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# SARS-CoV-2 most concerning variants: A review on their complications, pathogenicity, transmissibility, and immune responses

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## Abstract:

Since the emergence of the coronavirus disease 2019 (COVID-19) pandemic, several different variants and strains of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been identified. Each of these variants has several mutations in different constituents of the original virus, such as the spike (S) glycoprotein, receptor-binding domain, N-terminal domain, and furin cleavage site region. These mutations mainly influence the virulence, infectivity, and transmission of the virus. Also, they can help the virus escape the natural- or vaccine-induced immunity in the host body. The Centers for Disease Control and Prevention categorized these variants into three major classes: variants of interest, variants of concern (VOC), and variants of high consequence. In this review, four VOCs, i.e., B.1.1.7, B.1.351, P.1, and B.1.427/B.1.429, have been presented, and their potential complications, pathogenicity, transmissibility, and capability of escaping natural- or vaccine-induced immunity are discussed. Moreover, the novel B.1.617 variant and its known characteristics are also demonstrated. In conclusion, this review can help clinicians and scientists better understand the most critical properties of the mentioned concerning variants of SARS-CoV-2 and guide them to conduct future studies on new preventive and therapeutic approaches in fighting COVID-19.

## Keywords:

COVID-19, mutation, SARS-CoV-2, strain, variant

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## Introduction

Several variants have been identified since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with more than 4000 mutations occurred only in the spike (S) glycoprotein of this virus.<sup>[1]</sup> These mutations can influence the virulence, infectivity, and transmission of virus.<sup>[2]</sup> Moreover, they can make the virus less likely to be diagnosed with current methods and more likely to be unresponsive to current therapies. Therefore, they have been categorized into variants of interest, variants of concern (VOC), and variants of high consequence by the Centers for Disease Control and Prevention.<sup>[3]</sup> The most concerning current variants are B.1.1.7 (20I/501Y.V1), B.1.351 (20H/501.V2), P.1 (20J/501Y.V3), B.1.427/B.1.429 (20C/S:452R),<sup>[4]</sup> and B.1.617 (VUI-21APR-01).<sup>[5]</sup> Still, many unknown mutations and new variants may be identified to induce other future pandemics.<sup>[6]</sup> In this review, some of the most prominent variants of SARS-CoV-2 are mentioned, and their potential complications, pathogenicity, transmissibility, and capability of escaping natural- or vaccine-induced immunity are discussed.

## History and epidemiology

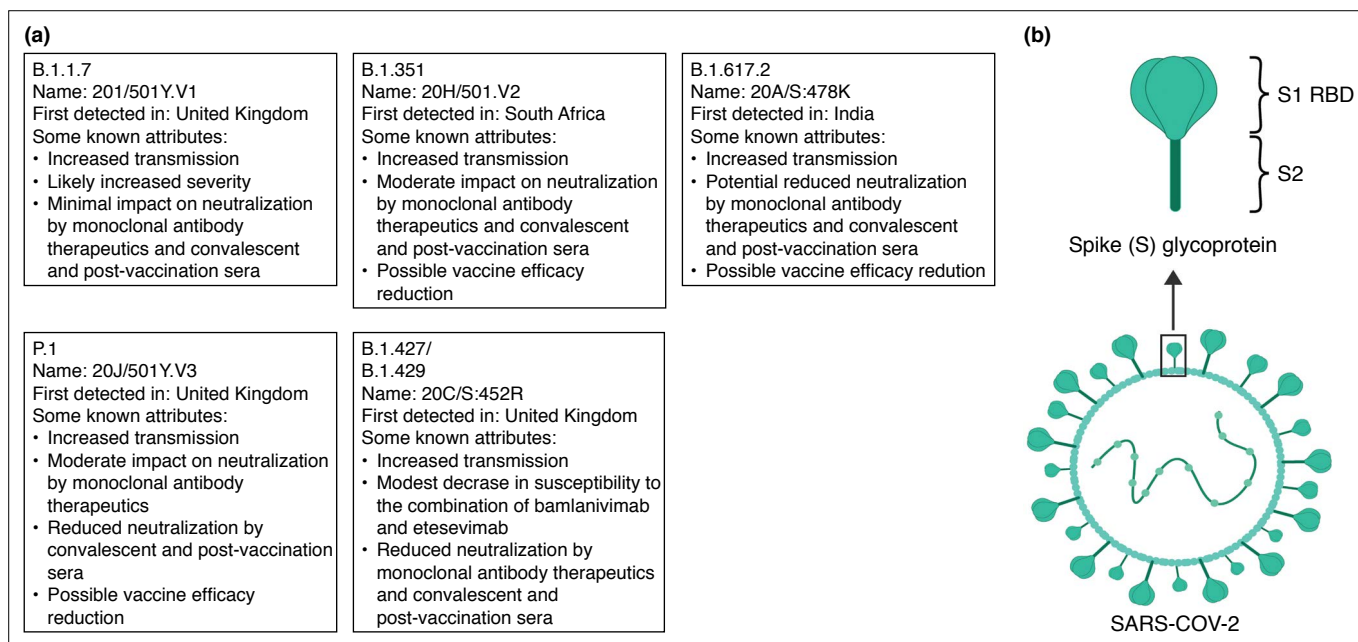
The first identified SARS-CoV-2 mutation was the D614G substitution that emerged in April 2020 and did not cause any prominent antigenic difference.<sup>[7]</sup> However, the first challenging mutation, B.1.1.7 (20I/501Y.V1), was detected in southeast England in October 2020 and spread rapidly to become the dominant strain throughout the UK.<sup>[8]</sup> In the last days of 2020, another SARS-CoV-2 variant named B.1.351 (20H/501.V2) emerged in South Africa. Although this strain was more locally concentrated in Africa, it was expected to spread worldwide due to its high transmissibility, similar to B.1.1.7.<sup>[9]</sup> Another variant, known as P.1 (20J/501Y.V3), was first discovered in Brazil in March 2020, but soon, patients infected with this variant were detected in the USA, France, Italy, Denmark, Singapore, Norway, Argentina, Ireland, and Canada.<sup>[10]</sup> Then, in January 2021, another less dangerous lineage, P.2 (20J), was discovered in Brazil.<sup>[11]</sup> Recently, two new SARS-CoV-2 variants, B.1.427/B.1.429 (20C/S:452R), were detected in California, whose characteristics are still under investigation.<sup>[12]</sup> The most novel SARS-CoV-2 lineage, B.1.617, comprising two significant sublineages, B.1.617.1 (20A/S:478K) and B.1.617.2 (20A/S:478K), was detected on October 5, 2020, in India, became the most common variant

