Tracing the trajectories of SARS-CoV-2 variants of concern between December 2020 and September 2021 in the Canary Islands (Spain)

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Several variants of concern (VOCs) explain most of the severe acute respiratory
syndrome coronavirus 2 (SARS-CoV-2) epidemic waves in Europe. We aimed
to dissect the spread of the SARS-CoV-2 VOCs in the Canary Islands (Spain)
between December 2020 and September 2021 at a micro-geographical level.
We sequenced the viral genome of 8,224 respiratory samples collected in the
archipelago. We observed that Alpha (B.1.1.7) and Delta (B.1.617.2 and
sublineages) were ubiquitously present in the islands, while Beta (B.1.351) and
Gamma (P.1/P.1.1) had a heterogeneous distribution and were responsible for
fewer and more controlled outbreaks. This work represents the largest effort
for viral genomic surveillance in the Canary Islands so far, helping the public
health bodies in decision-making throughout the pandemic.

Introduction

The continuous emergence and international widespread of variants of concern (VOCs) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have revealed the occurrence of multiple viral spike gene mutations that promote increased transmissibility and some degree of immune escape (Tao et al., 2021). In response, the public health system activated the organization of centers for routine viral genome surveillance starting in mid-January 2021 in our laboratories, which were later distinguished as the Reference Centre for the Network of COVID-19 Genomic Surveillance in the Canary Islands.

We have previously tracked the entrance and surge of one of the three most widely distributed VOCs, B.1.1.7 [Pango lineage nomenclature (Rambaut et al., 2020)], or Alpha variant (WHO, 2022), in December 2020 in Tenerife (Alcoba-Florez et al., 2021) due to the island direct flight connections with the United Kingdom where it may have originated. This lineage has been associated with increased transmissibility (Davies et al., 2021; Volz et al., 2021) compared to the previously circulating variants, a feature that has been linked to the presence of the mutation N501Y in the Spike (S) receptor-binding domain (RBD). Other VOCs that have also emerged in late 2020 are B.1.351, or the Beta variant, and P.1/P.1.1, or the Gamma variant, firstly identified in South Africa (Tegally et al., 2021) and in Brazil (Faria et al., 2021), respectively. These lineages have been associated with increased transmission (Faria et al., 2021; Pearson et al., 2021; Tegally et al., 2021) and carry multiple mutations affecting the RBD, most importantly the N501Y (such as Alpha), as well as K417N/K417T and E484K that reduce the effectiveness of some vaccines (Garcia-Beltran et al., 2021) and specific monoclonal antibody treatments (Greaney et al., 2021; Harvey et al., 2021). Later in time, lineage B.1.617.2, or the Delta variant, was identified in India where it was responsible for a surge of coronavirus disease 2019 (COVID-19) cases in April 2021 (Dhar et al., 2021). The Delta (B.1.617.2) variant presented additional mutations, such as the L452R in the RBD and the P618R, and has been characterized by higher transmissibility (Campbell et al., 2021b) and reduced sensitivity to antibody neutralization (Planas et al., 2021; Wall et al., 2021) and vaccine effectiveness (Lopez Bernal et al., 2021; Planas et al., 2021). From the Delta variant, numerous sublineages have emerged, reporting the presence of additional mutations such as the Y145H and the Y222V in the N-terminal domain of the S protein found in the AY.4.2 lineage (Gangavarapu et al., 2022), which was suggested to be more transmissible than the original variant (Public Health England, 2021). Delta and its sublineages became prevalent and completely displaced Alpha worldwide throughout the summer of 2021 (WHO, 2022).

Here, we describe the introduction and temporal evolution of these four VOCs in the Canary Islands (Spain). The archipelago is formed by eight islands, four occidental

(Tenerife, La Palma, La Gomera, and El Hierro) belonging to the Tenerife province and four oriental islands (Gran Canaria, Fuerteventura, Lanzarote, and La Graciosa) belonging to the Gran Canaria province (Figure 1). Throughout the study period (18 December 2020 to 29 September 2021), there were a total of 70,401 reported COVID-19 cases and 489 COVID-19 deaths in the archipelago, with the islands of Tenerife and Gran Canaria accounting for most of them (60,069 COVID-19 cases and 421 deaths) (https://opendata.sitcan.es/dataset/datos-epidemiologicos-covid-19).

