

Molecular dynamics of the COVID-19 pandemic in Espírito Santo (Brazil) and border States

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ABSTRACT

This study represents the first overview of the epidemiological dynamics of SARS-CoV-2 in Espírito Santo (ES) State, Brazil, filling in knowledge on this topic, observing data collected in the State, and aiming at understanding the epidemiological dynamics of the virus in ES, as well as its possible routes of transmission and dissemination. . Our results highlight that, so far, nine lineages have been identified with ES State. The B.1.1.33 lineage was the first with the highest occurrence in ES, remaining predominant until September 2020. The second predominant lineage was *Gamma*, representing 45% of the samples. The *Delta* lineage appears on the State scene, proving to be the next dominant lineage. This research allowed us to understand how the lineages advanced and were distributed in the State, which is important for future work, also making it possible to guide sanitary control measures. Data analyses were made through the GISAID database for ES State showed that the pandemic in the State has been evolving dynamically with lineage replacements over the months since the first notification.

KEYWORDS: SARS-CoV-2. COVID-19. Lineages. Espírito Santo. Brazil.

INTRODUCTION

More than two years after the first notification of an outbreak of respiratory crisis caused by a new coronavirus (SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2), this syndrome, which received the name coronavirus disease (COVID-19)¹, has already contaminated more than 400 million people in the world, and has killed more than 5.7 million² (more than 635,000 people in Brazil)³. In Brazil, the first case of SARS-CoV-2 infection was identified in Sao Paulo State, on February 25, 2020, in a 61-year-old Brazilian man who had traveled to Lombardy, Northern Italy⁴.

Due to the transmission potential and aggressiveness of COVID-19, scientists have been working to obtain effective and safe vaccines at an unprecedented rate⁵. The effectiveness of several vaccines were reported in late December 2020, for the population to start immunization to fight the pandemic^{6,7}.

Brazil is territorially divided into five regions (North, Northeast, Midwest, Southeast, and South), in which the disease spread rapidly, following the same epidemiological patterns reported in European countries such as Italy, Spain and the United Kingdom⁸. The Southeast region of Brazil covers four States: Sao Paulo - SP (41 million inhabitants), Rio de Janeiro - RJ (15 million inhabitants), Minas Gerais - MG (19 million inhabitants) and Espírito Santo - ES (3 million and 800 thousand

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inhabitants). The Brazilian Southeast region has the highest population concentration in the country, being ES, the 14th State in the national ranking, with a population density of 76.25 inhabitants/km² (2010).

The metropolitan area of Vitoria, capital city of ES, is composed of seven cities (Cariacica, Fundao, Guarapari, Serra, Viana, Vila Velha and Vitoria), and has 1,276,113 inhabitants according to the IBGE - Brazilian Institute of Geography and Statistics in the 2010 Demographic Census⁹. The first reported case of COVID-19 in Latin America¹⁰, and most confirmed cases in Brazil (more than 27 million infections and 635,000 deaths by February 10, 2022) are from the Southeast region of the country.

In ES State, however, there is a lack of studies on the COVID-19 data collected. Understanding how lineages advance and are distributed in the State cannot only provide data for future research, but also guide health control measures. The first case was reported on March 5, 2020 by the ES Health Department (SESA)¹¹. The epidemiological data of COVID-19 in the State registers more than 13,700 deaths, and more than 950 thousand cases of the disease¹¹. Nevertheless, exploratory and evolutionary studies were only conducted in some States of the country, such as Minas Gerais - MG¹², Rondonia - RO¹³ and Pernambuco - PE¹⁴. Therefore, taken into account this bottleneck of reported information, this study aimed at understanding the epidemiological dynamics of the virus in ES State, as well as its possible routes of transmission and dissemination.

MATERIALS AND METHODS

Complete and genotyped genomes of ES State residents were downloaded from the GISAID database using the “complete genome”, “high coverage”, and “low coverage excluded” filters. In addition, genomes from neighboring States were also downloaded, namely: Bahia (BA), Minas Gerais (MG) and Rio de Janeiro (RJ). Using these sequences, two databases were assembled. The first one containing only samples from ES State, dated between February 29, 2020 and August 19, 2021 (data collection period) in addition to the NCBI Reference sequence NC_045512.2 SARS-CoV-2, which was used to conduct the analysis of lineages and mutations present in the State. The second database, used for phylogenetic analysis, was constructed using sequences from ES together with sequences from the neighboring States (RJ, MG, BA).