reported in this country, and soon spread to other countries like Singapore, Nepal, and Thailand. First, the B.1.617 was defined as a double mutation variant, referring to the simultaneous presence of E484Q and L452R mutations in its S glycoprotein.<sup>[13]</sup> However, recently, it has become evident that another lineage, B.1.618, has an additional mutation called V382L in the spike protein, which is the reason to use the term “triple mutant.”<sup>[14]</sup> Figure 1a encompasses these five most concerning variants, their country of origin, and most critical clinical attributes.

## Genetic

It is better to describe the terms “variant,” “strain,” and “lineage” first. Whenever specific mutations are selected through multiple viral replications, a new variant evolves. However, if this new variant has a distinctly different phenotype, it is named a strain. In addition, a new lineage is evolved if genetic sequencing detects a new variant as a different branch on a phylogenetic tree.<sup>[15]</sup> Most concerning mutations occur in the S glycoprotein of the virus, but they can emerge anywhere in the virus genome, such as domains coding the receptor-binding domain (RBD), N-terminal domain, and furin cleavage site region. These mutations lead to higher angiotensin-converting enzyme 2 (ACE2) receptor binding affinity.<sup>[16]</sup> Figure 1b illustrates the S glycoprotein of SARS-CoV-2 and its significant subunits. Early in the coronavirus disease 2019 (COVID-19) pandemic, the only detected mutation was D614G substitution, which did not seem to affect the virus’s characteristics significantly. However, soon after, it became evident that even a single amino acid substitution can significantly alter its properties.<sup>[17]</sup>

In addition to the D614G substitution mutation, eight other mutations have been described for the S glycoprotein of the B.1.1.7 variant, including two deletions and two other substitutions. One of the mutations, N501Y, increased the spike protein and ACE2 receptor interactions.<sup>[18,19]</sup> B.1.351 was evolved as a result of nine mutations mainly composed of substitutions. 20H/501.V2 harbors three substitutions, i.e., N501Y, E484K, and K417N. This new variant has two similar mutations (D614G and N501Y) with the B.1.1.7 variant.<sup>[20]</sup> Brazilian lineage, B.1.1.28, consists primarily of two variants P.1 and P.2. P.1 variant contains the E484K mutation,<sup>[21]</sup> whereas the P.2 variant has 11 mutations in its S glycoprotein gene, in addition to the original E484K mutation.<sup>[22]</sup> The California variants B.1.427/B.1.429 harbor three



