REVIEW

DOI: 10.4274/eamr.galenos.2021.93695
Eur Arch Med Res 2021;37(3):134-40

COVID-19 Vaccines

Serkan Aydemir[1], Hatice Rumeysa Selvi[2], Muhammet Rıdvan Dumlu[1], Seçil Arıca[2], Funda Şimşek[1]

[1]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Family Medicine, İstanbul, Turkey

Abstract

The World Health Organization declared coronavirus disease-2019 (COVID-19) as a "Public Health Emergency" of international importance on January 30, 2020, and as a "Pandemic" on March 11, 2020. In the fight against coronavirus, the most important strategy in protection from the disease is the "Vaccine", due to the fact that the coronavirus is very contagious, the complications and death it causes. In this review, there is information about current vaccines, their effectiveness and studies that play a role in protection against COVID-19.

Keywords: COVID-19, vaccine, efficacy

INTRODUCTION

Inactivated Vaccines

Inactivated vaccine production is a more traditional method. Many inactivated vaccines have been developed for various viruses, such as influenza, hepatitis A, and poliovirus (1). Inactivated vaccines contain killed pathogens through physical or chemical processes; therefore, they cannot cause disease and are considered safe (2). Adjuvants are used to strengthen the immune response to vaccines (3), and their storage and transportation conditions are easier to achieve than in those of other vaccine types. They can be stored at 2 °C-8 °C. However, there are some disadvantages: i) Large amounts of virus or bacteria are needed to produce vaccines; ii) during the inactivation process, the immunogenicity of the pathogen can be affected; and iii) booster doses are generally needed to produce adequate immune response (2,4). Since the start of the coronavirus disease-2019 (COVID-19) pandemic, nine inactivated vaccines have been authorized for emergency use by many countries, so far, including CoronaVac developed by Sinovac Biotech (China), BBIBP-CorV by Sinopharm (China), and BBV152 (Covaxin) developed by Bharat Biotech (India) (5). Only two of them were approved by the World Health Organization (WHO), i.e., CoronaVac and BBIBP-CorV, as of August 2021 (6).

Phase III clinical trials of CoronaVac were conducted in China, Brazil, Turkey, Chile, Indonesia, Philippines, and Hong Kong (6), and some of them are still ongoing. The Brazilian trial demonstrated an efficacy of 51% [95% confidence interval (CI) 36-62] against symptomatic disease, whereas the Indonesian and Turkish trials presented 65% (95% CI 20-85) and 84% (95% CI 65-92), respectively. By contrast, the efficacy of vaccines against hospitalization was 100% in Turkey (95% CI 20-100) and Brazil (95% CI 56-100). In Chile, a cohort study of more than 10 million individuals was conducted. They were followed for 2 months after vaccination, and vaccine effectiveness was assessed. The efficacy rates against symptomatic COVID-19, hospitalization, intensive care unit admission, and death were 67% (95% CI 65-69), 85% (95% CI 83-97), 89% (95% CI 84-92), and 80% (95% CI 73-86), respectively (7-9). On June 1, 2021, the WHO validated the vaccine for emergency use, and 39 countries including Turkey were granted emergency use of authorized vaccines as of August 12, 2021. The efficacy of BBIBP-CorV (Sinopharm) was evaluated in the COVIV-02 study. It is being conducted in

Address for Correspondence: Funda Şimşek, University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
Phone: +90 212 221 77 77-5700 **E-mail:** fundasimsek67@gmail.com **ORCID ID:** orcid.org/0000-0002-7387-5057

Received: 27.08.2021
Accepted: 31.08.2021

Cite this article as: Aydemir S, Selvi HR, Dumlu MR, Arıca S, Şimşek F. COVID-19 Vaccines. Eur Arch Med Res 2021;37(3):134-40

