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MINI REVIEW

Recombinant vaccines for COVID-19

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ABSTRACT

SARS-CoV-2, the causative agent of COVID-19, has imposed a major public health threat, which needs effective therapeutics and vaccination strategies. Several potential candidate vaccines being rapidly developed are in clinical evaluation. Considering the crucial role of SARS-CoV-2 spike (S) glycoprotein in virus attachment, entry, and induction of neutralizing antibodies, S protein is being widely used as a target for vaccine development. Based on advances in techniques for vaccine design, inactivated, live-vectored, nucleic acid, and recombinant COVID-19 vaccines are being developed and tested for their efficacy. Phase3 clinical trials are underway or will soon begin for several of these vaccines. Assuming that clinical efficacy is shown for one or more vaccines, safety is a major aspect to be considered before deploying such vaccines to the public. The current review focuses on the recent advances in recombinant COVID-19 vaccine research and development and associated issues.

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Introduction

A novel coronavirus (CoV) was recently identified in December 2019 in Wuhan in Hubei province, China. This novel coronavirus was rapidly spread and therefore was declared as a public health emergency of international concern by the World Health Organization (WHO) on January 30, 2020.[1–4] Considering the high sequence similarity of novel coronavirus with Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), the virus was renamed as SARS-COV-2 which causes the pandemic Coronavirus disease (COVID-19). To date, the COVID-19 pandemic has resulted in over 25 million confirmed infections and almost one million deaths worldwide, with the number of cases increasing rapidly[3] Despite having a fatality rate lower than that recorded for SARS-CoV during the epidemic in 2003, SARS-CoV-2 is associated with severe respiratory malfunction and has a high mortality rate among the elderly and in individuals with chronic health issues, including diabetes and hypertension.[5,6] SARS-CoV-2 is believed to have originated in wild bats, although the intermediate hosts have yet to be identified.[7–9] Furthermore, SARS-CoV-2 has been found to share high levels of genomic similarity (spike glycoprotein sequence similarity 87.2%) with SARS-CoV,[10,11] providing a basis for the development of a vaccine. Efforts are currently underway to obtain further information on SARS-CoV-2 and its mechanism of rapid transmission to promote the development of effective control measures. In February 2020, experts on infectious diseases met at the WHO headquarters in Geneva to share their findings on SARS-CoV-2 and agreed to address the pandemic together to hasten the research process to curb the current outbreak and to prepare for potential pandemics in the future.[3]

Both the current pandemic and the threat of future epidemics underline a prerequisite for the development of precautionary strategies to fight coronaviruses (CoVs). In this context, vaccines represent an effective measure for the control of widespread viral infections associated with high morbidity and mortality. Research and development (R&D) organizations and institutes worldwide are currently using various vaccine platforms in attempts to develop a treatment against SARS-CoV-2 infection.[12] In addition to live vectored and inactivated viruses, novel recombinant technologies are being used in the development of COVID-19 vaccine. The advantage of recombinant vaccines is their greater response predictability and improved efficacy. This review focuses on the current state of recombinant vaccines, in particular within the context of the COVID-19 pandemic, with discussions on their efficacy and effectiveness as well as the safety issues associated with their implementation. As the research literature on recombinant vaccines remains limited, a significant amount of information has been collected from official websites and publicly available documents.

SARS-CoV-2 structure and potential targets for vaccine development

SARS-CoV-2 belongs to the *Betacoronavirus* genus of the *Coronaviridae* family and shares close genomic similarities with SARS-CoV, an earlier endemic virus that first emerged in

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2002–2003. SARS-CoV-2 and SARS-CoV are both positive-sense single-stranded RNA viruses with a genome size of ~30 kilobases that encode several structural and non-structural proteins. The structural proteins contain the spike (S) glycoprotein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein.[10,13,14]

The absence of proofreading during genome recombination among existing CoVs has played a key role in the evolution of novel CoVs.[7] Furthermore, the rate of recombination has been found to be higher in the S genes that code for the S protein.[10] Studies have suggested that the association of the S protein of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE-2) is stronger than that of the S protein of SARS-CoV; this may have resulted in its rapid transmission and more infectious nature.[15,16] The S1 subunit of the receptor-binding domain (RBD) of the S protein initially interacts with the ACE2 receptor for attachment, thereafter entering the host cell by fusing the viral and host membranes with the help of the S2 subunit.[10,17–20] In this manner, the S protein plays a key role in the internalization of the virus, receptor binding, membrane fusion, tissue tropism, and host range and has thus emerged as an important target for vaccine development.[21] Prior studies on the development of vaccine against SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) also points out the significance of the S protein as a potential target for vaccine development against SARS-CoV-2.[22,23] In proposed vaccine, the antibodies produced against S protein are expected to obstruct its binding with ACE2 and neutralize the virus.

