Journal of Pharmaceutical Research International

33(47A): 469-488, 2021; Article no.JPRI.75109
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Vaccines against COVID-19 – Catching the Rays of Hope

Suresh Kumar Srinivasamurthy[1] and Laxminarayana Kurady Bairy[2*]

[1]Department of Pharamcology, RAK College of Medical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, B.O.Box No.11172, United Arab Emirates.
[2]Dean and Chairperson of Pharmacology, RAK College of Medical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, B.O.Box No.11172, United Arab Emirates.

Authors' contributions

This work was carried out in collaboration between both authors. Both final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i47A33035
Editor(s):
(1) Debarshi Kar Mahapatra, Rashtrasant Tukadoji Maharaj Nagpur University, India.
(2) Begum Rokeya, Bangladesh University of Health Sciences, Bangladesh.
(3) Y.C. Tripathi, Forest Research Institute - University, India.
(4) Sung-Kun Kim, Northeastern State University, USA.
Reviewers:
(1) Ali Jaber, Lebanese University, Lebanon.
(2) Yash Jain, IIHMR University, India.
(3) Indla Ravi, Kerala University of Health Sciences, India.
(4) Rakhamaji Dattarao Chandane, Lady Hardinge Medical College, Delhi University, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/75109

Review Article

Received 24 September 2021
Accepted 25 October 2021
Published 27 October 2021

ABSTRACT

COVID-19 pandemic has affected the world in all its dimensions. With herd immunity being a distant and non-practical possibility, vaccination remains most tractable approach to reduce morbidity and mortality. Several early phase clinical trials have proved the immunogenicity of vaccines. The efficacy trials have shown reduction in chance of acquiring COVID-19 disease after vaccination. The vaccines approved for emergency use have reported efficacy above 50% thus making them important public health tool in controlling the pandemic. Nevertheless, several questions remain elusive such as whether these approved vaccines are effective against newer variants of the virus; whether vaccination prevents transmission of the virus in the community; clinical impact of vaccination on morbidity and mortality. This review aims to elucidate the status of vaccine candidates in advanced trials along with the vaccines, which have been granted emergency approvals. Further, we collate the data on vaccines efficacy phase 3 trials and their probability of efficacy against newer variants.

**Corresponding author: E-mail: kurady@rakmhsu.a.c.ae;*

Keywords: *Prevention of COVID-19; COVID-19 vaccines; prevention of SARS-CoV-2; COVID-19 vaccine immunogenicity.*

ABBREVIATIONS

CEPI : Coalition for Epidemic Preparedness Innovations;
CI : Confidence interval;
COVID : Corona Virus Disease;
DNA : Deoxy ribonucleic acid;
GAVI : Global Vaccine Alliance;
IV : Inactivated Virus;
LAV : Live Attenuated Virus;
NAAT : nucleic acid amplification test;
NTD : N terminal;
PCR : Polymerase chain reaction;
PS : Protein Subunit;
RBD : receptor binding domain of spike protein;
RNA : Ribonucliec acid;
SARS : Severe Acute Respiratory Syndrome;
Saran : Self-amplyfying RNA;
VLP : Virus Like Particles;
VVnr : Non-Replicating Viral Vector;
VVr : Replicating Viral Vectors.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic that has practically paralyzed the whole world in terms of economy, education and people movement has seen second and third waves in different regions of the globe. The total global cases involving 221 countries and territories have crossed 227,923,887; with more than 4,686,061deaths [1]. Although many existing drugs have been repurposed, none of them is proved to be effective in preventing COVID-19 [2]. At this stage, the crucial strategy to control pandemic is by vaccination and infection control measure such as physical distancing. The development of safe and effective vaccine for COVID-19 has been on war footing since the advent of pandemic. Various challenges have been overcome for accelerating the process of vaccine development. Many vaccine candidates have been granted emergency use authorization in several countries, while many more are in clinical trials and preclinical phases. Thus, pandemic has overburdened not just public health systems of countries but also the clinical development process.

Nearly 21 candidate vaccines are in public use under emergency use authorization (EAU) and 107 in various phases of clinical trials [3]. As per World Health Organisation (WHO) landscape of COVID-19 candidate vaccines 117 are in clinical development and 194 are in preclinical development [4]. The vaccine platforms being evaluated are by conventional approaches such as protein/adjuvant, inactivated and live attenuated vaccines; and novel approaches such as viral vectors, DNA, mRNA vaccines [5]. The United States Food and Drug Administration (US FDA) has put forward that essential efficacy of at least 50 % for any COVID-19 vaccine candidate for emergency approval [6]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) structural proteins, which can be targeted for generating neutralizing antibodies, have been characterized by Lee et al. [7] (Fig. 1) The antigenic receptor-binding domain (RBD) within the spike protein is considered as the prime target of most of neutralizing antibodies [8]. However, emerging evidence suggests other regions on spike protein targetable by novel monoclonal antibodies for better efficacy. The SARS-CoV-2 spike protein and that of severe acute respiratory syndrome associated corona virus (SARS-CoV) of 2003 have reported to be having 75.5% homology, with several novel epitopes [8]. The antibodies against SARS-CoV spike protein is shown to be not beneficial against SARS-CoV-2 spike protein due to these variations [8,9]. The conventional approach used hitherto would have taken longer duration for development of vaccines. However, novel approaches such as mRNA platform have the advantages of fastening clinical development and was employed by several vaccine candidates. Thus, COVID-19 pandemic has not only paved way for historic fast-track development of vaccines but also brought perspectives for use of novel vaccine platforms (Fig. 2).

We searched databases such as PubMed and Google Scholar, for terms COVID, coronavirus, delta covid variant; vacccine; trials; prevention. The relevant and crucial articles were seelcted for this narrative review.

2. VACCINE PLATFORMS AND THEIR CANDIDATES IN CLINICAL TRIALS

Live Attenuated Virus (LAV): Codagenix/Serum Institute India was engaged in developing live

attenuated vaccine against covid-19 and at present early clinical trials are going on [4].

Inactivated Virus (IV): The virus is killed using a method such as heat or formaldehyde. Whole virus vaccines use the entire virus particle, fully destroyed using heat, chemicals, or radiation. Sinopharm/ Beijing institute of biological products/ Wuhan institute of biological products, Bharat Biotech, Institute of Medical Biology/ Chinese Academy of Medical Sciences, Research Institute for Biological Safety Problems and Sinovac are involved in development of inactivated virus vaccine [11].

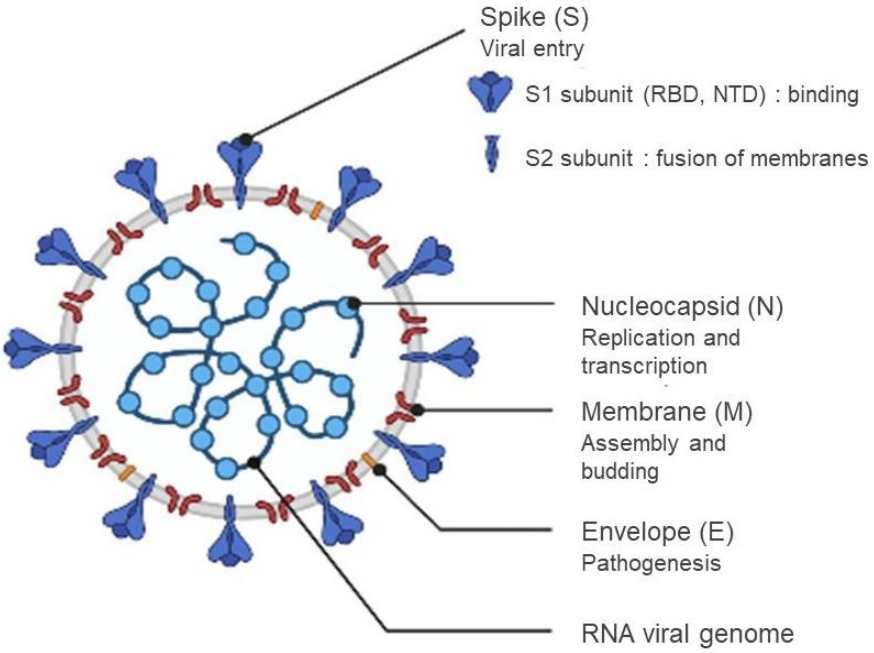

Fig. 1. Schematic diagram of SARS CoV-2; RBD: receptor binding domain of spike protein; NTD: N terminal domain. Modified and adopted from Walls et al. [10] (Created with BioRender.com)

