JMID/
Journal of Microbiology and Infectious Diseases

2022; 12 (1):38-51
doi: 10.5799/jmid.1086226

REVIEW ARTICLE

Comparative Analysis of B.1.617.2 (Delta) Variant of SARS-CoV-2

Mohd Fardeen Husain Shahanshah, Saloni Jain, Bhawna Sharma, Ananya Grewall, Shalini Swami

Ram Lal Anand College, University of Delhi, New Delhi, India

ABSTRACT

The emergence of numerous variants of SARS-CoV-2 has caused massive setbacks and prolonged the COVID-19 pandemic. Some of the variants are still under investigation, while some have become a reason of grave concern. One such variant is B.1.617.2, known as the Delta variant, which was first detected in India. A comprehensive analysis and comparison of this particular variant have been done to the original Wuhan strain, and the possible reasons behind rapid mutation have also been discussed.

A comprehensive literature search was done to summarize the information on the variants of SARS-CoV-2 and the reasons behind their mutation, with a significant focus on the B.1.617.2 variant. Data were collected from various online sources such as PubMed, Google Scholar, MEDLINE, Worldometer, WHO, CDC, and GISAID. In addition, 3D structures of spike proteins were obtained from Protein Data Bank (PDB).

The data shows that the spike protein of the B.1.617.2 strain is highly mutated and has accumulated eight amino acid changes. Besides spike protein, changes in non-structural proteins (nsP2, nsP3, nsP4, nsP12, and nsP15), other structural proteins (nucleocapsid and membrane protein), and accessory proteins (ns3, ns7a) have been observed as well. Furthermore, in almost all the variants of SARS-CoV-2, D614G mutation occurs, suggesting its role in increased infectivity and transmission.

New variants are continuously emerging on which we have no control. Spike mutations are more favored and essential in the evolution of new variants because it increases the transmissibility and infectivity of the virus. Therefore, to maximally protect public health, knowledge of different variants is essential. *J Microbiol Infect Dis 2022; 12(1):38-51.*

Keywords: *SARS-CoV-2, Spike, Mutation, Variants, B.1.617.2 variant*

INTRODUCTION

Since its first appearance in Wuhan, China, in late November 2019, the novel coronavirus, SARS-CoV-2, has transcended all borders and continues its rampage across the world by prolonging the ongoing COVID-19 pandemic [1, 2].

As of 30 November 2021, 1:47 am, 262,136,650 cases of coronavirus have been reported globally. Of these, 236,709,323 people have recovered, and 5,221,506 people have succumbed to the illness [3,4].

SARS-CoV-2 possesses a 30 kb long, positive sense, single-stranded RNA (ssRNA) molecule as its genome. Surrounding that RNA molecule is the Nucleocapsid (N) protein and the viral envelope, which is collectively made up of three other structural proteins, namely Spike (S), Envelope (E), and Membrane (M) [5, 6]. Its expansive genome consists of 14 open reading frames (ORFs) encoded for 27 different proteins. This betacoronavirus shares homology with other important zoonotic viruses such as SARS-CoV and MERS CoV, both of which have caused severe outbreaks in the past [1,2,7,8].

The virus particle gets transmitted via respiratory aerosols, fomites, and human contact and manifests a range of nonspecific

Correspondence: Dr. Shalini Swami, Department of Microbiology, Ram Lal Anand College, University of Delhi, Benito Jaurez Marg, South Campus, New Delhi, India
E-mail: dr.shaliniswami@gmail.com
Received: 28 July 2021 Accepted: 24 January 2022

signs and symptoms. Fever, cough, fatigue, loss of taste and smell, diarrhea, and shortness of breath are the most common indications of the illness. The mild infection may develop into severe complications like Acute Respiratory Distress Syndrome (ARDS) or severe pneumonia and increase the chances of fatality in patients with comorbidities. Additionally, some individuals may remain asymptomatic and effectively transmit the pathogen [1,2,7,8].

Through concerted efforts of different nations and organizations, several effective prophylactic strategies have been successfully developed and proposed for combating COVID-19. However, the pandemic is still escalating, and the fight against it persists. The rampant rise of COVID-19 can be attributed to its high infectivity, ease of transmission, and the rapid advent of mutants. For a pandemic to end, herd immunity is required. However, the rate of mass immunization cannot cope with the emergence of fast-evolving new viral mutants, resulting in a disproportion. SARS-CoV-2 being an RNA virus, is highly susceptible to mutations. A mutation is inevitable if the virus is allowed to propagate within the population. Multiple variants of the novel coronavirus have been reported, some of which have higher transmissibility and may be much more virulent. These mutated lineages of SARS-CoV-2 have dominated the second wave of the pandemic and severely impacted healthcare institutions [6].

The damaging consequences of the COVID-19 pandemic have greatly distressed the world. Consequently, the rise of new variants poses a significant threat and demands a prompt response. This paper aims to provide an insight into the different variants of SARS-CoV-2 that have emerged within a brief period with a significant focus on one of the most special variants, i.e., B.1.617.2, also known as the delta variant.

2. Mutation

Mutation brings about various genetic constitutions in an evolving populace. Assuming that mutations will happen in a population, accurate and precise mutation rates are vital. It serves an essential purpose in quantitative genetics and phylogenetic analysis of RNA viruses [9]. RNA viruses mutate faster than DNA viruses; single-stranded viruses undergo rapid mutations [10]. The primary reason is the poor fidelity of RNA-dependent RNA-polymerases (RdRps). RdRps of RNA viruses errs and contribute to the highest mutation rates, permitting them to evolve swiftly [10]. Polymerase's built-in fidelity and exonuclease activity alter the mutation rates [10]. The number of mutations that can attenuate the phenotype of the virus and alter the fidelity of its RdRp suggests that the mutation rates of RdRps are highly regulated. Specific mutations result in infidelity and recombination-deficient mutants [9]. Furthermore, the mutation rate is inversely proportional (negatively correlated) to the length of the genome, i.e., the higher the mutation rate, the shorter the length of the genome. This correlation has been illustrated in figure 1.

