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SARS-CoV-2 Variants Distribution and Infections in Vaccinated and Unvaccinated Hospitalized Individuals in the Dominican Republic.

Paulino-Ramírez, Robert[1*]; Rojas-Fermín, Rita[2,3*]; Cuevas, Paula[1]; Tapia, Leandro[1]; Vallejo Degaudenzi, Alejandro[1]; Mueses, Sayira[1]; Calderón, Victor Virgilio[1]; Jabier, Maridania[1]; Ruiz, Ingrid[1]; Guzmán -Marte, Anel[4]; Tolari -Jacobo, Gilda[4]; Sánchez -Marmolejos, Ann[2]; Cuevas Lantigua, Gabriella[2].

[1]Instituto de Medicina Tropical & Salud Global, Universidad Iberoamericana (UNIBE), Santo Domingo 22333, Dominican Republic

[2]Clinical Research Department, Hospital General de la Plaza de la Salud (HGPS), Distrito Nacional, Santo Domingo, Dominican Republic

[3]Infectious Disease Department, Hospital General de la Plaza de la Salud (HGPS), Distrito Nacional, Santo Domingo, Dominican Republic

[4]Microbiology Laboratory, Hospital General de la Plaza de la Salud (HGPS), Distrito Nacional, Santo Domingo, Dominican Republic

Correspondent: Robert Paulino-Ramírez, Instituto de Medicina Tropical & Salud Global, Universidad Iberoamericana (UNIBE), Santo Domingo, 22333, Dominican Republic.

E-mail: r.paulino1@unibe.edu.do

Author´s List

Robert Paulino-Ramirez- r.paulino1@unibe.edu.do

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SARS-CoV-2 Variants Distribution and Infections in Vaccinated and Unvaccinated Hospitalized Individuals in the Dominican Republic.

ABSTRACT

First cases of coronavirus disease 2019 (COVID-19) in the Dominican Republic (DR) were reported in early 2020. During the first trimester of 2021 a national vaccination campaign was deployed, including whole-virus inactivated, adenovirus-based, and mRNA vaccines platforms. To better understand the effectiveness and efficiency of vaccines to reduce COVID-19 related deaths, among vaccinated (2-doses), unvaccinated and partially vaccinated (1-doses), and SARS-CoV-2 variants we analyzed clinical and molecular data obtained from breakthrough infections in hospitalized individuals. Samples from SARS-CoV-2 infected hospitalized patients were collected for viral sequencing. During the study period, we analyzed the data of thirty-three (n=33) COVID-19 case-patients from June to September 2021. Studied cases reported receiving a whole-virus attenuated vaccine (CoronaVac) in 36.8%. The survival rate among two-dose vaccinated individuals was 73% (95% CI, 70.8 to 74.2) compared to 65% in unvaccinated individuals. Molecular variant analysis of variant circulation among infections was initially due to B.1.621 (Mu) and rapidly shifting to B.1.617 (Delta) variants. No differences in outcomes between Mu, Iota, or Delta infections were observed. This suggests that VOIs can also have a deleterious impact on vaccinated individuals.

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INTRODUCTION

First cases of coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), in the Dominican Republic (DR) were reported in early 2020 being the ancestral D614G the most prevalent [1] (Figure 1A); since that, a cumulative mortality rate has been ranging 0.87%-1.03%[2]. These indicators have been associated with the "Stay at Home" policy, generalized lockdowns, circulation impediments from and out large cities, population age and health status, a resilient health care system, and more recently the impact on vaccination campaigns[3]. During the first trimester of 2021 a national vaccination campaign was deployed, including whole-virus inactivated, adenovirus-based, and mRNA vaccines platforms. However, many barriers have caused stagnation in vaccine coverage. As of February 2022, less than 65% has a complete or partially complete protocol with either vaccine platform[4]. These figures have been representing a public policy challenge in the DR, reinforced with the fast identification of virus variants that provokes pressing importance to better understand host neutralizing antibodies and viral evasion.