Identification of lineages

The sequences from both databases were submitted

to the Pangolin COVID-19 software version v1.2.56 (Pangolin, Centre for Genomic Pathogens Surveillance, USA) to identify the lineages present in ES State¹⁵.

Phylogenetic inference

For the second database used in the phylogenetic analysis, samples from ES (n=487), MG (n=627), BA (n=942) and RJ (n=5,747) were downloaded from the database. From the total sample collected, the selection of sequences was performed randomly with the aid of a specific script prepared using the Python language software (Python Software Foundation, Wilmington, DE, EUA), resulting in the following values of “n” for each State: ES (n=49), MG (n=53), BA (n=50) and RJ (n=50), with a total of 202 samples for the construction of the phylogenetic tree. Furthermore, the software MAFFT, version 7 (Osaka University, Osaka, Japan) and the Multiple alignment program for amino acid or nucleotide sequences were used to perform the database sequence alignment. The maximum likelihood tree was calculated using the IQ-TREE platform, version 1.6.12 (University of Vienna, Vienna, Austria) with 15,000 bootstraps. The GTR+F+I evolutionary model was selected by the platform. For the Bayesian inference, the evolutionary model was calculated using the software MrModelTest2, version 2 (Boston, MA, USA). The evolutionary model generated was the GTR+I+G. Then, the sequences were submitted to the CIPRES platform, version 3.3 (New Orleans, LA, USA) to generate the phylogenetic tree. A consensus tree between the Bayesian inference and the maximum likelihood inference was used for phylogenetic analyses.

RESULTS

The GISAID database in which the SARS-CoV-2 sequences from the genomic identification of the virus in the world are deposited, was consulted to obtain the date of collection of the first SARS-CoV-2 genome sequences from the States that belong to the Southeastern region of Brazil, considering the following dates in ascending order: Sao Paulo (2020/02/25), Espirito Santo (2020/02/29), Rio de Janeiro (2020/03/05) and Minas Gerais (2020/05/21). Thus, it determined that the first Brazilian SARS-CoV-2 sequence submissions correspond to samples from the Southeast region. In the study period, a total of 487 samples of SARS-CoV-2 genomes isolated in ES State from February 2020 to September 2021 was analyzed. As a result, the presence of nine lineages was observed in the State, according to the classification provided by the Pangolin software: B.40, B.1.1.33, B.1.1.28, Zeta (P.2), P.7, Alpha (B.1.1.7), Gamma (P.1; P.1.2; P.1.7; P.1.9 P.1.10;

P.1.11), N.9, and *Delta* (AY.13; B.1.617.2; AY.26; AY.32; AY.4; AY.5). Among the variants found in the period of this study, the most frequent were: *Gamma*, (44.5%), *Delta* (19.0%), *Zeta* (14.8%), B.1.1.33 (11.3%), B.1.1.28 (5.1%), and *Alpha* (4.5%).

The dynamics of the lineages present in ES State during the months, evaluated in the database (Figure 1) starts with the first sample collected, from a resident in Vila Velha (an ES State municipality), who had arrived from a trip to Italy. The collection of the sample from this case was carried out on February 29, 2020, and it was classified within the B.40 lineage. This lineage is related to other lineages of the “large clade B”, as is the case of lineage B.1.1.33, which was considered the first lineage with the highest occurrence in the State, remaining as the main lineage until September 2020, when the B.1.1.33 lineage became predominant. The predominance of the B.1.1.33 lineage in ES occurred until the advance in the number of cases caused by the *Zeta* variant. This variant was detected for the first time in the State in October 2020, and became the main cause of infections between December 2020 and February 2021.

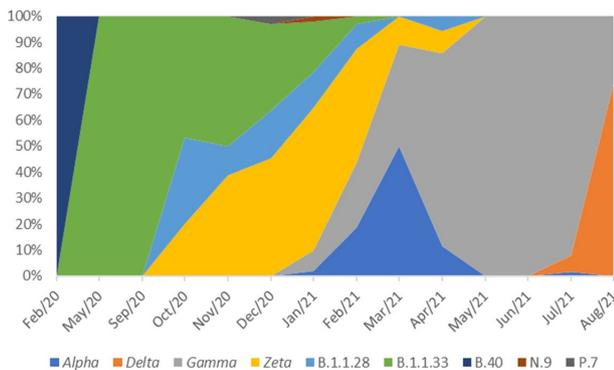


Figure 1 - Emergence of lineages in ES State over time.