Bahrain, Egypt, United Arab Emirates, and Jordan (clinicaltrials.gov, NCT04510207). Interim results showed an efficacy of 78.1% (95% CI 64.8-86.3%) against non-severe COVID-19. The WHO approved BBIBP-CorV for use on May 7, 2021, and it is being used in 59 countries as of August 12, 2021 (7). BBV152 (Covaxin) vaccine demonstrated an efficacy of 77.8% (95% CI 65.2-86.4) against symptomatic disease and 93.4% (57.1-99.8) against severe disease in a phase 3 clinical trial in India (10). This vaccine has been approved in nine countries, including Guyana, India, Iran, Mauritius, Mexico, Nepal, Paraguay, Philippines, and Zimbabwe, as of August 2021.

Variants of concern: A study revealed that serum samples obtained from individuals who received two doses of CoronaVac showed nearly the same neutralization activity against alpha (B.1.1.7) variant but significantly reduced activity against beta (B1.351) and gamma (P.1) variants (11). In another study, Wang et al. (12) revealed similar results for BBIBP-CorV vaccine against alpha and beta variants.

A report evaluating the efficacy of BBV152 showed a decreased neutralization activity against beta, gamma, delta (B.1.617.2), and kappa (B.1.617.1) variants, whereas the activity was quite similar against the alpha variant. In the same study, vaccine effectiveness was 65.2% (95% CI 33.1-83.0) against the delta variant (10). Further studies are warranted to get a better understanding of the efficacy of inactivated vaccines against new variants.

Nucleic Acid Vaccines

Nucleic acid vaccines are DNA and mRNA vaccines. DNA vaccines enable the expression of target proteins in the individual who was vaccinated. These vaccines consist of plasmid DNA containing the gene of the target protein and mammalian expression promoter regions. Its routine usage has been avoided because of drawbacks, such as low immunogenicity, reliance on mRNA for function, and possibility of being mutagenic by interacting with the recipient DNA (13). Although mRNA vaccines were originally utilized during the COVID-19 pandemic, the first studies on these vaccinations were conducted in 1989. The ability of mRNA packaged in a cationic liposomal nanoparticle (LNP) to enter multiple eukaryotic cells was first demonstrated; subsequently, when naked (unprotected) mRNA was injected into mouse muscle cells, it remained stable for several days and generated target antigens (14). These findings show that using an *in vitro* transcription mRNA molecule rather than plasmid DNA to enable the production of a targeted protein in living tissue without the use of a viral carrier is safer (vector) (14,15). Because the mRNA molecule acts in the cytoplasm rather than in the nucleus, there is no risk of insertional mutagenesis when it joins the host genome, and its structure can be destroyed by normal cellular activity; thus, its half-life can be controlled by various chemical modifications (16).

One of the most significant advantages of the molecule is that it can be turned into a more effective molecule by modifying it chemically to make it more stable and translatable (17). It is not dependent on a viral vector for *in vivo* activity and does not induce side effects caused by antivector immunization as it allows rapid uptake and expression into the cytoplasm with carrier molecules (18,19). Self-amplifying and self-replicating vaccines and conventional (non-replicating) vaccines are two types of MRNA vaccines. RNA-dependent RNA polymerases are commonly used in self-replicating mRNA vaccines to promote mRNA amplification and target antigen expression. Long-term antigen production is guaranteed in this manner; however, the vaccine has a huge molecular structure because it comprises numerous promoter regions and necessitates transport by viral vector (20).

In contrast, traditional mRNA vaccines are synthetic molecules made *in vitro* from plasmid DNA and bacteriophage RNA polymerase (15,16) The created unprotected mRNA molecules must be packed with lipid nanoparticle carriers so that they can enter the target cells via endocytosis. LNPs also shield these compounds from enzymatic degradation (21,22). Furthermore, lipid nanoparticles enable the regulated distribution of mRNA molecules in the body, allowing them to reach their target cells (16).