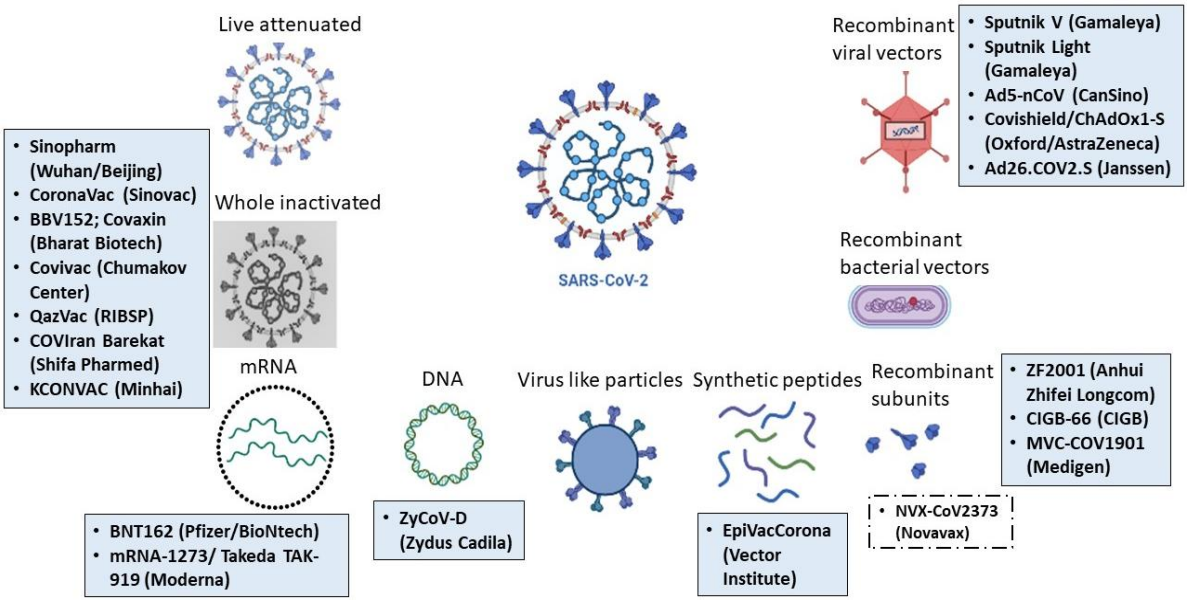

Fig. 2. Vaccine platforms against SARS-CoV-2 and their vaccines in use, within line boxes; vaccine in the process of approval in dotted line box (Created with BioRender.com)

mRNA Vaccines: mRNA vaccines are a novel vaccine platform to protect against infectious diseases. To trigger an immune response, many vaccines put a weakened or inactivated organism into human bodies. Pfizer vaccine became first completely approved vaccine to be in this platform for any disease [12]. Several countries including USA, UK, Canada, Saudi Arabia, UAE, Switzerland, Qatar, Kuwait, Oman and many other countries have approved the same vaccination. The challenge for its effective implementation is its storage requirements of -80°C and -60°C, where it is stable for up to 6 months. For temporary storage, vaccine can be at 2^0 C and 8^0 C up to five days. However, recent study show that the shelf life of vaccine is much better than previously thought, enabling the storage at -25°C to -15°C for maximum of 2 weeks [13].

National Institute of Allergy and Infectious Disease (NIAID) (USA) is also conducting phase 3 trial of NCT04470427 and is being approved for vaccination by many countries such as USA, European countries. Another mRNA vaccine is developed by Cure Vac, Germany and currently in phase 3 trial. People's Liberation Army, China is aslo developing the vaccine, which is undergoing phase I trial ChiCTR2000034112 [11].

Self-amplyfying RNA (saRNA) vaccines are another next generation RNA vaccine platform capable of self-replication with the help of replicase, inserted in the synthetic RNA transcript itself [14]. The saRNA vaccines would be more effective in triggering immune response, even at lower doses [15]. Imperial College London/ VacEquity Global Health, United Kingdom is developing self-amplyfying RNA (saRNA) vaccine which is undergoing phase I/2 trials. Similarly, Arcturus, Singapore NCT04480957 vaccine which is in phase I trial.

DNA Vaccine: Genexine (Korea), Inovio (USA), Osaka University/ AnGeS (Japan and Zydus-Cadila (India) are developing DNA vaccines and all are undergoing phase 2/3 trials [11].

Virus Like Particles (VLP)/Nanoparticles: Medicago/ GSK and Serum Institute India are involved in virus like particles vaccine (VLP) and in phase I and 2 clinical trials. Medicago has designed live plant based bioreactors to produce noninfectious VLP, which retains all the structure of the COVID-19 virus except for genetic material [16].

Synthetic Peptides: EpiVacCoronais designed on synthetic peptide platform. The vaccine is approved in Russia [17].

Protein Subunit (PS): Adimmmune, Anhui Zhifei, Clover Biopharm/ GSK, Covaxx +United Biomedical Inc, Instituto Finlay, Kentucky Bioprocessing, Medigen, Sanofi/ GSK, University of Queensland/ CSL/ Sequirus, and Vaxine Pty are working on protein subunit vaccine and they are in phase I, 2 and clinical trials [11].

Bacterial Vector: Symvivo of Canada has developed bacterial vector vaccine and phase I trials on NCT04334980 is underway. The platform is actually oral DNA vaccine given as combined plasmid with probiotic bacterium. Orally delivered bacTRL-Spike contains bacterial medium with either 1 billion, 3 billion or 10 billion colony-forming-units of live *Bifidobacterium longum*. These probiotic bacterium has been engineered to deliver plasmids containing synthetic DNA encoding spike protein from SARS-CoV-2 [18].

Non-Replicating Viral Vector (VVnr): Here viral vectors are used to develop vaccines. CanSino, Bharat Biotech, Gamaleya Research Institute, Janssen, ReiThera and University of Oxford/ AstraZeneca are developing non-replicating viral vector. They are in different phases of clinical trials.

Replicating Viral Vectors (VVr): Jiangsu Provincial Center for disease prevention and control, China and Pasteur/Themis/Merck/University of Pittsburgh are developing replicating viral vectors and currently in phase I/2 trials. Jiangsu Provincial Center is developing the influenza virus vector based vaccine to deliver the COVID-19 antigens in the form of intranasal Spray.

3. VACCINES THAT HAVE OBTAINED EMERGENCY USE AUTHORIZATION

Nearly, 190 countries have approved the COVID-19 vaccines under emergency use authorization (EUA) [3]. Some of the vaccines such as Pfizer/BioNTech, Moderna, Oxford/AstraZeneca, CanSino, EpiVac, Sinopharm and Sinovac have received full authorization in specific countries [3]. (Table 2) However, only seven vaccines namely Moderna (mRNA-1273), Pfizer/BioNTech (BNT162b2), Janssen (Johnson & Johnson) (Ad26.COV2.S), Oxford/AstraZeneca (AZD1222), Serum Institute of India - Covishield

(Oxford/AstraZeneca formulation), Sinopharm (Beijing) (BBIBP-CorV), Sinovac (CoronaVac) have received WHO Emergency use listing (EUL) [3].

Sinopharm: First approved for emergency use in China for age group of 18-59 years. The vaccine has to be stored at 2-8 degrees centigrade. It is administered on day 0 and booster dose on day 21. It is shown to be having 95-100 % seroconversion. The adverse effects reported are fever, nausea and local reactions [19].

Sinovac: First approved for emergency use in China for the age group of 18-59 years. The vaccine needs to be stored at 2-8 degrees centigrade. First dose is given on day 0 and booster dose on day 28. The seroconversion rate is 97-100%. Mild local effects are seen in few patients [20].

