robust humoral immune response that efficiently neutralized both the original SARS-CoV-2 strain and the D614G variant | No adverse events are reported | - | Intramuscular |
| EpiVacCorona | The vaccine contains small portions of viral proteins, known as peptides. In February, Tass reported that the immune response from EpiVacCorona lasted "for approximately a year" | No life-threatening adverse events were reported | Stable in refrigerator for up to 2 years | Intramuscular |
| Novavax/ NVX-CoV2373 | It is a stabilized prefusion viral protein subunit vaccine which is based upon the molecular clamp technology and uses AS03 adjuvant system from GSK | No adverse events were reported | Stable in refrigerator 2-8°C | Intramuscular |
| PittCoVac | Micro-needle array-based delivery of the recombinant SARS-CoV-2 S1 induced a statistically significant antigen-specific antibody response within 2 weeks of administration in the mice models | No adverse events were reported | - | The patch goes on like a Band-Aid and the needles, which are made entirely of sugar and protein pieces, simply dissolve into the skin |
| Triple-antigen vaccine | The 4-week placebo controlled, randomized, blinded to be conducted in mice, will seek to evaluate safety in the rodent model and examine immune response by dose titration | - | - | Intramuscular |
| CoVLP | A recombinant SARS-CoV-2 protein (undisclosed) VLP produced in tobacco | No adverse side effects were reported | Stable in refrigerator | Intramuscular |

ADE: Antibody-dependent enhancement, DC: Dendritic cell, MNA80: Micro-neutralization assay, PRNT: Plaque reduction neutralization, VLP: Virus like particles, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RBD: Receptor binding domain, mRNA: Messenger RNA, nAb: Neutralizing antibodies, LV-SMENP-DC: Lentiviral - Synthetic minigene - dendritic cell, CTL: Cytotoxic TLymphocytes, GSK: Glaxo Smith Kline

## Vectored vaccines

Vectored vaccines are generally constructed for a carrier virus, such as an adeno or pox virus, and are engineered to carry a relevant gene from the virus, usually the S-gene for SARS-CoV-2.

### *Ad5-nCoV/CONVIDICEA*

It is a recombinant, replication defective adenovirus type 5 vector (Ad5) expressing the recombinant spike protein of SARS-CoV-2.[2] It was prepared by cloning an optimized full length gene the S-protein along with the plasminogen activator signal peptide gene in the Ad5 vector devoid of E1 and E3 gene developed by CanSino Biologics named Convidicea.[2] The two lower doses of $5 \times 10^{10}$ and $1 \times 10^{11}$ viral particles were found to have an acceptable safety and immunogenicity profile and were selected for a Phase 2 trial.[8] No serious adverse reactions were reported and those reported are mild to moderate and resolved within a short period of time maximum by 48 h of reaction onset. The preliminary report suggests the acceptable safety.[2] It can be stored at 2°C–8°C temperature.

### *Ad26COV2.S/JNJ-78436735*

It is nonreplicating viral vector vaccine developed by Janssen Pharmaceutical Companies using their AdVac and PER C6 systems, which were also used to develop the company's Ebola vaccine.[9] The DNA in the adenovirus is modified so that it produces a key part of the SARS-CoV-2 virus particle to which the body then develops an immune response.[14] From the Phase ½ study in humans, a single dose of the vaccine was given intramuscularly that showed immunogenicity and good safety profile. Only mild side effects are reported such as fatigue, fever headache, and pain at injection site, which generally resolve within a day or 2. It was found to be 72% effective in the vaccine candidates. It can be stored up to 2 years frozen at −4°C (−20°C) and up to 3 months refrigerated at 36°F–46°F (2°C–8°C) [Table 2].

### *CoroFlu (University of Wisconsin-Madison/Flugen/Bharat Biotech)*

M2SR is a self-limiting version of the influenza virus, which is modified by insertion of the SARS-CoV-2 gene sequence of the spike protein. It is able to enter into the cell, thereby inducing the immunity against the virus.[2] It shall be administered intranasally mimicking the natural route of viral infection and had higher immunogenicity as compared to the intramuscular injections. No adverse events were reported.

### *LV-SMENP-DC (Shenzen Geno-Immune Medical Institute)*

The LV-SMENP-DC vaccine is prepared by engineering the dendritic cells (DCs) with the lentiviral vector expressing the conserved domains of the SARS-CoV-2 structural proteins and the protease using the SMENP mini genes. The subcutaneous inoculation of the vaccine presents the antigen presenting cells that ultimately activate the cytotoxic T-cell and generate the immune response.[2]

### *ImmunityBio*

ImmunityBio is developing a COVID-19 adenovirus vaccine candidate that targets both spike and nucleocapsid DNA in SARS-CoV-2 with no name announced so far. The interim Phase 1 results showed no serious adverse events in the low-dose group. Route of administration is subcutaneous.

