Incidence and Cluster Analysis of SARS-CoV-2 Variants of Concern, Belize, August 2021 – July 2022

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Abstract

Background. Variants of Concern (VOC) of the SARS-CoV-2 virus challenged prevention and control measures against COVID-19 especially as Omicron became the dominant VOC globally. The VOC behavior has not been studied in Belize. Our objective was to describe the prevalence and high-risk clusters of VOC.

Population and Methods. An ecologic study. We described the incidence and high-risk clusters of VOC circulating in Belize. These were defined as per the US Centers for Disease Control and Prevention. The Central Medical Laboratory of Belize provided the database. Prevalence rates were estimated by sex, age, district, and VOC. Space-time analysis identified high risk community clusters using SaTScan with a Discrete Poisson probability model. The Autoregressive Integrated Moving Average (ARIMA) model was applied in XLSTAT to describe and predict the temporal behavior of VOC for one year.

Results. Of 645 confirmed cases of COVID-19, 0.2%, 31.2% 0.5% and 68.2% were Alpha, Delta, Gamma, and Omicron, respectively. The median age of the cases was 33 years. Highest prevalence rates (cases per 10,000 persons) were reported in: females – 16.6 (95% CI: 14.9-18.3); age group of ≥60 years – 33.7 (95% CI: 27.2-41.2), and Omicron – 10.2 (95% CI: 9.3-11.2). The 12-month cumulative incidence was 15.0 cases/10,000 persons (95% CI: 13.9-16.2). Of four clusters identified, the fourth (Caye Caulker) had the highest relative risk (67.8). The ARIMA analysis indicated infections would gradually decrease but would continue to occur.

Discussion. Females, elderly persons, and the Cayo district were most affected. Omicron predominated. Sample sequencing criteria possibly introduced selection bias. Sustained surveillance of VOC is vital for early detection and public health response. Bivalent vaccines should be promoted. The study period needs to be extended.

Keywords: incidence, SARS-CoV-2, clustering, time series, Belize

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in Wuhan City, China in December 2019 as a novel Coronavirus [1]. It causes the COVID-19 disease. This resulted in millions of infections and deaths, and social and financial turmoil. The World Health Organization (WHO) declared a pandemic in March 2020 [2]. This global crisis was further exacerbated with the appearance of SARS-CoV-2 variants.

Mutations developed which could have upgraded the viral replication capabilities or allowed the virus to avoid detection by naturally acquired immune response or that conferred by vaccines. Increased viral transmission may have resulted from the adaptation of the virus [3]. Such changes threatened the public´s health by resulting in increased transmission, disease severity, number of hospitalizations and deaths. These variants are known as Variants of Concern (VOC). In January 2021, the WHO issued a draft report on COVID-19 variants [4.] The paper outlines the importance of such viral mutations, or changes in the genetic makeup of the virus and underscores the need for research.

Several studies aimed to understand the public health impact of selected variants. For example, a study in France found that the Omicron Variant may have been responsible for 3.8% of re-infections [5]. A new variant in England led to a surge in COVID-19 infections [6]. Persons infected with a VOC had higher odds of hospitalization and admittance into the Intensive Care Unit (ICU) than persons not infected with a VOC [7].

In August 2021, the circulation of VOC was first detected in Belize [8]. The country suffered varying degrees of disease incidence, hospitalization rates, and mortality rates with each COVID-19 wave [9]. However, to our knowledge, no previous published report has described the circulation and behavior of these variants in Belize. This was the first study focused on describing and analyzing the incidence of SARS-COV-2 VOC and its circulation in Belize over space and time.

We provide information on circulating SARS-CoV-2 VOC to identify affected areas of the country and their impact of the population over a 12-month period of study. We had hoped this information could guide the strengthening or implementation of targeted prevention and control measures. The timely implementation of prevention strategies against COVID-19, especially in the presence of VOC, was essential for the protection of especially vulnerable populations with greater risk for more severe outcomes [10]. This study can also serve as a basis for further analyses to consider associated factors with VOC circulation and possible application to other respiratory diseases such as Influenza.

