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Update on the effectiveness of COVID-19 vaccines on different variants of SARS-CoV-2

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ABSTRACT

It has been more than three years since the first emergence of coronavirus disease 2019 (COVID-19) and millions of lives have been taken to date. Like most pandemics caused by viral infections, massive public vaccination is the most promising approach to cease COVID-19 infection. In this regard, several vaccine platforms including inactivated virus, nucleic acid-based (mRNA and DNA vaccines), adenovirus-based, and protein-based vaccines have been designed and developed for COVID-19 prevention and many of them have received FDA or WHO approval. Fortunately, after global vaccination, the transmission rate, disease severity, and mortality rate of COVID-19 infection have diminished significantly. However, a rapid increase in COVID-19 cases due to the omicron variant in vaccinated countries has raised concerns about the effectiveness of these vaccines. In this review, articles published between January 2020 and January 2023 were reviewed using PubMed, Google Scholar, and Web of Science search engines with appropriate related keywords. The related papers were selected and discussed in detail. The current review mainly focuses on the effectiveness and safety of COVID-19 vaccines against SARS-CoV-2 variants. Along with discussing the available and approved vaccines, characteristics of different variants of COVID-19 have also been discussed in brief. Finally, the currently circulating COVID-19 variant i.e Omicron, along with the effectiveness of available COVID-19 vaccines against these new variants are discussed in detail. In conclusion, based on the available data, administration of newly developed bivalent mRNA COVID-19 vaccines, as booster shots, would be crucial to prevent further circulation of the newly developed variants.

1. Introduction

The first emergence of SARS-CoV-2 infection and COVID-19 disease was reported in Wuhan city of China in late 2019. COVID-19 soon became a pandemic [1] and to date (October 30th 2022), more than 635 million cases have been identified to be infected with SARS-CoV-2 among which at least 6.59 million cases died due to COVID-19. Numerous complications including respiratory symptoms and lung involvement [2], acute respiratory distress syndrome (ARDS) [3], cytokine release syndrome [4], septic shock [5], gastrointestinal disorders [6], psychotropic and mood disorders [7,8], neurologic dysfunction [9,10], hematologic complications [11], and renal dysfunction [12] were associated with COVID-19. In this regard, COVID-19 complications and multi-organ failure were most commonly reported in patients with predisposing diseases [13]. Various therapeutic options have been considered in the management of COVID-19 with different severities [13,14] including antiviral [15], anti-inflammatory [16,17], anticoagulant [18], and immunomodulatory agents [19,14]. Furthermore, several miscellaneous agents [20–22] and supplementary micronutrients [23–25] are also considered in order to minimize COVID-19 complications. Besides all the efforts made in the management of COVID-19 infection, pharmacotherapy in these individuals still remains a challenge [26]. In this regard, the recruitment of COVID-19 vaccines to prevent SARS-CoV-2 infection and/or reduce its severity and

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transmissibility was a pivotal task. Different vaccine platforms have been considered in the design and development of COVID-19 vaccines including inactivated vaccines, nucleic acid-based vaccines (mRNA and DNA vaccines), protein-based vaccines, and adenovirus-vectored vaccines [27–29]. In this regard, Food and Drug Administration (FDA) approved the first COVID-19 vaccine, the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®), an mRNA-based vaccine, on 23rd August 2021 [30]. Various COVID-19 vaccines with different platforms were considered and received approval by the FDA and/or World Health Organization (WHO) [31]. Although the role of COVID-19 vaccines in the prevention of SARS-CoV-2 infection and/or reduction of hospitalization and mortality rates has been confirmed, still, concerns remained regarding their effectiveness against various newly emerging SARS-CoV-2 variants that may significantly affect vaccines' effectiveness and the level of neutralizing antibody titers [32]. This review mainly focuses on the effectiveness of COVID-19 vaccines against different SARS-CoV-2 variants. At first, available and approved vaccines are reviewed in brief. Characteristics of different variants of COVID-19 including *Alpha*, *Beta*, *Gamma*, *Epsilon*, *Zeta*, *Eta*, *Theta*, *Lota*, *Kappa*, *Lambda*, and *Mu*, and Delta have been discussed thereafter. Finally, the currently circulating COVID-19 variant, *i.e. Omicron*, as the current variant of concern (VOC), along with the effectiveness of available COVID-19 vaccines against these new variants are discussed in detail.

2. Methods

Literature was reviewed on PubMed, Google Scholar, and Web of Science databases using the key search terms of "COVID-19", "SARS-CoV-2", "COVID-19 vaccines", "vaccine platforms", "vaccine effectiveness", "vaccine coverage", "SARS-CoV-2 variants", and "SARS-CoV-2 sublineages" from January 2020 until January 2023. In this regard, first titles and abstracts of the peer-reviewed articles were reviewed and the relevant papers were included and discussed in more detail if appropriate. In addition, SARS-CoV-2 variants and sublineages have been categorized according to the latest update of the WHO website.

3. A review of the currently available and approved COVID-19 vaccines

Since the emergence of SARS-CoV2 and the consequences driven by this pandemic, the worldwide effort has been made to develop therapies and prophylactic vaccines against SARS-CoV-2. Therapeutic goals were focused on efforts that could shorten the hospitalization period and increase the survival of infected patients [14], while prophylactic vaccines aim to generate protective immunity against SARS-CoV-2 [27]. Given the urgent pandemic setting with its associated consequences, such as limited ventilators and hospital capacity, it was critical to develop successful prophylactic vaccines against SARS-CoV-2. There are mainly five types of COVID-19 vaccine that have been used for global vaccination, including the whole virus (inactivated), nucleic acid (DNA and RNA), viral vector (replicating and non-replicating), protein subunit, and virus-like particles (VLPs) vaccines. As of June 2021, a total of 287 candidate vaccines were launched in clinical or preclinical settings. The latest update of COVID-19 vaccines with WHO Emergency Use Listing (EUL) are summarized in Table 1 [33].

AstraZeneca vaccine (AZD1222) is globally the most used vaccine which is administered in 182 countries, followed by Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Sinopharm vaccine, being administered in 115, 68, and 66 countries, respectively [34].

3.1. Subtypes of COVID-19 vaccine

3.1.1. mRNA vaccines

3.1.1.1. Pfizer-BioNTech (BNT162b2) COVID-19 vaccine. BNT162b2 has been developed and manufactured by BioNTech and Pfizer. BNT162b2 is an mRNA-based vaccine that encodes for the viral spike glycoprotein of SARS-CoV-2, encapsulated in lipid nanoparticles (LNPs). Gene-based vaccines (mRNA vaccines and DNA vaccines) carry the genetic information for triggering the production of the antigen by the cells of the vaccine recipients. The target antigen for COVID-19 is the surface spike protein, which is used by the virus to bind and fuse with host cells. In BNT162b2, the mRNA encodes the SARS-CoV-2 spike protein and embraces mutations that stabilize the spike protein [35].

Regarding adverse reactions, the BNT162b2 vaccine showed two dose-dependent systemic or local reactions, such as grade 1 and 2. A common adverse event was pain at the injection site, and other systematic events were also reported [27].

3.1.1.2. Moderna COVID-19 (mRNA-1273) vaccine. Another mRNA-based COVID-19 vaccine is the Moderna mRNA-1273. Like BNT162b2, mRNA-1273 vaccine also utilizes a modern technology, in which the mRNA that codes SARS-CoV-2 spike protein is enveloped in lipid nanoparticles and passes through the cell membrane, and reaches the cytosol producing a spike protein for later antigen presentation and activation of the immune system [36].

Regarding adverse reactions, pain at the site of injection was the

Table 1
COVID-19 vaccines with WHO Emergency Use Listing (EUL) [33].