The relative geographical isolation of the archipelago and its islands and their central role as a hub for international tourism and in the European migratory crisis have shaped the COVID-19 pandemic and delineated the introduction and spread of these VOCs in the territory. In fact, the first SARS-CoV-2 outbreaks in Spain were detected in La Gomera and Tenerife islands (January and February 2020, respectively; available reports from: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Informes%20COVID-19/Informe%20COVID-19.%20N%c2%ba%201_11febrero2020_ISCIII.pdf).

Methods

Design and sample collection

The study was conducted at the University Hospital Nuestra Senãora de Candelaria (HUNSC) (Santa Cruz de Tenerife, Spain). The institutional review board approved the study (approval number: CHUNSC_2020_24). We assessed nasopharyngeal swabs from COVID-19/SARS-CoV-2 patients from 18 December 2020 to 27 September 2021. Routine COVID-19 testing in the centers was conducted using diverse commercial RT-qPCR alternatives, as described elsewhere (Alcoba-Florez et al., 2020). In line with the guidelines indicated by the ECDC (European Centre for Disease Prevention and Control, 2021) and assuming a prevalence of 10,000 positive cases per month in the territory (https://opendata.sitcan.es/dataset/datos-epidemiologicos-covid-19), we estimated the sequencing of 12,000 samples a year for accurate tracking of viral variants (at 50% accuracy in prevalence estimates).

Viral genome sequencing and classification

Samples were selected for sequencing if they showed a cycle threshold (Ct) ≤30 for any of the amplicon targets included in the COVID-19 diagnostic kits. Libraries were prepared following either the Midnight protocol v.4 (Freed et al., 2020) by means of the Rapid Barcoding kit (SQK-RBK004, Oxford Nanopore Technologies) and sequenced on a MinION and an R9.4 flow
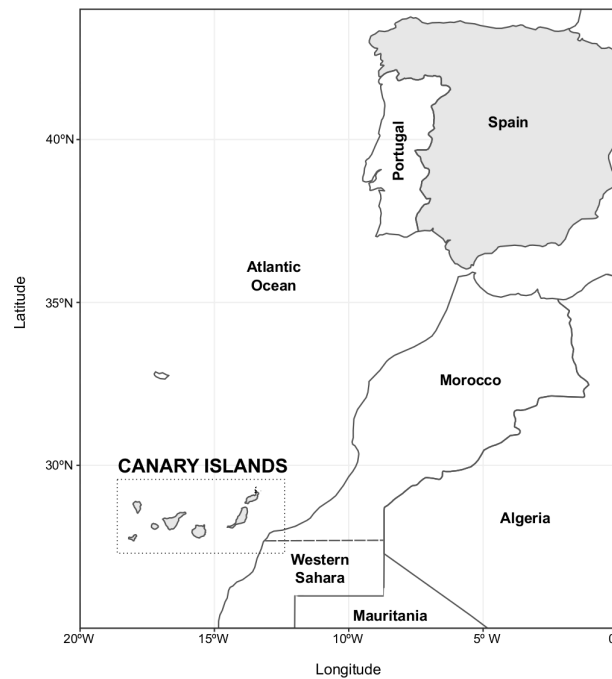
FIGURE 1
Geographical location of the Canary Islands with respect to the Iberian Peninsula and Northwest Africa.

cell (Oxford Nanopore Technologies) for 6 h or the COVIDSeq Test (Illumina, Inc.) protocol based on the ARTIC V3 amplicons and sequenced on a NextSeq 550 (Illumina) instrument on High Output mode with 36-bp single- or pair-end (after 7 September 2021) reads following the procedures described elsewhere (Alcoba-Florez et al., 2021; Ciuffreda et al., 2021). Positive and negative amplification controls were included in each run (one for each fraction of 94 samples).

The RAMPART (v.1.2.0) software package was used for real-time monitoring of the MinION sequencing run. Reads were basecalled and demultiplexed with Guppy 4.2.2 (high-accuracy mode), and the ARTIC Network bioinformatics procedures (https://github.com/artic-network/artic-ncov2019) were used for read filtering (by length, 250–1,500 bp), consensus assembly, and variant calling (nanopolish workflow with maximum coverage of 200×). The COVIDSeq Test reads were processed as described elsewhere (Alcoba-Florez et al., 2021) based on the DRAGEN COVIDSeq Test v1.2.2 pipeline and the DRAGEN Lineage v3.5.3 (Illumina, Inc.). Nextclade v.0.14.3 (Aksamentov et al., 2021) was used for variant calling and functional predictions. In the final analysis, sequences having a genome coverage less than 70% of the entire SARS-CoV-2 sequence and having a QC classified as "bad" by Nextclade software were excluded. Pangolin v3.1.1 (O'Toole et al., 2021b) was used for the classification of the consensus sequences. Microbetrace v0.8.2 (Campbell et al., 2021a) was used for

cluster investigation together with epidemiological data from the public health authorities.

