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SARS-CoV-2 Mutations and Variants: what do we know so far?

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Abstract

With the circulation of the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOC), there is a worry that an increase in transmission, hospitalisations, and deaths may occur efficacy of some vaccines may be compromised. Recently the WHO has recommended the use of labels with letters of the Greek alphabet. Then, the variants of concern are now called Alpha, Beta, Gamma, and Delta. So that the classification of the variants is more accessible and more practical when they are discussed in non-scientific audiences. In addition, the variants can be classified into three large groups according to their clinical capacity to affect global public health: variants of interest (VOI), variants of concern (VOC), and High consequence variant (VOHC). This review aims to explore the molecular and epidemiological characteristics of SARS-CoV-2 mutations and variants.

Key word: SARS-CoV-2, COVID-19, variants, pandemic, mutations

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Introduction

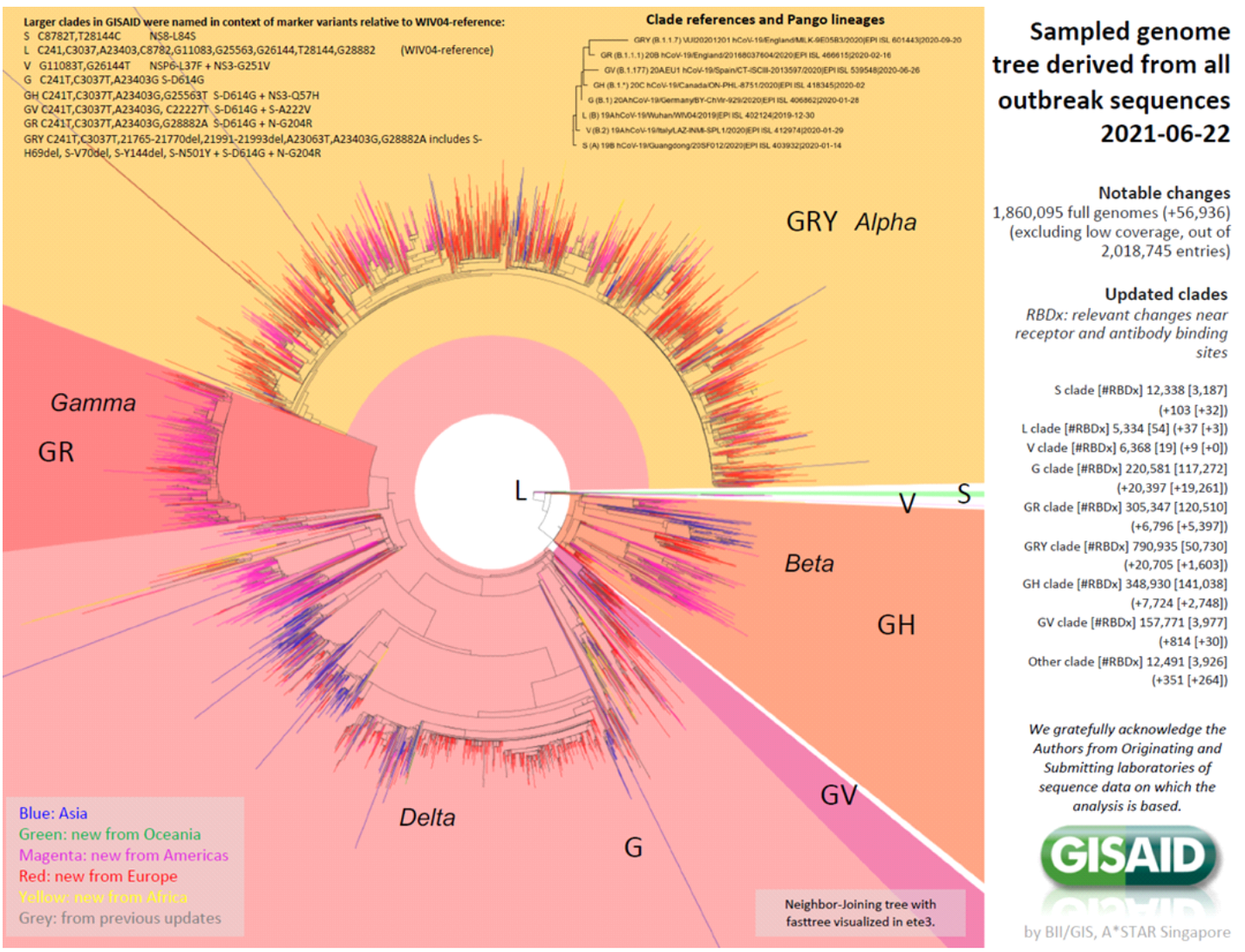
The Coronavirus Disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) belonging to the Betacoronavirus genus in the family Coronaviridae. This virus jumped to the human population at the end of 2019 from an animal reservoir currently not thoroughly characterised (1,2). SARS-CoV-2 is a positive-sense single-stranded ribonucleic acid (RNA) virus that shares significant homology with SARS-CoV but with only 75% similarity in its sequence encoding the "S" proteins (prS); both viruses use the Angiotensin-Converting Enzyme 2 Receptor (ACE2) to gain entry into the cell and establish infection (3).