Like many Low-to-Middle Income Countries (LMIC), genomic surveillance systems are scanty and costly in the DR, requiring trained personnel, resources, and sophisticated platforms that have an impact in previously affected economies[5,6]. Data collection on epidemic metrics are incomplete hence the rapid mutational variability of SARS-CoV-2 variants, therefore, decision-makers are aimed to rapidly conduct public health interventions. During the half first year of the pandemic, viral phylogenetic and phylodynamic were slowly progressing in mutational variability, however, viral diversity increased when in December 2020 the first variant of concern (VOC) B.1.1.7, later named Alpha by the World Health Organization (WHO) was detected[7]. VOC and variants of interest (VOI) are hierarchized for global monitoring based on their increase in transmissibility,

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virulence, and decrease in the effectiveness of public health measures including vaccines and therapeutics.

Some studies have reported differences in infection outcomes related to circulating variants in different scenarios. Moreover, VOCs like B.1.617.2 (Delta) and B.1.351 (Beta) have been associated with an important immune evasion of pre-existing circulating antibodies, and therefore affecting vaccine-induced immunogens. In contrast, some studies demonstrated that infections, hospitalizations, and death rates are largely associated with vaccination status and it seems not to be affected by the circulating variant[8]. However, transmissibility does occur among vaccinated individuals but exhibits faster clearance[9]. Which might be associated to rapid neutralization and circulation among specific populations. On January 2021, a VOI B.1.621 named Mu was reported in Colombia[7] (Global Influenza Surveillance and Response System (GISAID) accession number EPI_ISL_1220045. This VOI rapidly replaced P.1 (Gamma) transmission chains in Colombia and was first reported in the DR on April 23rd, 2021 (EPI_ISL_3188597), and VOC B.1.617.2/AY.X (Delta) and its lineages were reported on January 13th, 2021. Most of Mu variants harbor the T95I and YY144-145TSN mutations in the N-terminal domain; and the D614G, P681H, and D950N mutations in other regions of the spike protein, the R346K, E484K, and N501Y mutations in the receptor-binding domain, of these E484K has been associated to antibody evasion, and cross-neutralization of infection-induced antibody responses[10]. Assays performed with serum samples from BNT162b2 vaccine recipients showed similar neutralization when compared with the ancestral variant B.1[11].

These findings are of particular importance for LMIC like DR, where vaccination coverage is still low, and existing genomic surveillance data indicates co-circulation of several VOCs and VOIs since December 2020[12]. (Figure 1B) To better understand the effectiveness and efficiency of vaccines, among vaccinated (2-doses), unvaccinated and partially vaccinated (1-doses), and SARS-CoV-2 variants we analyzed clinical and molecular data obtained from infections in hospitalized individuals.

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METHODS

Clinical Isolates

A total of 33 samples were obtained from polymerase-chain-reaction (PCR)-confirmed SARS-CoV-2 infection at *Hospital General Plaza de la Salud* (HGPS) located in Santo Domingo, Dominican Republic. Demographic and clinical data were collected during admission and posterior hospitalization. Criteria for case selection among 18 years old with a positive SARS-CoV-2 PCR test performed on-site and breakthrough infection defined as a confirmed infection after vaccination with coronavirus infectious disease 2019 (COVID-19). Sample selection criteria were based on a cycle threshold of 32 (Ct <32) to assure better sequencing quality. Samples were collected during June-September 2021. The institutional review board at *Universidad Iberoamericana* (UNIBE) (CEI# 2020-16), and *Hospital General Plaza de la Salud (HGPS)* approved this study.

Extraction and amplification

Samples were processed at the molecular biology laboratory at *Instituto de Medicina Tropical & Salud Global* (IMTSAG-UNIBE) for the amplification of SARS-CoV-2 RNA. RNA was extracted and purified with automated liquid handling workstations for nucleic acid e xtraction nucleic acid extractor automat (AdvanSure ™ E3 System; LG Chem, Seoul, Korea) following the manufacturer's instructions. Subsequent amplification was carried out on a Tianlong Gentier 96E/96R Real-time PCR system (Xián Tianlong Technology Co., Ltd, China). We utilized Virella SARS-CoV-2 seqc RT-PCR Kit (Gerbion GmbH & Co, Germany) following the instructions of the manufacturer.