Results

An overview of COVID-19 cases and sequenced samples in the Canary Islands throughout the study period is presented in Figures 2, S1. Of the 70,588 positive samples collected in the archipelago from 18 December 2020 to 27 September 2021, 11,956 (16.9%) were sequenced using either Illumina sequencing (11,936) or Oxford Nanopore Technologies (20). Of these, 8,224 samples passed the QC filtering steps and had an assigned lineage. In the period, 3,447 samples (41.9%) were assigned to Alpha, 138 (1.7%) to Beta, 47 (0.6%) to Gamma, and 3,262 (39.7%) to Delta and sublineages of Delta [1,066 (12.9%)], while 1,330 (16.1%) were assigned to other non-VOC lineages. Within the Delta sublineages, AY.4 (153) and AY.12 (119) were the most commonly found throughout the period. None of the Delta sublineages was assigned to AY.4.2 (also known as Delta plus).

The temporal distribution of the different VOCs in the Canary Islands is represented in Figure 3. Since there were relatively few samples sequenced from two of the smallest islands [La Gomera (n = 17) and El Hierro (n = 50)] (Figure S1) and the samples from La Graciosa were collected within those from Lanzarote, we excluded these islands from the following
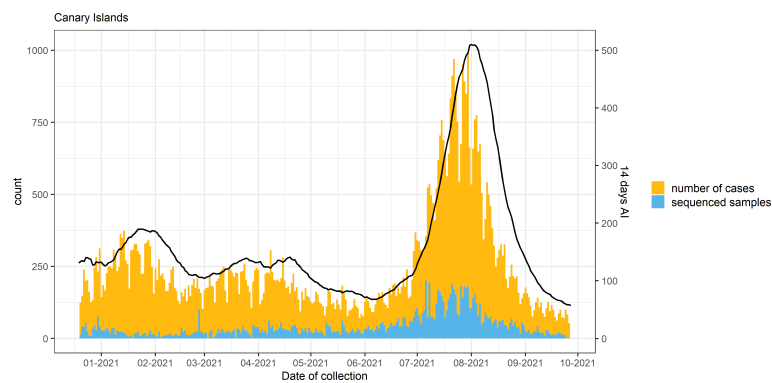
FIGURE 2
Number of cases, sequenced samples, and the 14-day accumulated incidence (AI; continuous line) throughout the study period in the Canary Islands archipelago.

description. As it was previously reported for Tenerife alone (Alcoba-Florez et al., 2021), the first description of Alpha in the Canary Islands occurred around 23 December 2020 and was associated with an increase in the 14-day accumulated incidence (Figure 3A). After that, the replacement of non-VOC lineages by the Alpha variant occurred more sharply in Gran Canaria and Lanzarote than in the other islands (Tenerife, Fuerteventura, and La Palma) with almost the totality of sequenced cases belonging to Alpha already by early February 2021 (Figures 3B, C).

Apart from a first imported case in La Palma at the end of January 2021 due to a traveler returning from Cameroon, community transmission of the Beta variant in the archipelago was first identified in the island of Gran Canaria, where a large cluster of 46 cases was observed between the end of March and mid-May 2021. At the beginning of April, a second small cluster of six cases was observed in Gran Canaria with no apparent connection to the first one. In Tenerife, three small clusters of an average of four cases were observed, one at the beginning of April and two throughout June. In mid-May, a second big cluster of 58 cases was observed in Gran Canaria that lasted up to the beginning of August, when the last case of this variant was observed. Almost no cases of the Beta variant were found on any other island throughout the study period. Cases of the Gamma variant were scarce and observed in Tenerife, Gran Canaria, La Palma, and Lanzarote up to the end of May 2021, when a cluster of 24 P.1.1 cases was observed in Fuerteventura. The Fuerteventura outbreak was associated with a religious celebration involving local residents and foreign visitors and lasted up to the middle of June. An overview of the Canary Islands archipelago geography and of the heterogeneous distribution of Beta and Gamma variants in the archipelago is presented in Figure 4.