The main objective of the study was to describe the incidence and high-risk clusters of SARS-CoV-2 VOC in Belize from August 2021 to July 2022. We specifically: 1) describe the prevalence of VOC cases by person (age and sex), place (address by district and/or community), and time (month-year); 2) generate a risk map of geographic groupings (clusters) of VOC over time; and 3) predict the temporal behavior of the VOC by use of time series analysis.

Population and methods

This ecological analysis described the epidemiological characteristics and spatial-temporal behavior of the occurrence of SARS-CoV-2 VOC from August 2021 to July 2022 in Belize. Secondary data was obtained from the Belize Health Information System (BHIS) and the Central Medical Laboratory (CML). The laboratory data was jointly produced by the Baylor College of Medicine (BCM) and the CML in a collaborative effort with the Ministry of Health and Wellness (MOHW). Community population estimates were obtained from the Statistical Institute of Belize (SIB), the Health Education and Community Participation Bureau (HECOPAB) in the MOHW, the Vector Control Unit in the MOHW, and the National Association of Village Councils (NAVCO) in the Ministry of Rural Transformation, Community Development, Labor, and Local Government. These population estimates varied by the most recent census for each community.

BCM had been conducting a study to monitor acute febrile illnesses (AFI) and included testing for respiratory viruses. With the advent of the COVID-19 pandemic, the study expanded to include testing for SARS-CoV-2 and later gene sequencing. The study applied eligibility criteria and a consent form to all patients who formed part of the study. Results were entered in the BHIS.

Study population

The CML received specimens from all over the country. There was a greater consideration given to patient samples meeting at least one of the following criteria: hospitalization, death, children, pregnant, fully vaccinated, or clusters of institutionalized persons. There was an intentional effort to include samples from as many communities as possible.

Laboratory testing

The CML carried out real-time polymerase chain reaction (RT-PCR) on specimens obtained by nasopharyngeal/oropharyngeal swabs of suspect cases to detect SARS-CoV-2 RNA using the cycle threshold (Ct) values of the viral load of 25.0 to deem the test as a positive test.

Case definition

A SARS-CoV-2 variant was defined as “a viral genome that may contain one or more mutations” [11]. A variant of interest (VOI) was defined as a variant with “changes to receptor binding domain (RBD);

reduced neutralization by antibodies generated against previous infection or vaccination; reduced efficacy of treatments, or tests; and predicted increase in transmissibility or disease severity" [11]. A VOC was classified as such because of its increased transmissibility, greater disease severity, increased evasion or resistance to treatments or vaccines (including diagnostics), and "significant reduction in neutralization by antibodies generated during previous infection or vaccination" [11]. A case was defined as a person with a gene sequencing of the SARS-CoV-2 identified as one the Alpha, Beta, Delta, Gamma, or Omicron VOC.

Selection criteria

All specimens yielding a Ct cut-off value equal or above 25.0 were excluded. During the study period, 685 samples yielded a sequencing result. Of these results, 647 were VOC and 38 were VOI. Two VOC cases were excluded: one was a Delta variant identified in a visitor from the United States of America. The second one was an Omicron case with an unknown address. We excluded from the analysis the 38 VOI. The 645 remaining VOC included those listed above and remained in the analytic set.