Covaxin: The complete virus inactivated vaccine developed by Bharat biotech (India) has received emergency use authorization under clinical trial mode. The immunogenicity and safety data were acceptable [21,22].

CoviVac: Another inactivated (whole virion) vaccine CoviVac is approved in Russia, developed by Chumakov Center and is administered in two doses, 14 days apart. It is transported and stored at normal fridge temperatures of 2 to 8 degrees Celsius [23]. However, these vaccine are not comparable due to different age groups, geographical locations, setting and differing variants [24]. The vaccine is currently undergoing phase 3 clinical trial.

QazVac (RIBSP): Research institute for biological safety problems, has developed QazCovid-in (QazVac) which has shown to be well tolerated and produce humoral immunity lasting for 6 months [25]. The phase 1 study, showed 59% of subjects positive for neutralsing antibodies after one dose and 100% showing antibodies after 2 doses. Similarly, in phase 2 study, subjects aged 18-49 showed 100% seroconversion even after one dose and 92-94% of those aged 50 and above, after one dose and 100% after two doses at day 0 and 21 [25]. The adverse events reported are injection site pain, fever, weakness, malaise and drowsiness [25].

COVIran Barekat (Shifa Pharmed): COVIran Barekat is inactivated whole virus vaccine reported to show immunogenicity in up to 93% of subjects during early phase of clinical trials. It has received EUA and phase 3 study is ongoing [26].

KCONVAC (Minhai): KCONVAC is developed jointly by Minhai Biotechnology and Shenzhen Kangtai Biological Products. It is inactivated vaccine obtained from Vero cells, with emergency use approval in China [27].

Sputnik V: Approved for age group from 18-60 years. The vaccine has to be stored at 2-8 degrees centigrade. It is administered on day 0 (rAd26-S) and booster dose on day 21 (rAd5-S). It is reported to be having 100% seroconversion. The adverse effects are local reactions and mild fever [28].

Oxford/AstraZeneca: The viral vector based vaccine has showed good humoral and cellular response in early clinical trials. The safety data were also acceptable, however prophylactic paracetamol was used to prevent the adverse reactions such as fever, chills and myalgia [29]. The immune response including humoral and cellular responses lasted even up to 8 weeks after single dose of vaccine [30]. The vaccine was also shown to be similarly immunogenic in elderly (>70 years) with better tolerability [31]. It was also shown that booster dose is better tolerated with good antibody response [32]. However, the two dose regimen showed least vaccine efficacy of 10.4% (95%CI: −76.8; 54.8) for COVID-19 B.1.351 variant [33].

CanSino: This vaccine is approved for use in China for the age group of over 18 years. This vaccine needs to be stored a 2-8 degrees centigrade. Administered on day 0 and booster dose on day 28. It is claimed to be having 59-61% seroconversion. Common adverse effects are injection site pain and fever [34].

Pfizer/BioNTech: This vaccine is approved by United Sates of America, United Kingdom, Canada, Saudi Arabia, United Arab Emirates, Switzerland, Qatar, Kuwait and Oman for the age group of 18-55 years. The vaccine needs to be stored at -80°C and -60°C. It is administered on day 0 and boaster dose on day 21. Common adverse effects are local reactions, fatigue, head ache, nausea etc. Raised antibodies 1-8-2.8 fold convalescent serum panel and 95% effective in preventing infection [35–37]. Vaccine and Related Biological Products Advisory Committee, or VRBPAC has recommended for booster doses only among those aged above 65, and others who are at risk of severe disease [38].

Table 1. The vaccine platforms and their advanced vaccine candidates

Vaccine platform	Organisation/company involved in vaccines development	Candidate	Immune response against viral antigen/ whole virus	Countries involved in manufacturing	Key advanced trials
RNA based vaccine (mRNA)	BioNTech/Pfizer	BNT162(3LNP-mRNAs)	Spike protein; S-2P (full length with proline substitutions, K986P and V987P)	Germany/United States	Phase 3 NCT04368728
	Moderna/ National Institute of Allergy and infectious diseases (NIAID)	mRNA-1273	Spike protein; S-2P (full length with proline substitutions, K986P and V987P)	United States	Phase 3 NCT04470427
	CureVac	CVnCoV Vaccine	Prefusionstabilised full length spike protein	Germany	Phase 3 NCT04674189
DNA based vaccine (DNA)	Inovio pharmaceuticals + International vaccine institute + AdvaccineBiopharmaceuticals	INO-4800+Electroporation	Full length spike protein	United States	Phase 2/3 NCT04642638
	AnGes+Takara Bio +Osaka university	AG0301-COVID19	Spike protein	Japan	Phase2/3 NCT04655625
	ZydusCadila	nCov vaccine (ZyCoV-D)	Spike protein	India	Phase 1/2 CTRI/2020/07/026352
Non-Replicating Viral Vector (VVnr)	CanSino	Novel corona virus vaccine(adenovirus type 5 vector)	Full length spike protein	China	Phase 3 NCT04526990
	Gamaleya Research Institute	Sputnik V Gam-COVID-Vacadenobased (rAd26-S+rAd5-S)	Full length spike protein	Russia	Phase 3 NCT04530396
	Janssen	Ad26.COV2.S	Full-length S with two proline substitutions (K986P & V987P) and two mutations at furin cleavage site (R682S &	USA	Phase 3 NCT04505722

Vaccine platform	Organisation/company involved in vaccines development	Candidate	Immune response against viral antigen/ whole virus	Countries involved in manufacturing	Key advanced trials
			R685G)		
	University of Oxford/ AstraZeneca	ChAdOx1-S-(AZD1222)	Full length spike protein	UK	Phase 3 NCT04516746
Replicating Viral Vectors (VVr)	Jiangsu Provincial Center for disease prevention and control	DelNS1-2019-nCoV-RBD-OPT1	Spike protein	China	Phase 2 ChiCTR2000039715
Inactivated Virus (IV)	Sinopharm/ Beijing institute of biological products/ Wuhan institute of biological products	SARS-CoV-2 vaccine (verocell)	Whole virus	China	Phase 3 ChiCTR2000034780
	Bharat Biotech	Whole virion inactivated SARS-CoV-2 vaccine (BBV152)	Whole virus	India	Phase 3 NCT04641481
	Institute of Medical Biology/ Chinese Academy of Medical Sciences,	SARS-CoV-2 vaccine (verocell)	Whole virus	China	Phase 3 NCT04659239
	Sinovac	CoronaVac	Whole virus	China	Phase 3 NCT04456595
	Chumakov Center	CoviVac	Whole virus	Russia	-
	Shifa Pharmed	COVIranBarekat	Whole virus	Iran	Phase 2/3 IRCT20201202049567N3
	Minhai Co	KCONVAC	Whole virus	China	Phase 3 NCT04852705
	Research institute for biological safety problems,	QazCovid-in	Whole virus	Rep of Kazakhstan	Phase 3 NCT04530357
Live Attenuated Virus (LAV)	Codagenix/Serum Institute India	COVI-VAC	Whole virus	India	Phase 1 NCT04619628

Vaccine platform	Organisation/company involved in vaccines development	Candidate	Immune response against viral antigen/ whole virus	Countries involved in manufacturing	Key advanced trials
Protein Subunit (PS)	Anhui Zhifei	Recombinant SARS-CoV-2 vaccine (CHO cell)	RBD dimer (as tandem repeat residues 319–537)	China	Phase 3 NCT04445194
	CIGB	CIGB 66	RBD + aluminium hydroxide	Cuba	Phase 1/2 RPCEC00000345
	Medigen	MVC-COV1901	Spike protein with aluminium hydroxide and CpG1018	Taiwan	Phase 2 NCT04695652
	Novavax	SARS-CoV-2 rS (CHO) /Matrix M1 adjuvant (NVX-CoV2373)	Full-length Spike protein with two proline substitutions (K986P and V987P) and three mutations at cleavage site (R682Q, R683Q, R685Q)	Unites States of America	Phase 3 NCT04611802
	Clover Biopharm/ GSK,	SCB 2019 +AS03 or CpG 1018 adjuvant plus alum adjuvant	Ectodomain of wild-type S with fusion to trimer-tag	Australia	Phase 2/3 NCT04672395
	Covaxx +United Biomedical Inc	UB 162	Multitope S1-RBD peptide based	China	Phase 2/3 NCT04683224
Virus Like Particles (VLP)/Nanoparticles	Medicago/ GSK	Corona virus like particle COVID-19(CoVLP) with AS03 adjuvant	Living plant based platform to produce noninfectious VLP	Canada	Phase 2/3 NCT04636697
Bacterial vector	Symvivo	bacTRL-Spike Vaccine	Spike protein	Canada	Phase 1 NCT04334980
Synthetic peptide	Vektor State Research Center of Virology and Biotechnology	EpiVacCorona	Spike protein	Russia	Phase1/2 NCT04527575

