SARS-CoV-2 variants of concern: a review

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Abstract

The virus that causes severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belongs to the genus Beta coronavirus and the family Coronaviridae. The SARS-CoV-2 virus is a positive sense, non-segmented single-strand RNA virus that causes coronavirus disease 2019 (COVID-19), which was first reported in December 2019 in Wuhan, China. COVID-19 is now a worldwide pandemic. Globally, several newer variants have been identified; however, only a few of them are of concern (VOCs). VOCs differ in terms of infectivity, transmissibility, disease severity, drug efficacy, and neutralization efficacy by monoclonal antibodies, convalescent sera, or vaccines. VOCs reported from various parts of the world include B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617/B.1.617.2 (Delta), P.1 (Gamma), and B.1.1.529 (Omicron). These VOCs are the result of mutations, with some based on spike proteins. Mutations may also cause molecular diagnostic tests to fail to detect the few VOCs, leading to a delayed diagnosis, increased community spread, and delayed treatment. We searched PubMed, EMBASE, Covariant, Stanford variants database, and CINAHL from December 2019 to February 2022 using the following search terms: Variant of Concern, SARS-CoV-2, Omicron, *etc*. All types of research were chosen. All research methods were considered. This review discusses the various VOCs, as well as their mutations, infectivity, transmissibility, and neutralization efficacy.

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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a positive sense, non-segmented single-strand RNA virus that belongs to the genus of Beta coronavirus, and family of coronaviridae [1]. The genome of SARS-CoV-2 is approximately 30 kb. The virus enters the human host by binding on the human cell-surface protein angiotensin-converting enzyme 2 (ACE2). The receptor binding domain (RBD) of spike protein (S protein) of SARS-CoV-2 binds ACE2 with high affinity [2]. Viral tropism and pathogenicity can be explained by the expression and tissue distribution of ACE2 receptors. The S protein mediates major receptor binding and membrane fusion. The S protein consists of the S1 and S2 subunits; the S1 subunit binds the receptor and the S2 subunit anchors the S protein to the virion membrane and mediates membrane fusion [2]. Host protease activation plays an important role in viral entry. The Transmembrane serine protease2 (TMPRSS2)facilitates cell entry via the S protein by fusion at the cellular or endosomal membrane [3]. Another pathway for host cell entry is the endocytic pathway within the endosomal–lysosomal compartments mediated by lysosomal cathepsins [4]. The virus uses the endosomal–lysosomal pathway in the absence of TMPRSS2 [5]. Subsequently, in the cytoplasm, the virus releases its RNA genome which first translates to polyprotein 1a/1ab (pp1a/pp1ab) that encode for the replicase-transcriptase complex. Synthesis of structural proteins helps in the completion of assembly and release of viral particles [6]. The single-stranded RNA genome of SARS-CoV-2 is replicated and transcribed by the viral RNA-dependent RNA polymerase (RdRp). The SARS-CoV-2 RdRp enzymes do not contain a proofreading exonuclease domain to ensure high fidelity unlike the high-fidelity cellular DNA polymerases [7].

The low replication fidelity allows the RNA viruses to quickly

adapt to different host environments and selection pressures and contributes to viral replication.[8]RNA virus replication is typically characterised by a high error rate resulting in the virus existing as diverse populations of genome mutants or "quasispecies" [9]. However, the low replicative fidelity is associated with an increased chance of error leading to viral extinction. Therefore, a finely tuned balance is required between low replicative fidelity and replicative fitness for viral virulence and evolution [9]. However, the SARS-CoV-2 encodes a 3'-to-5' exoribonuclease (ExoN) in nsp14 which functions as the proofreading machinery by excising mismatched nucleotides during the replication process [9]. The RNA proofreading activity does not only ensure high replication fidelity but also impairs the therapeutic effects of anti-virus agents such as Remdesivir which are incorporated into the viral genome to induce premature replication termination. The virus was first reported in China in December 2019 [10], and subsequently, it spread globally and rapidly became a pandemic of devastating nature. On 16 May 2022, there have been 521 million confirmed cases of COVID-19, including 6.2 million deaths, reported to the World Health Organization (WHO) [11]. Similar to the evolutionary mechanism found in all other microorganisms, SARS-CoV-2 accumulates mutations as it passes through its human hosts [12]. Variants are a group of coronaviruses that may contain one or more mutations. The variants are designated as a variant being monitored (VBM), variant of concern (VOC) or a variant of interest (VOI) due to shared attributes and characteristics that may require public health action [13]. The emergence of the SARS-CoV-2 variants may pose a significant global public health concern as it has implications on transmissibility, infectivity, disease severity, diagnosis, neutralization efficacy by vaccines and therapeutics, and reinfections capability. The SARS-CoV-2 virus accumulates 2-3 single-nucleotide (nt) mutations in its genome per month, which is slower than influenza (4 nt/month) and the human immunodeficiency virus (HIV) (8 nt/month) [14,15]. There are various nomenclature systems used by the scientific community worldwide for the SARS-CoV-2 variants such as the Global Initiative on Sharing Avian Influenza Data (GISAID), NextStrain, and Phylogenetic Assignment of Named Global Outbreak (Pango) [16]. The WHO defined the VOC as a SARS-CoV-2 variant that meets the definition of a VOI and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance. There is an increase in transmissibility or detrimental change in COVID-19 epidemiology, or an increase in virulence or change in clinical disease presentation, or a decrease in the effectiveness of public health and social measures or available diagnostics, vaccines, and therapeutics [17]. The VOI is a SARS-CoV-2 variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; and Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside an increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health [17].

Methods

We searched PubMed, EMBASE, Covariant, Stanford variants database, and the CINAHL from December 2019 to July 2022 using the following search terms: variant of concern, SARS-CoV-2, omicron, *etc*. We have selected all types of the study. A total of 3000 studies were reviewed. The objective of this review was to enumerate the various VOCs and their mutations, infectivity, transmissibility, and neutralization efficacy.

