

Coronavirus disease 2019 vaccine: An overview of the progression and current use

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ABSTRACT

On December 31, 2019; unidentified pneumonia cases were reported from China. It was soon announced that these cases were of viral origin and the cause was a new coronavirus (CoV). Initially, the virus was called “novel CoV ” and then defined as “severe acute respiratory syndrome CoV 2 (SARS-CoV-2)” after more detailed investigations. The disease caused by SARS-CoV-2 was named CoV disease 2019 (COVID-19) by the World Health Organization. The rapid spread of the disease in a few months has resulted in a global pandemic and it continues. However, there are no specific effective anti-viral drugs for SARS-CoV-2 infection, some antiviral drugs are using in the therapy of COVID-19 with limited success. Currently, for the prevention of the pandemic, global vaccination seems to be important. Antiviral protection of vaccines is provided by the development of antibodies that can neutralize the virus. Antibody response develops against spike protein and nucleocapsid protein but neutralizing antibodies are formed against the receptor-binding domain of the spike protein. It has also been shown that most viral proteins are recognized in T-cell responses. Vaccine discovery trials for COVID-19 have begun all over the world since the outbreak began. More than 100 vaccine studies against COVID-19 have been published in the last year. Some of them were urgently approved and used worldwide. The current study aimed to review the progression and current use of COVID-19 vaccines.

Keywords: Clinical phases; clinical trials; coronavirus disease 2019; severe acute respiratory syndrome coronavirus 2; vaccine.

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BACKGROUND OF CORONAVIRUS DISEASE 2019 (COVID-19)

On December 31, 2019, an outbreak of pneumonia was reported with unidentified etiology in Wuhan by the World Health Organization (WHO) China Office. The symptoms of these patients are fever, dry cough, dyspnea, and malaise and are diagnosed as viral pneumonia. Severe acute respiratory syndrome (SARS) has been observed in some patients. The fact that the first cases were related to the Huanan seafood

wholesale market suggested that the disease was an animal origin. The WHO first announced on January 07, 2020, that these complaints were caused by a new type of coronavirus (CoV) [1]. The virus, defined as “novel” CoV (2019-nCoV), in the sense of a nCoV that has not been detected in humans before, has become the 7th CoV that causes infection in humans. The virus was named “SARS-CoV-2” by the International Virus Taxonomy Committee Coronaviridae Working Group. The WHO named this disease “COVID-19” on February 12, 2020 [2]. COVID-19, which is transmitted from



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person to person, has become a global danger that has spread from China to other countries within months. The WHO declared a pandemic on March 11, 2020. From this date to May 08, 2021, 156,496,592 confirmed cases and 3,264,143 deaths due to COVID-19 have been reported in 223 countries [3]. In Turkey, a total of 5,016,141 cases were recorded and 42,746 death with a 3.2% mortality rate due to COVID-19 on May 8, 2021, by the Ministry of Health [4].

Although some antiviral drugs such as favipiravir, remdesivir, etc. are using in the therapy of COVID-19 with limited success, currently, there is no specific and effective anti-viral drug for SARS-CoV-2 infection. For the prevention of the disease, respiratory control measures are widely used. To prevent the pandemic, global vaccination seems to be important. Vaccine preparation studies worldwide which started with the onset of the pandemic have shown important progression. Some of these vaccine studies have completed phase 3 and started to be widely used with emergency use approval. This review aims to summarize the progression of SARS-CoV-2 vaccine studies and current use worldwide. The data of vaccines produced against COVID-19 are summarized in this study from the WHO, the National Health Institute of America, PubMed, and Web of Science database.

SARS-COV-2 VIRAL CHARACTERISTICS

Coronaviruses are enveloped positive-polarity single-stranded RNA viruses. They were named "CoV", meaning "corona" in Latin, meaning "crown" due to the rod-like extensions on their surface. Coronaviruses are a large family of viruses that can cause serious consequences such as mild cold, pneumonia, bronchitis, SARS leads to multiple organ failure, coagulopathy, and death. Coronaviruses are divided into four genera: alpha, beta, gamma, and delta coronaviruses. The majority of them have zoonotic character and they also cause diseases in humans. There are many types of CoV detected in bats, pigs, cats, dogs, rodents, and poultry. Types of coronaviruses that cause mild respiratory infections are HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1-CoV. SARS-CoV, the etiologic agent of SARS, was transmitted from civet cats and bats to humans, and Middle East respiratory syndrome CoV (MERS-CoV), the etiologic agent of MERS, from dromedary camels to humans. The 8098 cases and 774 deaths due to SARS-CoV were recorded in 29 countries, which started in South China