Data analysis

The data was obtained from the BHIS in Microsoft® Access® format. It was then entered on to Microsoft® Excel® 2019 for data editing. The laboratory data also included the cut-off values for each case and the quality control values so that the data quality could be validated. Further cleaning and analysis were performed using R i386 4.1.1 Software [12]. Data on the following variables were collected:

- BHIS ID: Unique Patient Identification Number generated by the BHIS
- Test Request ID: Unique Sample Identification Number generated by the BHIS
- Address: community (village, town, city, district) identified where the case lives
- Date of Collection: year, month, and day of when sample was reported as collected
- Age: Age of Patient in Years (0-11 months = 0 years)
- Sex: Gender of Patient (Masculine or Feminine)

- Population: Official count of number of persons living in a given community
- Coordinates: Latitude and Longitude coordinates of the patient's residential address

We verified the address for each VOC case using an official map of Belize. This ensured the quality of the data for an accurate description of the spatial distribution of the cases. The occurrence of VOC was estimated using the cumulative incidence ($\frac{newly\ diagnosed\ cases}{Population\ at-risk}$), risk, or attack rate. It was considered the best estimate of the occurrence although the dates when an individual recovered from the disease were not available. Moreover, re-infections could not be identified. Graphs and tables were generated to present the types of variants and their individual frequencies, proportions per month, sex, and district of residence, and annual cumulative incidence rates. All cumulative incidence rates were reported along with their 95% Confidence Intervals (95% CI).

The spatial-temporal analysis employed a Discrete Poisson probability model obtained using the algorithms available in SaTScan software version 10.1 [13]. The risk map was generated to identify VOC geographic clusters with high risk using spatial point pattern sets. These clusters were defined as the maximum spatial groupings of communities with a minimum of 12% of the population at risk based on a 12% national SARS-CoV-2 occurrence during the study period. The date of sample collection was used to determine the temporal distribution of the clusters. The log likelihood value was compared with a null distribution using 999 replicates in the simulation to derive the statistical significance of each cluster. Statistical significance was considered when the two-sided *P* value was <0.05. One set of coordinates were allowed per location unique identification (ID) number for each locality. We used the location ID generated by the BHIS per location.

The Autoregressive Integrated Moving Average (ARIMA) using XLSTAT (XLSTAT [2007] Statistical Software for Excel. https://www.xlstat.com) was applied to describe and predict the temporal behavior of the VOC by time series. This model converted the "moving" time series into stationary or snapshots of the series to predict future "movement" of values based on historical data.

Protection of Human Subjects

The protocol was approved by the National Ethics Committee of Belize. Data obtained from the Epidemiology Unit and the use CML laboratory data was deidentified, and procedures were in place to prevent the disclosure of private information.

Results

Overall incidence of VOC, and by age, sex and residence

Of the 645 VOC results analyzed, Omicron accounted for 440 (68.2%); Delta accounted for 201 (31.2%); Gamma accounted for 3 cases (0.5%); and Alpha for 1 (0.2%) case. The median age for the total VOC cases was 33 years. Overall, females had a higher rate. The age group of 60 years and over yielded the highest cumulative incidence rate. For the 12-month study period, the VOC cumulative incidence rate was 15.0 cases per 10,000 persons (95% Confidence Interval: 13.9-16.2). Four clusters of high risk were identified, and these were in five of the six districts. The time series analysis indicated a slight and gradual decreasing trend.

Females accounted for the higher cumulative incidence rate at 16.6 cases per 10,000 persons (95% CI: 14.9-18.3); males accounted for a rate of 13.4 cases per 10,000 persons (95% CI: 12.0-15.1). The age group of 60 years and over accounted for the highest cumulative incidence rate of VOC at 33.7 cases per 10,000 persons (95% CI: 27.2-41.2). The expanded age group from 20 to 59 years accounted for 68.7% of the total cases. Children (<5 years old) accounted for only 4% of the VOC cases (Table 1.)

The Cayo District saw the highest cumulative incidence rate at 20 cases per 10,000 persons (95% CI: 17.4-22.8). This was higher than the national cumulative incidence rate. Toledo accounted for the lowest rate at 7.4 cases per 10,000 persons (95% CI: 5.1-10.4). Cayo also saw the highest proportion of cases (32.6%).