**Figure 1:** (a) Spike (S) glycoprotein of SARS-CoV-2 comprises two major subunits: S1 and S2. They, in turn, consist of several domains, including receptor-binding domain (RBD), which mediate virus entry into host cells via binding of this domain to the human angiotensin-converting enzyme 2 (ACE2) receptor. (b) Five most notable SARS-CoV-2 variants, B.1.1.7, B.1.351, P.1, B.1.427/B.1.429, and B.1.617.2, their formal names, country of origin, and some notable clinical attributes

mutations in the S glycoprotein, including an L452R substitution known as the 20C subclade.<sup>[23]</sup> All the mentioned new variants share the N501Y mutation, which affects the RBD of the spike protein. Moreover, the B.1.351 and P.1 variants have two other RBD mutations, known as K417N/T and E484K, which further increase the binding affinity to the ACE2 receptor.<sup>[24]</sup> Besides those VOCs, the novel Indian variant, B.1.617, has caused significant concerns worldwide. It possesses three key mutations: E484Q, which causes stronger binding to ACE2 receptor and more capability of escaping the host immune system;<sup>[13]</sup> L452R, which boosts S glycoprotein and ACE2 receptor binding and reduces the chances of recognition by the host immune system;<sup>[13]</sup> and P681R, which may increase virus infectivity in cellular levels.<sup>[25]</sup> However, three sublineages, B.1.617.1, B.1.617.2, and B.1.617.3, have been defined for this new variant with different substitutions and deletions. Nevertheless, it is noteworthy that this newly diagnosed SARS-CoV-2 variant is still under investigation, and more studies should be performed to fully understand its characteristics and its interactions with the immune system and different vaccines.

### Transmissibility

The D614G mutation was reported to affect viral replication, transmissibility, and infectivity of SARS-CoV-2.

In general, this higher transmissibility has led to an increased incidence of the virus.<sup>[26]</sup> The B.1.1.7 variant, initially detected in the UK, has been reported to have 30%–80% increased transmissibility.<sup>[27]</sup> The B.1.1.7 variant has spread quite rapidly all over the UK and then to most countries. Moreover, its intrafamilial distribution implies the higher transmissibility of this variant. The reasons for higher transmissibility of the B.1.1.7 variant might be the higher viral load suggested by lower cycle threshold values, more prolonged viral shedding, a shorter generation time than the preexisting variants and higher growth rate, and immune escape, all of which led to more secondary cases per contact with an index case.<sup>[28]</sup> The B.1.351 variant has raised concerns in South Africa because of multiple mutations in its spike glycoprotein. This strain is also thought to have higher infectivity and transmissibility, which may be related to the N501Y mutations that involved the RBD of the S glycoprotein, leading to a 40%–70% higher transmission than the primary virus.<sup>[29]</sup> There is little information about the transmissibility of the P.1 variant, but it is expected to have the same characteristics as the B.1.1.7 and the B.1.325 variants due to the same acquired mutations (N501Y, K417N/T, E484K, N501Y) they have in common.<sup>[30]</sup> California B.1.427 and B.1.429 lineages are approximately 20% more transmissible than the previ-

ous variants.<sup>[23]</sup> It has been estimated that the transmissibility of the B.1.617 variant is up to 50% more than other variants, which could be due to its increased spike protein structural stability and hACE2 binding affinity.<sup>[31]</sup>

### Age- and sex-related characteristics of variants

Up to the present time, the emerging variants have been reported to involve both sexes with comparable rates.<sup>[32]</sup> However, it has been forecasted that B.1.1.7 might involve children more prevalently and severely than the previous variants. The spread of this variant during school season in England may explain the higher susceptibility of children to B.1.1.7 compared with the preexisting strains. However, no study indicative of this variant's more severity has been published yet.<sup>[33]</sup>

### Virulence, severity, and mortality

It is observed that the new variants have not affected the severity of the disease despite the higher incidence they have caused.<sup>[34]</sup> Moreover, some studies have concluded that mutations with increased transmissibility are associated with lower disease severity.<sup>[35]</sup> Nonetheless, reports are conflicting, as some studies have mentioned an increased virulence and higher risk of mortality (32%–104%) for the B.1.1.7 variant than the previous ones due to its higher nasopharyngeal viral loads.<sup>[32,36]</sup> Due to multiple mutations, the B.1.617 variant is expected to have increased virulence and a more severe course. Besides, some authorities believe that the increased mortality of the new strains could be due to their rapid spread, which may fill the hospitals, exhaust medical staff, and cause resources shortage.<sup>[37]</sup> Moreover, the lack of testing and molecular sequencing capacity of current diagnostic tools can result in delayed detection and treatment and, therefore, more rapid progression in novel variants. Nonetheless, these estimates should be interpreted with caution because of their new emerging nature since more time is needed to carefully assess the consequences and burden of these new variants.<sup>[28]</sup>

