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REVIEW ARTICLE

Current State of Developed COVID-19 Vaccines; Light at the End of the Tunnel

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Abstract

COVID-19 pandemic has posed a dire threat to global health. Safe and effective vaccination can play an important role in preventing the transmission of the virus, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus type 2). The right choice of vaccine type, carrier, or vector as well as the dosage of vaccine can have a direct impact on the resulting effectiveness against the illness, COVID-19. Therefore, there is tremendous pressure on researchers to develop safe and effective vaccines against the virus SARS-CoV-2 and the resultant illness. In addition, this pandemic is an alarm to the world that we have to prepare ourselves for various consequences of SARS-CoV-2 or another unpredictable pandemic in the future. This review described leading vaccines developed against SARS-CoV-2; Comirnaty, mRNA-1273, Sputnik V, Ad26.COV2.S, Vaxzevria, NVX-CoV2373, BBIBP-CorV, CoronaVac, Convidecia, and BBV152.

Key Words: *COVID-19; Pandemic; Prevention; Vaccine*

Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus type 2) was first isolated in Wuhan, China, in December 2019. The World Health Organization (WHO) called the virus coronavirus disease 2019 (COVID-19) in February 2020. The genome of the virus is 96% the same as bat coronavirus (RaTG13) and no evidence of the manipulation in the genome has been found up to this time [1].

The world is currently grappling with an unprecedented global pandemic caused by SARS-CoV-2, which spreads through inhaling virus-infected droplets and thus it is considered as a threat to global health due to its easy transmission. SARS-CoV-2 is a positive-sense single-stranded RNA virus completely enveloped in a complex protein and bilipid shell. These viruses are relatively large, consisting of 26 to 32 kilobase pairs and four main structure proteins, namely spike, envelope, membrane, and nucleocapsid. The spike protein facilitates the transmission of the virus; in fact, the attachment protein, *i.e.,* spike uses the same ACE2 and the cellular protease TMPRSS2 for the activation of the virus in our body [2-4].

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There are many ways to prevent the transmission of viruses, including using medical masks, social distancing, and lockdowns. However, vaccination is considered the most effective way to avoid an infectious disease. Thus, developing, manufacturing, and distributing high-performance vaccines play a major role against COVID-19, significantly reducing morbidity and mortality rate associated with COVID-19 as well as decreasing the negative economic impact [2,3,5]. The aim of this review is to summarize some of the leading vaccines already developed against SARS-CoV-2; Comirnaty, mRNA-1273, Sputnik V, Ad26.COV2.S, Vaxzevria, NVX-CoV2373, BBIBP-CorV, CoronaVac, Convidecia, and BBV152.

Types of vaccines

Inactivated virus: The first idea for vaccines with inactivated viruses was put forward in the 1950s by Jonas Salk, who developed polio vaccine and later utilized it for rabies and hepatitis A. The same mechanism was used for COVID-19 vaccine. To extract the inactivated virus, first a pile of coronaviruses was doused *via* beta-propiolactone, a chemical that bonds to viruses' genes and disables them. The resulting inactivated virus could not replicate; nonetheless, the proteins of the virus, including spike stayed intact. After extracting the inactivated virus, it was combined with a small amount of adjuvant, which is an aluminum-based compound. After injecting vaccines developed *via* the mentioned technology, the immune system's response to the vaccine is to produce antibodies. This method was used to develop the following vaccines: BBIBP-CorV, CoronaVac, Covaxin [6,7].

Adenoviral vectors: Another technology for developing vaccines is based on adenoviruses, a type of virus that causes cold. To develop Sputnik V, Ad26.COV2.S, and Convidecia, the gene of the spike protein was inserted into the genome of human adenovirus type 26 and 5, 26, and 5 respectively. Moreover, chimpanzee adenovirus was used for the development of Vaxzevria. Since adenoviruses are able to induce both innate and adaptive immune responses, they are the best vectors to carry antigens. This technology was also used to develop vaccines versus *Ebola* and *Zika* viruses. Given that adenovirus is genetically modified, it is unable to create replicas of itself. However, the DNA gene of the spike protein can be deciphered and read by mRNA and afterwards it can begin to assemble spike proteins. After injection, the vaccine stimulates the immune system to react more strongly to the spike proteins of COVID-19 [6].