Highlight key points

- Current structural features of the SARS-CoV-2 virus were discussed. Current and important vaccines produced against COVID-19 were discussed. The latest situation of COVID-19 in the world and in Turkey was discussed.

in 2003, and the estimated case fatality rate was 14–15%. The outbreak of MERS has been started in Saudi Arabia in 2012, 2,494 cases were recorded in 27 countries with 858 deaths. The case fatality rate was reported as 34.4%. The last SARS-CoV case was seen in 2004, but MERS-CoV has been ongoing as multiple sporadic cases in different countries since 2012 [5]. SARS-CoV-2 is transmitted from person to person by close contact or respiratory droplets of an infected person. SARS-CoV-2 also belongs to the Betacoronavirus genus such as SARS-CoV and MERS-CoV. Coronaviruses also have the largest genome of all RNA viruses [6, 7]. Since the virus is of positive polarity, the genome is used as a direct template, and various non-structural and structural proteins are encoded. The genome of a typical CoV contains at least six open reading frames (ORF). The first ORFs (ORF1a /b) constitute approximately two-thirds of the entire genome length and encode 16 non-structural proteins (nsp 1-16), Gamacoronaviruses without nsp-1 are the exception. Non-structural proteins include viral RNA polymerase, protease, and other virus-specific enzymes involved in viral replication. From the other ORF regions that make up the remaining one-third of the genome, at least four structural proteins are encoded: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. In addition to structural proteins, in different coronaviruses, accessory proteins specific to that virus are also encoded. When CoV genome sequences were compared in different coronaviruses, 58% identity was found between regions encoding non-structural proteins, 43% between regions encoding structural proteins, and 54% at the level of the whole genome. These results suggest that non-structural proteins are more protected and maybe more diverse due to the need for adaptation to new hosts [8].

ANTIGENIC STRUCTURE FOR VACCINE CANDIDATES

Antibodies produced by a vaccine that neutralize the virus protection from viral infection. Neutralizing antibodies prevent the virus from binding to the receptor or fusing

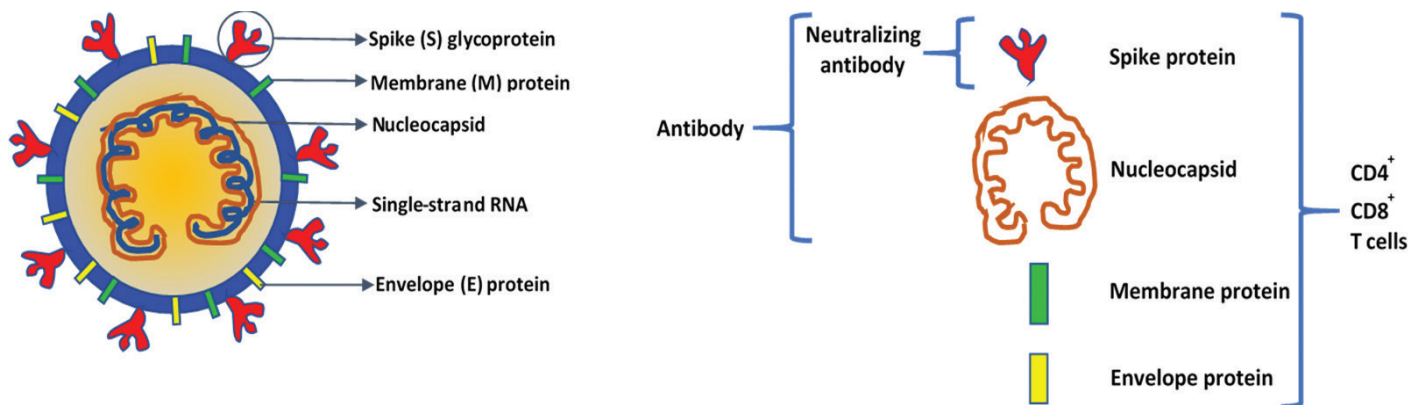


FIGURE 1. Severe acute respiratory syndrome coronavirus 2 virion structure and structural proteins.

to the cell membrane. Antibodies and immunity developed against SARS-CoV-1 have been studied in detail in previous studies [9]. Previous preclinical vaccine trials on SARS-COV-1 pioneered covid vaccine studies. Examination of the immune response to SARS-COV-2 has also accelerated vaccination studies [10]. Immune system cells target the four structural proteins of SARS-COV-2. Antibody response develops against spike (S) protein and nucleocapsid protein. Neutralizing antibodies are formed against the receptor-binding domain (RBD) of the spike protein. It has also been shown that most viral proteins are recognized in T-cell responses (Fig. 1) [11].

