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SARS-CoV-2 epidemic in Brazil: how the displacement of variants has driven distinct epidemic waves

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A R T I C L E I N F O

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A B S T R A C T

Brazil ranks as third in terms of total number of reported SARS-CoV-2 cases globally. The COVID-19 epidemic in Brazil was characterised by the co-circulation of multiple variants as a consequence of multiple independent introduction events occurring through time. Here, we describe the SARS-CoV-2 variants that are currently circulating and co-circulating in the country, with the aim to highlight which variants have driven the different epidemic waves. For this purpose, we retrieved metadata information of Coronavirus sequences collected in Brazil and available at the GISAID database. SARS-CoV-2 lineages have been identified along with eleven variants, labelled as VOCs (Alpha, Gamma, Beta, Delta and Omicron) VOIs (Lambda and Mu) VUMs (B.1.1.318) and FMVs (Zeta, Eta and B.1.1.519). Here we show that, in the Brazilian context, after 24 months of sustained transmission and evolution of SARS-CoV-2, local variants (among them the B.1.1.28 and B.1.1.33) were displaced by recently introduced VOCs firstly with the Gamma, followed by Delta and more recently Omicron. The rapid spread of some of those VOCs (such as Gamma and Omicron) was also mirror by a large increase in the number of cases and deaths in the country. This in turn reinforces that, due to the emergence of variants that appear to induce a substantial evasion against neutralizing antibody response, it is important to strengthen genomic effort within the country and how vaccination still remains a critical process to protect the vulnerable population, still at risk of infection and death.

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Introduction

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an emerging RNA Betacoronavirus first detected in China by the end of 2019, is considered a major public health threat. Since the onset of the COVID-19 pandemic, SARS-CoV-2 variants have been emerging and circulating around the world and have made major contributions to the recurring epidemic waves that occurred asynchronously in different regions through time. During late 2020, the emergence of variants that posed an increased risk to the global public health prompted the implementation of major monitoring programs in order to inform the ongoing response to the COVID-19 pandemic. This in turn yielded the generation as of the end of February 2022 of more than 8 million genomes through sequencing-based surveillance (Khare, 2021).

Currently, lineages that may require public health actions have been classified by the WHO as variant of concern (VOC), variant of interest (VOI), variant under monitoring (VUM) and as formerly monitored variant (FMV) (World Health Organization 2022).

The classification of variants occurs dynamically according to the evolution of the virus and follows the Greek letter system that denominates variants in a non-stigmatising manner, as advised by WHO (World Health Organization 2022).

VUMs generally require epidemiological or phenotypic assessment to investigate suspicious genetic changes that may enhance viral fitness. If it is predicted or established that defined genetic changes may affect diagnostic and therapeutic strategies, immune escape, transmissibility, and disease severity, the investigated VUM starts to be considered as a VOI. Additionally, when genetic properties are associated with increased transmissibility and virulence, detrimental change in clinical presentation and a decrease in effectiveness of public health measures, the VOI starts to be classified as a VOC (World Health Organization 2022).

As the spectrum of knowledge regarding the variants may rapidly evolve, variants can further be reassigned as FMVs. This happens when those variants start to be associated with reduced public health significance due to low frequencies of circulation, undetected impact in a long-term period and when they are no longer associated with factors of concern (World Health Organization 2022).

In Brazil, the COVID-19 epidemic had huge impact. According to the National health report Brazil reported more than 27 million confirmed cases and a death toll exceeding 640 thousand by the end of February of 2022, making it one of the countries hardest hit by COVID-19 pandemic (World Health Organization 2022, Giovanetti et al., Oct 2021).

In this study we provide insights regarding the spread of SARS-CoV-2 variants in the Brazilian territory, highlighting how the replacement of several variants of concern have dictated the different epidemic waves in the country.

