

Epidemiological Characterization of Patients in the First Eight Weeks Following Detection of SARS-CoV-2 B.1.1.529 (omicron) Variant in Cuba

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ABSTRACT

INTRODUCTION In November 2021, omicron—a new SARS-CoV-2 variant—was identified in South Africa and almost immediately, WHO declared it a ‘variant of concern’. In view of its rapid worldwide spread and its imminent introduction in Cuba, genomic surveillance was strengthened.

OBJECTIVE Describe cases during the first eight epidemiological weeks (epiweeks) of SARS-CoV-2 infection attributable to omicron variant in Cuba by clinical and epidemiological variables.

METHODS From epiweek 48, 2021 to epiweek 4, 2022, 288 nasopharyngeal swabs were processed for sequencing of a 1836 bp fragment of the S gene. Variants were identified according to GISAID database and confirmed by phylogenetic analysis. Variants’ association with clinical and epidemiological outcomes was assessed.

RESULTS The first cases of omicron variant were imported, mostly from African countries and the United States. During

the period studied, omicron was detected in 83.0% (239/288) of cases processed, while the delta variant was found in 17.0% (49/288). Most persons infected with omicron were symptomatic (63.2%; 151/239) and fully vaccinated (65.3%; 156/239); severe cases and deaths occurred mainly among patients aged ≥ 65 years (92.9%; 13/14), and 12 of these deaths occurred in fully vaccinated persons (92.3%; 12/13). Omicron spread rapidly throughout the country (from 10% of cases in epiweek 48, 2021, to 100% by epiweek 4, 2022), displacing the formerly predominant delta variant.

CONCLUSIONS Omicron’s rapid expansion in Cuba was associated with increased incidence but not with a higher case fatality rate. The relatively milder disease in those infected with this variant could be influenced by the high vaccination coverage, along with the natural immunity acquired as a consequence of previous virus infection.

KEYWORDS Pandemics, epidemiology, epidemiological monitoring, COVID-19 testing, COVID-19, SARS-CoV-2, COVID-19 vaccines, Cuba

INTRODUCTION

Several SARS-CoV-2 variants have circulated worldwide. On May 31, 2021, WHO introduced labels for SARS-CoV-2 variants of concern (VOC) and variants of interest (VOI) to be used with the scientific nomenclature. WHO updates the existing and emergent variants according to their detection frequency, transmissibility, severity or immune response.[1]

On November 24, 2021, South Africa reported detection of a new SARS-CoV-2 variant, designated as B.1.1.529. Two days later, WHO recognized this variant as a new VOC, named omicron.[2] Omicron has numerous mutations that could increase transmissibility, confer resistance to therapeutics, or partially escape from infection or vaccine-induced immunity.[3–5] Preliminary evidence suggested that infection with the omicron VOC might have a milder clinical presentation compared to delta. However, further analysis showed

that clinical evolution was more influenced by previously achieved immunity levels, rather than the intrinsic characteristics of the SARS-CoV-2 variant.[6,7] More recently, different omicron subvariants have been described, such as BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5, according to WHO.[8]

In Cuba, genetic surveillance of SARS-CoV-2 was started at the beginning of the Cuban epidemic, in March 2020. Circulation of 18 variants was detected in 2021 including: the Wuhan virus (Clade L), D164G (Clade G); the VOCs alpha, beta, gamma and delta; one VOI (lambda); and two previous VOIs (A.2.5.1 and Zeta/P.2). However, beta (34.8%), delta (24.9%) and D614G (19%) variants were the most frequently detected in 2021. Co-circulation of different predominant variants was observed in all epidemic waves; however, delta increased from 1.4% in May 2021 to 27.1% by June, 70.1% in July and 94.1% in August. By September, 100% of the studied samples were classified as delta, displacing the other variants circulating in the country; this suggested that delta had genetic advantages over other previously circulating variants.[9–11]

Immediately after detection of omicron in South Africa, Cuba’s Ministry of Public Health (MINSAP) intensified genetic surveillance of SARS-CoV-2.[12,13] This study aims to summarize the characteristics of the first SARS-CoV-2 cases in Cuba attributable

IMPORTANCE This is the first description of SARS-CoV-2 infection by the omicron variant in Cuba, including the variant’s association with epidemiological and clinical variables during the first omicron surge, December 2021–January 2022.

to the omicron variant, detected during epidemiological weeks (epiweeks) 48, 2021–4, 2022.