Moderna: Approved for use in United State of America for individuals under 18 years of age. It needs to be stored at 2-8 degrees centigrade. First dose administered on day 0 and booster dose on day 28. It is shown to be having 100% seroconversion [39,40]. Local reactions, fever, fatigue etc. are reported as common adverse effects. The mRNA-1273 also showed good titers of binding and neutralising antibodies even at 90 days after the second dose of vaccine [41].

Ad26.COV2.S (Johnson and Johnson): Also known asAd26COVS1, JNJ-78436735, is approved as single shot vaccine for prevention COVID-19 by US FDA [42].

ZyCoV-D (ZydusCadila): ZyCoV-D is the world's first DNA based vaccine approved for humans [43]. The intradermal vaccine is showed to provide 67% protection against symptomatic COVID-19 and 100% against moderate disease among subjects aged 12 and above [43]. The vaccine is approved under EUA in India based on clinical trial conducted during second wave of COVID-19 of 2021. The phase 1 study has proved tolerability and immunogenicity when 3 doses are administered at 28 days intervals (days 0, 28, 56) [44]. The trial included both needle based administration and needle free injection by PharmajetTropis®. The reported adverse events included tenderness at injection site, joint pain, and fever.44 The neutralisation antibody titres based on live virus assay showed that 50% and 80% of subjects showed antibodies at day 84 after receiving 2mg needle based and 2mg needleless administration respectively [44].

EpiVacCorona: Peptide based vaccine EpiVacCorona is approved in Russia. The vaccine is claimed to be immunologically effective in 100% of participants. EpiVacCorona is developed by Vektor State Research Center of Virology and Biotechnology. It consists of SARS CoV2 antigen conjugated with protein carrier with aluminium adjuvant given as two doses with 21 day interval [45]. The vaccine has reported no major safety concerns.17 Turkmenistan has given complete authorization for its use [46].

ZF2001 (Anhui ZhifeiLongcom): Is protein subunit based vaccine developed by Anhui ZhifeiLongcom. The phase1/2 data suggest tolerability and immunogenicity [47]. The seroconversion rate of neutralizing antibodies after 14 days of third dose is 93-97%.47 The vaccine is reported to be 81.7% efficacious against alpha variant disease and 77.5% against disease caused by delta variant in a phase 3 study [48,49]. It is given as three doses schedule (day 0, 30, and 60) and found to be retaining neutralizing activity against delta variant of SARS CoV2 [50].

CIGB-66 (CIGB): Center for Genetic Engineering and Biotechnology (CIGB), Cuba has developed protein subunit based vaccine CIGB-66 also known as Abdala. CIGB-66 is approved under emergency use in Cuba and Venezuela [51]. The phase 1/2 clinical trial indicated a good tolerability and immunogenicity and results of phase 3 study is awaited [52]. It is given intramuscularly at day 0, 14 and 28.

MVC-COV1901 (Medigen): it is a protein subunit vaccine containing S-2P antigen adjuvanted with aluminium hydroxide and CpG1018 jointly developed by Medigen and Dynavax. The vaccine has obtained emergency use approval in Taiwan [53]. MVC-COV1901 is given intramuscularly at day 0 and 28 has shown tolerability and immunogenicity in phase1 and phase 2 studies with seroconversion rate of 99.8% after 28 days of second dose [54,55]**.**

4. EFFICACY STUDIES OF VACCINES APPROVED FOR EMERGENCY USE

4.1 Pfizer-BioNTech

BNT 162b2 evaluated in multinational placebo controlled observer blinded pivotal efficacy trial (NCT04368728) [58]. The primary endpoint was COVID-19 occurring at least 7 days after the second dose The published study showed that 8 participants among 21728 in vaccine group and 162 participants among 21728 in placebo group developed COVID-19. Thus, the vaccine efficacy is reported to be 95%. The adverse reactions reported were injection site reactions, fatigue, headache. Polack et al*.* study calculated vaccine efficacy as 100X (1-IRR) [58]. Incidence rate ratio (IRR) is ratio of confirmed COVID-19 per 1000 person-years of follow up in vaccine group to respective illness rate in placebo group [58].

Table 2. The list of vaccines obtained emergency use authorization and their published data of immunogenicity

Vaccines	Age group	Schedule	Storage	Safety data	Seroconversion rate	Published studies
Sputnik V	18-60 years	Day 0 (rAd26-S) and day 21 (rAd5-S)	2-8 degrees centigrade	Local reactions, mild fever	100% seroconversion	Logunov et al. [28[
Sinopharm*	18-59 years	Day 0 and 21	2-8 degrees centigrade	Local reactions;	95-100% seroconversion	Xia et al. [19]
Sinovac*	18-59 years	Day 0 and 28	2-8 degrees centigrade	Mild local effects	97-100 % seroconversion	Zhang et al. [20]
CanSino*	>18 years	Day 0 and 28	2-8 degrees centigrade	Injection site pain, fever	59-61% seroconversion	Zhu et al. [56]
Pfizer/BioNTech*	18-55 years	Day 0 and 21	-80°C and -60°C	Local reactions, fatigue, head ache, nausea	Raised antibodies 1-8-2.8 fold convalescent serum panel	Mulligan et al. [35] Sahin et al. [36] Walsh et al. [37]
Moderna*	>18 years	Day 0 and 28	2-8 degrees centigrade	Local reactions, fever, fatigue	100% seroconversion	Jackson et al. [40] Anderson et al. [39]
Oxford/AstraZeneca*	18-55 years	Single dose and two dose schedule 28 days apart	2-8 degrees centigrade	Mayalgia, fever, chills	90-100% seroconversion	Folegatti et al. [29] Ewer et al. [30] Ramaswamy et al. [31] Barrette et al. [32]
Covaxin	12-65 years	Day 0 and day 28	2-8 degrees centigrade	Injection site pain, fever, chills, anorexia, myalgia	92-98% seroconversion	Ella et al. [21]
Ad26.COV2.S (Janssen)	18-55 years and >65 years	One dose & two dose schedule (56 days apart)	2-8 degrees centigrade	Headache, fatigue, muscle aches, nausea and fever	90% seroconversion	Sadoff et al. [57]
ZyCoV-D	12 years and older	Day 0, 28 and 56	2-8 degrees centigrade	Tenderness at injection site, fever, joint pain	100% seroconversion in 2mg (needless) administration arm at day 84	Momin et al. [44]
ZF2001	21-58 years	Day 0, 30, and 60	2-8 degrees centigrade	Pain, swelling, redness, rashes, and pruritus	93-97% after 14 days of third dose	Yang et al. [47]

**Vaccines that have currently obtained full authorization; Pfizer/BioNTech is currently approved by the USFDA; Moderna is approved in Switzerland; AstraZeneca/Oxford in Brazil; and Cansino, Sinopharm, Sinovac in China [46]*

The BNT 162b2 has also shown efficacy in mass-vaccination setting in a large population of 596,618 participants in each group [59]. The vaccine effectiveness was calculated as one minus the risk ratio, using the Kaplan–Meier estimator (Table 3). At days 14 through 20 after the first dose, the estimated effectiveness for documented infection, was 46% (95% [CI], 40 - 51); for symptomatic Covid-19, 57% (95% CI, 50 - 63); for hospitalization, 74% (95% CI, 56 - 86); for severe disease, 62% (95% CI, 39 - 80); for preventing death 72% (95% CI, 19 - 100) respectively. The effectiveness at 7 or more days after the second dose for documented infection, was 92% (95% CI, 88 - 95); for symptomatic Covid-19, 94% (95% CI, 87 - 98); for hospitalization, 87% (95% CI, 55 - 100); and for severe disease, 92% (95% CI, 75 - 100), respectively.