Genome sequencing

Library preparation was performed using an automated version of the NEBNext ARTIC SARS-CoV-2 companion kit (NEB# E7660S/L) with an Opentrons liquid handler. To optimize sequencing, we modified the standard protocol with incubation time for cDNA synthesis was

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changed to 25 minutes; modified incubation time for end preparation was changed to 15 minutes each; for barcode, ligation was increased to 40 minutes; and increased released incubation time for adapter-ligated step by 5 minutes. We assessed the purity and concentration of each sample by using a NanoDrop spectrophotometer. Flow cell priming was performed with Oxford Nanopore SQK-109 ligation sequencing Kit as recommended by the manufacturer.

The Artic Network protocol was reproduced completely choosing a run time of 24 hours to ensure representation. Data processing began with base calling the raw Fast5 data produced by the sequencer. Base-calling was performed post-sequencing with Guppy Basecaller version 5.0.7. https://community.nanoporetech.com/). Run configuration was "-c dna_r9.4.1_450bps_fast.cfg". Demultiplexing and read filtering were performed so both barcodes at each end have a read length between 400 and 700 base pairs. Demultiplexed and filtered reads were then processed through the *artic minion* pipeline (https://github.com/artic-network/fieldbioinformatics) Genomes obtained were visually curated with IGV genome browser[13]. Consensus genomes obtained from these processes were compared to NextStrain[14] clade tool (https://clades.nextstrain.org) where the proper clade was identified. To perform phylogenetic analysis, other relevant genomes were downloaded from the GISAID database. Phylogenetic and molecular evolutionary analyses were conducted using MEGA version 11[15].

Data analysis

The primary endpoint was to identify the sequence of breakthrough cases of SARS-CoV-2, the baseline characteristics, and the impact of prior vaccination on their outcome. For our analysis, we represented continuous and categorical measurements and compared them with Anderson Darling and D'Agostino-Pearson omnibus to assess normality. We also utilized a multiple regression model for the analysis of our covariates (adjusting for age and sex, days of hospitalization, ICU admission, vaccination status, pregnancy, and smoking history) to investigate the association of previous vaccination with hospitalization outcomes and sequenced

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genome of SARS-CoV-2. All analyses were performed using GraphPad Prism version 9.3.0 for Windows, GraphPad Software, San Diego, California, USA (www.graphpad.com).

RESULTS

During the study period, we analyzed the data of thirty-three (n=33) COVID-19 case-patients from June to September 2021. We analyzed the cases into 2 groups: Living (n=25) and deceased (n=8) with reported clinical records and outcome of infection (Figure 1C). All cases during the study period were included in the demographic analysis (Table 1). The locality of Santo Domingo represented the highest percentage of living patients 64% (n=16) and deceased patients 62.5% (n= 5). We found a slightly uneven distribution of male to female ratio in survival with 48% (n=12) living males and 52% (n=13) living females. While the deceased outcome frequency in males was higher 63% (n= 5) compared with females 38% (n=3). The mean age of study participants was 65 years (SD =16.2).

Among the 33 studied patients, 74% (n=14) with a complete vaccination scheme (2-doses) and 25% (n=5) with an incomplete vaccination scheme (1-dose). None of them reported having a booster jab of either whole-virus attenuated, adenovirus, or mRNA vaccine, despite being recommended by the local health authorities at the moment. Of these, 68% received a 2-doses of CoronaVac, and Oxford/AstraZeneca (5%). Among those with a 1-dose schedule, 21% received CoronaVac, and 5% received BioNTech/Pfizer. Prevalence of ≥1 underlying comorbidities was reported for all age groups, and cardiovascular diseases were among the top (70.6%). Only 7.8% (n=4) did not report any comorbidities and therefore were excluded from the related analysis (Tables 1, 2).

Molecular variant analysis of variant circulation among infections was mainly due to B.1.621 (Mu), a phenomenon observed also in the national reporting at GISAID (Figure 1B) and rapidly shifted to B.1.617 (Delta) variants. Infections among vaccinated (n=19), the Mu and Delta variant identification did not show any gender differences.

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DISCUSSION

More than one year going through SARS-CoV-2 pandemic and six months after initiating a national COVID-19 vaccination, the Dominican Republic struggles with vaccine hesitation, with less than 65% of the population fully vaccinated[16] and multiple variants of concern and interest emerging all around the world[7]. Among thirty-eight admitted patients to *the Hospital General Plaza de la Salud* (HGPS), we found that only 40.4% of patients were fully vaccinated, despite a high prevalence of reported comorbidities in 89.5%.