With the aid of its proofreading and/or post-replicative mechanisms, the viruses can rectify and modify the genomic mismatches. However, such refurbishments can also lead to mutations. Additionally, certain distinctive and unique genetic elements are encoded by viruses with an outstanding ability to fabricate novel and colossal mutations [10]. Another primary reason behind their quick evolution is the activity of the host editing enzymes that can alter the mutation rates. These enzymes rope in Apolipoprotein B Editing Complex (APOBEC) and Adenosine Deaminase, RNA-specific (ADAR) [9].

During viral infections, there is an exhilaration of highly reactive chemical molecules, Reactive Oxygen Species (ROS), along with various other chemical metabolites, which are responsible for commanding mutations in viruses and the host cell. Single-stranded viruses are much more likely to suffer from oxidative deamination and other types of spontaneous chemical damage. Other factors responsible for determining the mutation rates of viruses are the template sequence and its secondary structure, proteins (other than the polymerase) of replication mechanisms, the replication mode, cellular microenvironment, and discrepancy in nucleotide pools [10].

The assorted genetic constitution brought about by mutation could be eliminated with the help of natural selection and genetic drift. However, the two factors are also necessary to maintain the equilibrium among the evolving diversity, reduce the impact of deleterious

mutations, and increase fitness. Also, there must be a balance between the limited genetic capacity, high mutation rates, and how the population of a species changes over a while. This crafts a closely acquainted and familiar relationship between RNA virus biology and evolutionary game theory. Hence, it is essential to interrupt this reputable balance through a well-known antiviral strategy indulging the use of enzymes. One such pharmacological mutagen/drug is ribavirin, a nucleoside analog (rGTP). But due to the change in mutation rate of RdRps, resistance has developed against this treatment [9].

Like all other viruses, SARS-CoV-2 also accumulates changes in its genetic code as it replicates over time. It has been speculated that the novel coronavirus mutates at a rate of $\sim 1.1 \times 10^{-3}$ substitutions per site per year [6]. Some genetic alterations may result in the emergence of a much more virulent strain, whereas some can diminish the infectivity.

In the succeeding sections, different variants of SARS-CoV-2 have been discussed in detail. They have been classified into different categories for quick identification and characterization of emerging variants.

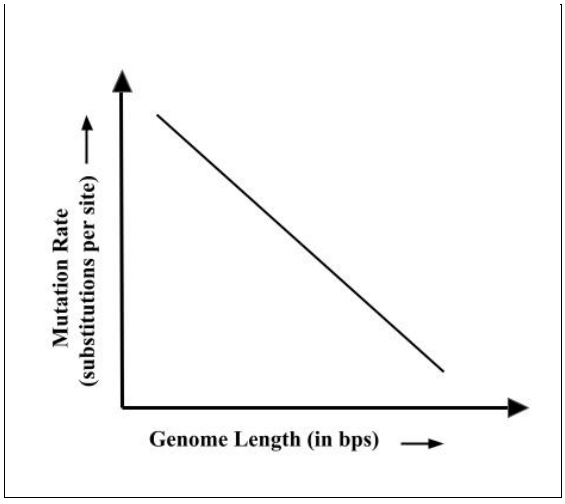

Figure 1. Graph representing the negative correlation between mutation rate and genome length.

3. Different variants of SARS-CoV-2

3.1 Variant of Interest (VOI)

Variants of Interest (VOI) are the variants that possess alterations in specific genetic markers that are linked to receptor binding affinity. These mutations have heightened the transmissibility and disease severity. It has also made the virus less receptive to treatments. These variants can also escape the immune action of neutralizing antibodies (nAb). Therefore, high sequence surveillance, epidemiological investigation to check its global spread, laboratory characterization, approximation of its severity and illness rates, and effectiveness of therapeutics and other treatment alternatives are required [11]. A specific missense mutation, D164G mutation, is shared among all the variants of B.1 lineage under VOI [12]. The CDC classified VOI are mentioned in Table 1.

3.2 Variants of Concern (VOC)

Variants that have shown an increase in transmissibility and disease severity diminished protection from nAbs generated during previous infection or vaccination, reduced susceptibility to different treatments or vaccines, or diagnostic detection failures have been characterized as Variants of Concern (VOC). The occurrence of such variants demands for astringent and prompt response to prevent further spread of the disease and ensure its containment. Antivirals such as ribavirin, lopinavir, and ritonavir are being actively prescribed as a therapeutic. Besides these, steroids like prednisolone and methylprednisolone are being administered to alleviate the symptoms of inflammation. Another modality of treatment that is widely in use is the administration of convalescent plasma and mAbs. The efficacy of the former is still under contention. A cocktail of mAbs (combination of bamlanivimab and etesevimab or casirivimab and imdevimab) has been found to be potent against VOCs. CDC classified VOCs have been tabulated in the following table (Table 2).

In the spike protein, B.1.617 and its sub-lineages possess common signature mutations T19R, G142D, L452R, E484Q, D614G, P681R, and D950N, including within the RBD region, out of which mutations at positions 452, 614, and 681 are present globally in all lineages.

Any mutations within the amino acid positions 438-506 of B.1.617 strain could significantly alter the properties of the virus, thereby augmenting its infectivity transmissibility and aiding in its escape from the immune system. Both E484Q and L452R amino acid substitutions raised concerns as both are found in the RBD of the Spike protein. RBD is a leading functional component responsible for

binding SARS-CoV-2 to ACE2. Mutation in this region provides the SARS-CoV 2 variant with a reformed and updated version of virulence and pathogenicity [19].

3.3 Variants of High Consequence (VOHC)

Variants of High Consequence (VOHC) are the variants that significantly impact the medical countermeasures (MCM). Efficacy of vaccines decreases, and vaccine-induced protection is also diminished significantly. All the diagnostic measures fail and give more false-negative results due to poor specificity and sensitivity. Therapeutics fail to work. More cases of severe illness and hospitalization are observed. As of now, there are no variants of SARS-CoV-2, which fall under the category of VOHC [11].

