

COVID-19 vaccine landscape

Seneviratne SL^{1,2,3}, Jayarajah U², Abeysuriya V³, Rahman A², Wanigasuriya K⁴

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is currently pandemic, and as of 15th November 2020, there have been 53.7 million confirmed cases worldwide and around 1.3 million deaths. The availability of an effective vaccine is the best long-term answer to the current COVID-19 pandemic. More than 210 candidate vaccines have come into development since the start of the pandemic. Eleven vaccines (ten of them specifically directed against SARS-CoV-2) have entered phase 3 clinical trials. Five of these vaccines have also been approved for early or limited use. This review outlines information on the current COVID-19 vaccine pipeline, discusses the pros and cons of different vaccine delivery systems and the steps involved in getting a safe and effective vaccine to the global population.

Key words: COVID-19, vaccine, SARS-CoV-2, Coronavirus, Coronavirus disease 2019, Severe acute respiratory syndrome coronavirus 2, pandemic

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ This virus originated in Wuhan, China in December 2019.² It is currently pandemic, and as of 15th November 2020, there have been more than 53 million cases worldwide and over 1.3 million deaths.³


COVID-19 causes harm in three broad ways: death or long-term organ damage, constrains on the operation of effective healthcare systems and adverse effects on national/regional economies.⁴⁻⁸ The availability of an effective vaccine is the best long-term answer to the current COVID-19 pandemic.^{9,10} There has been an international response to COVID-19 vaccine development. More than 210 candidate vaccines have come into development since the start of the pandemic. Eleven vaccines (ten of them specifically directed against SARS-CoV-2) have entered phase 3 clinical trials (Table 1). Five of these vaccines have also been approved for early or limited use. In this review, we have described the different COVID-19 vaccine candidates, their mechanism of action and the human clinical trial findings published so far.

Vaccine development cycle

Vaccine development occurs in several stages known as the vaccine development cycle (Figure 1). This includes: preclinical, clinical (phase I, II and III) and the manufacturing (phase IV) stages. In the preclinical stage, the vaccine target is identified and assessed for feasibility and safety by means of *in vivo* and animal studies. During the clinical stages, safety, immunogenicity and efficacy are assessed in a step wise manner using increasing numbers of individuals. At the end of phase III, the properties of the vaccine and administration protocols would be defined and it should be suitable for large scale manufacturing. During Phase IV, comparative clinical studies and post-marketing surveillance should take place. In general,

¹*Institute of Infection and Immunity, Royal Free Hospital and University College London, London, UK*, ²*Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka*, ³*Nawaloka Hospital Research and Education Foundation, Nawaloka Hospitals PLC, Colombo, Sri Lanka*, ⁴*Department of Medicine, Faculty of Medicine, University of Sri Jayewardenepura, Sri Lanka*.