Alpha, Beta, and Gamma lineages were replaced by the Delta variant that started circulating in Tenerife at the beginning of June 2021 (the first case detected in Tenerife on the 17th of May)

followed by its identification in all other islands probably due to multiple introductions of this variant in the archipelago. The presence of Delta was associated with a rapid surge of COVID-19 cases in all islands when the archipelago entered the fifth wave, and the highest number of cases was reached since the beginning of the pandemic. From the end of July 2021, the previous heterogeneous distribution of VOCs in the different islands converged to a similar figure, with Delta becoming prevalent and almost completely displacing all other variants circulating in the archipelago. At the beginning of August, the sublineages of Delta (mainly AY.4 and AY.12) started circulating in the islands, completely superseding Delta by the end of September 2021.

Discussion

In this work, we dissected the spread of VOCs in the Canary Islands archipelago in the period between mid-December 2020 and late September 2021. Through genome sequencing and lineage assignment of more than 8,000 SARS-CoV-2-positive nasopharyngeal swab samples, we were able to track the spatiotemporal distribution of the variants Alpha, Beta, Gamma, and Delta in the archipelago. We observed that the viral sequences detected in the islands were characterized by a diverse epidemiological background and variant distribution throughout the study, which can be largely explained by their geographical isolation and heterogeneous population size. While Alpha spread ubiquitously across the archipelago early after its first appearance in the island of Tenerife, Beta and Gamma variants were observed only in some of the islands and not in others. Beta was observed in the archipelago from late January up to August 2021, and its spatial distribution was mainly circumscribed to the islands of Gran Canaria and Tenerife, even though it was already present in several European
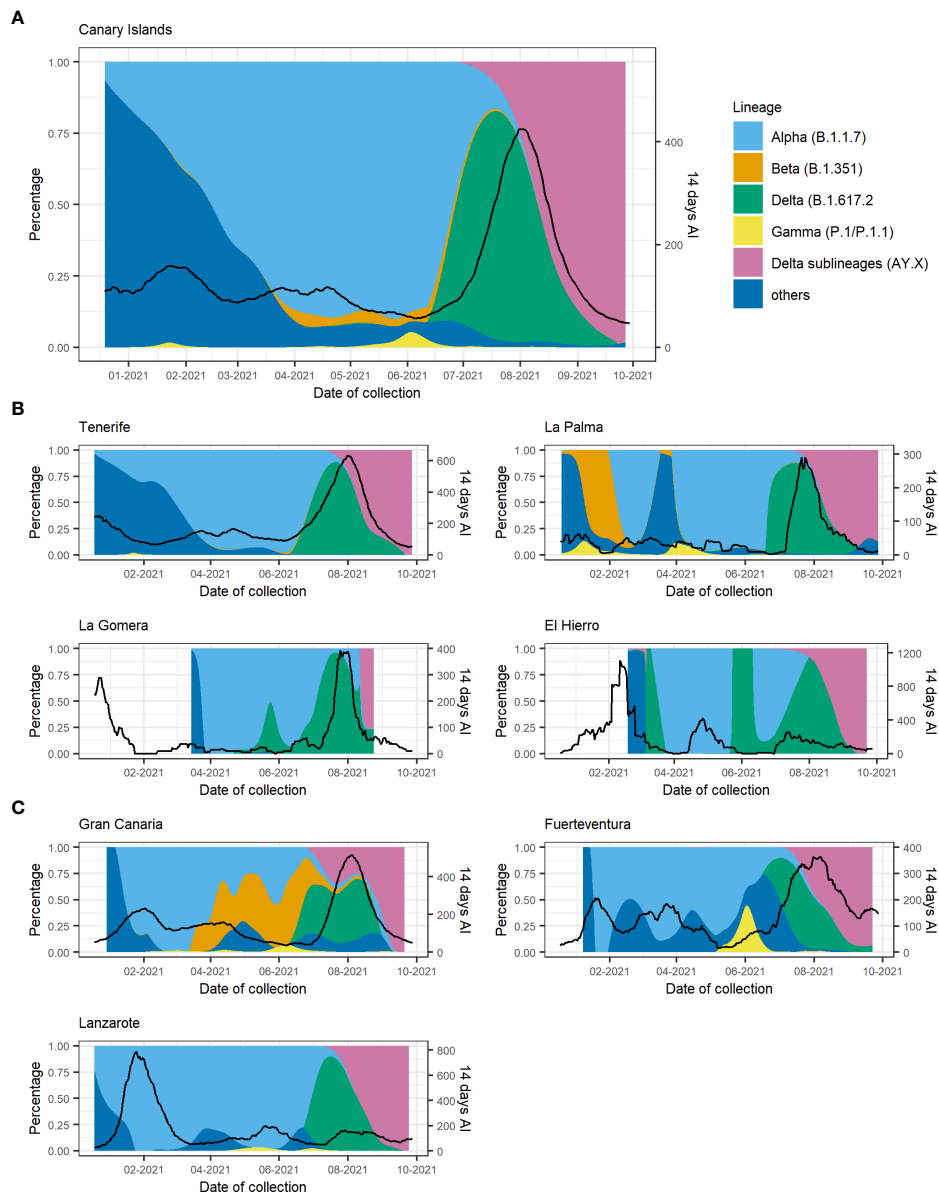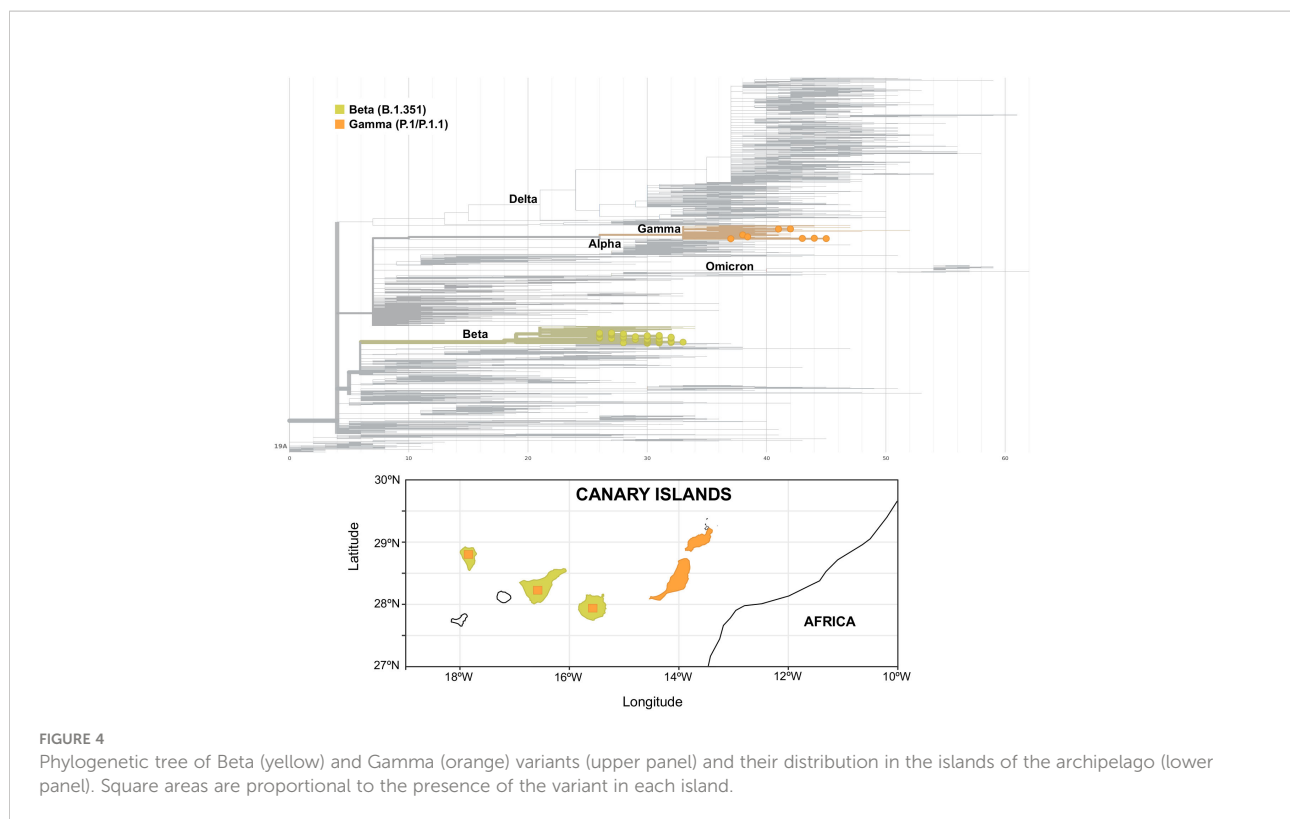
FIGURE 3
Proportion of variants of concern (VOCs) and the 14-day accumulated incidence throughout the study period for **(A)** the Canary Islands as a whole and disaggregated by island for **(B)** the Tenerife province and **(C)** the Gran Canaria province. Black lines depict the 14-day accumulated incidence. AY.X denotes the sublineages of Delta (B.1.617.2).

