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Emerging variants of SARS-CoV-2 and its public health implications

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All viruses, including SARS-CoV-2 (Severe Acute Respiratory Syndrome, CoronaVirus 2) mutate. These genetic changes happen as the virus makes new copies of itself to spread and thrive. Most mutations are irrelevant and some can even be harmful to the perpetuation of the virus (negative selective pressure), but others can facilitate its spread (positive selective pressure) or make it more pathogenic to the host (humans).

Among the most relevant mutations of SARS-CoV-2 from a clinical and epidemiological point of view are those that affect S protein (spike), which plays an important role during the infectious process facilitating the entry of the coronavirus into cells human. The infection process occurs when the virus enters the cell after the connection between the RBD domain (receptor binding domain) of S protein and the target cell receptor, which is the angiotensin-converting enzyme 2 (ACE-2) [1] .

Much of the protection against COVID-19 (COronaVIrus Disease 2019) is mediated by the immune response directed against this same protein. Neutralizing antibodies to the virus bind to S protein, usually in the RBD region, preventing the virus from attaching to the ACE-2 receptor on human cells. Most, if not all, of the vaccines currently in use or under study are based on inducing the production of antibodies directed to these sites [1].

Mutations that alter the S protein that increase the amount of virus eliminated by an infected person or that increase their affinity for RBD for the ACE-2 receptor may be associated with increased virus transmission. An example is the D614G mutation, which is associated with higher viral loads and greater transmissibility. Strains with this mutation became prevalent worldwide from mid-2020, replacing the original strains [2]. Other mutations can alter S protein and impair the binding of neutralizing antibodies and, consequently, increase the risk of reinfections or decrease the effectiveness of vaccines. Another aspect to be considered for mutations is the loss of sensitivity to diagnostic tests, which raises concerns about the need for continuous monitoring of new variants to allow the continuous updating of diagnostic methods used in molecular or even serological screening.

In recent weeks, a great concern has arisen in the scientific community regarding three variants of the SARS-CoV-2 virus, known in the dynamic nomenclature, recently proposed by Rambaut et al., [3] as: i) B.1.1.7 (or VUI - 202012/01), ii) B.1.351 (or 501Y.V2) and iii) P.1, initially identified in infected patients in the United Kingdom, South Africa and Manaus, Brazil respectively [4–6].

These variants are considered worrisome due to the presence of a set of mutations that have led to increased transmissibility and to the deterioration of epidemiological situations in the areas where they have recently established themselves. Despite having different origins, they share a constellation of mutations, which reinforces the possibility that these mutations offer relevant competitive advantages.

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Variants of concern (VOC)

On December 14, 2020, UK authorities notified WHO of a variant referred to by the UK as SARS-CoV-2 VOC 202012/01 or B.1.1.7. This strain carries 14 defining mutations, including seven in S protein (Table 1). Among these 7 is the N501Y mutation, which is associated with greater affinity of the virus for the ACE-2 receptor, which may explain its rapid expansion [4]. The name of the mutation refers to the nature of its change: the amino acid at position 501 in S protein has changed from N (asparagine) to Y (tyrosine). In addition, this strain carries some deletions, including those that exclude amino acids 69 and 70 from S protein. Recent experiments have shown that this "elimination" of amino acids allows the new coronavirus to infect cells more successfully. To date, this strain has been found in 70 countries, of which 29 are locally transmitted. It was responsible for the worsening of the epidemiological situation in the United Kingdom, Portugal and other European countries between December 2020 and January 2021. Although the first reports did not find evidence of an impact on the severity of the disease, an update published in January 2021 of NERVTAG (New and Emerging Respiratory Virus Threats Advisory Group) from the British agency Public Health England found, among others, a cohort study that found a relative risk of death of 1.65 (95% CI 1.21-2.25) among individuals infected with the B .1.1.7 deformation compared to non-B.1.1.7 cases [7]. Another worrying data regarding this strain was the increase in the proportion of cases between children and young adults [8].