METHODS

Study design This is a cross-sectional study, with viral genome analysis of nasopharyngeal swabs obtained from patients confirmed with infection by SARS-CoV-2 from epiweek 48, 2021 to epiweek 4, 2022. Samples included travelers from various countries and all Cuban provinces. Samples were collected at different points in the period studied, from patients exhibiting differences in clinical severity, from within areas with a significant increase of cases, and from diverse age groups (Table 1). Samples were sent to the Reference Laboratory for Influenza and Respiratory Viruses, in the Virology Department of the Pedro Kourí Tropical Medicine Institute (IPK), in Havana, Cuba, where genomic analysis was performed. As not all samples fulfilled the required quality attributes for amplification or sequencing, the number of samples with valid sequences varied by week.

Sequencing and variant designation Total RNA was extracted using the QIAcube Automated DNA/RNA Purification System and the QIAamp Viral RNA mini Kit (QIAGEN, Germany), following manufacturer's instructions. cDNA synthesis and amplification of a 1836 bp fragment of the S gene (positions 21,976 to 23,812) was performed using the commercial kit One Step RT-PCR (QIAGEN, Germany), following manufacturer's instructions. Primers for RT-PCR were those described in Protocols for SARS-CoV-2 Sequencing by the US Centers for Disease Control (CDC, Atlanta, USA).[14] The Dye Terminator Cycle Sequencing (DTCS) Quick Start commercial kit (Beckman Coulter, USA) was used for the sequencing reaction, with four primers spanning the entire amplified fragment of the S gene (positions 21,976 to 23,812).

Sequencing products were purified also according to the DTCS Quick Star Master Mix kit (Beckman Coulter, USA) and analyzed in a Beckman Coulter automatic sequencer model CEQTM8800 using the raw data analysis procedure for PCR products. Obtained sequences were assembled and edited using the Sequencher program (Sequence Analysis Software, Version 4.10.1, Gene Codes Corporation, USA). The complete Wuhan-Hu-1 sequence (NC_045512.2) was used as the reference nucleotide sequence. Mutations were identified using the CoVsurver interpretation algorithm: Mutation Analysis of hCoV-19, from the GISAID database (<https://www.gisaid.org/epiflu-applications/covsurver-mutations-app>). Cuban variants were named according to the mutational profile described in the GISAID database,[15] and confirmed by phylogenetic analysis, using the bioinformatics tool NGPhylogeny (<https://ngphylogeny.fr>).

Statistical analysis Descriptive statistics and graphics were obtained using Microsoft Office Excel 2010.

Ethics IPK's Ethics Committee approved the study protocol. Epidemiological and clinical information was obtained from the case registry of MINSAP's surveillance system fully protecting patient identities. WHO guidelines for clinical management of COVID-19[16] were used as criteria for clinical classification of asymptomatic and symptomatic (mild and severe) patients.

RESULTS

During the study period, 288 nasopharyngeal swab specimens from persons with confirmed SARS-CoV-2 infection were

sequenced. Table 1 describes the epidemiological and clinical characteristics of these first omicron cases detected in Cuba, during epiweeks 48, 2021–4, 2022.