Protein: In developing NVX-CoV2373, modified spike gene was used to simulate the immune system to produce antibodies. To develop this vaccine, researchers first inserted the modified spike gene to baculovirus, waiting for moth cells to be infected with it. The infected cells produced spike proteins, which researchers harvested from the moth cells and then put together in the form of nanoparticles. The spike nanoparticles could not replicate or cause SARS-CoV-2 despite having the molecular structure of the coronavirus. The vaccine contains spike nanoparticles and immunity-priming compound capable of activating the immune system versus COVID-19 [6].

mRNA: mRNA technology has been used for two vaccines namely, Comirnaty and mRNA-1273. The genetic material *i.e.,* mRNA, is fragile and after injection it is broken down by natural enzymes. In developing the two above-mentioned vaccines, lipid nanoparticles were used to surround and protect the mRNA based on mRNA technology. Upon injecting the vaccine, its particles collide with cells and fuse into them, as a result of which mRNA is

released. The cell's molecules read the released mRNA and produce spike proteins; the mRNA is destroyed by the same molecules. After vaccination, the response of immune system is to produce antibodies against spike protein in case of infection with COVID-19 [6].

Vaccines

Comirnaty: This vaccine has been co-produced by two companies, BioNTech and Pfizer. The U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the vaccine on December 11, 2020. Lipid nanoparticles (mRNA-LNP) proved to have high immunization effect versus infectious diseases and their efficacy has also been confirmed for SARS-CoV-2 in humans. Comirnaty consists of two 15 μg dosages. To address the issue of storing the vaccine at low temperature (-94°F (-70°C)), the company has constructed special containers with dry ice and thermal sensors. Phase III trial of the vaccine was performed on over 43,000 participants. Given the satisfactory results, Comirnaty was approved by the World Health Organisation (WHO) [8,9].

mRNA-1273: Six days after the approval of Pfizer BioNTech vaccine by the US FDA, an Emergency Use Authorization (EUA) was also issued for mRNA-1273 vaccine. Similar to Pfizer-BioNTech, mRNA technology was used in the manufacturing process of the mRNA-1273 vaccine by an American pharmaceutical and biotechnology company (Moderna) located in Cambridge, Massachusetts. mRNA-1273 vaccine requires two doses (100 μg, 0.5 mL each). Phase III trial of the vaccine was completed with approximately 30,000 voluntary participants. Like Comirnaty, mRNA-1273 vaccine is highly effective against the virus and was approved by WHO [10].

Sputnik V: The Gamaleya Research Institute of Epidemiology and Microbiology of Russia developed the first vaccine named Sputink V against SARS-CoV-2. On August 11, 2020, Sputnik V was issued for emergency use in Russia (before going through phase III clinical trial) and therefore, the safety and efficacy of the vaccine was questionable at the time. Sputnik V uses two different adenoviral vectors, namely Ad26 and Ad5; to ensure long-lasting immunity and increasing the efficacy of the vaccine, a single dose of rAd26-S was given for the first vaccination and one dose of rAd5-S after 3-4 weeks. Currently, Sputnik V is one of the three vaccines proven to be 90% effective against COVID-19. As of December 2020, Belarus issued an emergency use authorization of this vaccine and 68 more countries have started using Sputnik V. Moreover, WHO has contacted Gamaleya Research Institute for Epidemiology and Microbiology, encouraging it to apply for approval [6,11,12].

Ad26.COV2.S: On February 27, 2021, the U.S. Food and Drug Administration issued an Emergency Use Authorization (EUA) for Ad26.COV2.S vaccine which was developed by Janssen Pharmaceuticals (Belgium), a subsidiary of American medical company Johnson & Johnson. The human adenoviral vector 26 provides complete or almost complete protection against SARS-CoV-2. While all other vaccines require patients to receive two separate doses spaced weeks apart, Ad26.COV2.S, similar to Convidecia, is delivered in a single dose. Ad26.COV2.S can also be shipped while being refrigerated (not under frozen conditions as required for transporting other vaccines). In March 2021, WHO added Ad26.COV2.S as a safe vaccine against COVID-19 [8,13].

Vaxzevria: UK issued an Emergency Use Authorization (EUA) of the Vaxzevria vaccine on

December 30, 2020. The Oxford-AstraZeneca group utilized a modified type of a chimpanzee adenovirus in making the vaccine, which reduces the transmission of future infections [14-16]. The vaccine has been reviewed and approved by the European Medicines Agency (EMA) [14]. WHO stated that the Vaxzevria has an efficacy of 63% against symptomatic SARS-CoV-2 infection, which will be increased with longer dose intervals, 8 to 12 weeks [15]. However, the company reported that the vaccine showed a significant increase in efficacy (up to 90%) in patients who first received a half a dose (20 mg) and after a four-week interval a full dose of 40 mg, whereas two full doses with the same interval has shown the efficacy of approximately 62% [16]. Moreover, on March 22, 2021, phase 3 trial of Vaxzevria in the United States showed that the efficacy of the vaccine was 76% in preventing symptomatic COVID-19 and 85% in elderly participants who are 65 years and older [17].

