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Effectiveness of COVID-19 Vaccines and Antiviral Therapies in the Era of SARS-CoV-2 Variants

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ABSTRACT

Since December 2019, the respiratory infection coronavirus disease 2019 (COVID-19) has been responsible for a major pandemic. Several mutations and variants have emerged and been seen throughout the pandemic. They eventually spread to various continents and nations. The most effective method of preventing illnesses from the past till the present has been vaccination. As a result of the advancement of vaccinations, numerous nations have begun immunizing global target groups. From the start of COVID-19 to the present, there aren't many possibilities for therapy. Data indicate that the rapid evolution and transmission of SARS-CoV-2 variants poses a danger to the effectiveness of currently available medications. As a result, the COVID-19 pandemic brought to light a serious public health issue that had an impact on everyone in the world. Along with the pandemic's rapid speed, new targeted vaccinations and medical therapies have reduced fears to some extent. Clinical phase studies are still being conducted in various areas because it is evident that the initial antiviral medications approved for use in the treatment of COVID-19 are ineffective in severe cases. Anti-vaccination, however, is one of the most serious barriers to vaccination, which is thought to be vital in the prevention of illnesses. Lack of information, incorrect information, and misguided religious beliefs can all contribute to anti-vaccination. With the advent of SARS-CoV-2 variants, we review the literature to provide an up-to-date overview of the features and efficacy of antiviral therapy and vaccines.

Keywords: Antiviral therapy, COVID-19, SARS-CoV-2, vaccine, variants

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INTRODUCTION

Since December 2019, a dangerous pandemic caused by the respiratory infection coronavirus disease 2019 (COVID-19) has been ongoing. With an upsurge in instances during the past 2 years, it has been the source of substantial morbidity and mortality (1, 2).

Positive-stranded RNA virus SARS-CoV-2, which causes COVID-19, is a member of the Betacoronavirus subgroup. The pointed structures in the glycoprotein structure emerging out of the envelope are called S (spike) proteins. The envelope and the M (membrane) proteins buried therein are important in the formation and separation of virions within the cell. The SARS-CoV-2 virus binds to angiotensin-converting enzyme-2 (ACE2) receptor in organs such as the heart, kidney, and lung via the receptor binding region of the S protein. The cellular transmembrane protease serine 2 (TMPRSS2) is also crucial for SARS-CoV-2 cell entrance. Viral antigens entering the host cell are presented by antigen-presenting cells. MHC-I and MHC-II molecules also contribute to antigen presentation. Antigen presentation virus specific B and T cell stimulates mediated humoral and cellular immunity, and a cytokine storm develops release of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL6) and chemokines (CCL2, CCL3, CCL5). A significant systemic inflammatory reaction occurs, which can progress from acute respiratory distress syndrome to multiple organ failure and death. SARS-CoV2, which is an RNA virus, cannot correct errors that occur during replication as in DNA molecules, so many more variants could emerge (3).

In this review, we reviewed the literature to conduct an up-to-date analysis of the features and efficacy of antiviral medication and vaccines in the era of SARS-CoV-2 variants. We searched for relevant studies in the PubMed, UpToDate, Web of Science, and Google Scholar databases between December 30, 2020 and September 10, 2022. The search terms used were "SARS-CoV-2," "variants," "COVID-19 vaccines," and "COVID-19 antiviral therapy."

SARS-CoV-2 Variants

Mutation in the SARS-COV-2 virus is described as the sequence changes that develop in the RNA during replication, and the variant refers to new viruses that evolve as a result of various mutations. In COVID-19, the D614G mutation was initially discovered in the receptor binding location of the S protein. It was found that this mutation increased the binding of the S protein to the ACE2 receptor and increased infectiousness. During the pandemic, several mutations and variants have surfaced. N501Y, E484K, K417N, K417T, Y453F, and

L452 mutations were observed, respectively. These are known to boost the affinity for ACE2 7–19 times. N501Y was first seen in B.1.1.7 and later in B.1351 and P1 variants. E484K, K417N, and K417T mutations were also seen in B.1.351 and P.1 variants. The variants were divided by the WHO on June 15, 2021, into two groups, Variant of Concern (VOC) and Variant of Interest (VOI). VOCs are defined as Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28.1 or P.1), Delta (B.1.617.2), and Omicron (B.1.1.529), respectively. VOIs are defined as Epsilon (B.1.427/B.1.4 29), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), and Lambda (C.37). Over time, they spread to various continents and countries (4, 5).