Vaccine platforms	COVID-19 vaccine	National Record of Achievement	Date of EUL approval
mRNA vaccines	COMIRNATY®/Pfizer BioNTech (BNT162b)	• EMA[a]	Dec 2020
		• FDA[b]	Jul 2021
	SPIKEVAX®/Moderna (mRNA-1273)	• EMA	Apr 2021
		• MFDS[c]	Dec 2021
		• FDA	Aug 2021
	COMIRNATY®Original/ Omicron BA.1	EMA	Oct 2022
	COMIRNATY®Original/ Omicron BA.4–5	EMA	Nov 2022
Adenovirus-vectored vaccines (Recombinant)	VAXZEVRIA®/ Oxford–AstraZeneca (ChAdOx1 nCoV-19)	• EMA	Apr 2021
		• Ministry of Health, Labour and Welfare	Jul 2021
			Jul 2021
			Aug 2021
		• Therapeutic Goods Administration	Dec 2021
			Dec 2021
		• Health Canada	
		• COFEPRIS (DP)	
		• ANMAT (DS)	
	COVISHIELD™/ Oxford–AstraZeneca (ChAdOx1 nCoV-19)	Central Drugs Standard Control Organization	Feb 2021
	Janssen/Johnson & Johnson (Ad26.COV2.S)	EMA	Mar 2021
	CONVIDECIA/CanSino (Ad5-nCoV-S)	NMPA[d]	May 2022
Protein-subunit vaccines	NUVAXOVID™/Novavax (NVX-CoV2373)	EMA	Dec 2021
	COVOVAX™/Novavax (NVX-CoV2373)	Central Drugs Standard Control Organization	Dec 2021
Inactivated vaccines	COVAXIN®/Bharat (BBV152)	Central Drugs Standard Control Organization	Nov 2021
	CoronaVac®/Sinovac	NMPA[d]	Jun 2021
	Sinopharm®/Beijing (BBIBP- CorV)	NMPA	May 2021

[a] European Medicines Agency.
[b] Food and Drug Administration.
[c] Ministry of Food and Drug Safety.
[d] National Medicinal Products Administration.

most common side effect reported. Tiredness, headache, and muscle and joint ache were also reported which mostly resolved after one or two days after injection [37,38]. The most adverse reactions of concern reported with mRNA-1273 were myocarditis, pericarditis, and chest pain after both doses of the vaccine. It is noteworthy that the rate of adverse reactions in both mRNA-1273 and BNT162b2 vaccines was 12.6 per million doses which do not need any medical care either [39,40].

In addition to the monovalent mRNA vaccines, FDA authorized the emergency use of the bivalent formulations of the mRNA COVID-19 vaccines including Moderna (Spikevax® bivalent original/Omicron BA.4–5) and Pfizer-BioNTech (Comirnaty® bivalent original/Omicron BA.4–5) COVID-19 vaccines. These bivalent COVID-19 vaccines, also known as updated boosters, contain two mRNA components of SARS-CoV-2. One of these components is from the original strain of SARS-CoV-2 and the other one is the common strain of BA.4/BA.5 sub-lineages of the Omicron variant [41].

3.1.2. Viral vectors: Adenovirus (Ads) vaccines

3.1.2.1. Oxford/AstraZeneca (ChAdOx1-S vaccine). Another platform of COVID-19 vaccines is the use of vectors, such as ChAdOx1 nCoV-19 or AstraZeneca vaccine (AZD1222) which was developed by Oxford University and the pharmaceutical company, AstraZeneca. AZD1222 is a non-replicating viral vector containing the virus structural surface glycoprotein antigen gene which encodes the spike glycoproteins [42,43]. AZD1222 evokes both humoral and cellular immunity. To date, Oxford/AstraZeneca vaccine seems to be better tolerated in older ages than in younger adults and provides comparable immunogenicity in all ages after the administration of a booster dose [44].

Pain at the site of injection as well as systematic reactions such as fever, chills, joint and muscle aches, headache, fatigue, and nausea were the most common adverse reactions reported with AZD1222 which did resolve after 4–5 days of occurrence [37,44]. Surprisingly, the reactions were more frequent in younger adults than in older individuals [44]. A rare but serious side effect observed after the first dose of the vaccine was thrombosis with thrombocytopenia syndrome [45].

3.1.2.2. Janssen Ad26.COV2.S COVID-19 vaccine. Ad26.COV2.S is a non-replicating, single-dose, recombinant human adenovirus type 26. Ad26.COV2.S encodes a full-length and stabilized SARS-CoV-2 spike protein which causes an antibody response against the SARS-CoV-2 infection [46].

Humoral and cellular immune responses remained after 8 months of Ad26.COV2.S vaccination [47]. Its effectiveness after the first dose injection was 66% against the mild to moderate COVID-19 infection (wild type SARS-CoV-2) and 100% against COVID-19-related mortality [27]. Adverse effects mostly reported were pain at the injection site as well as systemic signs such as fever, myalgia, nausea, and headache [46].

3.1.2.3. Sputnik V COVID-19 vaccine. Gam-COVID-Vac, also known as Gamaleya's Sputnik V vaccine, is a recombinant adenovirus-vectored vaccine. Sputnik V is a two-dose heterogeneous recombinant COVID-19 vaccine (rAd26/ rAd5) that is injected 21 days apart. Overall 92% effectiveness has been reported for this vaccine with 100% effectiveness against severe COVID-19. Sputnik V vaccine was well tolerated among recipients and no severe adverse reactions has been reported. The most commonly reported adverse reactions were fever, pain at the injection site, headache, and weakness [27].

3.1.3. Protein sub-unit vaccines

3.1.3.1. Novavax vaccine against COVID-19 (Nuvaxovid, NVX-CoV2373). NVX-CoV2373 is the first recombinant protein-based vaccine against the SARS-CoV-2, to receive regulatory approval [48]. NVX-CoV2373 is a nanoparticle-based immunogenic vaccine. It is developed by the use of the recombinant expression of SARS-CoV-2 spike protein. This vaccine is composed of trimeric full-length spike glycoproteins of SARS-CoV-2 and is assembled into nanoparticles co-formulated with a saponin-based adjuvant (Matrix-M) [49]. Doses of vaccine and adjuvant administered include 5 μg rsSARS-CoV-2 adjuvant with 50 μg Matrix-M1 given at two doses with the interval of 21 days.

To date, no serious adverse reaction has been assessed following vaccination with Nuvaxovid. The most common solicited systemic adverse reactions were fatigue, headache, and muscle pain. The mean duration of such adverse reactions lasted as long as 3 days [50].

3.1.4. Inactivated vaccines

3.1.4.1. Sinovac-CoronaVac COVID-19 vaccine. Inactivated virus vaccines are globally among the most widely used vaccines. Given their less strict cold chain requirements for preservation as well as ease of transportation along with their lower costs compared with mRNA vaccines, they are mostly applied in low- and middle-income countries. The most commonly used inactivated virus vaccines are CoronaVac, Sinopharm, and Bharat Biotech, with more than 4.5 billion doses of these vaccines have been delivered worldwide as of 14 December 2021 [51]. CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China), which has been reported to provide an immunity response. CoronaVac is given in two doses, 2 weeks apart [52].

The most common adverse reactions observed with CoronaVac were pain at the site of injection, headache, high blood pressure, dizziness, fatigue, and rash [53].

3.1.4.2. Sinopharm COVID-19 vaccine. The Sinopharm COVID-19 vaccine is an inactivated vaccine against SARS-CoV-2 which was developed by the Beijing Bio-Institute of Biological Products (BBIBP) and is the first Chinese COVID-19 vaccine approved by WHO for urgent use [54]. The Sinopharm vaccine is administered in two separate doses of 4 μg 28 days apart [55,56]. The vaccine has been reported to be well-tolerated and safe [57]. Regarding the most common adverse reactions with the Sinopharm vaccine, fever, nausea, vomiting, headache, fatigue, and dizziness along with allergic dermatitis were mostly observed. Some mild to severe adverse reactions have been reported within 28 days of vaccination, leading to no serious events [55].

3.1.4.3. Bharat Biotech BBV152 COVAXIN vaccine against COVID-19. BBV152/Covaxin is an inactivated COVID-19 vaccine and India's first indigenous COVID-19 vaccine which was developed and manufactured by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV). BBV152 vaccine has shown an acceptable safety profile, with similar safety results to other inactivated COVID-19 vaccines. Regarding adverse reactions, the most common of all were pain at the injection site, fever, nausea, vomiting, and fatigue [58].

4. A brief review of early COVID-19 variants

SARS-CoV-2 has evolved into different variants since 2019. Mutations occurred in the spike protein (S protein) are called key S mutations due to the role of the S protein in binding to angiotensin 2 (ACE2) receptor, antigenic effect, cell entry, transmissibility, virulence, and escaping from host cell immunity. Neutralizing antibodies binding to S protein are important in the humoral immune response against SARS-CoV-2 [59]. In late 2020, WHO classified the new SARS-CoV-2 variants based on significant amino acid substitution. There are Global Initiative on Sharing All Influenza Data (GISAID), Nextstrain, and Pango genetic lineages nomenclature. WHO has utilized Greek alphabetic to classify new variants. Based on the latest update on June 7th, 2022, different SARS-CoV-2 variants are classified as variants of concern

(VOC), variants being monitored (VOB), variants of interest (VOI), VOC lineages under monitoring (VOC-LUM), and variants of high consequences (VOHC) [60].