Variants of concern

Alpha (B.1.1.7 lineage)

The B. 1.1.7 variant also known as the UK variant/Kent variant, was first detected in southeast England in September 2020 and quickly became the dominant lineage in the UK [18]. The B.1.1.7 variant is characterized by multiple spike protein mutations (Δ69/Δ70, Δ144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H) as well as mutations in other genomic regions [19]. Besides these, E484K, S494P, and N501Y mutations are present in the RBD. The B.1.1.7 variant became the predominant variant in many countries subsequently, including the United States till it was replaced by the B.1.617.2 variant [19]. The B.1.1.7 variant showed increased transmissibility and increased disease severity (some studies) [18,20]. The B.1.1.7 variant is 43 to 90% (range of 95% credible intervals, 38 to 130%) more transmissible than pre-existing variants in the UK [18]. Volz *et al*. [21] showed a 50% to 100% higher transmissibility over other lineages. Similarly, Li *et al*. [22] reported a 50 to 75% higher transmissibility with R_0 value of 1.75-fold higher than the origin lineage. The B.1.1.7 variant is not only more transmissible but may also cause more severe illness than the pre-existing SARS-CoV-2 variants with the hazard of death 55% (95% confidence interval, 39-72%) higher than that in cases without SGTF after adjustment for age, sex, ethnicity, deprivation, residence in a care home, and test date [23]. The increased transmissibility of the B.1.1.7 variant could be due to the N501Y mutation and an additional Δ69/Δ70 that increases the binding affinity to ACE2 [21,24]. It has also been observed that the B.1.1.7 variant harboring D614G, N501Y mutations is more infectious than the B.1.1.7 variant containing D614G mutations alone [25-27]. The P681H mutation located adjacent to the highly variable S1/S2 furin cleavage site also enhances transmissibility [28,29]. Moreover, the Δ69/Δ70 in NTD also impart a conformational change in the spike protein and increases transmissibility. The proofreading activity of the SARS-CoV-2 virus cannot correct deletions. McCarthy *et al.* [30] observed that recurrent deletions in the spike protein of SARS-CoV-2 caused antibody escape and increased human-to-human transmission. The mutations located on the S gene may cause SGTF and a false negative diagnostic assay that targets the s gene only [21]. The B.1.1.7 variant shows no impact on neutralization by mABs, but shows a minimal impact on neutralization by convalescent and/or post-vaccination sera [31]. This indicates that a prior infection or vaccination with wild-type SARS-CoV-2 may still protect against the B.1.1.7 variants.

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B.1.1.7 variants may also acquire E484K mutation that causes a significant additional loss of neutralization efficacy by the monoclonal and polyclonal antibodies. Collier *et al*. [36] reported a 6-fold and 11-fold decreased sensitivity to immune sera from individuals vaccinated with the Pfizer/BioNTech mRNA vaccine and convalescent sera respectively in B.1.1.7 variant harboring the E484K mutation. Further immune evasion may occur with a combination of E484K and various NTD mutations (particularly deletions) [37].

Beta (B.1.351; GH/501Y.V2)

Tegally *et al*. [38] detected this variant in South Africa in late 2020 and was subsequently known as B.1.351. These variants are characterized by 17 critical mutations such as seven substitutions (D80A, D215G, K417N, E484K, N501Y, D614G, A701V) in the spike protein, ORF1a mutations (T265I, K1655N, K3353R, ΔS3675, ΔG3676, and ΔF3677), ORF1b mutations (P314L) and ORF3a mutation (Q57H) along with N protein (T205I) and E protein (P71L) mutations. There are three deletions (Δ241, Δ242, Δ243) in the N5 loop [39,40]. These variants also possess transmissibility similar to the B.1.1.7 variants. Besides increased transmissibility, B.1.351 variants also show immune escape properties. The B.1.351 variants showed a significant decrease in neutralization efficacy by some monoclonal antibody therapies. Bamlanivimab-etesevimab showed a 45-fold decreased susceptibility, however, casirivimab-imdevimab and sotrovimab showed no change in susceptibility [33-35]. There is also a moderate reduction in neutralization by convalescent and post-vaccination sera [41]. Variants with triple combinations of K417N, E484K, and N501Y are responsible for reduced susceptibility to vaccine-induced and convalescent sera [40,42]. N501Y mutation allows a higher binding affinity for the ACE2 receptor, whereas K417N and E484K may help in immune escape from neutralizing antibodies [43]. Studies from South Africa reported that Lys417Asn, Glu484Lys, and Asn501Tyr substitutions in the RBD, and Leu18Phe, Asp80Ala, Asp215Gly, 242–244del, and Arg246Ile in the NTD of the B.1.351 variant are responsible for reduced susceptibility to neutralization by convalescent sera taken from individuals exposed to earlier variants, in either live virus or pseudo virus neutralization assays [42,44]. Wibmer *et al*. reported a complete loss of neutralizing activity in 48% of the samples [44]. Butt *et al*. [45] reported that patients infected with the B.1.617.2 variant experience more severe disease compared to the B.1.351 variant with more hospitalization (27.3% *vs* 20.0%) and a higher odds of experiencing any adverse outcome. However, vaccinations are highly protective against severe disease for both variants.

Gamma (P.1; GR/501Y.V3)

The P.1 variant or the Brazilian variant was reported by Faria *et al*. [46] from Manaus, Brazil in late 2020. Later on, it became the predominant variant in Brazil and several other South American cities rapidly. The P.1 variants have 17 mutations including three in the spike proteins RBDs such as K417T, E484K, and N501Y. Both the beta and gamma variants contain the triple mutation combinations of K417N, E484K, and N501Y in the critical RBD of the S gene except K417 is substituted by N instead of T in the beta variant. The gamma variant also differs from SARS-CoV-2 and beta variants by the absence of deletion sites in the NTD domain [47]. This variant has increased transmissibility and immune escape properties. The P.1 variant is 1.7 to 2.4-fold higher transmissible than previous (non-P.1) infections. The immunity evasion is 21-46% more than the non-P.1 variant. The P.1 variants are 1.2 to 1.9 times more likely to result in mortality compared with previous lineages [48]. The P.1 variants show a >511-fold decreased susceptibility to bamlanivimab-etesevimab but do not show any change in susceptibility with casirivimab-imdevimab and sotrovimab [33-35]. Convalescent and post-vaccination sera showed a reduced neutralization function [48]. In the Manaus areas, 25-61% of the people who were already infected with SARS-CoV-2 previously, had reinfection. This indicates a high reinfection rate, and the mutations confer the ability to escape the anti-SARS-CoV-2 immune memory established in the previous infection [22]. Wang *et al*. [49] studied the impact of SARS-CoV-2 variant mutations on immune escape mechanisms. They found the B.1.351 variant as the most resistant to neutralization followed by P.1 and B.1.1.7. The B.1.351 variant was resistant to many mAbs and COVID-19 convalescent plasma (6.9-fold decreased). The triple-mutant K417N-E484K-N501Y that is present in the B.1.351 and P.1 variants showed resistance to class I and II mAbs. The NTD supersite mutations such as Y144del and 242-244del seen in B.1.1.7 and B.1.351 variants substantially reduced the neutralizing efficacy to supersite antibodies and convalescent plasma.