3.4 Variants Under Investigation (VUI)

The variants of SARS-CoV-2 that have reported multiple pathogenic, immunological, and epidemiological properties are placed in the VUI category. Once they have been thoroughly researched and the associated risk has been assessed/calculated, they may get classified into other categories such as VOC or VOI. Table 3 encapsulates the different VUI that have been identified so far.

4. Comparison of B.1.617.2 strain with the original Wuhan strain

The analysis was done using the CoVsurver of GISAID and PyMOL. For this study, we selected the sequence hCoV-19/India/TN-Seq_999_S84_R1_001/2021 with the accession number EPI_ISL_2272937 compared it hCoV-19/Wuhan/WIV04/2019 Refseq [47]. The information obtained has been summarised in Table 4. In addition, the differences between the S glycoproteins of Wuhan and the Delta variant of SARS-CoV-2 has been depicted in figure 2a and 2b.

The data shows that the spike protein of the B.1.617.2 strain is highly mutated and has accumulated 8 amino acid changes. Besides spike protein, changes in non-structural proteins (nsP2, nsP3, nsP4, nsP6, nsP12 and nsP15), other structural proteins (N and M) and accessory proteins (ns3, ns7a) has been observed as well. No mutations (100% similarity) were observed in rest of the proteins - nsP1, nsP5, nsP7, nsP8, nsP9, nsP10, nsP11, nsP13, nsP14, nsP16, envelope (E), ns6, ns7b, and ns8.

Spike protein plays a crucial role in viral attachment and entry into the host cell. It also serves as an epitope for neutralizing antibodies. Mutation of the spike protein has the potential to change the entire course of pathogenesis and infection. In case of the Delta variant (B.1.617.2), the high transmissibility, immune evasion and reduced effectiveness of therapeutics against the virus can be attributed to its heavily mutated spike protein. The NTD (N terminal domain) and the RBD of the spike protein harbours diverse mutations like T19R, L452R, T478K. Other defining Single Nucleotide Polymorphisms (SNPs) of the Delta variant are S:D614G, S:P681R, S:D950N, ORF3a:S26L, M:I82T, ORF7a:V82A, ORFa:T120I, N:D63G, N:R203M and N:D377Y.

However, this particular variant has less transmissibility and hACE2 receptor binding affinity as compared to other two sub-lineages of B.1.617 (B.1.617.1 and B.1.617.3) due to absence of an important mutation, E484Q in the RBD region (mentioned in table 5).

Searching Method

A comprehensive literature search was carried out to condense the information about the different variants of SARS-CoV-2 by retrieving data from freely available online databases like PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar and MEDLINE. The keywords used were ‘RNA virus mutation’, ‘SARS-CoV-2 Variants’, and ‘SARS-CoV-2’. Research papers focusing on the variants of SARS-CoV-2 were only included. We restricted ourselves to recent publications dating from 2016 to 2021 and manually performed abstract screening and study selection. Abstracts from commentaries were excluded and any discrepancies were resolved through consensus. The global data on COVID-19 cases was obtained from Worldometer and WHO. The classification of the variants was done as per the CDC (https://www.cdc.gov/). The thorough analysis and comparison of the B.1.617.2 variant with the original Wuhan strain was performed using the resources offered by Global Initiative on Sharing All Influenza Data (GISAID), Protein Data Bank (PDB) and visualization software PyMol. Additionally, the possible reasons behind rapid mutation of the novel coronavirus has also been exemplified in this article and supported with appropriate/relevant references.

