SARS-CoV-2 vaccine challenge based on spike glycoprotein against several new variants

The coronavirus disease 2019 pandemic has not ended, and several variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus continue to emerge. The emergence of new variants is worrying because higher transmission leads to spikes in infections, vaccine efforts, and other therapeutic developments. Existing literature reports that with new variants affecting vaccine efficacy, hospitalization and risk of a recurrent infection increase. In this review article, we describe the latest variants of SARS-CoV-2, and the impact of each new variant on the efficacy of the developed vaccines reported in the literature and findings. The report concludes that the emergence of a variant that completely evades the immune response and reduces neutralizing antibodies.

Keywords: COVID-19 vaccines, SARS-CoV-2 variant, COVID-19

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious and pathogenic coronavirus (CoV) that has caused a pandemic of acute respiratory disease, named “coronavirus disease 2019” (COVID-19) [1]. COVID-19 was initially characterized as an unknown form of pneumonia [2]. Like SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and animal CoVs, SARS-CoV-2 infection is not limited to the respiratory system but can trigger an exaggerated immune response, leading to multiple organ failure and death [3]. Since the COVID-19 pandemic first hit on December 31, 2019, it has spread worldwide and resulted in more than 3.8 million deaths worldwide [4,5].

Like other CoVs, the SARS-CoV-2 genome encodes a spike (S) glycoprotein, which protrudes from the surface of the mature virion [6]. Glycoprotein S plays an essential role in viral attachment, fusion, and entry into host cells [7]. Each trimeric S protein monomer is approximately 180 kDa and contains two subunits, S1 and S2, which mediate membrane attachment and fusion, respectively [8]. The surface-exposed location of glycoprotein S allows it to carry out membrane fusion and makes it a direct target for the host immune response, making it a prime target for neutralizing antibodies [9]. Due to its central role in viral infection and eliciting humoral and cellular immune responses mediated in the host during infection [6], protein S is a significant target for current vaccine development because antibodies directed against these proteins can neutralize infection [7].
Various countries have developed several SARS-CoV-2 vaccines (i.e., inactivated vaccine, recombinant protein vaccine, adenovirus vector vaccine, DNA vaccine, and RNA vaccine). This vaccine has achieved vaccine efficacy of up to 95% in clinical trials. However, concerns have been raised regarding the reduction of vaccine efficacy against globally emerging variants [10-13]. Viruses are constantly changing through mutations, and new variants are expected to continue to emerge. Some variants appear and disappear, while others may appear and persist [14]. The SARS-CoV-2 variant is thought to or is known to affect viral characteristics such as transmissibility, disease severity, immune shedding, and diagnostic or therapeutic release. In addition, genetically altered SARS-CoV-2 variants were identified as causing significant community or multiple-cluster transmission of COVID-19, in many countries with increasing relative prevalence as the number of cases increased over time, or other significant epidemiologic impacts suggesting emerging risks to global public health [15,16]. This review focuses on using S glycoproteins as potential antigens, mutations, and characteristics of the SARS-CoV-2 variants of concern (VOC), effectiveness, and immunogenicity of currently available vaccines against existing variants.

The Structure of the Coronavirus and Its Role

CoV is a subfamily Coronavirinae of the Coronaviridae family. The CoV genome is 27–32 kb in size and is single-stranded positive-sense RNA. CoV genome size is larger than other RNA viruses. All CoVs are highly pathogenic, including SARS-CoV-2, which belongs to the Betacoronavirus. The SARS-CoV-2 particles are spherical or pleomorphic, and the SARS-CoV-2 genome sequence is 80% similar to the SARS-CoV genome and 50% to MERS-CoV. The genome consists of 14 open reading frames (ORFs). Two-thirds encode 16 non-structural proteins (nsp1-16), the remaining one-third encode nine accessory subunits, namely the S1 and S2 subunits. The S1 subunit consists of an N-terminal domain (NTD) and a receptor-binding domain (RBD), which bind to host cell receptors. The S1 domain acts as the primary surface antigen. The S2 protein mediates the entry of CoV into the host cell. Transmembrane glycoprotein (S) forms a homotrimer that protrudes from the viral surface. There are 15–30 freely rotating S proteins on the viral envelope. Spike glycoproteins are so important for the entry of CoV that they are attractive antiviral targets. The S protein consists of two functional subunits, namely the S1 and S2 subunits. The S1 subunit consists of an N-terminal domain (NTD) and a receptor-binding domain (RBD), which bind to host cell receptors. The S1 domain acts as the primary surface antigen. The S2 subunit consists of a fusion peptide, heptad repeat 1 (HR1), heptad repeat 2 (HR2), transmembrane domain, central helix, connector domain, and cytoplasmic tail [17,18]. HR1 and HR2 form a six-helical (6-HB) bud responsible for membrane fusion dominated by the SARS-CoV and SARS-CoV-2 spike proteins, making HR1 and HR2 attractive drug targets. 6-HB in SARS-CoV-2 can increase the interaction between HR1 and HR2, thereby increasing the infectivity of SARS-CoV-2 [17].

