



## Evolution of SARS-CoV-2 variants and their impact on the epidemic period in Villa Clara, Cuba

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### Abstract

Epidemiological and clinical aspects of COVID-19 are modified according to the variant circulating, hence the importance of identifying the variables in each epidemic period. The objective of the research consisted in characterizing the evolution of SARS-CoV-2 variants, and its repercussion in the epidemic period in Villa Clara province, Cuba. A cross-sectional descriptive observational study was carried out in the Laboratory of Molecular Biology of Villa Clara, in the period from December 2020 to May 2023. In the province, the epidemic period was divided into three, in the first one, the circulation of D614G was detected; in the second one, the one with the highest incidence and mortality, the beta and delta variants were identified, and in the third one, omicron and its sublineages were sequenced. It is concluded that in Villa Clara the D614G, beta, delta and omicron variants were the ones that originated the epidemic waves. The most intense epidemic period was concentrated in four months, from July to October 2021. The responsibility for this high incidence and mortality was attributed to the beta and delta variants, without being able to specify whether it was one or both of them.

**Keywords:** Coronavirus infections; Genetic variants; SARS-CoV-2; Villa Clara

### 1. Introduction

The genetic variability of SARS-CoV-2 increased markedly when the pandemic was declared (Aguilar *et al.*, 2021). Wuhan-Hu-1 was the original strain, which initiated the pandemic in December 2019. Between January and February 2020, a variant with a D614G substitution emerged; a mutation that conditioned the pandemic, replacing the one initially detected in China; by June 2021 it was globally dominant (Expósito *et al.*, 2021).

During the pandemic, viral variants continued to appear, some of which caused sudden increases in infection (Shiehzadegan *et al.*, 2021; Tao *et al.*, 2021). The WHO classified viral variants into those of interest and concern (Aguilar *et al.*, 2021).

Variants of concern show evidence of increased transmissibility, disease severity and diagnostic interference, reduced susceptibility to therapies, and significantly decreased neutralizing antibodies; named alpha (British), beta (South African), gamma (Brazilian), delta (Indian) and omicron (Botswana) (Aguilar *et al.*, 2021; Expósito *et al.*, 2021; Shiehzadegan *et al.*, 2021). In February 2020, Cuba established laboratory surveillance for SARS-CoV-2, including genomic surveillance (Guzman *et al.*, 2022).

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The first confirmed cases of COVID-19 in Cuba were reported on March 11, 2020, and the country's first autochthonous case was detected in Villa Clara province on March 12 of that year (Durán, 2022; Pérez *et al.*, 2022). The D614G variant was identified in almost 100% of the samples sequenced in the country during 2020 (Guzmán *et al.*, 2022; Portal, 2022).

On October 25, 2020, Cuba reopened its borders and new variants of the virus were introduced into the country due to the entry of infected travelers. As of January 2021, the variants of greatest concern, beta and delta, were introduced (Portal, 2022). In 2021, the circulation of 18 variants was detected (Pérez-Santos *et al.*, 2022).

On May 5, 2023 the director of the World Health Organization (WHO) declares the end of the global health emergency for COVID-19; and notes, in more than three years of COVID-19 almost seven million deaths have been reported to WHO, but this figure is known to be several times higher, and the number of deaths is at least 20 million (WHO, 2023a).

COVID-19 has not ceased to represent a global public health concern; disease severity is decreasing, transmissibility is increasing; therefore, the virus has developed a successful strategy to continue infecting many people (Farid and Amin, 2023; WHO, 2023b).

There is a risk of the emergence of new variants causing a new increase in cases and deaths (WHO, 2023a); hence the need for each region to characterize the phylogenetic evolution of the virus in order to detect the presence of genomic variants. In this context, the present research aims to characterize the genetic variants of SARS-CoV-2 causing the COVID-19 pandemic in Villa Clara, Cuba.