NVX-CoV2373: The protein nanoparticle technology was used in the development of the vaccine. On January 28, 2021, Novavax Company reported that the final analysis (phase 3 trial) of the efficacy of NVX-CoV2373 versus COVID-19 in the UK was 89.7%. In addition, the efficacy of the vaccine versus new variants was promising. Novavax is currently (August 2021) not on the WHO list [6,18].

BBIBP-CorV: The BBIBP-CorV vaccine was approved in China, Bahrain, and UAE and used as an emergency measure in more than 44 countries. The vaccine has already been approved by the WHO [6,8].

CoronaVac: The CoronaVac was approved for use in China and used in emergency conditions in more than 28 countries. The efficacy of the vaccine is satisfactory, and it has received the approval of WHO [6].

Convidecia: This vaccine requires a single dose like Ad26.COV2.S. Phase III clinical trial has begun in Pakistan, Russia, Mexico, and Chile with the participation of 40,000 volunteers. The vaccine was approved for vaccination in China; also, an emergency use authorization was issued in Chile, Hungary, Mexico, Moldova, Pakistan, Argentina, Ecuador, and Malaysia. Phase III interim analysis data showed that the vaccine has satisfactory effect against COVID-19. Currently, Convidecia is not listed by WHO [6,8].

Covaxin: The result of the vaccine efficacy evaluation in first and second phases showed that the vaccine provides satisfactory defence versus COVID-19, without any serious side effects. Thus, the vaccine was issued for emergency use in India and 13 more countries. Covaxin leads to tolerable immune effects and improves immune responses [6].

It should be noted that the WHO recommends the interval of 21-28 days between doses of vaccines and depending on the vaccine, it may be increased up to 12 weeks [19]. (Table 1) demonstrates the 10 leading COVID-19 vaccines discussed above. Details about the efficacy of the vaccines are depicted in (Figure 1). As mentioned earlier in the article, the efficacy of some vaccines was evaluated in different countries under variety of conditions; therefore, for some vaccines, the diagram demonstrates more than one result.

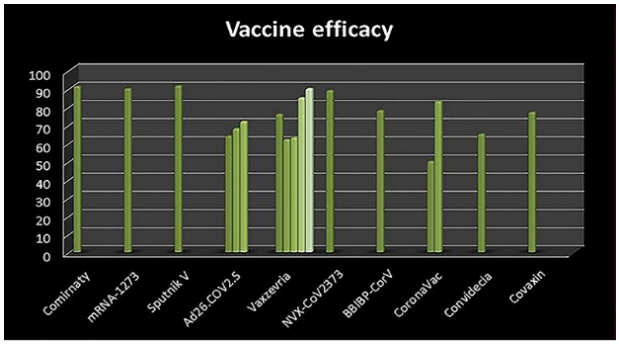

Figure 1) *Demonstrates Vaccines Efficacy.*

TABLE 1

Shows vaccines details.

Vaccine name	Manufacturer	Technology	Dosage	Vaccine efficacy
Comirnaty (BNT162b2)	Pfizer BioNTech; Pfizer (USA) /BioNTech (Germany)	mRNA	2 doses, 3-4 weeks apart	≥ 90%
mRNA-1273 (Spikevax)	Moderna (USA)	mRNA	2 doses, 4 weeks apart	≥ 90%
Sputnik V (Gam-Covid-Vac)	Gamaleya Research Institute (Russia)	Human adenoviral vectors 26 and 5	2 doses, 3-4 weeks apart	≥ 90%
Ad26.COV2.S (JNJ-78436735)	Johnson & Johnson (USA)	Human adenoviral vector 26	Single dose	≥ 64%
Vaxzevria (AZD1222, ChAdOx1)	University of Oxford/ Astra Zeneca (UK/ Sweden)	Chimpanzee adenoviral vector	2 doses, 4 to 12 weeks apart	≥ 76%
NVX-CoV2373	Novavax (USA)	Protein	2 doses, 3 weeks apart	≥ 89%
BBIBP-CorV	Sinopharm (China)	Inactivated virus	2 doses, 3 weeks apart	≥ 78%
CoronaVac (PiCoVacc)	SINOVAC (China)	Inactivated virus	2 doses, 2 weeks apart	≥ 50%
Convidecia (PakVac, AAd5-nCoV)	CanSinoBIO (China)	Human adenoviral vector 5	Single dose	≥ 65%
Covaxin (BBV152 A, B, C)	Bharat Biotech (Indian)	Inactivated virus	2 doses, 4 weeks apart	≥ 77%

Variants of SARS-CoV-2

Variant of Interest (VOI)

This type of mutation of the virus might neutralize the immunity which is built by antibodies or an effective routine treatment. It might also increase the severity of the disease and its transmissibility [20,21].