To induce immunogenicity, mRNA vaccines must first reach the ribosomes and ensure the production of target antigens. After this target intracellular endogenous antigen is synthesized, it is presented to CD8+ T-cells by major histocompatibility complex (MHC) class I molecules, which sensitize them. Additionally, antigen-presenting cells use MHC class II molecules to activate CD4+ T lymphocytes. This is very important in the induction of humoral immunity as well as cellular immunity. In addition, antigen-presenting cells transport the antigens to the lymph nodes, where they are transferred to non-sensitive B-cells, triggering the immunological process that leads to antibody production. Memory B-cells are activated when a vulnerable individual is exposed to target antigens again. In conclusion, mRNA vaccines provide cellular and humoral immunity by activating CD4+, CD8+ T-cells, and B lymphocytes (23-25). According to the WHO, 184 vaccine candidates are in preclinical development and 112 are in clinical trials for COVID-19, with 11 and 18 being DNA and RNA vaccines, respectively (26). Of

these vaccines, Pfizer/BioNTech BNT162b2 has been licensed by the Food and Drug Administration (FDA) for use in individuals aged >16 years and has been approved for emergency use for individuals aged 12-16 years (27). Moderna's mRNA-1.273 vaccine also has been licensed for emergency use to prevent COVID-19 (28).

BNT162b1 and BNT162b2 mRNA vaccines were created by Pfizer/BioNTech. The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) spike protein is encoded in both vaccines, which are packed with LNP and undergo nucleotide modification. In phase I/II trials, both vaccines were proven to be efficacious and safe in prime and boost vaccine regimens, and BNT162b2 was able to advance to phase II/III studies (NCT04368728) because it has milder adverse effects (29). In a phase III study including 43,000 patients aged ≥16 years, the case group received 30 µg of the vaccine, and the control group received the same quantity of saline solution at 3-week interval. Vaccine efficacy was measured 7 days after the second dose, with rates of 95% and 94.6% in those without and with a history of COVID-19, respectively. The findings of this investigation show that BNT162b2 is efficacious and safe against COVID-19 (30). The vaccine's efficacy against symptomatic disease declined with time, from 90% at the end of the second month to 84% at the end of the sixth month, according to an unpublished follow-up report that included phase III participants (31). Although the vaccine's neutralizing antibody levels were lower against beta and delta variants, investigations have indicated that it maintains neutralizing effectiveness against variants of concern (32,33). The BNT162b2 vaccination should be given in two intramuscular doses of 0.3 mL each at an interval of 3 weeks. The time between the two doses can be extended up to 42 days, but not less than 3 weeks. If the vaccine was not administered at this time, the schedule should be re-established (34,35). Because most studies involved two doses, the protective effectiveness and durability of a single dose are uncertain. Furthermore, a single-dose vaccine was found to be ineffective against the alpha, beta, and delta forms (36,37). In immunocompromised groups, such as recipients of chemotherapy, patients with hematological malignancies, recipients of hematopoietic stem cell and solid-organ transplantation, patients with human immunodeficiency virus (HIV), and others, a third dose has been advised, provided that it is given at least 28 days after the second dose (38). Local adverse effects such as redness, swelling, and pain at the injection site are common after the second dosage, whereas serious postvaccine reactions are rare. The majority of these reactions are mild and generally resolve within 2 days.

Fever, fatigue, headache, arthralgia, and myalgia are other symptoms that have been described (39). Anaphylaxis following vaccination was observed in five cases per million doses (40). Although Bell's palsy occurred during phase III clinical trials, no link between immunization and Bell's palsy was discovered (41). The surveillance system found no thrombosis-related events connected with mRNA vaccinations (42). Moderna's mRNA-1273 is another mRNA vaccination that has been licensed by the FDA for emergency use. The recommendation was to take two doses at 28 days apart. It contains the target antigen and spike protein lnp packed with the mRNA molecule (43).