Table 1: Demographic and clinical characteristics of persons studied, by SARS-CoV-2 variant: Cuba, epiweeks 48, 2021–4, 2022

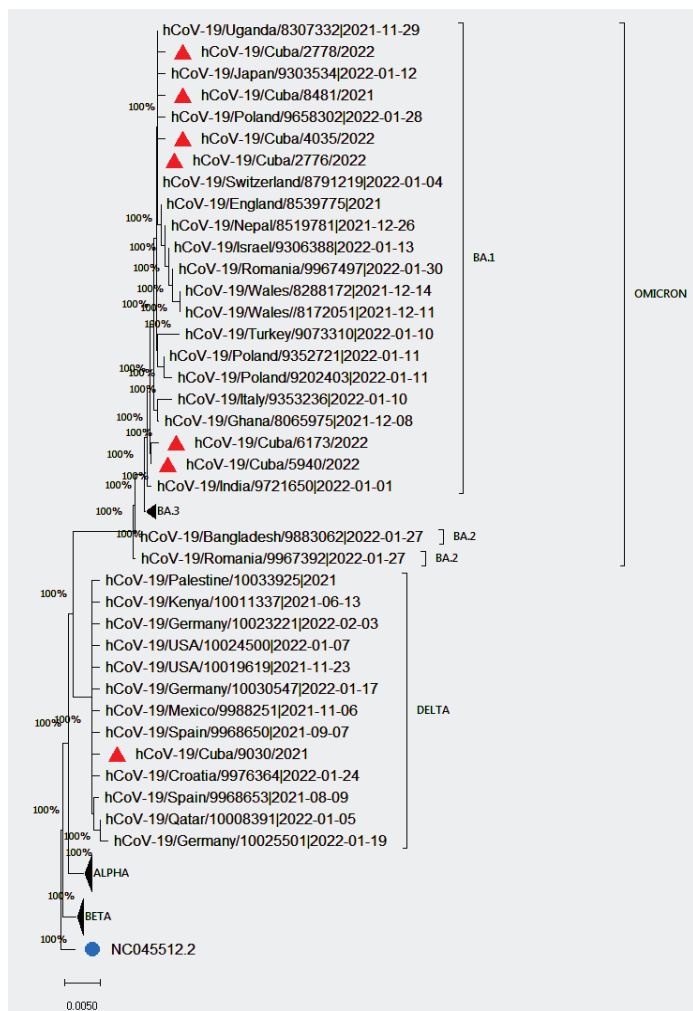
Characteristics	Delta	Omicron	Total
Persons studied	49 (100%)	239 (100%)	288 (100%)
Dates of SARS-CoV-2 diagnosis (epiweek)			
Nov 28–Dec 04, 2021 (48)	10 (20.4)	1 (0.4)	11 (3.8)
Dec 05–11, 2021 (49)	6 (12.2)	0 (0.0)	6 (2.1)
Dec 12–18, 2021 (50)	3 (6.1)	7 (2.9)	10 (3.5)
Dec 19–25, 2021 (51)	15 (30.6)	58 (24.3)	73 (25.3)
Dec 26–Jan 1, 2022 (52)	11 (22.4)	44 (18.4)	55 (19.1)
Jan 2–8, 2022 (1)	0 (0.0)	36 (15.1)	36 (12.5)
Jan 9–15, 2022 (2)	4 (8.2)	41 (17.2)	45 (16.6)
Jan 16–22, 2022 (3)	0 (0.0)	19 (7.9)	19 (6.6)
Jan 23–29, 2022 (4)	0 (0.0)	33 (13.8)	33 (11.5)
Age group (years)			
≤18	0 (0.0)	22 (9.2)	22 (7.6)
19–39	8 (16.3)	77 (32.2)	85 (29.5)
40–64	11 (22.4)	75 (31.4)	86 (29.9)
65–80	4 (8.2)	32 (13.4)	36 (12.5)
>80	2 (4.1)	18 (7.5)	20 (6.9)
Unknown	24 (49.0)	15 (6.3)	39 (13.5)
Sex			
Male	29 (59.2)	113 (47.3)	139 (48.3)
Female	20 (40.8)	126 (52.7)	149 (51.7)
Recent International Travel			
Yes	12 (24.5)	54 (22.6)	66 (22.9)
No	37 (75.5)	185 (77.4)	222 (77.1)
COVID-19 vaccination status			
Unvaccinated		6 (2.5)	6 (2.1)
Partially vaccinated	0 (0.0)	14 (5.8)	14 (4.8)
Fully Vaccinated*	26 (53.1)	156 (65.3)	182 (63.2)
Vaccinated plus booster dose	0 (0.0)	32 (13.4)	32 (11.1)
Unknown	23 (46.9)	31 (13.0)	54 (18.8)
Symptom profile			
Symptomatic	27 (55.1)	151 (63.2)	178 (61.8)
Asymptomatic	1 (2.0)	78 (32.6)	79 (27.4)
Unknown	21 (42.9)	10 (4.2)	31 (10.8)
Outcomes			
Severe case	0 (0.0)	19 (7.9)	19 (6.6)
Death	0 (0.0)	5 (2.1)	5 (1.7)

