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REVIEW

Brief Overview of the Currently Available COVID-19 Vaccines

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ABSTRACT

The ongoing pandemic COVID-19, coupled with the absence of an effective antiviral treatment against SARS-CoV-2 is forcing the world community to focus on the specific prevention of COVID-19. Mass immunization, along with other public health measures, can reduce morbidity and mortality and reduce the burden of economic and social losses due to the global spread of Covid-19. Currently, more than 30 vaccines have already been authorised, and more than 60 candidates are now in clinical trials phases III. This review summarises and classify the current information about available vaccines and briefly describes their mechanisms of action, safety, and potential benefits and drawbacks. This paper also provides a brief overview of the present data of phases III COVID-19 vaccines clinical trials, summarised in the table and focusing mainly on their demographic data and clinical effectiveness.

KEYWORDS: Covid-19, Vaccine, Vaccine types, Clinical trials, Vaccine efficacy, Vaccine safety

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) pandemic continues to claim victims worldwide and imposes enormous burdens on all public spheres, particularly on health care and the economy. As of January 31, 2022, WHO announced more than 370 million confirmed cases of COVID-19 with more than 5.5 million deaths [1].

The current spike of omicron variant in Malaysia causes severe concern, despite the implementation of strict SOPs and various restrictive measures. Thus, the total number of COVID-19 cases in Malaysia has reached almost 3 million cases by February 2022, and the total number of deaths exceeding 30 thousand [2]. The situation is getting more complicated as there is still no specific antiviral treatment for COVID-19, and the antiviral drugs that are used have controversial data of their clinical efficacy and produce a number of adverse drug reactions (ADRs) [3]. Even the drugs that have proved their benefits for COVID-19 treatment, such as corticosteroids and anticoagulants, are well known to cause severe ADRs.

Massive vaccination campaign worldwide is designed to stop the spread of COVID-19 and significantly reduce the number of severe cases and mortality rate. The rate and extent of vaccination vary greatly in different countries and depend on many factors, including the availability of vaccines, duration of the vaccination campaign, the capacity of the health care system, as well as the awareness and general willingness of the population for vaccination. Thus, immunisation for frontliners was initiated in Malaysia at only the end of February 2021, and the massive vaccination for the general public was started only in June 2021 [4]. Thus, from the end of February until the end of May 2021, 3,027,466 doses were reported to be administered; however, in June, the number of the administered doses doubled, and the total number of the

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reported doses reached 8,239,107 [5]. Despite the delay in the start of mass vaccination by early August, more than 7 million people in Malaysia have completed both doses of the COVID-19 vaccines, and more than 14 million have already received their first dose. The unprecedented mobilisation of the Ministry of Health of Malaysia and efforts of the healthcare providers and volunteers resulted in impressive achievements. The total number of vaccine doses administered by early February 2022 was more than 64 million, which is about 78 percent of the total population [6], including 37.5 percent that received booster doses. The total number of the COVID-19 vaccines are currently authorised worldwide exceeded 30 (Table 1) [7], and seven of them are currently available in Malaysia [8]. Moreover, more than 60 vaccine candidates are currently at phases III clinical trials [7] and are expected to be authorised soon.

Table 1: List of COVID-19 vaccines approved on 31st January 2022 according to their mechanism of action (modified from COVID-19 vaccine tracker [7])

	Name	Type	Developer	Country of origin	Countries approved	WHO approval
	DNA vaccines					
1.	ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	India	India	_
	mRNA vaccines					
2.	Comirnaty / BNT162b2	RNA vaccine	Pfizer; BioNTech; Fosun Pharma	Germany, China, USA	More than 130	Yes
3.	Spikevax / Moderna COVID-19 Vaccine /mRNA-1273 / TAK-919 (Japan)	RNA vaccine	Moderna; BARDA; NIAID	USA	More than 80	Yes
4.	TAK-919	RNA vaccine	Moderna; Takeda	Japan, USA	Japan	_
	Adenovirus vector vaccines					
5.	Oxford–AstraZeneca COVID-19 vaccine /AZD1222/ Vaxzevria	Chimpanzee Adenovirus (ChAdOx1) vector vaccine	Oxford/AstraZeneca	UK	More than 130	Yes
6.	Covishield	Chimpanzee Adenovirus (ChAdOx1) vector vaccine	Serum Institute of India; Oxford/AstraZeneca	UK	More than 40	Yes
7.	Sputnik V	Recombinant Adenovirus (rAd26 and rAd5) vector vaccine	Gamaleya Research Institute; Acellena Contract Drug Research and Development	Russia	More than 70	_
8.	Sputnik Light	Recombinant Adenovirus (rAd26) vector vaccine	Gamaleya Research Institute; Acellena Contract Drug Research and Development	Russia	More than 20	_