Coronavirus vaccines: development and achievement

Vaccines are the primary intervention strategy in the control of coronavirus transmission and infection. Several methods are available for the development of a vaccine against SARS-CoV -2, including the use of inactive or live-attenuated viruses, virus-like particles (VLPs), viral vectors, and protein-based, DNA-based, and mRNA-based vaccines. However, the development of a vaccine typically spans 10–15 years. However, owing to the rapid identification and publication of the SARS-CoV-2 gene sequence, it was only a matter of months before the first vaccine candidate was ready for clinical testing. Currently, more than 60 SARS-CoV-2 vaccines are being developed at different clinical trial phases.[3] The following sections provide a brief outline of the main platforms for the development of a SARS-CoV-2 vaccine, namely inactivated, live-attenuated, and recombinant vaccines. Figure 1 represents a pictorial outline of various recombinant vaccine strategies.

Inactivated coronavirus vaccine

The development of inactivated vaccines requires a target virus to be initially inactivated, either chemically or by irradiation. This allows the nucleic acids of the virus to be destroyed, while keeping the viral antigens intact. The immunological characteristics and effectiveness of inactivated CoV vaccines were investigated in animal models during the emergence of the first SARS virus. An inactivated vaccine against SARS-CoV was first evaluated in rhesus monkeys, which was found to induce humoral and mucosal immunity, highlighting its potential for use in clinical trials.[24] A double-inactivated, candidate whole-virus vaccine against SARS-CoV was also developed using sequential exposure to formaldehyde and ultraviolet radiation to ensure its safe use. The immunogenicity of this vaccine was verified using a mouse model, which showed high antibody titers against the CoV S protein and enhanced neutralizing antibodies, highlighting its potential for application as a platform for the development of a SARS-CoV-2 vaccine.[25] Recently Gao et al (2020) developed PiCoVacc, a purified inactivated SARS-CoV-2 virus vaccine, that was found to incite SARS-CoV-2-specific neutralizing antibodies in mice, rats, and non-human primates. The generated antibodies were found to neutralize 10 representative strains of SARS-CoV-2, holding up its broad-ranged applicability against the virus.[26] However, there is a potential public health risk associated with incomplete inactivation, which leads to undesired immune or inflammatory responses. Currently, Sinovac Biotech has secured approval in China to conduct a human clinical trial using an inactivated vaccine candidate against SARS-CoV-2.[27] The Beijing Institute of Biological Products/Wuhan Institute of Biological Products, the Research Foundation for Microbial Diseases of Osaka University (BIKEN), and the National Institutes of Biomedical Innovation, Health, and Nutrition (NIBIOHN) are also working toward the development of inactivated vaccines.[28]

Live-attenuated coronavirus vaccine

Live-attenuated vaccines are being developed from live coronaviruses whose virulence has been reduced under laboratory conditions. This technique allows for the virus to replicate in the host while producing only mild pathogenesis, if any. Live-attenuated vaccines are one of the basic technologies used for the development of licensed human vaccines. However, the spread of CoV via the feces of individuals who have received a live-attenuated vaccine and the risk of its recombination with wild-type CoV are among its major safety concerns. Another issue is its suitability for the older population, who are at a higher risk of severe disease.[17]

The Serum Institute of India has allied with Codagenix Inc., a major US pharmaceutical company, to develop a live-attenuated vaccine against SARS-CoV-2, which is presently in the preclinical stage.[28] However, owing to its safety concerns, in particular with regard to elderly individuals (at a higher risk of COVID 19), the use of live-attenuated virus vaccines is unlikely to represent the best approach.