The Alpha variant, which was defined in the United Kingdom, had been one of the most prevalent variants until the Delta variant emerges and had been contagious at a rate of 50%–75%. Beta variants are defined as 20H/501Y.V2. It has been first discovered and propagated in South Africa; however, it has not become a global dominant variant. Gamma identified as 20J/501Y.V3 did not become a globally dominant variant. Only increased infectivity due to some mutations in variant and its impacts on the immune system have raised concerns. Delta is extremely contagious and causes hospitalizations for serious illnesses. Studies have shown that while the efficacy of the vaccines decreases over time in symptomatic cases developing with the Delta variant, it remains effective in preventing hospitalizations (1, 2, 6).

The Omicron variant appeared to spread more quickly than the initial SARS-CoV-2 strain, causing significant infection. The original Omicron variant was the BA.1 subline, but in several nations, the BA.2.12.1, BA.4, and BA.5 subline BA.2 have become the worldwide common variants. Information on the severity of infections brought on by the Omicron subtypes BA.4 and BA.5 are still lacking (2, 6). However, according to the most recent CDC data, as of August 2022, about 88% of COVID-19 patients in the United States were infected with the BA.5 strain. Recently, worldwide monitoring information revealed the appearance of the new Omicron variant BA.4.6. It is stated that it spreads quickly in the United Kingdom and 3% of cases are infected with this variant. In addition, it was reported that the spreading rate was 36 times greater than Omicron BA.5. As of CDC reports, it is currently at the level of 7.5%. It was discovered that the virus developed due to an R346T mutation in the spike protein (7, 8).

COVID-19 Vaccines

It is widely acknowledged that effective vaccines from the past to the present are the most crucial prevention methods for infections. Since its inception, multiple vaccines have been created and proven to be safe and effective for immunization against COVID-19. With the advancement of vaccines, numerous nations have begun to immunize global target groups (9).

The usefulness of vaccines, one of the most crucial protection strategies against COVID-19, in lowering the risk of SARS-CoV-2 infection has been determined by clinical investigations (10). Particularly its effectiveness has been demonstrated to be better in healthcare personnel who can receive complete dose vaccination. At the time of this research, 199 vaccines are preclinical, and 172 vaccines are now under clinical development according to global data (11).

It has been declared by the WHO that the vaccines manufactured by AstraZeneca/Oxford, Johnson and Johnson, Moderna, Pfizer/BioNTech, Sinopharm, Sinovac, Covaxin, Covovax, Nuvaxovid, and CanSino meet the safety criteria for efficacy against COVID-19 on April 8, 2022. There are four different COVID-19 vaccines that have been licensed for use in the United States: two mRNA vaccines (mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech)), an adenoviral vector vaccine (Ad26.COV2.S (Janssen/Johnson &Johnson)), and an adjuvanted recombinant protein vaccine (NVX-CoV2373 (Novavax)). However, only four vaccines have been approved by the European Medicines Agency in the European Union. These are BioNTech, Moderna, Vaxzevria (formerly COVID-19 Vaccine AstraZeneca), and Janssen. Additionally, three vaccines remain in the research phase, namely, CVnCoV (CureVac AG, Tübingen, Germany), NVXCoV2373 (Novavax CZ AS, Gaithersburg, MD, USA), and Sputnik V (Gam-COVID-Vac, Gamaleya National Center for Epidemiology and Microbiology, Moscow, Russia) (1, 9).