SARS-CoV-2 variant distribution in the DR has been characterized by a broad array of circulating variants associated to social and political dynamics, being the founder effect related to the B and B.1 (D614G) variants[1]. Global distribution of variants responded to local transmission chains, and viral characteristics, in many countries viral waves have been caused mainly by Alpha, Delta, and more recently Omicron. In contrast, our study reported that the major reason for hospitalization was associated to VOI Mu (Table 1, 2) (Figure 1C) As seen in other studies this VOI has shown to have a strong resistance to current vaccine schemes[17], presenting three spike mutations in common with the B.1.351(Beta) variant; considered a VOC, firstly reported in South Africa in late 2020[18].

Studied cases reported receiving a whole-virus attenuated vaccine (CoronaVac) in 36.8%. Previous real-time vaccine studies with the same vaccine platform revealed that a scheme of a two-dose schedule has an effectiveness of 65.9% (95% confidence interval [CI], 65.2 to 66.6) for the prevention of COVID-19, 87.5% (95% CI, 86.7 to 88.2) for the prevention of hospitalization and 86.3% (95% CI, 84.5 to 87.9) for the prevention of COVID-19–related death[19]. Our study found that with this vaccine schedule survival rate among two-dose vaccinated individuals was 73% (95% CI, 70.8 to 74.2) compared to 65% in unvaccinated individuals, and no differences outcomes between Mu, Iota, or Delta infections were observed. This suggests that VOIs can also have a deleterious impact on vaccinated individuals.

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A study conducted in the DR explored neutralizing antibodies (NAb) detection in plasma from those who received CoronaVac vaccines (2-doses), and the effects of a booster using a heterologous platform. It demonstrated that half-maximal plaque reduction neutralizing assays (PRNT50) exposed to several variants including Delta and Omicron, NAb titers were reduced (IC50 mean, 1.4;7.1-and -3.6-fold reduction) for Omicron compared to the ancestral and Delta SARS-CoV-2 variants, unfortunately, this study did not assess neutralizing reaction compared with Mu either cellular induced response[20], but supported the policy of a third booster shot using a heterologous means, or revaccinating schedules with an mRNA vaccine platform.

Our study presented several limitations including the small sample size of hospitalized breakthrough cases and the retrospective nature of it, especially with the constant emergence of mutant strains as the pandemic continues to evolve and vaccines are not yet available to most of the world population. To counteract our small cohort limitations, we limited our results to patients' outcomes instead of exploring specific symptoms and severity scales.

CONCLUSION

As breakthrough infections are a major risk of lately SARS-CoV-2 variants more studies are needed to investigate the protective efficacy of current COVID-19 vaccines, in the light of the basic immune status of recipients, history of immunosuppressive therapy, the molecular diversity of viruses, innovative approaches in therapy and vaccine platforms.

The virus will be constantly changing to become the fittest version of itself whether that is through increased transmissibility or the ability to outwit naturally acquired or vaccine-induced immunity. Interactions of several VOC and human transmission have been explored further, however, many VOI has been circulating in Latin America and the Caribbean and its interactions with critical indicators like death, intensive care, and intubation have not been well described. Data suggest that VOI B.1.526 (Iota) in New York City was not associated to severe outcomes, in the DR, Iota

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was registered in January 2021 along with Alpha and other variants under investigation (VUI), moreover, by mid-March and April 2021, Iota represented near 25% of the total registered non-ancestral variants circulating in the country. Preliminary data indicate a lower reinfection rate with B.1.526 carrying E484K mutation compared with those with infections without this landmark mutation[21,22].

The nearly absent genomic surveillance system in both the Dominican Republic and more accentuated in Haiti will facilitate the cryptic circulation of new variants that might affect regional global efforts in vaccination campaigns, rapid deployment of non-pharmacological interventions, and medical response to those requiring hospitalization. With these results, based on a small cohort of patients, we propose future studies should consider bigger cohorts to assess these differences and describe their significance based on public health implementation strategies.

As SARS-CoV-2 variants have come to be more frequent, and many countries are relaxing restrictions, is of utmost importance to further explore the role of local variant distributions and clinical outcomes, including the long-COVID-19 spectrum.