countries by mid-January (O'Toole et al., 2021a), representing up to 20% and 8% of cases in Austria and France, respectively, at that moment (Hodcroft, 2021). Cases associated with the Gamma variant were also relatively few, with a small cluster of cases observed in Tenerife in late January 2021, followed by isolated cases in the other islands. The largest Gamma cluster was a P.1.1 cluster observed in Fuerteventura. Both Beta and

Gamma did not spread throughout the archipelago such as Alpha did, something that was also observed in other European countries (Hodcroft, 2021). We can attribute this to two factors: 1) Alpha was largely spread in Europe and worldwide at that time, something that increases the likelihood of multiple introductions of this variant in the different islands of the archipelago; 2) travel restrictions were in place during the

FIGURE 4
Phylogenetic tree of Beta (yellow) and Gamma (orange) variants (upper panel) and their distribution in the islands of the archipelago (lower panel). Square areas are proportional to the presence of the variant in each island.

early months of 2021 (up to May 2021) and limited the spread of Beta and Gamma once they were introduced. When Delta emerged, it was associated with a surge of cases in the archipelago throughout the summer, mimicking what occurred in the United Kingdom (Riley et al., 2021) and in the rest of Europe (Hodcroft, 2021). We attribute this not only to the intrinsically higher transmissibility of the Delta variant compared to the previously circulating VOCs (Campbell et al., 2021b) but also to the concurrent lifting of COVID-19 restrictions in the archipelago and nationwide. Since August 2021, we observed the emergence of diverse Delta sublineages (AY.4 and AY.12), similar to what occurred worldwide throughout the summer (Angeletti et al., 2021; Eales et al., 2021).

In summary, as a response to the COVID-19 pandemic, we established a network for genomic surveillance of SARS-CoV-2 in the Canary Islands based on two sequencing technologies, leveraging homogeneous and centralized processing of samples, efficient sequencing workflows, rigorous data quality control, and accurate sequence classification. To do so, we relied on both previously existing capacities and human resources in the involved laboratories and the rapid dissemination of information over VOCs and open-source bioinformatics tools made available by researchers worldwide. We managed to sequence more than 15% of COVID-19 cases of the archipelago in the study period, aligning our sequencing strategy to the WHO and the ECDC recommendations. We

recognize sampling bias as a limitation of our study, with sample collection being not proportional to the number of cases in all islands. In fact, the island of Tenerife always had the highest percentage of sequenced samples mainly because the network was physically located in the island and therefore sample logistics was easier. Despite this, we managed to efficiently identify and track all VOCs in the Canary Islands since December 2020 and promptly inform the public health authorities in the region.

Data availability statement

Sequences in FASTA format have been deposited in GISAID with EPI_ISL codes ranging in the following intervals: 14072942-14073924, 14076844-14076860, 14091532-14092460, 14094040-14094110, 14094631-14095630, 14100149-14101148, 14102007-14103006, and 14103347-14103889.

Ethics statement

The study was conducted at the University Hospital Nuestra Senãora de Candelaria (HUNSC) (Santa Cruz de Tenerife, Spain). The institutional review board approved the study (approval number: CHUNSC_2020_24). Written informed consent for participation was not provided by the participants'

legal guardians/next of kin because: For Public Health reasons linked to the COVID-19 emergency.

Author contributions

JA-F and CF planned the experiments and supervised the project. LC, RG-M, DG-MdA, HG-C, HR-P, AI-C, IDM-M, TT-N, OD-G, and JL-S collected the samples and conducted the sequencing experiments. LC, JL-S, AV-F, and CF performed the analysis and interpreted the results. CF obtained the funding. LC, JL-S, and CF drafted the first version of the manuscript and prepared the figures. All authors contributed to manuscript revision and read and approved the submitted version.

Funding

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

The Supplementary Material for this article can be foundonline at: https://www.frontiersin.org/articles/10.3389/fcimb.2022.919346/full#supplementary-material

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