On December 18, 2020, national authorities in South Africa announced the detection of a new variant of SARS-CoV-2 called B.1.351 (or 501Y.V2), due to the presence of the N501Y mutation. Although variant B.1.1.7 also has the N501Y mutation, phylogenetic analyzes have shown that variant B.1.351, detected in South Africa, has a different origin. Genomic data showed that the 501Y.V2 variant quickly replaced other strains circulating in South Africa, becoming the dominant strain in the region [5]. The B.1.351 strain has multiple changes in S protein, of which three stand out in the RDB domain (K417N, E484K and N501Y) (Table-1). The variant N501Y mutation is associated with increased infectivity, since it appears to increase the link between S protein of the virus and the host receptor. The E484K mutation alters the region of the spike where neutralizing immunoglobulins are coupled, allowing viral escape (when the virus is not neutralized by the antibody) and increasing the risk of reinfection [9]. This lineage was first identified in Nelson Mandela Bay, along the east coast of South Africa and spread rapidly to the other districts of the Eastern Cape and to the Western Cape and KwaZulu Natal (KZN) provinces, becoming the dominant lineage in the Eastern Cape and Western Cape provinces in weeks [5]. It has been found so far in 31 countries, 13 of which with local transmission, and is associated with the second wave of COVID-19 that started in December 2021 in South Africa (https://cov-lineages.org/global_report.html, accessed on 6 / feb / 2021).

On January 9, 2021, Japan notified the WHO of a new variant of SARS-CoV-2, P1 (initially reported as B.1.1.248), detected in four travelers from Brazil. This variant is not genetically related to the variants SARS-CoV-2 B.1.1.7 and B.1.351, having been identified in December 2020 in Manaus, capital of the state of Amazonas, in Brazil. This variant has 12 mutations in S protein, including three mutations of common interest with B.1.351, that is, K417N / T, E484K and N501Y, which can affect the host's transmissibility and immune response (Table 1).

The fact that these strains have different origins, but have the same mutations, suggests a process called evolutionary convergence, which is the name given when yesilar characteristics are selected in different locations because they represent clear advantages such as greater transmissibility, success in replication or even immune escape.

This new strain of SARS-CoV-2 was absent in the samples collected between March and November in Manaus, but was identified in 42% of the December 2020 samples and in 91% of the samples collected in the same city in January 2021 (Figure- 1), suggesting a strong and recent increase in the frequency of this strain associated with the second and largest wave of COVID-19 in the city [6]. Seroprevalence in Manaus observed in June 2020 was 52.5% (95% CI = 47.6–57.5), right after the first epidemic wave indicating that this new strain was also subjected to strong selective pressure [10].

Also worth mentioning, the Brazilian P.2 strain, carrying the E484K mutation, first identified in October 2020, was already the most prevalent among the sequenced strains of patients who developed symptoms in November in the state of Rio de Janeiro, too in Brazil. [11]. Analyzing

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the data from the Fiocruz Genomic Network, which brings together researchers from various institutes of the Oswaldo Cruz Foundation, we find that since the beginning of the emergence of P.1 and P.2 strains in October 2020, in just 4 months these strains corresponded together for 75 % of all strains sequenced throughout Brazil (Figure 1). In the city of Manaus, these two strains together corresponded to 97.8% of the virus samples sequenced in January 2021 (Figure 1).

In addition to the variants already mentioned, Brazil, Europe, the United States of America, Japan and other countries have already notified the detection of many other new variants, whose scope and importance for public health require further epidemiological and laboratory research.

Reinfections

The fact that new strains cause epidemics in places already affected by previous severe epidemics raises some concerns, such as the increase in transmissibility and the possibility of antigenic escape [12]. Pointing in this sense, in Brazil several cases of reinfection by the new strains have also been described [13–15].

The discovery of cases of reinfection serves as a warning and reinforces the need to maintain pandemic control measures, with social distance and the need to accelerate the vaccination process, to reduce the possibility of circulation of this and possible future strains that, accumulate mutations, may become more infectious, even for individuals who have already had the disease [12]. In this sense, it has recently been demonstrated in vitro that the B.1.351 strain has greater space to neutralization by antibodies in patients who had a natural infection [16].

Vaccines

Studies on protection among people who received vaccines against COVID-19 are still few, but they already demonstrate that the response to these strains is different from the responses to the original strains. Researchers estimated that the Novavax vaccine was 95.6% effective against the virus that originally circulated in the UK and 85.6% against the B.1.1.7 strain [17]. In fact, the N501Y mutation, associated with this strain, raised less concerns about the capacity for immune escape. The studies carried out with this vaccine in South Africa demonstrate an overall efficacy of 49.4% against the B.1.351 strain, excluding the HIV-positive population from that group from the analysis, the vaccine was 60% effective [17]. The plasma activity of individuals 8 weeks after the second dose of the Modern mRNA (mRNA-1273) or Pfizer-BioNTech (BNT162b2) vaccines against SARS-CoV-2 variants that carry the E484K or N501Y mutations or the K417N combination: E484K: N501Y has been reduced by a small but significant margin. [18].