SARS-CoV-2 is approximately 60-120 nm in size and comprises structural and non-structural proteins (4). Like all RNA viruses, it is susceptible to mutations or minor changes in some genes that synthesise proteins or virus compounds without generating a new strain. Mutations refer to changes in genetic makeup that occur naturally over time. Some mutations can change the ability to cause infection and disease (5).

The prS is a class I fusion glycoprotein structural protein that, together with the "Receptor Binding Domain" (RBD), are essential for this anchoring to ACE2 (6). In addition, the genes that encode these proteins are the most susceptible to mutation due to the adaptive pressures that the virus must endure in its race to infect human cells and avoid human immunity and the treatments or vaccines to which it is exposed (7).

Data from complete viral genome sequencing collected from patient samples worldwide indicate the changing prevalence of different genetic variants and mutations over time (Figure 1).

Figure 1. Phylogenetic clades classification of SARS-CoV-2 based on full-genome sequences by GISAID, June 22, 2021



This review aims to explore the molecular and epidemiological characteristics of SARS-CoV-2 mutations and variants.

Mutations of SARS-CoV-2

The complete sequencing of the SARS-CoV-2 genome was carried out on January 7, 2020, with the first draft of the new coronavirus genome being made public on January 10, 2020 (8). By June 27, 2021, more than 1.86 million SARS-CoV-2 genomic sequences have been made (Figure 1), and the scientific community has gained much knowledge with these sequencing (9). The first ten genomic sequencings of SARS-CoV-2 showed a 99.98% agreement between them, indicating that despite being an RNA virus, it had low mutability, which continues to be the case (10).

At the beginning of the pandemic, three variants of the virus genome were reported that can be phylogenetically classified into different clades: type A and C that were present in Asia, Europe and the United States, and type B, which is the most frequent variant in Asia (11). These clades are groups of variants that share a common ancestor. Some minor clade types have also been described, such as the L type that showed greater aggressiveness and transmission speed and the S type that was structurally more stable (12).

When a variant has very different characteristics from the original virus, such as differences in its ability to spread or cause severe disease, it is called a strain. All strains are variants, but not all variants are strains. To date, no new strain of SARS-CoV-2 has been detected (13).