Recombinant COVID-19 vaccines

Nucleic acid-based coronavirus vaccine

The greatest advantage of DNA- and RNA-based vaccines is their potential for rapid development and reduced side effects. DNA vaccines have shown strong potential to trigger immune responses against CoVs in animal models. However, clinical data on the efficacy of DNA vaccines in humans remain limited. In a previous study on mice, a DNA vaccine encoding the S protein of SARS-CoV was found to induce T cells, a neutralizing antibody response, and protective immunity.[29] A group of prototype DNA vaccines expressing various SARS-CoV-2 S proteins has

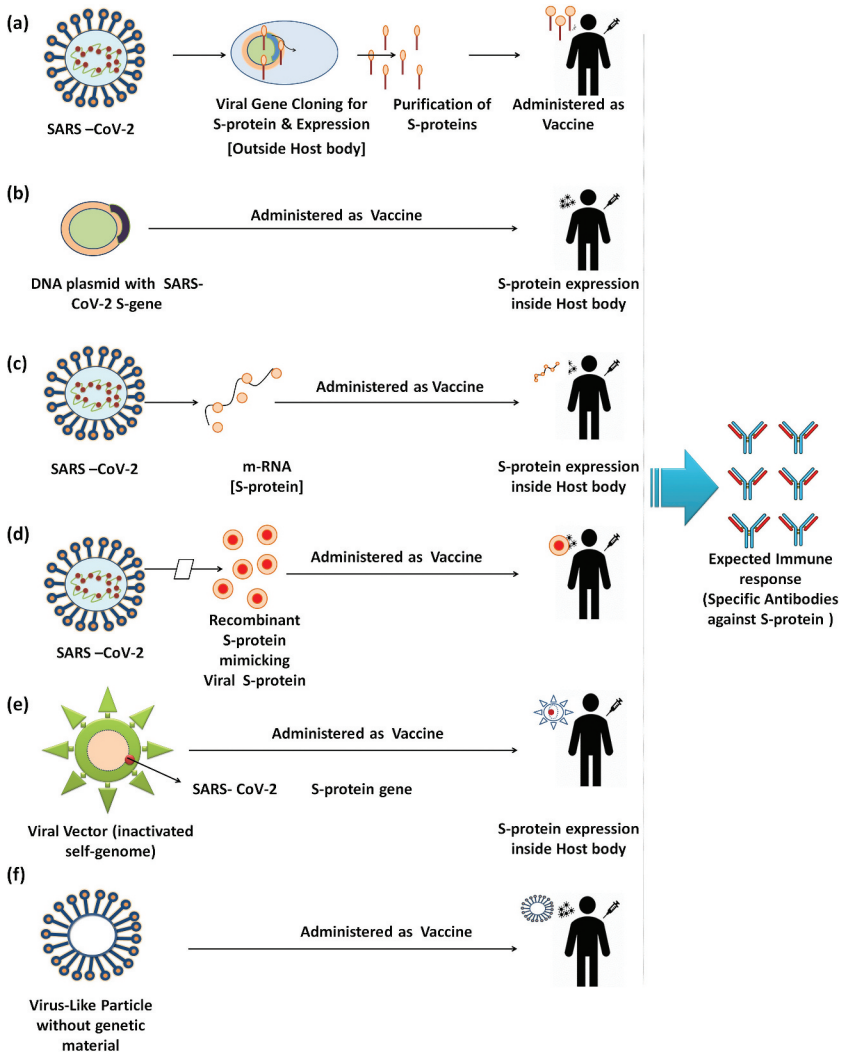

Figure 1. Various strategies for recombinant vaccine development. (a) DNA-based vaccine developed by cloning SARS-CoV-2 S-protein; (b) Development of vaccine using DNA plasmid containing SARS-CoV-2 S gene; (c) Vaccine development by S protein mRNA; (d) Use of recombinant S-protein mimicking SARS-Cov-2 S protein as a vaccine; (e) Use of vector without self-replicating machinery containing SARS-CoV-2 S protein gene as vaccine; (f) Virus-Like Particle equivalent to SARS-CoV-2 without genetic material as a vaccine. Most of the vaccines target S protein that is expected to sensitize the host cellular and humoral immune response leading to immunization.