Correspondence: SLS, e-mail: suran200@yahoo.co.uk

 <https://orcid.org/0000-0002-6548-5673>

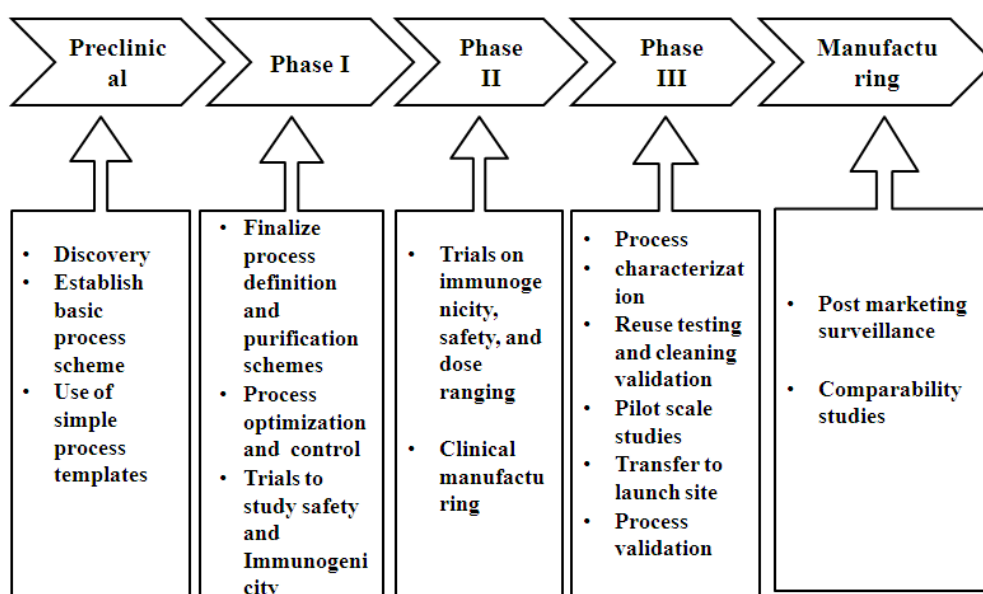
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Table 1. Vaccines that have entered Phase 3 Trials

<i>Class of vaccine</i>	<i>Vaccine candidate</i>	<i>Developer</i>	<i>Vaccine platform</i>
Genetic vaccines	mRNA-1273 BNT162	Moderna/NIAID BioNTech/Fosun Pharma/Pfizer	LNP-encapsulated mRNA Three LNP-mRNAs
Viral vector vaccines	Ad5-nCov	CanSino Biological Inc/ Beijing Institute of Biotechnology	Non-replicating viral vector
	AZD1222 (formerly ChAdOx1 nCov-19)	University of Oxford/Astra Zeneca	Non-replicating viral vector
	Adeno-based (rAd26-S+rAd5-S)	Gamaleya Research Institute	Non-replicating viral vector
	Ad26COVS1	Janssen Pharmaceutical Company	Non-replicating viral vector
Protein based vaccines	Protein subunit	Novavax	Full length rSARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M
Inactivated coronavirus vaccines	Inactivated	Beijing institute of Biological Products/SinoPharm	Inactivated virus
	Inactivated	Wuhan Institute of Biological Products / SinoPharm	Inactivated virus
	Inactivated	Sinovac	Inactivated virus
Repurposed vaccines	Bacillus Calmette- Guerin (BCG)	Murdoch children's Research Institute	Attenuated Mycobacterium bovis

Stages of vaccine development**Figure 1. Stages of vaccine development cycle.**

completion of the different stages of vaccine development takes over a decade. However, during pandemic situations such as the COVID-19 pandemic, this process has been significantly shortened (to around one year) because several steps are carried out in parallel rather than sequentially. Prior to this, the shortest time for vaccine development was four years, with the mumps vaccine.

Potential targets for a COVID-19 vaccine

SARS-CoV-2 is an enveloped β coronavirus.¹¹ The viral envelope consists of the spike (S) glycoprotein

and the envelope (E) and membrane (M) proteins (Figure 2). The S glycoprotein mediates host cell attachment and is required for viral entry. It consists of two subunits; S1 and S2 (Figure 3). The S1 subunit is responsible for attachment to the ACE receptor present on host cells and S2 for the subsequent fusion of the cell membranes of both virus and the host.¹² The S1 subunit has a receptor-binding domain (RBD). The S protein has been identified as the major immunogenic target for vaccine development.¹³ Most of the COVID-19 vaccines in development are intended to induce antibody responses that neutralise SARS-CoV-2. The expectation is that this would