4.2 Moderna

Lipid nanoparticle encapsulated mRNA-1273 vaccine is designed to encode fll length spike protein once injected into the body. The phase 3 randomised observer blinded placebo controlled trial involving vaccine and placebo arms with 15210 participants in each has been conducted during July 27, 2020 to October 23, 2020 [60]. Symptomatic COVID-19 after 14 days of 2nd dose was 56.5 per 1000 person years (95% CI 48.7-65.3) in placebo group and 3.3 per 1000 person years (95% CI 1.7 – 6.00) in vaccine group. The vaccine efficacy was shown to be 94.1% (95% CI 89.3- 96.8%). Efficacy was defined as percentage reduction in hazard ratio for primary end point (Table 3). Severe COVID-19 occurred in 30 participants and were all in placebo group. The local and systemic reactions were transient and found prominently in vaccine group. The adverse reactions included injection site pain, erythema, induration, headache, fever, myalgia and arthralgia. Serious adverse events were similar in incidence among the groups.

4.3 AstraZeneca/Oxford

ChAdOx1 nCoV-19 vaccine (AZD1222) has been studied in four phase 3 blinded, randomised controlled trials at Brazil, South Africa and UK. The interim analysis of these pooled data is published [61]. ChAdOx1 nCoV-19 is studied in two standard doses (SD) (5X 10^{10} viral particles each) in SD/SD cohort, a subset of participants in UK were recruited for half dose as first dose (low dose LD) and standard dose as second dose in LD/SD cohort. Symptomatic COVID-19 confirmed by nucleic acid amplification test (NAAT) swab test 14 days after second dose was considered as primary efficacy endpoint. The data of period of nearly 6 months (April 23rd to Nov 4th 2020) showed enrollment of 23848 participants. In SD/SD cohort, 27 of 4440 participant (0.6%) in ChAdOx1 nCoV-19 vaccine group and 71 of 4455 (1.6%) in control group developed the primary efficacy end point. The vaccines efficacy calculated as 1-relative risk from Poisson regression model adjusted for age was showed to be 62.1% (Table 3).

Among LD/SD cohort there were three of 1367 (0.2%) in vaccine group vs 30 of 1374 (2.2%) in control group met the primary efficacy end point. The vaccine efficacy was calculated to be 90.0%. The overall vaccine efficacy was calculated to be 70.4% (95% CI, 54.8-80.6%). The safety analysis during the median follow up of 3.4 months there were 84 events in vaccine group and 91 in control group. Voysey et al. also showed that vaccine efficacy was higher in participants who had more than six weeks between the two does (65.4%) than among participants who had second dose in less than six weeks (53.4%) [61].

The recent study showed the efficacy of single dose vaccines of both BNT162b2 or ChAdOx1 COVID-19 in causing significant reduction of symptomatic cases and severe COVID-19 infection in elderly participants [62].

4.4 Sputnik V

Heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V) had showed 91.6% efficacy as per interim analysis of phase 3 trial [63]. The study involved 19866 participants included for primary outcome analysis. From the day of 2nd dose of vaccine (21st day) 0.1% of 14964 participants of vaccine group and 1.3% of 4902 in placebo group were found to be COVID-19 positive, with vaccine efficacy of 91.6% [63] (Table 3). Among a total of 21977 participants, 16501 were in vaccine group and 5476 were in placebo group and were considered for safety analysis. Commonly reported adverse events were grade 1. Serious adverse events (SAEs) reported were, 0.3% of vaccine group and 0.4% of placebo group and none were considered related to vaccination. There were three deaths in vaccine group and one death in placebo group and were considered not related to vaccination.

Table 3. The phase 3 efficacy data of vaccines, which are in wide public use

	Primary endpoint	Vaccine group		Control group		Vaccine efficacy% (95% CI)	References
		a	b	c	d		
AstraZeneca/Oxford ChAdOx1nCoV-19 vaccine (SD/SD)	NAAT-positve symptomatic COVID-19 after 14 days of second dose	27	4440	71	4455	62.1% (95% CI of 41-75.7%)	Voysey et al. [61]
AstraZeneca/Oxford ChAdOx1nCoV-19 vaccine (LD/SD)	NAAT-positve symptomatic COVID-19 after 14 days of second dose	3	1367	30	1374	90.0% (95% CI of 67.4-97%)	Voysey et al. [61]
Moderna mRNA -1273	Symptomatic COVID-19 after 14 days of 2nd dose	11	14134	185	14073	94.1% (95% CI of 89.3-96.8%)	Baden et al. [60]
Pfizer-BioNTech BNT162b2	Laboratory confirmed COVID-19, 7 days after 2nd dose	8	18198	162	18325	95% (95% CI of 90.0-97.9%)	Polack et al. [58]
Sputnik V	COVID-19 positive from the day of 2nd dose (21st day after 1st dose)	16	14964	62	4902	91.6% (95% CI 85.6 - 95.2%)	Logunov et al. [63]

Vaccine efficacy is 1- odds ratio expressed as percentage; a is number of participants meeting primary endpoint in vaccine group; b is total number of participants in vaccine group; c and d are respectively participants meeting primary endpoint and total number of participants in placebo group; odds ratio is ad/bc; NAAT nucleic acid amplification test; SD - standard dose; LD - low dose

5. EFFICACY DATA OF VACCINES AS PUBLICLY AVAILABLE

CoronaVac (Sinovac): The inactivated vaccine has shown to have overall efficacy of 50.65 and, 83.70% in preventing medical treatment, and 100% for prevention of hospitalization, severe, and fatal disease [64,65]. The vaccine has received conditional marketing authorization in China [64].

Sinopharm: The phase 3 efficacy data is yet to be published by the sponsors. However the efficacy data released to the public domain show 79.34% in multinational study [66]. The data available in public domain also indicate that the vaccine is 100% effective in preventing moderate and severe disease [67].

Johnson and Johnson Vaccine: Ad26.CoV2.S of Janssen Pharmaceuticals (Johnson and Johnson) when given as single injection has showed overall efficacy of 66% [68]. The promising results are the vaccine also showed 57% efficacy in South Africa where B.1.351 is becoming a dominant variant. The study also demonstrated 100% prevention of hospitalization. Further, asymptomatic infection was also prevented with an efficacy of 88%. The common adverse reactions included headache, fatigue, muscle aches, nausea and fever.

Cansino: vector based vaccine developed as a single dose shot. The vaccine was approved for emergency use among military in China last year, and later by Mexico [69,70]. The vaccine efficacy is claimed to be of 65.7% [70].

Covaxin: The Bharat biotech has released the phase 3 efficacy data of their inactivated vaccine [22]. The phase 3 study involved 25,800 participants aged between 18-98 years of age.

The primary endpoint being RT-PCR-confirmed symptomatic COVID-19 occurring at least 14 days after the 2nd dose. First interim released to public domain show that 36 cases of COVID-19 were found in the placebo group as compared to 7 cases in vaccine group. The reported vaccine efficacy is 80.6%. the safety data were found to be similarly distributed between the groups [22].

6. EFFICACY DATA OF VACCINES IN PROCESS OF APPLYING FOR EUA AS PUBLISHED ON COMPANY WEBSITES

NVX-CoV2373, from Novavax demonstrated in phase 3 UK trial: 89.3% overall efficacy (95.6% against the original strain). In another phase 2b South Africa trial the vaccine showed 60% efficacy against new variant virus [71,72]. The vaccine is well tolerated and showed good immunogenicity as compared to human convalescent sera in phase1/2 clinical trials.