been developed and tested in 35 rhesus macaques. The vaccinated macaques demonstrated specific humoral and cellular immune responses. Further upon being challenged with SARS-CoV-2, the animals showed a remarkable reduction of viral replication in the upper and lower respiratory tract. The data displayed the significant role of DNA vaccine against SARS-CoV -2 infection.[30] Smith et al (2020) reported the immunogenicity of a synthetic DNA-based vaccine against SARS-CoV-2, INO-4800 in multiple animal models. The immunized animal showed specific T cell responses, and antibodies that not only neutralized SARS-CoV-2 and blocked S protein-ACE2 interaction, but also circulated through the lungs. The study emphasized on its further evaluation as a potential contender for COVID-19 vaccine.[31] Presently, Inovio Pharmaceuticals are evaluating a DNA plasmid-based prophylactic vaccine (INO-4800) against SARS-CoV-2 in a phase 1 trial. Similarly, Karolinska Institute/Cobra Biologics, Osaka University/Anges/Takara Bio, and Takis/Applied DNA Sciences/Evvivax are currently in the preclinical phase of the development of DNA-based vaccines.[28] Recently, OncoSec collaborated with the Cancer Institute to conduct the first in-human trial of OncoSec's CORVax12, a trial vaccine against SARS-CoV-2. This vaccine involves the co-administration of TAVO™ (plasmid IL-12) with a DNA-encodable variety of the SARS-CoV-2 S glycoprotein to increase the immunogenicity of the module, developed by scientists at the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID-NIH) Vaccine Research Center. It is designed to induce a harmonized response via innate, adaptive humoral, and cellular immunity.[32]

Messenger RNA (mRNA)-based CoV vaccines are considered to be more advantageous than DNA-based vaccines since they do not require entry into the host cell nucleus to be transcribed. Therefore, a lower dose can be used, without the need for any special delivery mechanisms. Moreover, mRNA-based vaccines avoid the risk of integration with the host cell genome and are able to produce pure viral protein. The technology associated with this vaccine is also capable of bypassing time-consuming standardization processes, thus speeding up its commercial production. Moderna Inc., a biotechnology firm, recently declared that mRNA-1273, a COVID-19

mRNA vaccine, has entered in phase 3 clinical trials with ~30,000 subjects. This vaccine program was funded by the Coalition for Epidemic Preparedness Innovations (CEPI) in association with the NIAID. mRNA-1273 encodes for a stable form of the SARS-CoV-2 S protein.[33,34] One of the RNA-based vaccine developed by Pfizer/Biotech BNT162b1 and BNT162b2 has entered in large phase 3 clinical trial with 29481 participants. BNT162b1 is nucleoside-modified mRNA encoding trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) has been prepared as a lipid nanoparticle-formulated vaccine (https://clinicaltrials.gov/ct2/show/study/NCT04368728?term=vaccine&cond=covid-19&draw=3).

Protein-based coronavirus vaccine

As discussed in the section above, owing to the role of the S protein in host cell receptor binding and membrane fusion, a SARS-CoV-2 vaccine based on the S protein may efficiently induce the production of antibodies and virus neutralization. Thus, the S protein is a good candidate target for vaccine development. Tazehkand and Hajipour (2020) fused an envelope and nucleocapsid protein with multi epitopes (B and MHC I epitopes) derived from the S protein and RNA-dependent RNA polymerase to construct a fusion vaccine. Although the vaccine was verified for its structural stability as well as physicochemical and immunological properties during a preliminary screening, the authors anticipated the need for further experiments with laboratory animals.[35] Recently, GlaxoSmithKline (GSK) collaborated with Clover Biopharmaceuticals to establish a COVID-19 vaccine aspirant. This joint venture aims to associate Clover's protein-based CoV vaccine candidate (COVID-19 S-Trimer) with GSK's adjuvant system. Clover has developed an S-Trimer subunit vaccine candidate using their Trimer-Tag technology and a rapid mammalian cell culture-based expression system.[36,37] Antigen Express Inc., a subsidiary of Generex (patent application US20060002947) disclosed the production of hybrid peptides comprising three elements: (a) an invariant chain (Ii) key peptide for antigen appearance-enhancing activity, (b) a chemical structure linking the Ii to the antigenic epitope, and (c) an antigenic epitope that binds to an MHC class II molecule. Recently, Generex also declared the development of a COVID-19 vaccine in association with a Chinese consortium, comprising China Technology Exchange, Beijing Zhonghua Investment Fund Management, Biology Institute of Shandong Academy of Sciences, and Sinotek-Advocates International Industry Development. The company will utilize its Ii-Key immune system activation technology to produce a SARS-CoV-2 viral peptide for use in human clinical trials.[37,38] Novavax Inc. recently introduced its COVID-19 vaccine candidate NVX-CoV2373, a stable, prefusion protein prepared using Novavax's proprietary nanoparticle technology, for phase 1 clinical trials in May 2020. This vaccine candidate has shown high immunogenicity and the stimulation of high levels of neutralizing antibodies in preclinical studies. Novavax proprietary Matrix-M™ adjuvant will be incorporated with NVX-CoV2373 to enable an immune response and the stimulation of high levels of neutralizing antibodies.[28,39] An attempt was made to design a multiepitope peptide vaccine against SARS-CoV-2 using envelope protein as a target with the help of immunoinformatics and comparative genomic approach. Such an approach assists the rapid development of potential vaccine although there is a need to validate it clinically.[40]