Non-structural proteins

Nsp1 mediates RNA processing and replication. Nsp2 modulates the survival signaling pathway of host cells. Nsp3 is believed to separate the translated protein. Nsp4 contains transmembrane domain 2 (TMT2) and modifies the endoplasmic reticulum (ER) membrane. Nsp5 participates in polyprotein processes during replication. Nsp6 is thought to be a transmembrane domain. Nsp7 and Nsp8 significantly increased the combination of nsp12 and template-primary RNA. Nsp9 functions as an ssRNA binding protein. Nsp10 is essential for cap methylation of viral mRNA. Nsp12 contains RdRp (RNA-dependent RNA polymerase), an essential component in CoV replication/transcription. Nsp13 is bound to adenosine triphosphate, and the zinc-binding domain of nsp13 participates in replication and transcription. Nsp14 is an exoribonuclease proofreading domain. Nsp15 has Mn (2+) dependent endoribonuclease activity. Nsp16 is a 2'-O-ribose methyltransferase. One study showed that several NSPs mediate the effects of splicing, translation, and protein trafficking to inhibit host defense. After SARS-CoV-2 infection, Nsp16 binds to the mRNA recognition domain of the U1 and U2 snRNAs to suppress mRNA splicing. Nsp1 binds to the 18s ribosomal RNA at the ribosomal mRNA inlet to interfere with mRNA translation. Nsp8 and Nsp9 bind to 7SL RNA located in the signal recognition particle to damage trafficking proteins to cell membranes [17,18].

Structural proteins

Spike glycoprotein (protein S) mediates the entry of CoV into the host cell. Transmembrane glycoprotein (S) forms a homotrimer that protrudes from the viral surface. There are 15–30 freely rotating S proteins on the viral envelope. Spike glycoproteins are so important for the entry of CoV that they are attractive antiviral targets. The S protein consists of two functional subunits, namely the S1 and S2 subunits. The S1 subunit consists of an N-terminal domain (NTD) and a receptor-binding domain (RBD), which bind to host cell receptors. The S1 domain acts as the primary surface antigen. The S2 subunit consists of a fusion peptide, heptad repeat 1 (HR1), heptad repeat 2 (HR2), transmembrane domain, central helix, connector domain, and cytoplasmic tail [17,18]. HR1 and HR2 form a six-helical (6-HB) bud responsible for membrane fusion dominated by the SARS-CoV and SARS-CoV-2 spike proteins, making HR1 and HR2 attractive drug targets. 6-HB in SARS-CoV-2 can increase the interaction between HR1 and HR2, thereby increasing the infectivity of SARS-CoV-2 [17].
The function of the S2 subunit is to fuse the viral and host cell membranes. The cleavage site at the boundary between the S1 and S2 subunits is called the S1/S2 protease cleavage site. In all CoVs, host proteases cleave spike glycoproteins at the S2 cleavage site to activate critical proteins for viral and host cell membrane fusion through irreversible conformational changes. N-linked glycans for precise folding, neutralizing antibodies, and extensively decorating spike protein trimmers. There is a furin cleavage site at the boundary of the S1 and S2 subunits (RRAR). This site distinguishes SARS-CoV-2 from other SARS-CoV and CoVs. Another remarkable feature of SARS-CoV-2 is the addition of a proline residue at the start of the furin cleavage site. This incorporated proline creates changes that are predicted to result in O-linked glycosylation at positions S673, T678, and S686 [17,18].

The SARS-CoV-2 spike protein contains RBD that explicitly recognizes the angiotensin-converting enzyme 2 (ACE2) receptor and is an important target for antiviral and antibody components [17]. The region that interacts with ACE2 is highly conserved among CoVs. The identity of SARS-CoV-2 and SARS-CoV decreased in the RBD region. Only 74% identical RBD explains why the two viruses attach to different receptors on the host cell. In SARS-CoV, mutations in RBD can occur in cell cultures. Thus, it is theoretically possible for SARS-CoV-2 to acquire mutations in RBD as an adaptation during cross-species transmission. Mutations in RBD increase in structural protein S and bind antibodies to other strains. Following the initial interaction between the S1 domain and the host ACE2 receptor, the S2 segment mediates the fusion of the host and viral membrane, allowing the viral RNA genome to enter the host cell [18].

Protein E

Glycoprotein M is the most abundant component of CoVs. The M protein is a multi-span membrane protein characterized by three transmembrane domains: an inside C-terminus and an outer N-terminus. The third transmembrane domain contains the amphipathic region at the end. This region was highly conserved in all members of the Coronaviridae. The M protein plays a role in viral assembly and its internal homeostasis. Transmembrane participates in interactions between proteins. M protein CoV can interact with RNA that encodes information about genomic packing signals. These findings support their primary role in virion particle assembly. As one of the main proteins of CoVs, M protein is thought to be involved in the regulation of RNA replication and packaging into mature viral particles. The M protein of SARS-CoV was reported to interact with host cell nuclear factor (NF)-B, decreasing the cyclooxygenase 2 (Cox 2) gene expression. In addition, M protein may contribute to pathogenesis by hijacking the NF-B- and Cox-2-mediated host inflammatory response [18].

N proteins

N proteins range from 43 to 50 kDa and bind to gRNA. Overall, N proteins are divided into three conserved domains: N arm, central linker (CL), and C tail. NTD and C-terminal domain (CTD) are essential structural and functional domains. The function of NTD is to bind to RNA and is mainly occupied by positively charged amino acids. CTD mediates N protein dimerization via self-association and contains a nuclear localization signal. CTD plays an important role in the oligomerization of nucleocapsid proteins and the interaction of N and M proteins. The CL region is thought to interact specifically with the M protein. The amino acid sequence of the N protein in SARS-CoV-2 is estimated to be 90% identical to that of the N protein in SARS-CoV. The functions of N proteins include viral RNA replication and transcription, formation, and maintenance of ribonucleoprotein complexes. N protein has also been reported to be involved in the interaction of the virus with the host, namely regulating the host cell cycle, including apoptosis to facilitate viral multiplication and spread. Recently three nuclear localization signals (NLS1-NLS3) and two nuclear export signals (NES1 and NES2) were reported in the SARS-CoV-2 N protein, which is supposed to play an essential role in viral protein assembly [18].

