Minireview *Highlight article*

SARS-CoV-2 variants: A double-edged sword?

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Impact statement

Due to the relentless efforts of the scientific communities and healthcare workers, we now have the effective vaccines to fight the COVID-19 pandemic, and managed to bring down the number of cases, hospitalizations, and mortality. However, the emergence of new viral variants during the last few months has posed new challenges. To that end, understanding various types of variants and mutations, the rate of transmission within the population, their impact on our daily lives, and the efficacy of the available vaccines become crucial. In this review, we have discussed these and other important aspects such as genomic surveillance as well as virus characterization, which will prove useful in mitigating the spread of SARS-CoV-2 variants.

Abstract

Since the worldwide emergence of the COVID-19 outbreak, there have been international concerns about the possible viral evolution into variants with underlying mutations that may contribute to their increased transmissibility, disease severity, risk of death, and their potential escape from the immune response or may even lead to its extinction. Rigorous surveillance has revealed the variants harboring mutations in the spike protein, the main target of neutralizing antibodies generated through vaccination or herd immunity. In this review, we have highlighted major SARS-CoV-2 variants as well as other local strains along with their specific mutations, suspected changes in their characteristics, and their impact on the current pandemic and vaccine efficacy. We have also emphasized the need to develop widely protective interventions to curb further transmission of variants.

Keywords: COVID-19, SARS-CoV-2, spike protein, mutations, variants, B.1.1.7

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Introduction

A year after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus first emerged in Wuhan, China, we are beginning to gain control over the coronavirus disease (COVID-19) pandemic with the help of efficient vaccines developed at an unprecedented speed and stringent social distancing protocols put in place by countries worldwide. However, the new SARS-CoV-2 variants that originated in United Kingdom (UK), South Africa, Brazil, and a few other countries have recently caused a surge in infections, thereby dampening these efforts and making the recovery harder. It has also prompted new lockdowns in Europe. In order to efficiently fight these variants, it is important to gain a better understanding of viral evolution.

Viruses mutate or change their genetic material every time they undergo replication, thereby creating variants.[1] Unlike DNA viruses, the frequency of mutations is higher in RNA viruses such as coronaviruses. Over time, the mutations that are beneficial to the viral propagation are retained via natural selection or a chance event, while others are eliminated. In the case of SARS-CoV-2, the same mutation has emerged independently in different countries, indicating its potential benefit for viral fitness.[2] Besides, all variants exhibit a host of mutations, suggesting rapid evolution within a short time.[2] It is critical to understand how these mutations affect viral transmissibility and virulence.

B.1.1.7 (501 y.V1)

Although the spike protein of SARS-CoV-2 has displayed around 4000 mutations throughout the pandemic,[3] most of them did not impact viral function. However, B.1.1.7, also referred to as the UK variant, first emerged in September

2020, and was found to have 23 mutations which have greatly benefitted its transmissibility (Table 1, Figure 1). Public Health England has named it as a Variant of Concern 202012/01 (VOC).[4] B.1.1.7 variant is 56% more transmissible than other variants, indicating its competitive advantage.[5] Studies also suggest that the variants containing 501Y mutation may have been going around since August 2020 but were detected in September 2020.[6] According to a recently published report, B.1.1.7 can increase the risk of death by 61% and also disease severity.[7] B.1.1.7 has shown resistance to monoclonal antibodies directed to the spike protein's N-terminal domain and a few that target receptor-binding domain (RBD).[7] Studies suggest that antibodies triggered by B.1.1.7 infection do

Table 1. Summary of SARS-CoV-2 variants and underlying mutations.