DATA AVAILABILITY

Sequences of the SARS-CoV-2 variants were deposited on the GISAID database (https://www.gisaid.org) (accession numbers: EPI_ISL_5587611, EPI_ISL_5587613, EPI_ISL_5587617, EPI_ISL_5587621, EPI_ISL_5587623, EPI_ISL_5587633, EPI_ISL_5587645, EPI_ISL_9590663, EPI_ISL_9590848, EPI_ISL_5587651, EPI_ISL_5587660, EPI_ISL_5587664, EPI_ISL_5620856, EPI_ISL_5621195, EPI_ISL_5621287, EPI_ISL_5621494, EPI_ISL_5621499, EPI_ISL_5621502, EPI_ISL_5687427, EPI_ISL_5687696, EPI_ISL_5687945, EPI_ISL_5688222, EPI_ISL_5689590, EPI_ISL_5689672, EPI_ISL_5689763, EPI_ISL_5689766, EPI_ISL_5689767, EPI_ISL_5689768, EPI_ISL_5689772, EPI_ISL_5689774,

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EPI_ISL_5587703, EPI_ISL_5587688, EPI_ISL_5587695, EPI_ISL_9591620, EPI_ISL_5587688, EPI_ISL_5587680, and EPI_ISL_5587676.

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AUTHOR CONTRIBUTIONS

R.P.R. and R.R.F. conceived the study. R.P.R., R.R.F., P.C., S.M., M.J., I.R., A.G.M., G.T.J. A.S.M., and G.C.L. designed and implemented data collection. A.G.M., G.T.J., P.C. A.V.D., V.V.C., M.J., and A.S.M. collected and processed samples for molecular and virus sequencing analysis. R.P.R., R.R.F., P.C., S.M., I.R., L.T., A.S.M., and G.C.L. designed, managed, and analyzed epidemiological data. Drafted the manuscript, R.P.R. and R.R.F. supervised the project, and are the guarantors of the data.

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TABLES AND FIGURES

Table 1. Characteristics of SARS-CoV-2 infected patients hospitalized in HGPS, Dominican Republic, From June to September of 2021

Characteristics	Living, n= 25	Deceased, n= 8
Locality, no. (%)		
Santo Domingo	16(64%)	5(62.50%)
Santo Domingo Este	2(8%)	1(12.50%)
Santo Domingo Oeste	1(4%)	0
Santo Domingo Norte	0	1(12.50%)
Azua	1(4%)	0
San Cristóbal	1(4%)	1(12.50%)
Elías Piña	2(8%)	0
La Altagracia	1(4%)	0
Monte Plata	1(4%)	0
Sex, No. (%)		
Female	13(52%)	3(38%)
Male	12(48%)	5(63%)
Age group, no. (%)		
32-52	9(36%)	0
52-72	10(40%)	4(50%)
72-92	5(20%)	3(38%)

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93-100	1(4%)	0
100+	0	1(13%)
Mean age, (SD) all age groups	64.09 (16.15)	65.03(16)
Age group and comorbidities (%)		
32-52	8(32%)	0
53-73	8(32%)	4(50%)
74-94	8(32%)	4(50%)
95-115	1(4%)	0
all age groups	25(71%)	8(23%)
Mean days of Hospitalization (SD)	9.12(5.84)	10.75(8.65)
Median days until death	N/A	8.5

*SD refers to the Standard Deviation of the analyzed variables

Table 2. Characteristics and comorbidities of SARS-CoV2 infected patients hospitalized in HGPS, Dominican Republic, From June to September of 2021

Covariates	**|t|**	**P-value**
Sex (Male=17, Female=16)	3.394	0.0024
Age (years)	2.333	0.0283
Hospitalization (days)	1.532	0.1387
ICU admission (yes=1, no=32)	0.5971	0.5560
Vaccinated (yes=19, no=14)	1.362	0.1858
Vaccine dose (no dose=14, 1-dose=5, 2-dose=14) *	1.698	0.1024
Outcome (deceased =8, living=25)	2.654	0.0139
Pregnancy (Yes=1, No=32)	2.595	0.0159
Smorkers (Yes=5, No=28)	0.2820	0.7803
Normality of residuals		
Anderson-Darling		0.5565
D'Agostino-Pearson omnibus		0.6207
Comorbidities n (%)	**Hospitalized patients n= 33**	