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9.	Sputnik M	Recombinant Adenovirus (rAd26 and rAd5) vector vaccine	Gamaleya Research Institute; Acellena Contract Drug Research and Development	Russia	Russia	_
10.	COVID-19 Vaccine Janssen / JNJ-78436735 / Ad26.COV 2.S	Non-replicating Adenovirus (rAd26) vector vaccine	Johnson & Johnson	The Netherlands, USA	More than 100	Yes
11.	Convidecia / PakVac /Ad5-nCoV	Non-replicating recombinant Adenovirus (rAd5) vector vaccine	CanSino Biologics	China	10	_
	Subunit vaccines					
12.	EpiVacCorona	Protein subunit vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Russia, Belarus, Turkmenistan Cambodia Venezuela	_
13.	Zifivax / ZF2001 / RBD-Dimer	Protein subunit vaccine	Anhui Zhifei Longcom; Institute of Microbiology at the Chinese Academy of Sciences	China, Uzbekistan	China, Uzbekistan, Indonesia	_
14.	Abdala / CIGB 66	Protein subunit vaccine	Center for Genetic Engineering and Biotechnology	Cuba	Cuba, Mexico, Nicaragua, Saint Vincent and the Grenadines, Venezuela, Viet Nam	_
15.	MVC-COV1901 / Medigen COVID-19 vaccine	Protein subunit vaccine	Medigen Vaccine Biologics Corporation	Taiwan	Taiwan, Somaliland	_
16.	Soberana 02 / FINLAY-FR-2 / Pastu Covac	Conjugate vaccine	Finlay Institute of Vaccines; Pasteur Institute of Iran	Cuba, Iran	Cuba, Iran, Nicaragua, Venezuela	_
17.	Soberana Plus / FINLAY-FR-1A	Conjugate vaccine	Finlay Institute of Vaccines	Cuba	Cuba	_
18.	Razi Cov Pars	Recombinant protein vaccine	Razi Vaccine and Serum Research Institute	Iran	Iran	_
19.	Corbevax / BECOV2A	Protein subunit vaccine	Biological E Limited	India, USA	India	_
20.	Nuvaxovid / NVX-CoV2373	Protein nanoparticle vaccine	Novavax	USA	More than 30	Yes

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21.	Covovax	Protein nanoparticle vaccine	Serum Institute of India; Novavax	India, USA	India Indonesia Philippines	Yes
22.	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	Recombinant vaccine	National Vaccine and Serum Institute	China	United Arab Emirates	_
23.	SpikoGen / Vaxine/ COVAX-19	Monovalent recombinant protein vaccine	Vaxine; CinnaGen	Iran	Iran	_
	Inactivated vaccines					
24.	Covilo / BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	More than 80	Yes
25.	WIBP-CorV	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China, Philippines	_
26.	CoronaVac	Inactivated vaccine	Sinovac	China	More than 50	Yes
27.	Covaxin / BBV152	Inactivated vaccine	Bharat Biotech; Indian Council of Medical Research (ICMR) – National Institute of Virology (NIV)	India	More than 10	Yes
28.	CoviVac	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Russia	Russia, Belarus, Cambodia	_
29.	QazVac / QazCovid-in	Inactivated vaccine	Research Institute for Biological Safety Problems	Kazakhstan	Kazakhstan, Kyrgyzstan	_
30.	COVIran Barekat	Inactivated vaccine	Shifa Pharmed Industrial Group	Iran	Iran	_
31.	KCONVAC/ SARS-CoV-2 Vaccine (Vero Cells) / KconecaVac	Inactivated vaccine	Minhai Biotechnology Co.; Kangtai Biological Products Co. Ltd.	China	China, Indonesia	_
32.	Turkovac / ERUCOV-VAC	Inactivated vaccine	Health Institutes of Turkey	Turkey	Turkey	_
33.	FAKHRAVAC (MIVAC)	Inactivated vaccine	Organization of Defensive Innovation and Research	Iran	Iran	_