4.1. Alpha variant (B.1.1.7 and Q lineages)

B.1.17 variant (20I/501Y.V1 in Nextstrain nomenclature system) also known as Alpha variant, is a previously circulating VOC. This variant was first introduced on December 19th, 2020, in the United Kingdom (UK) and was the predominant variant on September 2020 in the UK. The B.1.1.7 variant was spread more easily and faster than other variants [61]. To date, 17 mutations have been found in the Alpha variant including 10 key amino acid sequencing changes in S protein (deletion 69–70, deletion 145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H). N501Y mutation increases S glycoprotein binding to the ACE2 receptor and results in more transmissibility and infectivity in animal models. Deletion 69,70 of spike protein caused failure in polymerase chain reaction (PCR) diagnostic tests [59,62]. In addition, results of an observational study on 31,390B.1.1 sequences in the UK revealed that the B.1.1.7 variant seems to have substantial transmissibility over other VOCs between November 2020 and January 2021 [62]. In a retrospective match case-control study, the more severe clinical presentation including mechanical ventilation requirement and medical treatment necessity, and also higher mortality rates were observed in hospitalized patients with B.1.1.7 variant [63]. In another experiment on vaccinated hospital workers, it was observed that the Alpha variant could induce serious illness in comparison to the wild-type SARS-CoV-2 [63]. In a comparative cohort study in China, higher viral load and more serious inflammatory disease and pneumonia due to COVID-19 infection were observed. These clinical and laboratory findings regarding the Alpha variant were fever above 38 °C and high levels of C-reactive protein (CRP), serum amyloid A (SAA), creatine kinase (CK), and $CD4^+$ T lymphocytes [64].

4.1.1. The effectiveness of different vaccines against the B.1.1.7 variant

Different studies have been performed on the effectiveness of vaccines against the Alpha variant. In one study, no change in antibody-neutralizing activity in sera of Pfizer-BioNTech-vaccinated individuals was found against pseudoviruses bearing the B.1.1.7 variant [65]. Although reports of a small cohort study indicate that Pfizer-BioNTech may have reduced effectiveness against B.1.1.7 variant transmission and enhanced viral load in the nasopharyngeal tract [66], however, in a vaccination program, the effectiveness of 95% was reported for Pfizer-BioNTech vaccine during the Alpha variant outbreak in winter 2020–2021 [67]. Furthermore, in a comprehensive study on the vaccination program between December 2020 and August 2021 in Ontario, Canada, the effectiveness of Pfizer-BioNTech Comirnity, Moderna Spikevax, and AstraZeneca Vaxzevria vaccines effectiveness were evaluated against symptomatic SARS-CoV-2 infection, hospitalization due to COVID-19 infection, and also effectiveness against the mortality due to COVID-19 were assessed after 14 and 21 days of the first dose vaccination and 7 and 14 days after the second dose vaccination. The results of different vaccines' effectiveness against the Alpha variant are summarized in Table 2 [68].

Results of phase 3 clinical trial on NVX-CoV2373 (Nuvaxovid) vaccine showed effectiveness of 83.4% and 86.3% against the B.1.1.7 variant after 7 and 14 days of the first and second dose of injection, respectively [69]. In an experiment on the effectiveness of Ad26.COV2.S (Johnson & Johnson] vaccine against the Alpha variant, 69.7% effectiveness was reported [70]. Covaxin, by Bharat Biotech company, could effectively neutralize B.1.1.7 variant [59]. Among inactivated COVID-19 vaccines CoronaVac and Sinopharm vaccines showed a significant reduction in B.1.1.7 serum neutralization geometric mean titer (GMT] by 0.5 times and 1.4 times, respectively [71].

4.2. Beta variant (B.1.351 and descendent lineages)

B.1.351 variant (20H/501Y.V2) also known as the Beta variant, the previous circulating VOC, was first detected in South Africa on late December 2020 and showed an increment in the transmissibility of the virus. This variant is capable of re-infect people with a previous history of COVID-19 infection. The B.1.351 variant had 8 key S protein mutations of D80A, D215G, 241/243del, K417N, E484K, N501Y, D614G, and A701V [72]. E484 and K417N mutations have been shown to contribute to the induction of a stronger affinity to ACE2 receptors. Increased affinity to the receptor results in more infectivity in comparison to the wild-type SARS-CoV-2 [73]. The US Centers for Disease Control and Prevention (CDC) has announced 50% more transmission of the Beta variant [74]. E484K mutation could reduce the neutralizing effect of convalescent sera [59]. In addition, neutralizing antibodies were not detected in 48% of convalescent sera after B.1.135 COVID-19 infection [65].

4.2.1. The effectiveness of different vaccine platforms against the B.1.351 variant

Although results of a randomized clinical trial performed by Pfizer and BioNTech reported effectiveness of 100% against the Beta variant [75]. However, some other reports are suggestive of lower effectiveness rates [67]. In a *meta*-analysis design study, the effectiveness of 36% and 61% were observed after 7 days after the first dose of Pfizer-BioNTech and Moderna injection [76]. In addition, the effectiveness of 86%, 92%, and 87% against the Beta variant was achieved in symptomatic

Table 2
The effectiveness of available COVID-19 vaccines against the Alpha (B.1.1.7) variant.

Vaccine name	Effectiveness against symptomatic SARS-CoV-2 infection after the 1st dose of vaccine	Effectiveness against COVID-19 hospitalization or death after the 1st dose of vaccine	Effectiveness against symptomatic SARS-CoV-2 infection after the 2nd dose of vaccine	Effectiveness against COVID-19 hospitalization or death after the 2nd dose of vaccine	Ref.
Pfizer-BioNTech (BNT162b2)	67% after 14 days	82% after 14 days	89% after 7 days	96% after 7 days	[68]
Moderna (mRNA-1273)	82% after 14 days	80% after 14 days	92% after 7 days	95% after 7 days	[68]
AstraZeneca-Oxford (ChAdOx1 nCoV-19)	63% after 14 days	87% after 14 days	91% after 7 days	82% after 7 days	[68]
Janssen/ Johnson & Johnson (Ad26.COV2.S)	70.2% effectiveness against moderate to severe infection after 14 days of single-dose vaccine				[70]
Novavax (NVX-CoV2373)	86.3% effectiveness against symptomatic mild, moderate or severe COVID-19 infection after 7 days of 2nd dose vaccine				[69]

patients after full vaccination with Pfizer-BioNTech, Moderna, and AstraZeneca-Oxford in Ontario vaccination program. In addition, 84% and 73% vaccine effectiveness was observed against symptomatic infection and hospitalization or death due to COVID-19 after 14 days of the first shot of AstraZeneca-Oxford [68]. In another study, the effectiveness of AstraZeneca-Oxford against the Beta variant was 10.4% [72]. Effectiveness of 51.9% and 64.7% were reported for the Janssen vaccine against the Beta variant [70,72]. It was claimed that the Sputnik V vaccine was highly effective against the Beta variant. No data regarding the effectiveness of the Sinopharm vaccine against the Beta variant is available. Furthermore, an effectiveness of 70% in comparison to the wild-type of SARS-CoV-2 was reported for the CoronaVac vaccine [77]. The effectiveness of various available vaccines against the Beta variant is summarized in Table 3.

4.3. Gamma variant (P.1 and descendent lineages) (VOC202101/02)

P.1 lineage (20 J/501YV3), also known as Gamma variant, the previously circulating VOC, was first reported in Manaus, Brazil on January 2021 and further reported in Japan, Korea, and the Faroe Islands [65]. This variant has 17 mutations including L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G H655Y, T1027I, and V1176F [72]. The key mutations are E484K and D614G N501Y in S protein that contribute to the stronger binding affinity to the ACE2 receptor, higher transmissibility, and enhanced immune escape [79]. Results of previous studies suggest that the Gamma variant interacts with ACE2 receptor more efficiently and thus it is a more infectious variant in comparison to the Alpha and Beta variants [59,73].

4.3.1. The effectiveness of vaccines against the Gamma variant

Effectiveness of Moderna, AstraZeneca-Oxford, and Pfizer-BioNTech vaccines against the Gamma variant was reported as 89%, 41%, and 63%, respectively after receiving the first dose [68]. Because of the limitation of the number of available cases in some studies, the effectiveness of vaccines against the Beta/Gamma variants was reported together. Efficacies of Janssen**,** Novavax, and CoronaVac vaccines in symptomatic COVID-19 patients were 52%, 60%, and 65.5 %, respectively. Effectiveness of 65–66% and 91–95% was reported for the Janssen vaccine against hospitalization and death due to COVID-19, respectively. The effectiveness of 87.5% was reported against severe illnesses with the CoronaVac vaccine [80]. In a match test-negative case-control study, the effectiveness of the CoronaVac vaccine in healthcare workers during the era of the Gamma variant epidemic in Manus was 49.6% and 36.8% in a 14-day period after the first dose as well as the second dose vaccination, respectively [81].

Effectiveness of various vaccines against the Gamma variant are summarized in Table 4.

