

Emergency use of COVID-19 vaccines recommended by the World Health Organization (WHO) as of June 2021

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SUMMARY In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the outbreak of coronavirus disease 2019 (COVID-19), and the resulting pandemic has caused widespread health problems and social and economic disruption. Thus far in 2021, more than 4 million people worldwide have died from COVID-19, so safe and efficacious vaccines are urgently needed to restore normal economic and social activities. According to the official guidance documents of the World Health Organization (WHO), vaccines based on four major strategies including mRNA, adenoviral vectors, inactivated viruses, and recombinant proteins have entered the stage of emergency use authorization and pre-certification evaluation. The current review summarizes these vaccines and it looks ahead to the development of additional COVID-19 vaccines in the future.

Keywords COVID-19, vaccine research, mRNA, adenoviral vectors, inactivated viruses, recombinant proteins

On March 11, 2020, the World Health Organization (WHO) declared novel coronavirus disease 2019 (COVID-19) a global pandemic (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has now infected more than 200 million people and caused more than 4 million deaths. A promising avenue for human beings to overcome epidemics, the research and development of vaccines has been compressed from the usual 10-15 years to 1-2 years as a result of joint efforts worldwide; these efforts are encouraging and fruitful (2). Earlier documents from the WHO described seven platforms or strategies for COVID-19 vaccine development (3). As of June 2021, there are four major categories of vaccines including mRNA vaccines, adenovirus-vectored vaccines, inactivated virus vaccines, and recombinant protein vaccines. Vaccines have been produced by 23 businesses and research institutions in 8 countries, leading to the 19 vaccines in the 'emergency use listing/pre-qualification evaluation process' as shown in Table 1 (4).

mRNA vaccines An mRNA vaccine encapsulates the mRNA that encodes the SARS-CoV-2 spike protein (S protein) into lipid nanoparticles, and these nanoparticles are then injected into the human body. After the nanoparticles enter cells, antigen information will be presented on the surface of the cell membrane and an immune response will be induced. Examples of mRNA vaccines are BNT162b2 (produced by Pfizer &

BioNTech) and mRNA-1273 (produced by Moderna). An mRNA vaccine has many advantages such as being noninfectious, being easy to production, and being easy to standardize (5,6). BNT162b2 was granted emergency use authorization by the WHO on December 31, 2020. It is the first mRNA vaccine that was approved for human use. In Israel, more than 6.5 million people over the age of 16 have been vaccinated once BNT162b2 was authorized for emergency use. Its efficacy is as high as 95.3% within 7 days of 2 rounds of vaccination (7). A study of nearly 4,000 frontline healthcare workers at eight locations in the United States from December 2020 to March 2021 indicated that the rate of infection dropped sharply after 2 rounds of vaccination within 14 days, and vaccine efficacy was 90% according to the Centers for Disease Control and Prevention (CDC) (8). Another study indicated that neutralizing antibodies and memory B cells remain stable over a period of 6-12 months after BNT162b2 is injected twice. These findings indicate that mRNA vaccines can confer long-lasting protection (9) and still remain efficacious against mutants (10).

Adenovirus-vectored vaccines When the S protein gene of SARS-CoV-2 is injected into a nonpathogenic adenovirus, it will express the antigen once it enters the human body, thereby inducing both humoral immunity and cellular immunity. An adenovirus-vectored vaccine should be transported and stored at low temperatures (2-8°C) (11). Examples of adenovirus-vectored vaccines

Table 1. Emergency use/pre-certification list of COVID-19 vaccines according to the WHO as of June 2021

Platform	Name of Vaccine	Manufacturer	Country
mRNA vaccine	BNT162b2/COMIRNATY Tozinameran (INN)	Pfizer & BioNTech	USA, Germany
	mRNA-1273	Moderna	USA
	CVnCoV/CV07050101	CureVac	Germany
Adenovirus-vectored vaccine	AZD1222	AstraZeneca & University of Oxford	UK
	Covishield (ChAdOx1_nCoV-19)	Serum Institute of India Pvt. Ltd.	India
	Ad26.COV2.S	Janssen (Johnson & Johnson)	USA
	Sputnik V	The Gamaleya National Center	Russia
	Ad5-nCoV	CanSinoBIO	China
Inactivated vaccine	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	Sinopharm/BIBP	China (Beijing)
	CoronaVac	Sinovac	China
	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Sinopharm/WIBP	China (Wuhan)
	COVAXIN	Bharat Biotech	India
Recombinant protein vaccine	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	IMBCAMS	China
	NVX-CoV2373/Covovax	NOVAVAX	USA
	CoV2 preS dTM-AS03 vaccine	Sanofi Pasteur	France
	EpiVacCorona	SRC VB VECTOR	Russia
	Recombinant Novel Coronavirus Vaccine (CHO Cell)	Zhifei Longcom	China
	SCB-2019	Clover Biopharmaceuticals	China
	Soberana 01, Soberana 02, Soberana Plus, Abdala	BioCubaFarma	Cuba