Variant	First identified	Countries with sequences	Types of mutations[a]
B.1.1.7	United Kingdom	102	aa:orf1ab:T1001I, aa:orf1ab:A1708D aa:orf1ab:I2230T, del:11288:9, del:21765:6, del:21991:3, aa:S:N501Y, aa:S:A570D, aa:S:P681H, aa:S:T716I, aa:S:S982A, aa:S:D1118H, aa:Orf8:Q27, aa:Orf8:R52I, aa:Orf8:Y73C, aa:N:D3L, aa:N:S235F
B.1.351	South Africa	58	aa:E:P71L, aa:N:T205I, aa:orf1a:K1655N aa:S:D80A, aa:S:D215G, aa:S:K417N aa:S:A701V, aa:S:N501Y, aa:S:E484K
P.1	Brazil	26	aa:orf1ab:S1188L, aa:orf1ab:K1795Q del:11288:9, aa:S:L18F, aa:S:T20N, aa:S:P26S aa:S:D138Y, aa:S:R190S, aa:S:K417T, aa:S:E484K, aa:S:N501Y, aa:S:H655Y, aa:S:T1027I, aa:orf3a:G174C, aa:orf8:E92K aa:N:P80R
A.23.1	Uganda	27	aa:S:F157L, aa:S:V367F, aa:S:Q613H, aa:S:P681R
B.1.525	Multiple Countries	30	aa:orf1ab:L4715F, aa:S:Q52R, aa:S:E484K aa:S:Q677H, aa:S:F888L, aa:E:L21F, aa:E:I82T del:11288:9, del:21765:6, del:28278:3

[a]cov-lineages.org/global_report.html.

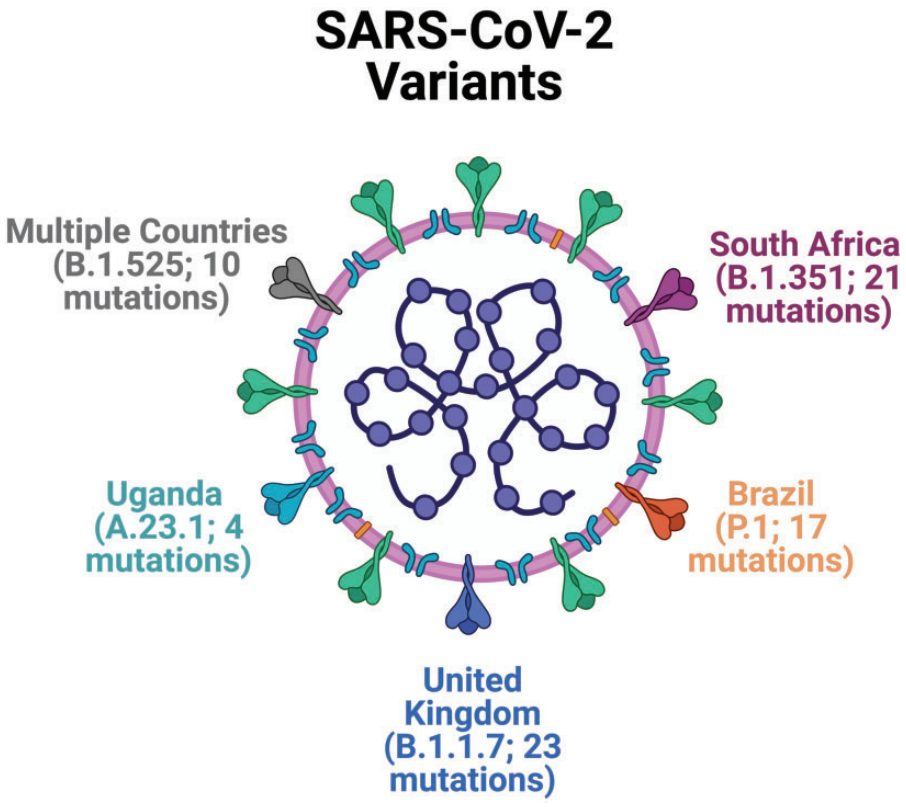

Figure 1. SARS-CoV-2 variants and associated mutations. Five SARS-CoV-2 variants, B.1.1.7, B.1.351, P.1, A.23.1, and B.1.525, each containing multiple mutations, originated in multiple countries and soon started spreading worldwide, due to their increased transmissibility, immune-escaping behavior, and the ability to cause severe illness. Created with BioRender.com. (A color version of this figure is available in the online journal.)

not work well against other variants including B.1.351, an aggressive South African variant.[8] On the contrary, B.1.351 infection elicits the production of antibodies, which are effective against P.1 (emerged in Brazil) and earlier variants.[8]