4.4. Epsilon variant (B.1.427 and B.1.429)

B.1.427/B.1.429 lineages (GH/452R.V1) CAL.20C, also known as the Epsilon variant, was first reported in the United States of America, in July 2020. The Epsilon variant is now classified as the previous VOI. The Epsilon variant is classified into two separate lineages of B.1.427 and B.1.429. The key mutations in the S protein include L452R, D614G in B.1.427, and S13I, W152C, L452R, and D614G in B.1.429 sublineage [60,82]. The L452 mutation in the S protein results in a stronger affinity of the S protein with the ACE2 receptor. Transmissibility of the Epsilon variant was enhanced by 18.6–24% in comparison to the wild type because of the occurrence of L452R and D614G mutations [82]. The S131I and W152 mutations contribute to viral escape from the therapeutic monoclonal antibodies [83]. Additionally, the infectivity of the Epsilon variant is reported to be significantly higher than the Alpha variant [84]. Results of a study have shown that an acceptable cellular and humoral immune response of Ad26.COV2.S vaccine was achieved against the Epsilon variant [85]. In an observational retrospective study, the Epsilon variant induced a 2.9 to13.4-fold reductions in serum neutralizing antibodies titers in comparison to the wild-type of SARS-CoV-2 after 35 days of BNT162b2 full vaccination [86]. The neutralization effect of the mRNA-1273 vaccine against the Epsilon variant was 2.8-fold less than the wild-type virus [27]. Convalescent sera neutralization showed reduced neutralization after vaccination with Pfizer-BioNTech and Moderna vaccines against B.1.427 and B.1.429 variants with neutralization efficiency of 2.05 and 2.96, respectively [87]. A 7.6-fold reduction in serum neutralization titers in vaccinated patients with Pfizer-BioNTech and Moderna vaccines undergoing hemodialysis was seen compared to the Delta variant [88].

4.5. Zeta variant (P.2)

P.2 variant (GR/484 K.V2) also known as the Zeta variant is now classified as previous VOI. It was first detected in Brazil on April 2020. The key S mutations are L18F; T20N; P26S; F157L; E484K; D614G; S929I; and V1176F [82]. The E484K mutation in the Zeta variant contributes to viral escape from host immune cells. In addition, the D614g mutation induces higher infectivity and viral load. This mutation has also been proposed as a possible cause of anosmia in infected patients [83].

Table 3
The effectiveness of available COVID-19 vaccines against the Beta (B.1.351) variant.

Vaccine name	Effectiveness against symptomatic SARS-CoV-2 infection after the 1st dose vaccine	Effectiveness against COVID-19 hospitalization or death after the 1st dose vaccine	Effectiveness against symptomatic SARS-CoV-2 infection after the 2nd dose vaccine	Effectiveness against COVID-19 hospitalization or death after the 2nd dose vaccine	Ref.
Pfizer-BioNTech (BNT162b2)	50% after 14 days	64% after 14 days	87% after 7 days	93% after 7 days	[68]
Moderna (mRNA-1273)	75% against Beta/Gamma after 14 days	59% after 14 days	89% against Beta/Gamma after 7 days	NA*	[68]
AstraZeneca-Oxford (ChAdOx1 nCoV-19)	84% after 14 days	61% after 14 days	NA*	NA*	[68]
Janssen/ Johnson & Johnson (Ad26.COV2.S)	51.9% effectiveness against moderate to severe infection after 14 days of single-dose vaccine 64.7% (54.1 to 73%) against symptomatic infection after 14 days of single-dose vaccine in Latin American population				[70,72]
Novavax (NVX-CoV2373)	51.1–60% effectiveness against symptomatic infection after 7 days of 2nd dose vaccine				[72,78]

* Data not available.

Table 4
The effectiveness of available COVID-19 vaccines against the Gamma (P.1) variant.

Vaccine name	Effectiveness against symptomatic SARS-CoV-2 infection after the 1st dose vaccine	Effectiveness against COVID-19 hospitalization or death after the 1st dose vaccine	Effectiveness against symptomatic SARS-CoV-2 infection after the 2nd dose vaccine	Effectiveness against COVID-19 hospitalization or death after the 2nd dose vaccine	Ref.
Pfizer-BioNTech (BNT162b2)	63% after 14 days	80% after 14 days	88% after 7 days	89% after 7 days	[68]
Moderna (mRNA-1273)	89% after 14 days	88% after 14 days	89% against Beta/Gamma after 7 days	NA*	[68]
AstraZeneca-Oxford (ChAdOx1 nCoV-19)	41% after 14 days	89% after 14 days	NA*	NA*	[68]
Janssen/ Johnson & Johnson (Ad26.COV2.S)	36.5% effectiveness against moderate to severe infection after 14 days of single-dose vaccine				[70]
Sinovac (CoronaVac)	46.8%, 55.5%, and 61.2% effectiveness against symptomatic infection, hospitalization, and death after 14 days of 2nd dose vaccine				[79]

* Data not available.

4.6. Eta (B.1.525) and Lota (B.1.526) variants

B.1.525 and B.1.526 lineages (G/484 K.V, GH/253G.V1 respectively) also known as the Eta and Lota variants, respectively, have common mutations in the S protein. The Eta variant was first identified in Nigeria on December 2020 and Lota was first reported on November 2020 in the United States of America. They are now classified as the previous VOI. B.1.525 key S mutations are A67V, H69-, V70-, Y144-, E484K, D614G, Q677H, and F888L [83].

4.7. Theta variant (P.3)

P.3 variant (GR/1092 K.V1) also known as the Theta variant was first identified on January 2021 in the Philippines and now is classified as the previous VOI. The key S mutations of the Theta variant are 141–143 deletion, E484K, N501Y, and P681H [89].

4.8. Lota variant (B.1.526)

B.1.526 (GH/253G.V1) also known as the Lota variant was first identified in Nigeria on December 2020. The key S mutations of the B.1.526 variant are L5F, D80G, T95I, Y144-, F157S, D253G, L452R, S477N, E484K, D614G, A701V, T859N, D950H, and Q957R. Results of a previous study reported 54% serum neutralization for the Lota variant in those who received 2 doses of the Moderna vaccine [90].

4.9. Kappa variant (B.1.17.1)

B.1.617.1 variant (G/452R.V3) also known as the Kappa variant was first identified on October 2020 in India and is now classified as a previous VOI. Harbor key mutations of the Kappa variant are T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H(83). In one study, 85% serum neutralization for the B.1.617.1 variant was observed in those who received 2 doses of the Moderna vaccine [90]. In another study, an 8-fold reduction in the neutralization of convalescent sera was obtained against the Kappa variant in comparison to the wild-type of SARS-CoV-2 in those who were vaccinated with Pfizer-BioNTech and Moderna vaccines. In addition, this study suggested that more immune escape occurred for the Kappa variant in comparison to that of the Epsilon variant [87]. In hemodialysis patients vaccinated with Pfizer-BioNTech or Moderna vaccines, a 6.8-folds reduction in neutralizing sera was observed compared to the Delta variant [88].

4.10. Lambda variant (C.37)

C.37 (GR/452Q.V1) also known as the Lambda variant was first found on December 2020 in Peru and is now classified as the previous VOI. It has key S mutations of L452Q, F490S, and D614G [83]. L452R/Q mutation could increase the binding affinity to the ACE2 receptor and enhance viral infectivity. A 2.5–4 fold and 3.2–4.9 fold reduction in sera neutralization against the Lambda variant compared to the wild-type of SARS-CoV-2 was observed for mRNA vaccines as well as Ad26.COV2.S vaccine, respectively [91]. Furthermore, a 3.1-fold reduction in neutralizing sera was seen in hemodialysis patients who received the mRNA vaccines [88].

4.11. Mu variant (B.1.621)

B.1.621 (GH) also known as the Mu variant was first identified on January 2021 in Columbia and became the predominant variant in that period. It is now classified as the previous VOI. It has 21 mutations including 9 key S protein mutations of T95I, Y144S, R346K, E484K, N501Y, D614G, P681H, and D950N [92]. WHO has announced that the Mu variant is capable of immune escape [93]. A 3.1-fold reduction in neutralizing sera compared to the wild-type virus was observed in hemodialysis patients who received the mRNA vaccines [88]. The effectiveness of Ad26.COV2.S vaccine against the Mu variant was less than the reference strain (B.1.D614G) [70]. The effect of key S mutations on clinical and laboratory findings of various SARS-CoV-2 variants are summarized in Table 5.