The primary target in COVID-19 vaccines is the surface spike protein, which binds to the ACE2 receptor on host cells and subsequently promotes membrane fusion. These antibodies produced after vaccination bind to the receptor binding site of the S protein and may stop the virus from adhering to the host cell. These recently designed vaccines create antibodies specific to S proteins and can induce anti-S Ig G antibodies with neutralizing efficacy. Available evidence also suggests that the humoral immune response to the virus receptor binding region and S protein appears to be especially protective (6).

In COVID-19, after receiving the first vaccine dose, the immune system recognizes the virus and gets the body ready for battle. Following the second dose, immunity is improved by producing many antibodies again, and memory cells are also stimulated. In clinical investigations, it has been demonstrated that the booster dose raises the level of antibodies and strengthens immunity to COVID-19. Studies have shown that mRNA-1273 stimulates CD4 T cells roughly 6 months after the second dose, whereas BNT162b2 promotes memory B cells 6 months after two doses. These particular cells are necessary for the long-term protection of SARS-CoV-2. But the duration of mucosal immunity for the protection against COVID-19 is unknown. Initial investigations examine whether COVID-19 vaccines include three crucial criteria to evaluate their long-term efficacy. These are the immune response to novel SARS-CoV-2 variants of infection, long-term antibody response to the virus, and vaccine adverse effects (1, 12, 13). Data from the Pfizer/BioNTech vaccine trial found that the effectiveness of the vaccine against symptomatic COVID-19 was 52% and 95% after the first and second doses, respectively (14). It was found that the Oxford/Astra Zeneca vaccine offered 76% protection in a single dose and 81% protection after the second dose (15).

Numerous studies have published results reporting the effectiveness of the COVID-19 vaccine around the world, but the findings are still debatable in the age of variations. Particularly, thorough meta-analyses would be more accurate to assess the effectiveness of vaccines against mutant strains (1). The data on vaccine efficacy against Omicron are from studies performed when sublineages BA.2 and BA.1 were taken and are limited to subgroups BA.4 and BA.5 which emerged recently. The vaccine potency for the Omi-

cron compared with other variants wanes after several months; but effectiveness against serious illness has remained largely high, among those who received a booster dose. The neutralizing antibody level in the serum of previously vaccinated individuals is also supported by study findings, which are reduced against Omicron when compared to the original Wuhan strain and Delta variant. There was no detectable neutralizing effect against Omicron in the majority of fully vaccinated and noninfected individuals. It is reported that vaccinated and infected individuals maintain sufficient neutralizing antibody titer against Omicron subgroups BA.1 and BA.2; although it is lower in BA.4 and BA.5 subgroups of these species, it is still above the expected level. According to unpublished findings, booster doses of investigated forms of current mRNA vaccines appear to elicit higher levels of neutralizing action against other variants (including the Omicron subgroup B.4 and B.5) than booster doses with the original vaccines (16, 17).

In the completely immunized groups, vaccine effectiveness (VE) for the prevention of Alpha, Gamma, and Delta variants was reported at 85%, 54%, and 74%, respectively (18). Only one trial provided evidence of the 75% effectiveness of the vaccine in preventing infection caused by the Beta variant of SARS-CoV-2 infection. BNT162b2 vaccine efficiency was the highest in each variant group globally: 92% for the Alpha, 62% for the Gamma, and 84% for the Delta variants. The mRNA-1273 vaccine also exhibited the highest VE of 97% for variant strains. In another study, the effectiveness of the Sputnik V vaccine against the Delta variant was found to be 83% effective (19). In a research conducted in Brazil, where SARS-CoV-2 is known to be present and 75% of the agents are P.1 variant, the efficiency of Sinovac-CoronaVac in symptomatic infections was found to be 49.6%. The efficacy of vaccine against Alpha/Gamma/D614G strain was 36.8%–73.8% (20, 21). Ad26.COV1.S vaccine demonstrated an efficacy of 60%–85% against Delta variants. The effectiveness of the AstraZeneca-Oxford vaccine in symptomatic COVID-19 illness was 67% against Delta variants and 74.5% against Alpha variants. Collie et al., in their study assessing the impact of the AstraZeneca-Oxford vaccine on variants, found that the vaccine provided more limited protection for variant B.1.351 compared to B.1.1.7. However, insufficient data are still available for the effects of both vaccines on the Omicron variant (21, 22).