A total of 8 out of 23 mutations of B.1.1.7 were detected in the spike protein including D796H,[2] del69-70, P681H, and N501Y in the six critical amino acids in the RBD. These mutations seem to have increased the affinity of the spike protein towards human angiotensin-converting enzyme 2 (ACE2), enabling tighter binding, easier viral entry, and its propagation.[5] Since N501Y mutation is also observed in strains that spread slowly, scientists suspect that it may be operating in conjunction with other mutations observed in the B.1.1.7 variant.[9] In addition, the strain with mutations D796H and del69-70 showed lesser sensitivity to convalescent plasma than wild-type virus *in vitro*.[2] While the mutation del69-70 confers high infectivity to the virus, P681H alters the spike protein cleavage site prior to viral entry into the host.[2]

D614G is one of the most important mutations found in B.1.1.7, which arises as a result of a substitution of aspartic acid with glycine at position 614 in the spike protein that binds to ACE2 to facilitate viral entry.[5] D614G augments SARS-CoV-2 replication in human lung epithelium and primary airway tissues as well as the upper respiratory tract in animal models, and stabilizes virions, increasing their ability to transmit to a new host.[10,11] D614G has managed to spread across multiple countries since its detection in March 2020. Individuals infected with D614G were found to be associated with lower RT-PCR cycle threshold (Ct) values, indicating higher titers in the upper respiratory tract and increased infectivity than that caused by D614 but were not associated with increased disease severity.[12] Population genetic studies showed a higher incidence of 614 G as compared to that of 614 D.[13] D614G was also accompanied by a higher viral load in younger population.[13,14] In this scenario, school closures may help in preventing further transmission and evolution of the virus into highly virulent strains.[15] However, it is important to consider the psychological burden of closing schools on the younger population before taking such a step.[16] The impact of 614 G on mortality and severity of COVID-19 is still unclear. In addition to 614 G, B.1.1.7 has shown another mutation known as E484K in some recently diagnosed cases in the UK.[17]

B.1.351 (501 y.V2)

B.1.351 emerged in October 2020 in South Africa,[4] and was found to have 21 mutations[18] (Figure 1). Similar to B.1.1.7, B.1.351 showed several alterations in the spike protein including N501Y, and is likely ~50% more transmissible.[9] Additionally, there are two other substitution mutations—E484K and K417N—in the spike protein of the virus (Table 1).

Of particular note is the E484K mutation detected in the receptor-binding motif of the spike protein. In a concerning development, E484K has conferred immune escape capabilities to B.1.351 via evasion of antibody neutralization by convalescent plasma and vaccines,[19] and monoclonal antibodies,[7] although there is a lot of inter- and intra-person heterogeneity in terms of the effect of E484K on antibody binding.[20] In some cases, the potency of plasma was even reduced by 10-fold.[21] In particular, the antibody response directed towards the N-terminal and receptor-binding domains of the spike protein was weakened. Interestingly, studies conducted using the HIV virus containing a full set of 501Y.V2 mutations revealed complete resistance of the virus to convalescent plasma obtained from 21 out of 44 people enrolled in the study.[21] Based on these findings, there is a realistic possibility of reinfection in people who have had COVID-19 before or have been vaccinated. However, the impact of the mutation on the severity of the disease remains unknown.

P.1 (501 y.V3)

The P.1 variant emerged in December 2020 in Brazil as a bifurcation of the B.1.1.28 lineage and was first detected in January 2021 in the United States (Table 1). P.1 had accumulated 17 mutations by the time it was identified in the population[22] (Figure 1). Three out of 17 of these mutations—N501Y, E484K, and K417N—are consistent with those observed in B.1.351, making it resistant to neutralizing antibodies.[9] Evidence also suggests that P.1 is twice as transmissible as the wild-type virus, and has led to reinfections of 25–61% of the Manaus people who have been previously infected with the virus.[22] However, the study cautions that these findings are only applicable to the specific cohort in Manaus, and cannot be generalized for any other population.[22] P.1 is responsible for the newest surge in COVID-19 infections in Brazil, which has overwhelmed their healthcare system.[23]

Other variants

A.23.1 is a relatively new variant that emerged in Uganda with a mutation profile similar to that of the UK (P681) and South African variants (E484K)[17] (Table 1, Figure 1). The proportion of lineage A variants jumped from 25% in June-October 2020 to 98% in December 2020 in the Ugandan population and they have since been identified in multiple countries.[17] Scientific communities worldwide are investigating the impact of these mutations on the disease severity and mortality.