Protection rates for vaccines against new emerging strains have not yet been fully and definitively tested in phase 3 studies, nor do we know what protection will be induced by any vaccine over time (Table 2). But there is a warning that protection from natural infections (and vaccines, by extension) may not be as long-lasting or that protection against new strains may not be as effective.

Virological surveillance, contact tracing and quarantine

The start of vaccination around the world has been widely celebrated and it is indeed a very positive fact, however, caution is needed with the relaxation of control measures for this disease and especially with the risky media, since the population needs to become aware of the need to maintain social exclusion care and individual care to reduce the risk of transmission of SARS-CoV-2.

Considering the occurrence of major epidemics where serious epidemic waves had already occurred, the increased risk of reinfections and even the possibility of decreasing the effectiveness of vaccines, it is essential to reinforce virological and genomic surveillance to identify early and monitor the spread of new strains, whether they are Brazilian or newly introduced [19].

Specific surveillance seeking to properly investigate and sequence the viruses that cause infections in vaccinees or reinfections is mandatory so that new strains and / or immune escape can be identified early and containment measures are taken.

In Brazil the control of COVID-19 has been fundamentally based on collective measures of social withdrawal, the tracking and quarantine of contacts has not been applied systematically by the Brazilian public health agency at any of the three levels of government, whether federal, state or municipal . Considering that

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almost 50% more of the transmission occurs before the onset of symptoms, the tracking and quarantine of contacts becomes essential for the containment of these new strains and is strategic to ensure the control of the disease, or at least to reduce the speed of transmission while more studies can be done to increase the knowledge and capacity to face these new strains.

Considering what has been presented, we believe that the challenge imposed by SARS-CoV-2 does not end with the introduction of vaccines, much remains to be done in the coming months and years in terms of epidemiological, virological surveillance and studies in the areas of epidemiology, clinic, immunology, virology and other areas of knowledge to ensure the safety of the world population in relation to COVID-19.

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Table 1. Emerging variants of SARS-CoV-2 that cause concern today. (Source: https://cov-lineages.org/ accessed on 6 / feb / 2021)

Linhagem	Mutações	Países que já sequenciaram a variante e número de sequencias
P.1	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	Brazil 66, Japan 4, USA 3, Italy 3, France 3, Netherlands 2, South_Korea 1, Faroe_Islands 1, Peru 1
P.2	Spike D614G, Spike E484K, Spike V1176F, N A119S, N G204R, N M234I, N R203K, NSP5 L205V, NSP7 L71F, NSP12 K426M, NSP12 P323L	Brazil 30, Japan 4, Italy 3, Faroe_Islands 1, USA 1, South_Korea 1
B.1.1.7	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	UK 46042, Denmark 1076, France 472, Netherlands 466, USA 404, Belgium 402, Spain 350, Ireland 276, Switzerland 211, Portugal 201, Italy 169, Austria 140, Turkey 116, Israel 78, Germany 77, Australia 71, Sweden 66, Finland 42, Singapore 40, Jordan 40, Slovakia 37, Norway 33, Luxembourg 32, New_Zealand 26, India 22, United_Arab_Emirates 21, Iceland 20, Brazil 19, Mayotte 18, Romania 13, Nigeria 13, Czech_Republic 13, South_Korea 13, Poland 9, Ecuador 6, North_Macedonia 5, Hungary 5, Greece 4, Jamaica 4, Latvia 4, St._Lucia 3, Thailand 3, Canada 3, Hong_Kong 3, Bangladesh 3, Gambia 3, Malaysia 2, Pakistan 2, Mexico 1, Slovenia 1
B.1.351	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	South_Africa 642, UK 114, Belgium 37, Netherlands 31, France 29, Mayotte 21, Mozambique 19, Botswana 14, Switzerland 11, Germany 10, Australia 10, Ireland 9, New_Zealand 7, Denmark 5, USA 5, United_Arab_Emirates 5, Finland 2, Turkey 2, Spain 2, Kenya 2, Luxembourg 2, Portugal 1, South_Korea 1, Sweden 1, Gaborone 1, Norway 1, Panama 1, Austria 1, Bangladesh 1