According to a report from an African health system, the effectiveness of two doses of BNT162b2 was 33% against any infection of variant, and effectiveness against the hospitalization associated with the Omicron surge was 70%, but VE against hospitalization during the Delta surge was 93%. Another US study found that a three-dose mRNA vaccine's protection against hospitalization during the Omicron spike ranged from 82% to 90%, while the Delta variant's efficiency was 94% (23, 24).

A strong humoral reaction to the Beta variant and other unsettling variants has been observed after booster doses of Moderna and Pfizer vaccines (at least 6 months after the second doses) (22). In a study testing the efficacy of the mRNA-1273 vaccine against Delta, the effectiveness was 57.4% 2 weeks after the first dose and 80.2% 2 weeks after the second dose (23). In the phase II study of the NVX-CoV2373 vaccine, it was found that the neutralizing antibody titer increased four times following the booster doses. A sixfold increase in antibodies against the Delta has also been reported (25).

Omicron BA.5, which first appeared in January 2022, has been demonstrated to spread more quickly than other subvariants. When monoclonal antibody responses were studied, it was shown that BA.4/5 had a two- to threefold decrease in neutralization antibody levels in sera from those who received three doses of BioNTech or AstraZeneca vaccines compared to BA.1 and BA.2 (26).

Against the BA.4.6 variant, one of the Omicron subvariants that has been on our agenda recently, Oxford University reported that people vaccinated with three doses of Pfizer had a lower response rate than BA.4 or BA.5. This troubling circumstance suggests that COVID vaccines would be less effective against BA.4.6 (27).

Finally, bivalent mRNA vaccines, popularly known as "Variant Vaccine," were given emergency use approval on August 31, 2022, by the US Food and Drug Administration (FDA). These are bivalent vaccines that allow the production of antibodies against the original Wuhan strain as well as the Omicron BA4/BA5 variants. Vaccination is advised for persons aged 18 years or older who have finished their primary vaccination, have been vaccinated with mRNA vaccine, and have had their last vaccination at least 2 months prior. Bivalent vaccines are advised as a booster dose in people who have received at least two doses of mRNA vaccine. It is comparable to current vaccines in terms of side effects (7, 28). In the table below, we have attempted to summarize the effectiveness of vaccines against COVID-19 mutations according to studies (Table 1).

COVID-19 Therapies

Few therapy options are available from the beginning of COVID-19 to the present. According to data, the rapid evolution and transmission of SARS-CoV-2 variants threaten to reduce the effectiveness of currently available medications. Studies are still ongoing for numerous antiviral therapies that are directly effective against SARS-CoV-2.

These antiviral medicines used for COVID-19 can be divided into two categories: compounds that act on viral replication and monoclonal antibodies (mAbs) that target spike protein. It is known that there is a mutation in RNA-dependent RNA polymerase (RdRp), which is essential for antiviral medicines, in the Omicron variant. In preclinical investigations, three antiviral medications (remdesivir, nirmatrelvir, and molnupiravir) which are expected to be effective against the Omicron variant have been discovered. Remdesivir, an RdRp inhibitor, has been approved by the FDA for use in symptomatic hospitalized COVID-19 patients. This medication can be utilized in the first stages of high-risk patients with COVID-19. The most significant drawbacks are emerging resistance to particular forms, variable plasma concentrations, and intravenous delivery. Some statistics indicate that some new antiviral medications are being developed, such as plitidepsin, because remdesivir has not sufficiently responded to the treatment of variants. More research determining the effectiveness of combination therapy with remdesivir in the treatment of immunocompromised patients and attenuated SARS-CoV-2 strains are required (29). In a study from Türkiye, although remdesivir is a well-tolerated medication, advanced age, inadequate oxygenation, and hospitalization in the intensive care unit were indicated to be risk factors independent of mortality in moderate/severe COVID-19 patients receiving remdesivir therapy (30). Molnupiravir (MK-4482 or EIDD-2801) and Paxlovid are oral antiviral medications that have