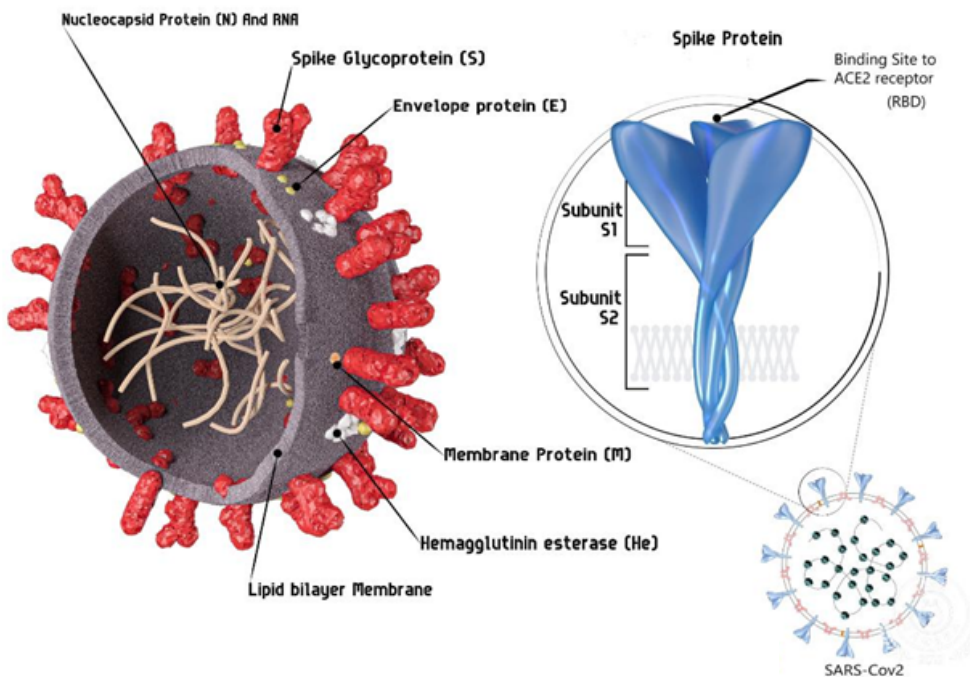


Figure 2. Structure of SARS-CoV-2 virus.

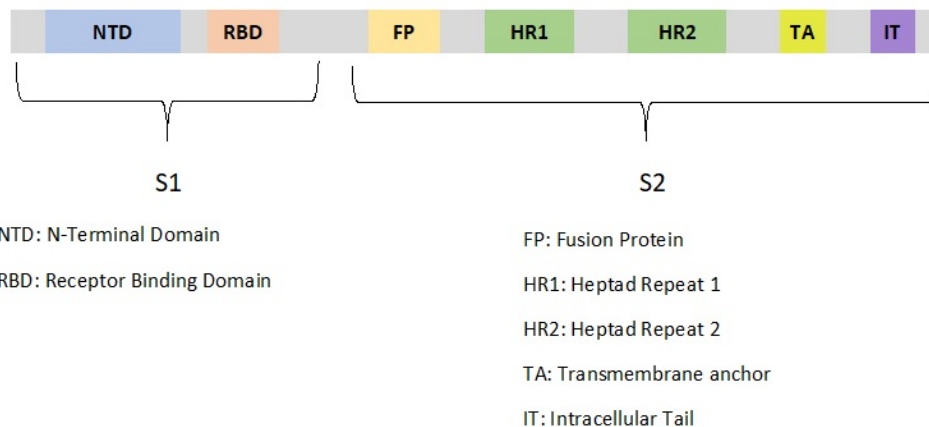


Figure 3. SARS-CoV-2 Spike glycoprotein

prevent the virus from entering target cells and infecting the host. In some cases, the vaccines may also induce antibody and/or cellular immune responses that can kill and eliminate already infected cells. A major driving force behind many of the existing programs appears to be the speed at which a vaccine product can be manufactured at scale using existing production facilities.

Categories of COVID-19 vaccines in development

The categories of vaccines for protection against SARS-Cov-2 infection and/or disease includes the following: genetic/nucleic acid (mRNA or DNA) vaccines, viral vector (non-replicating or replicating) vaccines, recombinant spike or RBD-protein vaccines, inactivated virus vaccines and live attenuated virus vaccines (Table 2). Some important features of each of these categories are outlined below.