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## 2. Methodology

### 2.1. About the study

A cross-sectional descriptive observational study was carried out from March 2020 to May 2023 in Villa Clara province, Cuba. The population consisted of 60141 samples of nasopharyngeal exudates from patients confirmed with SARS-CoV-2 by RT-PCR at the Molecular Biology Laboratory of Villa Clara. From this population, 106 samples were sent for sequencing to the National Reference Laboratory of Influenza and respiratory viruses of the Virology Department of the "Pedro Kourí" Institute of Tropical Medicine (IPK), for the genomic surveillance of the country.

The Sanger method was used for partial sequencing of the S and N genes of SARS-CoV-2. The sequences obtained were assembled and edited with the Sequencher™ 4.10.1 software tool (Genes Codes Corporation, USA). The data generated were used for the identification and subsequent molecular characterization of the genetic variants of the virus using the Coronavirus Typing Tool, SARS-CoV-2 Program ([www.covdb.stanford.edu](http://www.covdb.stanford.edu)) and CoVsurver Mutation App.

Samples with a mutation pattern not previously described by GISAID, detected in five or more patients (Guzman *et al.*, 2024), were called mutational patterns.

### 2.2. Statistical analysis

Microsoft Excel 2016 and SPSS, version 22 were used for data processing and analysis. Absolute and relative frequencies were used as summary measures for qualitative variables.

### 2.3. Ethical Aspects

The research was approved by the Ethics Committee of the institution, Provincial Center of Hygiene, Epidemiology and Microbiology of Villa Clara (CPHEM-VC), and was subject to ethical norms that made it possible to minimize the possible harm to the technical and laboratory personnel involved in the research, in order to generate new knowledge without violating the ethical principles established for these cases. On the other hand, all authors involved in the research, publication and dissemination of the results are responsible for the reliability and accuracy of the results shown (DHAMM, 2013).

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## 3. Results

In Villa Clara, from March 2020 to May 2023, 60141 cases of COVID-19 were reported; of these, 446 patients died. A total of 106 samples were sequenced, in which 7 variants and two mutational patterns were detected.

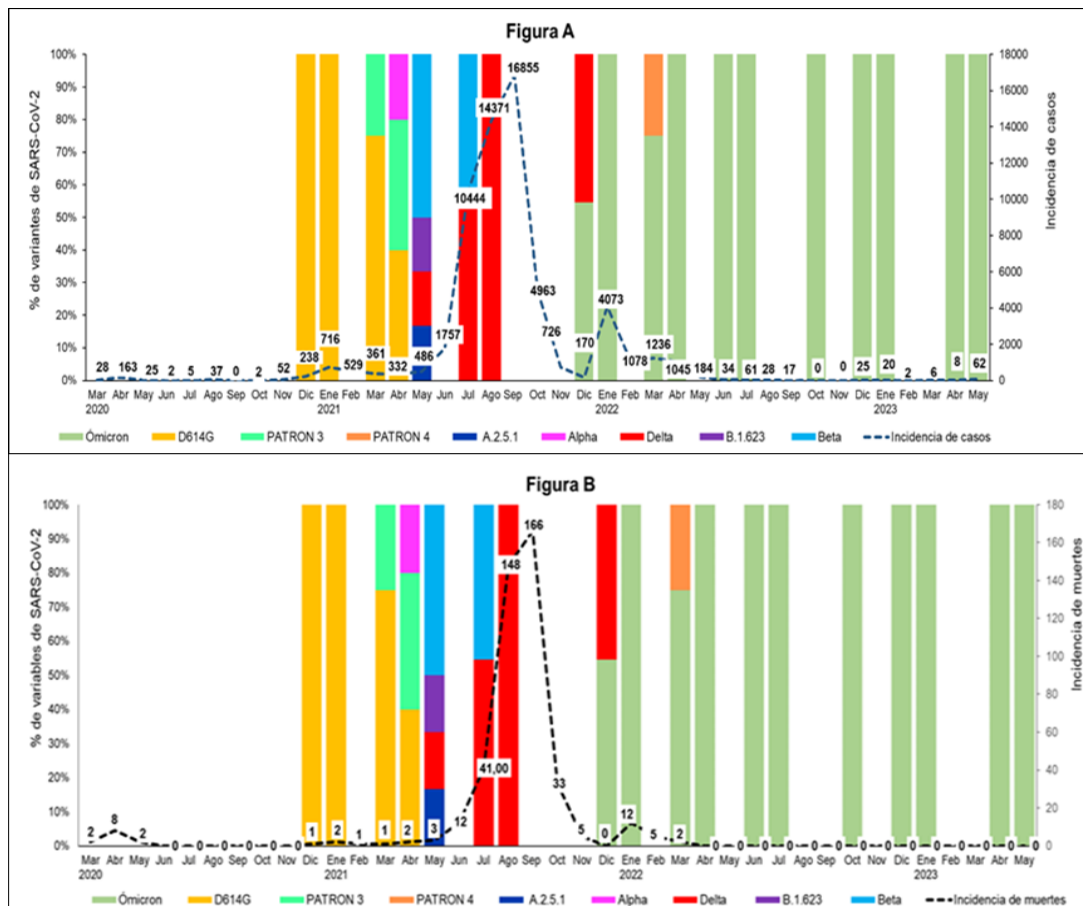
In the province, the epidemic period was divided into three. The first, from March 2020 to April 2021, fourteen months; where the circulation of the D614G variant was detected and 4.1% (2490/60141) of cases and 4.3% (19/446) deaths were diagnosed in the province. The first wave occurred in January 2021 with 716 confirmed cases in the month (Table 1), (Figures 1 A and B).