Materials and methods

We retrieved metadata information of Brazilian SARS-CoV-2 sequences available at the GISAID (Khare, 2021) database collected up to February 19th, 2022. To ensure the quality of the data analysed in this study and to guarantee the highest possible accuracy of the obtained results, only genomes >29,000bp and <1% of ambiguities with a variant assignment provided by the Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) (O'Toole et al., 2021), were considered (n = 111,626). For convenience, the geographical locations were aggregated in five Brazilian macro regions: North, Northeast, Southeast, Midwest and South. North macro region includes the states of: Acre, Amapá, Amazonas, Pará, Rondônia, Roraima, Tocantins. Northeast macro region includes the states of: Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Rio Grande do Norte, Sergipe. Southeast macro region includes the states of: Rio de Janeiro, Espirito Santo and Minas Gerais. Midwest macro region include the states of: Goias, Federal District, Mato Grosso and Mato Grosso do Sul. South macro region includes the states of: Parana, Santa Catarina and Rio Grande do Sul.

In addition, daily cases of SARS-CoV-2 in Brazil were retrieved from the Official National repository available at covid.saude.gov.br. The National network releases daily updates on the number of confirmed new cases, deaths, and recoveries, with a breakdown by states and regions.

Results

As a consequence of efforts to generate genomic data that would contribute to the mitigation of the pandemic, by the end of February 2022, a total number of 240 different lineages had been identified in Brazil. Eleven of them were assigned as: VOCs (Alpha, Gamma, Beta, Delta and Omicron); VOIs (Lambda and Mu); VUMs (B.1.1.318) and FMVs (Zeta, Eta and B.1.1.519). Ancestral relationships among these variants and main lineages identified in Brazil are represented as a diagram in (**Fig. 1**).

The Brazilian epidemic has been characterized by three distinct epidemic waves, causing more than 27 million cases and 670 thousand deaths as of 19th February 2022 (**Fig. 2 and Fig. S1**) (COVID-19 Situation Reports - PAHO/WHO). The first wave from February 2020 to November 2020 was characterized by the co-circulation of different lineages because of multiple introduction events occurring through time (**Fig. 2A**) (Giovanetti et al., Oct 2021). The second epidemic wave (December 2020 up to December 2021) was fuelled by the emergence and circulation of several VUMs, such as P.2 (i.e., Zeta), and VOCs such as Gamma (i.e., P.1), which started to be detected from January 2021 (**Fig. 2A** and **Fig. S1**). We detected several additional VOCs, VOIs, VUMs and FMVs sporadically during this wave period, including the Alpha, Mu and Eta, C.1.2, B.1.1.318, Lambda and B.1.1.519 variants from January 2021 onwards, but they remained at a low frequency nationally and were not associated with a significant resurgence of cases in any regions (**Fig. S2**). In April 2021, the Delta VOC started to be detected in the country. This VOC was able to displace the Gamma variant becoming the dominant viral circulating variant in the National scenario by the end of October 2021 (**Fig. 2A and Fig. S1**) (Giovanetti et al., Dec, 2021).

The months following the detection of this emerging VOC in Brazil, between September 2021 and December 2021, were marked by lower levels of transmission as indicated by a low incidence of reported COVID-19 cases and deaths (**Fig. 2**). It is nonetheless challenging to identify the exact cause of this trend, but it is likely that immunity acquired by prior infection with previous variants (e.g. Gamma) together with a successful vaccination coverage (more than 50%) played a role in the declining numbers of reported cases and deaths in the country (**Fig. 2**) (Giovanetti et al., Dec, 2021).

After the emergence of Omicron in South Africa and Botswana, in late November 2021, the first Omicron imported cases was also detected in Brazil (Viana et al., 2021, Campos Soares et al., 2022). Since then, we observed a striking growth in the prevalence rate of this emerging variant from early January 2022. As already described before, it can be noted a clear trend of Delta's replacement by Omicron (**Fig. 2A**) at the national and international level (Campos Soares et al., 2022, Callaway, 2021). The Omicron variant (B.1.1.529) raised a world alert due to its constellation of mutations (30 mutations (Campos Soares et al., 2022, Saito et al., 2021)), most of them located in the spike protein (Saito et al., 2021, Gong et al., 2021) and likely-associated with increased risk of infection (Wolter et al., 2021). Several Omicron's sublineages (BA.1, BA.2, BA.3, among others) have been already described (World Health Organization 2022), with BA.3 as the least prevalent. Studies have shown that BA.2 has a growth advantage over BA.1, which currently remains the most common Omicron sublineage reported worldwide (World Health Organization 2022). This in turn reinforce how crucial appear to be following their realtime evolution worldwide.