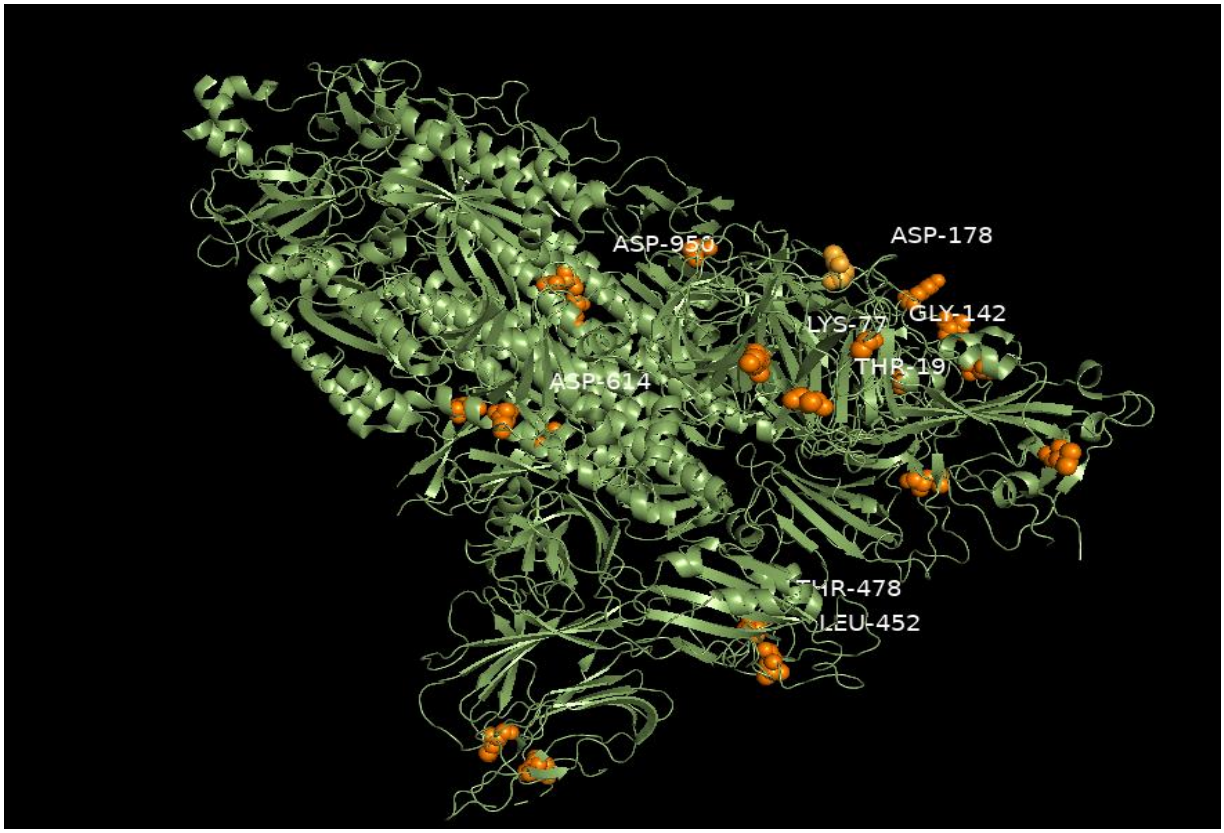

Figure 2a. Spike glycoprotein of Wuhan variant (PDB: 7DK3).

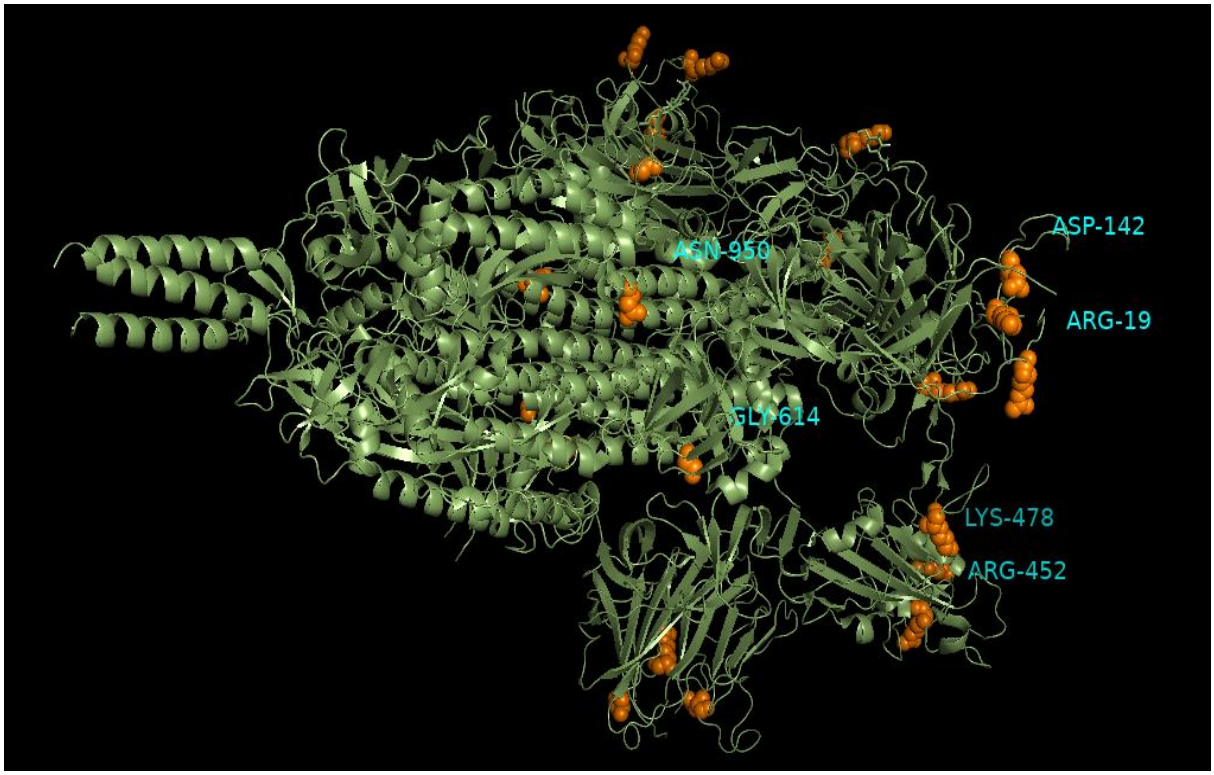

Figure 2b. Spike glycoprotein of Delta variant (PDB: 7SBO). The variations are displayed in orange color in the structure. Variations shown are T19R, G142D, L452R, T478K, D614G, G614R, and D950N.

Table 1. SARS-CoV-2 Variants of Interest (VOI).

S. No	Variant/ Country of detection/ Date of detection	Mutation	Virulence	Potential Prophylactics	Reported Complications	References
1	B.1.525 (previously UK1188) (Eta)/ United Kingdom/ December 2020	Spike mutations: A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L	More risk of reinfection due to decreased sensitivity to antibodies	All approved vaccines	Reduction in neutralization by some EUA mAb treatments, convalescent and post-vaccination sera	[11, 13]
2	B.1.526/ United States (New York) (Iota) / November 2020	Spike mutations: (L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*) Non-spike mutations:nsP2 -T85I; nsP4 - L438P; nsP6-9bp (Δ106–108) deletion; nsP12-P323L; nsP13-Q88H; ORF3a - Q57H; N gene-P199L and M234I	High transmissibility, no major increase in the comorbidities as compared to the wild type, more chances of hospitalization	Moderna and Pfizer vaccines	Reduction in neutralization by mAb treatment (bamlanivimab+etesevimab) , convalescent and post-vaccination sera	[11,14]
3	B.1.526.1/ United States (New York)/ Unclear	Spike mutations: D80G, Δ144, F157S, L452R, D614G, (T791I*), (T859N*), D950H	Increased transmissibility and disease severity	Moderna and Pfizer vaccines	Reduction in neutralization by some EUA mAb treatments, convalescent and post-vaccination sera	[11,15, 16]
4	B.1.617.1 (VUI- 21 APR-01)/India/ December 2020	Spike mutations: (T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	Increased hACE2 receptor binding affinity and possible escape from nAb due to RBD mutations L452R and E484Q along with P681R in the furin cleavage site, high transmissibility due to the high rate of S1-S2 cleavage, more chances of hospitalization. Level of infectivity and severity under investigation	Neutralization by convalescent sera of the COVID-19 cases and recipients of BBV152 (Covaxin), Moderna, and Pfizer vaccines	Reduction in neutralization by some EUA mAb treatments and post-vaccination sera	[11,17-20]