Variant of Concern (VOC)

In this variant, the transmission rate of the virus significantly increases (more than 50%); so does the mortality and morbidity rate, and hospitalization. Also, this variant decreases the effectiveness of vaccines or treatment, destroying antibodies formed during vaccination or previous infections [20,21].

Variant of High Consequence

This variant leads to a much more acute illness. It can completely refrain the antibodies, which are already produced either by vaccination or by previous infection. Up to present time, no SARS-CoV-2 variant on this level has been found [20,21]. (Table 2) demonstrates the VOI and VOC.

Vaccination in Pediatrics and its Correlation with the Third Clinical Trial

According to WHO, it is essential for children to receive the recommended childhood vaccines. Children show milder infection or side effects of COVID-19 compared to adults. Thus, vaccination for children, except for children with chronic diseases or other heath conditions, is

TABLE 2

Current variants of SARS-CoV-2.

Variant of Interest (VOI)			
Variant	**Pango lineages**	**First occurrence in a country**	**Date of designation**
Eta	B.1.525	various countries,12/1/2020	17.03.2021
Iota	B.1.526	USA, 11-2020	24.03.2021
Kappa	B.1.617.1	India, 10-2020	04.04.2021
Lambda	C.37	Peru, 12-2020	14.06.2021
Variant of Concern (VOC)			
Variant	**Pango lineages**	**First date of occurrence in country**	**Date of designation**
Alpha	B.1.1.7	09-2020/ United Kingdom	18.12.2020
Beta	B.1.351, B.1.351.2, B.1.351.3	05-2020/ South Africa,	18.12.2020
Gamma	P.1, P.1.1, P.1.2	11-2020/ Brazil	11.01.2021
Delta	B.1.617.2, AY.1, AY.2	10-2020/ India	VOI 04.04.2021, VOC 11.05.2021

not a priority. WHO recommended Comirnaty from Pfizer/BionTech for children at the age of 12 and older who are at high risk of getting infected. However, there is insufficient evidence on the effectiveness of different types of vaccines in children and adolescents. It is suggested that given the satisfactory and safety immunogenicity results of vaccines, clinical trials in pediatrics should begin in parallel with phase 3 clinical trials for adults [22,23].

Fact Versus Myth of Vaccination

There are many questions asked by the common people about COVID-19, some of which are: 1. Did researchers rush to make the vaccines and is therefore the efficacy of vaccines questionable? 2. Can women's fertility be impaired after vaccination? 3. Are the side effects of vaccines in some cases fatal? 3. Can vaccines manipulate our DNA? 4. Have COVID-19 vaccines been produced with controversial materials?

Johns Hopkins University (JHU) reported that the source of all these questions and similar ones is social networks that spread misleading information. Developing vaccines has the following phases: 1. Discovery phase. 2. Preclinical phase. 3. Clinical phase. 4. Approval. 5. Manufacturing phase. 6. Quality control. The use of developed vaccines across the globe confirms their efficacy by decreasing the spread of the virus and the rate of mortality and morbidity. Thus, the facts triumph over the myths about COVID-19 vaccines [6,24,25].

COVID-19 Vaccine Boosters

The aim of vaccination is to reduce the spread of the virus as well as to protect individuals who have received full dose of vaccines from infection with SARS-CoV-2. According to the information in (Table 1), so far vaccines showed satisfactory results against COVID-19. Delta variant is categorized as a variant of concern and can spread the virus significantly more than the previous variant types. However, it is not clear whether a third dose or revaccination is required to support the fall of the first two doses and essentially to deal with viral variants particularly delta. Therefore, further investigation is required [26].

Who Needs Vaccination?

According to the WHO Strategic Advisory

Group of Experts on Immunization (SAGE), the priority of vaccination is as follows: 1. Health workers at high risk of getting sick or transmitting SARS-CoV-2 infection. 2. Older population with comorbidities. 3. Socio-demographic groups with higher morbidity and mortality risk in areas with high transmission of the virus [27].

Conclusion

Currently, there is extraordinary pressure on researchers to develop safe and effective vaccines to counter COVID-19. To do so, the selection of the proper antigen and understanding the biophysical properties of the vaccine are of great importance. The evaluation of the efficacy of a vaccine is a very complex process, particularly in the case of COVID-19. Since a new variant of SARS-CoV-2 has emerged with a large number of mutations, long-term investigation is required to confirm the safety and efficacy of novel vaccines produced versus COVID-19. Therefore, the current review is not able to report a firm conclusion regarding the efficacy and safety of the novel vaccines at this point. However, the developed vaccines can significantly reduce the morbidity and mortality rate and the spread of COVID-19.

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