Table 1. Cumulative Incidence Rate of SARS-CoV-2 Variants of Concern by Sex, Age Group and District, Belize, August 2021 – July 2022

Variable	n (%)	Cumulative Incidence Rate (x 10,000 persons)	95% CI
Sex			
Male	289 (44.8)	13.4	12.0-15.1
Female	356 (55.2)	16.6	14.9-18.3
Age Group			
<1	4 (0.6)	4.0	1.4-9.6
1-4	22 (3.4)	5.4	3.5-78.1
5-9	27 (4.2)	5.2	3.5-7.4
10-14	31 (4.8)	6.2	4.3-8.6
15-19	29 (4.5)	6.3	4.3-8.9
20-24	88 (13.6)	21.6	17.4-26.5
25-29	81 (12.6)	22.9	18.3-28.3
30-34	60 (9.3)	19.7	15.2-25.2
35-39	58 (9.0)	21.0	16.1-27.0
40-44	51 (7.9)	22.0	16.6-28.7
45-49	40 (6.2)	20.1	14.5-27.0
50-54	42 (6.5)	26.9	19.6-35.9
55-59	23 (3.6)	20.0	13.0-29.4
≥60	89 (13.8)	33.7	27.2-41.2
District			
Corozal	59 (9.1)	11.4	8.8-14.7
Orange Walk	98 (15.2)	18.1	14.8-21.9
Belize	205 (31.8)	15.6	13.6-17.9
Cayo	210 (32.6)	20.0	17.4-22.8
Stann Creek	43(6.7)	9.1	6.7-12.1
Toledo	30 (4.7)	7.4	5.1-10.4
Total/National	645 (100)	15.0	13.9-16.2

Data Source: Belize Health Information System and Central Medical Laboratory

Distribution by time of VOC

The proportions of VOC were presented by month and year as per Table 2. January of 2022 accounted for the highest VOC proportion at 14.7% (95% CI: 12.2-17.7). April of 2022 saw the least proportion at 3.7% (95% CI: 2.5-5.5). September of 2021 only had one sample positive and is considered an outlier.

For Delta, October 2021 accounted for the highest proportion at 40.3% (95% Confidence Interval: 33.8-47.2) representing 81 cases. January 2022 accounted for the lowest proportion at 2.5% (95% CI: 1.1-5.7) representing 5 cases. For Omicron, January 2022 accounted for the highest proportion at 20.5% (95% CI: 16.9-24.5) representing 90 cases. April 2022 accounted for the lowest proportion at 5.5% (95% CI: 3.7-8.0) representing 24 cases. A transition was observed from Delta to Omicron from December 2021 to January 2022.

Table 2. SARS-CoV-2 Variants of Concern Proportion by Month-Year, Belize, August 2021 – July 2022

Month-Year	All SARS-CoV-2 VOC*			Delta			Omicron		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Aug-21	60	9.3	7.3-11.8	56	27.9	22.1-34.4	0		
Sep-21	1	0.2	0.0-0.8	1	0.4	0.1-2.8	0		
Oct-21	81	12.6	10.2-15.3	81	40.3	33.8-47.2	0		
Nov-21	36	5.6	4.1-7.6	36	17.9	13.2-23.8	0		
Dec-21	66	10.2	8.1-12.8	22	10.9	7.3-16.0	44	10.0	7.5-13.2
Jan-22	95	14.7	12.2-17.7	5	2.5	1.1-5.7	90	20.5	16.9-24.5
Feb-22	51	7.9	6.1-10.2	0			51	11.6	8.9-14.9
Mar-22	25	3.9	2.6-5.7	0			25	5.7	3.9-8.3
Apr-22	24	3.7	2.5-5.5	0			24	5.5	3.7-8.0
May-22	88	13.6	11.2-16.5	0			88	20.0	16.5-24.0
Jun-22	44	6.8	5.1-9.0	0			44	10.0	7.5-13.2
Jul-22	74	11.5	9.2-14.1	0			74	16.8	13.6-20.6
Total	645	100		201	100	4.1-5.4	440	10.2	