While India is ranked second and third worldwide in terms of the number of COVID-19 cases and deaths respectively, the country has one of the lowest per capita infection and mortality rates in the world.[24] Therefore, a rapid increase in infections over the last few months has caught everyone's attention. Evidence suggests the emergence of 240 new strains including a double mutant B.1.617 that may be responsible for causing re-infections in people recovered from their previous encounter with the virus or in those that were vaccinated.[25] Either way, the virus seems to escape immune protection by neutralizing antibodies. It remains to be seen whether the reinfections are the result of a weaker immune system or an impact of the mutation.[21]

Viral outbreaks associated with mink farms in Denmark and Netherlands led to the identification of a novel variant

known as cluster 5 around summer 2020.[26] Viral transmission from animals to humans and vice versa is particularly concerning.[27] The cluster 5 variant exhibits four mutations in the spike protein namely, Y453F, del69-70, I692V, and M1229I, which may have enhanced its avidity for mink ACE2[5]. Evidence suggests that cluster 5 is able to escape immune protection offered by convalescent plasma.[26] The transmission pattern of the virus is alarming, since it indicates that the virus may be using mink as an animal reservoir in order to evolve before infecting humans. Continued surveillance and taking appropriate precautions would be critical to prevent further transmission.

In the United States, B.1.526 variant first emerged in November 2020 in New York.[28] It started spreading slowly by the end of December 2020 and then rapidly by February. It currently represents ~25% of all viral sequences in the dataset.[28] Studies are ongoing to determine the effect of mutations present in its spike protein, its antigenicity, and whether the variant has the potential to escape an immune response elicited by monoclonal antibodies and vaccines.[28]

B.1.525 variant has spread to at least 11 countries after originating in December 2020 in Africa and Europe[29] (Figure 1). It has a mutation profile similar to that of other variants found in the UK, Brazil, and South Africa (Table 1). Further investigation is needed to determine if it is capable of evading immune protection afforded by vaccines and monoclonal antibodies.

B lineage variants, B.1.427/B.1429, have become dominant in California, representing >50% of total cases across 44 counties, and suggesting rapid transmission.[28] Los Angeles reported a new strain called CAL.20C followed by the fresh surge in COVID-19 cases in Southern California. The five mutations associated with the variant include ORF1a: I4205V, ORF1b: D1183Y, and three spike protein mutations namely, S13I, W152C, and L452R. CAL.20C has shown 35% and 44% higher incidence in January 2020 alone in the state and Southern California, respectively. It has also spread worldwide and across the United States. Further investigation is needed to determine the effect of this strain on COVID-19 prognosis and transmission.[30]

More recently, a new variant called Pelican carrying a mutation Q677P emerged in New Mexico, and is responsible for a fresh surge in COVID-19 cases in the state.[31] Q677P is localized close to the spike protein site that is cleaved in order for the virus to enter its host.[31] A similar mutation has been found in many other variants in the United States (Table 1) and is being investigated.

Vaccine activity against variants

Since the emergence of the viral variants, one question that is being commonly asked is whether the newly developed vaccines are effective. Based on the vaccination data from Israel, the country with the highest vaccination rate, the Pfizer Inc.-BioNTech SE vaccine was 92% effective against all kinds of infections including those caused by B.1.1.7, which is a majority variant in the population.[32] Although B.1.1.7 did not completely escape the immune protection, reduced antibody neutralization was observed in 40 participants immunized with Pfizer Inc.-BioNTech vaccine shots.[33] Further large-scale studies are warranted to determine the potency of the vaccine against the variants. The difference between the spike protein of the UK variant and the one that's encoded by the Pfizer vaccine is only nine amino acids.[2] While the Moderna vaccine demonstrated efficacy against the UK (B.1.1.7) and South African (B.351) variants *in vitro*, a significant decline in neutralizing antibody levels was observed against B.1.351, P.1, and B.1.1.7 variant containing E484 mutation.[23,34] Both Moderna and Pfizer-BioNTech vaccines elicited strong antibody response in people recovered from their previous encounter with the virus, even with a single dose. The antibody concentration in the blood was found to be high enough to neutralize the 501Y.V2 and earlier variants.[32] It is possible that the vaccine enhanced already established broad immune response in previously infected people.[8]