RNA vaccines

DNA is the genetic code of living structures and proteins are the building blocks. mRNA translates DNA into protein. An mRNA vaccine against COVID-19 would instruct the body's cells to produce specific coronavirus proteins (and not the virus per se). These proteins would then trigger an antibody and cellular immune response. mRNA technology is relatively new (only about 20 years old). Presently, three firms lead the field (two German firms – BioNTech and Curevac and the US biotech company Moderna).¹⁴⁻¹⁹ BioNTech has teamed up with Pfizer and Fosun from Japan and Curevac and is developing its vaccine with the Centre of Epidemic Preparedness Innovation (CEPI). Two Belgian firms (eTheRNA and Ziphus therapeutics) and Sanofi/Triamtbio have also recently entered this arena.

Normally, it would take around 18 months to design a vaccine and get it to phase 1 testing. This is because complex proteins or inactivated viruses need to be designed, produced and then tested. This time period is shortened with mRNA vaccines. For instance, Moderna took around two months to enter phase 1 trials, after the SARS-CoV-2 viral sequence was released. mRNA vaccines are designed using the sequence of virus. Thus, the lab does not need to work with the virus itself. Industrial production of mRNA is also easier and faster. mRNA consists of simple chains of nucleosides and no complex proteins need to be made. The persons own body cells become factories when mRNA is delivered into cells. mRNA is better than DNA at activating the immune system and has better access to cells. It is safer than the delivery of

foreign DNA to an individual and does not carry the risk of integration into the genetic material of the target cell. It could also be directly taken up by cells of the immune system without additional stimulation. However, one needs to remember that no mRNA vaccine or therapeutic has still been approved. Furthermore, the amount of animal data on this aspect is still comparatively small.

Very recently, BioNTech/Pfizer announced their mRNA-based-vaccine candidate BNT162b2 was more than 90% effective in preventing COVID-19 in participants at seven days after the second dose of vaccine. The study has enrolled 43,538 participants and the first interim efficacy analysis evaluated 94 confirmed COVID-19 cases in the trial participants. No serious safety concerns were announced. Approximately 42% of the global participants and 30% of the US participants have racially and ethnically diverse backgrounds.²⁰ One needs to remember that the BioNTech/Pfizer vaccine comes with special storage challenges, as it needs to be stored at -70 degrees centigrade. An update earlier this week stated the BNT162b2 vaccine was 94% effective among adults over the age of 65 years. Moderna also announced the findings of an interim analysis of their phase 3 trial. They found their vaccine candidate mRNA-1273 to be safe and well tolerated and to have a vaccine efficacy of 94.5%.²¹

DNA vaccines

With DNA vaccines, double-strand DNA is injected into the recipient (intradermal injection using an electroporation device).²²⁻²³ It has a better safety profile than live attenuated vaccines. Furthermore, the manufacturing process is well defined and a freeze-dried formulation is possible. Inovio pharmaceuticals and Cobra biologics have initiated trials with DNA vaccines for COVID-19. In April 2020, Inovio announced the initiation of phase 1 human clinical trials in the US and in June, the trials were extended to South Korea and China. In July 2020, the company announced positive interim data when the vaccine was given to non-human primates. However, at the end of September 2020, the FDA requested more information about the vaccine and its delivery device prior to granting approval for the commencement of the phase 2/3 trial.

Viral and bacterial vector-based vaccines

Potentially immunogenic parts of the SARS-CoV-2 virus may be inserted into a viral or bacterial vector and this could then be used as a vaccine. The common vectors in use at present includes: adenovirus, adeno-associated virus, lentivirus and lactic acid bacteria.

