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Effectiveness of COVID-19 vaccines in Ecuador: A test-negative design

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A B S T R A C T

Background: The COVID-19 pandemic poses a significant global health threat, characterized by high morbidity, severity, and the emergence of concerning variants. Latin America has been greatly affected, with high infection and mortality rates. Vaccination plays a crucial role in mitigating severe disease and controlling the pandemic. This study aims to assess the effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 severe acute respiratory infections (SARI) in hospitalized vaccination target groups in Ecuador.

Methods: This is a test-negative design study. We used data reported through sentinel surveillance of SARI between May 2021 and March 2022 in Ecuador. Patients with case criteria of SARI and hospitalized for a minimum of 24 hours were included in the study. Cases were defined as patients with SARI with a positive RT-qPCR test for SARS-CoV-2 and controls were those with a negative result. Information on vaccination status was obtained from the national vaccination registry, a valid dose of vaccination was considered when it was administered at least 14 days prior to symptom onset. Vaccine effectiveness (VE) (1-OR/OR) was calculated using a logistic regression.

Results: A total of 1,277 patients were included in the analysis of VE. The adjusted vaccine effectiveness (aVE) in preventing hospitalization, adjusted for sex, age group, presence of one or more comorbidities, and period of the predominance of the omicron variant, was 44.5% for the partial primary schedule, 74.7% for the complete primary schedule, and 79.9% for the complete primary schedule plus booster doses. The aVE in avoiding ICU admissions was close to 80% with both the complete primary schedule and the booster doses, and in avoiding deaths, the aVE was 89% and 98%, respectively.

Conclusions: In Ecuador, COVID-19 vaccination prevents hospitalizations, ICU admissions, and deaths. The effectiveness of the vaccines improves with more doses, offering increased protection across all age groups.

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2, began in late 2019 and spread rapidly globally. The virus has caused many ambulatory infections, hospitalizations, and deaths, and has also brought about other health concerns, such as sequelae of the disease and mental health problems [1–3]. In response to this, an accelerated production of COVID-19 vaccines occurred involving governments,

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pharmaceutical companies, research institutions, and international organizations [4].

The first COVID-19 vaccines were licensed for emergency use in December 2020, and several other vaccines subsequently become available [5]. The availability of vaccines has varied across different countries and regions, leading to significant disparities in health outcomes during the pandemic. These discrepancies are influenced by factors such as the level of disease transmission and access to healthcare services [6].

The COVID-19 pandemic has had a significant impact in Latin America, with many countries in the region experiencing high rates of infection and death. To respond to this, governments and organizations in the region have been working to acquire and distribute COVID-19 vaccines to their populations. These concerted efforts have resulted in a remarkable surge in the rates of intention to vaccinate within the population across most Latin American countries, reaching an approximate rate of 78 % in 2021 [7,8].

In Ecuador, COVID-19 vaccines became available in January 2021, and since then, four vaccine platforms - Pfizer-BioNTech, AstraZeneca, CanSino, and Sinovac - have been administered. In the first phases of vaccination in the country, immunization of healthcare workers, people over 60 years of age, and vulnerable groups including those with catastrophic illnesses such as cancer, individuals at high risk of mortality due to preexisting conditions like coronary heart disease and diabetes, and individuals with disabilities, were prioritized [9]. By the end of 2021, immunization has been expanded to include children aged 5 years and older. Subsequently, in 2022, vaccination has further extended to children from the age of 3 years, with the administration of booster doses recommended from the age of 12 years. At the beginning of 2022, the primary series vaccination rates for COVID-19 had impressively reached 88 % [10].

Given that the different COVID-19 vaccine platforms have demonstrated high efficacy in clinical trials, it is important to assess whether these technologies work equally well in the real world, in different social, health, and economic contexts, with regards to their effectiveness [11]. This study presents the first analysis of the early effect of vaccination against COVID-19 in Ecuador. In this analysis, we estimated the effectiveness of vaccination against COVID-19 in preventing hospitalization, intensive care unit (ICU) admission, and death from SARS-CoV-2 from May 1, 2021 to March 31, 2022.