Table 1. Efficacy of COVID-19 vaccines against variants

COVID-19 vaccines	Manufacturer	Type of vaccine	Author	Efficacy against COVID-19 variants
BNT162b2	Pfizer/BioNTech	RNA-based	Liu et al. Abu-Raddad LJ et al.	• Effectiveness was 92% for the Alpha, 62% for the Gamma, and 84% for the Delta variants
mRNA-1273	Moderna	RNA-based	Abu-Raddad LJ et al.	• Effectiveness was 97% for different strains
AZD1222 ChAdOx1 nCoV-19	AstraZeneca/ University of Oxford	Nonreplicating viral vector	Fiolet et al. Gavin et al. Hung et al.	• Effectiveness was 74.5% against Alpha, 67% against Delta variant • More limited protection for variant B.1.351 compared to B.1.1.7
Gam-COVID-Vax Sputnik V	Gamaleya Research Institute	Nonreplicating viral vector	https://www.reuters.com/ business/ healthcare pharmaceuticals/ russias-sputnik-v-shotaround-83-effective-against-delta-variant-health-minister-2021- 08-11/. (Accepted 16.09.2022)	• Efficiency was 83% against Delta variants
Ad26.COV2.S	Johnson&Johnson	Nonreplicating viral vector	Fiolet et al.	• Efficacy was 60%–85% against Delta variants
CoronaVac	Sinovac Biotech	Inactivated virus	Supasa et al.	• Efficacy in symptomatic infections was shown to be 49.6% • Efficiency was 36.8%–73.8% against Alpha/ Gamma/D614G strain

received FDA approval intended for high-risk outpatients with mild to moderate COVID-19. Molnupiravir prevents replication of the virus, similar to remdesivir, and is used in the early stage of the illness. The clinical application of molnupiravir, due to the potential for prenatal damage, cartilage growth, and genotoxicity abnormalities, has largely been constrained. Studies show that molnupiravir keeps its *in vivo* activity against Beta and Alpha strains and *in vitro* activity against Delta and Omicron strains. Additionally, the data demonstrating *in vivo* activity against Delta or Omicron variants are currently not available, and there is uncertainty that a high replication rate may change the effectiveness of the medication (31). Nirmatrelvir which is used in the treatment of mild to moderate instances of COVID-19 prevents the SARS-CoV-2 protease, thereby inhibiting virus proliferation. Regardless of vaccination status, nirmatrelvir is advised by the National Institutes of Health as the first choice of antiviral medication for outpatients at risk for infection. In clinical investigations, hospitalization and death rates from COVID-19 were significantly lower in patients 65 years of age and older who took nirmatrelvir than those who did not. No discernable difference was found in young people. Nirmatrelvir exhibits antiviral efficacy when used with ritonavir, an HIV protease inhibitor. The medication in its packaged form with the pharmacokinetic enhancing agent ritonavir is identified by the name Paxlovid. Nirmatrelvir has *in vitro* activity against the BA.1 Omicron variant and its *in vivo* effects have not yet been reported. Paxlovid, an active 3C-like (3CL) protease inhibitor, is an oral broad-spectrum antiviral effective against COVID-19 and has 90% protection against hospitalization. Potential drug-drug interaction is a major drawback of Paxlovid. Although Paxlovid has been demonstrated to be effective for Delta and Omicron, effects on Omicron subgroups have not yet been established. Clinical research is still being conducted. EIDD-1931 (β-D-N4-hydroxycytidine) is another RdRp inhibitor created to combat several RNA viruses (32, 33).

One of the biggest issues in the future with new variants in the treatment of COVID-19 is drug resistance. For instance, it is believed that the use of antiviral medications targeting the host, such as plitidepsin, may prevent future resistance. Plitidepsin is an inhibitor of eukaryotic translation elongation factor 1 alpha, which is also essential in virus replication. In preclinical investigations, this medication, known to be effective against SARS-CoV-2, has been shown to suppress growth, and there are also precautions with its use (34).