The second period, May to December 2021, two circulating variants, beta and delta, were detected. The incidence was 82.8% (49772/60141) and 91.5% (408/446) deaths. In this eight-month interval, the quarter of July, August and September stands out, which gave rise to the second wave, with an incidence of 69.3% (41670 / 60141) and 79.6% (355 / 446) deaths (Table 1), (Figures 1 A and B).

The third period was from January 2022 to May 2023. The circulating variant was omicron, with its multiple sublineages; in this interval the incidence was 13.1% (7879) and mortality was 4.3% (19/446). The third wave occurred in January, with the notification of 4073 cases (Table 1) (Figures 1 A and B).

**Table 1** Epidemic periods and variants of SARS-CoV-2 in Villa Clara March 2020 - May 2023

Epidemic periods	Date	NO. of months	Incidence	%	Deceased	%	Detection Variants
First	Mar 2020-April 2021	14	2490	4.1	19	4.3	D614G
Second	May 2021-decem 2021	8	49772	82.8	408	91.5	beta, delta
Third	Juan 2022-may 2023	17	7879	13.1	19	4.3	omicron
Total	Mar 2020-may 2023	39	60141	100	446	100	--



**Figures 1A and B** Percentage of SARS-CoV-2 genetic variants in relation to the incidence of cases and deaths, Villa Clara March 2020-May 2023

In Villa Clara the first SARS-CoV-2 variant to be sequenced was D614G in December 2020 and detected until April 2021. In March 2021, in addition to the D614G variant (75%), mutational pattern 3: D614G + T732A (25%) was detected. In April 2021, circulating D614G (40%), mutational pattern 3: D614G + T732A (40%), and variant Alpha Lineage B.1.1.7. was detected (20%). In May 2021 four variants were identified co-circulating, A.2.5.1 (16.7%), beta lineage B.1.1.351 (50%) delta, lineage B.1.1.617.2 (16.7%) and B.1.623 (16.7%). In July 2021, the variants beta lineage B.1.1.351 (45.5%) and delta lineage B.1.1.617.2 (54.5%) remained in co-circulation. In August 2021, only delta lineage B.1.1.617.2 (100%) was identified and in December 2021 delta lineage B.1.1.617.2 (45.5%) was again detected in cocirculation with the omicron variant B.1.1.529 (54.5%).

From that date and for the remaining 17 months of the study, only the omicron variant or one of its subvariants was detected in the sequenced samples, except in March 2022, where pattern 4 was also identified: D614G + Q677H (Figures 1 A and B).

Figure 1A relates the variants to the number of confirmed cases of SARS-CoV-2, the highest incidence was in September 2021 with 16855 (27.6%) cases. Figure 1 B shows that, in this series, the highest number of deaths (166) was in September.