Data Source: Belize Health Information System and Central Medical Laboratory

**Includes: Omicron cases (440), Delta cases (201), Gamma cases (3), and Alpha case (1)*

Omicron had a cumulative incidence rate more than twice that of Delta in both sexes. Regarding Delta, the Orange Walk District accounted for the highest cumulative incidence rate at 5.7 cases per 10,000 persons (95% CI: 4.0-8.0). The Belize District accounted for the highest proportion of cases at 35.8%. Regarding Omicron, the Cayo District accounted for the highest cumulative incidence rate at 15.6 (95% CI: 13.3-18.1). The Belize District accounted for the highest proportion of cases at 54.6%.

Table 3. Prevalence Rate of Major Variants of Concern by Sex, District, and Month, Belize, August 2021

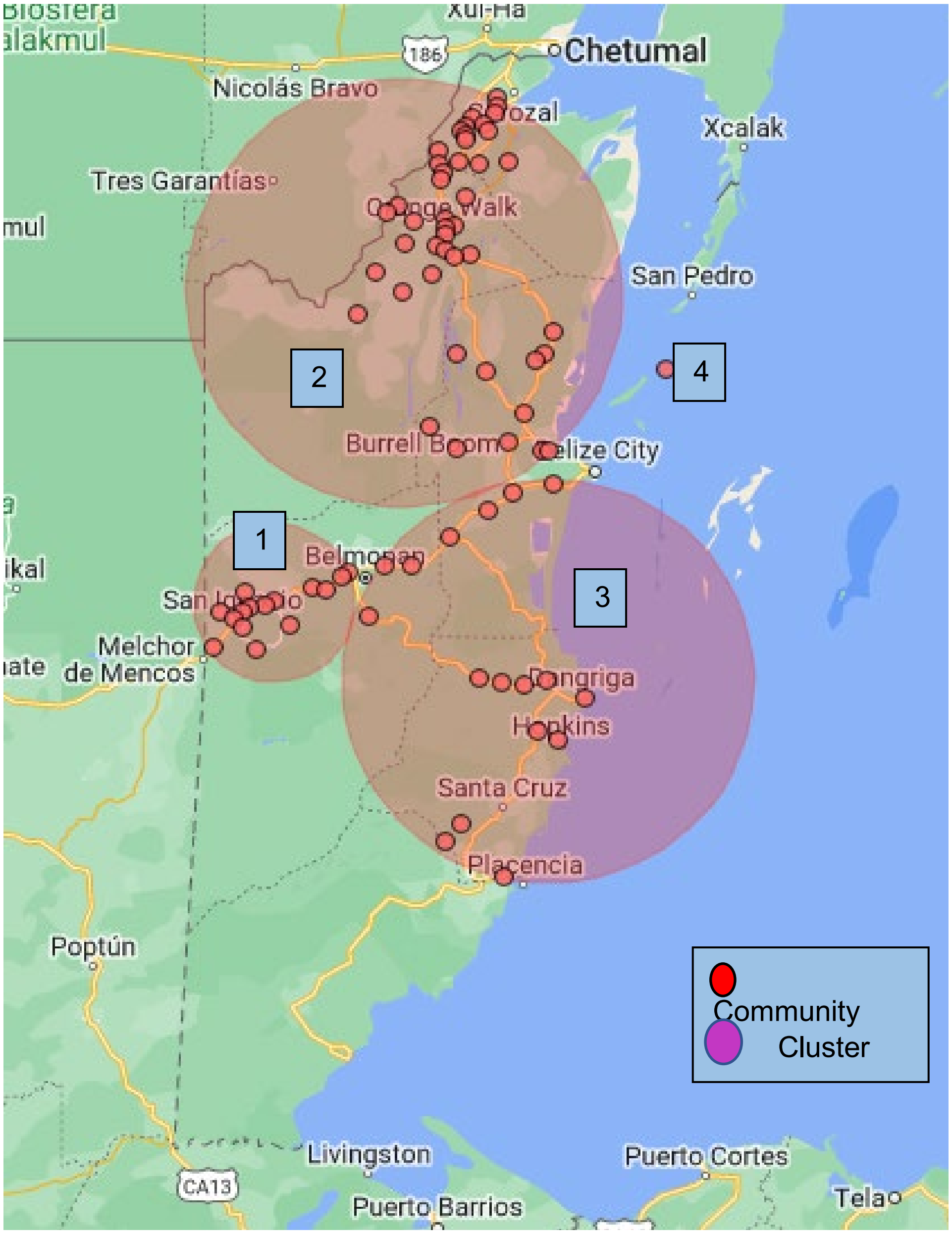
Variable	Delta			Omicron		
	N (%)	Prevalence (x 10,000)	95% CI	N (%)	Prevalence (x 10,000)	95% CI
Sex						
Male	91 (45.3)	4.2	3.3-5.2	195 (44.3)	9.1	7.9-10.4
Female	110 (54.7)	5.1	4.2-6.1	245 (55.7)	11.4	10.0-12.9
District						
Corozal	17 (8.5)	3.3	2.2-4.8	42 (9.5)	8.1	6.0-10.9
Orange Walk	31 (15.0)	5.7	4.0-8.0	66 (27.5)	12.2	9.5-15.4
Belize	72 (35.8)	5.5	4.3-6.9	131 (54.6)	10.0	8.4-11.8
Cayo	46 (22.9)	4.4	3.2-5.8	164 (37.2)	15.6	13.3-18.1
Stann Creek	19 (9.4)	4.0	2.5-6.1	23 (5.2)	4.9	3.2-7.2
Toledo	16 (8.0)	3.9	2.3-6.3	14 (3.2)	3.5	2.0-5.6
Total/National	201 (100)	4.7	4.1-5.4	440 (100)	10.2	9.3-11.2