Individuals aged 18-55, as well as those aged >55 years were studied in a phase I clinical trial. Despite the decline in CD8+ T-cell response, considerable CD4+ T-cell response was seen in both the groups, and they had comparable and sufficient effectiveness and safety profiles (44,45). In a phase III clinical trial, vaccination activity was shown to be 94.1% effective (14 days after the second dose) in avoiding symptomatic illness; however, adults aged >65 years accounted for 86.4% of this activity. This vaccine has also been studied with two doses, and the efficiency and safety of a single dosage are unknown (46). The side effects are comparable with those of BNT162b2 and are usually local reactions including pain, redness, and swelling at the injection site, which usually resolve within 2 days of vaccination. Fever, fatigue, headache, arthralgia, and myalgia are other symptoms that have been described. Although adverse effects are less likely to occur in individuals aged >65 years, they have been considered in this vaccine (47). Anaphylaxis was found in 2.8 cases per million doses after vaccination. A history of allergy was noted in 86% of these cases, and 90% of allergies occurred within half an hour after vaccination. In the United States, some cases of Bell's palsy are assumed to be related to the vaccine, but no link has been identified between vaccination and Bell's palsy because the rate is lower than the general population (48,49). In the United States, a case of postvaccine sinus vein thrombosis with thrombocytopenia was recorded; however, it was unclear if the link was accidental or causal and has been reported as an extremely rare side effect (49-51).

Viral Vector Vaccines

Although the traditional approach is being used when developing a vaccine to control the COVID-19 pandemic, viral vector vaccines have also been used based on molecular techniques. The basic characteristic of viral vector vaccines is that a genetic piece of the virus is transferred into another virus, and immunity is produced following administration of a vaccine to the body (52). In vaccines obtained through this method, an immune response resembling a real viral infection occurs (53). The characteristics of the carrier virus of a known structure

determine the side effects and production details of the vaccine. Thus, vaccine studies against a new and unknown pathogen can be conducted more securely. Replicable (attenuated) viruses and non-replicating (inactivated) viruses are used as carriers in these vaccines (53). Although vesicular stomatitis virus is most frequently used as a replicating carrier virus, adenoviruses are most often preferred as the non-replicating carrier virus (54). At present, carrier viruses are used in the vaccine production studies for Ebola, hepatitis C, influenza, tuberculosis, and HIV (55). By activating both cellular and humoral immunity, these vaccines produce long-term immunity. They are advantageous because they can be produced easily, can be applied to the mucosa, and are of low cost (56). In contrast, COVID-19 viral vector vaccines are based on the transfer of genes encoding the spike protein of SARS-CoV-2 via adenovirus. Although this technology was used in 17 vaccine candidates, only three adenoviral vector vaccines have been approved for use (57).

Oxford/AstraZeneca Vaccine: At the beginning of the pandemic, a viral vector vaccine, which is a gene technology product developed by transferring the genes encoding the spike proteins of SARS-CoV-2 into the non-replicating chimpanzee adenovirus, was produced in collaboration with the Oxford University and AstraZeneca (58,59). In the preclinical trials of the vaccine, high antibody levels were observed in pigs (8-59). Phase I/II studies of the vaccine, codenamed AZD1222, were conducted in England and South Africa, phase II/III studies were performed in England, and phase III studies were conducted in Brazil. A total of 23,848 volunteers aged >18 (7,548 from England and 4,088 from Brazil) participated in the four blinded, randomized controlled phase III study conducted in these three countries. In these studies, wherein vaccine efficacy was assessed based on symptomatic disease and polymerase chain reaction test, the vaccine was found to be effective against symptomatic COVID-19. As a result of the phase III trials, the efficacy rate was 62.1% in the group that received two full doses of vaccine, whereas it was 90% in the group that received half dose in the first dose and full dose at the second dose. Two doses of the vaccine are administered intramuscularly at 28 days apart (59). In the phase I/II study conducted with 1077 volunteers in England, the most common side effects associated with the vaccine were pain, fever, chills (shaking), muscle pain, headache, and weakness (58,59). Similar adverse effects were reported in phase II/III studies conducted in England, in two different centers with 560 patients, and no serious side effects were observed once again (58). Transverse myelitis developed in two individuals in the group that received two doses of the Oxford/AstraZeneca vaccine and in one individual in the control group that received meningococcal vaccine; however, no direct association with the vaccine was found (60).