### Response to current medications

The mutations leading to the evolution of these variants may make current therapeutic and prophylactic interventions partially useless. As a result of the mentioned muta-

tions in the S glycoprotein gene, these new variants have developed antigenic changes leading to current therapeutic options and the ineffectiveness of vaccine candidates.<sup>[24]</sup> Some monoclonal antibodies, such as bamlanivimab, have been investigated to treat SARS-CoV-2 infection.<sup>[38]</sup> The interaction between the B.1.1.7 variant and neutralizing antibodies seems to be affected, making this variant refractory to neutralization by most monoclonal antibodies.<sup>[39]</sup> Moreover, therapeutic antibodies may also be ineffective on B.1.351 and P.1 variants.<sup>[40,41]</sup> The B.1.351 variant is shown to be refractory to monoclonal antibodies, convalescent plasma, and serum of vaccinated people.<sup>[42,43]</sup> Fortunately, the P.1 clade is not resistant to monoclonal antibodies. However, due to the E484K substitution, resistance to convalescent plasma is expected for this variant, similar to B.1.351 variant. Nevertheless, it is noteworthy that entry inhibitors, such as maraviroc and fostemsavir, seem to inhibit all existing variants.<sup>[41]</sup> Little is known about the California variant. However, it is expected that the S glycoprotein L452R mutation in this variant might make it resistant to some anti-S glycoprotein monoclonal antibodies.<sup>[44]</sup> Due to the two spike protein mutations of B.1.617 in the RBD, any neutralizing antibody used for COVID-19 treatment, such as bamlanivimab, could be ineffective against this variant.<sup>[45]</sup> Also, it has been shown that this variant is six- to eightfold more resistant to neutralization by sera from COVID-19 convalescent and Moderna and Pfizer vaccinated individuals.<sup>[46]</sup>

### Vaccines or natural immunity

The most important triggering factor in the emergence of new variants of SARS-CoV-2 can be its extensive transmission and mutability. Vaccines are currently the mainstay of limiting the pandemic progression and new variants' emergence.<sup>[47]</sup> However, their unknown duration of protection and efficacy against the new emerging variants has raised concerns about the role of current vaccine candidates in preventing the disease as antigenic changes are expected to affect the immunity. Some believe that vaccination-induced neutralizing antibody titers are so high that they can protect against the new variants.<sup>[15]</sup> Nevertheless, the solution to this critical problem might be the rapid manufacturing and distribution of new vaccines with efficacy on the new strains.<sup>[48]</sup> Another strategy can be developing booster shots to defend against novel mutations, such as Moderna's most recent trial to design a third dose of the current vaccine with the mRNA

incorporating B.1.351's mutations.<sup>[49,50]</sup> As the virus mutates and produces different variants, there is an ongoing concern that current vaccine candidates would not be effective on these new strains. Unfortunately, this issue is already experienced with the South Africa B.1.351 variant, on which many current vaccines have lower efficacies. Thus, as with Influenza, the need for a vaccine that can induce immunity against all strains of SARS-CoV-2 is strong. This task is complex, and a stepwise approach is required from COVID-19 to pan-coronavirus to universal coronavirus vaccines.<sup>[51]</sup> Nevertheless, currently, some researchers are trying to overcome this issue. For example, researchers at the Walter Reed Army Institute of Research are developing a peptide-based version of a vaccine that can bind to several coronavirus antigens.<sup>[52]</sup>

Moreover, a mosaic vaccine containing several antigens of different variants can be utilized. In this regard, a recent study on homotypic nanoparticles displaying the RBD of SARS-CoV-2 or co-displaying SARS-CoV-2 RBD and RBDs from animal beta-coronaviruses was conducted in which mosaic nanoparticles with four to eight distinct RBDs were utilized. Their findings revealed that a single dose of mosaic RBD nanoparticles could induce the production of antibodies with superior cross-reactive recognition of heterologous RBDs. This promising study demonstrated the potential of mosaic vaccines as a strategy to simultaneously protect against SARS-CoV-2 and emerging zoonotic coronaviruses.<sup>[53]</sup> Whether natural or acquired immunity induced by previous SARS-CoV-2 infection or vaccination could protect against new variants is a question. It is believed that natural antibody protection has partial efficacy against reinfection with the B.1.351 variant.<sup>[29]</sup> Moreover, studies have indicated that antibodies in the serum of previously infected individuals are likely ineffective against the new variants. The reported data imply that an S glycoprotein-based vaccine might do less favor in the cases of new variants which harbor S glycoprotein mutations.<sup>[54]</sup>