Monoclonal antibodies are new medications created for use in the treatment of COVID-19, which bind to the virus and neutralize it. They are recombinant proteins made from B cells of humanized mice or post-COVID patients and provide passive immunization. It is also believed to be efficient for prophylaxis in severe COVID-19 patients. The neutralizing monoclonal antibodies that LY-CoV555 (bamlanivimab), COV2-2196 (tixagevimab), REGN10987 (mdevimab), S309 (sotrovimab precursor), REGN10933 (casirivimab), COV2-2130 (cilgavimab), LY-CoV016 plus LY-CoV555, REGN10987 plus REGN2109-2196 plus COV2-2130 (35).

In the treatment of mild to moderate COVID-19 patients, bamlanivimab was initially licensed for emergency use as monotherapy by the FDA, and later it was approved for use in combination therapy with etesevimab. In a randomized clinical investigation, a significant reduction in viral load was detected in combination therapy compared to monotherapy. The efficacy and safety of

Table 2. Effectiveness of antiviral medications against COVID-19 variants

Antiviral drugs	Mechanism of action	Author	Efficacy against COVID-19 variants
Remdesivir	RdRp inhibitor	Vangeel et al.	• Effective *in vitro* against all VOCs including Omicron
Molnupiravir	RdRp inhibitor and deadly mutagenesis	Painter et al. Vangeel et al.	• Effective *in vivo* against Alpha and Beta variants • Effective *in vitro* against Delta and Omicron variants
EIDD-1931	RdRp inhibitor created to combat several RNA viruses	Vangeel et al.	• Effective *in vitro* against all VOCs including Omicron
Nirmatrelvir/ritonavir (Paxlovid)	Nirmatrelvir: 3CL protease inhibitor Ritonavir: CYP 3A4 inhibitor	Hung et al.	• Effective against Alpha, Beta, Gamma, Delta, Lambda, and Omicron variants *in vitro* • Real-world evidence of antiviral effect of Paxlovid against Omicron variants has not yet been documented
Plitidepsin	eEF1A inhibitor	White et al.	• Effective against B.1.1.7 variants
Monoclonal antibodies			
Bamlanivimab (LY-CoV555)	Neutralizing monoclonal antibody intended for the treatment of mild to moderate COVID-19	Gottlieb et al. Vangeel et al. Kumar et al.	• Resistant to Omicron BA.1 • Against Delta, it is understood that bamlanivimab loses activity *in vitro*
Etesevimab	Bind to the overlapping epitopes in RBD		• Resistant to Omicron BA.1 • Against Delta, it is well-established that etesevimab provides protection
Casirivimab plus imdevimab (REGN10933 plus REGN10987)	Combination of two neutralizing immunoglobulin gamma 1 (IgG1) recombinant human monoclonal antibodies against the SARS-CoV-2 spike protein		• Resistant to Omicron BA.1 • Against Beta and Gamma variants, it is known that casirivimab loses its efficacy *in vitro*, while imdevimab protects it
Sotrovimab S309 (sotrovimab precursor)	mAb that binds to conserved epitope on the spike protein RBD		• Resistant to Omicron BA.2 • Omicron BA.4 and BA.5 unlikely to be active • Active against the Omicron BA.1 and BA.1.1 subvariants
Bebtelovimab	mAb that binds to the spike protein and is unmodified in the Fc region		• Omicron BA.1 and BA.2 active • Omicron BA.4 and BA.5 active
Tixagevimab plus cilgavimab (COV2-2196 plus COV2-2130)	mAbs that attach to nonoverlapping epitopes of the spike protein RBD		• Only for pre-exposure prophylaxis • Tixagevimab component is ineffective against any of the Omicron subgroups • Cilgavimab component is ineffective against BA.1 and BA.4/BA.5 while still being effective against BA.2