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The availability of such a large number of different vaccines challenges the choice and contributes to confusion in understanding the differences between vaccines in terms of their mechanism of action, efficacy, safety, and, therefore, possible clinical applications. The current review aims to summarise the available data on registered COVID-19 vaccines and briefly discuss their mechanisms of action, effectiveness, potential advantages, drawbacks, and safety.

Types of COVID-19 vaccines and the principles of their mechanisms of action

There are five types of COVID-19 vaccines based on their mechanism of action: Inactivated virus, subunit or protein, non-replicating adenovirus vector-based, mRNA-based vaccines, and DNA vaccines.

The inactivated COVID-19 vaccines belong to conventional or classical vaccines. They are produced from the whole coronavirus particles grown in Vero cells first and then are inactivated by beta-propiolactone or other methods [9]. The inactivated virus has lost its ability to replicate but still consists of all types of antigens, including spike protein which is considered the primary target for immune response. This vaccine type is stable, well studied, and uses pre-existing technology and infrastructure required for its development [10]. Conventional inactivated virus vaccines commonly contain some adjuvants (aluminium salts, oil emulsion adjuvants, etc.) to boost their immunogenicity [11] [12]. The presence of the adjuvants is a particular concern since they are associated with a higher risk of excess reactogenicity, allergic and toxic reactions [13]. There are data on the associations between the use of vaccines containing specific adjuvants and the development of rare autoimmune or chronic degenerative disorders [13]. Thus, the use of squalene emulsion–adjuvanted vaccines is associated with narcolepsy [14] and the use of aluminium adjuvants can cause chronic granulomatous inflammation macrophagic myofasciitis [15] or Alzheimer's disease [16].

The subunit COVID-19 vaccines consist not of the whole viral particles but the subunits of selected viral protein such as the spike protein (S protein), which was identified as the most suitable target for developing COVID-19 vaccines [17]. SARS-CoV-2 S protein is a typical viral fusion protein responsible for the recognition and entry of the virus into the host cells and it consists of two subunits S1 and S2 [18]. The S1 subunit recognises the human angiotensin-converting enzyme 2 (hACE2) receptor via its receptor-binding domain (RBD), and the S2 subunit is responsible for membrane fusion and virus entry [18] [19] [20]. Several structural and functional studies recognised distinct epitopes on RBD of S protein (SRBD) as the binding sites for most of the neutralising antibodies to SARS-CoV-2 [21] [22] [23].

There are several currently approved subunit COVID-19 vaccines. Most of them comprise several different epitopes of S_{RBD} that are able to induce production of neutralising antibodies. Thus, EpiVacCorona comprises three short immunogenic peptides conjugated to a carrier protein and mixed with aluminium hydroxide as adjuvant [20]. The subunit vaccines are safe as they have no whole coronavirus particles; however, they also require adjuvants due to low immunogenicity. Moreover, the duration of the immune response and its efficacy for this vaccine type is doubtful [10].

Compared to conventional attenuated virus and subunit vaccines, the novel viral vectored vaccines as well as mRNA and DNA vaccines are focused neither on delivery antigens (proteins) but the delivery of the genetic instructions (DNA or RNA) for the host's cells to make them produce the antigens. Thus, this approach allows production of the antigenic viral proteins by host cells, which in case of natural viral infections are introduced by the invading virus. Hence, these vaccines are considered to generate immune response that mimics a natural infection and does not require the addition of adjuvants to enhance the immunogenicity compared to inactivated and subunit vaccines [24]. There are several COVID-19 virus vector vaccines such as Sputnik V, Oxford–AstraZeneca COVID-19 vaccine (AZD1222), Janssen COVID-19 vaccine, Convidecia (AD5-nCOV), etc (Table 1). They all share the same principle of action. Double-stranded DNA coding for the SARS-CoV-2 S protein is incorporated into the

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inactivated adenovirus genome and delivered to the host cells using adenovirus (Ad) as a vector. Thus, SARS-CoV-2 DNA directly delivered to the host cells and copied into mRNA, which offers a long-term and high level of antigenic protein (S protein) expression but no entire virus particles are formed [25]. The endogenous antigen production ensures both humoral and cellular immune responses.

