

REVIEW ARTICLE

SARS-CoV-2 Leading Vaccine Candidates: Progress and Development

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ABSTRACT

The coronavirus disease 2019 (COVID-19) outbreak that originated in China in December 2019, spread globally and was declared a public health emergency of international concern by WHO. The genome sequence of novel coronavirus (SARS-CoV-2) was made available publicly in an unprecedented time that allowed rapid research and development to combat this deadly virus. Due to the absence of therapeutics, vaccines could be a promising solution towards the control and prevention of SARS-CoV-2 infections. As a quick response to this pandemic, the already established vaccine platforms are being explored for development of an effective vaccine against SARS-CoV-2. Thus, the clinical trials to evaluate the safety and efficacy of experimental vaccines are emerging in a record time. In this review various vaccine strategies that include nucleic acid (mRNA and DNA), viral vector based, partial or complete genome based inactivated, and protein subunit vaccines are summarized. We have also highlighted the status of clinical trials currently in progress and the preliminary findings of these frontrunner vaccine candidates. To eradicate the current COVID-19 pandemic and to prevent future outbreaks, successful vaccine platforms should be capable of scalable manufacturing and global distribution.

Key Words: *Clinical Trials, COVID-19, SARS-CoV-2, Vaccines.*

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Introduction

Since the novel coronavirus disease 2019 (COVID-19) outbreak, the disease has severely affected more than 100 countries, with over 13 million confirmed cases and 570, 288 deaths globally within the first 6 months of the outbreak.¹ COVID-19 is caused by the novel coronavirus of Coronaviridae family and is also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).² SARS-CoV-2 is an enveloped virus with approximately 30 kb long single stranded, positive sense RNA genome, similar to beta-coronaviruses such as SARS-CoV and Middle East Respiratory Syndrome CoV (MERS-CoV).^{3,4} The genome is predicted to consist of 14 open reading frames encoding four major structural proteins; spike (S), membrane (M), envelope (E), nucleocapsid

(N), 16 non-structural proteins (nsps) and eight accessory proteins (3a, 3b, 6, 7a, 7b, 8b, 9b, and orf 14) (Figure 1).⁵ The S glycoprotein has a central role in host tropism and is also the major protein involved in receptor binding and membrane fusion. It has been revealed that the SARS-CoV-2 S protein has close resemblance with the structure of spike protein of SARS-CoV and also uses the same receptor i.e. angiotensin-converting enzyme 2 (ACE-2) for internalization into human cells.⁶ Information available from vaccine development against SARS and MERS has aided in the vaccine progress against COVID-19. It has been found that the SARS-CoV-2 S glycoprotein is involved in eliciting a potent polyclonal antibody response, neutralizing the S mediated entry into cells thus making S protein an important vaccine target.⁷ Most of the vaccine candidates that are currently in clinical and pre-clinical stages of development are using S protein as the core antigen.

According to a WHO document on COVID-19 vaccine progress, 29 vaccine candidates have entered different stages of clinical trials, while 138 candidates are under pre-clinical evaluation as of August 13, 2020 (Figure 2, 3).⁸ Here, we review the

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current status of leading vaccine candidates in different phases of clinical evaluation and the platform technologies used in the design of these

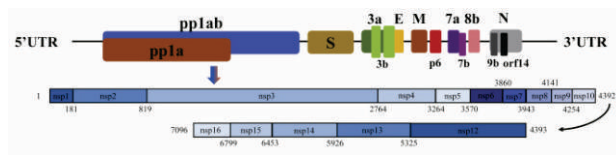


Fig 1: Schematic diagram of the SARS-CoV-2 genome⁵ vaccines (Table 1).