Table 2. Categories of vaccines for COVID-19

<i>Platform</i>	<i>Target</i>	<i>Are there existing licenced human vaccines using the same platform</i>	<i>Pros</i>	<i>Cons</i>
Genetic vaccines - RNA vaccines	S protein	No	No infectious virus needs to be handled Rapid production possible Typically immunogenic	Some safety issues with reactogenicity
Genetic vaccines - DNA vaccines	S protein	No	No infectious virus needs to be handled Rapid production possible Easy to scale up Low production costs High heat stability	Needs specific delivery devices to reach good immunogenicity
Viral vector based vaccines	S protein	Yes - Ervebo (for Ebola virus disease - using the Vesicular Stomatitis Virus)	No infectious virus needs to be handled Excellent pre-clinical and clinical data	Vector immunity may negatively affect vaccine effectiveness
Recombinant protein vaccines	S protein	Yes (HPV, Influenza, HBV)	No infectious virus needs to be handled Adjuvants can be used to increase immunogenicity	Global production capacity might be limited Antigen integrity needs to be confirmed
Inactivated vaccines	Whole virion	Yes	Striaightforward manufacturing process Used for several licenced human vaccines Existing infrastructure can be used Adjuvants can be used to increase immunogenicity	Large amounts of infectious virus need to be handled Antigen integrity needs to be confirmed
Live attenuated vaccines	Whole virion	Yes	Striaightforward manufacturing process Used for several licenced human vaccines Existing infrastructure can be used	Creating infectious clones for attenuated coronavirus vaccine takes time Extensive safety testing will be needed

Oxford University and Astra Zeneca have developed a chimpanzee adenovirus vectored vaccine, which encodes the spike protein.²⁴ It was found to be immunogenic and efficacious in non-human primate studies. Phase 1/2 human trials found humoral and T cell responses in most recipients after the first dose of the vaccine with further boosting of the antibody responses after the second dose. A large phase 3 trial is ongoing. The Gamaleya Research Centre have developed a vaccine consisting of recombinant adenovirus serotype 26 and 5 vectors.²⁵ A phase 1/2 human trial reported seroconversion in 100% of recipients and a CD4+ and CD8+ T cell immune response in all subjects that peaked at 28 days post-vaccination. Surprisingly, on August 12th 2020, this vaccine (now named Sputnik V) was granted approval for limited use in Russia, prior to the completion of the phase 3 trials. CanSino Biologics and Johnson and Johnson have developed recombinant adenovirus 5 and adenovirus 26 vectored vaccines respectively and have ongoing phase 3 human trials.²⁶⁻³⁰ A recent update from the Oxford vaccine suggests it produces similar neutralising antibody titres and T cells responses across all three age groups (18-55, 56-69 and 70+ years).

Recombinant protein-based vaccines

When recombinantly synthesised SARS-CoV-2 viral proteins or protein fragments (such as the RBD) are injected, they stimulate an immune response. This technique mainly induces a humoral immune response and needs appropriate adjuvants to increase immunogenicity. The NVX-CoV2373 nanoparticle vaccine contains recombinant full length wild-type SARS-CoV-2 (rSARS-CoV-2) and the Matrix M1 adjuvant (a saponin based adjuvant).³¹

Inactivated virus vaccines

These vaccines require an adjuvant to boost immunogenicity. For instance, the vaccine candidate from SinoVac uses aluminium hydroxide (Alum). This induces a predominantly humoral based immune response. Other adjuvants such as monophosphoryl Lipid A (MPL) may help stimulate a cellular immune response too. Sinovac Biotech and Sinopharm are at present conducting phase 3 trials on inactivated vaccines.³²⁻³⁴

Trained immunity-based vaccines

Trained immunity-based vaccines stimulate the innate immune system and provides protection to unrelated pathogens. The BCG vaccine is currently under evaluation for its ability to induce trained immunity against SARS-CoV-2.

COVID-19 vaccine clinical trial findings

Several human clinical trials have reported their phase 1 and 2 findings (a summary of their main findings are shown in Table 3). The USA, UK, Germany, Russia and China have been the leading countries carrying out these studies. The 11 human COVID-19 vaccine trials that have reported their results have included 3586 participants (range - 40 to 1192), age range: 18 to 80 years. The SARS-CoV-2 spike protein has been the vaccine target for most of the trials, whilst a group from China used whole virion as the target. Nine of the eleven were randomized trials. Some were phase 1 trials and others were combined phase 1/2 or phase 2 trials. Only a few mild to moderate adverse effects were noted.

