Short review

SARS-CoV-2 variants — Evolution, spike protein, and vaccines

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ARTICLE INFO

ABSTRACTS

Despite the rising natural and vaccines mediated immunity, several countries have experienced a resurgence of the Coronavirus disease of 2019 (COVID-19) due to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. From Alpha to Omicron, the variants of concern (VOC) have evolved several spike protein mutations that may have an impact on virus characteristics, such as transmissibility and antigenicity. In this review, we describe the evolution of SARS-CoV-2, summarize current knowledge of epidemiological and clinical features of the variants, and discuss the response strategies in terms of vaccines to reduce the burden of COVID-19.

Coronavirus disease of 2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. It has since spread globally and has had a significant impact on public health and the economy. As a result, many countries have adopted several measures to prevent the expansion of the pandemic, such as launching nationwide vaccination campaigns and extensive lock-down of civil activities. However, after initially containing SARS-CoV-2, many countries are experiencing a resurgence of COVID-19 due to the emergence of new variants. These emerging variants have sets of mutations that could have an impact on virus characteristics, such as increased transmission rate, disease severity, and risk of reinfection, thereby enhancing the level of difficulties in reducing the COVID-19 burden. In this review, we describe the evolution of SARS-CoV-2, summarize the key spike mutations reported in different variants, and discuss the response strategies for emerging variants in terms of vaccines.

Evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

At the beginning of the pandemic (December 2019 to October 2020), SARS-CoV-2 expanded globally with little evidence of selective evolutionary pressure. SARS-CoV-2 evolves slowly with a rate of 1×10^{-3} substitutions/site/year (or around 2 substitutions per genome per month) [2,3] due to the proof-reading function of an exonuclease enzyme encoded by nonstructural gene nsp14 [4]. This rate is slower than that of most RNA viruses. Nonetheless, selective evolutionary pressure was evident with the detection of a viral variant containing spike mutation D614G. This particular variant was initially found in early 2020; it then spread globally, outcompeted previous viruses, and became the dominant form with a prevalence of almost 100% by June 2020 [5].

Following the emergence of D614G substitution, several novel lineages with mutations occurring primarily, but not exclusively, in spike proteins have been reported [Table 1]. Most of these mutations are convergent, meaning they occur independently in different lineages, possibly due to a response to the changing immune profile or chronic infections in individuals who are immunocompromised [6,7] or individuals receiving partially effective interventions [8]. In December 2020, the B.1.1.7 variant, presenting with numerous genetic changes, emerged in the United Kingdom (UK) [9]. Almost concurrently, two other variants, B.1.351 and P.1 emerged independently and caused a surge of new cases in South Africa [10] and Brazil [11], respectively. In January 2021, Manaus, Brazil, experienced a resurgence of COVID-19 due to the emergence of variant P.1 despite its high seroprevalence from the first epidemic wave [12]. Similarly, in April 2021, with the seroprevalence around 50% after enduring three waves of the SARS-CoV-2 pandemic, India encountered the fourth wave caused by the B.1.617.2 variant [13]; this variant then spread globally and displaced other variants in multiple countries [14—16]. At the beginning of November 2021, a highly divergent variant B.1.1.529 with a high number of mutations was detected in Botswana, South Africa [17]. Since then, South Africa has experienced a surge of cases, increasing from 280 to 800 cases per day; spreading rapidly and displacing B.1.617.2., B.1.1.529 has become the dominant variant in South Africa [18].

SARS-CoV-2 variants that have expanded widely and displayed the potential to be associated with increased transmissibility, disease severity, or change in interactions with host immunity are classified as variant of concern (VOC)

by the WHO. Variants that display similar mutations as VOC but spread less widely are classified as variant of interest (VOI). As of April 1, 2022, there are five VOCs classified by WHO and are designated as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). Although most mutations observed are expected to be either neutral or mildly deleterious, the spike protein mutations that may alter the antigenicity of the SARS-CoV-2 are of particular importance. Nevertheless, whether these mutations will alter the variants' pathogenicity, infectivity or antigenicity remains to be determined.