4.12. Delta variant (B.1.617.2)

Delta variant, also known as B.1.617.2 variant, was first detected in India in October 2020 and considered as the previously circulating VOC on 7th June 2022 [95]. SARS-CoV-2 VOCs including the Delta variant are those with one or more mutations that induce easier viral transmission and less treatment responsiveness of the virus and also they can influence the vaccines' effectiveness against COVID-19 infection [96]. Delta variant was rapidly spread throughout the world and caused a large number of infections, hospitalization, and mortality rates. In many countries such as the United Kingdom (UK), the viral spread during the Delta variant wave was significantly high despite the high vaccine coverage. However, the disease severity, hospitalization, and mortality rates were lower in vaccinated patients [96]. At first, this phenomenon was attributed to the delay in the second dose of COVID-19 vaccine administration in some of these nations. In addition, it has been reported that the Delta variant is 60% more transmissible than the Alpha variant with a basic reproduction rate (R_0) of 5 to 8 [96] or 3.2 to 8 with a mean value of 5.08 [97]. Furthermore, it has been shown that through *in vitro* conditions, the Delta variant was 6-fold and 8-fold less responsive to the serum-neutralizing antibodies of the recovered patients and vaccine-

Table 5
The potential effects of key S mutations on characteristics of various SARS-CoV-2 variants.

SARS-CoV-2 Variants	Mutation	Potential effects	Ref.
Alpha	H-69 and V70	Increased infectivity and reduced serum neutralization	[83,94]
	Y144	Reduced affinity to antibody binding	
	L452r	Increased binding ability to ACE2* receptor, reduced binding of vaccine simulated antibodies	
	E484k	Escape from the host immune system	
	N501y	Enhanced Binding to ACE2, immune escape	
	P681h	Enhanced transmissibility	
	D614g	Loss of smell, higher infectivity, higher viral load	
Beta	K417N	Resistance to antibodies	
	E484k	Escape from the host immune system	
	N501y	Enhanced Binding to ACE2, immune escape	
	D614g	Loss of smell, higher infectivity, higher viral load	
Gamma	K417T, L18F	Resistance to antibodies and immune escape	
	E484k	Escape from the host immune system	
	N501y	Enhanced Binding to ACE2, immune escape	
	H655y	Enhanced transmissibility	
	P681h	Enhanced transmissibility	
	D614g	Loss of smell, higher infectivity, higher viral load	
Epsilon	L452r	Increased binding ability to ACE2 receptor, reduced binding of vaccine simulated antibodies	
	D614g	Loss of smell, higher infectivity, higher viral load	
Zeta	E484k	Escape from the host immune system	
	D614g	Loss of smell, higher infectivity, higher viral load	
Eta	H-69 and V70	Increased infectivity and reduced serum neutralization	
	Y144	Reduced affinity to antibody binding	
	E484k	Escape from the host immune system	
	Q6777h	Enhanced transmissibility	
	D614g	Loss of smell, higher infectivity, higher viral load	
Theta	E484k	Escape from the host immune system Enhance	
	N501y	Binding to ACE2, immune escape	
	P681h	Enhanced transmissibility	
	D614g	Loss of smell, higher infectivity, higher viral load	
Lota	Y144	Reduced affinity to antibody binding	
	D253G	Resistance to neutralizing antibodies	
	S477n	Escape from monoclonal antibodies	
	E484k	Escape from the host immune system	
	D614g	Loss of smell, higher infectivity, higher viral load	
Kappa	L452r	Increased binding ability to ACE2 receptor, reduced binding of vaccine simulated antibodies	
	e484q	Reduced sera neutralization	
	F490s	Reduced susceptibility to antibody neutralization	
	P681r	Enhanced transmissibility	
	D614g	Loss of smell, higher infectivity, higher viral load	
Lambda	L452q	Increased viral infectivity	
	D614g	Loss of smell, higher infectivity, higher viral load	
Mu	D614g	Loss of smell, higher infectivity, higher viral load	

* Angiotensin converting enzyme 2.

induced antibodies in comparison to the wild-type SARS-CoV-2, respectively [98]. Also, the Delta variant showed a higher replication rate and spike-related entry in comparison to the Kappa variant [98].

Delta plus variant emerged from the previous Delta variant in which 5 key spike mutations including T95I, A222V, G142D, R158G, and K417N were more prevalent in comparison to the Delta variant, and also 3 spike mutations including K417N, V70F, and W258L were solely presented in Delta plus variant. These mentioned mutations could significantly affect the antibody binding site and induce lower sensitivity to vaccine-elicited antibodies [99]. Therefore, the Delta and Delta plus variants could escape from the receptor-binding domain (RBD) and non-RBD targeting antibodies through these new spike mutations and the wide expansion of these variants throughout the world could be attributed to this possible mechanism [100].

5. Currently circulating COVID-19 variant

According to the WHO, the currently circulating SARS-CoV-2 VOC is the Omicron (B.1.1.529) variant.

5.1. Omicron variant (B.1.1.529)

Omicron, also known as B.1.1.529, was first detected in Botswana and South Africa and soon distributed in multiple countries in November 2021 and was considered as VOC on 26th November 2021. In comparison to the Delta variant, the Omicron variant mostly affected the younger population and those with higher rates of vaccination. COVID-19 due to the Omicron variant presented with lower respiratory symptoms, diminished inflammatory responses, and lower rates of lung involvement in Computed tomography (CT) scan [101]. In addition, the Omicron variant in comparison to the Delta variant was accompanied by better hospital outcomes [101].

The Omicron variant itself has been divided into various subgroups including BA.1, BA.2, BA.3, BA.4, BA.5, and also a recombinant form of BA.1/BA.2 known as XE [95]. The mutations related to the Omicron variant including 69-70del, T95I, G142D/143-145del are responsible for higher binding affinity, enhanced transmissibility, and also higher rates of antibody escape of this new SARS-CoV-2 variant [102]. Protection against COVID-19 infection has been defined as the titer of neutralizing antibodies produced against the SARS-CoV-2 and also the binding of these antibodies to the S protein and its receptor-binding domain (RBD) [103]. In this regard, since the currently available vaccines are designed against the S protein of the wild-type SARS-CoV-2, reducing the neutralizing potential of vaccines against the Omicron variant would be predictable. Memory B cells are responsible for recall response to antigens after COVID-19 infection or booster vaccine administration. Therefore, their role is crucial in the protection against various SARS-CoV-2 variants. The results of a recent study revealed that the BNT162b2 vaccine showed strong neutralizing potential against the BA.1 and BA.2 Omicron subgroups and other VOCs, while its neutralizing potential was significantly reduced against the BA.4 and BA.5 sublineages. BA.4 and BA.5 Omicron subgroups induced 5-fold lower antibody titer in comparison to the wild-type SARS-CoV-2 [103]. The amounts of produced memory B cells against the S protein of BA.1 Omicron variant were comparable to the titer produced against the Wuhan type or other VOCs, while the memory B cells against the RBDs of the BA.1 sublineage were slightly lower in comparison to the others [103]. Results of this study confirmed that those who were vaccinated with the BNT162b2 vaccine showed augmented neutralizing activity against the BA.1, BA.2, and other VOCs. However, these vaccinated individuals failed to show enhanced neutralizing potential against the BA.4 and BA.5 sublineages of the Omicron variant [103]. Similar results were reported for those who received the CoronoVac vaccine, in whom the BA.4 and BA.5 could bypass the boosted humoral immunity regenerated against the BA.1 Omicron subgroup. Also, it has been reported that the BA.2.12.1, BA.2.13, BA.4, and BA.5 Omicron sublineages

showed higher transmission potential in comparison to BA.2. This can be attributed to the L452 mutation that was reported in these newly emerged Omicron sublineages. In addition, the rate of neutralization evasion against the sera of individuals who received two vaccine shots and an additional booster dose was significantly higher for BA.2.12.1, BA.4, and BA.5 in comparison to BA.2. Furthermore, these new emerging Omicron sublineages can escape the humoral immunity produced through the BA.1 infection [104].

BA.3 Omicron sublineage showed no specific mutation in the S protein, however, it is considered as a combination of mutations that occurred in both BA.1 and BA.2 sublineages. All these three lineages were first found in South Africa and approximately appeared at the same time (on November 2021). According to the published data, the most dominant sublineage of the Omicron variant was the BA.1 and BA.3 which had the lowest dominancy among the others. It has been reported that 37, 31, and 33 mutations occurred in BA.1, BA.2, and BA.3 sublineages, respectively, in which 21 of them were most responsible for the enhanced transmission rate in comparison to the wild-type virus. In this regard, it has been mentioned that the N501Y and Q498R mutations are related to the enhanced binding to the ACE2 receptor, while the H655Y, N679K, and P681H mutations are more responsible for spike cleavage that can lead to enhanced transmission [105].