Delta (G/478 K.V1; B.1.617.2)

TheB.1.617.2 variant was first detected in Maharashtra, India, in October 2020 and quickly became the dominant variant in India and globally until the emergence of the B.1.1.529 variant. The B.1.617.2 variant was responsible for the second wave in India. The B.1.617 lineage has three sub lineages including B.1.617.1, B.1.617.2, and B.1.617.3. The B.1.617.2 variants show increased transmissibility compared with the B.1.617.1 [50], a minimal reduction in neutralization by mAbs [34,35] and a moderate reduction in VE against symptomatic COVID-19 infection without significant impact on VE against severe disease·[33,51-53]. B.1.617.2 variant is 40-60% more transmissible than B.1.1.7 and almost twice as transmissible as the original Wuhan strain [54]. The B.1.617.2 variants have replication fitness as the viral loads increase rapidly in a person infected with B.1.617.2 variant. Li *et al*. [55] demonstrated that people infected with B.1.617.2 variant developed viral loads of 1260 times higher than those for the 2020 infections with clade 19A/19B viruses. Moreover, B.1.617.2 variants replicate more quickly, making the patient infectious more rapidly. The B.1.617.2 variants are associated with an increased severity of the disease [50,56] and an increased risk of hospitalization compared to the B.1.1.7 cases [56,57]. Sheikh *et al*. [56] reported a 2-fold rise in the risk of COVID-19 hospitalization in those with the B.1.617.2 variant. The risk of hospitalization was particularly higher in patients with five or more comorbidities. Twohig *et al*. [58] in a cohort study from the UK reported a higher hospital admission or emergency care attendance risk for patients with COVID-19 infected with the B.1.617.2variant. Following mutations have been identified such as T19R, V70F, T95I, G142D, Δ156, Δ157, R158G, A222V, W258L, K417N, L452R, T478K, D614G, P681R, and D950N [11,13]. The common signature mutations are D111D, G142D, L452R, E484Q, D614G, and P681R located in the spike protein. Of these, the mutations at residue positions 452, 484 and 681 have been reported in other lineages also. The L452R, E484Q, and P681R mutations explain the increased transmissibility of this variant. The E484Q and P681R mutations also influence the antibody binding. Cherian *et al*. [59] reported the following three mutations L452R, E484Q, and P681R, from patients in the second wave of COVID-19 in Maharashtra, India. Another sub-lineage of B.1.617.2 is the Delta plus variant (AY.1 and B.1.617.2.1) which was first detected in April 2021 from India. Later on, it was detected

in different parts of the world [60]. The AY.1 sub-lineage has an additional K417N mutation in the spike protein. Yadav *et al*. [61] had shown a reduced neutralization titer for the Delta AY.1 sera of vaccinees (BBV152/Covaxin) COVID-19 naïve, recovered cases with full vaccination and breakthrough cases. The AY.1 sub-lineage also shows resistance to the monoclonal antibody cocktails (casirivimab and imdevimab and bamlanivimab and etesevimab) [62,63]. Several high-prevalence mutations (≥20%) are present in a significant number in the Delta Plus variant compared to that in the Delta variant. These include G142D, A222V, and T95I mutations in the spike protein. Following spike protein mutations such as K417N, V70F, and W258L are exclusively present in the Delta Plus variant. Moreover, a new mutation in ORF1a (A1146T) was only present in the Delta Plus variant with ~58% prevalence [64]. The Delta Plus variant may spread more easily than the regular B.1.617.2 variant and has a greater affinity to the mucosal lining of the lungs compared to other variants [62,64]. Another sub-lineage of the B.1.617.2 variant reported from Vietnam is Delta-V. It contains deletions at positions H67, V70, and/or Y144 which are also seen in the B.1.1.7variant [63]. The B.1.617.2 variant was initially considered a variant of interest on 4th April 2021. Subsequently on 11th May 2021 WHO classified it as a VOC due to its rapid spread globally. One of the mechanisms of B.1.617.2 immune evasive function is the 156/157 deletions which remove amino acidsin the supersite and change the 158th amino acid from arginine to glycine, thereby eliminating a direct contact point for antibody binding on the variant [65]. The P681R mutation promotes cell-to-cell fusion, leading to the formation of larger syncytia, and has been linked to disease pathogenesis as it makes the virus more infective [66]. The immune evasion is due to the RBD mutations L452R, T478K, and E484Q and their combination with NTD mutations and deletions, particularly in the case of B.1.617.2.

Omicron (B.1.1.529 lineage) variant

Table 1 is showing the characteristics of various VOCs. Omicron is now the dominant variant globally characterized by high transmissibility and immune escape from most mABs, convalescent plasma, and immunity after full vaccination. This new SARS-CoV-2 variant was first reported from Botswana on 11th November and then was detected in South Africa three days later. The WHO labeled it variant a VOC on 26th November and named it as Omicron [67]. Table 2 is showing the four VOCs and their mutations. Subsequently, the omicron variant was identified from different parts of the world, rapidly became the dominant strain. This is the highly mutated variant so far, containing up to 59 mutations in its genome, including 36 occurring within the spike protein [68]. These mutations are responsible for increased transmissibility and reduced neutralization by vaccine-induced immunity [69]. The RBD within the spike protein is one of the main targets of neutralizing antibodies, explaining the reduced neutralization efficacy [42,70]. Phylogenetic analysis reports that the B.1.1.529 variant is closely related to the P.1 variant. Kannan *et al*. [71] studied the prevalence and nature of mutations by using the NextClade CLI and/or an in-house Python script on the sequences of the B.1.1.529 variant downloaded from the GISAID repository. Mutations with a prevalence of more than 50% were described as signature mutations. They reported 30 signature mutations such as A76V, T95I, Y145del, G339D, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K,P681H,

Table 1. Showing the characteristics of various variants of concern.

Variants	Transmissibility	Disease severity	Evasion of antibodies
Alpha (UK)	50% to 100% higher transmissibility compared to pre-existing lineages [14]	More severe illness in few studies. Davies *et al.* [16] estimated the hazard of death of 55% (95% confidence interval, 39-72%) higher than in cases without SGTF after adjustment	No impact on neutralization by mABs, but minimal impact to neutralization by convalescent and/or post-vaccination sera [24]. However, E484K and/or various NTD mutations (particularly deletions) may cause a significant fall in neutralization efficacy. [109,110]
Beta (South Africa)	Increased transmissibility	Less severe than Delta variant [37]	Bamlanivimab-etesevimab showed a 45-fold decrease in susceptibility. Casirivimab-imdevimab and sotrovimab showed no change in susceptibility [25-27]. There is also a moderate reduction in neutralization by convalescent and post-vaccination sera [33]
Gamma (Brazil)	The P.1 variant is 1.7 to 2.4-fold higher transmissible than previous (non-P.1) infection. Increased risk of reinfection	1.2 to 1.9 times more likely to result in mortality compared with previous lineages [38]	The immunity evasion is 21-46% more than the non-P.1 variant. More than 511-fold decreased susceptibility to bamlanivimab-etesevimab but no change in susceptibility with casirivimab-imdevimab and sotrovimab [25-27]. Reduced neutralization to convalescent and post-vaccination sera [40]
Delta (India)	40-60% more transmissible than and almost twice as transmissible as the original Wuhan strain [46]	Increased severity of the disease [42,48] and an increased risk of hospitalization [48,49]	Minimal reduction in neutralization by monoclonal antibody therapies. Moderate reduction in vaccine effectiveness against symptomatic COVID-19 without significant impact against severe disease [33]
Omicron	Highly transmissible, it may cause increased risk of reinfection/ breakthrough infection	Less severe disease compared to Delta variant	Reduced or absent neutralization efficacy by vaccines and monoclonal antibody therapies