In January 2021, the first sample containing the *Gamma* lineage was found in the State, and from March onward it became the main culprit in ES cases of COVID-19. However, the *Gamma* lineage ceased to predominate after the spread of the *Delta* variant.

The variant that first gave rise to the *Delta* lineage was the B.1.617.2, but AY.4, AY.5, AY.13, AY.26, AY.32 are also within the *Delta* lineage. These variants are closely related to B.1.617.2 in terms of genotype. Between July and August 2021, the period in which this lineage was identified in the State, there was a significant increase in the prevalence of the *Delta* lineage (Figure 1), which was identified in more than 73.0% of the samples tested in the month of August.

Regarding the samples available in the database for phylogenetic analysis (Figure 2), the only sample from ES

State related to lineage B.1.1.7 was collected on March 2, 2021. This sample shares a common ancestor that gave rise to the clade that also contains samples from MG and RJ States with 99.0% bootstrap support. The samples from both States were collected after the data collection period in ES State (March 2, 2021), on March 8, 2021 for MG State, and April 26, 2021 for RJ State.

In Figure 3, A highlights a close relationship between the genomes of *Delta* lineage virions collected in ES, MG and RJ States. This relationship points to the possibility that the samples collected in ES on August 19, 2021 may share a common ancestor that gave rise to the sequenced virions from MG and RJ States, bearing in mind that samples from MG and RJ were collected on August 26, 2021 and June 29, 2021, respectively. In Figure 3, B highlights the possibility that the first sample is related to the *Delta* lineage in ES State, collected on July 19, 2021 (EPI_ISL_3801883). This viral lineage would share a common ancestor that gave rise to the two samples from BA State, both collected on August 6, 2021, whose clade obtained a bootstrap support of less than 70.0%.

DISCUSSION

In the present study, we corroborated that the outbreak of COVID-19 in Latin America began in Brazil, in Sao Paulo State, with the beginning of the viral spread among other States and Southern countries. The high air connectivity through the Sao Paulo-Guarulhos International Airport (the largest in Brazil), and the maritime connection through the most important ports in the country, such as the iron ore exporting port in Vitoria, the capital city of ES State, and the Brazilian largest port located in Rio de Janeiro, are important points to understand the beginning of the transmission and significant expansion of the virus from the Southeast region, where the first epidemic phase began in Brazil, to the rest of the country. However, published reports highlight the relevance of mobility between States as a key factor in the local and interregional spread of SARS-CoV-2, with the Southeast region being the main source of virus exports in the country^{4,10}.

In this context, we analyzed some information about the circulation of SARS-CoV-2 variants in ES, as well as the phylogenetic correlation between the different variants of the virus that circulate in bordering States, making it possible to understand the viral dynamics of transmission and dissemination.

It is known that SARS-CoV-2 is a single-stranded RNA virus whose genome is very unstable, favoring the occurrence of mutations and the emergence of variants¹⁶. Given the diversity of viral strains with mutations in their