On March 2022, three recombinant forms of the Omicron variant were introduced including XE, XD, and XF. The XF and XD subvariants are recombinant forms of the Delta variant and the Omicron BA.1 sublineage, while the XE subvariant is a recombinant form of BA.1 and BA.2 Omicron sublineages. The growth rate of the XE recombinant variant has been enhanced by about 9.8% in comparison to the BA.2 sublineage. Special attention has been paid to the XE subvariant due to the higher transmissibility than the previously reported SARS-CoV-2 variants which can be attributed to the various mutations that occurred in its S protein [106]. Therefore, escape from the produced neutralizing antibodies of the convalescent plasma and vaccination would be predictable. Since these mutations can facilitate viral replication in the upper respiratory tract, higher transmissibility and lower virulence potential were seen with the Omicron XE subvariant. It has been reported that the Omicron variant has a multiplication and infection rate of approximately 70-fold higher than the wild-type or the Delta variant, while its lung involvement and lower respiratory tract destruction is reduced by more than 10-fold in comparison to the wild-type SARS-CoV-2. In addition, the Omicron infection lower severity can be attributed to the pre-existing immunity that occurred due to vaccination and/or previous COVID-19 infection(s). Therefore, the Omicron variant transmitted faster with lower severity worldwide [106]. The most recently circulating Omicron sublineages are BA.4, BA.4.6, BA.5, BA.2.75.2, BQ.1, BQ.1.1, XBB, and XBB.1. Although these new sublineages were not associated with enhanced COVID-19 disease severity, however, due to their additional S-protein mutations, vaccine evasion and reduced antibody neutralization, and reduced vaccine effectiveness are predictable with these subvariants [107,108]. In this regard, it has been reported that BQ.1, BQ.1.1, XBB, and XBB.1 are the most resistant SARS-CoV-2 sublineages. Effectiveness of both parental and bivalent mRNA vaccines have been significantly reduced against these sublineages. In addition, they are resistant to all clinical monoclonal antibodies. However, the ACE2 affinity of these new sublineages are the same as the other Omicron sublineages [109].

6. Effectiveness of vaccines against the previously circulating VOC

6.1. Effectiveness of vaccines against the Delta variant

In general, the effectiveness of vaccines used in the USA including Pfizer-BioNTech, Moderna, and Janssen vaccines against hospitalization due to Delta variant infection was 82 to 95% with a mean value of 89%. Meanwhile, the rates were reduced to 64–84% with an average value of 76% in older adults who were over 75 years old [110]. Also, results revealed that the Moderna, Pfizer BioNTech, and Janssen vaccines' effectiveness against hospitalization due to the Delta variant were 92%, 77%, and 65%, respectively [110]. Therefore, the effectiveness of the Moderna vaccine was significantly higher than the Pfizer-BioNTech or Janssen vaccines [111]. In addition, it has been declared that unvaccinated individuals were at risk of death due to the Delta variant of COVID-19 infection about 11 times more than the vaccinated individuals [110]. According to the results of a recent systematic review, the effectiveness of Pfizer-BioNTech, Moderna, and CoronaVac vaccines, after the 3rd dose administration, against the Delta variant were 97.2%, 97%, and 63.8%, respectively [112].

6.1.1. Pfizer-BioNTech (BNT162b2)

The effectiveness of the Pfizer-BioNTech vaccine, an mRNA-based vaccine, against SARS-CoV-2 infection (confirmed through PCR positive test) was reduced by about 10–13% in adults in comparison to the Alpha variant [113].

The effectiveness of the Pfizer-BioNTech vaccine against SARS-CoV-2 infection in adolescents was completely time-dependent. In this regard, it has been reported that the effectiveness of this vaccine during 14–20 days and 21–27 days after the first shot was 59% and 66%, respectively. While its effectiveness in 7–14 days after the second shot was increased to 90%. In addition, effectiveness against symptomatic COVID-19 was reported 57%, 82%, and 93%, respectively [114].

6.1.2. Moderna (mRNA-1273)

Among various vaccines used in the USA, including Pfizer-BioNTech, Moderna, and Janssen, the Moderna vaccine showed the highest effectiveness (95%) against the life-threatening Delta variant [111]. In addition, the Moderna vaccine with an effectiveness of 92% showed the highest effectiveness against hospitalization or need to emergency units or urgent care clinics due to the Delta variant infection [110].

6.1.3. AstraZeneca-Oxford (ChAdOx1 nCoV-19)

The AstraZeneca-Oxford vaccine is an adenovirus-vectored vaccine. The effectiveness of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection (confirmed through PCR positive test) was reduced by about 16% in adults in comparison to the Alpha variant [113]. This decline in vaccine effectiveness was more significant in older patients who were $\geq$ 65 years of age which can be attributed to their reduced immunity [110]. It has been reported that the effectiveness of two-dose vaccination was approximately equal to the protection that comes from the natural SARS-CoV-2 infection. In addition, results revealed that although the effectiveness of the AstraZeneca-Oxford vaccine was lower than the Pfizer-BioNTech vaccine, the effectiveness of the former lasted much longer. Vaccines' effectiveness against the previously circulating Delta variant of SARS-CoV-2 are summarized in Table 6. As is noticeable in Table 6, vaccines' effectiveness against SARS-CoV-2 infection and also COVID-19 infection was significantly enhanced after the second shot administration [115].

6.1.4. Janssen/Johnson & Johnson (Ad26.COV2.S)

Janssen vaccine is an adenovirus-vectored vaccine. Among the vaccines administered in the USA, the single-dose Janssen vaccine showed the lowest effectiveness against the Delta variant with the rate of about 60% at least 14 days after the vaccine shot [111]. While these rates were 95% and 80% after the second dose administration of the Moderna and Pfizer-BioNTech vaccines, respectively [111]. Furthermore, the Janssen vaccine's effectiveness against hospitalization and the need for emergency care due to the Delta variant infection was 65% which was significantly lower than the effectiveness of mRNA vaccines including the Pfizer-BioNTech and the Moderna [111].

6.1.5. Sinovac-CoronaVac COVID-19 vaccine

CoronaVac vaccine, an inactivated COVID-19 vaccine, has been

Table 6
Vaccine effectiveness against the Delta variant of SARS-CoV-2.

Vaccine name	Effectiveness against SARS-CoV-2 infection	Effectiveness against COVID-19 death	Ref.
Pfizer-BioNTech (BNT162b2)	• After the first vaccine shot: Insufficient protection against symptomatic COVID-19 infection (20% effectiveness) • After the second vaccine shot: 84 or 88% effectiveness • In adolescents the effectiveness, 7 days after the second dose, was 90%	95% effectiveness 14 days following the second dose	[96,115,122]
AstraZeneca-Oxford (ChAdOx1 nCoV-19)	• After the first vaccine shot: Insufficient protection against symptomatic COVID-19 infection (39% effectiveness) • After the second vaccine shot: 64 or 67% effectiveness	88% effectiveness 14 days following the second dose	[96,115,122]
Janssen/ Johnson & Johnson (Ad26.COV2.S)	• Vaccine effectiveness: 60% after the single-dose administration	NA*	[111]
Moderna (mRNA-1273)	• Vaccine effectiveness: 95% after the second dose	98.3% effectiveness after the 3rd dose	[111–112]
Sinovac (CoronaVac)	• Vaccine effectiveness after the first dose: 13.8% or <50% • Vaccine effectiveness following the second dose: 59–60%	75.3% effectiveness after the 3rd dose	[112,117]
Bharat Biotech BBV152 COVAXIN	• 65.2% effectiveness after the 2nd dose	NA*	[112]
Sputnik V (Gam-COVID-Vac)	• 81% effectiveness after the 2nd dose (in 18–50 years old recipients) • 68% effectiveness after the 2nd dose (in 50 + years old recipients)	• 95% (in 18–50 years old recipients) • 74% (in 50 + years old recipients)	[123]
Sinopharm	• 95% effectiveness in fully vaccinated individuals against hospitalization and critical admission due to COVID-19 infection	NA	[124]

* NA: Data not available.

developed by Sinovac Company in China. The neutralizing antibody titer of this vaccine against the Delta variant was reduced by 31.6 times in comparison to the wild-type SARS-CoV-2. Also, this reduction in neutralizing effect was significantly higher than that of Alpha and Beta variants [116]. It has been reported that the effectiveness of the CoronaVac vaccine against the Delta variant was less than 50% after the first dose administration. However, the effectiveness was increased to 60% after the second shot. Surprisingly, the CoronaVac effectiveness against the Delta variant was reported at the highest levels, about 98%, when the two-dose CoronaVac was accompanied by a BNT162b2 vaccine booster dose. In addition, the vaccine effectiveness was increased to 86% after the two-dose CoronaVac followed by a single ChAdOx1 nCoV-19 booster shot [117]. Therefore, booster doses were crucial in the period of Delta variant-dominant pandemic to reach desirable vaccine effectiveness.

6.1.6. Sinopharm COVID-19 vaccine

The BBIBP-CorV (Sinopharm) COVID-19 vaccine is a type of inactivated vaccine. Results of a recent study from the United Arab Emirate (UAE) on the effectiveness of the Sinopharm vaccine in comparison to the Pfizer-BioNTech mRNA vaccine against the Delta variant reported the effectiveness of 95% and 98% against hospitalization due to COVID-19 infection for those who were fully vaccinated with Sinopharm and Pfizer-BioNTech, respectively. Results of effectiveness for partially vaccinated individuals were 62% and 83%, respectively [118].