are AZD1222 (developed by the Jenner Institute of Oxford & AstraZeneca), Ad26.COV2.S (produced by Johnson & Johnson), and Ad5-nCoV (produced by CanSinoBIO). Numerous studies involving hundreds of thousands of people in Great Britain have indicated that AZD1222 and BNT162b2 are both effective at preventing infection and severe symptoms of COVID-19 (12-14). A phase 3 trial randomized double-blind study involving tens of thousands of people has indicated that Ad26.COV2.S was equally effective at preventing infection and at treating severe-critical disease (including hospitalization and death) (15). Data from a phase 3 trial on Sputnik V (developed by the Gamaleya National Center of Epidemiology and Microbiology) will be released later (16,17).

Inactivated vaccines An advantage of an inactivated vaccine is that it retains immunogenicity while lacking the infectivity of a virus. Vaccination with an inactivated virus can stimulate the body to generate a humoral immune response to defend against SARS-CoV-2 (18). The main manufacturers of inactivated vaccines against COVID-19 are Sinopharm/BIBP, Sinovac, and Sinopharm/WIBP. Clinical data indicate that the vaccine produced by Sinopharm/BIBP has an efficacy of 79% (19). In one study, 13,459 individuals received an initial injection with a vaccine by Sinopharm/WIBP, and 13,066 individuals received the second injection (20). High titers of antibodies developed within 14 days of the second injection, resulting in effective protection, positivity for neutralizing antibodies higher than 99%, and a protective efficacy of 72.8%. The vaccine produced by Sinovac was the second Chinese vaccine approved by the WHO. Although it had an initial efficacy of only 51%, its efficacy at preventing severe illness and mortality was 100% (19). Inactivated vaccines from Bharat Biotech and the Institute of Medical Biology, Chinese Academy

of Medical Sciences (IMBCAMS) have also entered phase III clinical trials or are in development.

Recombinant protein vaccines A target gene (like that encoding a SARS-CoV-2 antigen) is expressed *in vitro*, transfected into bacteria, yeast, mammal, or insect cells using specific protein vectors, and then the expression of large amounts of antigenic protein is induced under certain conditions. Once the protein is collected and purified, a recombinant protein vaccine can be prepared. There are currently two strategies to prepare recombinant protein vaccines against COVID-19: expression of the S protein and expression of virus-like particles (VLPs). The former ultimately uses purified S protein. An example is NVX-CoV2373/Covovax (produced by NOVAVAX), which was used to vaccinate more than 2,000 volunteers in a phase III clinical trial. Results indicated that the vaccine was 100% efficacious at preventing moderate to severe disease and that it had an overall efficacy of up to 90.4% (21). The latter is still being developed and is in the early clinical stage. An example is AS03 (Medicago Inc.), which contains VLPs self-assembled from capsid proteins of SARS-CoV-2 within a heterologous system. VLPs are similar to SARS-CoV-2 since they have its outer shell, but VLPs are hollow since they do not contain the virus' genetic material, so they have no infectivity or replicative capacity. However, VLPs can effectively trigger cellular immunity and humoral immunity (22,23).

In addition to the four main types of vaccines described thus far, several novel manufacturing approaches are being developed. As an example, the diversity and spread of coronaviruses spurred a research team at the Duke University School of Medicine to recently develop several 'mixed' mRNA vaccines with multiple immunogenicity (24). Results from animal trials indicated that these vaccines can target 2-3 different

coronaviruses at the same time

There are nearly 300 COVID-19 vaccine projects in the research and development stage worldwide, and more than 100 have entered the clinical trial stage (25). More vaccines will appear, and global vaccine production is continually expanding. The resulting vaccines will be able to cover more countries and regions and provide safety and effective protection from this global pandemic.

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