A summary of seven reported animal COVID-19 vaccine trials are shown in Table 4. Six were conducted in USA and the other in China. The US trials targeted the SARS-CoV-2 spike protein and the study from China targeted the whole virion. Mice, non-human primates, guinea pigs and hamsters were used in the studies. All the animal trials showed promising protection against COVID-19.

Vaccine efficacy

Vaccine efficacy involves the study of outcome data from randomized controlled trials (RCT) between participants that are vaccinated or not. Outcomes that may be assessed include: a reduction in infection, effect on severity of clinical disease or on duration of infectivity.³⁵ Large scale prospective studies would help evaluate the effectiveness and immunogenicity in different strata of the population. Standardized approaches for assessing efficacy endpoints are important for making comparisons between the different vaccine candidates. Instead of measuring only clinical outcomes, validated and robust immunological correlates of protection may be used as surrogate markers. For this, properly designed in-vitro immune based assays would be needed. Reinfections have been reported in a subset of individuals thus raising the possibility of waning of long-standing immunity. Furthermore, the efficacy of antibody generating vaccines in immunocompromised or immunodeficient patients may be sub-optimal.

Controlled human challenge studies involve the exposure of human volunteers to infectious pathogens. Recently, the human challenge consortium was convened to explore the feasibility and ethics of such studies. Proponents of such studies argue they would allow rapid assessment of vaccine efficacy and thus discontinue any that are found to be ineffective.

Table 3. Summary of reported human COVID-19 vaccine trials

Author and country	Funding source	Developer	Target	Study design Number of participants Age	Phase	Vaccine candidate	Vaccine platform	Actual findings
Jackson USA	NIAID and others	Moderna/NIAID	SARS-CoV-2 spike protein	Dose-escalation, open-label trial 18 to 55 years	Phase 1	mRNA-1273	LNP-mRNA	Vaccine induced anti-SARS-CoV-2 immune responses developed in all participants.
Anderson USA	NIAID and others	Moderna/NIAID	SARS-CoV-2 spike protein	Open-label trial N=40 56 years and above	Phase 1	mRNA-1273	LNP-mRNA	Adverse events associated with the vaccine were mainly mild or moderate.
Mulligan USA	BioNTech/Pfizer	BioNTech/Pfizer	SARS-CoV-2 spike protein	Randomized placebo-controlled trial N= 45 18-55 years of age	Phase 1	BNT162b1	LNP-mRNA	Neutralizing antibody titers 1.9 – 4.6-fold that of a panel of COVID-19 convalescent human sera.
Sahin Germany	BioNTech/Pfizer	BioNTech/Pfizer	SARS-CoV-2 spike protein	Randomized placebo-controlled observer-blinded trial N= 60 Age 20-56 years	Phase 1 & 2	BNT162b1	LNP-mRNA	Induces functional and pro-inflammatory CD4+ and CD8+ T cell responses in almost all participants, TH1 polarization of the helper response.
Walsh USA	BioNTech/Pfizer	BioNTech/Pfizer	SARS-CoV-2 spike protein	Randomized placebo-controlled observer-blinded trial N=195 Age 18 to 55 years and 65 to 85 years	Phase 1 & 2	BNT162b1	LNP-mRNA	Safe and immunogenic.
Folegatti UK	UKR&I/CEPI/NIHR	University of Oxford/ Astra Zeneca	SARS-CoV-2 spike protein	Single-blind, randomized controlled trial N=1077 Age 18-55 years	Phase 1 & 2	ChAdOx1 nCoV-19	Non-replicating viral vector	Acceptable safety profile, homologous boosting increased antibody responses.