5	B.1.617.3 (VUI-21 APR-03)/ India/ February 2021	Spike mutations: T19R, G142D, L452R, E484Q, D614G, P681R, D950N	Increased hACE2 receptor binding affinity and possible escape from nAb due to RBD mutations L452R and E484Q along with P681R in the furin cleavage site. High transmissibility due to the high rate of S1-S2 cleavage. More chances of hospitalization. Level of infectivity and severity under investigation	Neutralization by convalescent sera of the COVID-19 cases and recipients of BBV152 (Covaxin), Moderna, and Pfizer vaccines	Reduction in neutralization by some EUA mAb treatments and post-vaccination sera	[11,17-20]
6	P.2 (B.1.1.28.P2) (Zeta)/ VUI-21 JAN-01/ Brazil/ January 2021	Spike mutations: E484K, (F565L*), D614G, V1176F	More contagious variant; leads to reduced immunity after the previous infection with earlier variants or following vaccinations. The severity of illness under investigation	mRNA based (Pfizer-BioNTech) and Covaxin	Reduction in neutralization by some EUA mAb treatments and post-vaccination sera	[11, 21]

EUA: Emergency Use Authorization; hACE2: Human Angiotensin-Converting Enzyme 2; RDB: Receptor Binding Domain; mAB: monoclonal antibody; nAB : neutralizing antibody, (*) shows that these mutations are detected in some sequences but not all.

Table 2. SARS-CoV-2 Variants of Concern (VOC)

S. No	Variant/ Country of detection/ Date of detection	Mutation	Virulence	Potential Prophylactics	Reported Complications	References
1	B.1.1.7 (20I/501Y.V1) (Alpha)/ United Kingdom/ 14th December 2020	Spike mutations: Δ69/70, Δ144, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	~50% increased transmission, no change in severity in comparison to the original strain	Combination mAb therapy	Relatively resistant to a few mAbs against the RBD	[22-25]
2	P.1 (20J/501Y.V3) (Gamma)/ Brazil/ 6 January 2021	Spike mutations: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	-	-	Reduction in neutralization by mAb treatment (bamlanivimab+etesevimab), convalescent and post-vaccination sera	[26]
3	B.1.351 (20H/501.V2) (Beta) /South Africa/ 18th December	Spike mutations: D80A, D215G, Δ241/242/243, K417N, E484K,	~50% increased transmission	mAbs (casirivimab +imdevimab)	Reduction in neutralization by mAb treatment (bamlanivimab+etesevimab), convalescent and post-vaccination sera	[23, 27]

	2020	N501Y, D614G, A701V				
4	B.1.427 (20C/S:452R) (Epsilon) /USA(California)/ February 2021	Spike mutations: L452R, D614G	~20% increased transmissibility	mAb treatment available, antivirals used	Reduction in neutralization by convalescent and post-vaccination sera	[28]
5	B.1.429 (Epsilon) /USA (California)/ February 2021	Spike mutations: S13I, W152C, L452R, D614G	~20% increased transmissibility	mAb treatment available, antivirals used	Reduction in neutralization by convalescent and post-vaccination sera	[28]
6	B.1.617 (G/452R.V3) (Kappa, Delta) / India/ 5 October 2020	Spike mutations: Seven mutations in S1 subunit - R21T, E154K, Q218H, L452R, E484Q, D614G, P681R. In S2 domain - H1101D Non-spike mutations: Mutation in each of the replication enzymes (nsP3, nsP6, nsP13, nsP15, nsP16) and in the accessory proteins (ORF3a, ORF6, and ORF7a)	Increased ability to evade the immune system. Maybe more transmissible	BBV152 (Covaxin), mRNA-based vaccines (Moderna and Pfizer). Neutralization of variant by convalescent sera of the COVID-19 cases	Reduction in neutralization by some EUA mAb treatments (bamlanivimab) and post-vaccination sera	[11,17-20, 29]
7	B.1.617.2 (VOC-21 APR-02)/ India/ December 2020	Spike mutations: T19R, (G142D), Δ156, Δ157, R158G, L452R, T478K, D614G, P681R, D950N. Lacks E484Q from the other two sub-lineages	Less transmissibility and hACE2 receptor binding affinity as compared to the other two sub-lineages. Highly contagious, more than 2x as contagious as previous variants, increased the chances of hospitalization	BBV152 (Covaxin), mRNA-based vaccines (Moderna and Pfizer). Neutralization of variant by convalescent sera of the COVID-19 cases	Reduction in neutralization by some EUA monoclonal antibody treatments and post-vaccination sera	[11,17-20]
8	B.1.1.529 (Omicron)/ South Africa/ 24 November 2021	Spike mutations: 30 mutations on spike protein, three small deletions and	Immune evasion and increased transmissibility with an almost complete	Currently, available vaccines may offer some level of protection	S-gene target failure in PCR diagnostic tests was observed, so sequence confirmation is required. Can potentially dodge immunity conferred by	[30,31-33]

		one small insertion (A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F) Non-spike mutations: nsP3 – K38R, V1069I, Δ1265, L1266I, A1892T; nsP4 – T492I; nsP5 – P132H; nsP6 – Δ105-107, A189V; nsP12 – P323L; nsP14 – I42V; E – T9I; M – D3G, Q19E, A63T; N – P13L, Δ31- 33, R203K, G204R	escape from convalescent and vaccine sera. Increased risk of reinfection compared to other VOCs.	against hospitalization and death, but further investigation is required	memory T cells	

EUA: Emergency Use Authorization; hACE2: Human Angiotensin-Converting Enzyme 2; RDB: Receptor Binding Domain; mAB: monoclonal antibody; nAB: neutralizing antibody