S protein is an important viral protein that determines host cell tropism and transmission capacity and has also been targeted for vaccine and antiviral development studies [12]. S protein; It is in the form of protrusions on the viral envelope and allows membrane fusion by binding to host cell receptors and the entry of the virus into the host cell [13]. SARS-CoV-2 enters human cells with angiotensin-converting enzyme 2 (ACE2) receptor, which is mostly found in the gastrointestinal and respiratory systems. The binding capacity of SARS-CoV-2 to the ACE2 receptor was approximately 10–20 times stronger than SARS-CoV. The higher incidence of ACE2 in adults than children also explains that adults have a higher susceptibility to infection and severe disease than children [14]. The S protein is cleaved by host cell proteases into two polypeptide fragments called S1 and S2. S1 protein is responsible for binding to the host cell receptor, and S2 protein is responsible for membrane fusion [15]. S1 subunit has N-terminal domain and C-terminal domain (CTD) and RBD is located in CTD of S1. The RBD is the main part that binds to the host cell receptor. Membrane fusion between viral and host cell membranes occurs with the S2 subunit. Both the S protein and the

RBD domain have been studied for use as antigens in vaccines. The S protein is the most common target used in most vaccines developed for SARS-CoV-2 [14].

M protein; It is the most abundant membrane protein that plays an important role in virus formation and release. The M protein, which has three transmembrane located parts, shapes the virions and provides the stabilization of the nucleocapsid protein. Thus, it provides the formation and continuation of the nucleocapsid-RNA complex. Through multiple protein-protein interactions, the M protein plays an important role in viral intracellular homeostasis. This protein is also important in the sensitization of the host cell by the virus, enabling the activation of the Interferon-beta (IFN-beta) pathway by a Toll-like receptor-dependent mechanism [6, 7].

E protein; is the smallest structural protein involved in the assembly of viral parts, virus release, and pathogenesis. Although its role in pathogenesis is not known exactly, it has been determined that the oligomerization of E proteins causes the formation of ion channels called viroporin. E protein, which makes protein activation by interacting with other proteins in the cell, is an important virulence factor that plays a role in the separation of the virus from the cell by budding. It has been found that if there is no E protein in the virus, the viral load in the host is lower. N protein; It is a protein that forms the nucleocapsid and functions primarily to bind to the CoV RNA genome. This protein plays a role in the regulation of replication and transcription of viral RNA. The N protein also acts as an IFN antagonist, thereby inhibiting the virus from trying to be destroyed by the immune system [13]. Due to its antigenic nature, N protein has been previously shown to stimulate antibody formation and cytokine production with the SARS-COV-1 virus [16].

GENERAL MECHANISMS OF ACTION OF VACCINES THAT ARE PRODUCING OR DEVELOPING AGAINST COVID-19

Vaccine discovery trials for COVID-19 have begun all over the world since the outbreak began. More than 100 vaccine studies against COVID-19 have been published in the last year, according to the reports. Based on their mechanism of action, these vaccine studies can be divided into four categories [17].

Inactivated Whole Virus Vaccines

Some conventional vaccines accomplish this by weakening or disabling the virus so that when it is introduced to the body, an immune response to the antigen can be produced without the virus causing disease. The immune system's defenses, such as antibodies and T cells, destroy the virus or infected cells when it comes into contact with the damaged virus. During this step, the immune system is primed to produce cells and antibodies that will easily attack these proteins by the specialized memory cells. As a result, the immune system will be able to combat the virus the next time it is encountered [18].

Protein Based Vaccines

Instead of using the whole virus particle, only fragments of it, such as the spike proteins, can be used to promote immunity. Since these fragments are unable to infect host cells, these subunit vaccines have the advantage of being relatively simple and inexpensive to manufacture. They are also incapable of causing disease. They are, however, less likely to be recognized by immune cells that are meant to kill infected cells, resulting in a weakened immune response. As a result, chemical adjuvants are often used in subunit vaccines. Booster shots, which are intended to stimulate a stronger immune response, may also be needed [19].