The main difference among currently available virus vector-based vaccines is the serotypes of adenovirus used. Thus, Janssen COVID-19 vaccine uses recombinant Ad26 strain, Convidecia uses Ad5, and Oxford–AstraZeneca is based on Chimpanzee adenovirus (ChAdOx1). These vectors are highly efficient in gene transduction and efficiently induce the immune response [26]; however, they may cause immunity against adenovirus vectors themselves, reducing the efficacy of the vaccines when they are used again [10]. Thus, it may explain the reason to use only one single dose, or, like Astra Zeneca vaccine, to split the jabs by increasing the interval between them up to 12 weeks. In contrast, Sputnik V comprises two doses containing the different serotypes; Ad26 for the first and Ad5 for the second dose. The presence of different Ad serotypes prevents the destruction of the booster dose of the vaccine by the antibodies against the first dose vector.

The mRNA vaccines are a new type of vaccines that were recently developed for Zika virus, Ebola virus, influenza virus, as well as for personalised cancer treatment [27]. The mRNA COVID-19 vaccines as Comirnaty (BNT162b1) and Moderna (mRNA-1273) COVID-19 vaccines are composed of synthetic mRNA (Moderna) or nucleoside-modified mRNA (Comirnaty) cording the full-length, pre-fusion S protein of SARS-CoV-2, which is enclosed in a lipid nanoparticle capsule [28] [29]. After injection, the vaccine particles fuse to the host cells, releasing synthetic viral mRNA. The host cells read its sequence and produce viral S proteins. The presence of S proteins on the surface of live cells and the debris of the dead host cells is recognised by the immune system and stimulates the development of the immune response [27].

This vaccine type is considered to be relatively safe as it contains neither the inactivated pathogen nor the sub-units of the live pathogen and does not require the use adjuvants [30]; however, mRNA is fragile and unstable and is rapidly and easily degraded so it must be incorporated into pegylated lipid nanoparticles [27]. The presence of nanoparticles as vectors may produce some toxic and adverse effects. Thus, lipid nanoparticles are highly inflammatory and cytotoxic [31], that may explain the local adverse drug reactions commonly associated with those vaccine type. Moreover, pegylated nanoparticles are known to trigger immune reactions including type I hypersensitivity and type IV autoimmune reactions especially in genetically predisposed individuals [32]. Another issue for mRNA vaccines is the requirement to be kept and transported in ultracold temperature [10] [27]. Thus, the Moderna COVID-19 vaccine requires transporting and keeping at -15 to -50 ^{o}C [33] and Comirnaty even at -60 to -80^{o}C [34], which significantly complicated the supply logistics and substantially increased the cost of vaccine.

The first authorised for COVID-19 DNA vaccine ZyCoV-D is composed of non-replicating and non-integrating plasmids carrying S protein gene and IgE signal peptide gene [35]. The plasmids gain entry into host cells without integrating into the host DNA. Once the plasmids enter the cells, they are converted into mRNA, which translates into S protein itself. Thus, plasmids act as a vector for viral DNA similar to adenovirus vector for virus vector-based vaccines.

Dose regimens and administration

Except for Comirnaty, which is approved for use in children 5 years of age and older, all other vaccines currently available are approved for use starting from 12-18 years (Table 2); however, several clinical studies are undergoing to determine the effectiveness and safety of covid-19 vaccines in children and adolescents [36], [37]. Most of the registered vaccines are administered intramuscularly (IM) in 2 doses with the intervals of 14 to 28 days apart (Table 2).