Data Source: Belize Health Information System and Central Medical Laboratory

Space distribution of VOC

Four VOC high-risk clusters were identified as shown in the spot map displayed in Figure 1. All four were statistically significant (*P* <0.001). The first cluster included 13 communities during the period of July 01 to July 31, 2022, with a relative risk of 15.9 and a log likelihood ratio of 28185.6. The second cluster included 43 communities during the period June 01 to June 30, 2022, with a relative risk of 11.3 and a log likelihood ratio of 18559.4. The third cluster included 15 communities during the period of May 01, 2022, to May 31, 2022, with a relative risk of 19.0 and log likelihood ratio of 27324.0. The fourth cluster included only one community during the period of July 01 to July 31, 2022, with a relative risk of 67.8 and a log likelihood ratio of 1764.7. This was the island of Caye Caulker in the Belize District.

Figure 1. High Risk Clusters of SARS-CoV-2 Variants of Concern, Belize, August 2021-July 2022

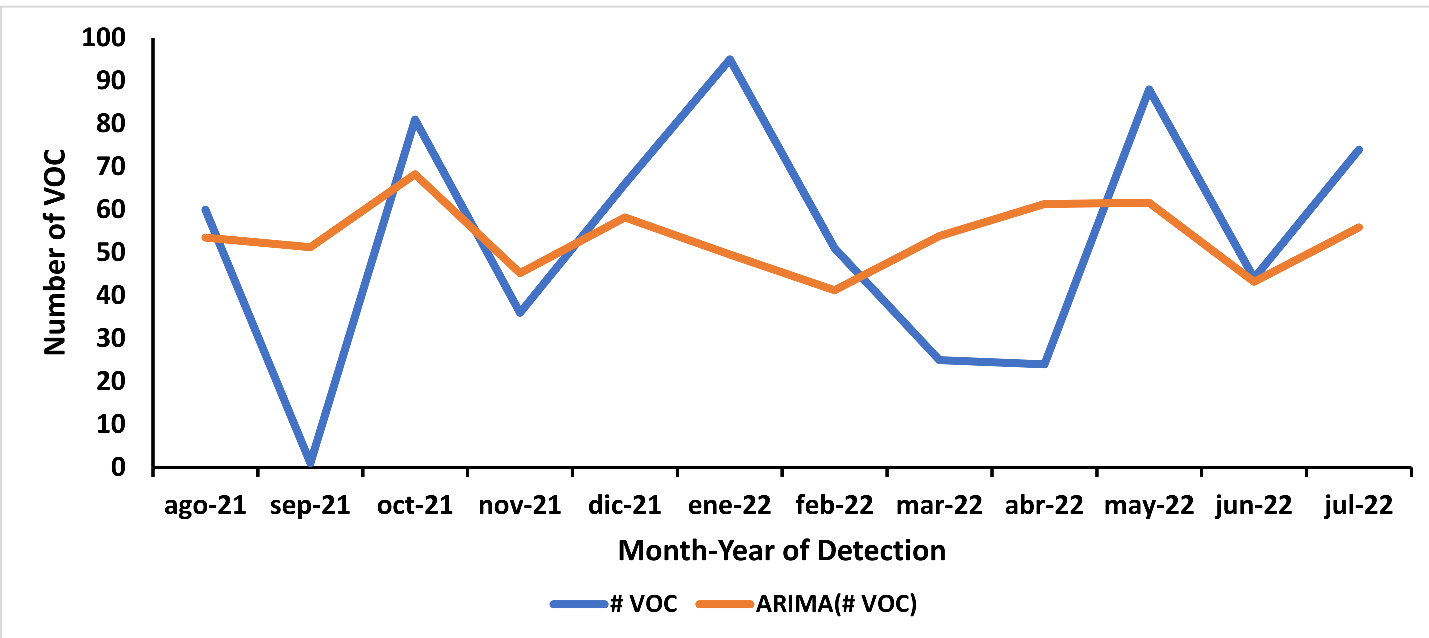


Data Source: Belize Health Information System and Central Medical Laboratory

Time series analysis

The time series distribution of VOC cases (blue line) in the line chart displayed in Figure 2, indicated a pronounced and constant variation of the actual number of cases throughout the study period. The highest peak of cases was in January 2022. There was an overall increasing trend especially towards the end of the study period. The predicted behavior (red line) of the VOC over the space of one year indicated a peaking of the cases in October for the following year. The prediction was for less variation in number of cases for the rest of the year. Infections would decrease but persist through time.

Figure 2. Autoregressive Integrated Moving Average of Number of Variants of Concern Cases, Belize, August 2021 – July 2022



Data Source: Belize Health Information System and Central Medical Laboratory

Discussion