Sputnik V (Gam-COVID-Vac): The Sputnik V vaccine, one of the first registered COVID-19 vaccines, was developed in Russia by the Gamaleya Institute. It is a vector vaccine developed by transferring the genes encoding the spike proteins of the SARS-CoV-2 genome into adenovirus type 26 at the first dose and adenovirus type 5 at the second dose. It was named Gam-COVID-Vac by Russia in August 2020. Sputnik V has now reached 61 countries as of December 2020, including Russia, Argentina, Belarus, Hungary, Serbia, and United Arab Emirates (61). Sputnik V, which was recognized as safe based on the results of phase I and II clinical trials, produced a high cellular and humoral immune response. Following that, in a double-blind randomized placebo-controlled study conducted in 25 clinics in Russia, 21,977 volunteers aged ≥18 years were assigned to the vaccinated group, whereas 5476 volunteers were assigned to the placebo group. The vaccine group received two doses of the vaccine at 21 days apart. The presence of COVID-19 at least 21 days following the first vaccination was assessed. COVID-19 was detected in 16 individuals (0.1%, n=14964) in the vaccinated group and in 62 individuals (1.3%; n=4902) in the placebo group; thus, its vaccine efficacy was 91.6%. The vaccine was 100% effective in preventing severe COVID-19 (62). Although mild and moderate local side effects were observed, no serious side effects were detected (62).

Johnson & Johnson (Ad26.COV2.S): This is a vaccine developed by delivering genes encoding spike proteins of SARS-CoV-2 virus via adenovirus type 26. It is the third COVID-19 vaccine to be approved for emergency use in the United States. The vaccine is administered intramuscularly as a single dose in individuals aged >18 years (63) Adverse effects and immune response were compared with the placebo group in a phase I/II trial wherein 402 volunteers aged 18-55 and >55 years were separated into two distinct cohorts. Although the most common local adverse effect is pain at the injection site, the most common systemic adverse effects were weakness, headache, and muscle pain. Neutralizing antibodies were detected in 90% of the participants 29 days after the first dose and 100% of them on day 57 (64). Phase III trials were conducted with 40,000 volunteers aged 18-100 years. Protective rates against symptomatic COVID-19 14 and 28 days after vaccination were 66.3% and 65.5%, respectively. The efficacy observed after 14 days varied by gender, age, race, and ethnic groups. The highest efficacy was 77% in the United States. Although some hospitalizations were associated with COVID-19 in 31 participants 14 days after the vaccination, 2 of them were in the vaccinated group, and no hospitalizations were noted in the vaccinated group 28 days after vaccination. The Janssen COVID-19 vaccine may be also protective against asymptomatic COVID-19 (63). Thrombocytopenia and cerebral venous sinus

thrombosis were reported in 42 women aged 18-49 years after receiving the Janssen vaccine for 1-2 weeks (60). The Centers for Disease Control and Prevention and FDA have warned against the risk of vaccine-induced thrombocytopenia and thrombosis, particularly in women aged 18-49 years (65).

Protein Subunit Vaccines

These vaccine types produce immunity by containing only the protein part of the virus without including the genetic material of the virus. Hepatitis B and pneumococcal vaccines are examples of protein subunit vaccines (66). There exist 38 vaccine candidates that are intended to produce immunity by transferring SARS-CoV-2 proteins to the human body using this method.