SARS-CoV-2 variant

To aid public discussion of variants, the World Health Orga-
nization (WHO) proposes using labels consisting of the Greek alphabet, e.g., Alpha, Beta, Gamma, as a practical way of discussing variants by non-scientific audiences [15]. As part of the WHO assessment of circulating variants, a clear understanding of the amino acid substitutions characteristic of each variant is required. A profile of amino acid changes in the spike protein was generated for each variant based on the first 1,000 genomes available at GISAID (genomes with less than 29,000 nucleotides and >5% Ns were excluded; https://www.gisaid.org/). Amino acid changes were present in 85% of the sequences shown. Of note, relevant amino acid changes may exist in other regions of the SARS-CoV-2 genome. Not all amino acid changes in the spike protein are associated with potential changes in the characteristics of viral variants [15].

The D614G mutation in the spike glycoprotein was first detected in March 2020 and spread throughout the world predominantly in the following month. In late January in China, the D614G mutation was detected by sequencing. The effect of this mutation occurs in receptor binding. Genetic and phylogenetic analyzes performed on more than 25,000 sequences from the United Kingdom found that viruses carrying D614G appeared to spread more rapidly and form larger phylogenetic clusters than viruses carrying D614D. Recent studies on experimental animals indicate that the virus-carrying D614G is more easily transmitted [21].

The spike N501Y mutation has been found in Alpha (B.1.1.7; 20I/501YV1), Beta (B.1.351; 20H/501YV2), and Gamma (P.1; 20j/501YV3) variants. The E484K mutation occurs in Beta and Gamma variants and has occurred independently in many other lineages, including Zeta (P.2; 20B/S.484K), B.1.1.318, Eta (B.1.525; 20A/S/484 K), and Iota [22]. K417N/T, E484K, and N501Y decreased the neutralizing activity of convalescent serum and vaccine mRNA [22].

Alpha variant (lineage B.1.1.7) was first reported in the United Kingdom [15]. The B.1.1.7 lineage, also called 501YV1 carries a mutation in the S protein (N501Y). These mutations affect the conformation of the RBD [21,23]. Thirteen B.1.1.7 lineage-determining mutations, some of which are in the S protein, including deletions at positions 69 and 70 (del69–70) that evolved spontaneously in other SARS-CoV-2 variants and are known to increase transmissibility [23]. Eight of the B.1.1.7 lineage mutations are in the spike glycoprotein, including N501Y at the RBS, the del69–70, and P681H at the furin cleavage site. All of these mutations can affect ACE2 binding and viral replication. The spike variant 501Y is predicted to have a higher affinity for human ACE2, and this mutated variant, along with other variants, is spreading rapidly in South Africa [21].

In May 2020, the earliest documented sample of the Beta variant (B.1.351) was South Africa [15]. A study conducted in Brazil found the B.1.351 (501Y) mutation characterized by: ORF1ab: T265I, R724K, S1612L, K1655N, K3353R, SGF 3675 F3677del, P4715L, E5585D; spike: D80A, D215G, L242 L244del, A282D, K417N, E484K, N501Y, D614G, A701V, C1247F; ORF3a: Q57H, S171L, E-P71L; ORF7b: Y10F; N:T205I; and ORF14: L52F [24]. Three substitutions (K417N, E484K, and N501Y) at residues in its RBD may be of functional importance [25]. The most important site is E484, where neutralization by multiple plasmas is reduced >10-fold by multiple mutations, including one in the emerging 20H/501YV2 lineage [25]. Mutations in this lineage are associated with increased transmissibility or immune flight [26].

Gamma (P.1) variant was first identified in Brazil [27]. The P1 lineage (20I/501Y) exhibits 17 mutations, including a trio of spike proteins (K417T, E484K, and N501Y) associated with increased binding to the human ACE2 receptor [28]. All lineages possessing the N501Y mutation in the RBD directly bind to the ACE2 receptor of the host cell, contributing to increased transmissibility [22]. Studies using a two-category dynamic model integrating genomic and mortality data estimate that P.1 maybe 1.7 to 2.4 times more infectious [26]. Case reports in Brazil had 3/5 cases of the P1 lineage reported developing as severe COVID-19, which required prolonged intensive care unit care with one associated death. The information interprets that the P1 lineage may assume an increased risk of severe infection or higher mortality. This association is still speculative, so further studies are needed to assess this possibility comprehensively [27].

The Delta (B.1.617) variant was first discovered in India with RBD L452R and E484Q mutations and P681R at the furin cleavage site. It was revealed that this might result in increased ACE2 binding and S1–S2 cleavage rates resulting in better transmissibility [29]. In vitro, B.1.617.2 was six-fold less sensitive to serum neutralizing antibodies than recovered individuals and eight-fold less sensitive to vaccine-evoked antibodies than Wuhan-1 wild-type containing D614G. B.1.617.2 had higher replication and spike-mediated entry than B.1.617.1, which could potentially explain the dominance of B.1.617.2. B.1.617.2 showed higher replication efficiency than B.1.1.7 in both the airway organoid and the human airway epithelial system, corresponding to the B.1.617.2 spike being in a primarily split state than the B.1.1.7 spike [30].