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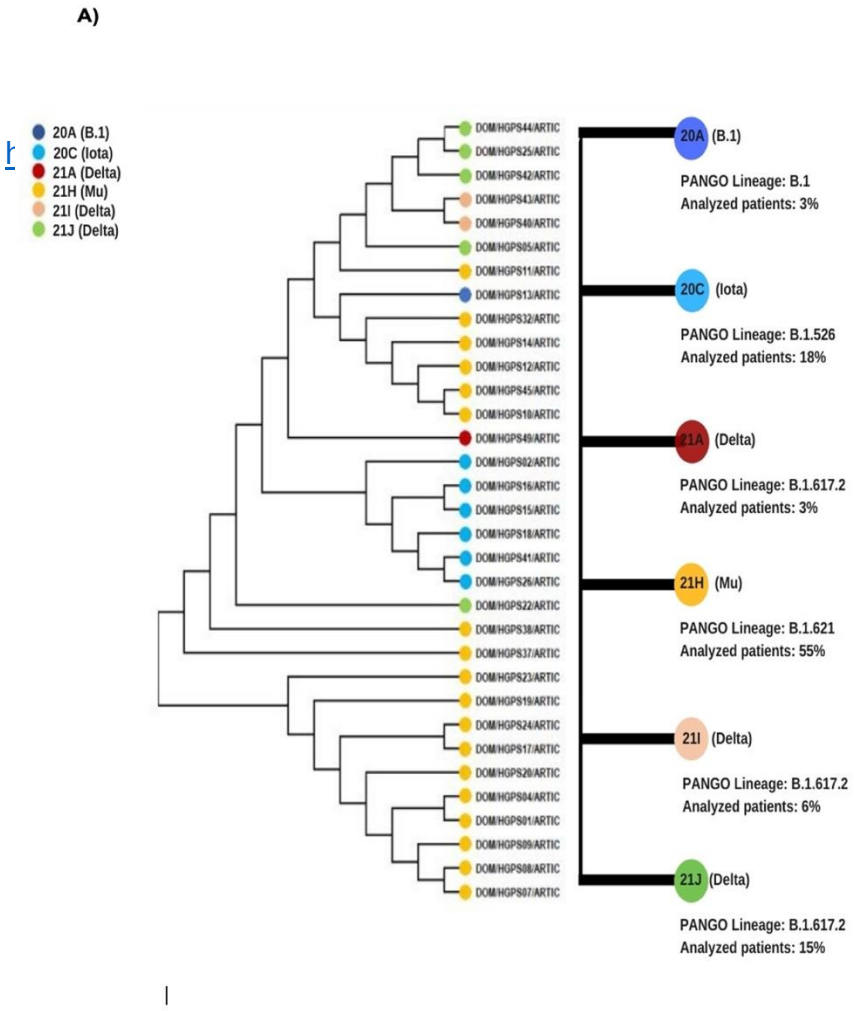
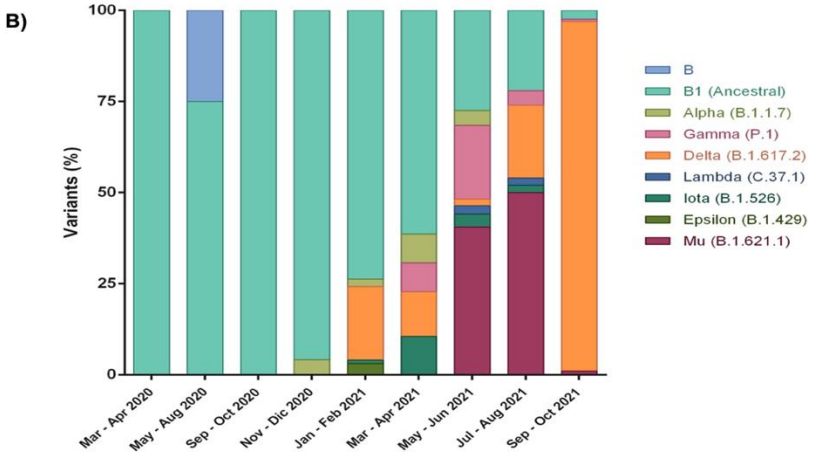
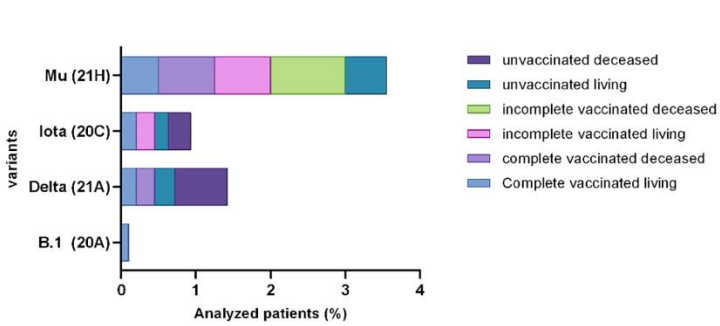
Autoimmune diseases	1(3%)
Metabolic bone diseases	2(6%)
Cancer	1(3%)
Cardiovascular diseases	22(67%)
Cerebrovascular diseases	3(9%)
Endocrine diseases	7(21%)
Gastrointestinal diseases	3(9%)
Neurodegenerative diseases	3(9%)
Pulmonary disease	4(12%)
Renal insufficiency	2(6%)
Other	4(12%)