By March 26, 2021, 827,572 viruses had been sequenced. Comparing these sequences with the original sequence of the "wild" virus, 17 million mutation events have been counted. Within this large group of mutations, some mutations of greater clinical interest or greater frequency have been identified:

The D164G mutation is the first mutation in early 2020, which is currently present in more than 98% of all SARS-CoV-2 isolates in the world (14). This mutation stabilises the union between prS and ACE2. That happened because the RBD located in the S1 subunit of the "S" protein "opens" more easily and

Table 1. Variants of SARS-CoV-2

WHO	Pango nomenclature	Total mutations and of greater interest	Country	Higher transmissibility	Higher lethality	Escape to NAb	Escape to MAb	CDC/WHO
	A.23.1	E484K	UK	Unknown	Unknown	Unknown	Unknown	Under investigation
	B.1.111	E383K L429S	Colombia	Unknown	Unknown	Unknown	Unknown	Under investigation
	B.1.1.22	T478K	Mexico	Unknown	Unknown	Unknown	Unknown	Under investigation
	B.1.1.207	P681H	Nigeria	Unknown	Unknown	Unknown	Unknown	Under investigation
Alfa	B.1.1.7 (501Y.V1)	23 (N501Y) +/- E484K	UK	Yes	Yes	Yes	No	Concern
Beta	B.1.351 (501T.V2)	21 (N501Y, E484K, K417T)	South Africa	Yes	No	Yes	Yes	Concern
Delta	B.1.617.2	L452R, E484Q	India	Yes	Yes	Yes	Unknown	Concern
Gamma	P.1 (501Y.V1)	17 (N501Y, E484K, K417T)	Brazil	Yes	No	Yes	Yes	Concern
Epsilon	B.1.427	L452R	USA (California)	Probable	No	Probable	Yes	Of interest
Epsilon	B.1.429	L452R	USA (California)	Probable	No	Probable	Yes	Of interest
Eta	B.1.525	G484K	USA (New York)	Unknown	No	Yes	Yes	Of interest
Iota	B.1.526	S484K	USA (New York)	Unknown	No	Yes	Yes	Of interest
Kappa	B.1.617.1	L452R, E484Q or P681R	India	Yes	Unknown	Unknown	Unknown	Of interest
Zeta	P.2	E484K	Brazil	Yes	No	Yes	Yes	Of interest
Lambda	C.37	G75V, T76I, L452Q, F490S, T859N	Peru, Chile	Probable	Unknown	Unknown	Unknown	Of interest

WHO: World Health Organization. NAb: neutralising antibodies. MAb: monoclonal antibodies. USA: United States of America CDC: Centers for disease control of USA.

quickly, and at least in the laboratory, allows it to infect more cells (15). It also allows you to have a higher number of viral copies in the upper airways but not in the lower airways and transmit the infection to more people. However, the severity of the disease is not altered or increased (16).

This mutation also increases the sensitivity to neutralisation generated by neutralising antibodies (NAb). That means that this mutation does not alter the response to vaccines that are mainly directed to the natural form D164 (17). The designation D164G means that the amino acid at position 614 of the prS has changed from "D" to "G". This mutation was initially described in the city of Houston in the United States of North America. All approved monoclonal antibodies such as bamlanivimab, etesevimab, casirivimab, imdevimab and now sotrovimab show high potency to neutralise the D614G variant (18).

The T478K mutation is located in prS, and its frequency has increased exponentially since the beginning of 2021, together with the previously described D614G mutation (19). Currently, 90% of the SARS-CoV-2 viruses circulating in the world have the D614G mutation. On the other hand, only 2% of circulating SARS-CoV-2 viruses have the T478K mutation (20).

The N501Y mutation occurs because the amino acid asparagine (N) has been replaced by tyrosine (Y) at 501 (21). This mutation is also located in the prS RBD and was initially observed by the monitoring service in England, following an increase in cases in Kent and London (22). This mutation quickly caught the attention of researchers because this mutation has been linked to an impressive increase in transmissibility and higher lethality (23).

The E484K mutation is also located in prS. It can generate an escape or lack of response to the NAb generated by the previous infection by SARS-CoV-2 or by those generated by vaccines, conferring a reduction of up to ten times in the neutralising activity of the serum of vaccinated persons (24).