Antigens are not always introduced into the body through vaccination. Some function by causing antigens to be generated by cells in the patient's body. Virus vector vaccines and messenger RNA (mRNA) vaccines are two examples. The aim of these approaches is to get a small piece of genetic code from the target pathogen, in this case, the SARS-CoV-2 virus that causes COVID-19, into the cells of the patient. This type of vaccine mimics how viruses naturally replicate during natural infection by hijacking cellular mechanisms. Rather than making copies of the virus, however, the

cells release large quantities of antigens, which normally cause a strong immune response [20].

Vector Based Vaccines

Viral vector vaccines do this by injecting the antigen's genetic code into a harmless virus that serves as a delivery mechanism for the code into the cells while causing no disease. While developing vector-based vaccines can be difficult, they can elicit strong immune responses without the use of adjuvants. In principle, one form of a vector may deliver code for a variety of antigens, potentially speeding up vaccine production [21].

Nucleic Acid Vaccines

Nucleic acid vaccines, including mRNA and DNA vaccines, generate antigens by injecting genetic code into cells. However, rather than using viruses to transmit the code, these vaccines take a more direct approach, injecting the code directly into cells. These vaccines can be developed quickly and at a low cost. They are, however, a relatively new technology [22].

VACCINE DEVELOPMENT PHASES

Vaccines are biological products that are used to improve the body's ability to fight infectious diseases by preventing and controlling their occurrence. Vaccines are very safe and provide the best defense against a variety of severe diseases, including COVID-19. According to published evidence, several people who receive various forms of COVID-19 vaccines develop disease immunity.

The aim of the COVID-19 vaccine process development is to create a manufacturing process that can reliably produce a safe and effective vaccine, and the vaccine development process can be broken down into two stages: preclinical development and clinical development.

Preclinical development is testing that takes place in laboratories and on animals, and it involves developing vaccine concepts and evaluating vaccine effectiveness in vitro and in vivo assays. Clinical development refers to the process of a vaccine being administered in humans for the 1st time. It is divided into four phases, beginning with phase 1 of human clinical trials and ending with phase 4 of post-market surveillance. The production of clinical trials is based on strict ethical standards of informed consent from volunteers, with a focus on vaccine safety as well as efficacy [23].

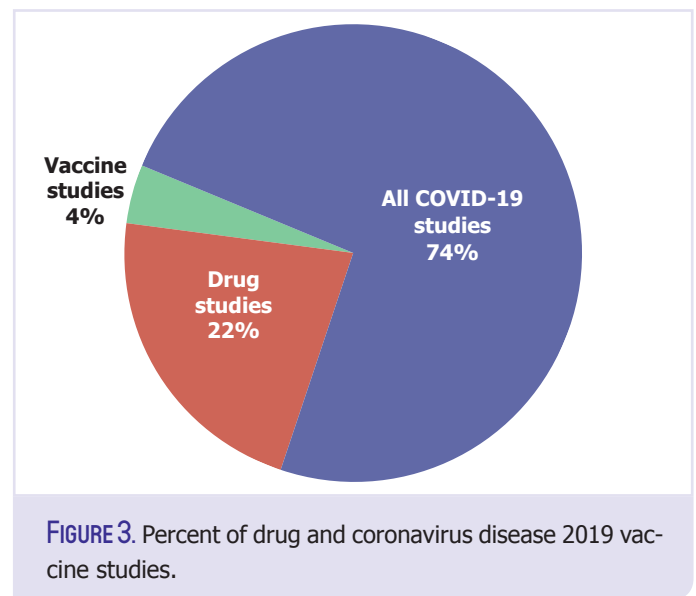
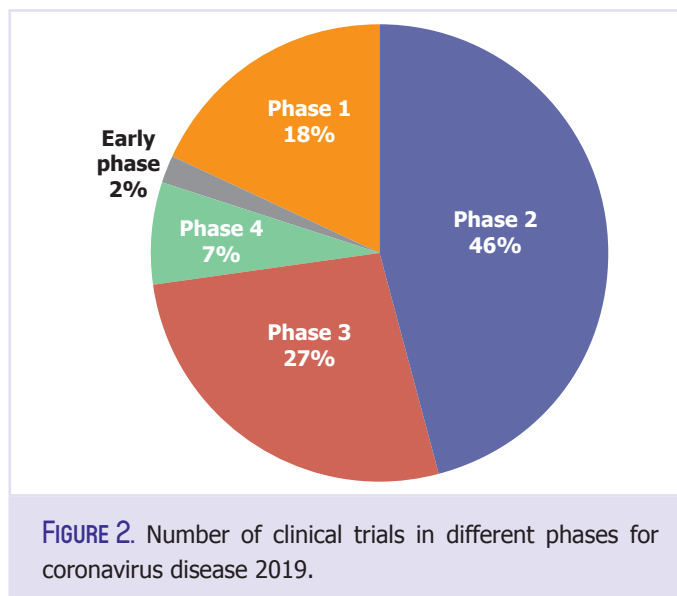