Novovax: Novavax, which is the first protein subunit vaccine to complete its phase III trial, was found to produce 89.7% protection in the original strain, as a result of a study conducted at 33 centers in the United Kingdom. Ten participants in the vaccinated group and 96 participants in the placebo group developed COVID-19 7 days after the second dose. Hospitalization and death were not observed in any of the 10 individuals who received the vaccine and subsequently became infected. Although a small number of mild and moderate adverse effects were observed, no serious adverse effects were detected (67).

Table 1 compares the characteristics of viral vector vaccines and protein subunit vaccines (67).

CONCLUSION

COVID-19 vaccines granted for EUA so far, are safe and effective. Vaccines are the most important tools in protection from the disease.

Development of new vaccines is still ongoing.

Table 1. Property of COVID-19 viral vector and protein subunit vaccines

Viral vector vaccines	**Advantage**	Faster and cheaper production		
	Disadvantage	Possibility of integrating the viral genome into the recipient genome, Low immune response in individuals who have previously encountered vector viruses		
	Other vaccines produced by this method	Hepatitis C, influenza, tuberculosis HIV vaccines		
Market name of vaccines	**Number of doses**	**Vaccine schedule (day)**	**Efficacy of vaccine**	**Developer country**
1. AstraZeneca, Oxford University (AZD1222, ChAdOx1)	2 doses 1. dose 1×(1/2) 2. dose 1×1	0, 28	90%	England
2. Sputnik V, Gamaleya Research Institute, Part of Russia's Ministry of Health (Gam-COVID-Vac)	2 doses	0, 21	91.6%	Russia
3. Janssen, Johnson & Johnson Pharmaceutical Company (Ad26. COV2.S)	2 doses	0, 56	74.4% (ABD) 64.7% (Latin America) 52% (South Africa)	ABD
	1 dose	0		
4. CanSino Biology, Military Academy of Medical Sciences (Ad5CoV)	1 dose	0	96-97%	China
Protein subunit vaccines	**Advantage**	Few side effects, Faster production		
	Disadvantage	Low immune response, booster vaccinatıon requirement		
	Other vaccines produced by this method	Pneumococcal vaccine, influenza, hepatitis B vaccine		
Market name of vaccines	**Number of doses**	**Vaccine schedule (day)**	**Efficacy of vaccine**	**Developer country**
1. Novavax (SARS-CoV-2 glycoprotein + matrix M)	2 doses	0, 21	89.7%	ABD
2. Medico Ing. (VLP)	2 doses	0, 21	-	Canada

HIV: Human immunodeficiency virus, COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus 2, VLP: Virus like particles