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Table 2 Approved COVID-19 vaccines: Storage, administration and dose regimen

	Name	Storage, ℃	Age for vaccination approved	Route of administration	Dose regimen
	DNA vaccines				
1.	ZyCoV-D	2–8	≥ 12	Intradermal using The PharmaJet needle-free system	3 doses 28 days apart
	mRNA vaccines				
2.	Comirnaty / BNT162b2	-70 -80	≥ 5	IM	2 doses 21 days apart. Booster dose 6 months post dose 2
3.	Spikevax / Moderna COVID-19 Vaccine /mRNA-1273	-20	≥ 18	IM	2 doses at least 29 days apart Booster dose at least 5 months post dose 2
4.	TAK-919	-20	≥ 18	IM	2 doses at 28 days apart
	Adenovirus vector vaccines				
5.	Oxford–AstraZeneca COVID-19 vaccine /AZD1222/ Vaxzevria	2–8	≥ 18	IM	2 doses 4-12 weeks apart
6.	Covishield	2–8	≥ 18	IM	2 doses 12-16 weeks apart. Booster dose 12 weeks post dose 2
7.	Sputnik V	2–8	≥ 18	IM	2 doses at least 21 days apart
8.	Sputnik Light	2–8	≥ 18	IM	Single dose
9.	Sputnik M	2–8	12-17	IM	2 doses at least 21 days apart
10.	COVID-19 Vaccine Janssen / JNJ-78436735 / Ad26.COV 2.S	2–8	≥ 18	IM	Single dose. Booster dose at least 8 weeks post dose 2
11.	Convidecia / PakVac /Ad5-nCoV	2–8	≥ 18	IM Intranasal	IM administration - single dose. Booster dose 6 months post primary dose Intranasal route of administration - 2 doses

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	Subunit vaccines				
12.	EpiVacCorona	2–8	≥ 18	IM	2 doses 14-21 days apart
13.	Zifivax / ZF2001 / RBD-Dimer	2–8	≥ 18	IM	2 and 3 dose schedules at 0, 1 and 4-6 months
14.	Abdala / CIGB 66	2–8	≥ 18	IM	3 doses (0, 14 and 28 days)
15.	MVC-COV1901 / Medigen COVID-19 vaccine	2–8	≥ 18	IM	2 doses 28 days apart
16.	Soberana 02 / FINLAY-FR-2 / Pastu Covac	2–8	≥ 8	IM	2 doses 28 days apart
17.	Soberana Plus / FINLAY-FR-1A	2–8	≥ 18	IM	Single dose as a booster dose
18.	Razi Cov Pars	2–8	≥ 18	IM and Intranasal	First 2 doses injected IM 21 days apart. The third dose is intranasal 51 post dose 2
19.	Corbevax / BECOV2A	2–8	≥ 18	IM	2 doses
20.	Nuvaxovid / NVX-CoV2373	2–8	≥ 18	IM	2 doses, minimum of 21 days apart. Booster dose 2-6 months post dose 2
21.	Covovax	2–8	≥ 18	IM	2 doses, minimum of 21 days apart
22.	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	–	–	–	–
23.	SpikoGen / Vaxine/ COVAX-19	2–8	≥ 18	IM	2 doses 21 days apart
	Inactivated vaccines				
24.	Covilo / BBIBP-CorV	2–8	≥ 18	IM	2 doses 21-28 days apart
25.	WIBP-CorV	2–8	≥ 18	IM	2 doses 21-28 days apart

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26.	CoronaVac	2–8	≥ 18	IM	2 doses at least 21 days apart
27.	Covaxin / BBV152	2–8	≥ 18	IM	2 doses 28 days apart
28.	CoviVac	2–8	≥ 18	IM	2 doses 14 days apart
29.	QazVac / QazCovid-in	2–8	≥ 18	IM	2 doses 21 days apart
30.	COVIran Barekat	2–8	≥ 18	IM	2 doses 28 days apart
31.	KCONVAC/ SARS-CoV-2 Vaccine (Vero Cells) / KconecaVac	2–8	≥ 18	IM	2 doses 14 days apart
32.	Turkovac / ERUCOV-VAC	2–8	≥ 18	IM	2 doses
33.	FAKHRAVAC (MIVAC)	2–8	≥ 18	IM	2 doses 14-21 days apart

Interestingly, the preliminary report of an open-label and randomised phase I clinical trial was published recently reported that two doses of aerosol formulation of Convidicea (Ad5-nCoV) vaccine elicited levels of neutralising antibody, comparable to one dose of intramuscular injection [38]. The use of an aerosol formulation was therefore proposed as a booster vaccination 28 days after the first intramuscular injection [38].