TABLE 1. Summary of emergency approved COVID-19 vaccines

Vaccine Name	Platform	Status	Number of doses	Storage	Manufacturer
BNT162b2/COMIRNATY	Nucleic acid vaccine	Finalized	2	-70°C	BioNTech with Pfizer
mRNA-1273	Nucleic acid vaccine	In progress	2	-20°C	Moderna
AZD1222	Vector based vaccine	In progress	2	2-8°C	AstraZeneca with Oxford University
CoronaVac	Inactivated vaccine	Finalized	2	Room temperature	Sinovac
Ad5-nCoV	Vector based vaccine	In progress	1	2-8°C	CanSino
Sputnik V	Vector based vaccine	Finalized	2	2-8°C	Gamaleya National Center
EpiVacCorona	Protein based vaccine	In progress	2	2-8°C	Vector State Research

Phase 1 clinical trials are small-scale tests used to see whether a vaccine is effective in humans and what kind of immune reaction it elicits. Phase 2 clinical trials take place later and are used to evaluate the vaccine's effectiveness against infection. Vaccine protection and side effects on the immune system are also investigated during this process. Phase 3 clinical trials are large-scale studies involving hundreds of participants in several locations to assess effectiveness under real-world disease conditions. If the vaccine remains safe and successful after these clinical trials, the manufacturer may apply for a commercial license. After the vaccine has been approved and put into use, the vaccine enters the fourth process, post-marketing.

According to NIH info, 42 COVID-19 vaccine and drug studies are in the early stages of development, 412 studies are in phase 1, 1050 studies are in phase 2, 629 studies are in phase 3, and 154 studies are in phase 4 (Fig. 2) [24].

EMERGENCY APPROVED VACCINES AT A GLANCE

Several vaccines have been approved under emergency use or conditional approval regulations (Pfizer 2020; Moderna 2020; Johnson and Johnson 2021; AstraZeneca 2021; Independent 2021), but not all of these vaccines have been approved in all countries, and the vaccines' long-term safety and effectiveness are uncertain. CoronaVac is approved for emergency use in Turkey (Independent 2021) [25]. In the NIH database, there were a total of 5316 COVID-19 trials, 1583 of which were drug and vaccine studies, and 275 vaccine studies (Fig. 3). Because of the pandemic situation, some of these vaccines were quickly tested and placed on the market (Table 1). This category includes the vaccines mentioned below [26].

BNT162b2/Comirnaty

Pfizer-Biontech has developed a new SARS-CoV-2 mRNA vaccine and emergency approved to use by some countries. The technology used by Pfizer-Biontech has never been used in humans before, but clinical trials have shown that it is 90% successful, which is truly remarkable. All of these factors combine to make this vaccine unlike any other previously produced vaccine. Rather than using a live virus, a dead virus, or an attenuated virus, this vaccine injects the genetic code for the S protein of the SARS-CoV-2 envelope protein into the body. Which is considered to be much better. As a result, the body believes it is being invaded by the virus and mounts an immune response that includes antibodies and T-cells. The vaccine developed by Pfizer and Biontech was also the first to be approved. The mumps vaccine was developed quickly, taking just five years, but this vaccine took less than a year to get from the lab bench to human use [27, 28].

mRNA-1273

Moderna COVID-19 Vaccine contains synthetic nucleoside-modified mRNA encapsulated in lipid nanoparticles that codes for the full-length, pre-fusion stable spike protein (S) of SARS-CoV-2.2. S glycoprotein is a large transmembrane protein involved in viral attachment, fusion, and entry into the host cell. Human cells express the SARS-CoV-2 S antigen after vaccination, and an immune response to the S antigen is elicited, resulting in defense against SARS-CoV-2 [29]. The Moderna COVID-19 Vaccine is approved for active immunization against COVID-19 caused by extreme SARS-CoV-2 in people aged 18 and up under an Emergency Use Authorization. It is given in two doses, 1 month apart (28 days) [30].