7. COVID-19 VARIANTS AS CHALLENGES TO VACCINES BEING DEVELOPED

Though RNA viruses are known to have higher mutation rates than DNA viruses, coronaviruses are show lesser mutation rates due to correction of errors by specific enzymes [73]. However, high rate of mutations are reported in a proteo-genomic analysis from COVID-19 patients [74]. A mutation indicate change in the sequence, as in D614G where aspartic acid to glycine substitution at 614 position of spike protein. Whereas, a variant is change in sequence of genome, which expresses phenotypic differences such as in antigenicity, transmissibility and virulence. D614G variants have been the predominant variant globally since June 2020.

SARS-CoV-2 VOC 202012/01 (Variant of Concern, year 2020, month 12, variant 01) also known as 20I/501Y.V1 or B.1.1.7 was detected in United Kingdom authorities. The variant is shown to be more transmissible with no effect on length of hospitalization and case fatality. B.1.1.7 variants are shown to be 36- 71% more transmissible than the native variant [75]. VOC 202012/01 variant consists 23 nucleotide substitutions, of which the deletion at position 69/70del was shown to affect the S gene targeted diagnostic PCR assays. However, globally PCR assays utilize multiple targets and hence variants are not postulated to affect diagnosis. Another variant 501Y.V2, (B.1.351) was detected in South Africa. The variant is characterized by rapid transmissibility (more than 50%) with no evidence on its association with disease adverse outcomes [75].

Both UK and South Africa variants have characteristic N501Y mutations. SARS CoV-2 N501Y is reported to increase the transmissibility in these variants [76]. The mutant has posed a new challenge to vaccine development process.

N501Y mutant S1-RBD binding to STE90-C11 is shown to increase significantly by in-silico Free energy of binding (FEP) and replica exchange solute tempering (REST) method [77]. STE90-C11 is a neutralizing antibody from convalenscent patients produced against COVID-19. STE90-C11 is shown to be effective against several RBD mutations as well previously [78].

Inactivated vaccine (Sinopharm) and recombinant dimeric ZF2001, RBD based protein subunit vaccine (Anhui Zhifei) immunized human sera neutralization studies have shown preserve activity against 501Y.V2 South African variants [79]. There is evidence from plaque reduction neutralization test (PRNT50) that whole virus inactivated vaccine, Covaxin (Bharat Biotech) could be effective against UK variant [80].

However several studies have shown loss of neutralization ability of human convalescent serum against SARS-CoV-2 variants containing the E484K mutations [81–83]. Further, convalescent and BNT162b2 mRNA vaccine immunised sera neutralized SARS-CoV-2 Brazilian (B.1.1.248) variants better than South African variants (B.1.351) even though both variants coded for E484 and N501 mutations. Thus distinct mutations in NTD regions of S protein may also have a role in development of viral resistance [83].

8. VACCINATION: PROTECTION AGAINST DISEASE OR INFECTION TRANSMISSIBILITY

Whether vaccinated persons spread, the infection is unclear currently. However, COVID-19 human challenge study being conducted in the UK would answer many such questions [84]. SARs-CoV-2 with doubling time of 2.3-3.3 days and R_0 (reproduction number) of 5.7 it is predicted that 82% of the population need to be immune either by vaccination or past infection to stop transmission and develop herd immunity [85]. However with rising cases of clinically

significant variants achieving herd immunity is a distant possibility. Rising cases of SARs CoV-2 variants, also pose threat to vaccine effectiveness.

Nevertheless, the data showing that vaccines prevent severe COVID-19 disease itself is the hope to begin “living” of global population, which was standstill due to pandemic [86] As indicated by the WHO, in spite of the available vaccines most effective stake to reduce the burden of infection still exists with social behavior of physical distancing and masks [86]. The data platform statistica had predicted that 50% reduction in number of new infections caused by a patient would translate to 27 fold reduction of number of infected after 1 month, which may be achieved by social behavioral changes [87].

9. VACCINATION CHALLENGES AND WAY AHEAD

With the world, witnessing the real time, fastest development of vaccines for a pandemic there are also several inadequacies so far and challenges ahead. Most of the countries showing lower vaccine coverage due to hindrances and voluminous task of vaccinating the populations worldwide [88]. The differences in regulatory status of vaccines among countries have adversely affected the international travelling during pandemic [89]. This has only resulted to add more to vaccine hesitancy and vaccine inequality due to injustice situation where vaccine of one country is not recognized by other country. Further, COVID-19 vaccine development is also characterized by commercial race, underreporting of data and mass pre-ordering instead of global collaboration [90]. Hence, global harmonization among countries in vaccine development, data reporting, production and distribution, along with suppressing of social-political, commercial interests are essential for equitable access of global vaccines which are safe and effective [90,91]. There is also need for harmonized surveillance and communication among countries for achieving herd immunity [90].

The global efforts led by WHO gave rise to COVAX, for ensuring equitable distribution of vaccines globally [92]. The WHO in collaboration with the Global Vaccine Alliance (GAVI), and the Coalition for Epidemic Preparedness Innovations (CEPI) has committed distribution of 2 billion doses by the December of 2021. COVAX initiative is aptly based on the motto “no one is safe unless everyone is safe” thus emphasing the concept of one safe world.

10. CONCLUSION

As reported, many pharmaceutical companies are involved in vaccine development for the prevention of COVID-19. Many of them have been approved for emergency use in various countries around the globe and several are in various phases of clinical trials. Of late, the new mutated form covid-19 is reported in many parts of the globe and posing new threat. The ray of hope is that the vaccines are effective in preventing severe disease. Further, the vaccines in pipeline are being studied against these mutated forms and would see the light in coming days. However, one has to exercise social restraint in the form of physical distancing and masking until that time.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The authors thank Dr. Gurumadhva Rao, President of RAKMHSU for support and guidance while preparing manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. COVID Live Update: 227,923,887 Cases and 4,686,061 Deaths from the Coronavirus - Worldometer.

Accessed September 17, 2021.
Available:https://www.worldometers.info/coronavirus/
2. Prevention of SARS-CoV-2. COVID-19 Treatment Guidelines.
Accessed October 16, 2021.
Available:https://www.covid19treatmentguidelines.nih.gov/overview/prevention-of-sars-cov-2/
3. COVID-19 vaccine tracker.
Accessed September 17, 2021.
Available:https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/
4. COVID-19 vaccine tracker and landscape.
Accessed September 17, 2021.
Available:https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
5. Tregoning JS, Brown ES, Cheeseman HM, et al. Vaccines for COVID-19. Clin Exp Immunol. 2020;202(2):162-192.
DOI: 10.1111/cei.13517
6. Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry. :24.
7. Lee CY-P, Lin RTP, Renia L, Ng LFP. Serological Approaches for COVID-19: Epidemiologic Perspective on Surveillance and Control. Front Immunol. 2020;11:879.
DOI: 10.3389/fimmu.2020.00879
8. Zheng M, Song L. Novel antibody epitopes dominate the antigenicity of spike glycoprotein in SARS-CoV-2 compared to SARS-CoV. Cell Mol Immunol. Published online. 2020;1-3.
DOI: 10.1038/s41423-020-0385-z
9. Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. 2020;9(1):382-385.
DOI: 10.1080/22221751.2020.1729069
10. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-292.e6.
DOI: 10.1016/j.cell.2020.02.058
11. Draft landscape of COVID-19 candidate vaccines.
Accessed December 22, 2020.
Available:https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
12. Commissioner O of the. FDA Approves First COVID-19 Vaccine. FDA.
Published August 23, 2021.
Accessed September 18, 2021.
Available:https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine
13. Pfizer and BioNTech Submit COVID-19 Vaccine Stability Data at Standard Freezer Temperature to the U.S. FDA | Pfizer.
Accessed February 26, 2021.
Available:https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-covid-19-vaccine-stability-data
14. Bloom K, Berg F van den, Arbuthnot P. Self-amplifying RNA vaccines for infectious diseases. Gene Ther. Published online October 22, 2020;1-13.
DOI: 10.1038/s41434-020-00204-y
15. Vogel AB, Lambert L, Kinnear E, et al. Self-Amplifying RNA Vaccines Give Equivalent Protection against Influenza to mRNA Vaccines but at Much Lower Doses. Mol Ther J Am Soc Gene Ther. 2018;26(2):446-455.
DOI: 10.1016/j.ymthe.2017.11.017
16. COVID-19 Programs.
Accessed February 23, 2021.
Available:https://www.medicago.com/en/covid-19-programs/
17. EpiVacCorona Vaccine.
Accessed February 23, 2021.
Available:https://www.precisionvaccinations.com/vaccines/epivaccorona-vaccine
18. Covid-19 and the Symvivo bacTRL Platform.
Accessed February 23, 2021.
Available:https://www.symvivo.com/covid-19
19. Xia S, Duan K, Zhang Y, et al. Effect of an Inactivated Vaccine against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. JAMA. 2020;324(10):951-960.
DOI: 10.1001/jama.2020.15543
20. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2020;0(0).
DOI: 10.1016/S1473-3099(20)30843-4
21. Ella R, Reddy S, Jogdand H, et al. Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of

immune responses from a phase 1 follow-up report. medRxiv. Published online December 22, 2020;2020.12.21.20248643. DOI: 10.1101/2020.12.21.20248643