*Vaccinated with the complete schedule according to different vaccine requirements (two or three doses)

On December 1, 2021 (epiweek 48), the first case of COVID-19 attributable to omicron variant was identified in a Cuban traveler from Mozambique. This variant expanded rapidly, replacing delta, which had been predominant since July 2021.[13] By January 29, 2022, 239 omicron samples had been reported through genomic surveillance, all classified as omicron BA.1 subvariant (Figure 1). The rapid extension of the omicron variant was accompanied by an increase in case numbers (Figure 2A). However, case fatality rates (CFR) did not increase significantly (Table 1, Figure 2B).

By the first epiweek of 2022, all sequenced samples were omicron, with the exception of four from the Isle of Youth Special

Figure 1: Phylogenetic tree with SARS-CoV-2 partial nucleotide S gene sequences of omicron and delta variants



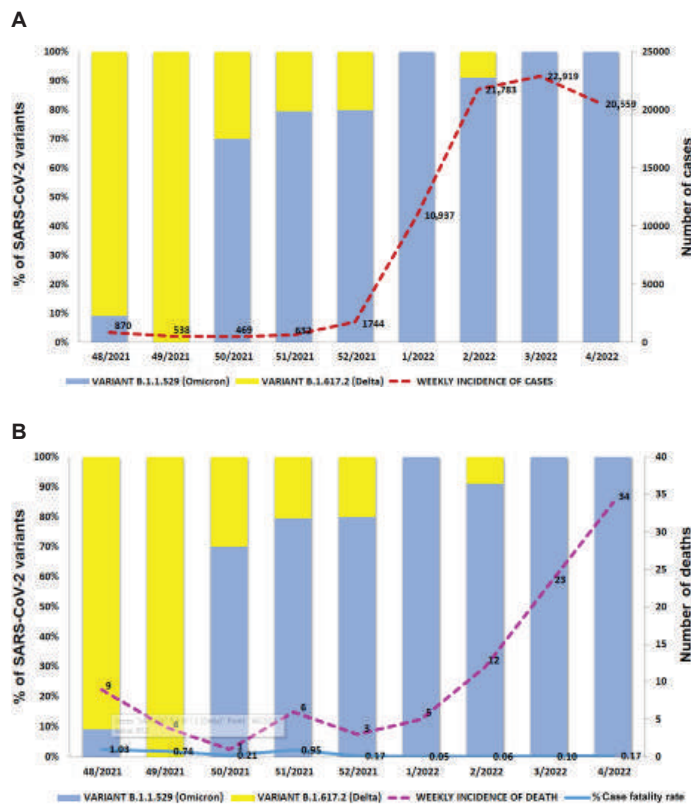
Analysis included 50 reference nucleotide sequences of the S gene, and 7 Cuban sequences from the present study (1836 bp). Duplicate sequences were removed using the elimdupes tool (<https://www.hiv.lanl.gov/content/sequence/elimdupesv2/elimdupes.html>). Sequences were aligned using the Mega version 11.0.11 and the bioinformatics tool NGPhylogeny (<https://ngphylogeny.fr/>). The evolutionary history was inferred using the NJ method (<https://ngphylogeny.fr/>). The consensus tree, inferred from 10,000 replicates, was used to represent the evolutionary history of the analyzed sequences. Our study samples are labeled with a red triangle. Sequences of alpha and beta variants are labeled with a black triangle. A blue circle shows the Wuhan-Hu-1 sequence, that was used as the outgroup.