Tree scale: 0.001

Lineages

- P.1
- B.1.1.28
- P.2
- Delta
- B.1 (B.1.1)
- B.1.1.7
- N.9
- B.1.1.33

Node Confidence

- 70
- 77.5
- 85
- 92.5
- 100

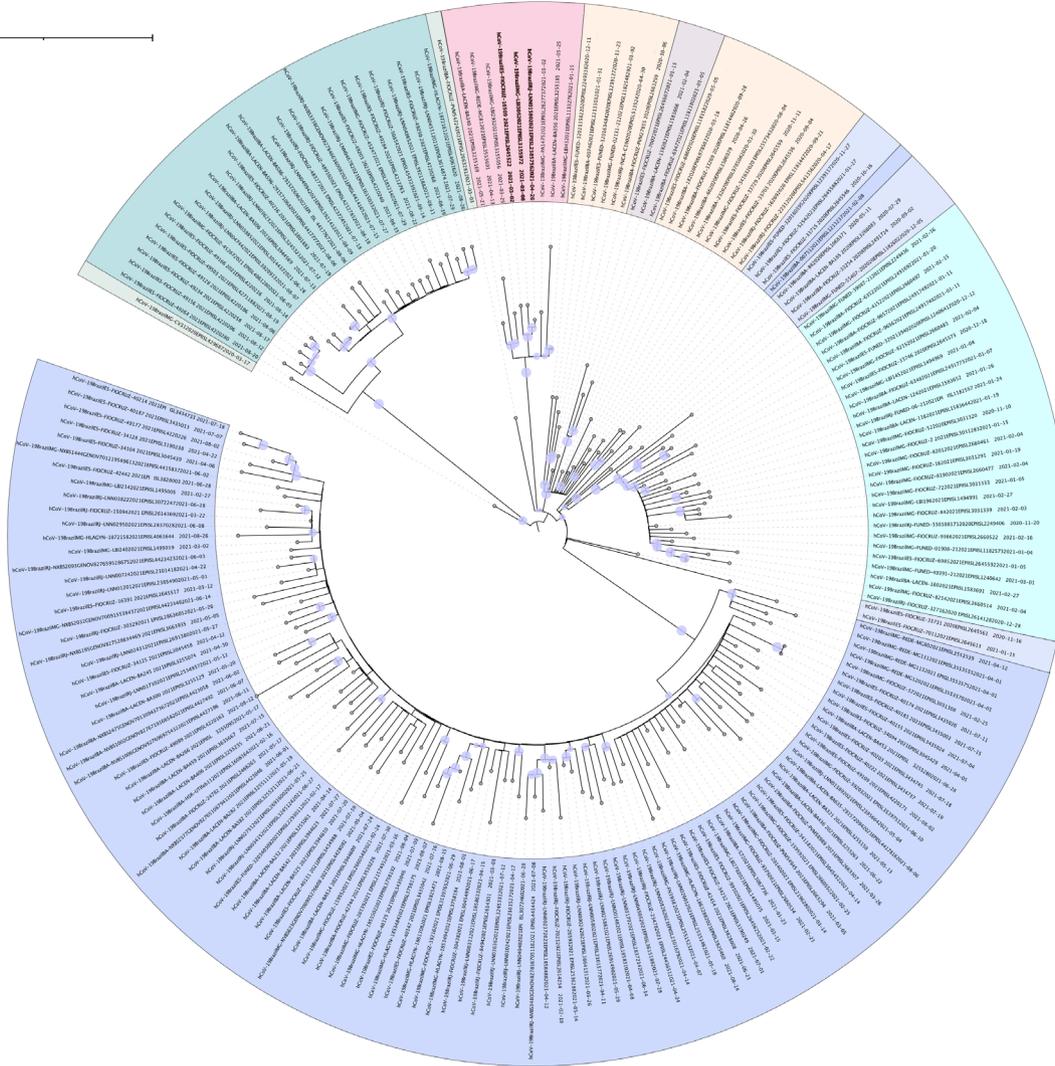


Figure 2 - Phylogenetic tree inferred by the Maximum Likelihood (ML) of 202 complete SARS-CoV-2 genomes from ES, BA, MG and RJ States.

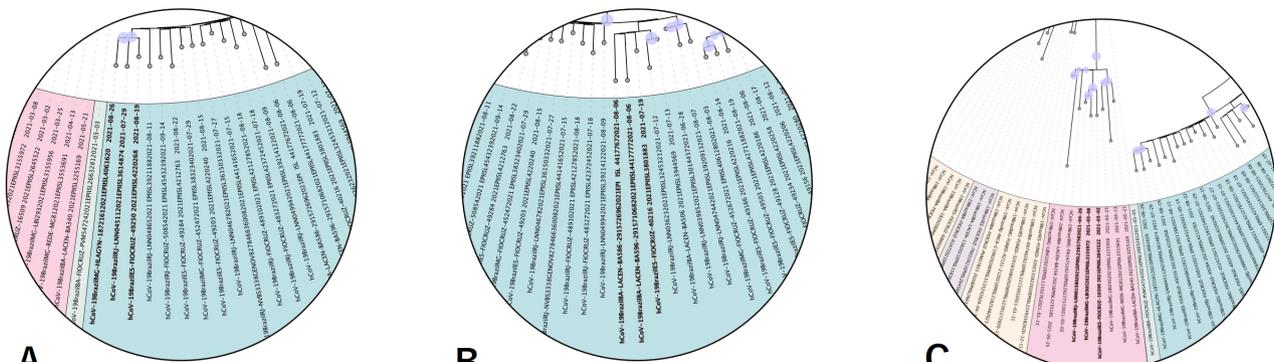


Figure 3 - Highlighting of interesting points on the phylogenetic tree: (A) Relationship between the genome of *Delta* lineage virions collected in ES, MG and RJ States; (B) The first sample referring to the *Delta* variant in ES State, collected on July 19, 2021 (EPI_ISL_3801883); (C) Single sample from ES State, lineage B.1.1.7 that make up the database.

genome, the World Health Organization (WHO) assigned a nomenclature to the SARS-CoV-2 strains that may harbor some important biological alterations. These lineages

are considered Variants of Concern (VOC) or Variants of Interest (VOI), which are identified using letters of the Greek alphabet¹⁷. During the analyzed period, in ES State,

out of the four VOCs, at least three were already present in the State, namely: *Gamma*, *Alpha*, and *Delta*.