Table 3. SARS-CoV-2 variants under investigation (VUI)

S. no	Variant/ Country of detection/ Date of detection	Mutation	Additional information	References
1.	B.1.214.2/ Switzerland/ December 2020	Spike mutations: Q414K, N450K, ins214TDR, D614G. A 9bp insertion (ACAGATCGA) at position 22204 in spike protein. A 30bp deletion in ORF3a (25448- 25478), ~60% of the samples have a 9bp deletion in ORF1a (11288-11297)	Contagiousness and severity are yet to be determined	[30,34,35]
2.	A.23.1 + E484K (VUI-21FEB-01, Liverpool variant)/UK/ December 2020	Spike mutations: V367F, E484K, Q613H Non-spike mutations: Altered nsP6, ORF8, and ORF9	E484K mutation helps to evade the antibodies, reducing antibody neutralization. Designated a "variant of concern" by	[30,36-38]

			PHE (Public Health England)	
3.	A.27/ Europe (France)/ December 2020	Spike mutations: L452R, N501Y, A653V H655Y	Neutralization of A.27.RN by BNT162b2 vaccine-induced antibodies but with reduced efficacy of ~2-3 times compared to the wild-type and B.1.1.7 strains. It affects immune response as well as transmissibility	[30,39,40]
4.	A.28/Unclear/ December 2020	Spike mutations: E484K, N501T, H655Y	Reduction in antibody neutralization	[30,36]
5.	C.16/Europe(Portugal)/October 2020	Spike mutations: L452R, D614G	Reduction in antibody neutralization	[30,36]
6.	C.37/South America (Peru)/December 2020	Spike mutations: L452Q, F490S, D614G Non-spike mutations: ORF1a (3675- 3677)	Shares the ORF1a mutation with the P.1 variant Details on transmissibility, virulence, severity, vaccine efficacy, and treatment under research	[30,41]
7.	B.1.351 + P384L/ South Africa/ December 2020	Spike mutations: P384L, K417N, E484K, N501Y, D614G, A701V	According to several lines of evidence, increased transmissibility escape from neutralization and, hence, loss of vaccine efficacy. Estimates of severity unclear	[30,42-44]
8.	B.1.351 + E516Q/ Unclear/January 2021	Spike mutations: K417N, E484K, N501Y, E516Q, D614G, A701V	According to several lines of evidence, increased transmissibility escape from neutralization and, hence, loss of vaccine efficacy. Estimates of severity unclear	[30,42-44]
9.	B.1.1.7 + L452R/ The United Kingdom/ January 2021	Spike mutations: L452R, N501Y, D614G, P681H	Affects immune response as well as transmissibility, more severe due to increased mortality in community-tested cases	[30,40,45,46]
10.	B.1.1.7 + S494P/ The United Kingdom/ January 2021	Spike mutations: S494P, N501Y, D614G, P681H	Affects immune response as well as transmissibility, more severe due to increased mortality in community-tested cases	[30,40,45,46]
11.	C.36 + L452R/ Egypt/December 2020	Spike mutations: L452R, D614G, Q677H	Affects immune response	[30,40]
12.	AT.1/Russia/ January 2021	Spike mutations: E484K, D614G, N679K, ins679GIAL	Reduction in antibody neutralization	[30,36]
13.	B.1.526.2/U.S.A/ December 2020	Spike mutations: S477N, D614G	-	[30]

14.	B.1.1.318/Unclear/ January 2021	Spike mutations: E484K, D614G, P681H	Reduction in antibody neutralization	[30,36]
15.	B.1.1.519/Mexico/ November 2020	Spike mutations: T478K, D614G	Affects immune response	[30,40]
16.	AV.1/United Kingdom/ March 2021	Spike mutations: N439K, E484K, D614G, P681H	Reduction in antibody neutralization	[30,36]

Table 4. Sequence Comparison.

S. No	SARS-CoV-2 Protein	% Identity	Mutation and its Implication
Spike Protein			
1	S (Spike)	99.4%	Substitution of Thr with Arg at 19th position (T19R) removes a potential N-glycosylation site, thereby affecting antigenic and other properties of this strain
			Substitution of Lys with Thr at 77th position (K77T)
			Substitution of Gly with Asp at 142nd position (G142D)
			Substitution of Leu with Arg at 452nd position (L452R), affecting the antibody recognition site
			Substitution of Thr with Lys at 478th position (T478K), affecting the antibody recognition site, also involved in host change, host surface receptor binding, antigenic drift, and viral oligomerization interface
			Substitution of Asp with Gly at 614th position (D614G), affecting the virulence and ligand binding
			Substitution of Pro with Arg at 681th position (P681R), affecting the furin cleavage site, thereby enhancing membrane fusion, internalization, and increasing transmissibility
			Substitution of Asp with Asn at 950th position (D950N), affecting the viral oligomerization interface
Non-Spike Mutations			
2	nsP2	99.8%	Substitution of Pro with Leu at 129th position (P129L)
3	nsP3	99.9%	Substitution of Pro with Leu at 882nd position (P822L), affecting the interaction between the host cell protein and viral RNA, also involved in the viral oligomerization interface
4	nsP4	99.6%	Substitution of Asp with Asn at 217th position (D217N)
			Substitution of Phe with Ser at 375th position (F375S)
5	nsP6	99.7%	Substitution of His with Glu at 11th position (H11Q)
6	nsP12	99.9%	Substitution of Pro with Leu at 323rd position (P323L), affecting the viral oligomerization interface
7	nsP15	99.7%	Substitution of Lys with Asn at 259th position (K259R) affecting the viral oligomerization interface

8	ns3	99.6%	Substitution of Ser with Leu at 26th position (S26L)
9.	M (Membrane)	99.5%	Substitution of Iso with Thr at 82nd position (I82T)
10.	ns7a	98.3%	Substitution of Val with Ala at 82nd position (V82A), related to antigenic drift
			Substitution of Thr with Iso at 120th position (T120I)
11.	N (Nucleocapsid)	99.3%	Substitution of Asp with Gly at 63rd position (D63G), related to antigenic drift and alters the viral oligomerization interface
			Substitution of Arg with Met at 203rd position (R203M)
			Substitution of Asp with Tyr at 377th position (D377Y)