Studies suggest that the antibody cocktail developed by Regeneron pharmaceuticals Inc. was effective against B.1.1.7 as well as B.1.351. It targets multiple epitopes of the virus, preventing the development of immune-evading variants.[32] The efficacy of Ad26COV2.S, the Johnson and Johnson's vaccine, was 72% and 57% in the United States and South Africa, respectively, while it offered modest protection (66%) in Latin America.[35] A clinical trial in South Africa involving the Novavax vaccine revealed that prior COVID-19 infection does not guarantee protection against the B.1.351 variant.[36] The AstraZeneca vaccine was found to be not as effective against B.1.351 (22%) compared to B.1.1.7 (74%).[37] As a result, South Africa has paused the distribution and administration of the AstraZeneca vaccine.[32]

Drugmakers have already started updating the existing vaccines to increase their potency, and the estimated time for production is about six weeks.[18] Multivalent vaccines work well against multiple lineages, and can be offered as booster shots.[23] Vaccine dosage can also be adjusted to ensure wider distribution.[28] It is possible that the approval process for new vaccines would be shorter, similar to that of the seasonal influenza vaccine, resulting in quicker distribution.[18]

In an effort to vaccinate the vast majority of the population, some countries are planning to extend the interval between the first and the second dose to 12 weeks instead of the standard three to four-week period, which is a cause of worry for a few scientists.[9] The rationale behind using the appropriate vaccine dosage regimen is that we eliminate the virus completely, instead of taming it and allowing it to become vaccine-resistant, a characteristic of seasonal influenza. However, not everyone shares this concern. Many believe that giving the wider community the chance to fight the virus is better than leaving half of them unprotected, while the other half is fully protected.

Future perspectives

The emergence of variants has prompted efforts to study their replication patterns, behavior, how each mutation

associated with the variant affects transmission and pathogenesis, and whether the existing interventions (e.g. antiviral treatments, vaccines, etc.) are effective, *in vitro* and in animal models.[23] Animal models should be selected carefully, taking into account their built-in characteristics and suitability to study the effect of mutations, although it is still unclear how translatable the animal data would be in humans.[2] Correlating the preclinical data with the epidemiological data will put us in a better position to predict the behavior of the virus. It would also be helpful to examine if there are any phenotype-specific mutations in proteins other than the spike protein, against which the vaccines are directed.[23]

In addition to studying the effect of mutations, it would be important to address any health disparities and factors associated with improved viral fitness in the population such as ACE2 expression. Although the proportion of children infected with the new variants seems to be higher in the UK, it is still unknown whether the new variants are particularly inclined to infect the children compared to the adult population. The younger population appears to be affected by both old and new variants. However, the disease severity and susceptibility were found to be lower in children and females of Asian descent, possibly due to higher ACE2 expression in that demographic.[38] Stronger immune response in children may also play a role.[39] Another explanation could be that the children continued going to schools, while the other places went into the lockdown again after reopening,[39] although schools have not been shown to play a role in viral transmission.[16] Further investigation is needed to identify the mechanism and sources underlying the transmission.

Conclusions

Evidence suggests that vaccines are effective against variants. While the variants may escape monoclonal antibodies, no virus has been shown to completely evade the broader immune response generated by vaccines.[2] Influenza virus stands out in this respect due to its high mutation rate and therefore needs a new vaccine to be generated each year.[2] Continued genomic surveillance is needed for early detection of any variants that may escape neutralizing antibodies,[9] so that vaccines can be updated accordingly. Currently, the proportion of cases sequenced in the UK and South Africa is 10% and 1%, respectively.[18] The sequencing capabilities of most countries are inadequate, with the exception of Denmark which sequences 20% of their cases.[14] In addition to updating vaccines, allowing their access worldwide and making them affordable are key aspects to consider. In order to study how viruses respond to antibodies, convalescent plasma and other patient materials should be readily available.[37] Data sharing is also equally important. Lastly, it is imperative to follow strict social distancing protocols to prevent the transmission of the virus, while the vaccines are being distributed and administered.

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MPJ, AV, and PG contributed to the conception, writing, and discussion of this review manuscript. MPJ, AV, and PG wrote the initial draft of the manuscript. The final version of the manuscript was approved by all authors.

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