Orf1ab and Orf1a genes at the 5'-terminus encode pp1ab and pp1a proteins respectively, comprising of 15 nsps (nsp1-nsp10 and nsp12-nsp16). The 3'-terminus of the genome comprises of four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) and eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and

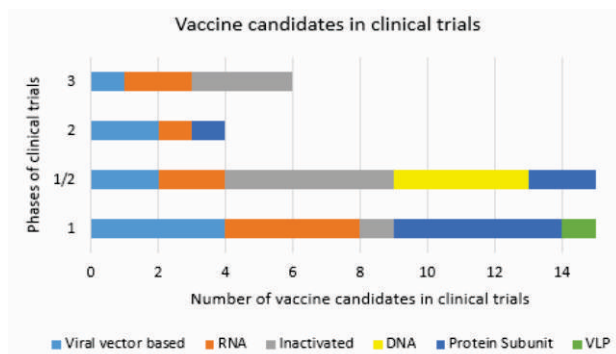


Fig 2: Landscape of SARS-CoV-2 vaccine development⁸

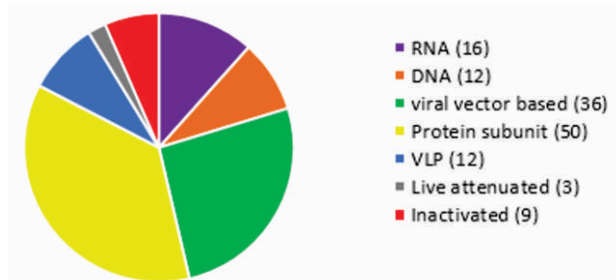


Fig 3: SARS-CoV-2 candidate vaccines in pre-clinical trials⁸ orf14) distributed among the structural proteins.

Viral Vector Vaccines

Viral vector-based vaccines use chimeric viruses (replicating or non-replicating) to deliver foreign genes encoding for one or more antigens responsible for inducing an immunological response, into host cells. Recombinant vector vaccines can efficiently elicit both antibody and cytotoxic T cell responses due to the high expression of the recombinant proteins and long-term stability of the vectors.⁹ A variety of viruses have been used as vectors for viral

Table 1: Landscape of leading candidate vaccines against SARS-CoV-2

Vaccine candidate	Vaccine platform	Developer/manufacturer	Status	Clinical trial registry
ChAdOx1-S	Non-Replicating Viral Vector	University of Oxford/ AstraZeneca	Phase I/II	PACTR202006922165 132 2020-001072-15
			Phase II	2020-001228032 ISRCTN89951424
			Phase III	
LNP-encapsulated mRNA	RNA	Moderna/ NIAID	Phase I	NCT04283461
			Phase II	NCT04405076 NCT04470427
			Phase III	
3 LNP-mRNA	RNA	BioNTech/ Fosun Pharma/Pfizer	Phase I/II	2020-001038 ChiCTR20000348
			Phase II	NCT04368728
			Phase III	
Inactivated	Inactivated	Sinovac	Phase I/II	NCT04383574 NCT04352608 NCT04456595
			Phase III	669/UN6.KEP/EC/2020
			Phase I/II	ChiCTR2000031809 ChiCTR2000034780
Inactivated	Inactivated	Wuhan Institute of Biological Products/ Sinopharm	Phase I/II	ChiCTR2000032459 ChiCTR2000034780
			Phase III	
			Phase I/II	
Adenovirus type 5 Vector	Non-Replicating Viral Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase I	ChiCTR2000030906 NCT04313127
			Phase II	ChiCTR2000031781 NCT04341389

LNP: lipid nanoparticle; NIAID: National Institute of Allergy and Infectious Diseases

vaccine development including adenoviruses, poxviruses (recombinant vaccinia Ankara virus), paramyxoviruses (such as measles virus, Newcastle disease virus, human parainfluenza virus), and rhabdoviruses (e.g. vesicular stomatitis virus).¹⁰ Adenovirus is currently the most commonly employed viral vector in the SARS-CoV-2 vector-based vaccine development. Leading viral vector vaccines under clinical evaluation against COVID-19 are based on non-replicating adenoviral vectors (Table 1).