Spike protein: structure, mutations, and antigenicity

The ability of VOCs to escape neutralization by antibodies elicited by infection, vaccination, or therapeutic application has been widely studied [19—21]. It is essential to know the structure and function of the spike protein in order to understand how mutations in the SARS-CoV-2 spike protein affect neutralization. The transmembrane spike glycoprotein is responsible for SARS-CoV-2 entry into the host cell. The spike protein is cleaved by furin into two subunits, S1 and S2. A part of the S1 subunit, named receptor-binding domain (RBD), can bind to the human angiotensin-converting enzyme 2 (ACE2) receptor and thus begin the process of entering cells. A part of RBD called receptor-binding motif (RBM) forms direct contact with the ACE2 receptor. Spike RBD is also the main target of neutralizing antibodies upon infection and is the key to a vaccine or other therapeutic development [22]. Similar to RBD, the S1 amino-terminal domain (NTD) is also exposed on the protein surface, and evidence shows that NTD plays a substantial role in antigenicity as well [23]. Most monoclonal antibodies (mAbs) bind to RBD, while others target the NTD. Furthermore, some neutralizing Abs may also bind to the S1 carboxy-domain or S2 subunit, but RBD-targeting and NTD-targeting Abs may be much more potent [24].

Several mutations in components of the spike protein may significantly affect the neutralizing activity of mAbs, thus enabling VOC and VOI to escape immunity and spread in a population with rising immunity. E484 is an important residue on RBD that can be recognized by polyclonal antibodies in convalescent sera. It has been demonstrated that amino acid substitution to K, Q or P can significantly reduce neutralization titers [25]. E484K, which is the substitution of amino acid

Table 1 Key mutations and proposed effects in different variants of concern.

Mutations and proposed effects	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Delta (B.1.617.2)	Omicron BA.1	Omicron BA.2	Omicron BA.4	Omicron BA.5	Omicron BA.2.12.1
D614, increase transmission	G	G	G	G	G	G	G	G	G
Δ69—70, increase transmission	Deletion				Deletion		Deletion	Deletion	
E484, K and Q decrease neutralization		K	K		A	A	A	A	A
K417, decrease neutralization		N	T		N	N	N	N	N
L452, decrease neutralization				R			R	R	Q
N501, increase transmission	Y	Y	Y		Y	Y	Y	Y	Y
P681, increase transmission	H			R	H	H	H	H	H

glutamic acid (E) with lysine (K) at position 484 of RBD, is an escape mutation that has been found in the Beta and Gamma VOCs and some of the VOIs. It facilitates escape from antibodies in convalescent plasma [25—27] and several mAbs such as casirivimab and bamlanivimab [28,29]. In addition, E484K has also been shown to escape from plasma samples collected from people vaccinated with mRNA vaccines [29]. Other RBD escape mutations include K417 N/T and L452R. K417N/T is found in the Beta, Gamma, and Omicron VOCs. They are related to escape from mAb such as etesevimab [30,31] but remain susceptible to convalescent plasma and plasma from persons vaccinated with BNT162b2 or mRNA-1273 [32]. L452R is present in Delta, Omicron subvariants BA.4 and BA.5, and it has been shown to reduce neutralizing activity by several mAbs [28,33] and convalescent plasma [33].

Several other mutations also contribute to the antigenicity of VOCs. For example, N501Y is another RBD mutation found in the Alpha, Beta, Gamma, and Omicron VOCs. It has been shown to increase ACE2 receptor affinity [30], but its antigenic impact is limited to a few monoclonal Abs. Furthermore, it is rarely associated with the reduced neutralizing activity of convalescent plasma or vaccine sera [32]. P681H/R is a mutation occurring close to the S1/S2 furin cleavage site. It has been shown to increase SARS-CoV-2 virulence by increasing S1/S2 cleavage [34]. P681H is reported in Alpha and Omicron VOCs, while P681R is found in the Delta VOC.

One of the NTD mutations, deletion at the position 69—70, has been shown to be associated with increased viral replication [35]. It is also used as a proxy to monitor certain VOCs [36]. One widely used PCR method for diagnosing SARS-CoV-2 amplifies three target genes. When one of the gene targets is missing (69/70 deletion), the spike gene target cannot be amplified on a specific PCR assay, and this creates a reproducible phenomenon called S gene target failure (SGTF). SGTFs have been seen in the Alpha and Omicron VOCs [18].