### *ChAdOX1 nCov 19/AZD122/Covishield/AstraZeneca*

It consists of the nonreplicating simian adenovirus vector ChAdOX1 containing the full length structure spike protein of SARS-CoV-2 developed by AstraZeneca and the Oxford Vaccine Group at the University of Oxford in collaboration with Serum Institute of India and goes by the name Covishield.[9] Two vaccines are administered in two doses between 4 and 12 weeks apart. 14 days after first dose of vaccine, cellular response was observed, and after 28 days, humoral responses to spike protein are seen. The vaccine has an overall efficacy of 70%, with vaccine efficacy of 62.1% in a group of participants receiving two standard doses and 90% in a group receiving one half dose followed by a standard dose.[9] No adverse events are reported, and those that are reported are mild to moderate such as fatigue, headache, fever, and pain at injection site which generally resolves within 1–2 days. It is stable in refrigerator for at least 6 months.

### *Gamaleya's Sputnik V*

It is the type of nonreplicating adenovirus (rAd26-S + rAd5-S) type vaccine developed by Gamaleya Research Institute Epidemiology and Microbiology, Health Ministry of the Russian Federation. The vaccine consists of the two components, one with the recombinant adenovirus vector based on the human adenovirus type 26 and another with the adenovirus vector based on the human adenovirus type 5, both containing SARS-CoV-2 S protein gene.[2] The interim results of the Phase 3 Gam-COVID-Vac trial show that the vaccine is 91.6% (95% confidence interval 85.6–95.2) efficacious against COVID-19 (from day 21 after first dose, the day of receiving second dose). rAd26-S and rAd5-S are administered intramuscularly separately with a 21-day interval.[16] No adverse side effects were reported and vaccine induced cellular immunogenic response. It can be stored at a temperature of 2°C–8°C [Table 2].

## Protein subunit vaccine

A subunit vaccine is one that is based on the synthetic vaccines or recombinant antigenic proteins, which are necessary for

invigorating long-lasting protective/or therapeutic immune response. The virus enters the cell via endocytosis by utilizing the S-protein–mediated ACE2 receptor.[2] Therefore, the S-protein and its antigenic fragments are the prime targets of subunit vaccine.

### *Molecular clamp-stabilized spike protein vaccine*

It is being developed by the University of Queensland in collaboration with GSK and Dynavax.[2] They are developing a stabilized preperfusion, recombinant viral protein subunit vaccine which is based on molecular clamp technology to induce the production of NAbs.

### *EpiVacCorona*

The Federal Budgetary Research Institution State Research Centre of Virology and Biotechnology in Russia has developed a peptide vaccine for COVID-19 called EpiVacCorona.[9] The vaccine relies on chemically synthesized peptide antigens of SARS-CoV-2 proteins, conjugated to a carrier protein and adsorbed on an aluminum-containing adjuvant (aluminum hydroxide). The EpiVacCorona vaccine contributes to developing protective immunity against SARS-CoV-2 coronavirus following two intramuscular administrations spaced 21–28 days apart. A Phase ½ trial for evaluating the efficacy of vaccine was done on 100 participants, and it was found to be 100% effective. No life-threatening adverse events were reported, and it is stable in refrigerator for up to 2 years.

### *NOVAVAX/NVX-CoV2373*

It is a nanoparticle-based immunogenic vaccine which is based upon the recombinant expression of the stable prefusion, coronavirus S-protein.[2] Phase 1 trial participants who received the vaccine developed an antibody response at multiple dose, and vaccine has a favorable safety profile with no adverse events with efficacy of 89%[17] [Table 1]. It is administered intramuscularly and can be stored at a temperature of 2°C–8°C [Table 2].

### *PittCoVacc (University of Pittsburgh)*

It is microneedle array-based recombinant SARS-CoV-2 vaccine which involves the administration of rSARS-CoV-2 S1 and rSARS-CoV-2 S1Frs09 (recombinant immunogens).[2] This array is a fingertip-sized patch of 400 tiny needles that deliver spike protein pieces into the skin, where the immune reaction is the strongest. PittCoVac is still in testing phases. No adverse side effects were reported so far.

### *Triple-antigen vaccines (Premas Biotech, India)*

It is a multigenic VLP vaccine prototype wherein the recombinant spike, membrane, and envelope protein of SARS-CoV-2 have been coexpressed in an engineered *Saccharomyces cerevisiae* expression platform.[2] It is thought to be safe and easy to manufacture on a mass scale, in a cost-effective manner. Its route of administration is intramuscular.

### *ZF2001*

It is the latest subunit vaccine candidate to enter Phase 3 clinical studies is the adjuvanted RBD-dimeric antigen designed by Anhui Zhifei Longcom Biopharmaceutical and the Institute of Microbiology of the Chinese Academy of Medical Sciences.[8] It is administered intramuscularly which utilizes a harmless fragment of SARS-CoV-2, instead of the complete germ.

## Plant-based vaccine

### *CoVLP*

Medicago Inc., recently developed a plant-derived recombinant quadrivalent VLPs coronavirus vaccine named CoVLP. It uses the virus-transfected plant *Nicotiana benthamiana* to express the prefusion trimeric subunit form of the SARS-CoV-2 S-protein and assemble it on the surface of VLPs, which are harvested and used for immunization.[8] No life-threatening adverse events were reported.