AZD1222

A virus that triggers the common cold in chimps is at the heart of the Oxford/AstraZeneca vaccine. The chimp virus has been improved to prevent it from multiplying and causing disease in humans. The gene for the CoV spike protein, the club-shaped component of the virus that dots the surface and is used to penetrate human cells, is then added. When the vaccine is given, the chimp virus transmits the CoV gene to human cells, which then begin to produce spike protein. When the immune system detects these, antibodies and other responses are generated, which can attack the real CoV if the individual becomes infected in the future.

The vaccine was found to be 70.4% protective in phase 3 trials in the United Kingdom and Brazil. The trials included over 20,000 volunteers, many of which were from the United Kingdom. Investigators found 30 cases of COVID-19 in people who received two doses of the vaccine and 101 cases in people who got a placebo. The vaccine was 62% effective in those who received two full shots. However, it tends to function best when administered as a half-dose first, then a full dose, with safety increasing to 90%.

CoronaVac

Sinovac Inc. is developing an aluminum vaccine that is formaldehyde-inactivated. This is a common method that uses killed viral particles to expose the body's immune system to the virus without triggering a severe disease response. Inactivated vaccines from China could be easier to distribute than any of the alternatives [31]. Pfizer's vaccine, for example, must be kept at -70°C , while Sinovac claims that its vaccine can be kept at $2-8^{\circ}\text{C}$ in a regular refrigerator.

Convidicea Vaccine (Ad5-nCoV)

In a clinical trial for COVID-19 in China, Convidicea (Ad5-nCoV) is the first novel CoV vaccine. CanSino-BIO's adenovirus-based viral vector vaccine technology platform is used to develop the candidate vaccine. An interim analysis of the international Phase 3 trial revealed that the vaccine was 65.7% effective, according to Pakistani officials [32]. Neutralizing antibodies and specific immunospot-assay-linked IFN responses were observed at all dose levels for most participants in the phase 2 trial, according to a paper published in *The Lancet*. The results of a phase 1 trial showed a humoral and immunogenic response to the vaccine, according to a article published in *The Lancet* [33]. Antibodies were also found to be elevated in another study conducted in Russia. Adverse reactions such as pain (54%), fever (46%), nausea (44%), headache (39%), and muscle pain (17%) occurred in 83 percent of patients in the low and medium dose groups and 75% of patients in the high dose group [34].

Sputnik V

Sputnik V is the world's first COVID-19 vaccine to be approved. It is a human vaccine that uses an adenovirus vector. Two human adenoviral vectors are injected with protein-coding genes from a CoV pulse. Vectors are vi-

ruses that have been genetically modified to prevent them from replicating, which is why they are safe for the body. Because vectors only carry protein-coding genes from the CoV spike, it is impossible to become infected during the first vaccination, vector enters a cell and immunity develops. The second vaccination with vector occurs after 21 days and boosts immunity. Sputnik V is built on a human adenovirus vector platform that has been thoroughly researched and proved to be healthy over the years. According to the manufacturer, the vaccine has a 90% efficacy score [34, 35].

EpiVacCorona

The Vektor State Virology and Biotechnology Research Center in Russia developed EpiVacCorona, a COVID-19 preventive vaccine. EpiVacCorona is an antigen-based vaccine that causes an immune response to COVID-19 and aids in the development of immunity. SARS-CoV-2 protein-peptide antigens are chemically synthesized, conjugated to a carrier protein, and adsorbed to an aluminum-containing adjuvant in the vaccine (aluminum hydroxide). After two intramuscular administrations of the EpiVacCorona vaccine, protective immunity against the SARS-CoV-2 CoV develops 21–28 days apart [36].

Conclusion

Despite intense studies and efforts, the COVID-19 epidemic, which started in the city of Wuhan in the past months of 2019, continues. It seems that our most important leverage in getting the epidemic under control and ending it will be by the vaccine. Globally, as of May 5, 2021, a total of 1,171,658,745 vaccine doses have been administered [37]. In Turkey due to health ministry 14,580,093 people received the first dose of vaccine, 10,329,269 people received the second dose, and a total of 24,909,362 people were vaccinated. Given the pandemic's scope, billions of people would undoubtedly need to be vaccinated, perhaps multiple times, and many approved vaccinations would be needed to satisfy this existing and continuing global demand.

In this review, the biological properties of the SARS-CoV-2 virus, as well as the latest vaccine studies on COVID-19 were summarized. Thanks to the intense studies carried out by different groups from different countries of the world It can be seen that humanity will overcome this pandemic with the development of more effective vaccines in the future.

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