Currently, the vaccine candidate at the most advanced stages of development employs a modified chimpanzee adenovirus vector which encodes SARS-CoV-2 spike protein.¹¹ This vaccine (ChAdOx1 nCoV-19), called AZD1222 has been

developed by the University of Oxford in collaboration with AstraZeneca and has now entered phase III trials. The first Phase III clinical trial of ChAdOx1 nCoV-19 vaccine was started in Brazil in June 2020 recruiting 4000 participants initially from across the country, while planning to recruit an additional 10,000 participants. The ChAdOx1 nCoV-19 vaccine trials are moving forward quickly, eventually to start clinical studies across United Kingdom, United States and South Africa in a larger population.^{12,13} Results from the phase I/II trials published in *The Lancet*, indicated that the vaccine induced strong T-cell (within 14 days of vaccination) as well as antibody response (within 28 days) after single dose of administration with no safety concerns or any serious adverse events.¹⁴ Using chimpanzee adenoviral vector (ChAdOx1) overcomes the challenges of pre-existing immunity associated with human adenoviruses as vaccine platforms. Thus, ChAdOx1 vector developed by the University of Oxford is considered as a promising and most suitable vaccine technology owing to its lack of pre-existing immunity in human.¹⁵

Another leading COVID-19 candidate vaccine, based on the non-replicating adenovirus type 5 (Ad5-nCoV) vector platform has been developed by CanSinoBIO in collaboration with Beijing Institute of Biotechnology. The phase II trial (NCT04341389) of this vaccine candidate began in April, 2020 after showing promising safety, tolerability and immunogenicity in healthy Chinese adults in phase I (NCT04313127) studies.¹⁶ The preliminary results of the phase II clinical trial have also been published and shows that the Ad5-nCoV vaccine is safe and induces strong immune responses, both humoral and T-cell, after a single immunisation with a dose of 5×10^{10} viral particles.¹⁷ Johnson & Johnson through its Janssen Pharmaceutical Companies with support from the Biomedical Advanced Research and Development Authority (BARDA), also expedited the development of the candidate vaccine based on non-replicating adeno-based viral vector (Ad26 CoV2-S). The company started Phase I/IIa clinical trials (NCT04436276) of its vaccine in July 2020 recruiting an estimated 1045 healthy adults from US and Belgium and also aiming to start phase III trials in September.^{18,19}

An adeno-based non-replicating viral vector vaccine

known as GAM-COVID-VAC LYO (NCT04437875) developed by Gamaleya Research Institute of Epidemiology and Microbiology, began its phase I trial in June 2020. The vaccine was approved from The Russian Health Ministry for use in Russia on August 11, 2020 without the critical phase III trials. However, the decision was condemned by scientists across the world for skipping the important step of testing safety and efficacy in larger trials prior approval.²⁰ Of the viral vector candidate vaccines in clinical trials, only one is based on a replicating measles-vector. Phase I of this trial was started in August 2020 (NCT04497298). The vaccine is being developed by Institute Pasteur/Themis/Univ. of Pittsburgh CVR/Merck Sharp & Dohme in collaboration with Coalition for Epidemic Preparedness Innovations (CEPI).

Adenoviral vectors have several advantages over other vaccine platforms including high level of recombinant protein expression, wide-ranging tissue tropism, intrinsic adjuvant properties and accommodation of large (up to 8 kb) transgenes.¹⁵

RNA Vaccines

mRNA based vaccine technology have remarkable potential to control infectious agents with outstanding safety. A mRNA sequence can encode for an antigen that is specific to the disease. Once delivered inside the target cells, the mRNA is translated into the antigen by utilizing host cell translation machinery.²¹ This antigen is then processed, displayed on the cell surface, recognized by the immune system and humoral and T cell immune response are activated. The intrinsic safety of mRNA is also associated with the fact that it does not interact with the genome. Unlike conventional vaccines, mRNA vaccines can be produced in the laboratory, faster and less expensively, and do not involve culture or fermentation for synthesis. This production process makes mRNA vaccines promising candidates in case of the emerging pandemic with the potential to quickly fill the gap between the desperate need for vaccine to control disease and scale-up manufacturing process to get rapid, abundant supply of effective vaccines. There are two major types of mRNA vaccines depending on translation ability of mRNA, 1) Conventional mRNA vaccines, which encode the specific antigen only, 2) Self amplifying mRNA vaccines (SAM), which have

the ability to encode for an engineered viral replicon in addition to the antigen of interest.²²