6.1.7. Bharat Biotech BBV152 COVAXIN vaccine against COVID-19

Results revealed that the neutralizing titer of BBV152 COVAXIN, an inactivated COVID-19 vaccine, against the Delta variant, was reduced by 4.6-fold in comparison to D614G. However, the BBV152 vaccine yet could maintain significant effectiveness against the Delta variant [119,120].

6.1.8. Novavax vaccine against COVID-19 (NVX-CoV2373)

The NVX-CoV2373 (Novavax) COVID-19 vaccine is a type of subunit vaccine. It is a recombinant SARS-CoV-2 glycoprotein (S protein) nanoparticle vaccine with M matrix as an adjuvant. Novavax showed an effectiveness of 95.6% against the wild-type virus and 85.6% against the Alpha variant. In addition, it has shown an effectiveness of 49.4% against the Beta variant. Since the Delta variant showed a higher evasion from the neutralizing antibodies, lower effectiveness values would be predictable. As it has been reported, approximately 8 to 20-fold sensitivity reduction to vaccine-induced antibodies was observed for the Delta variant. However, no published data is available till now regarding the exact effectiveness value of subunit vaccines including the Novavax vaccine against the Delta variant [121].

7. Effectiveness of vaccines against currently circulating VOC

7.1. Effectiveness of vaccines against Omicron variant

7.1.1. Pfizer-BioNTech (BNT162b2)

Results of a recent study on live-virus neutralization assay revealed that the Omicron variant could escape the antibody neutralization by the Pfizer-BioNTech mRNA vaccine [125]. The effectiveness of Pfizer-BioNTech vaccine against hospitalization due to the Omicron variant infection in South Africa was 70% during the period of Omicron variant predominance, while this effectiveness was 93% during the period of the Delta variant outbreak. These results were obtained from the subjects who received two doses of the Pfizer-BioNTech vaccine. Therefore, due to the significant reduction in vaccine effectiveness during the Omicron pandemic, the necessity of a booster dose for providing efficient protection and viral coverage has emerged [126]. A cohort study on the Danish adult population revealed that about 4 weeks after the second dose of Pfizer-BioNTech vaccine administration, the neutralization titer against the Omicron variant was 14 folds lower in comparison to the reported titer against the D614G SARS-CoV-2. In addition, the amount of Omicron-specific neutralizing antibody response was reduced rapidly from 76.2% to 53.3%, and to 18.9% at weeks 4 and 8 to 10, and weeks 12 to 14 post-vaccination, respectively [127]. Administration of the Pfizer-BioNTech vaccine booster dose was accompanied with 20.6 folds and 7.7 folds increase in neutralizing antibody titers after 3 and 4 weeks, respectively. Furthermore, according to the results of this cohort study, the neutralizing antibody titers against the Omicron variant was significantly reduced in individuals older than or equal to 65 years of age in comparison to those younger than 65 [127].

7.1.2. Moderna (mRNA-1273)

Two-dose vaccination with the Moderna vaccine was accompanied by 85% effectiveness against the Omicron variant about 1 month after the second dose. However, the neutralizing antibody titer against the Omicron variant was 35 folds lower than that of the D614G variant. The Moderna vaccine effectiveness against the Omicron variant was reduced to 55% after 7 months of the second dose [128]. It has been reported that administration of the Moderna booster shot (50 μg) was associated with a 20-fold higher neutralizing antibody titers against the Omicron variant in comparison to that of 1 month after the second dose of Moderna vaccine. This peak titer was observed 1 month after the third dose (booster shot) of the Moderna vaccine. Results of the comparison of the effectiveness of 50 μg-dose booster and 100 μg-dose booster shots of the Moderna vaccine revealed that the neutralizing titers of the latter were 2.5 to 2.6-fold higher against the Omicron variant [128].

7.1.3. AstraZeneca-Oxford (ChAdOx1 nCoV-19)

According to the results of the recent studies, about 5 months after vaccination with the second dose of AstraZeneca-Oxford COVID-19 vaccine, no specific neutralizing antibodies were detected in the sera of 90% of the individuals and no anti-viral activity occurred after exposure to the Omicron variant. These results were comparable to those who were vaccinated with the Pfizer-BioNTech mRNA vaccine. In addition, it has been reported that the neutralization effectiveness against the Omicron variant was reduced 6 to 23 folds, therefore a booster dose or vaccination of those who recovered from COVID-19 infection is highly recommended to protect against the Omicron infection [129].

A summary of vaccines' effectiveness against the Omicron variant in England are summarized in Table 7.

7.1.4. Janssen/Johnson & Johnson (Ad26.COV2.S)

The Janssen vaccine effectiveness against hospitalization due to the Omicron infection was 55%, 74%, and 72% within 13 days, 14 to 28 days, and 1 to 2 months after the second dose administration among the South African population. In addition, the Janssen vaccine effectiveness against ICU admission and critical care requirement due to the Omicron infection was 69% and 82% at 14 to 27 days and 1 to 2 month after the second shot. These results revealed that after the 2-dose vaccine administration the effectiveness of the Janssen vaccine was comparable and equal to that of the Pfizer-BioNTech vaccine to provide protection against the severe disease due to the Omicron variant [131]. CDC has recommended that all adults (age $\geq$ 18 years old) who have received a single-dose Janssen vaccine should receive a booster shot at least 2 months after the first dose. This booster shot can be a homologous booster (another dose of the Janssen vaccine) or a heterologous mRNA booster dose. Results of a recent study reported that the Janssen vaccine effectiveness against the emergency department/urgent care (ED/UC) visits due to the Omicron variant after the first Janssen dose was 24%. While its effectiveness after the booster dose of homologous 2nd dose of Janssen vaccine and heterologous mRNA booster shot was 54% and 79%, respectively. These rates for protection against hospitalization due to the Omicron infection were 31%, 67%, and 78%, respectively. In this study, those who received 3 doses of mRNA vaccine (two scheduled doses and a booster shot) were considered as the control group and showed an effectiveness of 83% against the ED/UC visits and 90% against hospitalization due to the Omicron variant infection. Therefore, booster doses are crucial to prevent against moderate to severe COVID-19 infection during the Omicron outbreak and administration of the heterologous mRNA booster shots would be preferred for those who received a single-dose Janssen vaccine. [132].

7.1.5. Sinovac-CoronaVac COVID-19 vaccine

Results of a prospective cohort study revealed that the Omicron neutralizing antibody titers was significantly higher among those vaccinated with either Coronavac or Pfizer-BioNTech vaccine in comparison to non-vaccinated individuals. In addition, it has been reported that the amount of neutralizing antibody titers against the Omicron variant was significantly higher in those who received a two-dose CoronaVac vaccine than in those with single-dose CoronaVac. Therefore, it has been concluded that in order to induce detectable amounts of neutralizing antibodies against the Omicron variant in those with the previous COVID-19 infection, administration of 2 doses of CoronaVac vaccine and one dose of Pfizer-BioNTech vaccine would be crucial [133].

7.1.6. Sinopharm COVID-19 vaccine

The Omicron variant emerged with at least 30 mutations in spike protein of which 15 of these mutations are on RBDs. These mutations are responsible for more than 50% reduction in the binding capabilities of the RBDs of the Omicron variant and can lead to viral escape from the produced neutralizing antibodies of the inactivated vaccines or convalescent plasma therapy. The reduction in binding capabilities of RBDs in the Omicron variant was much higher than that of the Delta variant [134].

7.1.7. Bharat Biotech BBV152 COVAXIN vaccine against COVID-19

A live neutralization assay study on the effectiveness of the COVAXIN vaccine revealed that in those who received a booster shot at least 6 months after the second dose, antibody-neutralizing activity was observed against the D614G, Delta, and Omicron variants. In addition, it has been reported that the neutralizing potential of the boosted COVAXIN against the Delta and Omicron variants was 100% and 90%, respectively among the participants. Therefore, the administration of the booster doses of COVAXIN would be essential in order to induce sufficient neutralizing antibody titers against the Omicron variant [135].

7.1.8. Novavax vaccine against COVID-19 (NVX-CoV2373)

FDA staff declared that although the Novavax vaccine, a protein-based recombinant vaccine, obtain sufficient effectiveness against the

Table 7
Vaccine effectiveness against BA.1 and BA.2 Omicron subvariants in those who received either Pfizer-BioNTech, Moderna, or Oxford-AstraZeneca vaccines as the 1st and 2nd doses of COVID-19 vaccines and Pfizer-BioNTech or half-dose Moderna vaccines as booster shots in England.