The majority of the mu (B.1.621) variant contains: The T95I
and YY144–145TSN mutations in the NTD. Mutations R346K, E484K, and N501Y in the RBD. D614, G, P681H, and D950N mutations in other regions of the spike protein. Some of these mutations are usually identified in the variant of concern. E484K is shared by beta and gamma variants [31]. Mu variant is known to be more resistant to antibody neutralization [31].

Variant B.1.1.28, notable by five single nucleotide variants (SNV): C100U, C28253U, G28628U, G28975U, and C29754U. SNV G23012A (E484K), in the spike protein receptor binding domain, was widespread throughout the sample. This mutation was previously associated with the release of neutralizing antibodies against SARS-CoV-2 [32].

The newest variant of B.1.1529, named Omicron, was first reported from South Africa on 24 November 2021 and is currently categorized as VOC. This variant has many mutations, some of which are worrying. Compared with other VOCs, preliminary evidence suggests an increased risk of reinfection with this variant. The number of new cases of this variant increases in almost all South African provinces. Several ongoing studies and the “Technical Advisory Group on SARS-CoV-2 Virus Evolution” will continue to evaluate this variant [33].

The Effectiveness of the SARS-CoV-2 Vaccine against New Variants

We summarize the efficacy and effectiveness of the COVID-19 vaccine shown in Table 1 [12,34-48]. This efficacy and effectiveness may differ between trials, even in terms of the definition of symptomatic disease. Vaccine effectiveness varies from vaccine efficacy in that it reduces the risk of infection or disease among vaccinated individuals. This can be affected by the effect of the vaccine depending on the population and vaccination schedule, and the handling/administration of the vaccine.

The efficacy of the ChAdOx1 nCoV-19 vaccine against the Beta variant analyzed as a secondary endpoint, was 10.4% (95% confidence interval [CI], -76.8% to 54.8%) [40]. The effectiveness of the ChAdOx1 nCoV-19 vaccine was 74.5% (95% CI, 68.45% to 79.4%) among people with the alpha variant and 67.0% (95% CI, 61.3% to 71.8%) among people with delta variant [34]. A study of 130 healthcare workers infected with SARS-CoV-2 at three centers in India found that the effectiveness of the ChAdOx1 vaccine was decreased against B.1,617.2 compared to non-B.1,617.2, with caveats. Against the Delta B.1.617.2 variant, the efficacy of highly susceptible compromised vaccines and immune evaders requires continued infection control measures in the post-vaccination era [30]. The study, conducted by Lopez Bernal et al. [34], showed that the vaccine’s overall effectiveness (BNT162b2 or ChAdOx1 nCoV-19) was high against symptomatic disease with delta variant after receiving two doses. The study combining the ChAdOx1 nCoV-19/BNT162b2 prime-boost heterologous vaccination found adjusted vaccine effectiveness of 67% [40]. The vaccine effectiveness adjusted for prime-boost vaccination of heter-

**Table 1.** Reported studies of the severe acute respiratory syndrome coronavirus 2 variant on vaccine efficacy and effectiveness

| Vaccine                   | Platform         | Vaccine effectiveness and efficacy against SARS-CoV-2 variant |
|---------------------------|------------------|--------------------------------------------------------------|
|                           |                  | Original virus/Alpha (B.1.1.7) | Beta (B.1.351) | Gamma (P1) | Delta (B.1.617.2) |
| BNT162b2 (Pfizer-BioNTech)| mRNA             | 95% after second dose [35]       | 93.7% [34]     | 49% [36]   | Unknown            | 51.9% after second dose [37]; 88.0% [34] |
| NVX-CoV2373 (Novavax)     | Protein subunit  | 95.6% [38]                        | Efficacy of 86.3% [39]; 85.6% [38] | 60% [38]   | Unknown            | Unknown |
| ChAdOx1 nCoV-19 (Oxford-AstraZeneca) | Viral vector     | Vaccine efficacy was 74.0% [12] | 74.5% [34]       | Vaccine efficacy was 10.4% [40] | 77.9% [41]       | 67.0% [34] |
| CoronaVac                 | Inactivated      | Vaccine efficacy was 50.7% – 83.5% [42] | -               | -               | 36.8% after second dose [43]; 55.5% – 83.3% after second dose [44] | -               |
| Ad26.COV2                 | Viral vector     | -                              | -               | 52.0% – 64% [45] | -               | -               |
| Moderna mRNA-127          | mRNA             | 88.7% after the 37 second dose [46] | 100% after second dose [47] | 96.4% after the second dose [47] | -               | 73.1% after second dose [37] |
| Gam-COVID-Vac             | Recombinant      | 85.7% after the 37 second dose [46] | -               | -               | -               | Efficacy of 69.85% after single-dose [48] |

It is not possible to directly compare studies because of differences in efficacy endpoints; data are provided to provide an idea of possible trends in the impact of variants on vaccines.
ologous ChAdOx1 nCoV-19/mRNA-1273 was 79% [40]. Another study by Nasreen et al. [49] estimated the effectiveness of BNT162b2, mRNA-1273, and ChAdOx1 vaccines against infection with SARS-CoV-2 variant Alpha, Beta, Gamma, and Delta in symptomatic patients and severe outcome (COVID-19 hospitalization or death) in Ontario, Canada. The results found that a single dose of these three vaccines provided substantial protection against the 4 SARS-CoV-2 variants [49].