N764K, D796Y, N856K, Q954H, N969K, L981F, L212I, S371L, S373P, S375F,K417N. Out of these 30 mutations, 23 are unique to the B.1.1.529 variant. They also reported following nine mutations in other genes that are >85% prevalent in the B.1.1.529 variant; ORF1a: K856R, ORF1a: L2084I, ORF1a: A2710T, ORF1a: T3255I, ORF1a: P3395H, ORF1a: I3758V, ORF1b: P314L, ORF1b: I1566V, and ORF9b: P10S. Locations of the mutations in the spike protein may affect the binding affinities of antibodies to the spike protein. Following mutations located at the S1-S2 furin cleavage site in the B.1.1.529variant may also increase transmissibility such as H655Y, N679K, and P681H [72]. The infectivity of SARS-CoV-2 depends on the binding affinity of the ACE2 and RBD complex and the furin cleavage site [73]. Using a variety of statistical and dynamic modeling approaches, Davies *et al*. characterized the spread of the B.1.1.7 variant in the UK. The authors found that the variant is 43 to 90% more transmissible than the predecessor lineage but saw no clear evidence for a change in disease severity, although enhanced transmission will lead to higher incidence and more hospital admissions. Large resurgences of the virus are likely to occur after the easing of control measures, and it may be necessary to greatly accelerate vaccine roll-out to control the epidemic.

Therefore, the H655Y, N679K, and P681H mutations located at the furin cleavage site and a large number of other RBD mutations explain the high infectivity of the omicron variant [74]. The R203K and G204R mutations in the nucleocapsid proteins also increase the infectivity. The B.1.1.529RBD contains many mutations that are shared by the other VOCs [75,76]. B.1.351 and P.1 contains three RBD mutations such as K417N, E484K, and N501Y that potentially diminished vaccine-induced neutralization efficacy [77]. The D614G mutation has been detected in all five VOCs [78]. Moreover, the N501Y mutation has also been shared with the B.1.351 and P.1 variants and it enhances transmissibility. B.1.1.529 also shares two RBD mutations with the B.1.617.2 variant. These include K417N (a lysine to asparagine substitution at amino acid position 417 in the spike protein), and threonine to lysine substitution at position 478 (T478K). The K417N mutation causes conformational changes in the Spike protein, which may aid in immune escape. The K417N mutation is also shared by the beta variants. The T478K mutation increases the electrostatic potential and steric interference of the residue, leading to an increased RBD binding affinity and immune escape [79]. Garcia-Beltran *et al*. [68] reported that the infection rates in the B.1.1.529-spike containing pseudo virus were four times higher than in the wild type and twice as efficient at infecting cells as B.1.617.2 variant. The B.1.1.529 variant may evade vaccine-induced humoral immunity and may increase the risk of reinfection/breakthrough infection. Compared to the previously circulating variants, the B.1.1.529 variant is more at ease in causing re-infection in convalescent individuals [73,80]. Kumar *et al*. [81] in a computational analysis had shown a higher binding affinity for human ACE2 in the B.1.1.529 variant compared to the B.1.617.2 variant due to the presence of a large number of mutations in the RBD, indicating a higher potential for transmission. They particularly noted Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K as responsible for the high binding affinity with ACE2. Moreover, the B.1.1.529 variant unlike the B.1.617.2 variant contains a large amount of hydrophobic amino acids such as leucine and phenylalanine, responsible for structural stability. Another important mechanism of resistance to neutralizing antibodies is the G142D mutation and deletion of residues 143-145 located in the antibody supersite [82,83].

Table 2. The various mutations and their locations in SARS-CoV-2 variants of concern.

Nomenclature	Spike protein and other mutations
Alfa/B.1.1.7	Spike protein:deletion 69-70, deletion 144, N501Y (RBD), A570D, D614G, P681H (located on the furin cleavage site), T716I (S2 mutation), S982A (S2 mutation), D1118H (S2 mutation) ORF8: Q27PST, R52I, Y73C N: D3L, R203K, G204R, S235F PLpro: T183I, A890D, I1412T nsp6: Δ106-108 RdRP: P323L
Beta/B.1.351	Spike protein: D80A, D215G, ΔL242, ΔA243, ΔL244, K417N, E484K, N501Y, D614G, A701V nsp2: T85I, nsp6: Δ106-108 PLpro: K837N 3CLpro: K90R RdRP: P323L ORF3a: Q57H, S171L E: P71L, N: T205I
Delta/B.1.617.2	Spike protein: T19R, T95I, G142D, Δ156, Δ157, R158G, L452R, T478K, D614G, P681R (located on the furin cleavage site), and D950N (S2 mutation) PLpro: A488S, P1228L, P1469S nsp4: V167L, T492I, nsp6:T77A, nsp13: P77L, nsp14: A394V RdRP: P323L, G671S ORF3a: S26L, M: I82T, ORF7a: V82A, T120I, ORF7b: T40I, ORF8: Δ119-120 N: D63G, R203M, G215C, D377Y
Gamma/P.1	Spike protein: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I PLpro: S370L, K977Q nsp6: Δ106-108,nsp13:E341D RdRP: P323L ORF3a: S253P, ORF8: E92K N: P80R, R203K, G204R

3CLpro, 3-chymotrypsin-like cysteine protease; N, nucleocapsid; nsp, non-structural proteins; ORF, open reading frames; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase.