Alpha variant (B.1.1.7)

The Alpha VOC has multiple mutations in RBD, most notably N501Y, P681H, and 69/70 deletion. SGTF has been used as a proxy to monitor this variant. It first emerged in the UK in September 2020 and had been detected in several other countries, including the USA, by early 2021 [37]. Data suggest that the Alpha VOC is 43—90% more transmissible than other pre-existing lineages circulating in the UK [36,38,39]. In terms of disease severity, although some reports demonstrated no clear evidence between the Alpha VOC and increase mortality [39,40], others have shown its association with more severe diseases [41—43]. Nevertheless, the Alpha variant is susceptible to most mAbs and convalescent and vaccine (mRNA-1273 and BNT162b2) sera [32,44,45]; however, its impact on antibody response in AZD1222 has been inconsistent [46,47].

Beta variant (B.1.351)

The Beta VOC has three RBD mutations (N501Y, E484K, and K417N) and some NTD mutations except 69/70 deletion. It was first identified in South Africa in October 2020, and cases have been found outside South Africa ever since. There is no clear evidence suggesting an association of this variant with increased mortality, but some reports have shown that E484K mutation may affect neutralization by several mAbs, including casirivimab, bamlanivimab, and etesevimab [28,32,48]. Furthermore, the Beta variant is more resistant to neutralizing activity by convalescent plasma [48] and sera from individuals immunized with mRNA-1273, BNT162b2 [32], and AZD1222 [49].

Gamma variant (P.1)

RBD mutations N501Y, E484K, and K417N were identified in the Gamma VOC. This variant caused a surge of infection in Manaus, where a majority of the population had already been infected with SARS-CoV-2, and it is associated with increased transmissibility, risks of reinfection, and mortality [11,12,50]. Similar to the Beta VOC, the Gamma variant is refractory to neutralizing the activity of several mAbs, convalescent plasma, and vaccine sera [48,51,52].

Delta variant (B.1.617.2)

The Delta VOC was first detected in India in early 2021. This variant contains RBD mutation L452R and furin cleavage site mutation P681. In addition, it has several other spike protein mutations (T19R, R158G, T478K, and D950N) and mutations within orf3, orf7a, and nucleocapsid genes [53]. Rapidly displacing the Alpha variant in multiple countries [14] and becoming the dominant global VOC, the Delta variant has shown increased transmissibility because of the following possible mechanisms: higher infectious viral load [54], longer duration of shedding infectious virus [55], and a higher rate of reinfection due to antibody escape [56]. The susceptibility of the Delta VOC to convalescent plasma and sera from recipients of BNT162b2 and AZD1222 is reduced [47,56,57], but one study showed that BNT162b2 offered more protection from the Delta variant than AZD1222 did [58]. Also, the Delta VOC may be resistant to bamlanivimab and some other mAbs [47].

Omicron variant (B.1.1.529)

On November 26, 2021, Omicron was first identified in Bostwana, South Africa. Within three weeks, new cases have also been detected in more than 50 countries worldwide [59]. This variant was later divided into six subvariants namely BA.1, BA.2, BA.3, BA.4, BA.5, and BA.2.12.1, and they are genetically and antigenically different from each other [60]. Due to increased transmissibility, BA.1 displaced Delta and become the globally dominant SARS-CoV-2 strain [61]. BA.2 later replaced BA.1 rapidly in several countries [59,62]. Nevertheless, new Omicron subvariants continue to emerge; BA.4/5 and BA.2.12.1 had become the dominant strain in South Africa and the United States [63—65], and they all present higher transmission advantage over BA.2 [66].

Omicron contains more than 30 mutations in its spike proteins; some of these mutations, particularly those involving

RBD and NTD, are predicted to influence antibody neutralization epitopes. Omicron subvariants share several common mutations, yet they also have many unique mutations of their own [67]. Shared mutations such as E484, K417N, T478K, N501Y, and P681H are found in other VOCs, and they are reported to be associated with increased transmissibility, higher ACE2 binding affinity, and higher antibody escape [59]. In addition to these common spike mutations, BA.1 carries 13 more unique amino-acid mutations while BA.2 carries 8 more mutations [68]. BA.4, BA5, and BA.2.12.1 display same RBD sequences to BA.2; in addition, BA.4 and BA5 contain L452R and F486V mutations while BA.2.12.1 has L452Q substitution [66]. Notably, similar to the Alpha variant, BA.1, BA.4, and BA.5 can be detected by SGTF due to 69/70 deletion, but BA.2 and BA.2.12.1 lack 69/70 deletion.