With the BNT162b2 vaccine, the two-dose effectiveness was 93.7% (95% CI, 91.6% to 95.3%) among those with the alpha variant and 88.0% (95% CI, 85.3% to 90.1%) among those with a delta variant [34]. The cohort study compared the effectiveness of two Spike full-length protein-coding mRNA vaccines from Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) when the prevalence of alpha or delta variants was very high. The results of the study showed that both vaccines were highly effective against SARS-CoV-2 infection (mRNA-1273: 86% [95% CI, 81.9–90.6%]; BNT162b2: 76% [95% CI, 69.3–81.1%]) and COVID-19 associated hospitalization (mRNA-1273: 91.6% [95% CI, 81.5–97.1%]; BNT162b2: 85% [95% CI, 73.8–93.3%]) [50]. Studies by Lefèvre et al. [36] found the effectiveness of the vaccine against all forms of beta infection estimated at 49% (95% CI, 14.4–69%) and 86% (95% CI, 67.0–94%) against severe forms of disease after the second dose of BNT162b2 mRNA COVID-19 vaccine for at least 7 days. These results were lower than those of a test-negative case-control study in Qatar, where effectiveness against beta infection was 75% (95% CI, 71.4–78.9%), and effectiveness against beta infection in severe disease was 97% (95% CI, 92.0–100%) [51]. In the study conducted by Charmet et al. [52], the second dose of vaccine mRNA (BNT162b2mRNA or Moderna mRNA-127) became 88% against the original virus, 86% against B.1.1.7, and 77% against the B.1.351/P.1 lineage. The study over the Delta period found that the effectiveness of the adjusted (Pfizer-BioNTech and Moderna) mRNA (Pfizer-BioNTech and Moderna) vaccines were 53.1% (95% CI, 49.1%–56.7%). Vaccine efficacy is lower after the Delta variant becomes the dominant circulating strain in the United States [53]. A study conducted in Scotland of 114,706 cases of SARS-CoV-2 infection detected in almost all infections of the delta variant found that the Oxford-AstraZeneca vaccine was 91% effective in preventing death in people who had been double vaccinated. In contrast, the Pfizer-BioNTech vaccine was 90% effective [54].

Preliminary data from clinical trials indicate the effectiveness of the Novavax vaccine against the original SARS-CoV-2 variant is 95.6% but also protects against the newer variants B.1.1.7 (85.6%) and B.1.351 (60%) [38]. In another trial of the NVX-CoV2373 vaccine against variant B.1.351, the vaccine efficacy was only 49.4% [55]. But the data carry mixed news, although Novavax was more than 85% effective against the COVID-19 variant identified in the United Kingdom, it was less than 50% effective against an alarming lineage called 501YV2 (B.1.351), which was detected in South Africa and spread worldwide. The researchers estimated that Novavax injection was more than 95.6% effective against the original virus, compared with 85.6% against B.1.1.7 [56].

In a single-dose test-negative case-control study in which the Gamma variant accounted for 86% of the SARS-CoV-2 genotype sample, the adjusted CoronaVac vaccine’s efficacy (49.6%; 95% CI, 11.3%–71.4%) on possible symptomatic SARS-CoV-2 infection for 14 days or more. The adjusted effectiveness of CoronaVac after receiving the second dose was 36.8% (95% CI, 54.9%–74.2%) against symptomatic SARS-CoV-2 infection for 14 days or more [43]. Another test-negative case-control study showed the effectiveness of CoronaVac against the gamma variant adjusted for COVID-19 symptoms was 24.7% at 0–13 days and 46.8% at 14 days after the second dose [44].

A study conducted in South Africa showed 86 out of 91 cases (94.5%) with consecutive viruses having the 20H/501YV2 variant, the efficacy of the Ad26.COV2.S vaccine was 52.0% and 64.0% against COVID-19 moderate to severe critical with onset at least 14 days and at least 28 days after administration, respectively—the efficacy of Ad26.COV2.S against critically severe COVID-19 was 73.1% and 81.7%, respectively [45]. Nonrandomized studies across US clinical practice demonstrated the effectiveness of the Ad26.COV2.S vaccine with a high incidence of Delta variant being 78% (73% to 82%) for infection and 85% (73% to 91%) for hospitalization [57].

The study conducted to assess the effectiveness of the adenovirus-based vaccine (recombinant adenovirus), Gam-COVIDVac (Sputnik V), for preventing laboratory-confirmed infections was 78.6% (95% CI, 74.8–81.7%). The effectiveness of the Sputnik V vaccine in reducing hospitalizations and mortality was 87.6% (95% CI, 80.3%–92.2%) and 84.8% (95% CI, 75.0%–90.7%), respectively [58].