Although, B.1.1.529 shows a decreased neutralization from the vaccine and prior infection, booster usually restores the protection [68]. Liu *et al*. [84] reported that the B.1.1.529 variants exhibit marked resistance to neutralization by serum not only from convalescent patients, but also from individuals vaccinated with one of the four widely used COVID-19 vaccines (BNT162b2/Pfizer, mRNA-1273/Moderna, Ad26.COV2. S/Johnson & Johnson, and ChAdOx1 nCoV-19/AstraZeneca). There was also a substantially diminished neutralizing activity against serum from persons vaccinated and boosted with mRNA-based vaccines and the neutralizing activity against the majority of the monoclonal antibodies was either abolished or impaired. They also identified four new spike mutations such as S371L, N440K, G446S, and Q493R that confer greater antibody resistance to the omicron variants. The S371L mutations cause a global resistance to many mAbs. B.1.1.529 variants are fully or largely resistant to each of the monoclonal antibodies and against the antibody cocktails (casirivimab and imdevimab and etesevimab and bamlanivimab). It may be explained by the presence of the following mutations such as K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, and Y505H, which are located within or close to the epitopes targeted by these antibodies. Therefore, the above two monoclonal antibody cocktails should not be used against the B.1.1.529 variants [85]. However, sotrovimab remains active against B.1.1.529 variants as it binds to epitopes not substantially altered by spike protein mutations [86]. Unlike the E484A and Y505H mutations having significant disruptive effects, the G339D mutation has a mild impact on antibody-mediated neutralization as it is located far away from the binding interfaces of most known antibodies [74]. Planus *et al*. [87] studied the sensitivity of the B.1.1.529 variant isolated in Belgium from a traveler returning from Egypt to 9 monoclonal antibodies (mAbs), and to antibodies present in 115 sera from COVID-19 vaccine recipients or convalescent individuals. They reported a complete or partial resistance to neutralization by all the mAbs tested. Similarly, the sera taken from individuals 5 months after complete vaccination with Pfizer or AstraZeneca vaccine, or convalescent sera showed drastically reduced neutralization. However, administration of a booster Pfizer dose generated an anti-Omicron neutralizing response, with titers 6 to 23-fold lower against Omicron than against Delta. The B.1.1.529 variant may also affect the diagnostic accuracy of the RT-PCR test. Testing with Thermo Fischer TaqPath RT-PCR COVID-19 assay had shown a specific SGTF or "S gene dropout" [69]. This is due to Δ69/Δ70 of the spike sequence as previously observed with the B.1.1.7variant [88]. Therefore, it is important to target at least two different genomic regions of the SARS-CoV-2 sequence to prevent false negativity of tests. However, SGTF can be used as a surrogate marker to suspect a B.1.1.529 infection in the present context. The SGTF has been reported with the BA.1 lineage.

Epidemiologically, B.1.1.529 is a highly transmissible variant showing a significant replication advantage, higher secondary attack rates, and a higher observed reproduction number compared to B.1.617.2 variant [89]. The doubling time reported from Gauteng province, South Africa and the UK was 3.38 days [CI 95%: 3.18–3.61 day] and 2-2.5 d, respectively with the basic reproduction number (R_0) above 3 [90,91]. The high R_0 is responsible for rapid spread and explains why the B.1.1.529 variant has become the dominant strain globally. The high R_0 is not only due to its increased transmissibility but also due to its immune evasion phenomenon [92]. Studies of households and contacts in the UK reported a higher risk of transmission to contacts from aB.1.1.529 index cases compared to B.1.617.2 index cases [93]. The adjusted odds ratio (aOR) of transmission from a B.1.1.529 index case compared to a B.1.617.2 index was 2.9)95% CI: 2.4-3.5), aOR of the risk of a close contact becoming a secondary case was 1.96 (95% CI: 1.77-2.16). The household secondary attack rate estimated using routine contact tracing data for B.1.1.529 and B.1.617.2 was 15.8% (95% CI: 14.3%-17.5%) and 10.3% (95% CI: 10.1%-10.5%) respectively. Preliminary data suggested a significantly lower risk of hospitalization, serious disease, and death in patients with B.1.1.529 infections as compared to B.1.617.2 infections [94-98].

Abdullah *et al*. [99] published the clinical profiles of patients admitted with B.1.1.529 variant in Tshwane, Gauteng Province, South Africa. They compared the clinical profile of 466 hospitalized patients admitted since 14th November 2021 with B.1.1.529 and compared it with 3962 admissions in the previous waves. The rates of ICU admissions (1% *vs* 4.3%, p<0.00001), in-hospital death (4.5% *vs* 21.3%, p<0.00001) and length of hospital stay (4.0 days *vs* 8.8 days) were lower among the 466 patients hospitalized with COVID-19 during the B.1.1.529surge compared with hospitalized patients from earlier surges. The average age was also lower during the B.1.1.529 surge (39 *versus* 50 years). Wolter *et al.* [94] reported an increased number of SGTF infections from 3% in early October to 98% in early December 2021. There were also lower odds of hospitalization among individuals with SGTF infection compared to non-SGTF infections (aOR 0.2, 95% CI: 0.1-0.3) on multivariable analysis. However, the severity of the disease among hospitalized patients did not differ between SGTF-infected individuals compared to non-SGTF individuals diagnosed during the same period (aOR 0.7, 95% CI: 0.3-1.4). When compared with B.1.617.2 infections, SGTF-infected individuals had lower odds of severe disease (aOR 0.3, 95% CI: 0.2-0.5). Maslo *et al*. [100] from South Africa evaluated the clinical characteristics of hospitalized patients with SARS-CoV-2 infection during the fourth wave and compared it with previous waves. The hospitalization rate was 41.3% in the fourth wave compared to 68% to 69% in the first 3 waves. Hospitalized patients in the 4th wave were significantly younger (median age, 36 years vs maximum 59 years in wave 3; p<0.001) and female predominance. A significantly lesser number of patients were hospitalized with an acute respiratory condition in the 4th wave (31.6% in wave 4 *vs* maximum of 91.2% in wave 3, p<0.001). Patients hospitalized in the 4th wave had a significantly decreased requirement of oxygen therapy (17.6% in wave 4 *vs* 74% in wave 3, p<0.001), significantly decreased requirement of mechanical ventilation and admission to intensive care. They also observed reduced mortality during the fourth wave i.e.,19.7% in wave 1 and 29.1% in wave 3 and 2.7% in wave 4. Similarly, a study from the UK reported that omicron was associated with approximately one-third the risk of hospital admission compared with B.1.617.2, irrespective of age, sex, vaccination status, and prior infection [101]. However, it is not clear whether the lower severity is due to the B.1.1.529 variant itself or the herd immunity at the population level due to prior vaccination and/or infection. McMahan *et al*. [102] in an animal study done on Syrian golden hamsters had shown that the spike protein variant resulted in more robust upper respiratory tract infection but less severe lower respiratory tract infection and milder clinical features (*e.g.*, weight loss) compared with prior SARS-CoV-2 variants. Infection of Syrian golden hamsters with the SARS-CoV-2 WA1/2020, Beta, or Delta strains led to 4-10% weight loss by day 4 and 10-17% weight loss by day 6, but the B.1.1.529infection did not show any detectable weight loss, even at high challenge doses. However, despite being a milder infection compared with previous COVID-19 variants, the sheer number of cases due to increased transmissibility may result in high rates of hospitalization and may compromise the overburdened healthcare system.