Efficacy and safety of the available COVID-19 vaccines based on phase III clinical trials

Due to pandemic and the need to start mass vaccination as soon as possible, some of vaccines were authorised for emergency use right after completing the second phase of the clinical trials. At this moment, about half of the registered vaccines have already passed at least partially their third phase of the clinical trials; however, the data of phase III have been published in the peer-reviewed journals only for several vaccines (Table 3). Some of the registered vaccines are still in phase III of the clinical trials, and a few recently registered vaccines have announced the third phase but still have not begun recruiting participants (Table 3).

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Table 3 Approved COVID-19 vaccines: Brief data of phase III clinical trials

	Name	Description	Efficacy	Location	References
	DNA vaccines				
1.	ZyCoV-D	Total 28,000 participants including 1,000 participants of age 12-18	Interim data 66.6% No severe cases or deaths due to COVID-19 occurred in the vaccine arm after administration of the second dose of the vaccine	India	[67]
	mRNA vaccines				
2.	Comirnaty / BNT162b2	Total 43,548 participants Vaccine : placebo ratio (1:1) Age 56-85 (41%-45%) Ethnic diversity 42%	95% (28 days after the first dose); 94% (among participants > 65 years)	USA, Germany, Turkey, South Africa, Brazil, Argentine	[52]
3.	Spikevax / Moderna COVID-19 Vaccine /mRNA-1273	Total 30,420 participants Age > 65 years (24.8%) Ethnic diversity 20.8%	94.1%	USA	[50]
4.	TAK-919	There are no trials for phase III announced			
	Adenovirus vector vaccines				
5.	Oxford–AstraZeneca COVID-19 vaccine /AZD1222/ Vaxzevria / Covishield	Total 11,636 participants Age > 55years (12.1%) Ethnic diversity 17.3%	Variable: Average 70.4% (after 2 dose) and 64.1% (after first dose)	Brazil, UK, South Africa	[51]
6.	Covishield	Comparative study of Covishield with Oxford/AZ-ChAdOx1 nCoV-19 and Placebo Total 1,600 participants	On-going	India	[68]
7.	Sputnik V	Total 21,977 participants Vaccine : placebo ratio (16,501 : 5,476) Age > 60 years (10.8%) Ethnic diversity (1.5%)	91.6%	Russia	[48]
8.	Sputnik Light	NCT04741061 6,000 participants Randomised, parallel, double-blind, placebo-controlled	On-going	International	[41]
9.	Sputnik M	Phase III clinical trial has been announced			

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10.	COVID-19 Vaccine Janssen / JNJ-78436735 / Ad26.COV 2.S	Total 43,783 participants. Vaccine : placebo ratio (19,630 : 19,691). Age ≥ 60 years 14,672 (33.5%) Ethnic diversity (51.3%)	Prevention of moderate to severe–critical COVID-19 66.9% and 66.1% (14 and 28 days after single dose administration) Prevention of severe–critical Covid-19 76.7% and 89.1% (14 and 28 days after single dose administration)	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, US	[43]
11.	Convidicea / PakVac, Ad5-nCoV	NCT04566770 Randomised, parallel, double-blind, placebo-controlled, phase 2b	On-going	International	[37]
		NCT04540419 500 participants Randomised, parallel, double-blind, placebo controlled			[54]
	Subunit vaccines				
12.	EpiVacCorona	NCT04780035 3,000 participants Randomised, parallel, double-blind, placebo controlled	On-going	Russia	[55]
13.	Zifivax / ZF2001 / RBD-Dimer	NCT04646590 29,000 participants Randomised, parallel, double-blind, placebo-controlled	On-going	China and outside	[56]
14.	Abdala / CIGB 66	48,000 participants Randomised, double-blind, parallel, placebo controlled	On-going	Cuba	[57]
15.	MVC-COV1901 / Medigen COVID-19 vaccine	NCT05011526 1,020 participants Randomised, double-blind, parallel, active-controlled	On-going	Paraguay	[58]
16.	Soberana 02 / FINLAY-FR-2 / Pastu Covac	44,031 participants Two doses of Soberana 02; two doses of Soberana 02 followed by a third dose of Soberana Plus; placebo (two doses) administered 28 days apart at a 1:1:1 ratio Age 19–80	Booster dose of Soberana Plus increased efficacy of Soberana 02 up to 92.4%.	Cuba	Preprint [59]
17.	Soberana Plus / FINLAY-FR-1A				
18.	Razi Cov Pars	IRCT20201214049709N3 41,128 participants Age ≥ 18 Randomised, parallel, double-blind, comparative vs Sinopharm vaccine	On-going	Iran	[69]