## Nasal sray

### *AdCOVID*

AdCOVID is a nasal spray developed by AltImmune a biopharmaceutical company for COVID-19, delivering the Ad5 adenovirus to the airway. On December 22, the company registered a Phase 1 clinical trial of a single dose of the vaccine, which is expected to deliver results in June 2021.[18]

### *BBV154*

This is a nasal spray developed by Bharat Biotech that contains a chimpanzee adenovirus developed by researchers at Washington University. They found that it could produce coronavirus antibodies in mice with just a single dose.[17] The vaccines mentioned in Tables 3 and 4 are in their Phase I and preclinical trials respectively.

## CONCLUSION

The world is in dire need of safe effective COVID-19 vaccine. According to the pandemic vaccine development paradigm, the conventional vaccine development has compressed from a time frame of 10–15 years to 1–2 years, with overlapping clinical, preclinical, and manufacturing process occurring in parallel. As a result, crucial information about the longevity and quality of vaccine-induced protective immunity is unavailable.

**Table 3: List of candidate vaccine in clinical evaluation: It can be assessed from World Health Organization: COVID-19 vaccine updates**

| COVID-19 vaccine developer/ manufacturer | Vaccine platform | Type of candidate vaccine | Number of doses | Timing of doses (days) | Clinical trial stage | Route of administration |
|---|---|---|---|---|---|---|
| Beijing Wantai Biological Pharmacy/ Xiamen University | Replicating viral vector | Intranasal-flu-based RBD | X1 | T | Phase I | Intranasal |
| City of Hope | Replicating viral vector | SARS-CoV-2 and MP genes inserted into a SMVA vector | X2 | 0-28 | Phase I NCT 04639466 | Intramuscular |
| Vaxart | Nonreplicating viral vector | Ad5-adjuvanted oral vaccine | X2 | 0-28 | Phase I NCT 04552366 | Intra-muscular/ mucosal |
| Codagenix/Serum Institute of India | Live attenuated virus | Codon-deoptimized LAV | X1 or X2 | 0 or 0-28 | Phase I NCT 04619628 | Intramuscular |
| Spybiotech/Serum Institute of India | VLP | RBD-HbsAg VLP's | X2 | 0-28 | Phase I/II ACTRN 1262000817943 | Intramuscular |
| Symvivo | DNA | BacTRL-Spike | X1 | | Phase I NCT 04334980 | Oral |
| Genexine Consortium | DNA | DNA vaccine (GX-19) | X2 | 0-28 | Phase I/II NCT 0445389 | Intramuscular |
| Sanofi and Pasteur/GSK | Protein Subunit | S protein (baculovirus production) | X2 | 0-21 | Phase I/II NCT 04537208 CTRI/2020/11/029032 | Intramuscular |
| Covaxx/United Biomedical Inc.Asia | Protein Subunit | Multiple peptides based S1RBD | X2 | 0-28 | Phase I NCT 04545749 | Intramuscular |
| Medigen Vaccine Biologics Corporation/NIAID/Dynavax | Protein Subunit | S-2P protein+ CpG1018 | X2 | 0-28 | Phase I NCT 04487210 | Intramuscular |
| PLA academy of Military Sciences/ Walvax Biotech | RNA | mRNA | X2 | 0-14 or 0-28 | Phase I ChiCTR 2000034112 ChiCTR 2000039212 | Intramuscular |
| Imperial College London | RNA | LNP-nCoV S RNA | X2 | - | Phase I ISCTRN 17072692 | Intramuscular |
| Shenzen Kangtai Biological Products | Inactivated | Inactivated | X2 | 0-28 | Phase 1/II NCT 04663472 ChiCTR 2000039462 | Intramuscular |
| Institute of Medical Biology, Chinese Academy of Medical Sciences | Inactivated | Inactivated | X2 | 0-28 | Phase I/II NCT 04470609 | Intramuscular |

VLP: Virus like particles, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, mRNA: Messenger RNA, PLA: People's liberation army, RBD: Receptor binding domain, NCT: National clinical trial, ChiCTR: Chinese clinical trail registry, ACTRN: Australian clinical trial registration number, LNP-nCoV: Lipid nano particle, LAV: Live attenuated virus, SMVA: Modified Vaccinia Virus, HbsAg: Hepatitis B surface antigen, ISCTRN: International standard for clinical trial registratio.

The COVID-19 vaccines are expected to provide at least some protection against new virus variants and are effective at preventing serious illness and death that is because these vaccines create a broad immune response, and any virus changes or mutations should not make vaccines completely ineffective. If any of these vaccines become less effective against one or more variants, it will be possible to change the composition of the vaccines to protect against these variants.

Therefore, along with focusing on the vaccine development, we should focus on containing the spread of the virus. Until widespread immunity halts the spread of SARS-CoV-2, physical distancing measures, covering a cough or sneeze in your elbow, frequently cleaning your hands, wearing a mask, and avoiding poorly ventilated rooms are needed to control COVID-19. However, control of pandemic coronavirus will only be achieved if the licensure, manufacturing, and distribution of these vaccines can be achieved at an unprecedented scale and vaccination is rolled out to all those who are vulnerable.

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## Conflicts of interest

There are no conflicts of interest.

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