Other frequent mutations are L452R and E484Q. Both are in the RDB, which independently seem to contribute to the lack of response to neutralising antibodies (25). The E484Q mutation only has a minor impact on the reduction of this activity (26). However, when the combined E484Q and L452R mutations are present in the same variant, the loss of sensitivity to the serum of vaccinated patients is statistically significant compared with the original or wild SARS-CoV-2 (27). However, a triple mutation made up of the E484Q / K mutations plus the P681R mutation can significantly increase the fusion capacity of SARS-CoV-2 to the ACE2 receptor of the human cell (25). The L452R or E484Q mutations appear responsible for the moderate decrease in neutralising antibodies produced from the Pfizer / BioNTech RNA vaccine (20).

Classification and variants of SARS-CoV-2

As we have mentioned, virus variants result from a simultaneous group of mutations (more than 2 to 3 generally) that can affect transmissibility, response to treatments, virulence, or simply change the selectivity for a species or disable the virus. When the mutations are significant in primordial regions of the virus and are grouped to express differences in proteins or structure, they can finally generate a substantial change that would mean a new strain; so far, there is no new strain SARS-CoV-2 (28).

Many mutations have generated approximately 600 variants, but few of them are of public interest. For the classification of the variants, the nomenclature systems established by GISAID, Nextstrain and Pango are used (29).

Recently the WHO has recommended the use of labels with letters of the Greek alphabet. Then, the variants of concern are now called Alpha, Beta, Gamma, and Delta. So that the classification of the variants is more accessible and more practical when they are discussed in non-scientific audiences. In addition, the variants can be classified into three large groups according to their clinical capacity to affect global public health (30).

Variants of Interest (VOI). Defined by genetic changes that suggest you might be more contagious or that may help you escape the immunity conferred by natural infection or vaccination. Therapies and tests may not work as well against you. Within this group are **B.1.427/B.1.429** (ε), **P.2** (ζ), **B.1.525** (η), P.3 (θ), **B.1.526** (ι), **B.1.617.1** (κ) and recently **C.37** (λ) (31).

Variants of concern (VOC). It is defined as associated with increased transmissibility, more severe disease, reduced neutralisation by antibodies generated by previous infection or vaccination, reduced efficacy of treatments or vaccines or evidence of test failure. The CDC is constantly tracking them: **B.1.1.7** (α), **B.1.351** (β), **P.1** (γ) and **B.1.617.2** (δ) (32).

High consequence variant (VOHC): To date (June 27, 2021), none of the emerging variants has met the CDC criteria for high consequence variants. These are defined as demonstrated failure of diagnostic tests, a significant reduction in vaccine protection, a significantly reduced susceptibility to authorised treatments, and more severe clinical illness and more hospitalisations (32,33).

Other variants have been recently discovered, and since their impact or clinical importance is not known, they are grouped as **variants under investigation (VUI)** (34).

Variant B.1.1.22

It was detected in Mexico in April 2020. The T478K mutation is present in around 65% of this variant. This variant is present in 38.1% of COVID-19 cases in Mexico and around 1.3% of cases in the United States of America, and sporadically within COVID-19 cases in Europe (35).

Variant B.1.1.7 or "British" variant (Alpha according to WHO) - Variant of concern

It was initially observed by England's monitoring service, following an increase in cases in the cities of Kent and London. The N501Y mutation was the first to be identified within this variant, which was initially called VUI-202012/01 and later renamed VOC-202012/01 (36). This variant was identified as the first variant investigated in December 2020. However, it was later known that this variant had already circulated in England since September 2020, and it was reported on December 14, 2020, to the World Health Organization (WHO). This variant is the dominant one in the United Kingdom and has already been reported in more than 90 countries (37).

Other mutations within the B.1.1.7 variant are the P681H mutation, whose function is not yet clear. Deletions at positions 69-70 in prS have also been reported to have been associated with immune leakage in immunosuppressed patients and increased viral infectivity in vitro (38). These deletions can reduce or alter the diagnostic sensitivity of some molecular tests (RT-PCR) that detect the S gene. However, most commercial RT-PCR tests use different genes, making it difficult for this to happen (37).