**Antibody Response of Vaccine Based on Glycoprotein against SARS-CoV-2 Variant**

Vaccination induces both humoral and cellular responses, but it is extensively thought that vaccine-induced neutraliz-
ing antibodies against the RBD of the SARS-CoV-2 S protein are a plausible protective mechanism. Animal studies show neutralizing antibodies against protein S can provide complete protection [59]. Spike mutations can affect susceptibility to neutralization by antibodies evoked by vaccination with the original spike sequence [60]. Different mutations varied the neutralizing potential of the serum antibody spike, and the mutants with the lowest neutralizing potential were K417N/E486K/N501Y and K417T/E486K/N501Y. The neutralizing potential of this infected person correlates with that of a previously uninfected vaccine, suggesting a similar susceptibility to spikes in antibody mutations elicited by natural infection or vaccination alone [60].

The serum neutralizing titer against B.1.617.2 was lower in the ChAdOx1 vaccine than in the BNT162b2 vaccine [29]. A cohort study involving volunteers who received a second injection of the mRNA-1273 or BNT162b2 vaccine against SARS-CoV-2 showed high levels of anti-SARS-CoV-2 immunoglobulin (Ig)M and IgG spikes 8 weeks after vaccine. In addition, plasma neutralizing activity and relative numbers of RBD-specific memory B cells from vaccinated volunteers were equal to those of individuals who had recovered from natural infection [22].

Several studies have shown that recipients of the Ad26.COV2.S vaccine has lower neutralizing activity against viral variants [61, 62]. In a study by Moore et al. [62], 501Y.V2 neutralization decreased significantly compared to Wuhan-1 D614G, with 22/27 (82%) serum showing no detectable 501Y.V2 neutralization on day 29. The study compared antibody titers of the Ad26.COV2.S vaccine against variants B.1.351 and P.1 was found 5.0-fold and 3.3-fold lower than WA1/2020 after vaccination on day 71. The binding antibody titers were 2.9-fold and 2.7-fold lower, against variants B.1.351 and P.1, respectively, compared to the original SARS-CoV-2 strain. These results indicate that the neutralizing antibody response induced by Ad26.COV2.S has reduced against B.1.351 and P.1 variants, but the functional non-neutralizing antibody response and the T-cell response were mainly preserved against the SARS-CoV-2 variant [63]. The B.1.351 variant was resistant to receptor binding of the RBD, mainly due to a mutation leading to the E484K substitution. B.1.351 was significantly more resistant to neutralization by convalescent plasma (9.4-fold) and serum than vaccinated individuals (10.3–12.4-fold) compared with wild-type SARS-CoV-2 [64].

Research shows that the neutralization potential of CoronaVac against alpha and gamma variants is low. Plasma samples showed more insufficient neutralization with variant alpha B.1.1.7 (geometric mean titer [GMT] = 18.5) and gamma P.1 (GMT = 10.0) compared to variant D614G (GMT = 75.1) at 60 days after treatment second dose of CoronaVac [65]. Another study comparing wild-type strains and post-vaccination serum showed similar effectiveness in neutralizing the D614G, B.1.1.7, and B.1.429 variants, whereas the serum neutralization efficiency decreased significantly for B.1.526 (by a factor of 4.03 [95% CI, 3.26–4.80]), P.1 (by factors of 3.92 [95% CI, 3.18–4.65]), and B.1.351 (by factors of 5.27 [95% CI, 4.19–6.34]). In addition, only a small proportion of post-vaccination serum was able to neutralize B.1.526 (24 [26%]; GMT = 29.0), P.1 (32 [34%]; GMT = 26.1), and B.1.351 (5 [5%]; GMT = 69.2) [66].

Research conducted by Wang et al. [64] found that B.1.1.7 was resistant to neutralization by most monoclonal antibodies against the NTD of the spike protein. However, B.1.1.7 is relatively resistant to some monoclonal antibodies to the RBD. It is no more resistant to plasma from individuals who have recovered from COVID-19 or serum from individuals who have been vaccinated against SARS-CoV-2 [64]. Collier et al. [68] assessed individual immune responses after vaccination with the BNT162b2 mRNA-based vaccine against pseudovirus expressing variant B.1.1.7. Serum from individuals receiving the vaccine showed slightly reduced neutralizing titers against wild-type pseudovirus against variant B.1.1.7. This decrease was also seen in the serum of some patients who had recovered from COVID-19. The appearance of the E484K substitution in the B.1.1.7 background poses a threat to the efficacy of the BNT162b2 vaccine [68]. In another study in the United Kingdom, for the Pfizer-BioNTech BNT162b2 vaccine, the reduction in neutralization titer against B.1.1.7 was 3.3-fold (geometric mean; n = 25, p < 0.0001) [69].

Study assessing sputnik V vaccine against internationally relevant genetic lineages B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.617.3, and Moscow endemic variant B.1.1.141 (T385I) and B.1.1.0.317 (S477N, A522S) with mutations in the RBD domain. The data obtained showed no significant difference in virus-neutraliz-
ing activity (VNA) against B.1.1.7, B.1.617.3 and local genetic strains B.1.1.141, B.1.1.317 with RBD mutations. Decreases in VNA for B.1.351, P1, and B.1.617.2 were observed to be statistically significant 3.1-, 2.8-, and 2.5-fold, respectively [70].

**Conclusion**

The variant of concern resistance and the variant of interest resistance to serum obtained from people who have recovered from COVID-19 and people who have been vaccinated can be associated with various mutations in the viral spike protein. All current vaccines appear to effectively prevent severe COVID-19, hospitalization, and death against all variants of concern. However, most of the effectiveness or efficacy decreases with the variant of concern. Questions remain regarding booster and reduced immunity doses, duration of immunity, and heterologous vaccination.