*Number of doses varies according to the vaccine that the patients chose to receive


A)
20A (B.1)
20C (Iota)
21A (Delta)
21H (Mu)
21I (Delta)
21J (Delta)
20A (B.1)
PANGO Lineage: B.1
Analyzed patients: 3%
20C (Iota)
PANGO Lineage: B.1.526
Analyzed patients: 18%
21A (Delta)
PANGO Lineage: B.1.617.2
Analyzed patients: 3%
21H (Mu)
PANGO Lineage: B.1.621
Analyzed patients: 55%
21I (Delta)
PANGO Lineage: B.1.617.2
Analyzed patients: 6%
21J (Delta)
PANGO Lineage: B.1.617.2
Analyzed patients: 15%


B)
Variants (%)
100
75
50
25
0
Mar - Apr 2020
May - Aug 2020
Sep - Oct 2020
Nov - Dic 2020
Jan - Feb 2021
Mar - Apr 2021
May - Jun 2021
Jul - Aug 2021
Sep - Oct 2021
B
B1 (Ancestral)
Alpha (B.1.1.7)
Gamma (P.1)
Delta (B.1.617.2)
Lambda (C.37.1)
Iota (B.1.526)
Epsilon (B.1.429)
Mu (B.1.621.1)


C)
variants
Mu (21H)
Iota (20C)
Delta (21A)
B.1 (20A)
0
1
2
3
4
Analyzed patients (%)
unvaccinated deceased
unvaccinated living
incomplete vaccinated deceased
incomplete vaccinated living
complete vaccinated deceased
Complete vaccinated living

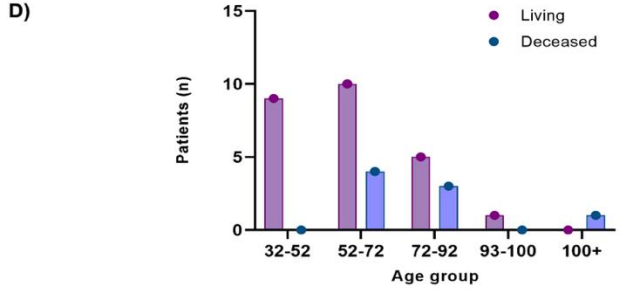

D)
Patients (n)
15
10
5
0
32-52
52-72
72-92
93-100
100+
Age group
Living
Deceased

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Figure 1. A) Phylogenetic analysis of SARS-CoV-2 and collected genome sequences in the Dominican Republic. Phylogenetic and molecular evolutionary analyses were conducted using MEGA version 11 (Tamura K, Stecher G, and Kumar S 2021). (B) SARS-CoV-2 variants registered at GISAID from the Dominican Republic from March 2020 to October 2021. (C) Analyzed variants and outcomes of SARS-CoV-2 in patients with or without prior vaccination. an incomplete vaccinated scheme patient outcome refers to someone who has received at least one dose of a vaccine. A complete vaccinated scheme outcome refers to someone who has received either a single-dose vaccine or both doses of a two-dose vaccine. Graph was generated using GraphPad Prism version 9.3.0 for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com. (D) Patient´s outcomes and age distribution. Graph was generated using GraphPad Prism version 9.3.0 for Windows, Graphpad Software, San Diego, California, USA. www.graphpad.com.