Vectored vaccines against coronavirus

Viral vectors represent one of the prospective strategies for the CoV vaccine platform. Their utility depends on their ability to infect cells. The main advantage of this platform is its efficient and gene-specific delivery as well as its initiation of healthy immune responses.[41] A recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing S protein of SARS-CoV-2 was assessed for phase 1 trial at Wuhan, China. The increase in specific neutralizing antibodies and T cell response were observed on day 14 after vaccination. The results remained promising and expect further evaluation.[42] Several groups have reported the results of preclinical trials of SARS-CoV-2 vaccines using other viruses as vectors, including measles replicating viral vector (Zydus Cadila, Institut Pasteur/Themis/University of Pittsburgh Center for Vaccine Research), influenza vector expressing RBD (University of Hongkong), and non-replicating viral vector adenovirus-based NasoVAX expressing the SARS-CoV-2 spike protein (Altimmune).[28] One of the Chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein developed by University of Oxford/AstraZeneca has entered in large phase 3 clinical trial with 2000 participants (http://www.isrctn.com/ISRCTN89951424).

Artificially synthesized protein-microarray

A recent study reported the development of a microneedle array-based recombinant SARS-CoV-2 S1 subunit vaccine. This vaccine was tested for its immunogenicity *in vivo* and was found to be able to induce an effective antigen-specific antibody response within two weeks post-immunization.[43]

Virus-like particle-based vaccine

Virus-like particles (VLPs) are multi-protein supra-molecular preparations with features equivalent to those of viruses. They represent a resourceful platform for vaccine development owing to their flexible immunological features, including suitable size, repetitive surface geometry, and stimulation of innate and adaptive immune responses. VLP-based vaccines target B lymphocytes and induce potent antibody responses, resulting in T helper cell activation and their presentation on MHC class II molecules via antigen-presenting cells (APCs).[44,45] Medicago Inc., a leading US-based biopharmaceutical company, recently developed a VLP-based vaccine against SARS-CoV-2. This vaccine is currently undergoing preclinical studies to determine its safety and efficacy. Saiba GmbH and Imophoron Ltd-Bristol University's Max Planck Center are also conducting preclinical tests using similar VLP-based vaccines in separate ventures.[28] These collaborative efforts aimed at gaining a fundamental understanding of SARS-CoV-2 have led to rapid technological advances that will aid in designing an effective vaccine against the virus. In addition to SARS-CoV-2-mimicking VLPs, another potential approach is the expression of SARS-CoV-2 epitopes in chimeric VLPs, allowing for viral presentation of the corresponding SARS-CoV-2 epitopes. Plants have long been used as a platform for biopharmaceutical

Table 1. COVID-19 candidate vaccines in clinical trials (WHO).