22. Press Releases - Bharat Biotech- A Leading Biotech Company. Accessed March 6, 2021. Available:https://www.bharatbiotech.com/press_releases.html
23. Ivanova P. Russia Approves Its Third COVID-19 Vaccine, CoviVac. The Wire Science. Published February 20, 2021. Accessed February 23, 2021. Available:https://science.thewire.in/health/russia-approves-its-third-covid-19-vaccine-covivac/
24. Ledford H. Why COVID vaccines are so difficult to compare. Nature. Published online February 23, 2021. DOI: 10.1038/d41586-021-00409-0
25. Zakarya K, Kutumbetov L, Orynbayev M, et al. Safety and immunogenicity of a QazCovid-in® inactivated whole-virion vaccine against COVID-19 in healthy adults: A single-centre, randomised, single-blind, placebo-controlled phase 1 and an open-label phase 2 clinical trials with a 6 months follow-up in Kazakhstan. EClinicalMedicine. 2021;0(0). DOI: 10.1016/j.eclinm.2021.101078
26. Mallapaty S. Iran hopes to defeat COVID with home-grown crop of vaccines. Nature. 2021;596(7873):475-475. DOI: 10.1038/d41586-021-02216-z
27. Kangtai Biological's COVID-19 vaccine gets emergency use approval in China. Reuters. Available:https://www.reuters.com/article/us-health-coronavirus-vaccine-kangtai-idUSKBN2CV1F6 Published May 14, 2021. Accessed September 18, 2021.
28. Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet Lond Engl. 2020; 396(10255):887-897. DOI: 10.1016/S0140-6736(20)31866-3
29. Folegatti PM, Bittaye M, Flaxman A, et al. Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: A dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. Lancet Infect Dis. 2020;20(7):816-826. DOI: 10.1016/S1473-3099(20)30160-2
30. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. Published online December 17, 2020. DOI: 10.1038/s41591-020-01194-5
31. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): A single-blind, randomised, controlled, phase 2/3 trial. Lancet Lond Engl. 2021;396(10267):1979-1993. DOI: 10.1016/S0140-6736(20)32466-1
32. Barrett JR, Belij-Rammerstorfer S, Dold C, et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nat Med. Published online December 17, 2020. DOI: 10.1038/s41591-020-01179-4
33. Madhi SA, Baillie V, Cutland CL, et al. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. medRxiv. Published online February 12, 2021:2021.02.10.21251247. DOI: 10.1101/2021.02.10.21251247
34. Zhu F-C, Li Y-H, Guan X-H, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: A dose-escalation, open-label, non-randomised, first-in-human trial. The Lancet. 2020;395(10240):1845-1854. DOI: 10.1016/S0140-6736(20)31208-3
35. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-593. DOI: 10.1038/s41586-020-2639-4
36. Sahin U, Muik A, Derhovanessian E, et al. Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine. medRxiv. Published online July 20, 2020:2020.07.17.20140533. DOI: 10.1101/2020.07.17.20140533
37. Walsh EE, Frenck RW, Falsey AR, et al. Safety and Immunogenicity of Two RNA-

Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-2450.
DOI: 10.1056/NEJMoa2027906

38. FDA advisory group rejects Covid boosters for most, limits to high-risk groups.
Accessed September 18, 2021.
Available:https://www.nbcnews.com/health/health-news/fda-advisory-group-rejects-covid-boosters-limits-high-risk-groups-rcna2074
39. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383(25):2427-2438.
DOI: 10.1056/NEJMoa2028436
40. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-1931.
DOI: 10.1056/NEJMoa2022483
41. Widge AT, Rouphael NG, Jackson LA, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med. 2021;384(1):80-82.
DOI: 10.1056/NEJMc2032195
42. Commissioner O of the. Janssen COVID-19 Vaccine. FDA.
Published online March 1, 2021.
Accessed March 6, 2021.
Available:https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine
43. Mallapaty S. India's DNA COVID vaccine is a world first – more are coming. Nature. 2021;597(7875):161-162.
DOI: 10.1038/d41586-021-02385-x
44. Momin T, Kansagra K, Patel H, et al. Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India. E Clinical Medicine. 2021;38:101020.
DOI: 10.1016/j.eclinm.2021.101020
45. Li D-D, Li Q-H. SARS-CoV-2: vaccines in the pandemic era. Mil Med Res. 2021;8(1):1.
DOI: 10.1186/s40779-020-00296-y
46. Zimmer C, Corum J, Wee S-L. Coronavirus Vaccine Tracker. The New York Times.
Available:https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html.
Published June 10, 2020.
Accessed October 16, 2021.
47. Yang S, Li Y, Dai L, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis. 2021;21(8):1107-1119.
DOI: 10.1016/S1473-3099(21)00127-4
48. New Chinese vaccine shows 82% effectiveness against serious Covid-19. The Straits Times.
Available:https://www.straitstimes.com/asia/east-asia/new-chinese-vaccine-shows-82-effectiveness-against-serious-covid-19
Published August 27, 2021.
Accessed September 19, 2021.
49. Reuters. China's Zhifei says unit's COVID shot shows 81.76% efficacy in late-stage trial. Reuters.
Available:https://www.reuters.com/world/china/chinas-zhifei-units-covid-19-shot-shows-8176-efficacy-late-stage-trial-2021-08-27/
Published August 27, 2021.
Accessed September 19, 2021.
50. Zhao X, Zheng A, Li D, et al. Neutralisation of ZF2001-elicited antisera to SARS-CoV-2 variants. Lancet Microbe.
Published online August 20, 2021.
DOI: 10.1016/S2666-5247(21)00217-2
51. Cuba – COVID19 Vaccine Tracker.
Accessed September 18, 2021.
Available:https://covid19.trackvaccines.org/country/cuba/
52. Development of the Abdala Vaccine Candidate in Cuba.
Published online September 18, 2021.
Accessed September 18, 2021.
Available:https://www.bmj.com/content/372/bmj.n309/rr-0
53. Medigen Vaccine Biologics Announces Launch of Its COVID-19 Vaccine MVC-COV1901 Adjuvanted with Dynavax's CpG 1018 Adjuvant.
Accessed September 18, 2021.
Available:https://www.medigenvac.com/public/en/news/detail/88?from_sort=2
54. Hsieh S-M, Liu W-D, Huang Y-S, et al. Safety and immunogenicity of a Recombinant Stabilized Prefusion SARS-CoV-2 Spike Protein Vaccine (MVC COV1901) Adjuvanted with CpG 1018 and Aluminum Hydroxide in healthy adults: A Phase 1, dose-escalation study. E Clinical Medicine. 2021;38.
DOI: 10.1016/j.eclinm.2021.100989