On the other hand, this particularity may be an advantage from the point of view of epidemiological surveillance since the absence of amplification of the S gene in samples positive for other targets or genes evaluated could be used as a screening to detect this new variant (39).

There is consistent evidence of cross-neutralisation between convalescent sera from individuals who have been infected with other variants and variant B.1.1.7. That means that this variant is affected by the immune response acquired after infection by other variants or by immunity secondary to vaccination, whatever this may be (40).

A subset of the B.1.1.7 variant has also been reported to have the E484K mutation. That has been reported from a small group of cases in the Southwest of England. No further hospitalisation or death has been reported with this variant with the E484K mutation (41). No international cases have been reported, but as described, this mutation can cause an escape or lack of response to NAbs generated by previous SARS-CoV-2 infection or those generated by vaccines (42). Except for etesevimab, the other four monoclonal antibodies actively neutralised variant B.1.1.7 (43).

In America, variant B.1.1.7 represents 20 to 30% of all viruses isolated from samples of patients with COVID-19 from the United States of North America and has already been reported in Mexico, Chile, Ecuador, Brazil, Peru, and Colombia others (44).

Reports up to January 21, 2021, indicated that this variant could cause 13 to 14 patients to die for every 1000 infected 60-year-old men. That means an increase of 10 patients out of every 1000 compared to the "wild" virus (45). That translates into an increase in average mortality from 60 to 100% and increased transmissibility of between 40 to 70% (14–16). B.1.1.7 / V1 is currently causing the majority of infections in Europe and North America (46).

Variant 501Y.V2 or B.1.351 or "South African" variant (WHO beta) - variant of concern

At the end of 2020, "The Network for Genomic Surveillance in South Africa" detected the variant 501Y.V2 or variant PANGO B.1.351, and it was reported to the WHO on December 18, 2020 (47). This variant is mainly characterised by the N501Y mutation (a mutation also present in the "British" variant). This variant is the dominant one in that country and has displaced the rest of the circulating variants in South Africa since October 2020 and is responsible for the high transmission speed of SARS-CoV-2 in the community in the second wave (48).

Phylogenetic analysis indicates that it has a different origin and is also different from variant B.1.1.7. This variant also has the E484K, K417N, and L18F mutation (49). By the end of December 2020, the variant had already been detected in 4 countries and is currently reported in more than 50. It is also characterised by increasing viral load and therefore having greater transmissibility. This variant to date has not shown adequate neutralisation from the immunity generated by vaccines (50).

Variant P.1 or Variant B.1.1.248 or "Brazilian" variant (gamma according to WHO) - variant of concern

It was initially identified in Japan in early January 2021 by four people from the Brazilian Amazon. This new variant has 17 mutations, of which three are located in prS (K417T, E484K and N501Y) (41). This variant shares the N501Y mutation with the "British" and "South African" variants and shares the E484K mutation with the "South African" variant and a subset of the "British" variant. These mutations result in antigenic changes in prS, reducing the effectiveness of the neutralising antibodies generated against SARS-CoV-2 (51).

Brazil has also reported this new variant in several sequences obtained from the Manaus region in the Brazilian Amazon collected in the second half of December 2020, so the transmission direction is assumed to have been from Brazil to Japan (52). This variant has already been shown to be more contagious, although not more lethal, and to escape the ability to neutralise the antibodies produced by a previous infection or by vaccines (31).

It is estimated that the "Brazilian" variant in the city of Manaus must have caused reinfections in 25 to 61% of those previously infected in 2020 (53). Additionally, in Brazil, a couple of cases infected with two different variants at the same time have been reported, which is concerned from the point of view of the possibility of generating more significant genetic variability. The V3 variant of the P.1 lineage has become dominant in Brazil and South America (21).