	Vaccine effectiveness against BA.1 after the 2nd dose	Vaccine effectiveness against BA.2 after the 2nd dose	Vaccine effectiveness against BA.1 after the booster shot	Vaccine effectiveness against BA.2 after the booster shot	Ref.
Effectiveness against symptomatic COVID-19	14.8% (25 weeks after the 2nd dose)	27.8% (25 weeks after the 2nd dose)	70.6% (7 days after the booster dose) 37.4% (15 weeks after the booster dose)	74% (7 days after the booster dose) 43.7% (15 weeks after the booster dose)	[130]
Effectiveness against hospitalization due to COVID-19	89% after 14 days	88% after 14 days	90.8% (7 days after the booster dose) 80.4% (15 weeks after the booster dose)	89.1% (7 days after the booster dose) 56.5% (15 weeks after the booster dose)	

Omicron variant, however a rare and severe cardiac adverse effects of myocarditis should be considered. Novavax is administered in 2 doses 3 weeks apart. On June 7th, 2022, the Novavax vaccine received the emergency use authorization (EUA) from the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the prevention of COVID-19. Results of phase 3 clinical trial on June 2021 reported effectiveness of 90% for the Novavax vaccine which was attributed to the era before the Delta and Omicron variants' dominance [136].

7.1.9. Sputnik V(Gam-COVID-Vac)

Several studies have suggested that the administration of the 3 doses of vaccines or a combination of vaccination and COVID-19 infection could significantly enhance neutralizing antibody titers against the Omicron variant. Results of a recent study revealed that the neutralizing antibody titers against the Omicron variant in individuals who received 2 doses of the Sputnik V vaccine were reduced 8.1 folds in comparison to the wild-type (D614G) SARS-CoV-2 variant. In addition, this study declared that these Omicron-specific neutralizing antibodies were detected in 74.2% of those vaccinated with the Sputnik V vaccine [137]. These results were comparable to that of the 2-dose BNT162b2 vaccinated individuals who showed a 21.4-fold reduction in neutralizing antibody titers. These neutralizing antibodies were detected in 56.9% of those vaccinated with the Pfizer-BioNTech mRNA vaccine. Although a stable level of IgG antibodies against the Omicron variant was observed in the Sputnik V vaccinated groups over time, however, the IgG level in sera of Pfizer-BioNTech vaccinated individuals was maximum at 2 weeks after the second-dose vaccine and diminished significantly at 3- and 6-month post-vaccination periods. Individuals who experienced a mild or asymptomatic COVID-19 infection and received 2 doses of Sputnik V vaccine showed 5 folds and 6.7 folds reduction in Omicron-specific neutralizing antibodies titers, respectively. Furthermore, the necessity of booster dose administration using the Sputnik Light booster shot is recommended to obtain better protection against the Omicron variant [137].

8. Discussion and conclusion

The COVID-19 pandemic during approximately the past 3 years had profound socio-economical and health complications globally. According to the formal reports of the National health authorities till this date (10.30.2022) at least 6.59 million people died due to COVID-19 infection, however, based on the significant rise in yearly mortality rate in different countries, WHO has estimated more than 18 million deaths due to the pandemic of COVID-19 [138,139]. Unfortunately, none of the approved antiviral drugs to date were effective enough to cure the infected patients and most of the therapeutic efforts focused on supportive therapy to control the COVID-19-related complications [140]. Enormous efforts were made to introduce effective vaccines in order to provide substantial protection against the infection and dozens of effective vaccines have been introduced during the last 3 years [29]. Although the introduced vaccines were of different platforms and showed different efficacies, the goal of global vaccination was achieved, although not equally in different regions, and now the COVID-19 pandemic is relatively under control [141]. However, the emergence of new variants of SARS-CoV2 is now a general concern. Despite the early start of the vaccination program in developed countries, unfortunately, due to vaccine shortages and the unavailability of vaccines in developing countries, the vaccination program started with a considerable lag time in many countries which was one of the main causes of the developing of new variants of COVID-19 which is a new challenge even in developing countries with considerable coverage of full vaccination program [142]. As mentioned in previous parts of this paper most of the mutations happened in the genes that code the S protein of the virus which is responsible for the cell internalization process of the virus. The consequences of these mutations were an increased rate of transmissibility of the virus [143]. Additionally, in most of these cases, antibody titers against COVID-19 were reduced considerably and vaccine effectiveness was reduced in mutated variants, especially in Delta and Omicron variants [144,145]. Although the reduction in vaccine effectiveness was evident in these newly circulating COVID-19 variants but due to the massive vaccination in 2021, the mortality rate of COVID-19 was diminished profoundly in 2022 [146]. Based on previous reports and the data discussed in the present review, the necessity of a booster dose is crucial in order to enhance COVID-19 vaccines' effectiveness against the newly emerging SARS-CoV-2 variants [32,147].

Recently, on 31st August 2022, FDA authorized the emergency use of bivalent formulations of the Moderna COVID-19 vaccine and Pfizer-BioNTech COVID-19 vaccine. These bivalent COVID-19 vaccines, also known as updated boosters, can be used as a single booster vaccine shot at least 2 months after the primary or booster vaccine doses. These updated boosters are containing two mRNA components of SARS-CoV-2. One of these components is from the original strain of SARS-CoV-2 and the other one is the common strain of BA.4/BA.5 sublineages of the Omicron variant. In this regard, the bivalent Moderna and the bivalent Pfizer-BioNTech COVID-19 vaccines have been authorized for use as a single booster shot for individuals $\geq$ 18 and $\geq$ 12 years old, respectively. All individuals with the mentioned years of age are eligible to receive the bivalent booster shot at least 2 months after completion of their primary COVID-19 vaccination or injection of previous monovalent booster doses [41]. Previous studies revealed that 3 to 4 doses of the parental mRNA vaccines (Pfizer-BioNTech or Moderna COVID-19 vaccine) failed to elicit robust neutralization against BA.4/5 sublineages [148,149]. Results of a recent study in the United States revealed that the BA.5 bivalent booster mRNA vaccines showed high neutralizing antibody titer against BA.4/5, while it could not induce robust neutralization against BA.2.75.2, BQ.1.1, and XBB.1 Omicron sublineages. The rate of neutralization evasion for the most recently emerged Omicron sublineages were as follows: BA.4/5 $<$ BA.4.6 $<$ BA.2.75.2 $\leq$ BQ.1.1 $<$ XBB.1 Furthermore, results of this study emphasized that a previous infection with SARS-CoV-2 could significantly enhance neutralization titer elicited with BA.5 bivalent booster shots. [108]. The possible cause of reduced neutralizing antibody titer and vaccine effectiveness against BQ.1.1 and XBB.1 sublineages can be attributed to R346T substitution that can lead to higher humoral immune evasion of these new sublineages in comparison to BA.5 and BA.2 [150].

This pandemic revealed that fast sharing of scientific findings regarding different aspects of such diseases will help us better control the pandemic and reduce mortality, morbidity, and socio-economical complications. Considering the possible development of new variants of this virus in the near future stipulates and highlights the necessity of early and prompt cooperation between scientists and pharmaceutical companies to respond properly and in a timely manner to provide smart preventive and therapeutic strategies to cease the possible dreadful infections.

According to the obtained data, efficient vaccination using updated bivalent mRNA vaccines (COMIRNATY® Original/Omicron BA.4–5 COVID-19 vaccine and SPIKEVAX® bivalent Original/Omicron BA.4–5 COVID-19 vaccine) would be crucial to prevent circulation of the newly developed variants. In addition, precise observation of the newly developing SARS-CoV-2 variants is essential for the early detection of VOCs which will hopefully prevent further global virus distribution. Close monitoring of the newly developing sublineages as well as performing preventive actions to reduce the risk of the disease burden would be pivotal.

The main limitation of this study was the unavailability of sufficient data regarding the vaccine effectiveness against some transient variants including Zeta, Eta, Theta, and Lota which did not last too long to be evaluated. In addition, the effectiveness of some vaccines, mostly used in Eastern countries, against the currently circulating SARS-CoV-2 variants were not available. Last but not least, the previous and currently

circulating variants were not distinguished in some nations, especially in developing countries, therefore, vaccine effectiveness against each of these variants was not assessed in those populations.

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Authors' contribution statement

Negar Firouzabadi contributed to study design, data gathering, writing-original draft, writing-review and editing. Parisa Ghasemiyeh contributed to study design, data gathering, writing-original draft, writing-review and editing. Fatemeh Moradishooli contributed to data gathering and writing-original draft. Soliman Mohammadi-Samani contributed to conceptualization, study design, supervision, data gathering, and writing-original draft, writing-review and editing.

CRediT authorship contribution statement

Negar Firouzabadi: Writing – original draft, Writing – review & editing. **Parisa Ghasemiyeh:** Writing – original draft, Writing – review & editing. **Fatemeh Moradishooli:** Writing – original draft. **Soliman Mohammadi-Samani:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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