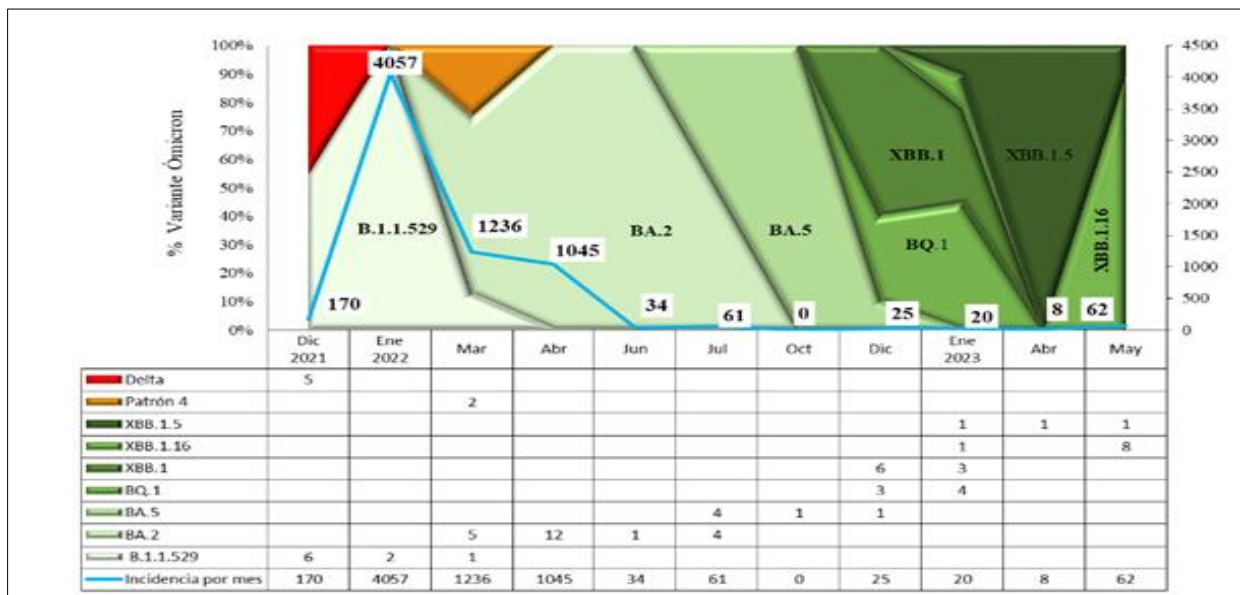
From December 2021 to May 2023 61.3% (65/106) of the sequenced samples corresponded to omicron or some of its sublineages.

Figure 2 shows the period from January to March 2022 where omicron B.1.1.529 was detected. In that quarter, the number of cases increased to 6371 and 19 deaths were reported, compared to November (726 cases and 5 deaths) and December (170 cases and 0 deaths) 2021.

Omicron BA.2 circulated from March to July 2022 and sublineage BA.5 was detected from July 2022 to December, a period in which 131 cases were diagnosed in the province. In December and January 2022, BQ.1 and XBB.1 sublineage are reported circulating in the province, months in which a slight increase in cases occurred.