Municipality, where the delta variant was still circulating. As of epiweek 3, 2022, all Cuban provinces had identified at least one omicron autochthonous case (Figures 2 and 3).

Most of the persons studied were aged 19–64 years (59.4%; 171/288), with no differences for those infected with delta and omicron variants; in children (≤ 18 years, 7.6%; 22/288), only the omicron variant was detected (Table 1).

Sixty six recently arrived international travelers were positive for SARS-CoV-2 infection and classified as imported cases (Table 1). Fifty-four of them (81.8%; 54/66) carried omicron variant. Countries most represented in the introduction of this variant were the United States (15), Angola (11), South Africa and Eswatini (6 each), and Canada (5) (Figure 4).

Figure 2: SARS-CoV-2 delta and omicron variants in Cuba, per number of cases and deaths, by epidemiological weeks



Omicron imported cases were predominant in epiweeks 48–52, 2021 (51/54); autochthonous cases increased rapidly starting in epiweek 51, 2021 (Figure 5).

One hundred and eighty two (63.2%; 182/288) persons infected had completed the full 3-dose COVID-19 vaccination schedule, mainly with the Cuban vaccine Abdala, and 32 (11.1%; 32/288) had received additional booster doses; 17 of 22 children had been fully vaccinated, the remaining 5 were aged <2 years and therefore not eligible for vaccination, since the Cuban regulatory agency had only provided emergency use authorization for the Cuban vaccines beginning at 2 years old.[17] Vaccination status could not be determined in 54 individuals (18.7%; 54/288), most of whom were imported cases (Table 1).

Overall, 178 (61.8%) patients presented with symptoms and 79 (27.4%) were asymptomatic. In those infected with the omicron variant, the percentage of symptomatic cases was slightly higher (63.2%; 151/239). Information on symptoms was lacking in a high proportion of those infected with the delta variant (46.9%; 23/49) (Table 1); 24 patients infected with the omicron variant developed severe disease and five of them died (Table 1). As described in Table 2, most severe or fatal cases (13/14, 92.9%) with documented age, were aged ≥ 65 years, and 12 of them had completed the vaccination schedule (Table 2).

DISCUSSION

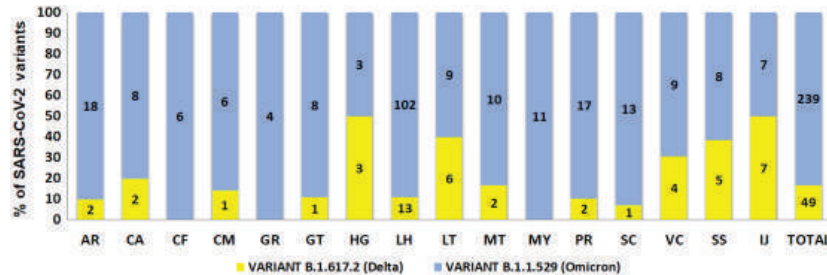
By epiweek 10, 2022, 446,987,500 COVID-19 cases and 6,022,374 deaths had been reported worldwide since the beginning of the

pandemic; Cuba had reported 1,072,560 cases and 8500 deaths. [18]

The first case of COVID-19 attributed to the omicron variant was detected in Cuba during epiweek 48, 2021, only a few days after

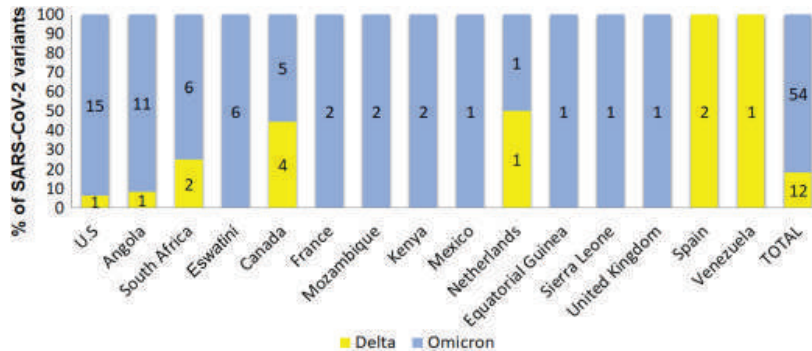
WHO declared this variant a VOC.[2,19] Initially, this variant was detected in travelers, arriving mainly from African countries (29 cases) or the USA (15 cases) where this variant had already been reported.[20,21] All Cuban isolates were classified as BA.1, as had been reported for most of the sequences worldwide.[8]