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Design: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Data Collection or Processing: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Analysis or Interpretation: S.Ar., F.Ş., Literature Search: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Writing: S.A., H.R.S., M.R.D., S.Ar., F.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369:77-81.
2. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines 2021;6:28.
3. Lee NH, Lee JA, Park SY, Song CS, Choi IS, Lee JB. A review of vaccine development and research for industry animals in Korea. Clin Exp Vaccine Res 2012;1:18-34.
4. Burrell CJ, Howard C, Murphy F, Burrell C, Howard C, Murphy F. Vaccines and vaccination. Fenner and White's Medical Virology 2017:155-67.
5. List of COVID-19 Vaccine Authorizations. Available from: https://en.wikipedia.org/wiki/List_of_COVID-19_vaccine_authorizations Accessed: 12 August 2021.
6. COVID-19 Vaccine Tracker. Available from: https://covid19.trackvaccines.org/agency/who/ Accessed: 12 August 2021.
7. Strategic Advisory Group of Experts on Immunization (SAGE) COVID-19 vaccines technical documents. Available from: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials Accessed: 12 August 2021.
8. Farma PB. Clinical Trial Report Interim II: A Phase III, Observer-blind, Randomized, Placebo-controlled Study of the Efficacy, Safety and Immunogenicity of SARS-CoV-2 Inactivated Vaccine in Healthy Adults Aged 18-59 Years in Indonesia. 2021.
9. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. The Lancet. 2021.
10. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial. medRxiv. 2021. doi: 10.1101/2021.06.30.21259439.
11. Chen Y, Shen H, Huang R, Tong X, Wu C. Serum neutralising activity against SARS-CoV-2 variants elicited by CoronaVac. Lancet Infect Dis 2021;21:1071-2.
12. Wang GL, Wang ZY, Duan LJ, Meng QC, Jiang MD, Cao J, et al. Susceptibility of Circulating SARS-CoV-2 Variants to Neutralization. N Engl J Med 2021;384:2354-6.
13. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science 2020;369:806-11.
14. Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, et al. Direct gene transfer into mouse muscle in vivo. Science 1990;247(4949 Pt 1):1465-8.
15. Duran T, Aydın Terzioğlu M, Çine N. Lipid nanoparçacık tabanlı mRNA aşı teknolojisi ve SARS-CoV-2 (COVID-19) mRNA aşıları. Canatan D, Alkan ŞŞ, editörler. Güncel COVID-19 Bilgileri. 1. Baskı. Ankara: Türkiye Klinikleri; 2021.p.47-56.
16. Verbeke R, Lentacker I, De Smedt SC, Dewitte H. Three decades of messenger RNA vaccine development. Nano Today 2019;28:100766.
17. Karikó K, Muramatsu H, Welsh FA, Ludwig J, Kato H, Akira S, et al. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther 2008;16:1833-40.
18. Kauffman KJ, Webber MJ, Anderson DG. Materials for non-viral intracellular delivery of messenger RNA therapeutics. J Control Release 2016;240:227-34.
19. Guan S, Rosenecker J. Nanotechnologies in delivery of mRNA therapeutics using nonviral vector-based delivery systems. Gene Ther 2017;24:133-43.
20. Kim J, Eygeris Y, Gupta M, Sahay G. Self-assembled mRNA vaccines. Adv Drug Deliv Rev 2021;170:83-112.
21. Midoux P, Pichon C. Lipid-based mRNA vaccine delivery systems. Expert Rev Vaccines 2015;14:221-34.
22. Zeng C, Zhang C, Walker PG, Dong Y. Formulation and delivery technologies for mRNA vaccines. In: Current topics in microbiology and immunology. Springer, Berlin, Heidelberg, 2020.
23. Sahay G, Alakhova DY, Kabanov AV. Endocytosis of nanomedicines. J Control Release 2010;145:182-95.
24. Van Nuffel AM, Benteyn D, Wilgenhof S, Pierret L, Corthals J, Heirman C, et al. Dendritic cells loaded with mRNA encoding full-length tumor antigens prime CD4+ and CD8+ T cells in melanoma patients. Mol Ther 2012;20:1063-74.
25. De Silva NS, Klein U. Dynamics of B cells in germinal centres. Nat Rev Immunol 2015;15:137-48.
26. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov 2018;17:261-79.
27. World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines Accessed on August 24, 2021.
28. Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus. Fact sheet for healthcare providers administering vaccine. https://www.fda.gov/media/144413/download Accessed on August 23, 2021.
29. Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19). Factsheet for healthcare providers administering vaccine. https://www.fda.gov/media/144637/download?utm_medium=email&utm_source=govdelivery Accessed on August 12, 2020.
30. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 2020;383:2439-50.
31. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med 2020;383:2603-15.

32. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. Available from: https://www.medrxiv.org/content/10.1101/2021.07.28.21261159v1.full.pdf

33. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. Lancet 2021;397:2331-3.

34. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 2021;596:276-80.

35. Edara VV, Pinsky BA, Suthar MS, Lai L, Davis-Gardner ME, Floyd K, et al. Infection and Vaccine-Induced Neutralizing-Antibody Responses to the SARS-CoV-2 B.1.617 Variants. N Engl J Med 2021;385:664-6.