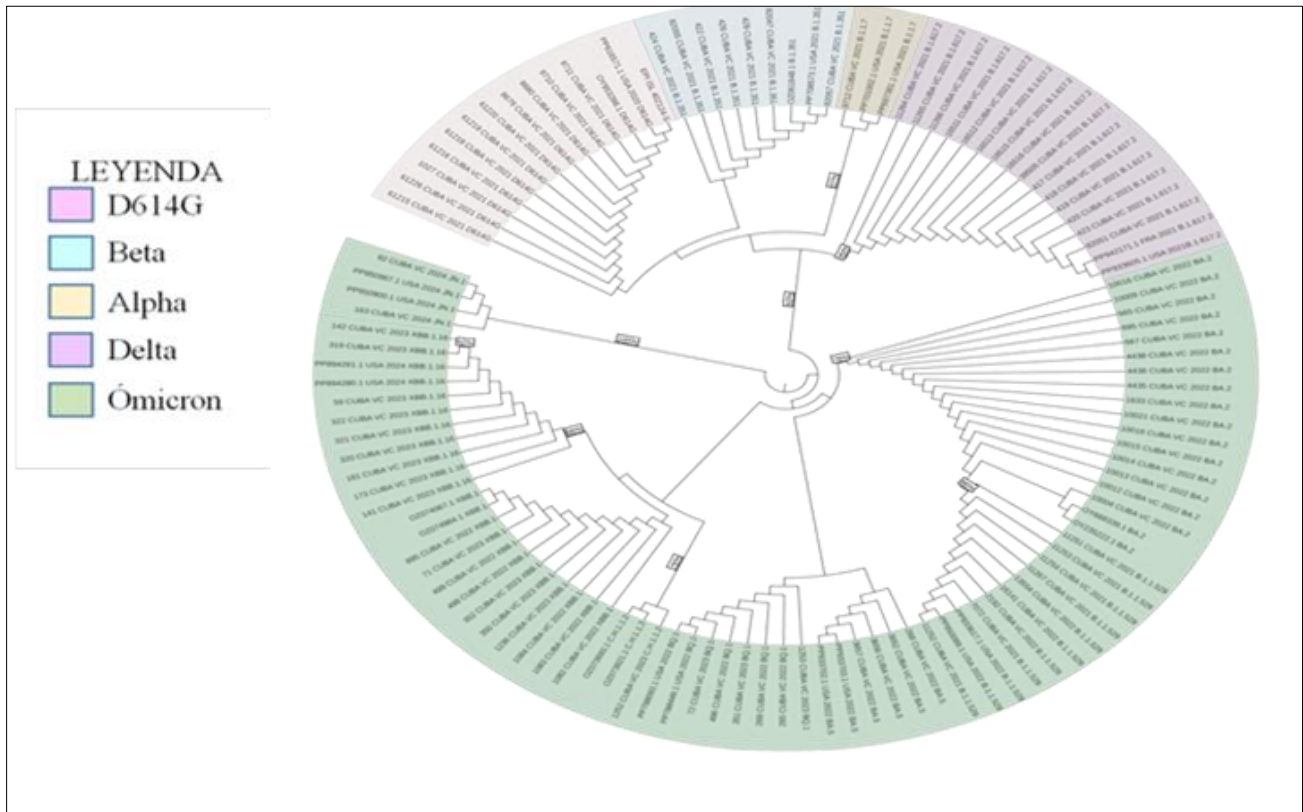
The XBB.1.16 and XBB.1.5 sublineages co-circulated from January 2023 until the end of the study in May, during which time the province reported 98 cases of COVID 19.

From June 2022 to May 2023, the completion date of the study, two-digit numbers of case incidences were reported and no deaths were reported (Figure 1 and 2). During this period, subvariants BA.2, BA.5, BQ.1, XBB.1, XBB.1.1, XBB.1.16, XBB.1.5 were detected circulating (Figure 2).



**Figure 2** Distribution of cases with omicron variant with its sublineages, detected by month in Villa Clara from December 2021 to May 2023. Patrón 4: D614G + Q677H

For the confection of the phylogenetic tree, and evolutionary history was inferred using the Maximum Likelihood method based on the three-parameter model of Tamura *et al.* (2013).



Source: registry of sequenced cases at LNR-IPK

**Figure 3** Phylogenetic tree with partial sequences of the SARS-CoV-2 S nucleotide gene

#### 4. Discussion

In Villa Clara, each variant of SARS-CoV-2 circulated in certain months; it was not detected that any variant was perpetuated over time simultaneously with others. The distribution of variants changes over time according to the emergence and expansion of those with greater evolutionary advantage (Machado *et al.*, 2024).

The variants detected in the province in the three epidemic periods did not have the same impact; the epidemiological and clinical aspects of COVID-19 are modified according to the variant circulating (Tao *et al.*, 2021; Guzmán *et al.*, 2022).