Figure 3: SARS-CoV-2 delta and omicron variants in Cuba by province, epidemiological weeks 48, 2021–4, 2022*



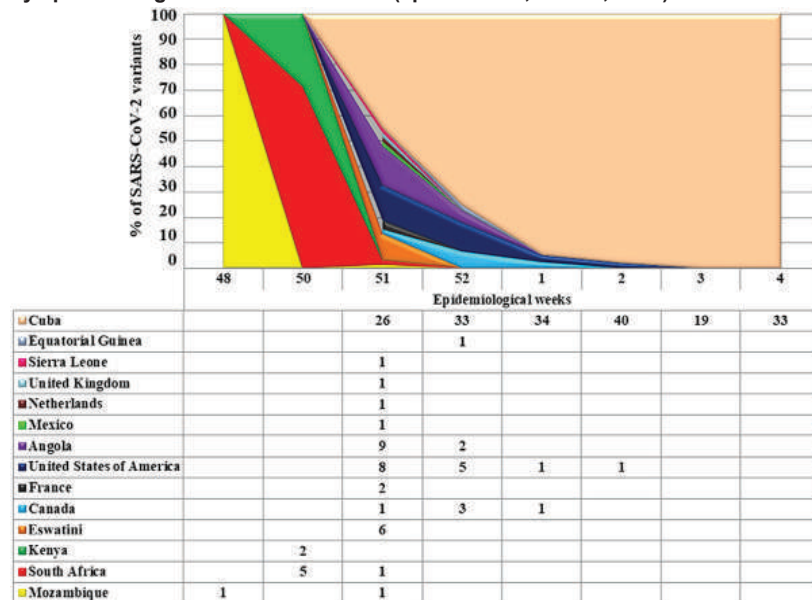
*Figures inside bars indicate number of cases of each SARS-CoV-2 variant
 AR: Artemisa; CA: Ciego de Ávila; CF: Cienfuegos; CM: Camagüey; GR: Granma;
 GT: Guantánamo; HG: Holguín; LH: Havana; LT: Las Tunas; MT: Matanzas; MY: Mayabeque;
 PR: Pinar del Río; SC: Santiago de Cuba; VC: Villa Clara; SS: Sancti Spiritus;
 IJ: Isle of Youth Special Municipality

Figure 4: SARS-CoV-2 delta and omicron variants introduced in Cuba, by percentage and country of origin, November, 28 2021–January 29, 2022*



*Figures inside bars mean number of cases of each SARS-CoV-2 variant

Figure 5: Distribution of omicron cases in Cuba by country of origin, stratified by epidemiological week of detection (epiweeks 48, 2021–4, 2022)



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.[22,23] At the time, Cuba was in a favorable epidemiological context with low numbers of new cases (7-day moving average of daily new cases: 67, in epiweek 50, 2021) and extremely low number of deaths (7-day moving average of daily deaths: 0 on epiweek 50, 2021), principally due to high levels of immunity achieved—attributable to high vaccination coverage—including pediatric immunization (2–18 years), and to the natural immunity acquired as a consequence of previous infection during the delta wave. When omicron was detected in Cuba (epiweek 48, 2021) 10,192,588 (91.1%) persons in Cuba had received at least one dose of the Cuban vaccines Abdala or Soberana and 83% of them had completed the 3-dose vaccination schedule. Only 3.9% had received a fourth (booster) dose.[24]

Emergence of the omicron variant in Cuba was accompanied by an increase in case numbers, but not higher CFR. By March 7, 2022, number of new cases had dropped to <600 cases per day (7-day moving average of daily new cases: 520).