DISCUSSION

Active monitoring of the emerging variants and their potential impact on critical SARS-CoV-2 countermeasures, including vaccines, therapeutics, and diagnostics is imperative. The high rates of mutations of RNA viruses are correlated with enhanced virulence and evolvability, traits considered beneficial for the selection of viruses but a harsh reality for us. Spike glycoprotein facilitates the entry of the virus into the host cells and serves as the primary target for antibodies. As a result, spike mutations are more favoured and important in the evolution of new variants because it increases the transmissibility and infectivity of the virus. A high rate of transmission allows the virus to propagate and persist in the population, paving way for new variants to evolve. The emergence of the heavily mutated Omicron variant confirms the same.

The Variants of Concern (VOC) can have major implications on public health and hence demand for a prompt and effective response. B.1.617 and its sublineage B.1.617.2 exemplified a perfect example of deadly threat to humans. From recent reports it has become evident that this delta variant is spreading faster than the original Wuhan variant or any other strain, and hence has been described as the fastest, fittest and formidable strain. Even though current vaccines are able to provide some protection to the infected individuals and prevent hospitalisation, the risk is significantly greater for unvaccinated populations. Furthermore, the disproportion in vaccination rates of different regions can result in hyperlocal outbreaks or even epidemics. Hence, equitable distribution of vaccines is vital. Some countries are even expecting a possible third wave of COVID-19 and are preparing for the same. If the current trend is allowed to continue, the pandemic will continue to linger. Surveillance, information, and research are the only key to winning this battle. New variants are continuously emerging on which we have absolutely no control. To maximally protect public health, knowledge of different variants is essential. Researchers are tracking the new mutations and trying to understand the consequences of these mutations on disease severity, transmissibility and vulnerability to vaccine induced immunity. The potential of variants to escape naturally induced and vaccine-induced immunity makes the development of next-generation vaccines that elicit broadly neutralizing activity against current and potential future variants a priority. The suppression of viral replication with both public health measures and the equitable distribution of vaccines is critical in reducing the risk of generation of new variants.

ACKNOWLEDGMENTS

The authors would like to express a special thanks of gratitude to Dr. Rakesh Kumar Gupta as well as the University of Delhi for supporting us on such an insightful project. All the authors contributed equally, reviewed and/or edited the manuscript before submission. The authors declare no competing interests.

Declaration of conflicting interest: The author(s) declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Financial disclosure: No financial support was received for this study

REFERENCES

1. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Research. 2020;198114. doi:10.1016/j.virusres.2020.198114
2. Sharma B, Shahanshah MF, Gupta S, Gupta V. Recent advances in the diagnosis of COVID-19: A bird's eye view. Expert Rev Mol Diagn. 2021;21(5):475-491. doi:10.1080/14737159.2021.1874354
3. Worldometer. COVID live update: 168,291,956 cases and 3,493,098 deaths from the Coronavirus. Available: https://www.worldometers.info/coronavirus/. (Accessed on May 25, 2021).
4. WHO Coronavirus (COVID-19) Dashboard. Available: https://covid19.who.int/. (Accessed on May 25, 2021).
5. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020;10(5):766-788. doi:10.1016/j.apsb.2020.02.008
6. Wu A, Peng Y, Huang B, et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe 2020; 27(3):325-328. doi:10.1016/j.chom.2020.02.001
7. Giovanetti M, Benedetti F, Campisi G, et al. Evolution patterns of SARS-CoV-2: Snapshot on its genome variants. Biochem Biophys Res Commun 2021; 538;88-91. doi:10.1016/j.bbrc.2020.10.102
8. Singh A, Gupta V. SARS-CoV-2 therapeutics: how far do we stand from a remedy? Pharmacol Rep 2021;73(3):750-768. doi:10.1007/s43440-020-00204-0
9. Dolan PT, Whitfield ZJ, Andino R. Mechanisms and Concepts in RNA Virus Population Dynamics and Evolution. Annu Rev Virol 2018; 5(1):69-92. doi:10.1146/annurev-virology-101416-041718
10. Sanjuán R, Domingo-Calap P. Mechanisms of viral mutation. Cell Mol Life Sci. 2016; 73(23):4433-4448. doi:10.1007/s00018-016-2299-6
11. SARS-CoV-2 Variant Classifications and Definitions. CDC; 2021. Available: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html (Accessed on May 16, 2021.)
12. What Mutations of SARS-CoV-2 are Causing Concern? 2021. Available: https://www.news-medical.net/health/What-Mutations-of-SARS-CoV-2-are-Causing-Concern.aspx. (Accessed on May 16, 2021).
13. Beskrivelse af udvalgte virus varianter. Statens Serum Institut (SSI); 2021. Available: https://covid19.ssi.dk/virusvarianter/virusvariantbeskrivelser. (Accessed on May 16, 2021).
14. Annavajhala MK, Mohri H, Zucker JE, et al. A Novel SARS-CoV-2 Variant of Concern, B.1.526, Identified in New York. medRxiv. February 2021. doi:10.1101/2021.02.23.21252259
15. Pfizer and Moderna vaccines effective against new NYC variant. Science X staff, Medical Xpress; 2021. Available: https://medicalxpress.com/news/2021-04-pfizer-moderna-vaccines-effective-nyc.html. (Accessed on May 16, 2021).
16. VDH (Virginia Department of Health); 2021 Available: https://www.vdh.virginia.gov/content/uploads/sites/8/2021/04/PartnerCall_Update_SARS-CoV-2_VariantsofConcern_04.30.2021. (Accessed May on 16, 2021).
17. Hoffmann M, Hofmann-Winkler H, Krüger N, et al. SARS-CoV-2 variant B.1.617 is resistant to Bamlanivimab and evades antibodies induced by infection and vaccination. bioRxiv.2021:442663. doi:10.1101/2021.05.04.442663
18. Cherian S, Potdar V, Jadhav S, et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv.2021:440932. doi:10.1101/2021.04.22.440932
19. Yadav PD, Sapkal GN, Abraham P, et al. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. bioRxiv.2021:441101. doi:10.1101/2021.04.23.441101
20. Fox News; 2021 Available: https://www.foxnews.com/health/pfizer-moderna-covid-19-vaccines-indian-coronavirus-variant-emory. (Accessed on May 16, 2021).
21. RIVM; 2021. Available: https://www.rivm.nl/en/news/brazilian-coronavirus-variants-p1-and-p2-found-in-netherlands. (Accessed on May 16, 2021).
22. Racaniello V. SARS-CoV-2 variant B.1.1.7 is not more virulent;2021. Available: https://www.virology.ws/2021/04/15/sars-cov-2-variant-b117-is-not-more-virulent/. (Accessed on May 25, 2021).
23. Wang P, Casner RG, Nair MS, et al. Increased resistance of SARS-CoV-2 variant P. 1 to antibody neutralization. Cell Host & Microbe 2021; 29(5):747-751. doi:10.1101/2021.01.25.428137
24. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, Yoon H, Li D, Haynes BF, Sanders KO, Gnanakaran S. SARS-CoV-2 variant B. 1.1. 7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines. Cell host & microbe. 2021; 29(4):529-539. doi:10.1101/2021.01.27.428516
25. Edara VV, Floyd K, Lai L, et al. Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. medRxiv. 2021.doi:10.1101/2021.02.02.21250799
26. Wang P, Casner RG, Nair MS, et al. Increased resistance of SARS-CoV-2 variant P. 1 to antibody neutralization. Cell host & microbe.