Methods

Aim, study design, and data source

This study aims to assess the effectiveness of COVID-19 vaccines in preventing severe acute respiratory infections (SARI) caused by SARS-CoV-2 among the targeted vaccination groups admitted to hospitals within the sentinel SARI network in Ecuador. This is a retrospective case-control study with a negative test design in sentinel hospitals of the intensified surveillance of SARI in Ecuador, including an adaptation for the country from the generic protocol REVELAC-COVID-19 of Evaluation of the effectiveness of the vaccine against COVID-19 in Latin America and the Caribbean [12]. The design of this study is similar to other studies, allowing us to be compared with them [13–15]. The sentinel SARI network is a comprehensive national surveillance system consisting of sixteen strategically selected sentinel hospitals distributed across different regions of the country. Its primary purpose is to monitor and analyze SARI cases nationwide, ensuring robust coverage and data collection [16,17]. The hospitals generate timely information regarding the transmission and positivity rates of various respiratory viruses, including influenza, adenovirus, parainfluenza, respiratory syncytial virus, and other respiratory viruses. The data is collected from SARI-related information recorded by the sentinel hospitals and laboratory results provided by the National Institute for Public Health Research (INSPI) [18].

Secondary data from the SARI network were used to conduct this study. The information hails from 12 hospitals in Ecuador located in six major cities: Cuenca, Ibarra, Guayaquil, Quito, Portoviejo, and Riobamba. The hospitals belong to the Ministry of Public Health and the Ecuadorian Social Security Institute, which are part of the country's comprehensive health network. The hospitals consist of six general hospitals, four specialized hospitals, and two specialty hospitals.

Population and study period

Information was included from patients 3 years of age and older hospitalized in the period between May 1, 2021, and March 31, 2022, with a diagnosis of SARI in any service of the selected sentinel hospitals. All identified SARI patients at the participant hospitals were tested.

Inclusion and exclusion criteria

The inclusion criteria consisted of patients who met the defined case criteria for SARI and were hospitalized for a minimum duration of 24 hours at one of the 12 participating hospitals. Additionally, eligible patients needed to meet the vaccination eligibility criteria and belong to the corresponding group or subgroup where vaccination had already commenced (e.g., specific age range, geographic area, professional group). We specifically included patients who had received their vaccination at least 14 days prior to symptom onset, considering them as having received valid doses for analysis.

Exclusion criteria comprised patients who had been hospitalized within the 14 days preceding their SARI admission, including those transferred between hospitals. Patients who developed symptoms after hospitalization, those with unknown vaccination status, and individuals experiencing symptom onset within 14 days after vaccination were also excluded from the analysis.

Definitions and data collection

A SARI case was defined as a patient admitted to one of the sentinel hospitals during the evaluation period, and who presented a history of fever or temperature $\geq$ 38 °C, cough, with onset of symptoms in the previous ten days, and who required hospitalization. This definition adheres to the standard definition outlined by the Surveillance System, which aligns with the criteria established by the World Health Organization (WHO) [19]. Hospitalization was defined as a minimum hospital stay of 24 h. A COVID-19 case was defined as any patient who met the definition of a SARI case and who presented a respiratory specimen with a positive result for SARS-CoV-2 by RT-qPCR at the time of admission. Patients hospitalized with SARI who had a positive test by RT-qPCR in the 14 days prior to hospitalization were also considered cases. For the analysis of vaccine effectiveness (VE) in preventing admission to intensive care units (ICU), patients with SARI who were hospitalized in the ICU and had a positive RT-qPCR result for COVID-19 were considered cases. In relation to VE in preventing death, cases were those with a positive RT-qPCR result for COVID-19 and who died during hospitalization.

Controls were defined as patients meeting the definition of a SARI case with a negative respiratory specimen for SARS-CoV-2 by RT-qPCR on admission. Controls must not have had a positive result for SARS-CoV-2 within the 14 days preceding hospitalization. For the analysis of VE in preventing admission to ICU, patients with SARI who were not hospitalized in the ICU and who had a negative RT-qPCR result for COVID-19 were considered controls. In relation to VE in preventing death, the controls were patients with negative RT-qPCR results for COVID-19 and who did not die during hospitalization.