The prevalence of VOC was slightly higher among women than in men. This was inversely different than what was seen in the country for the COVID-19 pandemic [14]. Sampling bias may have been the cause of this scenario because of the testing criteria. The age group of 60 years was the single age group most affected. We also indicate the age groups from 20 to 59 cumulatively account for the highest proportion

(68%) of all VOC cases. These age groups correspond to the working population. Hence, they would be the most exposed and at risk of becoming carriers. The median age of 33 supports these results. It is noteworthy that sampling for children less than five years was among the lowest in the age groups. This was also expected as the social measures included closure of schools and daycares [15]. Omicron was dominant in the USA by the end of 2021 [16]. In Belize, Omicron became by February 2022.

The Cayo District has the second highest population in Belize as per the Statistical Institute of Belize 2021 estimates. Yet, it accounted for the highest proportion of cases and the highest prevalence rate. Belize District has the highest population and accounts for 30% of the national population. Yet, this district accounted for the second highest proportion and third highest cumulative incidence rate of VOC cases. This was even though the only laboratory performing gene sequencing was in Belize City, Belize District. The Toledo District has the least population. It accounted for the lowest proportion and the lowest incidence rate of cases. Additionally, the communities in Toledo are quite widespread compared to the other districts. This dispersion may have impacted the sampling of persons and the integrity of the samples for testing. Samples had to be transported to Punta Gorda Community Hospital Laboratory (district capital) for further transportation to the CML in Belize City (Belize District). Additionally, the distance by road from Toledo to Belize City is the farthest among all the districts. Air transportation was difficult due to the closure of many businesses.