Omicron’s first-wave peak in Cuba took place in epiweeks 2–4, 2022. The Cuban wave was less intense compared to other countries, including those with high vaccination coverage. As of January 29, 2022, Cuba reported 268.08 new COVID-19 cases per million population (pmp), while the UK, USA and Germany reported 1307.72, 1589.32 and 1740.56 cases pmp, respectively.[25] European countries with higher vaccination rates were better prepared for the autumn 2021 wave, despite the emergence of the more transmissible SARS-CoV-2 delta and omicron variants.[6]

A relatively high number of omicron-infected individuals were asymptomatic, as reported in other countries,[4,23,26] which has been attributed to a preferential infection of the upper respiratory tract.[27] Cuba’s high immunization coverage also may have facilitated the mild disease occurrence observed during the first omicron wave.[24] In fact, it has been argued that a milder clinical evolution in omicron cases may be associated with acquired immunity due to virus circulation or vaccination, rather than to intrinsic characteristics of this SARS-CoV-2 variant.[7]

Nevertheless, severe disease and even fatal outcomes have been reported globally from the omicron variant, mainly in older adults and those with

Table 2: Demographic and clinical characteristics of persons infected by omicron, by COVID-19 vaccination status: Cuba, epiweeks 48, 2021–4, 2022^a

Characteristics	Fully vaccinated ^{b/} Vaccinated plus booster					Unvaccinated/ Incomplete vaccination					Unknown vaccination status	TOTAL
	<18	18–39	40–65	>65	Total	<18	18–39	40–65	>65	Total		
Age (years)	<18	18–39	40–65	>65	Total	<18	18–39	40–65	>65	Total		
Asymptomatic (%)	2 (11.8)	14 (21.9)	23 (38.3)	6 (14.3)	45 (24.6)	0 (0.0)	5 (62.5)	2 (50.0)	0 (0.0)	7 (38.9)	15 (68.2)	67 (30.0)
Mild symptoms (%)	15 (88.2)	50 (78.1)	36 (60.0)	24 (57.1)	125 (68.3)	5 ^c (100.0)	3 (37.5)	2 (50.0)	0 (0.0)	10 (55.6)	2 (9.1)	137 (61.4)
Severe cases (%)	0 (0.0)	0 (0.0)	1 (1.7)	9 (21.4)	10 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 ^c (100.0)	1 (5.6)	4 (18.2)	15 (6.7)
Deaths (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.1)	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	4 (1.8)
TOTAL (%)	17 (-)	64 (-)	60 (-)	42 (-)	183 (82.1)	5 (-)	8 (-)	4 (-)	1 (-)	18 (8.1)	22 (9.8)	223 (100.0)

^aDifferences observed between the information in Table 1 and the information analyzed in this table are due to missing data on patient age and/or clinical status.

^bVaccinated with the complete schedule according to the different vaccine requirements (two or three doses)

^cUnvaccinated

various comorbidities.[28] Coinciding with previous reports, most severe cases and deaths observed in our study occurred in elders, probably associated to a less robust vaccine immune response, and a shorter durability of omicron-neutralizing antibodies due to immunosenescence.[29]


This study has some limitations. The number of samples studied was determined by the laboratory sequencing capacity. A number of samples positive for SARS-CoV-2 proportional to the number of cases in the country was selected each week; nevertheless, not all resulted in the required quality either during amplification or sequencing; in consequence, the number of samples sequenced was not homogeneous each week.

Although whole-genome sequencing was not performed, the sequences obtained covering the S gene from positions 21,976 to 23,812 permitted identification of SARS-CoV-2 variants circulating in Cuba.

CONCLUSION

Beginning in late 2021 and into early 2022, the omicron BA.1 subvariant of SARS-CoV-2 rapidly replaced delta the variant in Cuba. Although the case numbers also increased, case fatality rates did not increase proportionally. The relatively milder form of the disease in individuals infected with this variant could be influenced by the high vaccination coverage achieved, including childhood immunization beginning at two years of age, along with the natural immunity acquired as a consequence of previous infection during the earlier delta wave.

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