In a Brazilian study that analyzed samples from March 2020, Franceschi *et al.*¹⁸ showed that the sequenced genomes were mainly from three lineages: B.1, B.1.1.28, and B.1.1.33. Lineages B.1.1.28 and B.1.1.33 had the highest percentages in the country (n=156, 31.01%, and 26.04%, respectively). In Rio de Janeiro, a study conducted with samples collected on December 1, 2020 and May 12, 2021¹⁹ identified lineages P.2 (43.44%), P.1 (36.47), B.1.1 (5.73%), B.1 (3.69%), B.1.1.28 (3.28%), P.1.2 (3.28%), B.1.1.33 (1.23%), B.1.1.7 (1.23%), P.4 (0.82%), B.1.407 (0.41%) and N.9 (0.41%). The predominant lineage in Rio de Janeiro was *Zeta*, which occurred between December 2020 and January 2021, followed by P.1, which was detected in the sixth week of 2021. In ES, during the period studied, the first lineage with the highest predominance was *Alpha*, identified for the first time on January 12, 2020, which was soon replaced by B.1.1.33, detected in the State on May 5, 2020.

The period during which our study was carried out captured the epidemiological profile and allowed us to correlate these data with the genetic profile of the SARS-CoV-2 population during the first three epidemic waves in ES, which occurred between June 2020 and August 2021¹¹.

The temporal analysis of the genetic frequencies of the SARS-CoV-2 epidemic population in ES demonstrated the predominance of B.1.1.33 lineage between May and November 2020, coinciding with the first wave of SARS-CoV-2, which occurred between June and July of the same year. The second epidemic wave in ES occurred between late November 2020 and early January 2021, coinciding with the cocirculation of the *Zeta* and B.1.1.28 lineages. During January 2021, there was a decline in the number of cases, however, in the period between March and April 2021, the third and most intense epidemic wave of the period analyzed in the present study was observed.

This third wave coincided with the initial detection of *Alpha* and *Gamma* variants, responsible for more than 49% of the samples from ES State analyzed in the period. A further increase in the number of SARS-CoV-2 cases, but with a lower intensity, occurred in September 2021, after the detection of the *Delta* variant circulation. These observations showed a scenario of great complexity of the epidemiological dynamics of SARS-CoV-2, which was aggravated by the emergence and cocirculation of new variants in addition to the speed of changes in the genetic profile of the SARS-CoV-2 population in ES. This outcome corroborated the results that had been previously found in other locations, such as SP State, RJ State and Amazonas State (mainly in the capital city of Manaus)^{10,20,21}.

The *Alpha* lineage in ES State was identified on January 12, 2021. It is possible to notice that the *Alpha* lineage (Figure 1) began to emerge in the State soon after its identification, with a peak in March 2021, corresponding to 50% of lineages found in the database in that period, which may reflect its transmission potential. This lineage harbors the N501Y mutation, detected for the first time in the United Kingdom on 2020/12/12, being considered the most transmissible lineage known so far²².

In ES, the *Zeta* lineage appeared for the first time in November 2020, being predominant until February 2021, according to the database. In Brazil, the *Zeta* lineage was identified for the first time in July 2020 in RJ²³, and it became predominant in this State from December 2020 until January 2021. This pattern changed after the emergence of the P.1 lineage, after its first detection¹⁹. As in RJ, in ES there was cocirculation of important lineages together with the *Zeta* lineage, such as B.1.1.33, B.1.1.28, *Alpha* and *Gamma*. In the period in which the *Gamma* lineage began to circulate (January to August 2021), there was a new increase in the number of deaths recorded in ES State, with a total of 1,249 deaths in March, and a peak of 2,081 deaths¹¹. Within this lineage, the *Gamma* variant associated with the N501Y.V3 mutation was reported for the first time in Japan, in four Japanese travelers from the city of Manaus (Amazonas State) on January 2, 2020²⁴. The *Gamma* variant, when compared to the ancestor (B.1.1.28), has 17 non-synonymous mutations, 10 out of which are found in the spike protein, being the most important N501Y, K417T and E484K²⁵. The *Gamma* variant was detected in a large percentage of samples from Amazonas in December 2020, what can be considered a possible cause of the worsening of the health situation in that. In January 2021, this lineage was already accounting for the majority of samples sequenced from that State²⁶.