Omicron sublineages

The SARS-CoV-2 B.1.1.529 lineage is divided further into sub-lineages: BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 [103]. The BA.1 (B.1.1.529.1) is the original SARS-CoV-2 omicron variant and is characterized by increased transmissibility and reduced severity of infection compared to the Delta strain. The BA.2 lineage has fewer mutations on spike proteins compared to BA.1 lineage. People infected with BA.2 lineage have greater infective power than people with BA.1 [104]. These large number of mutations over spike proteins might have compromised BA.1 ability to infect in contrast to fewer mutations in BA.2 lineages which explains its good transmissibility [104]. The BA.2 lineage does not develop SGTF due to a lack of deletions in position 69-70 [105]. The SGTF in the B.1.1.529 variant may lead to a delayed diagnosis and spread of infection. B.1.1.529 infection has also been shown to enhance the B.1.617.2 strain neutralization by 4.4 fold [106]. The sub-lineages BA.1 and BA.2 have shown reduced neutralization by sera from individuals with prior infection or from individuals vaccinated. The sublineages BA.1 have shown a reduced or absent neutralization efficacy by vaccines and monoclonal antibody therapies e.g., bamlanivimab-etesevimab, casirivimab-imdevimab, and tixagevimab-cilgavimab. However, sotrovimab and bebtelovimab show no change in susceptibility [34,35,107-109]. The BA.2 sublineage similarly shows a significant reduction in neutralization by certain monoclonal antibodies such as sotrovimab and casirivimab-imdevimab. However, bebtelovimab and tixagevimab-cilgavimab retained activity [34,35,107-109]. Sublineages BA.4 and BA.5 showed an uncertain impact on transmissibility compared with other Omicron sublineages. However, they have a similar disease severity as other Omicron sublineages. The sub-lineages BA.4 and BA.5 showed a reduced neutralization by sera from individuals with prior infection or from individuals vaccinated. However, vaccination with a booster dose appears to restore some neutralizing activity but to lower levels than with BA.1 and BA.2. Against these sub-lineages, only bebtelovimab and tixagevimab-cilgavimab retained activity [110]. Another Omicron variant BA.2.75 also known as "Centaurus" has been detected first in India in early May 2022 and was detected later on in UK, USA, Australia, Germany and Canada [111]. This variant has a potentially more transmissible power. However, it needs more surveillance and study. Clinically, patients infected with the Omicron BA.2.75 or Centaurus variant have shown mild headache, mild fever, shivering, minor cough, and cold symptoms [112]. Takashita *et al*. [110] recently studied the efficacy of monoclonal antibodies and antiviral drugs against the Omicron subvariants *in vitro*. They used strains BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4, and BA.5. The casirivimab and imdevimab combination is inactive against sublineages BA.1, BA.1.1 (>1013-fold decrease in susceptibility). However, against sublineages BA.2.12.1, BA.4, and BA.5, the combination showed a reduced efficacy. Tixagevimab-cilgavimab combination shows a reduced activity against BA.1 and BA.1.1 (12- to 30-fold decrease in susceptibility for BA.1 and 176-fold decrease for BA.1.1). The value against BA.2 is a 5.4-fold decrease so likely active. Compared with the ancestral strain, the 50% focus reduction neutralization testing (FRNT50) value was higher by a factor of 6.1 against BA.2.12.1, by a factor of6.0 against BA.4, and by a factor of 30.7 against BA.5. Sotrovimab was unlikely to be effective against BA.2, BA.2.12.1, BA.4 and BA.5 but is effective against the BA.1 variants. Bebtelovimab, however, was effective against all the lineages of Omicron. Similarly, Iketani *et al*. [113] studied the antibody-evasion properties of Omicron sublineages. Continuing surveillance of the evolution of Omicron has since revealed the rise in prevalence of two sublineages, BA.1 with an R346K alteration (BA.1+R346K, also known as BA.1.1) and B.1.1.529.2 (BA.2), with the latter containing 8 unique spike alterations and lacking 13 spike alterations found in BA.1. Here we extended our studies to include antigenic characterization of these new sublineages and demonstrated a substantial loss in neutralizing activity against both BA.1.1 and BA.2. The BA.2 variants also showed marked resistance sotrovimab but retained neutralization activity against BA.1 and BA.1.1 sublineages. Therefore, except bebtelovimab, other monoclonal antibodies do not cover all sublineages of the Omicron variant. Table 3 is showing various mutations and their locations in SARS-CoV-2 variants of concern [114].

Vaccine effectiveness

Table 4 is showing vaccine efficacy against the VOCs. The ChAdOx1 nCoV-19 (AstraZeneca) vaccine showed 70.4% effectiveness against the B.1.1.7 variant, however, there is a reduced neutralization activity against the B.1.1.7 variant compared to a non-B.1.1.7 variant [115]. Bernal *et al*. [52] evaluated the effectiveness of two COVID-19 vaccines, BNT162b2 vaccine (Pfizer-BioNTech) and ChAdOx1 nCoV-19 (AstraZeneca), against symptomatic disease caused by the B.1.617.2 or other variants. They reported lower effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) among persons infected with the B.1.617.2 variant (30.7%; 95% CI, 25.2 to 35.7) than among those infected with B.1.1.7variant (48.7%; 95% CI, 45.5 to 51.7). The vaccine effectiveness (VE) of the two-dose BNT162b2 vaccine was 93.7% (95% CI, 91.6 to 95.3) among persons with the B.1.1.7variant and 88.0% (95% CI, 85.3 to 90.1) among those with the B.1.617.2 variant. The two-dose ChAdOx1 nCoV-19 vaccine showed a 74.5% (95% CI, 68.4 to 79.4) and 67.0% (95% CI, 61.3 to 71.8) effectiveness against the B.1.1.7and B.1.617.2 variants respectively. Abu-Raddad *et al*. [116] reported VE at 14 or more days after the second dose of BNT162b2 Covid-19 Vaccine against any documented infection with the B.1.1.7 variant as 89.5% (95% CI, 85.9 to 92.3). The VE against any documented infection with the B.1.351 variant was 75.0% (95% CI, 70.5 to 78.9) and against severe, critical, or fatal disease due to infection with B.1.1.7 and B.1.351 variants was 97.4% (95% CI, 92.2 to 99.5).