Since the first cases of COVID-19 in the world, more than 20 variants, with multiple lineages, of SARS-CoV-2 have been described; with a predominance of one viral variant in each pandemic peak (Abu-Raddad *et al.*, 2022; Pérez *et al.*, 2022a; Machado *et al.*, 2024). In Villa Clara, each epidemic wave was characterized by competition between variables for the establishment of one of them.

In Villa Clara, from March 2020 to April 2021, months in which the circulation of D614G was estimated, was the epidemic period with the lowest incidence in the series; this could be determined by the rigor of confinement, the closure of airports, the use of masks and other sanitary measures; despite the fact that patients infected with the D614G mutation have higher levels of viral RNA (Pérez *et al.*, 2022a; Machado *et al.*, 2024). This mutation has been associated with increased virulence, transmissibility and viral survivability (Suarez, 2021; Perez *et al.*, 2022b; Machado *et al.*, 2024).

Regarding mortality due to D614G, 19 persons died in the province. Cuba from March to May 2020, presented the highest case fatality rate ranging between 2.83%, 4.38% and 3.79% respectively due to the low number of diagnosed cases and the lack of experience in the clinical management of this new disease (Guzmán *et al.*, 2022; Machado *et al.*, 2024).

The global prevalence of D614G during 2020 reached approximately 100%; due to the evolutionary genetic selection pressure of SARS-CoV-2 (Amanat and Krammer, 2020; Chowdhury *et al.*, 2021; Abu-Raddad *et al.*, 2022). In Cuba until November 2020, the D614G variant was detected in more than 90% of sequenced samples (Pérez *et al.*, 2022a, b; Guzmán *et al.*, 2024; Machado *et al.*, 2024); moreover, D614G predominated in the country from January to March 2021 (Pérez *et al.*, 2022b; Guzmán *et al.*, 2024).

In Cuba, Alpha was detected in December 2020 (Guzmán *et al.*, 2024), and was not associated with an increase in cases and deaths (Durán, 2022; Portal, 2022). In Villa Clara, even when the borders were open and vaccination had not been initiated in the country, no increase in cases was reported. This could be due to the fact that the beta and delta variants with greater infection capacity were beginning to circulate (Guzmán *et al.*, 2022).

However, Alpha in the USA and European countries was associated with increased transmissibility, increased risk of reinfection and reduced vaccine efficacy; it is estimated that mortality increased by 50% (Tao *et al.*, 2021).

Variant A.2.5, originally described in California, USA, was identified in Cuba at the end of December 2020 and spread throughout the country until May (Guzmán *et al.*, 2024). In Villa Clara, A.2.5 and B.1.623 did not change the incidence of cases or deaths in the province.

The beta variant was first reported in Nelson Mandela Bay, South Africa, in October 2020 (Aguilar *et al.*, 2021). Infection with the beta variant was associated with even higher risks of severe and critical illness and death related to COVID-19 (Abu-Raddad *et al.*, 2022; Vogt *et al.*, 2023).

In Cuba, this variant, initially detected in Havana at the end of December, progressively spread to the rest of the country (Durán, 2022; Guzmán *et al.*, 2024). Beta B 1.351 was associated with significant increases in the number of cases and decreased neutralizing antibody response to different vaccine formats, as well as a possible risk of hospitalization, clinical severity and mortality (Machado *et al.*, 2024).

In Villa Clara, the beta variant was detected co-circulating with the delta variant, and the incidence and deaths attributable to each variant separately could not be determined. In the period of beta and delta co-circulation in the province, the greatest increase in cases and deaths occurred in the present study; similar to what occurred in other studies (Expósito *et al.*, 2021; Suárez, 2021; Guzmán *et al.*, 2022; Machado *et al.*, 2024).

A study of severe and critical cases in Havana showed in 87.7% of patients the variant reported in South Africa (Pérez *et al.*, 2022b; Machado *et al.*, 2024); and it was detected in 80.4% of deaths. This variant was also present in 68.1% of the deceased in the country (Guzmán *et al.*, 2024; Machado *et al.*, 2024).