2021;29(5):747-51.doi:10.1101/2021.03.01.433466
27. Planas D, Bruel T, Grzelak L, et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nat Med. 2021;27(5):917-924. doi:10.1038/s41591-021-01318-5
28. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. MedRxiv. 2021.doi:10.1101/2021.03.07.21252647
29. Doucleff M. People Are Talking About A "Double Mutant" Variant In India. What Does That Mean? NPR 2021. Available: https://www.npr.org/sections/goatsandsoda/2021/04/24/988744811/people-are-talking-about-a-double-mutant-variant-in-india-what-does-that-mean.. (Accessed May 16, 2021).
30. SARS-CoV-2 variants of concern as of 29 November 2021. ECDC 2021. Available: https://www.ecdc.europa.eu/en/covid-19/variants-concern. (Accessed November 30, 2021).
31. Callaway E., Heavily mutated Omicron variant puts scientists on alert. Nature. 2021.DOI: https://doi.org/10.1038/d41586-021-03552-w (Accessed on 29 November 2021)
32. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. World Health Organisation.2021. https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern (Accessed on 29 November 2021)
33. Implications of the emergence and spread of the SARS-CoV-2 B.1.1.529 variant of concern (Omicron) for the EU/EEA. Threat Assessment Brief, European Center for Disease Prevention and Control. 2021. Available: https://www.ecdc.europa.eu/
34. Jerusalem Post Staff. New coronavirus variant identified in Europe. The Jerusalem Post 2021. Available: https://www.jpost.com/. (Accessed May 25, 2021).
35. GitHub. cov-lineages/pango-designation. 2021. Available: https://github.com/cov-lineages/pango-designation.(Accessed May 25, 2021).
36. Jangra S, Ye C, Rathnasinghe R, et al. SARS-CoV-2 spike E484K mutation reduces antibody neutralisation. The Lancet Microbe 2021.doi:10.1016/S2666-5247(21)00068-9
37. Bugembe DL, Phan MV, Ssewanyana I, et al. A SARS-CoV-2 lineage A variant (A. 23.1) with altered spike has emerged and is dominating the current Uganda epidemic. MedRxiv. 2021.doi:10.1101/2021.02.08.21251393
38. A coronavirus variant, with a "similar change" to the fast-spreading variant in the UK and US, has emerged in Uganda. Business Insider India 2021. Available: https://www.businessinsider.in/science/health/news/a-coronavirus-variant-with-a-similar-change-to-the-fast-spreading-variant-in-the-uk-and-us-has-emerged-in-uganda/articleshow/80881380.cms.(Accessed May 25, 2021).
39. Mallm JP, Bundschuh C, Kim H, et al. Local emergence and decline of a SARS-CoV-2 variant with mutations L452R and N501Y in the spike protein. medRxiv. 2021.doi:10.1101/2021.04.27.21254849
40. SARS-CoV-2 variants of concern and variants under investigation in England. PHE 2021. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/984274/Variants_of_Concern_VOC_Technical_Briefing_10_England.pdf.(Accessed May 25, 2021).
41. C.37, the new variant of COVID-19 that spreads in Peru and Chile | coronavirus | INS | UPCH | PERU. ARCHYDE 2021. Available: https://www.archyde.com/c-37-the-new-variant-of-covid-19-that-spreads-in-peru-and-chile-coronavirus-ins-upch-peru/. (Accessed May 25, 2021).
42. Tegally H, Wilkinson E, Giovanetti M, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature. 2021;592(7854):438-443. doi:10.1038/s41586-021-03402-9
43. Cele S, Gazy I, Jackson L, et al. Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. Nature. 2021;593(7857):142-146. doi:10.1038/s41586-021-03471-w
44. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. GitHub 2021. Available: https://cmmid.github.io/topics/covid19/reports/sa-novel-variant/2021_01_11_Transmissibility_and_severity_of_501Y_V2_in_SA. (Accessed May 25, 2021).
45. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538). doi:10.1126/science.abg3055
46. Davies NG, Jarvis CI, CMMID COVID-19 Working Group, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021;593(7858):270-274. doi:10.1038/s41586-021-03426-1
47. CoVsurver Analysis of the sequences. GISAID. Available: https://www.gisaid.org/. (Accessed Nov 29, 2021).