The VE of two-dose mRNA-1273 (Moderna COVID-19 vaccine) is 98.4% (96.9% to 99.1%) against B. 1.1.7 variant [117]. Moreover, the waning of VE was less pronounced for non-delta variants. The two-dose vaccine showed a VE against infection with the B.1.617.2 variant of 86.7% (95% CI 84.3% to 88.7%) and against hospital admission with the B.1.617.2 variant, the VE was 97.5% (92.7% to 99.2%). The VE against B.1.617.2 infection also waned from 94.1% at 14-60 days after vaccination to 80.0% after 151-180 days of vaccination [117]. Against the B.1.617.2 variant, the mRNA vaccine is highly effective. In contrast, the ChAdOx1 (AstraZeneca) and Ad26.CoV2-S (Johnson & Johnson) vaccine was 60% effective against B.1.617.2 infection [118]. The Novavax vaccine showed approximately 86% protection against infection in the UK (predominantly the B.1.1.7 variant) and against the B.1.351 variant, VE was 50% [119]. Against the B.1.351 variant, the two-dose ChAdOx1 (AstraZeneca) vaccine showed only 10.4% protection against mild-to-moderate disease [120]. The mRNA-1273 (Moderna) vaccine two-dose showed VE of 100% against B.1.1.7 variant ≥14 days after the second dose. The VE against the B.1.351 infection was 61.3% after the first dose and 96.4% after the second dose. Effectiveness against any severe, critical, or fatal COVID-19 disease (predominantly B.1.1.7 and B.1.351) was 95.7% after the second dose [121]. The single-dose Ad26.CoV2-S (Johnson & Johnson) vaccine showed 64% protection against moderate-to-severe disease in South

Africa (dominated by the B.1.351 variant), 66% protection against moderate-to-severe disease in the USA (mainly the Wuhan-1 variant with D614G), and 68% protection against the P.1 variant (at least 28 days after administration) [105]. The ChAdOx1 nCoV-19 (AstraZeneca) vaccine showed a VE of 64% against the P.1 variant, however, only 18 cases were enrolled for analysis [122]. The protection occurs despite the presence of the spike protein mutation E484K. The authors proposed that there would be a minimal reduction in protection when E484K mutation occurs isolated. The BNT162b2 Covid-19 Vaccine showed no evidence of reduced protection against the P.1 variant. Wu *et al*. [123] reported that the mRNA-1273 (Moderna) vaccine had no significant effect on neutralization against the B.1.1.7 variant. However, against the P.1 variant, B.1.1.7+E484K variant, and B.1.351 variant, reduced titers of neutralizing antibodies were observed and the B.1.351 variant showed the largest effect on neutralization. Andrews *et al*. [124] evaluated the VE against symptomatic disease caused by the Omicron and Delta variants in England and reported no effect after the two-dose ChAdOx1 vaccine against Omicron infection. After two-dose BNT162b2 vaccine, VE was 88.0% at 2-9 weeks after the second dose and it dropped to between 34 and 37% from 15 weeks post-second dose. However, from two weeks after a BNT162b2 booster dose, the VE increased to 71.4% for ChAdOx1 primary course recipients and 75.5% for BNT162b2 primary course recipients. The VE was 41.8% and 63.5% against Delta after two ChAdOx1 and BNT162b2 doses and increased to 93.8% and 92.6% two weeks after the BNT162b2 booster.

Collie *et al*. [125] reported a BNT162b2 (Pfizer-BioNTech) VE of 70% during the proxy omicron period which is significantly different from the comparator period when the rate was 93% against hospitalization. Khoury *et al*. [126] in a meta-analysis observed that the VE six months after primary immunization with an mRNA vaccine for Omicron was 40% against symptomatic disease and 80%

Table 3. The various mutations and their locations in SARS-CoV-2 Omicron variants.

Omicron/B.1.1.529 BA.1 sub-lineage:	Spike protein: A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, R214ins, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N764K, N679K (Mutations just upstream of the S1/S2 furin cleavage site), P681H (proximal to the S1/S2 furin cleavage site) D796Y, N856K, Q954H, N969K, L981F ORF1a: K856R, L2084I, A2710T, T3255I, P3395H, I3758V ORF1b: P314L, I1566V, P10S PLpro: K38R, S1265I, Δ1266, A1892T nsp4: T492I, 3CLpro:P132H, nsp6: Δ105-107, I189V,nsp14:I42V RdRP: P323L E: T9I, M: D3G, Q19E, A63T, N: P13L, Δ31-33, R203K, G204R
Omicron/B.1.1.529 BA.2 sub-lineage	Spike protein: T19I, L24S, Δ25-27, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K (just upstream of the S1/S2 furin cleavage), P681H (proximal to the S1/S2 furin cleavage site), N764K, D796Y, Q954H, N969K nsp1: S135R, nsp4: L264F, T327I, L438F, T492I, nsp6: Δ106-108, nsp13: R392C, nsp14: I42V, nsp15: T112I PLpro: T24I, G489S 3CLpro: P132H RdRP: P323L ORF3a: T223I, E: T9I, M: Q19E, A63T, ORF6: D61L N: P13L, Δ31-33, R203K, G204R, S413R
Omicron/B.1.1.529 BA.2.75 sub-lineage	Spike protein: T19I, L24S, Δ25-27, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H (Furin cleavage site), N764K, D796Y, Q954H, N969K nsp1: S135R, nsp4: L264F, T327I, L438F, T492I, nsp6: Δ106-108, nsp14: I42V, nsp15: T112I PLpro: T24I, S403L, G489S, D821S, 3CLpro: P132H, RdRP: P323L, G671S, nsp13: R392C ORF3a: T223I, E: T9I, M: Q19E, A63T, ORF6: D61L, N: P13L, Δ31-33, R203K, G204R, S413R
Omicron/B.1.1.529 BA.4sub-lineage	Spike protein: V3G, T19I, L24S, Δ25-27, Δ69-70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H (Furin cleavage site), N764K, D796Y, Q954H, N969K nsp1: S135R, Δ141-143, nsp6: Δ106-108, nsp13: R392C, nsp14: I42V, nsp15: T112I PLpro: T24I, G489S, nsp4: L264F, T327I, T492I 3CLpro: P132H RdRP: P323L ORF3a: T223I, E: T9I, M: Q19E, A63T, ORF6: D61L, ORF7b: L11F, N: P13L, Δ31-33, P151S, R203K, G204R, S413R
Omicron/B.1.1.529 BA.5 sub-lineage	Spike protein: T19I, L24S, Δ25-27, Δ69-70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H (Furin cleavage site), N764K, D796Y, Q954H, N969K nsp1: S135R, nsp4: L264F, T327I, T492I, nsp6: Δ106-108, nsp13: R392C, nsp14: I42V, nsp15: T112I PLpro: T24I, G489S 3CLpro: P132H RdRP: P323L ORF3a: T223I, E: T9I, M: D3N, Q19E, A63T, N: P13L, Δ31-33, R203K, G204R, S413R