In Qatar, beta infection was associated with increased risks of severe, critical illness and COVID-19-related death. Intensive care (ICU) admissions doubled during the beta wave, but ICU admissions and deaths quadrupled, with the disproportionately greater effect of this variant on critical illness and COVID-19-related deaths (Abu-Raddad *et al.*, 2022).

The delta variant B.1.617.2, was responsible for the second deadly wave of COVID-19 infections in April 2021 in India (Aguilar *et al.*, 2021). In August 2021, it became the dominant variant (Shiehzhadegan *et al.*, 2021). The increased infectivity of the variant is a combination of key mutations that give the spike protein a higher affinity to bind to ACE-II, reduced efficacy of vaccines against it, and higher viral loads in infected individuals (Nomier *et al.*, 2020; Shiehzhadegan *et al.*, 2021).

The delta variant, detected in Matanzas province, Cuba in late April 2021, within two months spread rapidly to the rest of the provinces (Guzmán *et al.*, 2024).

The delta variant, which had been circulating in Villa Clara since May 2021, was the only variant detected in August 2021, a month with a high incidence (14371/24%) and mortality (148/34%) in this series.

The first half of 2021 in Cuba was characterized by a difficult epidemiological situation due to the increase in serious, critical and deceased patients and the impossibility of purchasing vaccines against SARS-CoV-2 given the economic situation caused by the intensification of the blockade, commercial and financial measures imposed by the Government of the United States (Portal, 2022).

According to GISAID, 90% of the global sequences from June to September 2021 were delta (Guzman *et al.*, 2024). The delta variant was predominant until December 2021, thereafter it was being displaced by the omicron variant (Suarez, 2021; Guzman *et al.*, 2024); this variant, the first case had been reported on November 24, 2021 in Botswana (Aguilar *et al.*, 2021). In December 2021, the omicron variant (B.1.1.529) of SARS-CoV-2 rapidly became dominant worldwide (Monge *et al.*, 2022; Rodriguez *et al.*, 2023).

As in other countries, omicron emerged in Cuba when delta was the predominant circulating variant and rapidly displaced it, due to its higher transmission rate, infectivity and evasion of vaccine-induced immunity. At that time, Cuba was in a favorable epidemiological context with a low number of new cases and an extremely low number of deaths (Pérez-Santos *et al.*, 2022b; Portal, 2022).

On December 1, 2021 in Cuba, omicron was identified for the first time (Guzman *et al.*, 2024), and in the same month the first detection of this variant is made in Villa Clara; omicron drove an increase in diagnosed cases worldwide (Lewnard *et al.*, 2022; Strasser *et al.*, 2022).

In Villa Clara the arrival of omicron B.1.1.529 modified the clinical-epidemiological scenario; despite the fact that 91.8% of the population of the province had a complete vaccination schedule with Abdala and Soberana; cases increased in January 2022 in relation to the months of November and December 2021.

When only omicron was circulating in Cuba in January 2022 (Durán, 2022; Guzmán *et al.*, 2024), fatal cases increased in Villa Clara in relation to the two preceding months. Strasser *et al.* (2022) in New England report a mortality rate of 0.4% for omicron B.1.1.529, lower than the delta mortality rate.

In an investigation in Cuba, omicron was detected in 83.0% (239/288) of the cases processed. They were fully vaccinated (65.3%; 156/239); severe cases and deaths occurred mainly among patients aged  $\geq 65$  years (92.9%; 13/14), and 12 of these deaths occurred in fully vaccinated persons (92.3%; 12/13) (Pérez-Santos *et al.*, 2022c; Guzmán *et al.*, 2024). The study concludes that, although the number of cases also increased, case fatality rates did not increase proportionally (Guzman *et al.*, 2024).

The peak of the first wave of omicron in Cuba occurred in January of the second to fourth weeks of 2022. The Cuban wave was less intense compared to the United Kingdom, United States and Germany, with high vaccination coverage (Pérez-Santos *et al.*, 2022a, b).

In Cienfuegos, a province adjacent to Villa Clara, in a study in January and February 2022, during the circulation of the omicron strain in 50 adult patients with COVID-19 admitted to the Intensive Care Unit, 28.0% of the patients received mechanical ventilation and 21 died; this was attributed to the predominance of advanced age and the presence of comorbidities related to non-communicable diseases, which may have influenced the high lethality (Avello *et al.*, 2023).