36. Ohmit SE, Victor JC, Rotthoff JR, Teich ER, Truscon RK, Baum LL, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med 2006;355:2513-22.

37. Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - An overview. Vaccine 2017;35:4064-71.

38. Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021;385:187-9.

39. Lopez Bernal J, Andrews N, Gower C, Gallegher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385:585-94.

40. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/07-COVID-Oliver-508.pdf (Accessed on July 23, 2021).

41. Chapin-Bardales J, Gee J, Myers T. Reactogenicity Following Receipt of mRNA-Based COVID-19 Vaccines. JAMA 2021;325:2201-2.

42. CDC COVID-19 Response Team; Food and Drug Administration. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14-23, 2020. MMWR Morb Mortal Wkly Rep 2020.

43. Shimabukuro T. COVID-19 vaccine safety update, Advisory Committee on Immunization Practices (ACIP) meeting, January 27, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf (Accessed on January 28, 2021).

44. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021;385:187.

45. European Medicines Agency. EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu (Accessed on January 06, 2021).

46. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020;383:1920-31.

47. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383:2427-38.

48. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-16.

49. Normark J, Vikström L, Gwon YD, Persson IL, Edin A, Björsell T, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. N Engl J Med 2021.

50. Manisty C, Otter AD, Treibel TA, McKnight Á, Altmann DM, Brooks T, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet 2021;397:1057-8.

51. Sangli S, Virani A, Cheronis N, Vannatter B, Minich C, Noronha S, et al. Thrombosis With Thrombocytopenia After the Messenger RNA-1273 Vaccine. Ann Intern Med 2021;L21-0244.

52. Kahraman EP, Altındiş M. COVID 19 Vaccines; Towards the end of the Pandemic? J Biotechnol and Strategic Health Res 2020;4:240-9.

53. Afrough B, Dowall S, Hewson R. Emerging viruses and current strategies for vaccine intervention. Clin Exp Immunol 2019;196:157-66.

54. Azap A. COVID-19 Vaccines: Light at the end of the Tunnel. Archives Medical Review Journal 2020;29:94-100.

55. Yavuz E. COVID-19 Vaccines. Türk Aile Hek Derg 2020;24:227-34.

56. Haque A, Pant AB. Efforts at COVID-19 Vaccine Development: Challenges and Successes. Vaccines (Basel) 2020;8:739.

57. World Health Organization. Draft landscape and tracker of COVID- 19 candidate vaccines. [Internet]. Switzerland : World Health Organization; 2021 [Access date: 24 Ağustos 2021]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

58. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in youngand old adults (COV002): a single-blind, randomised,controlled, phase 2/3 trial. Lancet 2020;396:1979-93.

59. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single blind, randomised controlled trial. Lancet 2020;396:467-78.

60. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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 2021;397:99-111. Erratum in: Lancet 2021;397:98.

61. Montalti M, Solda G, Di Valerio Z, Salussolia A, Lenzi J, Forcellini M, et al. ROCCA observational study: Early results on safety of Sputnik V vaccine (Gam-COVID-Vac) in the Republic of San Marino using active surveillance. EClinicalMedicine (2021):101027.

62. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and immunogenicity 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 2021;397:671-81.

63. Oliver SE, Gargano JW, Scobie H, Wallace M, Hadler SC, Leung J, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine - United States, February 2021. MMWR Morb Mortal Wkly Rep 2021;70:329-32.

64. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021;384:1824-35.

65. Centers for Disease Control and Prevention (CDC). Selected Adverse Events Reported after COVID-19 Vaccination. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html (Access date: 25 August 2021).

66. Ho, Gibaldi. Biotechnology and Biopharmaceuticals (Transforming Proteins and Genes intoDrugs). Hoboken, New Jersey: John Wiley & Sons, Inc. ISBN 0-471-20690-3 Copyrght© 2003.

67. Heath PT, Galiza EP, Baxer DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. New England Journal of Medicine, 2021.