Regarding a published report²⁷ in which the transmission of the *Delta* lineage has been detected in almost every country in the world, including Brazil in July 2021, this lineage circulation in ES State was identified a month later when there was an increase in the number of sequences identified in August 2021. After the decline in the number of cases of the third wave of contagions, there was a new increase in September 2021 due to the circulation of the *Delta* variant, according to data provided by the COVID-19 panel¹¹, although much lighter than the previous ones. Thus, in August 2021, ES reached the lowest number of infected people since the first wave to date¹¹. Thus, we were able to observe the positive action of vaccination in the State, due to the fact that in the months of June and August 2021 around 52 to 66% of the population of ES had at least received one dose of the vaccine. It is also known that infection by the

Delta lineage is associated with an increase in both, the viral load in the infected subject and the time of viral elimination from the body, causing an increase in the transmissibility of the virus²⁸. In addition, recent studies have suggested that the *Delta* lineage is 40 to 60% more contagious than the *Alpha*²⁹ variant, justifying a change in the behavior of the virus in comparison with the previous variants and the one used as a reference.

Vaccination against COVID-19 in Brazil started in January 2021³⁰. In September 2021, 71% of the population had received one dose of the vaccine, whereas 43% had received two doses. The rate of vaccination in ES in the same period was slightly higher than in other Brazilian States, with 74,4% and 45,7% of the population vaccinated with one and two doses, respectively^{11,30}. The effectiveness of immunization was supported by the reduction in the positivity rates of tests performed after the beginning of the vaccination campaign. In ES, in January 2021, from the total RT-PCRs carried out, about 50% had a positive result and with the advancement of immunization and infection control measures, the positivity rate regressed over the months, reaching less than 12% in July 2021. However, in September 2021, this rate reached 21%, which may be related to the advance of the infection caused by the *Delta* variant, which showed a great potential for dissemination^{11,30}.

According to the phylogenetic analysis conducted in this study, it was possible to notice some relationships of the first samples collected among the States, suggesting a possible relationship of the origin of infections between the analyzed States, indicating possible influences of the entry of the virus in a previously unknown State (Figure 3). Finally, regarding the data analyses obtained in this study, we can infer that the *Delta* variant arrived first in RJ State, followed by BA, ES and MG, respectively.

This study has also shown that during the initial phase of the pandemic in Southeastern Brazil, the first SARS-CoV-2 sequence from ES (EPI_ISL_1181582), collected on May 5, 2020 and analyzed by the phylogenetic tree, corresponded to the lineage B.1.1.33, having an evolutionary relationship to the viruses sequenced in the other States. As they belong to the same 70% below supported monophyletic clade, we claim that the possible origin of that lineage in ES was introduced from a borderline State, since at that time the other States had already identified this lineage. However, globally, it was the first lineage with the greatest spread. In fact, a previous study³¹ estimated that B.1.1.33 is a widespread associated lineage to community transmission among Brazilian States.

In addition, the analysis of the phylogenetic tree of 202 SARS-CoV-2 sequences allowed to show a close evolutionary relationship between the viruses from different

States (ES, MG, RJ, BA), which were grouped within the same clade. Moreover, they have a tendency to form monophyletic groups as they belong to the same lineage.

CONCLUSION

Due to the limitations found for the sequencing of cases identified in ES, the analysis of data made available through the GISAID database for the State showed that the pandemic in ES has been evolving dynamically with lineage replacements over the months since the first notification. Thus, this study showed that the lineage *Delta* began to predominate the ES scenario after two events of great predominance caused by two other strains: B.1.1.33 and *Gamma*. Therefore, we claim that our study represents the first overview of the epidemiological dynamics of SARS-CoV-2 in ES State.

AUTHORS' CONTRIBUTIONS

STR, CVAM, ASJ, and DSHP performed the software analysis and performed data interpretation. STR, CVAM, ASJ, PMM, PGG, FBFT and DSHP performed the literature search, collected the data and wrote the manuscript, and made edits. PGG, FBFT and DSHP critically revised the manuscript for intellectual content and wrote the manuscript. All authors reviewed and approved the manuscript.

CONFLICT OF INTERESTS

The authors declare that the research was carried out without any conflict of interests.

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