Alpha virus replicon is an example of Self-amplification of mRNA having single-stranded, positive sense (+) RNA that encodes four non-structural proteins (nsP1-4) and their structural genes are substituted by antigen of interest, the resultant self-amplifying RNA after delivery into cytosol produces antigen in four phases 1) Genomic (+) RNA translates four nonstructural proteins (nsp1-4) encoding for RNA-dependent RNA polymerase (RdRp), 2) RdRp synthesizes complementary genomic (-) RNA intermediate, 3) Genomic (+) and subgenomic RNA generates from genomic (-) RNA intermediate, 4) subgenomic RNA is translated into antigen.^{22,23,24} Self-amplification of mRNA vaccine results in high levels of antigen expression in host cells, irrespective of cell division.²⁵

During the current pandemic of COVID-19, up to the end of August 2020, six mRNA-based vaccine candidates encoding SARSCoV-2 spike glycoprotein have entered clinical trials and sixteen candidates are being evaluated in preclinical studies. To date, no RNA vaccine has been licensed and approved for human use.²⁶ The US company, Moderna's messenger RNA (mRNA) therapeutics and vaccines technology platform is a pioneer and is functional against various infectious diseases.²⁷ Therefore, Moderna in partnership with US National Institute of Health was fastest to develop SARS-CoV-2 mRNA vaccine and launched phase I clinical trial in March 2020 just two months after sequence identification of the virus (NCT04283461). Moderna's mRNA-1273 vaccine consists of nanoparticle encapsulated mRNA encoding a prefusion stabilized full-length S protein of SARS-CoV-2.

Phase I trial involves 45 healthy adults of 18 – 55 years of age who received one of three doses; (25 µg, 100 µg, or 250 µg), administered as two vaccinations 28 days apart. Preliminary findings of phase I trial were published in *The New England Journal of Medicine*,²⁸ which reported that the vaccine induced an effective anti-SARS-CoV-2 immune response in all the study participants. In May, this vaccine advanced to phase II to assess the safety, reactogenicity, and immunogenicity in 600 healthy participants across 2 cohorts, 18-55 years and over 55 years of age, who will be given a placebo, 50 µg or 100 µg dose as 2

vaccinations with a one-year follow-up (NCT04405076).

Recently, a large Phase III trial of mRNA-1273 was started involving 30,000 healthy adults at various sites around the US (NCT04470427). Study participants will receive either placebo or 100 µg of mRNA-1273 on Days 1 and 29. Based on preliminary findings, the dose of 100 µg of mRNA-1273 is selected for Phase III trial with the aim to maximize the immune response and reduce adverse reactions. If successful, then mRNA-1273 will be the first mRNA vaccine to seek approval for marketing.

The German company BioNTech in collaboration with Pfizer and Fosun Pharma developed 4 mRNA vaccine candidates named as BNT162a1, BNT162b1, BNT162b2 and BNT162c2, each of which consist of unique mRNA design and antigen target. Two of the candidates comprise of a nucleoside modified mRNA (modRNA), one contains a uridine containing mRNA (uRNA), and the fourth candidate includes self-amplifying mRNA (saRNA). Full-length spike antigen is included in the two vaccines and the other two vaccines contains smaller optimized receptor binding domain (RBD) of the spike protein. All of them are formulated with lipid nanoparticles. Recently they reported preliminary results of phase I trial of BNT162b1 and BNT162b2, findings represent that both candidates have similar T cells and antibody responses, however BNT162b2 has shown lesser systemic reactogenicity therefore BNT162b2 has advanced into phase II/III safety and efficacy clinical trials.^{29,30} Researchers from Imperial College London have developed a self-amplifying RNA vaccine (LNP-nCoVsaRNA) encoding the S glycoprotein of SARS-CoV-2. Phase 1 trial begun on April, 2020 with the purpose to determine the safety of the vaccine (ISRCTN17072692). In June 2020, a German company Curevac launched Phase 1 trial of its mRNA vaccine (CVnCoV) to evaluate safety and immunogenicity profile (NCT04449276). Recently, Duke-NUS Medical School in collaboration with Biotech company Arcturus Therapeutics have also started Phase I/II trial of self-replicating mRNA vaccine that encodes for spike protein at Singapore General Hospital (NCT04480957).