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19.	Corbevax / BECOV2A	CTRI/2021/08/036074 2,140 participants Age 18-80 Randomised, single-blind, parallel group, active-controlled	On-going	India	[70]
		CTRI/2021/06/034014 1,268 participants Age 18-80 Phase 2/3, single arm	On-going	India	[71]
		CTRI/2021/10/037066 624 participants Age ≥5 - 18 Phase 2/3, randomised, double-blind, placebo-controlled	On-going	India	[72]
20.	Nuvaxovid / Novavax / NVX-CoV2373	15,187 participants Vaccine : placebo ration 1 : 1 Age ≥18 -84 Age ≥65 (27.9%)	89.7%	UK	[73]
		29,949 participants Vaccine (19,714): placebo (9,868) ratio two doses of 21 days apart. Age ≥18 years of age Age ≥65 (12.6%)	92.6%	USA, Mexico	[74]
21.	Covovax	CTRI/2021/02/031554 2,520 participants Age ≥2 - 99 Phase 2/3, randomised, observer-blind, controlled	On-going	India	[75]
22.	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	NCT05069129 1,848 participants Randomised, double-blind, controlled	On-going	United Arab Emirates	[76]
23.	SpikoGen / Vaxine/ COVAX-19	NCT05005559 16,876 participants Randomised, two-armed, double-blind, placebo-controlled	On-going	Iran	[77]
		NCT05148871 2,000 participants Phase 2/3b, randomised, open, 4 parallel groups	On-going	Australia	[78]
		NCT05175625 300 participants Randomised, two-armed, placebo-controlled, double-blind, parallel groups	On-going	Iran	[79]

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Inactivated vaccines

24. 25.	Covilo / BBIBP-CorV WIBP-CorV	Combined clinical Trial of 2 vaccine candidates WIV04: HB02 : adjuvant ratio (13,459 : 13,465 : 13,458)	WIV04 - 72.8% HB02- 78.1% (14 days after the second dose)	UAE, Bahrain	[49]
26.	CoronaVac	Turkey Total 10,214 participants. Vaccine : placebo ratio (6,646 : 3,568). No participants ≥ 60 years Brazil Vaccine : placebo ratio (9,823 : 12,396) Chile Total number of healthcare workers 434 participants Vaccine : placebo ratio (270 : 164) Age ≥ 60 years (37 participants)	Turkey: 83.5% (14 days after the second dose) Brazil: 50,7% (prevention of symptomatic cases) and 83,7% (prevention of moderate or severe cases) Chile: 90% - 100% (seroconversion rate at 28-42 days after first dose)	Turkey, Brazil, Chile, Indonesia	[60] [42] [61]
27.	Covaxin / BBV152	Total 25,798 participants Vaccine : placebo ratio (1:1) Age ≥18 Age ≥ 60 years (2,433)	77·8% (14 days after the second dose)	India	[62]
		NCT04918797 525 participants of ages ≤18 to ≥2 years. Phase 2/3, single group assignment, open label	On-going	India	[36]
28.	CoviVac	Details of the study are not announced	On-going according the information from the website of the Ministry of Health Russian Federation	Russia	[63]
29.	QazVac / QazCovid-in	NCT04691908 3,000 participants Randomised, parallel, blind, placebo-controlled	On-going	Kazakhstan	[64]
30.	COVIran Barekat	IRCT20201202049567N3 2,000 participants Phase 2/3, randomised, double-blind, parallel, placebo-controlled	On-going	Iran	[65]
31.	KCONVAC/ SARS-CoV-2 Vaccine (Vero Cells) / KconecaVac	NCT04852705 28,000 participants Randomised, double-blind, placebo-controlled	On-going	International	[66]