A month after the first identified Omicron case in the country, this emerging variant was associated with sustained transmission within all Brazilian regions and was also associated with an initial increase in

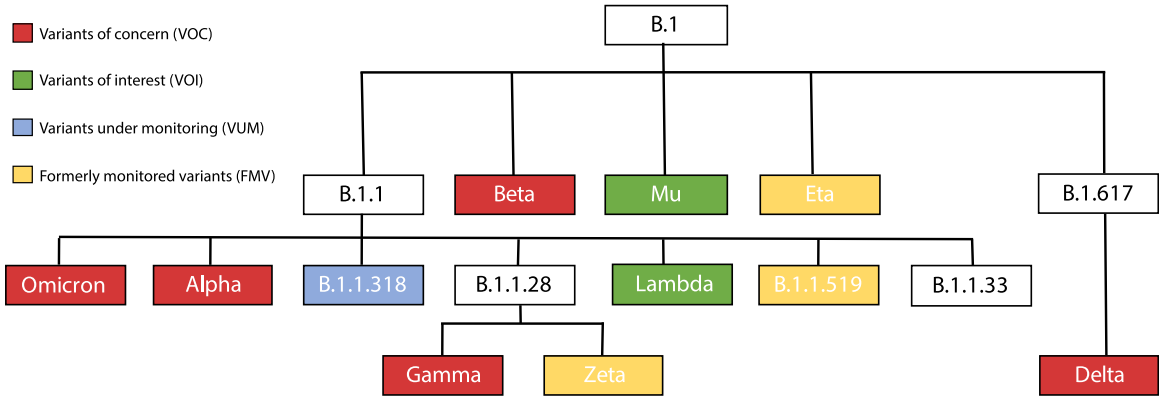

Fig. 1. Diagram of variants detected in Brazil. The diagram represents the evolutionary relation of the twelve VOCs (alpha, beta, gamma, delta, omicron), VOIs (mu, lamda), VUMs (B.1.1.318) and FMVs (zeta, eta and B.1.1.519 detected in Brazil since the beginning of the epidemic until the February 19th, 2022. Colours indicate WHO variant classification. Main ancestor lineage is B.1. Lineage B.1.1.28 had a crucial impact leading to variants that presented high frequency lately in Brazilian genomes (Gamma and Zeta).