a single dose of casirivimab and indevimab infusion were compared with a placebo in a phase I/II/III placebo-controlled study in patients who were COVID-19 positive, symptomatic, and not hospitalized within the following 3 days. Following the study, the FDA approved the combination medication of casirivimab and imdevimab for emergency use in COVID-19 (36). *In vitro* studies have found that bamlanivimab, etesevimab, and casirivimab plus imdevimab are resistant to Omicron BA.1 and sotrovimab was resistant to Omicron BA.2. Combination of tixagevimab plus cilgavimab was recommended only for pre-exposure prophylaxis based on research. It is known that while the tixagevimab component is ineffective against any of the Omicron subgroups, the cilgavimab component is useless against BA.1 and BA.4/BA.5 while maintaining its potency against BA.2. Also, against Beta and Gamma variants, it is known that casirivimab loses its activity *in vitro*, while imdevimab protects it. Against Delta, it is known that bamlanivimab loses effectiveness *in vitro*, but etesevimab offers protection. The main drawback of monoclonal antibody treatments is the unknown bioavailability of IgG produced in the tissues affected by the infection. Infusion-related allergic reactions have been reported in patients (37).

Clinical data on the effectiveness of monoclonal antibodies and antiviral medications in the treatment of patients infected with BA.4 or BA.5 subvariants are limited. In several tests, bebtelovimab has been proven to be effective against BA.4 and BA.5. However, these variants have been revealed to be less responsive to the combination therapies of casirivimab plus imdevimab and tixagevimab plus cilgavimab. It was also claimed that sotrovimab could not provide effective treatment against BA.4 or BA.5 (38). In the table below, we have attempted to summarize the effectiveness of antiviral medications against COVID-19 variants according to studies (Table 2).

Due to this, with the emergence of the COVID-19 pandemic, a significant global health issue that affected the whole world was brought to light. The new variants that appeared as a result of mutations of the virus raised serious concerns. Along with the speed of the pandemic, the development of new targeted vaccines and medical therapies has reduced fears to some extent. When the effectiveness of currently available COVID-19 vaccines was assessed, it was shown that they could offer some protection against illnesses and fatalities brought on by all current variants. However, it was shown that their effectiveness deteriorated over time due to the drop in antibody response rates. However, the goal of updated vaccines should be to offer broader and more durable protection against future variants. As a result, it can lower the likelihood of the spread and emergence of new variants in immunocompromised individuals. Bivalent vaccines created with this idea seem to be able to suit today's needs. Additionally, it is evident that the first approved antiviral medications for use in the treatment of COVID-19 are not effective in severe cases, and clinical phase studies are still ongoing in some. It has been noted that monoclonal antibody therapies used in the treatment of mild to moderate COVID-19 variant cases in hospitalize or outpatient treatment and in postexposure prophylaxis exhibit modest efficacy and good safety. Although monoclonal antibodies among these medications appear promising at this time, the necessity of the treatment may need to be reexamined in light of their high costs and potential side effects. For all of these reasons, additional research is required.

When seen broadly, one of the most significant barriers to vaccination, which is acknowledged as one of the crucial criteria for preventing illnesses all around the world, is anti-vaccination. The WHO views anti-vaccination as a serious public health threat, particularly in low-middle-income countries. Anti-vaccine may be due to misguided religious beliefs, lack of knowledge, and incorrect information. Although anti-vaccination percentages can vary in high-income countries, they have been estimated to be 30% or higher. Anti-vaccination behaviors due to misinformation in the population can cause disruptions in the vaccination program and an increased risk of epidemics. These opposing detrimental attitudes are founded on conspiracy theories that trigger autoimmune diseases, causing autism and infertility. Also, these theories include a history of not having the flu shot, belief in low risk of catching COVID-19, disbelief in the seriousness of COVID-19, less fear of infection, and safety concerns about the rapid development of vaccines. Therefore, efforts to offer correct information about COVID-19 vaccines and decrease conspiracy theories must be made to boost the acceptance of the COVID-19 vaccines (39).

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