Inactivated Vaccines

Among the various categories of vaccine candidates, the protein immunogens are traditional ones;

delivered as virus like particles (VLPs) or inactivated viruses. These are usually administered with an adjuvant to uplift the amplitude of the immune responses and durability. According to the preliminary results of trials involving an inactivated vaccine by Xia and team (2020), the first inactivated SARS-CoV-2 vaccine was reported.³¹ The clinical trial was randomized, alum controlled and double blind (ChiCTR2000031809). The vaccine contains β -propiolactone-inactivated SARSCoV-2 vaccine with aluminum hydroxide (0.5 mg) as an adjuvant. The phase I clinical trial included 96 healthy participants, vis 4 groups of 24 participants having a dose of 2.5 μ g, 5 μ g, and 10 μ g, and an alum adjuvant-only dose respectively. Three vaccine doses were administered at day 0, 28 and 56. The phase II clinical trials included 224 participants having a dose of 5 μ g to administer. The booster dose time was reduced to day 14 or 21 post immunization. Each group in the trial contains n=84 along with 28 participants having alum shot only in each schedule. The participants were traced for any local and systemic trouble. They were found to be safe in each trial. Upon these preliminary reports, the novel vaccine has been approved for Phase III clinical trials.

The other candidate inactivated vaccine that is under phase III clinical trial has been developed by Gao et al. 2020 namely PiCoVacc.³² It is purified inactivated novel coronavirus that induced specific neutralizing antibodies against SARS-CoV-2 in lab animals (rat, mice) and in non-human primates. These antibodies can neutralize broader range of SARS-CoV-2 strains. In macaques, three immunizations of two different doses vis 3 μ g and 6 μ g per dose resulted in partial or complete protection against SARS-CoV-2 infection. The other two candidates of inactivated vaccines are from Bharat Biotech and Chinese Academy of Medical Sciences. These vaccines are in Phase I/II clinical trials.

DNA vaccines

Among the new approaches for the control of an infectious disease, the DNA based vaccine is gaining popularity. This approach involves a plasmid having specific DNA sequence that encodes specific pathogen to induce immune responses. This approach ensures in-situ production of that specific antigen. The DNA vaccines have the best advantages of B- and T-cell immune responses, enhanced

stability of vaccine, diminish the chances of any other infectious agent and are easy to produce at large scale. The same approach has been incorporated for synthesis of DNA vaccine against SARS-CoV-2. The synthetic DNA based vaccines by Smith and colleagues (2020) engineered SARS-CoV-2 S-protein (INO-4800) based on their better results of MERS-CoV S-protein (INO-4700) as the S-protein is the immunogenic protein of coronaviruses.³³ The newly engineered construct, INO-4800 provides positive outcomes in protein expression (*in vitro*) as well as in inducing neutralizing antibodies (*in vivo*) in mice and guinea pig model. The novel candidate vaccine induces pathogen associated T-cell immunity and active antibodies that neutralize the viral infection and block the ACE2 binding receptor. On the basis of fruitful results, the candidate vaccine is being translated to Phase I/II clinical trials. It is a non-randomized trial. There are 120 participants with intradermal administration. This vaccine is proposed by Inovio Pharmaceuticals/ International Vaccine Institute with trial's accession number NCT04336410; NCT04447781.