During the study period, Alpha and Gamma variants were no longer a global threat. Delta had replaced them and became dominant from November 2021 to December 2021. Omicron emerged in November 2021 in Africa and became the dominant variant by December 2021 globally [17]. In Belize, Omicron was first detected in December 2021 and completely replaced Delta by February 2022. This may be explained by the greater transmissibility of Omicron [18] whereby subvariants emerged rapidly.

All the clusters were detected in the year 2022. None of the clusters included Belize City which is the community with the largest population (66,083 inhabitants). The second highest population center is

Belmopan City (26,906 inhabitants). Toledo was the only district not included in any cluster. This corelates with it having the lowest cumulative incidence rate and proportion. Of the four high risk clusters, persons living in Caye Caulker were 67.8 times more at risk of being infected with a VOC than those not living in this community. This cluster was composed of only one community which is an island with an estimated population of 2,000 inhabitants and an area of 3.88 km^2. The population density was at 515.5/km^2. This was far above the population density of Belize at approximately 18/km^2. Caye Caulker is a touristic island. In January 2022, tourists were allowed in the country within certain regulations as defined by Statutory Instrument 15 of 2022 with subsequent relaxation of public health measures and restrictions [19]. It may be that the low population in a compact area, leading to a high population density led to a higher risk in this community as observed in a study in the Brazilian island of Ilhabela [20].

The predictive model indicated that for the following year the “movement” of the VOC would have less fluctuation. We infer that there would be less variation in VOC incidence rates leading to a more stabilized circulation with a further gradual decreasing. This may be due to the persons developing immunity whether by previous infection or vaccination [21]. These would lead to decreased transmission of COVID-19.

We described the incidence of VOC in Belize with Delta and Omicron being most dominant. An expected result pertained to those who would be more affected – the working population and the elderly population. An unexpected result related to the identification of the high-risk areas, especially the fourth cluster in Caye Caulker. The forecast indicated a tendency towards a gradual decrease but persistence of cases for 2022.

We consider a few major limitations that may have affected our analysis. Notably, the criterium of a cut-off of 25 or less was inherent to the laboratory procedure. Therefore, may have favored samples of better quality due to collection and/or transportation. The other eligibility criteria for gene sequencing were determined by the health authorities. This skewed towards patients with more severe symptoms and/or outcomes. The ARIMA model requires from 20 to 50 observations but preferably more than 100.

However, we applied it for twelve months instead of 365 days with the intention to capture the health event – infection with VOC [22].

The identification of the high-risk clusters and the temporal behavior of the VOC can guide the targeted strengthening or implementation of prevention and control measures in these communities. Such measures should include greater dissemination of information relating to proper hand hygiene, cough etiquette, proper use of face masks, and patient isolation. The authorities would be able to prioritize allotment of more resources to such high-risk communities. The surveillance of variants through gene sequencing needs to continue. Furthermore, testing of SARS-CoV-2 needs to be integrated in the testing protocol for influenza. This would monitor the circulation of known variants and the emergence of new ones. The country needs to promote the bivalent vaccine to discourage viral transmissibility [23]. Furthermore, studies should be carried out to investigate association of VOC circulation/emergence with disease incidence and severity. The methodology described in this study can be applied to diseases such as dengue and influenza.

Declaration of potential conflicts of interests

The authors have no conflict(s) of interest to declare.

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Contribution of Authors

Aldo Sosa – data collection and analysis, conception and design of study, manuscript writing; Sylvia Sosa – design of the study and critical revision of manuscript.

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