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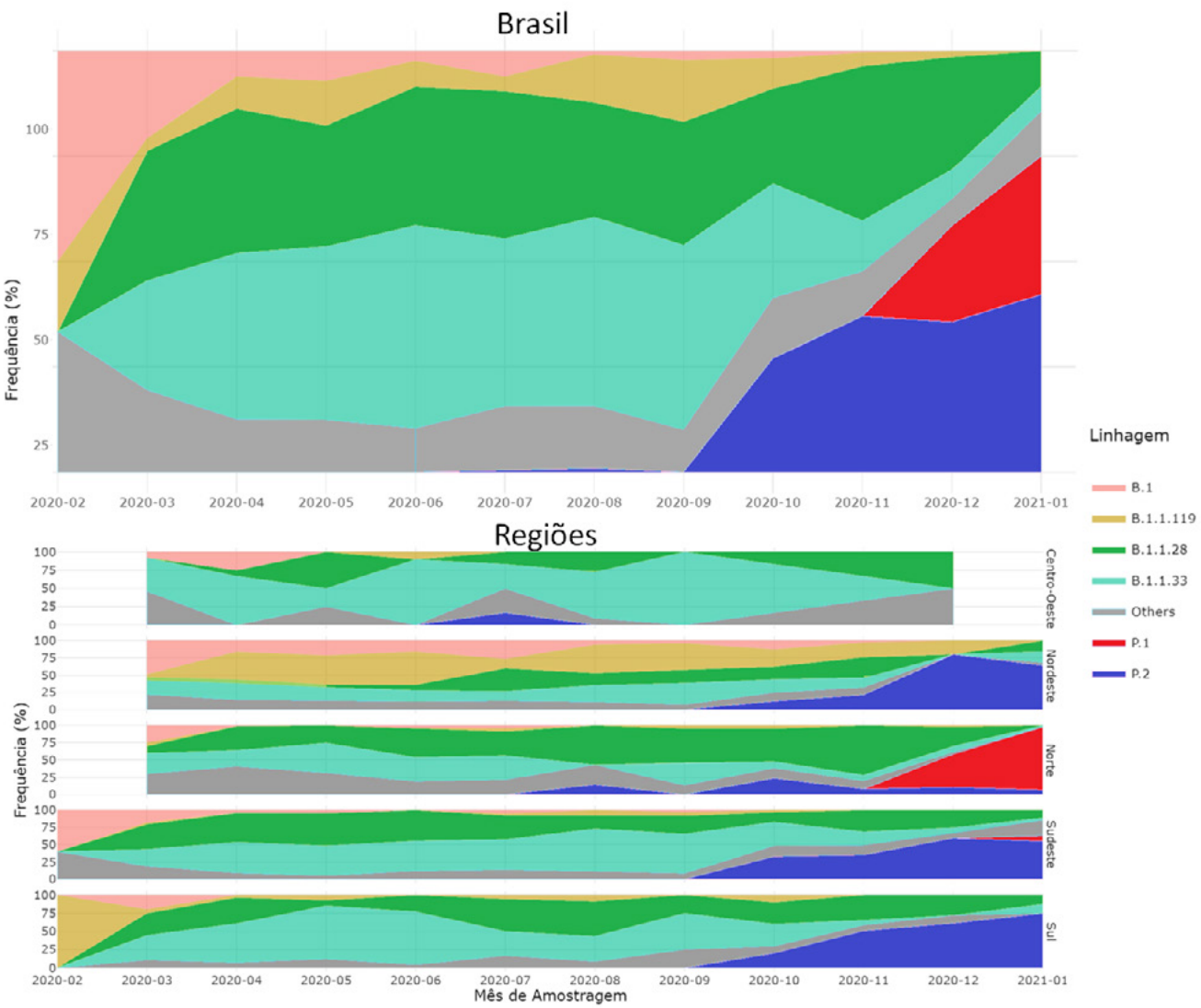

Figure 1. Proportions of the main strains of SARS-CoV-2 per month of sample. Brazil, February 2020 to January 2021. (Source: Rede Genômica Fiocruz. https://bit.ly/2YmCSjH. accessed on 7/feb /2021)

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Table 2. Summary of new emerging strains and their characteristics

			Mutações				**Características clínico-epidemiológicas**		
Lineage	Infection site of the first description	Description date	*N501Y*	*E484K*	*K417N*	*K417T*	Quickly expansion	Increased severity	Viral scape
B.1.1.7	United Kingdon	nov/20	Yes				Yes	Sim	little
B.1.351	South Africa	dez/20	Yes	Yes	Yes		Yes	not studied	Yes
P.1	Manaus	jan/21	Yes	Yes		Yes	Yes	not studied	Likely (not studied yet)
P.2	Rio de Janeiro	dez/20		Yes			Yes	not studied	Likely (not studied yet)

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