Another DNA vaccine is proposed by Genexine supported by South Korean government along with a consortium of Genexine, International Vaccine Institute, Genbio, Binex, Pohang University of Science & Technology (POSTECH), and the Korea Advanced Institute of Science & Technology (KAIST). This vaccine is named as GX-19.³⁴ The clinical trials are in phase-I/II stage to evaluate immunogenicity, safety and tolerability through intramuscular injection. In phase I, 60 participants were enrolled while phase II were double blind, randomized placebo control started with 150 subjects. This study will be completed in June, 2022 with accession number NCT04445389. The other two DNA based COVID19 vaccines have been proposed by Cadila Healthcare Limited and Osaka University/ AnGes/ Takara Bio with an accession numbers CTRI/2020/07/026352 and JapicCTI-205328, respectively.

Cadila Healthcare Limited has developed a plasmid DNA based vaccine which is under clinical trial phase I/II while Osaka University has developed DNA plasmid vaccine along with adjuvant. This vaccine is in phase I clinical trial.

Protein subunit vaccines

Protein subunit is another important platform technology that is currently employed for vaccine development against SARS-CoV-2. Seven out of the 29 vaccine candidates in clinical evaluation stages are based on the protein subunit methodology, while several are under pre-clinical trials.⁸ Subunit vaccines comprise of only components or protein antigens of a pathogen that can stimulate a protective immune response. The vaccines produced using this platform are therefore safer as the risks associated with handling the entire pathogen are eliminated. However, these vaccines often require specific adjuvants to induce a strong long-term immune response.³⁵ Protein subunit vaccines for COVID-19 rely on the full length S protein or S1/S2 subunits of the virus as antigen along with adjuvants to induce protective immunity in the host. Novavax, a US based company began the phase I/II trials of its vaccine candidate, NVX-CoV2373, in May 2020 (NCT04368988). The preliminary results from phase I part of this study have shown that the vaccine was well-tolerated eliciting robust antibody responses and has now advanced to phase II part expanding the age range to also include older adults.³⁶ The NVX-CoV2373 vaccine, constructed on the company's recombinant nanoparticle technology using SARS-CoV-2 S protein as antigen. Novavax vaccine has also been selected for participation in a US government sponsored program, Operation Warp Speed (OWS) for delivering millions of vaccine doses in 2021 to the US population. OWS has funded Novavax for the late stage clinical studies of its candidate vaccine including phase III trials to begin in late 2020.³⁷

Another protein subunit vaccine using RBD dimer of the S protein of SARS-CoV-2 has been developed by Anhui Zhifei Longcom Biopharmaceutical in collaboration with Chinese Academy of Sciences and initiated phase II clinical trial in July 2020 (NCT04445194, NCT04466085). Also the phase I trials of subunit vaccines by Clover Biopharmaceuticals/GSK/Dynavax (NCT04405908), Vaxine Pty Ltd/Medytox (NCT04453852) started in June 2020, and University of Queensland/CSL/Seqirus (ACTRN12620000674932) in July 2020. Others, including GSK/Sanofi Pasteur, Kentucky Bioprocessing and Medigen Vaccine Biologics Corp./NIAID/Dynavax are expected to start phase I clinical trials of their candidate vaccines

independently in the next couple of months.³⁸

Conclusion

Currently various academic institutions and pharmaceutical companies are in a race to develop the prophylactic SARS-CoV-2 vaccine. The platform technologies utilized in these candidate vaccines include mRNA, DNA, viral vector, protein subunit, attenuated and inactivated. Several candidate vaccines are being investigated in clinical trials against COVID-19, while a couple of them have already entered phase III trials. Various candidate vaccines have proven human safety and immunogenicity in short term trials. Although parallel and prompt efforts of scientists from academic laboratories and industries offer hope, however, an effective and safe vaccine is still months or at least a couple of years away from production to marketing. After successful completion of the phase III clinical trials, the next challenge is the production of the vaccine on a large scale to meet the global demand during current and/or post pandemic time. Therefore, intensive coordination and technology transfer is required among pharmaceutical industries, governments and regulatory bodies for mass scale global production with improved delivery system of effective vaccines to fight COVID-19.

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