Several studies have shown reduced neutralizing activity of vaccine serum against Omicron BA.1. These vaccines include two doses of the ChAdOx1-S vaccine [69,70], two doses of the mRNA vaccine (mRNA-1273 and BNT162b2 [69−71]), and heterologous vaccination with the ChAdOx1-S and BNT162b2 vaccines [69]. Convalescent serum from persons who had been infected with the Alpha, Beta or Delta VOC also showed low neutralizing activities against BA.1 [69,72]. However, the serum samples collected from individuals infected with SARS-CoV-2 and then vaccinated [69,72] and individuals vaccinated with boosters (third dose with mRNA vaccines) [61,70−72] showed detectable neutralizing antibodies against BA.1. The neutralizing activities of vaccine serum against BA.1 and BA.2 are similar [68,73], and the vaccine effectiveness of booster doses against symptomatic disease and hospitalization is also similar for BA.1 and BA.2 [74]. However, one study found that comparing to BA.1, BA.2 was associated with increased susceptibility of infection for unvaccinated, fully vaccinated and booster-vaccinated individuals [75]. BA.4/5 and BA.2.12.1, on the other hand, exhibit more neutralization evasion than BA.2 against the plasma from 3 doses of BNT162b2 [65] and CoronaVac [66].

Cross-reactivities between different VOCs and Omicron subvariants have been investigated. One study revealed that unvaccinated individuals who had no previous SARS-CoV-2 infections before infection with BA.1 developed neutralizing antibodies against BA.1 mostly, and no significant neutralizing activity against other VOCs was found [76]. Moreover, although one study showed a certain degree of cross-reactivity between BA.1 and BA.2 [68], others found poor cross-reactivity of BA.1/2-specific neutralizing Abs against BA.4/5 and BA.2.12.1 [66,77].

Several therapeutic mAbs, including bamlanivimab, imdevimab, casirivimab, and etesevimab, were evaded by BA.1, BA.2, BA.4/5 and BA.2.12.1 [78]. Sotrovimab, however, was able to maintain its function at a reduced efficacy against BA.2 as compared to Delta or D614G virus [64,78−80]. Although sotrovimab was less effective against BA.2 than the parental virus, BA.4/5 BA.2.12.1 were more sensitive to sotrovimab than BA.2 [78]. Few other mAbs, such as tixagevimab/cilgavimab and adintrevimab, were partly active against BA.2 and BA.4/5 [64,65,78,80].

Response strategies to emerging variants

Different SARS-CoV-2 variants have emerged independently around the globe against the background of increasing population immunity. Various strategies have been used to reduce the burden of VOCs and VOIs, and most of the strategies remain effective. For instance, no report shows that existing public health prevention measures, such as wearing masks, social distancing, and hand hygiene, are ineffective against various variants. Moreover, several therapeutic mAbs (e.g. sotrovimab) and antiviral agents (e.g. remdesivir and molnupiravir) remain active against most VOCs and VOIs [21,81]. The protection provided by the vaccines, however, may be the principal concern.

Several countries are experiencing the resurgence of COVID-19 due to emerging VOCs and waning vaccine-induced immunity. Studies indicate a progressive waning of immunity provided by previous doses of COVID-19 vaccines [82,83], and some emerging variants are less susceptible to neutralizing activity of these vaccines [84,85]. It is inferred that in response to waning immunity and the rise of new variants such as Omicron, vaccine boosters should be considered because they can increase immunogenicity after the initial course of vaccines. Affinity maturation of antibodies may be the underlying mechanism of the improved humoral response against SARS-CoV-2 [86]. Furthermore, several studies have shown that administering a booster dose using currently licensed mRNA vaccines can offer protection against symptomatic infection, hospitalization or mortality associated with emerging VOCs [74,87−89]. Although a heterologous prime-boost schedule can be more immunogenic and reactogenic than a homologous prime-boost schedule [90,91], policymakers should still consider administering a booster dose to reduce severe COVID-19-related outcomes.

Introducing modified and new vaccines with antigens that are effective against pre-existing variants is another possible solution to enhance protection against emerging VOCs that may become vaccine-resistant [92]. One study indicated that using an mRNA vaccine integrated with spike mutations from the Beta variant as a booster can increase both wild-type and Beta variant neutralization titers in mice [93]. However, more studies are required to determine whether new immunogens can elicit a wider and longer-lasting response to VOCs rather than boosting existing antibodies generated by previous infections or current vaccinations. Until then, genomic surveillance with continued sharing of data, public health prevention measures, and full vaccination with boosters may be the best strategies to alleviate the impact of emerging variants.

Funding

Conflicts of interest

We have no conflicts of interest to disclose.

Acknowledgement

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