against severe disease. A booster dose with an existing mRNA vaccine showed an efficacy of 86.2% (95% CI: 72.6-94) against symptomatic infection and 98.2% (95% CI: 90.2-99.7) against severe infection. Similarly, in a matched case-control study, Tseng *et al*. [127] assessed VE of mRNA-1273 against infection and hospitalization with omicron or delta in a large, diverse Southern California population. The two-dose vaccine effectiveness against Omicron was showed 42.8% (95% CI, 33.8%-50.7%) and it waned rapidly. However, after the 3rd dose, VE was 67.7% (65.5%-69.7%) against omicron infection. The VE falls further in immunocompromised individuals, 21.7% (0.0%-45.0%). Garcia-Beltran *et al*. [51] measured the neutralization potency of sera from 88 mRNA-1273 (Moderna),111BNT162b2 (Pfizer-BioNTech), and 40 Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine recipients against the wild type, Delta, and Omicron SARS-CoV-2 pseudoviruses. They reported an undetectable neutralization efficacy in the majority of vaccinated persons. Despite an immune escape from humoral immunity, vaccines may ameliorate the disease severity of breakthrough infections *via* pre-existing cellular and innate immunity. Moreover, a booster dose of the mRNA vaccines showed a potent neutralization efficacy (4-6-fold lower than wild type) by individuals with the Omicron variant. It indicates the importance of booster doses in tackling the Omicron variant. The South African Phase 3b Sisonke study showed a homologous (same vaccine) booster shot of theAd26.COV2.S (Johnson & Johnson/Janssen) vaccine demonstrated 85% effectiveness against COVID-19-related hospitalization among healthcare workers after Omicron became the dominant variant [128].

One important aspect of the COVID-19 vaccine benefit is the issue of waning vaccine protection. Therefore, duration of protection is an important component to decide pandemic policy interventions such as the need for and timing of booster doses. In the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study involving asymptomatic healthcare workers, Hall *et al*. [129] estimated VE after two doses of COVID-19 vaccine, according to the type of vaccine and dosing interval, in participants without previous infection. The majority of participants (95%) had received two doses (78% had received BNT162b2 vaccine with a long interval between doses, 9% BNT162b2 vaccine with a short interval between doses, and 8% ChAdOx1 nCoV-19 vaccine). The vaccine effectiveness of the long-interval BNT162b2 vaccine among previously uninfected participants increased from 85% 14 to 73 days post second dose to 51% at a median of 201 days (interquartile range, 197 to 205) after the second dose. Among the recipient of ChAdOx1 nCoV-19 vaccine, the adjusted vaccine effectiveness at 14 to 73 days after the second dose was 58%.

In a retrospective, population-based cohort study in Brazil and Scotland enrolling 1,972,454 adults in Scotland and 42,558,839 in Brazil who received two doses of ChAdOx1 nCoV-19, Katikireddi *et al*. [130] reported that in Scotland, VE decreased from 83·7% at 2 to 3 weeks, to 75.9% at 14 to 15 weeks, and 63.7% at 18 to 19 weeks. The corresponding figures in Brazil were 86.4%, 59.7%, and 42.2% at 2 to 3 weeks, 14 to 15 weeks, and 18 to 19 weeks respectively. The waning VE of ChAdOx1 nCoV-19 against COVID-19 hospital admissions and deaths developed within three months of the second vaccine dose. In a systematic review and meta-regression analysis, Feikin *et al*. [131] analyzed the duration of protection of COVID-19 vaccines against various clinical outcomes. They reported a decreased in protection against SARS-CoV-2 infection by 21.0% (95% CI 13.9-29.8) over a 6-month period from full vaccination across all ages and for all investigated vaccine types (Pfizer–BioNTechComirnaty, Moderna-mRNA-1273, Janssen-Ad26.COV2.S, and AstraZeneca-Vaxzevria). For severe COVID-19 disease, vaccine efficacy or effectiveness was decreased by 10 percentage points (95% CI 6.1-15.4) in people of all ages and 9.5 percentage points (5.7-14.6) in older people. However, vaccine efficacy or effectiveness against severe disease remained greater than 70% for 6 months. Against symptomatic COVID-19 disease, vaccine efficacy or effectiveness decreased by 24·9 percentage points (95% CI 13·4–41·6) in people of all ages.

Table 4. Vaccine efficacy against the variants of concern.

	ChAdOx1 nCoV-19 (AstraZeneca)	BNT162b2 vaccine (Pfizer–BioNTech)	mRNA-1273 (Moderna) vaccine	Ad26.CoV2-S (Johnson & Johnson)	Novavax vaccine
B.1.1.7	70.4% effectiveness [9]	Single dose: 48.7% - two doses: 93.7% [43]	Two doses: 98.4% [101]	69.7% [105]	86% [103]
B.1.351	Two-dose: 10.4% [104]	VE: 75.0% and against severe, critical, or fatal disease, VE 97.4% [100]	After first dose: 61.3% After second dose: 96.4%. Effectiveness against any severe, critical or fatal COVID-19 disease: 95.7% after the second dose [105]	64% protection against moderate-to-severe disease [105]	50% [103]
P.1	64% [187]	No evidence of reduced protection		68% [105]	
B.1.617.2	Two doses:67.0% [43]	Single dose: 30.7% - two doses: 88.0% [43]	Two doses: 86.7% and against hospital admission 97.5% [101]	60% [102]	
B.1.1.529	No effect after two doses. Two weeks after a BNT162b2 booster dose, the VE increased to 71.4% [108]	70% efficacy against hospitalization [109]. Second dose: VE 88.0% at 2-9 weeks and dropped between 34 and 37% from 15 weeks post second dose. After a booster dose, the VE increased to 75.5% [108]	After two doses: VE 42.8% and after the 3rd dose, VE was 67.7% (65.5%-69.7%) Immunocompromised individuals: 21.7% [111]	VE: 85% against COVID-19-related hospitalization [112]	

Limitations

COVID-19 variants are explosive and rapidly evolving areas. Newer variants have been detected many times in the past and will be detected in the future also. Therefore, this topic always needs modification in the future as it will become antiquated due to explosive scientific growth in this field.

Conclusions

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is evolving continuously since the beginning of the pandemic and several different variants of concern (VOC) have been identified from various parts of the world. The VOCs are characterized by an increased transmissibility compared to the original Wuhan strain. The VOCs differ from each other in terms of infectivity, transmissibility, disease severity, re-infectivity and evasion of immune responses induced by vaccine and natural infection. The VOCs are also differed from each other in terms of location and number of mutations. We need to constantly monitor the emergence of newer mutations and understand their impact for a robust public health response in the future.

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