Variant P.2 is also derived from variant B.1.1.248 (Zeta according to WHO) - variant of interest

E484K mutation presents allow escaping the neutralising activity of antibodies generated in past infections. It is less common and transmissible than the P.1 variant and is also found in the Brazilian Amazon (54).

In an experimental study, unmodified laboratory mice have been infected with two of the SARS-CoV-2 variants (B.1.351 and P.1), which did not occur with the "wild" variant, which suggests an increase interspecies transmissibility. If this news is confirmed, the door opens to the existence of new non-human reservoirs from which the virus can evolve independently (2,55).

Variant B.1.427 and variant B.1.429 (Epsilon according to WHO) - variant of interest

Discovered in California in the United States of North America, they are also called CAL.20C / L452R or B.1.427 / B.1.429. Both are approximately 20% more transmissible than "wild" SARS-CoV-2 and may not respond as well to specific treatments such as monoclonal antibodies for mild and moderate cases of COVID-19 (56). B.1.429 represents 8.1% of circulating SARS-CoV-2 in the United States of North America, while B.1.427 represents 3.3% (57). They were first detected in Southern California in October 2020 and then by the University of San Francisco in December 2020. However, we now know that they emerged in July 2020 in Los Angeles, California. As of February 24, 2021, this variant has already been identified in all the United States of North America and 19 countries (58).

In 4 months, the prevalence of this variant increased from 0% to 21.3% in California. B.1.427 and B.1.429 have three mutations in prS (59). Of the three mutations, the most worrisome is L452R, which allows the virus to adhere more closely to cells and escape monoclonal antibody treatments.

Variant B.1.1.207 - variant under investigation

It has two sequences that were first identified in Nigeria, although where it first emerged is unknown yet. The P681H mutation characterises this variant. There is currently no evidence to suggest that this variant has any impact on disease transmission or severity (60).

Variant B.1.525 (Eta according to WHO) - variant of interest

It was detected in people in Denmark since November 20, 2020, and is no longer circulating in humans. It was associated with the transmission of mink crops. The clinical implications of this new variant are not yet well understood; however, mutations in prS such as G / 484K.V3 have been reported. All minks from the affected farms were euthanised. Seven other countries have reported SARS-CoV-2 in farmed minks (Lithuania, Greece, Spain, Italy, the Netherlands, Sweden and the United States) (61).

Variant B.1.111 or "Colombian variant" - variant under investigation

It has the L249S and E484K mutations which would make it a variant of concern. As we have mentioned, these mutations give the virus the ability to escape the immune system. These mutations are associated with the "Brazilian" and "South African" variants (42).

Variant A.VOI.V2

Identified in Angola, this new variant has 31 amino acid substitution mutations and three deletion mutations. Of these, 11 of 31 substitution mutations and all deletion mutations were found in prS. Some mutations of interest in this variant are R346K, T478R, and E484K. Although this variant has been

identified in only three passengers from Tanzania, scientists believe that more research is urgently needed to control its transmission within and outside the country of origin (62).

Variant C.37 - variant under investigation

It has similar characteristics to variants of more significant concern due to its high transmission capacity, such as P.1, B.1.1.7 and B.1351. However, it is not yet possible to affirm that it is more contagious or lethal. This variant descends from variant B.1.1.1 that circulates throughout the world since the pandemic and reports in Peru and Chile. C.37 and P.1 share the ORF1a: 3675-3677 mutation. For this reason, many of the samples identified as P.1 may be C.37 (63).

Variant B.1.617 or "Indian" variant (Delta according to WHO) - variant of concern

It was initially identified in Maharashtra in India on October 5, 2020, known as the "double mutation" variant and previously named VOC-21APR02 (64). This variant has at least 15 mutations, nine of which have occurred in prS, two mutations in RBD, and one mutation in the S2 subunit of prS (65). However, the presence of two simultaneous mutations are the ones that generate the most significant concern: the E484Q mutation, which gives it more significant potential for binding to ACE2, as well as a better ability to evade the immune system, and the L452R mutation, which gives it a higher affinity for the prS to ACE2 and a lower recognition capacity of the immune system (66). The appearance of both mutations in the same variant is unique so far. It also has other mutations, including the P681R (67).