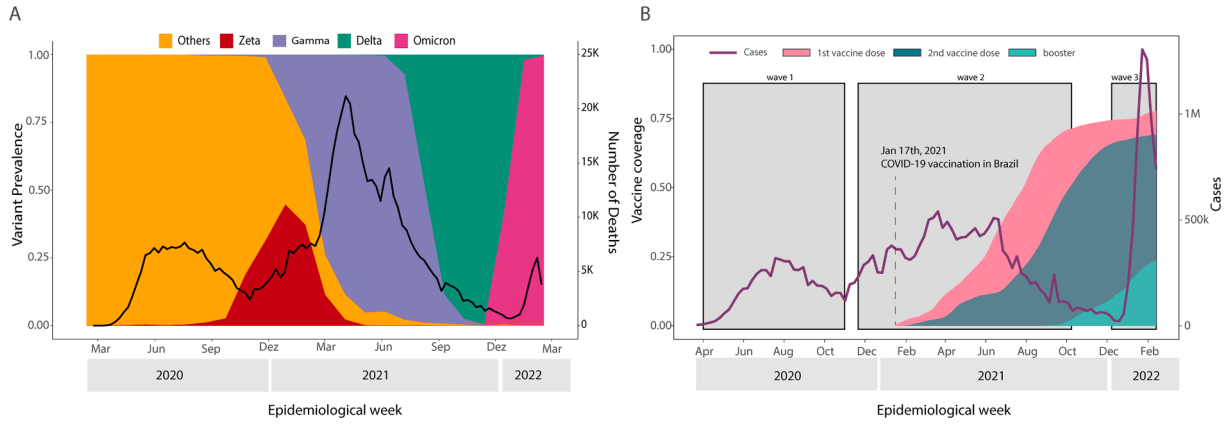

Fig. 2. Dynamics of the SARS-CoV-2 epidemic in Brazil. A) Number of daily COVID-19 cases and the vaccination rates in time; B) Progression in the proportion of circulating variants in Brazil over the first second and third waves of infection, showing the rapid replacement of different VOCs throughout time additionally showing the number of daily COVID-19 deaths.

COVID-19 cases and deaths (**Fig 2 and Fig. S1**). It is likely that the Omicron mutations allowed to better evade immune protection while spreading faster than any prior known variant (Viana et al., 2021). Despite this, it was observed that the Omicron's wave had a sharp peak and a swift decline, likely reflecting the successful impact of the vaccination programme together with the capacity of this unpredictable and very transmissible virus to quickly affect the proportion of susceptible population.

Discussion

Brazil has historically faced one of the worst COVID-19 scenarios worldwide and made South America the epicentre of the SARS-CoV-2 epidemic. Different sequencing efforts have been employed by Brazilian states thus resulting in differing numbers of available genomes for each state/region (totalizing $n = 113{,}681$ complete genome sequences available as of 19th February 2022), thus struggling our ability to describe in detail the progression of the epidemic in the country. Considering that since the beginning of the epidemic sustained lineage replacements over time have been observed (Giovanetti et al., Oct 2021, Giovanetti et al., Dec, 2021), our study reinforces how important it is to strengthen genomic monitoring in order to follow local time evolution of this viral pathogen.

In this study by combining epidemiological and genomic data we show that after 24 months of persistent transmission and evolution of SARS-CoV-2, local variants (among them the B.1.1.28 and the B.1.1.33) were subsequently displaced by recently described VOCs, firstly by Gamma, followed by Delta and Omicron, and how the rapid spread of some of those variants also dictated a large increase in the number of cases and deaths in the country. Understanding why cases are rising and falling is crucial for implementing adequate control measures.

Omicron drove a third wave of SARS-CoV-2 cases an deaths in Brazil, as it did rapidly worldwide. Additionally, the recent identification of Omicron's sub lineages (BA.1, BA.2, BA.3, among others) raises concern regarding their potential impact on the national and international health systems. Close monitoring of the Omicron's sublineages evolution appears to be necessary to better understand its transmissibility and the capacity of this variant to evade post-infection and vaccine-elicited cases. Our results finally highlight the need of more public investments to strength the genomic capacity across the country.

Author contribution

Conceptualization: LCJA, and MG; Curated metadata: EN, GS; ST.; Analysed the data: LCJA, EN, GS; ST., VF., and MG.; Helped with study design and data interpretation: LCJA; EN, GS, ST, HF, VP, SA, JASN, LLC, HF, SCS, MCE, SK, SNS, EC, MC, JL, VF, and MG; Wrote the initial manuscript, which was reviewed by all authors: EN, ST, HF ans MG.

Supplementary information

Supplementary Figure 1. Dynamics of the SARS-CoV-2 epidemic in each Brazilian microregion showing the number of daily COVID-19 deaths and the progression in the proportion of circulating variants in the country over time, showing the rapid replacement of several VOCs (Gamma, Delta and Omicron).

Supplementary Figure 2. Frequency and distribution of SARS-CoV-2 VOCs, VOIs, VUMs and FMVs in Brazil.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.virusres.2022.198785.

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