It is generally believed that the D614G mutation and the B.1.1.7 strain will not significantly diminish the efficacy of vaccines. In contrast, the B.1.351 and P.1 variants partially resist the current vaccines, such as the Pfizer and Moderna mRNA vaccines and the Novavax protein vaccine.<sup>[55]</sup> It is postulated that antibody recognition might be affected during the B.1.351 and the P.1 infection due to the E484K mutation they possess.<sup>[18]</sup> The double muta-

tions in B.1.617 (E484K and L452R) may cause immune protection evasion, which leads to less efficacy of natural- or vaccine-induced antibodies against the Indian variant.<sup>[14,45,46]</sup> Generally, various vaccine platforms have been suggested and manufactured, such as inactivated whole-virion vaccines (BBIBP-CorV [Sinopharm]), nanoparticles (e.g., NVX-CoV2373), mRNA-encapsulating liposomes (e.g., BNT162b2 and mRNA-1273, both from Moderna), and adenovirus vectors (e.g., ChAdOx1 nCoV-19 [AZD1222] from AstraZeneca and University of Oxford, CTII-nCoV, Sputnik V, and Ad26.COVS.2.S). The average efficacies of these vaccines range between 65% and 96%.<sup>[56]</sup> Studies have shown that the BNT162b2 and mRNA-1273 vaccines have had lower neutralizing activities against the P.1 variant.<sup>[50]</sup> Furthermore, the AZD1222 vaccine has had a higher efficacy against the UK and Brazilian variants than the South African one, whereas the NVX-CoV237 vaccine efficacy against the UK variant has been higher than the South Africa variant. Moreover, the Ad26.COVS.2.S vaccine was more efficient against the California variants than the South Africa variant.<sup>[57]</sup>

A single shot of the Johnson & Johnson vaccine was estimated to be 66% and 57% efficacy against the Brazil and South Africa variants, respectively.<sup>[58]</sup> It is also shown to be 57% and 89% efficient against moderate-to-severe and severe B.1.351 variants, respectively, approximately similar to its efficacy against its ancestral strains (72%).<sup>[59]</sup> On the other hand, Novavax was reported to provide 89% and 60% efficacy against the UK and South Africa variants, respectively.<sup>[60]</sup> It is also indicated that the Ad26.COVS.2.S vaccine has an efficacy of 85% against the B.1.351 strain.<sup>[61]</sup> In a study in Africa, the AstraZeneca ChAdOx1 vaccine, the protection against the South Africa variant-induced mild-to-moderate disease had been lower than expected, leading to its suspension in South Africa.<sup>[62]</sup> Even a two-dose regimen of this vaccine did not cause effective immunity against this variant.<sup>[62]</sup> However, its efficacy against the B.1.1.7 variant was partially acceptable.<sup>[63,64]</sup> Moderna was the first multivalent vaccine that seemed to be effective against the South Africa variant. However, it has been observed that the two mRNA vaccines (mRNA-1273 vaccine [Moderna] and BNT-162b2 vaccine [Pfizer/BioNTech]) had a neutralizing activity of lower than optimal against the B.1.351 variant while being effective against the UK variant similar to that of the previous variants.<sup>[65]</sup> It seems that the Indian-produced version of the Oxford-AstraZeneca vaccine called Covishield can somehow pro-

tect against the B.1.617 variant.<sup>[66]</sup> Moreover, convalescent plasma from Comirnaty/BNT162b2 or BBV152 (Covaxin)-vaccinated individuals have been shown to protect against COVID-19 efficiently.<sup>[66]</sup> In general, COVID-19 vaccines are believed to be most effective in preventing symptomatic infection. However, studies have demonstrated that the ChAdOx1 nCoV-19 vaccine can also diminish viral shedding and asymptomatic SARS-CoV-2 infections, leading to reduced transmission.<sup>[67]</sup>

## Conclusion

This study provides an overview of SARS-CoV-2 four VOC, i.e., B.1.1.7, B.1.351, P.1, and B.1.427/B.1.429, and their potential complications and pathogenicity transmissibility, and capability of escaping natural- or vaccine-induced immunity are discussed. Moreover, data on the novel concerning variant B.1.617, first discovered in India, is also described. In conclusion, it can be inferred that although different strategies are developed or under development to prevent and treat COVID-19, the emergence of new strains poses a severe challenge to these efforts. For instance, as already experienced with the South Africa variant, the efficacy of current vaccine candidates is lower on this new strain. Hence, the development of new preventive and therapeutic options, such as universal vaccines, should be the sole concern of the scientific society.

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