(Continued)

Author and country	Funding source	Developer	Target	Study design Number of participants Age	Phase	Vaccine candidate	Vaccine platform	Actual findings
Logunov Russia	MOH - Russian Federation	Gamaleya National Research Centred	SARS-CoV-2 spike protein	Non-randomized study N=76 Age 18-60 years	Phase 1 & 2	rAd26 and rAd5 vectors	Non-replicating viral vector	Good safety profile, induced strong humoral and cellular immune responses
Zhu (a) China	NPKRP/NSTMP/CanSino	CanSino Biologics	SARS-CoV-2 spike protein	A dose-escalation, single-centre, open-label, non-randomized. N=195 Age 18-60 years	Phase 1	rAd5 vector	Non-replicating viral vector	Tolerable and immunogenic at 28 days post-vaccination. Humoral response peaked at day 28 post-vaccination. Rapid specific T-cell responses noted from day 14 post-vaccination.
Zhu (b) China	NPKRP/NSTMP/CanSino	CanSino Biologics	SARS-CoV-2 spike protein	Randomized, double-blind, placebo-controlled, N=603 Age more than 18 years	Phase 2	rAd5 vector	Non-replicating viral vector	Safe, induced significant immune responses in the majority of recipients after a single dose.
Keech USA	CEPI	Novavax	SARS-CoV-2 spike protein	Randomized, placebo-controlled trial N=134 Age not mentioned	Phase1 & 2	Protein subunit	Nanoparticle subunit vaccine with Matrix M adjuvant	Appeared to be safe, elicited immune responses that exceeded levels in Covid-19 convalescent serum.
Xia China	NPKRP/NMP-ID/ NMP- NDC/ BSTP	BIBP	Whole virion	Randomized, double-blind, placebo-controlled trial N=1192 Age 18-80 years	Phase 1	BBIBP-CorV	Inactivated virus	Safe and well tolerated at all tested doses.

BIBP - Beijing Institute of Biological products BISTP - Beijing Science and Technology Plan. BISTP: Beijing Science and Technology Plan. CEPI: Coalition for Epidemic Preparedness Innovations. NIAID - National Institute of Allergy and Infectious Diseases. NPKRP - National Program on Key Research Project of China. NMP - National Mega Projects of China for Major Infectious Diseases. NMP - National Mega Projects of China for New Drug Creation. NPKRP: National Program on Key Research Project of China. NMP-ID: National Mega Projects of China for Major Infectious Diseases. NMP - NDC: National Mega Projects of China for New Drug Creation. NSTMP, National Science and Technology Major Project. UKR&I: UK Research and Innovation. NIHR: National Institute for Health Research.

Table 4. Summary of reported animal COVID-19 vaccine trials

Name and country	Funding source	Target	Type of animal	Vaccine candidate	Vaccine platform	Actual findings
Corbett USA	NIH	SARS-CoV-2 spike protein	Nonhuman primates	mRNA-1273	LNP-mRNA	Induced robust virus neutralizing activity, rapid protection in the upper and lower airways, no pathologic changes in the lung.
Tostanoski USA	HHS-BARDA	SARS-CoV-2 spike protein	Hamsters	rAd26 vector	Non-replicating viral vector	Demonstrated vaccine protection against virus
Hassan USA	NIH	SARS-CoV-2 spike protein	Mice	ChAd-SARS-CoV-2-S	Non-replicating viral vector	Protects against viral infection and pneumonia
King USA	Altimmune/BISF	SARS-CoV-2 spike protein	Mice	rAd5 vector (Intranasal Ad COVID)	Non-replicating viral vector	Promotes concomitant systemic and local mucosal immunity.
Smith USA	Inovio	SARS-CoV-2 spike protein	Mice, Hartley guinea pigs	DNA vaccine (INO-4800)	DNA plasmid	Demonstrated effective vaccine protection.
Yu USA	RHMGH/MIT/ Harvard/NIH	SARS-CoV-2 spike protein	Rhesus macaques	DNA vaccine	DNA plasmid	Demonstrated effective vaccine protection against virus
Seo China	CNU Korea	Whole virion	Mice	Cold adapted live-attenuated SARS-CoV-2 vaccine	Replicating viral vector	Mice were completely protected after a single dose