The lineage is in turn divided into three subgroups, all of them presenting the L452R mutation: 1) B.1.617.1 (with mutations: L452R, E484Q or P681R); 2) B.1.617.2 (with mutations: L452R, T478K, P681R and missing the E484Q mutation); and 3) B.1.617.3 (the E484Q mutation reappearing); of which variant B.1.617.2 has been designated as a variant of concern because it has the highest infectivity capacity (25). It is estimated that this variant is responsible for the high transmissibility in India and a large number of deaths. However, it has not been associated with a higher fatality in itself (3,24). The presence of B.1.617 has been reported in 40 countries. Of the three lineages, B.1.617.1 and B.1.617.2 are increasing worldwide, and the prevalence of the B.1.617.2 lineage has increased in the UK (68).

Concerning variant B.1.617.2, all monoclonal antibodies except Bamlanivimab retained their active virus neutralisation potency. The acquisition of the L452R mutation could cause the loss of effectiveness of Bamlanivimab against this variant (68).

Other variants

Other variants have been reported that to date have not been classified or are under investigation, such as the C.16 variant from Portugal, the variant of the viral clade 19B (with 18 mutations including the N501Y, L452R, H655Y mutations) (69) and the variant 20C both in France (70), variant B.1.298 with a predominant mutation Y453F (7,22), B1.1.318 and B1.324.1 (the latter two with E484K mutation), P.3 in the Philippines and recently identified GRL variant or B.1.1 / S lineage with the V1230L mutation (27); the clinical significance is still unknown, and they are classified as investigational (VUI). Recently, a study showed the increase in the transmissibility of the VUI and suggests that circulating viruses may soon be replaced by these variants in the geographic areas where they are present (71).

So, there is evidence that some variants have higher transmissibility, higher lethality, and the ability to reduce the action of neutralising antibodies. The greater the number of people with SARS-CoV-2 infection or COVID-19 disease, the more exposure patients, have to drugs, convalescent plasma and monoclonal antibodies or the longer global vaccination delays, together with nature itself to "survive", adapt and perpetuate the SARS-CoV-2, we will continue to witness increasingly frequent events of mutations and variants. Our objective should be to prevent VOHC variants and maintain active surveillance of genetic and antigenic changes in the world population.

Conclusions

Over the last months, corresponding to the first semester of 2021, there has been a great worry regarding the impacts of the emerging SARS-CoV-2 VOC (72). In particular, from India, the Delta variant is now distributed across multiple continents in different countries, is linked to an increase in transmission, and some breakthrough infections in vaccinated people, in countries such as Israel. Then, more than ever, their circulation called for the need to enhance genomic surveillance in all the countries, track the impact of the arrival and circulation of the VOI and the VOC, and be prepared for the High consequence variant (VOHC). The appearance and circulation of the VOHC in a world still moving unequally fast regarding COVID-19 vaccination seems imminent in highly vaccine coverage countries, but even worse in developing countries with poor proportions of people vaccinated and weak health systems that are already collapsed during new waves of the virus. At the same time, there is a clear need to develop everywhere studies specifically assessing the clinical impact of the variants, especially the VOC and the rest, and consider strategies to increase the mitigation of such impact. Unfortunately, the global situation of COVID-19 remains highly unstable; healthcare systems, then under significant pressure, and all of this occurs in a world with inequities that prolong the impact and duration of this situation. Then, although high vaccination coverage is desirable, as vaccines are vital for controlling this pandemic, vaccines are essential, and the rest of non-pharmaceutical interventions, the public health and social measures are of utmost importance for another long time.

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