The presence of the omicron variant also caused the highest incidence rates of COVID-19 ever recorded worldwide, even in countries with high vaccination coverage such as Spain (Monge *et al.*, 2022). In elderly residential centers in Spain, these rates were as high as three times those observed during the period of delta variant predominance (Monge *et al.*, 2022; Rodríguez *et al.*, 2023).

The severity of SARS-CoV-2 decreased in individuals infected with omicron could be influenced by treatments, vaccines and previous infections (Pérez-Santos *et al.*, 2022b; Strasser *et al.*, 2022; Guzmán *et al.*, 2024); however, the incidence was possibly increased because acquired immunity might not be as effective due to the significant number of mutations acquired by omicron compared to the other variants. As a result, omicron was able to infect people who still had immunity against the delta variant (Amanat and Krammer, 2020; Chowdhury *et al.*, 2021; Sunetra, 2023).

On the other hand, the milder behavior may have been due to the salient characteristics of coronaviruses, that immunity against infection is short-lived, whereas immunity against severe disease is long-lived; most people had already acquired immunity against severe disease (Sunetra, 2023).

In Villa Clara, the circulation of omicron subvariant BA.2 was detected in March 2022 until July; in those five months, 2 560 cases of COVID 19 were reported in the province, and in March, when BA.2 and omicron (B.1.1.529) were co-circulating, the last two deaths attributed to COVID 19 occurred in the province, up to the date of completion of this study. The BA.2 omicron subvariant lineage of SARS-CoV-2 is inherently less severe than the delta and omicron variants (Strasser *et al.*, 2022; Guzman *et al.*, 2024).

Many countries and regions experienced successive waves of infections caused by omicron sublineages, mainly BA.2 and BA.5 (Bordoy, 2024).

The first recombinant lineages, XBB and derivatives, which were successful enough to displace their relatives the XBB.1.5, XBB.1.16, XBB.1.9, XBB.2.3, EG.5.1 (XBB.1.9.2.5.1) and HK.3 (XBB.1.9.2.5.1.1.3) lineages coexist in a period of great genetic diversity and convergent evolution known as the "variant soup" (Bordoy, 2024).

SARS-CoV-2 variants differ in their transmission rates, disease severity and risk of reinfection (Fang *et al.*, 2020; Grubaugh *et al.*, 2020; Tao *et al.*, 2021). In Cuba, a greater association of the beta variant with clinical severity and the delta variant with greater transmissibility was observed (Guzmán *et al.*, 2024).

In Villa Clara, the most intense epidemic period was concentrated in four months, from July to October 2021; 46 633 (78.0%) cases and 388 (89.4%) deaths were reported.

The phylogenetic analysis of the sequenced samples from Villa Clara showed that the sequences identified are grouped into five major clades that are formed according to variants. Two of the sequences (61226 and 61215), of the D614G variant, presented a greater length of the branch, related to a greater number of substitutions, in critical patients. When analyzing the clade in which the beta variant sequences are grouped, most are genetically similar, only one (32057) showed a higher number of mutations, related to a deceased patient. It is noteworthy that the branch that grouped the omicron variant showed a high genetic diversity, two new branches arise from this clade, one of them showed higher variability. The branches formed are grouped according to the sublineages BA2, B.1.1.529, BA5, BQ1, XBB1, XBB.1.16, JN1).

#### *Limitations of the study*

Performance of sequencing studies not available in all months of the pandemic period as determined by laboratory sequencing capacity.

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## **5. Conclusion**

In Villa Clara, the D614G, beta, delta and omicron variants originated the epidemic waves. In the province, the most intense epidemic period was concentrated in four months, from July to October 2021. The responsibility for this high incidence and mortality was attributed to the beta and delta variants, without being able to specify whether it was one or both of them.

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## **Compliance with ethical standards**

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#### *Disclosure of conflict of interest*

No conflict of interest exists among the Authors.

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