BISF: Barbara Ingalls Shook Foundation, BIDMC: Beth Israel Deaconess Medical Center, Department of Health and Human Services Biomedical advanced Research and Development Authority, MLSF: Mark and Lisa Schwartz Foundation, MaaCPR: Massachusetts Consortium on Pathogen Readiness, JV-PVB: Janssen Vaccines & Prevention BV, HHS-BAR-DA: Department of Health and Human Services Biomedical advanced Research and Development Authority, RI-MGH: Ragon Institute of MGH.

However, such studies could be logistically difficult to arrange and may involve challenging a group of young otherwise healthy individuals that really does not represent the demographic to whom the vaccine would be first targeted. However, such studies may provide important immunological insights into the disease pathogenesis in a controlled manner.

Vaccine safety

Having safe vaccines are critical for any wide-spread vaccination programmes. The population at large, needs to be continuously updated on the safety aspects of all the evaluated COVID-19 vaccines. Furthermore, complete transparency in the reporting of findings from the various large-scale clinical trials is essential. Assessment of vaccine safety needs to be inbuilt into all stages of clinical development of the different vaccine candidates. Furthermore, they need to continue once a vaccine has been approved for use and then given to large population groups. With COVID-19 vaccines, this is especially important as some of the vaccine platforms are novel (mRNA, DNA, nanoparticle, viral vector) and thus need careful safety checks. Standardised definitions and lists of adverse effects of special interest have been discussed and agreed on. Human COVID-19 vaccine studies that have reported thus far, have shown acceptable safety profiles of the different vaccine platforms and constructs. Overall, the inactivated whole virus vaccine constructs were found to be the least reactogenic.

Access to COVID-19 vaccines

Equitable and simultaneous access to new COVID-19 vaccines is the hope for stopping the progression of the pandemic.³⁶ Once effective COVID-19 vaccines are developed and approved, questions of how to distribute them equitably across different countries would arise. Aspects relating to 'Vaccine Nationalism' should be strongly guarded against at all cost, by ensuring ethical and effective frameworks are in place for international COVID-19 vaccine allocation and distribution. Reducing premature deaths would take precedence in any COVID-19 vaccine allocation programme. It is likely that persons at greatest risk of COVID-19 (healthcare workers, nursing home residents, persons with underlying health conditions, the elderly) would be the first to be given access to a COVID-19 vaccine. COVAX is one of three pillars of the Access to COVID-19 Tools Accelerator. It is coordinated by the WHO, Global Alliance for Vaccines and Immunization (Gavi), and the Coalition for Epidemic Preparedness and Innovations (CEPI). It was set up to ensure research, purchase and distribution of any new vaccines is shared equally between the world's

rich countries and developing states. Since the first useful COVID-19 vaccines would be in short supply, any approved vaccines would be targeted to 3% of the population of each of the countries in the coalition. China has recently become a partner of this coalition.

Vaccine hesitancy

COVID-19 vaccine hesitancy is an important aspect to be discussed and considered.³⁷ Recent reports suggest between one sixth and one half of the UK population may refuse to receive a COVID-19 vaccine.^{38,39} This in turn would pose a serious threat to achieving widespread SARS-CoV-2 immunity.

Conclusions

The continuing COVID-19 pandemic and its adverse individual, societal and economic effects necessitate finding of effective control measures as an important and urgent global need. Effective and safe vaccines are known to reduce high disease burdens in other diseases and to have the greatest beneficial effects on a wide scale. The hope is that one or more of the presently evaluated COVID-19 vaccine candidates would prove to be safe, immunogenic and efficacious and would play its role in controlling this devastating pandemic.

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