Several VOC have emerged, namely Alpha (501Y.V1 and B.1.1.7), Beta (501Y.V2 and B.1.351), Gamma (501Y.V3 and P1), and Delta (G/478K.V1 or B.1.617.2). This variant has been associated with increased transmission or mortality of COVID-19 or escapes immunity compared to the original strain or D614G variant. The COVID-19 vaccine currently under development or approval is expected to protect against the new virus variant as it generates a broad immune response involving multiple antibodies and cells. Therefore, changes or mutations in the virus should not render the vaccine completely ineffective. If one of the existing vaccines proves to be less effective against one or more variants, then the vaccine’s composition needs to be changed to protect against those variants. Currently, the emergence of the latest variant, Omicron, has become a significant concern worldwide because of many mutations.

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**References**

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021;19:141-54.

2. Syahniar R, Purba MB, Bekti HS, Mardhia M. Vaccines against coronavirus disease: target proteins, immune responses, and status of ongoing clinical trials. J Pure Appl Microbiol 2020;14:2253-63.

3. da Rosa Mesquita R, Francelino Silva Junior LC, Santos Santana FM, et al. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr 2021;133:377-82.

4. World Health Organization. World Health Organization Emergencies Programme [Internet]. Geneva: World Health Organization; c2021 [cited 2021 Nov 24]. Available from: https://www.who.int/emergencies/overview.

5. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19) [Internet]. Treasure Island (FL): StatPearls Publishing 2021 [cited 2021 Nov 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.

6. Duan L, Zheng Q, Zhang H, Niu Y, Lou Y, Wang H. The SARS-CoV-2 spike glycoprotein biosynthesis, structure, function, and antigenicity: implications for the design of spike-based vaccine immunogens. Front Immunol 2020;11:57622.

7. Salvatori G, Luberto L, Maffei M, et al. SARS-CoV-2 SPIKE PROTEIN: an optimal immunological target for vaccines. J Transl Med 2020;18:222.

8. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 2020;11:1620.

9. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181:281-92.

10. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020: FDA briefing document. Silver Spring (MD): Food and Drug Administration; 2020.

11. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-16.

12. Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 vaccine. N Engl J Med 2021;385:2348-60.

13. Voysey M, Clemens SA, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111.

14. Centers for Disease Control and Prevention. What you need to know about variants [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2021 [cited 2021...
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Nov 19]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant.html.

15. World Health Organization. Tracking SARS-CoV-2 variants [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Nov 21]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.

16. World Health Organization. The effects of virus variants on COVID-19 vaccines [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Nov 20]. Available from: https://www.who.int/news-room/feature-stories/detail/the-effects-of-virus-variants-on-covid-19-vaccines.

17. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: structure, biology, and structure-based therapeutics development. Front Cell Infect Microbiol 2020;10:587269.

18. Kadam SB, Sukhramani GS, Bishnoi P, Pable AA, Barvkar VT. SARS-CoV-2, the pandemic coronavirus: Molecular and structural insights. J Basic Microbiol 2021;61:180-202.

19. Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 transmission and pathogenesis. Trends Immunol 2020;41:1100-15.

20. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbiol Immunol Infect 2021;54:159-63.

21. Lauring AS, Hodcroft EB. Genetic variants of SARS-CoV-2: what do they mean? JAMA 2021;325:529-31.

22. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature 2021;592:616-22.

23. Galloway SE, Paul P, MacCannell DR, et al. Emergence of SARS-CoV-2 B.1.1.7 Lineage: United States, December 29, 2020-January 12, 2021. MMWR Morb Mortal Wkly Rep 2021;70:95-9.

24. Slavov SN, Patane JS, Bezerra RD, et al. Genomic monitoring unveil the early detection of the SARS-CoV-2 B.1.351 (beta) variant (20H/S01YV2) in Brazil. J Med Virol 2021;93:6782-7.

25. Greaney AJ, Loes AN, Crawford KH, et al. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe 2021;29:463-76.

26. Legally H, Wilkinson E, Giovanetti M, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature 2021;592:438-43.

27. de Siqueira IC, Camelier AA, Maciel EA, et al. Early detection of P.1 variant of SARS-CoV-2 in a cluster of cases in Salvador, Brazil. Int J Infect Dis 2021;108:252-5.

28. Faria NR, Mellan TA, Whittaker C, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science 2021;372:815-21.

29. Cherian S, Potdar V, Jadhav S, et al. SARS-CoV-2 spike mutations, L452R, T478K, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. Microorganisms 2021;9:1542.

30. Mlcochova P, Kemp SA, Dhar MS, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature 2021;599:114-9.

31. Uriu K, Kimura I, Shirakawa K, et al. Neutralization of the SARS-CoV-2 Mu variant by convalescent and vaccine serum. N Engl J Med 2021;385:2397-9.

32. Voloch CM, da Silva Francisco R Jr, de Almeida LG, et al. Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. J Virol 2021;95:e00119-21.

33. World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Nov 21]. Available from: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern.

34. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021;385:585-94.

35. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603-15.

36. Lefevre B, Tondeur L, Madec Y, et al. Beta SARS-CoV-2 variant and BNT162b2 vaccine effectiveness in long-term care facilities in France. Lancet Healthy Longev 2021;2:e685-7.

37. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med 2021;27:2136-43.

38. Mahase E. COVID-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant. BMJ 2021;372:n296.

39. Heath PT, Galizia EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 COVID-19 vaccine. N Engl J Med 2021;385:1172-83.

40. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 COVID-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1885-98.

41. Hitchings MD, Ranzani OT, Dorion M, et al. Effectiveness
of ChAdOx1 vaccine in older adults during SARS-CoV-2 Gamma variant circulation in Sao Paulo. Nat Commun 2021;12:6220.

42. McMenamin ME, Cowling BJ. CoronaVac efficacy data from Turkey. Lancet 2021;398:1873-4.

43. Hitchings MD, Ranzani OT, Torres MS, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: a test-negative case-control study. Lancet Reg Health Am 2021;1:100025.

44. Ranzani OT, Hitchings MD, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of COVID-19 in Brazil: test negative case-control study. BMJ 2021;374:n2015.

45. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19. N Engl J Med 2021;384:2187-201.

46. Voko Z, Kiss Z, Surjan G, et al. Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary-the HUN-VE study. Clin Microbiol Infect 2022;28:398-404.

47. Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med 2021;27:1614-21.

48. Dolzhikova I, Gushchin V, Shcheblyakov D, et al. One-shot immunization with Sputnik Light (the first component of Sputnik V vaccine) is effective against SARS-CoV-2 Delta variant: efficacy data on the use of the vaccine in civil circulation in Moscow. medRxiv [Preprint] 2021 Oct 8 [Epub]. https://doi.org/10.1101/2021.10.08.21264715.

49. Nasreen S, Chung H, He S, et al. Effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. Nat Microbiol 2022;7:379-85.

50. Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv [Preprint] 2021 Aug 21 [Epub]. https://doi.org/10.1101/2021.08.06.21261707.

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

52. Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med 2021;27:1614-21.

53. Nanduri S, Pilishvili T, Derado G, et al. Effectiveness of Pfizer-BioNTech and Moderna vaccines in preventing SARS-CoV-2 infection among nursing home residents before and during widespread circulation of the SARS-CoV-2 B.1.617.2 (Delta) variant: National Healthcare Safety Network, March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1163-6.

54. Sheikh A, Robertson C, Taylor B. BNT162b2 and ChAdOx1 nCoV-19 vaccine effectiveness against death from the Delta variant. N Engl J Med 2021;385:2195-7.

55. Shinde V, Bhikha S, Hoosain Z, et al. Efficacy of NVX-CoV2373 COVID-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1899-909.

56. Callaway E, Mallapaty S. Novavax offers first evidence that COVID vaccines protect people against variants. Nature 2021;590:17.

57. Polinski JM, Weckstein AR, Batech M, et al. Effectiveness of the single-dose Ad26.COV2.S COVID vaccine. MedRxiv [Preprint] 2021 Sep 10 [Epub]. https://doi.org/10.1101/2021.09.10.21263385.

58. Gonzalez S, Olsevicki S, Salazar M, et al. Effectiveness of the first component of Gam-COVID-Vac (Sputnik V) on reduction of SARS-CoV-2 confirmed infections, hospitalisations and mortality in patients aged 60-79: a retrospective cohort study in Argentina. EClinicalMedicine 2021;40:101126.

59. Jin P, Li J, Pan H, Wu Y, Zhu F. Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. Signal Transduct Target Ther 2021;6:48.

60. Ibarrondo FJ, Hofmann C, Ali A, Ayoub P, Kohn DB, Yang OO. Previous infection combined with vaccination produces neutralizing antibodies with potency against SARS-CoV-2 variants. mBio 2021;12:e0265621.

61. Jongeneelen M, Kaszas K, Veldman D, et al. Ad26.COV2.S elicited neutralizing activity against Delta and other SARS-CoV-2 variants of concern. bioRxiv [Preprint] 2021 Jul 1 [Epub]. https://doi.org/10.1101/2021.07.01.450707.

62. Moore PL, Moyo-Gwete T, Hermanus T, et al. Neutralizing antibodies elicited by the Ad26.COV2.S COVID-19 vaccine showed reduced activity against 501YV2 (B.1.351), despite protection against severe disease by this variant. BioRxiv [Preprint] 2021 Jun 9 [Epub]. https://doi.org/10.1101/2021.06.09.447722.
63. Alter G, Yu J, Liu J, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature 2021;596:268-72.
64. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature 2021;593:130-5.
65. Fernandez J, Bruneau N, Fasce R, et al. Neutralization of alpha, gamma, and D614G SARS-CoV-2 variants by CoronaVac vaccine-induced antibodies. J Med Virol 2022;94:399-403.
66. Chen Y, Shen H, Huang R, Tong X, Wu C. Serum neutralising activity against SARS-CoV-2 variants elicited by CoronaVac. Lancet Infect Dis 2021;21:1071-2.
67. Vacharathit V, Aiewsakun P, Manopwisedjaroen S, et al. CoronaVac induces lower neutralising activity against variants of concern than natural infection. Lancet Infect Dis 2021;21:1352-4.
68. Collier DA, De Marco A, Ferreira IATM, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature 2021;593:136-41.
69. Supasa P, Zhou D, Dejnirattisai W, et al. Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera. Cell 2021;184:2201-11.
70. Gushchin VA, Dolzhikova IV, Shchetinin AM, et al. Neutralizing activity of sera from Sputnik V-vaccinated people against variants of concern (VOC: B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.617.3) and Moscow endemic SARS-CoV-2 variants. Vaccines (Basel) 2021;9:779.