S. No.	Plateform	Type	Developer	Current Stage	Trial Duration	Sample Size	Dose Level	Reference
1	Inactivated	Inactivated Novel Coronavirus Pneumonia vaccine (Vero cells)	Wuhan Institute of Biological Products/ Sinopharm	Phase 1/2	20 Months	8 to 84	Low to high, Placebo	http://www.chictr.org.cn/showprojen.aspx?proj=52227
2	Inactivated	Inactivated novel coronavirus (2019-CoV) vaccine (Vero cells)	Beijing Institute of Biological Products/ Sinopharm	Phase 1/2	20 Months	8 to 84	Not available	http://www.chictr.org.cn/showproj.aspx?proj=53003
3	Inactivated	Inactivated + alum	Sinovac	Phase 1/2	2 Months	422	Low to high, Placebo	https://clinicaltrials.gov/ct2/show/NCT04383574?term=covid-19&cond=vaccine&cntry=CN&draw=2
				Phase 1/2	9 Months	744	Medium to High, Placebo	https://clinicaltrials.gov/ct2/show/NCT04352608?term=Sinovac&cntry=CN&draw=2
4	Inactivated	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1/2	15 Months	942	50 U/0.5 ml to 150 U/ 0.5 ml, Placebo	https://clinicaltrials.gov/ct2/show/NCT04412538?term=vaccine&cond=covid-19&draw=2
5	DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals/International Vaccine Institute	Phase 1/2	21 Months	160	1–2 mg/dose + EP	https://clinicaltrials.gov/ct2/show/NCT04447781
6	DNA	DNA Vaccine (GX-19)	Genexine Consortium	Phase 1/2	24 Months	190	Not available	https://clinicaltrials.gov/ct2/show/NCT04445389?term=vaccine&cond=covid-19&draw=3
7	RNA	LNP-encapsulated mRNA	Moderna/NIAID	Phase 2	15 Months	600	50–100 mcg	https://clinicaltrials.gov/ct2/show/NCT04405076?term=moderna&cond=covid-19&draw=2&rank=1
8	RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	Phase 1/2/3	32 Months	7600	0.5 mL	https://clinicaltrials.gov/ct2/show/NCT04368728?term=vaccine&cond=covid-19&draw=3
9	RNA	LNP-nCoVsaRNA	Imperial College London	Phase 1	16 Months	320	Not available	http://www.isrctn.com/ISRCTN17072692
10	RNA	mRNA	Curevac	Phase 1	14 Months	168	2–8 µg, Placebo	https://clinicaltrials.gov/ct2/show/NCT04449276?term=vaccine&cond=covid-19&draw=6
11	RNA	mRNA	People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	Phase 1	19 Months	56	Low to High dose, Placebo	http://www.chictr.org.cn/showprojen.aspx?proj=55524
12	Protein subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 1/2	15 Months	131	5–25 µm with or without Matrix M	https://clinicaltrials.gov/ct2/show/NCT04368988?term=vaccine&recrs=a&cond=covid-19&draw=2
13	Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	Clover Biopharmaceuticals Inc./GSK/ Dynavax	Phase 1	10 Months	150	3–30 µg with or without adjuvant	https://clinicaltrials.gov/ct2/show/NCT04405908?term=clover&cond=covid-19&draw=2&rank=1
14	Protein subunit	Adjuvanted recombinant protein (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Phase 1	15 Months	50	25–50 µg/0.5 ml/ person, Placebo	https://clinicaltrials.gov/ct2/show/NCT04445194?term=longcom&draw=2&rank=2
15	Protein subunit	Recombinant spike protein with Advax™ adjuvant	Vaxine Pty Ltd/Medytox	Phase 1	12 Months	40	Spike antigen (25 µg) + 15 mg Advax-2 adjuvant, Placebo	https://clinicaltrials.gov/ct2/show/NCT04453852?term=vaccine&cond=covid-19&draw=5
16	Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	Phase 3	14 months	2000	Single dose of 5x10^10vp	http://www.isrctn.com/ISRCTN89951424
17	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 2	10 Months	250	Middle dose (1E11vp)	http://www.chictr.org.cn/showprojen.aspx?proj=52006
				Phase 2	10 Months	125	Low dose (5E10vp)	http://www.chictr.org.cn/showprojen.aspx?proj=52006
				Phase 2	10 Months	125	Placebo	http://www.chictr.org.cn/showprojen.aspx?proj=52006
18	Non-Replicating Viral Vector	Adeno-based	Gamaleya Research Institute	Phase 1/2	3 Months	38	Not available	https://clinicaltrials.gov/ct2/show/study/NCT04436471?term=vaccine&cond=covid-19&draw=4

production. To date, several plant-vaccine candidates have been considered for clinical trials. Currently, the existing expression method for foreign proteins in plants represents a potential platform for the generation of suitable vaccine candidates against SARS-CoV-2 with reservations.[46]

There are currently three listed interventional clinical trials for the treatment and prevention of COVID-19 in China. A pathogen-specific aAPC vaccine currently in phase 1 trials (NCT04299724, ICTRP) was developed using lentivirus minigenes to express SARS-CoV-2 antigens in APCs (where COVID-19/aAPCs are inactivated for proliferation) and has been extensively tested for its safety. Another platform uses the inhalation of inactive *Mycobacterium* (ChiCTR2000030016, ICTRP). The third vaccine, the LV-SMENP-DC vaccine (NCT04276896, ICTRP), was established by modifying dendritic cells with a lentivirus vector expressing COVID-19 minigene SMENP and immune-modulatory genes. The specific antigens have been designed to stimulate cytotoxic T lymphocytes.[47] Table 1 exhibits various COVID-19 vaccine in clinical trials as per WHO.[40]