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32.	Turkovac / ERUCOV-VAC	NCT04942405 1,290 participants Randomised, double-blind, parallel	On-going	Turkey	[80]
		NCT05077176 7,400 participants Non-randomised, open label	On-going	Turkey	[81]
33.	FAKHRAVAC (MIVAC)	IRCT20210206050259N3 41,128 participants Randomised, double-blind, controlled, parallel groups	On-going	Iran	[82]

Published results of phase III clinical trials for most vaccines indicate a reasonably high level of efficacy to prevent COVID-19 that varied for different vaccines from 50.1% to 95% (Table 3). All published data reported no meaningful differences in vaccines efficacy among sex, race, or ethnic groups. The extraordinarily high incidence of SARS-CoV-2 infection at the time of these clinical trials may be associated with seemingly lower level of vaccine efficacy [39] [40]. Although it should be taken into account that due to the urgency, the endpoints in the majority of the trials were settled at day 14 after the administration of the second dose (28-42 days from the beginning of immunisation) and indeed cannot fully indicate the effectiveness of vaccines for the long-term. In this regard, many developers continue to conduct a series of phase IIb and phase III trials to obtain data on efficacy over more extended periods [41], as well as in various cohorts of subjects, including adolescents and children [36], [37]. In addition to the efficacy to prevent SARS-CoV-2 illness, the prevention of severe-critical forms of the disease is also crucial. The published phase III data have shown a 70% - 90% reduction of severe–critical Covid-19 cases in the vaccinated groups compared to the placebo [42] [43]. Some more recent studies have shown that COVID-19 vaccines also prevent COVID-19 associated hospitalisations and death [44]. It should be noted that all of these studies have been done on alpha variant and do not include data of the efficacy against new delta and omicron variants. Some of the recently published studies have shown that the efficacy of the currently available COVID-19 vaccine against delta and omicron variants is significantly lower compared to that for alpha variant [45] [46].

Most of the vaccines that completed the phase III clinical trials showed a number of adverse drug reactions (ADRs); however, almost all ADRs reported were not severe and belonged to grades 1 and 2 of FDA Toxicity Grading Scale [47]. The list of the common ADRs included local reactions such as mild-to-moderate pain, redness, and swelling at the injection site and the systemic reactions including fatigue, myalgia, nausea, headache, and fever. In the majority of cases, these ADRs were self-limiting and resolved within 1 to 2 days. Serious adverse events were rare for all vaccines, and the incidence of ADRs grade 3 [47] has varied from decimal percentages; Janssen 0.2% [43], Sputnik V 0.4% [48], and BBIBP-CorV and WIBP-CorV 0.5% [49]; up to a few percentage points; 1.5% for both Moderna and Oxford–AstraZeneca [50] [51] and 2% for Comirnaty [52]. Hypersensitivity reactions, including anaphylaxis, as well as rare thrombosis and thrombocytopenia [53] were reported among serious ADRs associated with COVID-19 vaccines.

Generally, published data of the clinical trials indicate the short-term safety of the COVID-19 vaccines. However, long-term post-marketing surveillance data is required to ensure the safety of COVID-19 vaccines, particularly in vulnerable high-risk groups such as seniors, pregnant women, and children.

CONCLUSIONS

Based on the analysis of the published phase III data and more recently, from real-world data, it can be concluded that currently available COVID-19 vaccines prevent SARS-CoV-2 infection and significantly reduce severe-critical illness, including hospitalisation and death. The phase III clinical trials shown that different COVID-19 vaccines have similar profiles of local and systemic ADRs, and the rate of severe post immunisation ADRs is very low. However, further data from larger sample size and more extended duration studies are warranted to establish more detailed knowledge of COVID-19 vaccines effectiveness and safety on the general population and in an ethnically and geographically diverse population, including participants in regions with emerging SARS-CoV-2 variants as well as in high-risk groups with pre-existing conditions as well as seniors and children.

Conflict of Interest

Author declare none.

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