55. Szu-Min H, Liu M-C, Chen Y-H, et al. Safety and Immunogenicity of CpG 1018 and Aluminium Hydroxide-Adjuvanted SARS-CoV-2 S-2P Protein Vaccine MVC-COV1901: A Large-Scale Double-Blind, Randomised, Placebo-Controlled Phase 2 Trial.; 2021:2021.08.05.21261532.
DOI: 10.1101/2021.08.05.21261532
56. Zhu F-C, Guan X-H, Li Y-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: A randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. 2020;396(10249):479-488.
DOI: 10.1016/S0140-6736(20)31605-6
57. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med.
Published online January 13, 2021.
DOI: 10.1056/NEJMoa2034201
58. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-2615.
DOI: 10.1056/NEJMoa2034577
59. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021;0(0):null.
DOI: 10.1056/NEJMoa2101765
60. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020;0(0):null.
DOI: 10.1056/NEJMoa2035389
61. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet Lond Engl.
Published online December 8, 2020.
DOI: 10.1016/S0140-6736(20)32661-1
62. Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medRxiv.
Published online March 2, 2021:2021.03.01.21252652.
DOI: 10.1101/2021.03.01.21252652
63. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: An interim analysis of a randomised controlled phase 3 trial in Russia. Lancet Lond Engl.
Published online February 2, 2021.
DOI: 10.1016/S0140-6736(21)00234-8
64. Sinovac Receives Conditional Marketing Authorization in China for its COVID-19 Vaccine-SINOVAC - Supply Vaccines to Eliminate Human Diseases.
Accessed March 6, 2021.
Available:http://www.sinovac.com/?optionid=754&auto_id=923
65. Sinovac Announces Phase III Results of Its COVID-19 Vaccine-SINOVAC - Supply Vaccines to Eliminate Human Diseases.
Accessed March 6, 2021.
Available:http://www.sinovac.com/?optionid=754&auto_id=922
66. Sinopharm vaccine in UAE: how effective is it against Covid-19 and are there side effects? The National. Published March 1, 2021. Accessed March 5, 2021. https://www.thenationalnews.com/uae/health/sinopharm-vaccine-in-uae-how-effective-is-it-against-covid-19-and-are-there-side-effects-1.1175488
67. China grants conditional market approval for Sinopharm CNBG's COVID-19 Vaccine_HOME.
Accessed March 6, 2021.
Available:http://www.sinopharm.com/en/s/1395-4173-38862.html
68. Johnson & Johnson. Content Lab U.S.
Accessed March 6, 2021.
Available:https://www.jnj.com/
69. Staff R. CanSino's COVID-19 vaccine candidate approved for military use in China. Reuters.
Available:https://www.reuters.com/article/us-health-coronavirus-china-vaccine-idUSKBN2400DZ
Published June 29, 2020.
Accessed March 6, 2021.
70. China's CanSino Covid-19 vaccine wins emergency approval in Mexico. South China Morning Post.
Published February 11, 2021.
Accessed March 6, 2021.
Available:https://www.scmp.com/news/china/science/article/3121448/chinas-cansino-covid-19-vaccine-wins-emergency-approval-mexico
71. Mahase E. Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant. BMJ. 2021;372:n296.

DOI: 10.1136/bmj.n296
72. Novavax Announces Start of Rolling Review by Multiple Regulatory Authorities for COVID-19 Vaccine Authorization | Novavax Inc. - IR Site.
Accessed March 2, 2021.
Available:https://ir.novavax.com/news-releases/news-release-details/novavax-announces-start-rolling-review-multiple-regulatory
73. Lauring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2-What Do They Mean? JAMA. 2021;325(6):529-531.
DOI: 10.1001/jama.2020.27124
74. Tushir S, Kamanna S, Nath SS, et al. Proteo-Genomic Analysis of SARS-CoV-2: A Clinical Landscape of Single-Nucleotide Polymorphisms, COVID-19 Proteome, and Host Responses. J Proteome Res.
Published online February 8, 2021.
DOI: 10.1021/acs.jproteome.0c00808
75. WHO | SARS-CoV-2 Variants. WHO.
Accessed March 7, 2021.
Available:http://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/
76. KupferschmidtDec. 20 K, Pm 5:45. Mutant coronavirus in the United Kingdom sets off alarms, but its importance remains unclear. Science | AAAS; 2020.
Published December 20, 2020.
Accessed December 30, 2020.
Available:https://www.sciencemag.org/news/2020/12/mutant-coronavirus-united-kingdom-sets-alarms-its-importance-remains-unclear
77. Fratev F. The SARS-CoV-2 S1 Spike Protein Mutation N501Y Alters the Protein Interactions with Both HACE2 and Human Derived Antibody: A Free Energy of Perturbation Study. Molecular Biology; 2020.
DOI: 10.1101/2020.12.23.424283
78. Bertoglio F, Fühner V, Ruschig M, et al. A SARS-CoV-2 neutralizing antibody selected from COVID-19 patients by phage display is binding to the ACE2-RBD interface and is tolerant to known RBD mutations. bioRxiv.
Published online December 3, 2020:2020.12.03.409318.
DOI: 10.1101/2020.12.03.409318
79. Huang B, Dai L, Wang H, et al. Neutralization of SARS-CoV-2 VOC 501Y.V2 by human antisera elicited by both inactivated BBIBP-CorV and recombinant dimeric RBD ZF2001 vaccines. bioRxiv.
Published online February 2, 2021:2021.02.01.429069.
DOI: 10.1101/2021.02.01.429069
80. Sapkal GN, Yadav PD, Ella R, et al. Neutralization of UK-variant VUI-202012/01 with COVAXIN vaccinated human serum. bioRxiv.
Published online January 27, 2021:2021.01.26.426986.
DOI: 10.1101/2021.01.26.426986
81. Liu Z, VanBlargan LA, Bloyet L-M, et al. Identification of SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization. Cell Host Microbe.
Published online January 27, 2021.
DOI: 10.1016/j.chom.2021.01.014
82. Andreano E, Piccini G, Licastro D, et al. SARS-CoV-2 escape in vitro from a highly neutralizing COVID-19 convalescent plasma. bioRxiv.
Published online December 28, 2020:2020.12.28.424451.
DOI: 10.1101/2020.12.28.424451
83. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med.
Published online March 4, 2021:1-10.
DOI: 10.1038/s41591-021-01294-w
84. World's first coronavirus Human Challenge study receives ethics approval in the UK. GOV.UK.
Accessed March 5, 2021.
Available:https://www.gov.uk/government/news/worlds-first-coronavirus-human-challenge-study-receives-ethics-approval-in-the-uk
85. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2 - Emerging Infectious Diseases journal - CDC. 2020;26(7).
DOI: 10.3201/eid2607.200282
86. COVID-19 vaccines offer hope, other prevention measures must continue.
Accessed October 16, 2021.
Available:https://www.who.int/westernpacific/news/commentaries/detail-hq/covid-19-vaccines-offer-hope-but-other-prevention-measures-must-continue
87. Infographic: The Vital Importance of Social Distancing. Statista Infographics.
Accessed March 5, 2021.
Available:https://www.statista.com/chart/21198/effect-of-social-distancing-signer-lab/

88. Coronavirus (COVID-19) Vaccinations - Statistics and Research. Our World in Data.
Accessed February 21, 2021.
Available:https://ourworldindata.org/covid-vaccinations
89. FDA rejects emergency use authorization for Bharat Biotech's Covaxin jab. mint.
Published June 10, 2021.
Accessed October 16, 2021.
Available:https://www.livemint.com/news/india/fda-rejects-eua-for-bharat-biotech-s-covaxin-jab-11623349228701.html
90. Vaccines for covid-19: reasons for hope, but first for concern. The BMJ.
Published September 30, 2020.
Accessed October 16, 2021.
Available:https://blogs.bmj.com/bmj/2020/09/30/vaccines-for-covid-19-reasons-for-hope-but-first-for-concern/
91. Forman R, Shah S, Jeurissen P, Jit M, Mossialos E. COVID-19 vaccine challenges: What have we learned so far and what remains to be done? Health Policy. 2021;125(5):553-567.
DOI: 10.1016/j.healthpol.2021.03.013
92. COVAX.
Accessed February 21, 2021.
Available:https://www.who.int/initiatives/act-accelerator/covax

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/75109