SARS-CoV-2 vaccine: efficacy and safety

The development of a vaccine requires extensive planning and research with regard to its design, production, and purification as well as preclinical trials in model animals to confirm its safety and several stages of human clinical trials to determine its efficacy in disease intervention. There is currently an urgent need for the development of an efficient vaccine against SARS-CoV-2. An effective and safe vaccine will play a significant role in diminishing the escalating transmission and infection of SARS-CoV-2. Currently, the development of a SARS-CoV-2 vaccine is at the initial stages of building a robust platform with which to tackle COVID-19. Although there are similarities between SARS-CoV and SARS-CoV-2, detailed information on the clinical trials, immune responses, and tentative outcomes of a SARS-CoV-2-specific vaccine are necessary. While SARS-CoV vaccines have been found to be effective in animal models, the efficacy of SARS-CoV-2 remains to be verified in humans. Standard protocols are the prerequisites to safeguard human health. Therefore, the corresponding regulatory authorities should evaluate the safety profile of potential SARS-CoV -2 vaccines using an array of virus strains and a variety of animal models.[48]

One major issue in the development of a SARS-CoV-2 vaccine is the probability of quick disappearance of the antibody response generated against the vaccine. CoV infection has been previously found to be incapable of inducing a long-lived antibody response, resulting in the re-infection of individuals with a similar virus after a long period. Although this phenomenon is not widespread, it is worth noting.[17] The lack or lower incidence of high-affinity anti-SARS-CoV-2 IgG results in antibody-dependent enhancement (ADE), a condition where specific antibodies can potentiate, instead of protecting against a CoV infection. In this context, rather than the clearance of the antigen-antibody complex via a regular mechanism, the system follows an alternative route through which the host cell is infected. Unless vaccines are designed strategically, the risk of ADE exists among vaccinated individuals. However, data on this issue are currently lacking and requires further clarification.[49,50] Another concern with the development of a SARS-CoV-2 vaccine is in ensuring the prevention of disease enhancement. A vaccinated person may develop a more severe condition than a non-vaccinated person upon infection. This phenomenon is supported by a study on the experimental SARS vaccine, in which vaccinated ferrets developed critical liver inflammation in response to viral infection.[51] A potential COVID-19 vaccine needs to address such safety concerns in order to curb the current pandemic, its reemergence, and future epidemics.

Conclusions

There is an urgent need for a relatively safe and effective COVID-19 vaccine. Vaccines generally require experimental trials in animal models, followed by human clinical trials in subjects of various age groups before they can be approved for mass production and widespread implementation. With considerable efforts being made both at an individual level and in collaboration for the development of vaccines against COVID-19 using a variety of platforms, the time-frame is the most important factor to determine the efficacy of vaccine technology. Past and present experiences with CoVs have taught us what we lack in preparation and what we must prepare for in the future. The ultimate goal of current research should be the easy availability and access of vaccines to the lower section of society. The recombinant COVID-19 vaccine has a capability to overcome these social limitations and the safety concerns associated with other vaccines. Further, this promising platform may reduce the intricacy of mass production and time-frame once established.

Future perspectives

With huge information available on vaccine development for COVID-19, there are still some aspects to be focused on while designing a potential recombinant vaccine. The efficiency and safety are the two major characteristics of a vaccine that demand a number of preclinical and clinical trials. Therefore, we need to investigate more animal models and volunteers with varied health conditions and age. However, the period of trials can be deliberately reduced with the help of modern biotechnology platforms that may result in fast and effective vaccine development in this type of utmost emergency. The recurrence of coronaviruses in the last decades suggests possible future outbreaks and potential to become pandemic and therefore the process of vaccine development should focus on wide host-range against several of the circulating CoVs to get flexible products within a short period of time. This necessitates the alliance of recombinant platforms to bring more accuracy and predictable efficacy to the current vaccine technology.

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Author contributions statement

SKS conceived the idea. TY, NS, SK, and SKS collected the data, devised the initial draft, reviewed the final draft and finalized the draft for submission. TY, NS, GM, KD, SK, BP and SKS read and approved the final version of the manuscript.

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The authors declare no competing financial interest. The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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