The definition of vaccinated with the complete primary series was considered any patient who received two valid doses of Oxford-AstraZeneca ChAdOx1-S, Pfizer-BioNTech BNT162b2, or CoronaVac (Sinovac) vaccines or a valid dose of CanSino; that is to say that in

addition to having received the complete primary series, at least 15 days had elapsed from completion of the primary series to the onset of symptoms. A partial schedule was defined as any patient who had received only one valid dose for two-dose vaccines. A patient who had received one valid dose, specifically a dose administered at least 14 days prior to symptom onset, was classified as being vaccinated with at least one dose. Moreover, a booster dose was defined as an additional administration of the vaccine given after four months completing the full primary series [20].

We also analyzed the homologous schedule, considered when the product used for the first dose is the same used for the second dose (homologous primary schedule), and the homologous booster refers to the use of the same product placed to fulfill the homologous primary schedule. Heterologous schedule: the vaccine product used for the second dose differs from that used for the first dose (heterologous primary schedule). The heterologous booster schedule refers to the administration of a vaccine product that differs from the product(s) previously used for a primary schedule.

The variables extracted from the SARI surveillance databases were gender, age, diagnosed preexisting medical conditions, date of illness onset, date of respiratory specimen collection, virus variant period, ICU admission, death, and vaccination status.

Statistical analysis

Descriptive analysis was conducted by presenting frequency distribution tables for both cases and controls. The age variable was summarized using appropriate measures such as mean and standard deviation or median and quartiles. For the analysis of VE, age was categorized into groups: <16 years, 17–39 years, 40–59 years, 60–74 years, and ≥ 75 years. Comorbidities were summarized as totals, and for the analysis of effectiveness, they were categorized as the presence or absence of one or more comorbidities. VE was calculated as 1-odds ratio/odds ratio of cases versus controls, with a 95% confidence interval (95% CI). To control for confounding factors and to examine multiple interactions between factors, adjusted ORs were calculated using the statistical technique of logistic regression and, from these, the adjusted vaccine effectiveness (aVE). The information was analyzed with the SPSS v-24 statistical program.

Ethical considerations

The institutional review boards of the National Directorate of Health Research of the Ministry of Public Health of Ecuador and the Pan American Health Organization reviewed the protocol and considered it an evaluation of the effectiveness of vaccination (non-intervention study). No personal identifiers were collected.

Results

Patients with SARI (n=5154) were identified in the 12 sentinel hospitals, of whom 1445 met the inclusion and exclusion criteria (Table 1). The evaluation of VE was performed in 1,277 patients with valid doses (Fig. 1). The hospital that contributed to the highest number of SARI cases was Hospital Eugenio Espejo in the city of Quito with 25.5% (n=368), while the hospital that contributed to the lowest number of cases was the Hospital Verdi Cevallos, located in the city of Portoviejo with 1.0% (n=15) of all included SARI sentinel surveillance cases (Table 1).

Characteristics of SARI cases and controls

Table 2 describes the demographic and clinical characteristics of the participants. A total of 566 cases and 711 controls were included for evaluating VE. Among the cases, 11.5% (65/566) had a partial primary schedule, 20.8% (118/566) had a complete primary schedule, and 4% (27/566) had a primary schedule plus a booster dose; 62.9% (356/566) cases did not receive any vaccine dose. Of the controls, 10.1% (72/711) had a partial primary schedule, 45.3% (322/711) had a complete primary schedule, and 12.5% (89/711) had a complete vaccination plus a booster dose; 32.1% (228/711) controls did not receive any dose. None of those evaluated had a valid second booster dose.

The median age of the cases was higher than that of the controls (56 vs. 49 years). Likewise, the minimum age of the cases was 4 years, and the maximum age was 103 years, while in the controls it was 3 and 98 years respectively. The sample considered in the evaluation included a greater number of men than women. In the cases group, the highest number of COVID-19 cases was observed in the age group of 40 to 59 years (36.0%), followed by the age group of 60 to 74 years. In the controls, the highest number of COVID-19 cases was observed in individuals younger than 16 years (24.3%), followed by the age group of over 75 years (22.4%) (Table 2).

A total of 62.9% (356/566) of the cases were not vaccinated compared to 32.1% (228/711) of the controls. 20.8% (118/566) of the cases received the complete primary series compared to 45.3% (322/711) of the controls, and the primary schedule plus booster with one dose was administered to 4.8% (27/566) of the cases and 12.5% (89/711) of the controls (Table 2). When analyzing the administration by the type of vaccine in cases and controls, there was less inoculation in cases than in controls. The most administered vaccine was CoronaVac (Sinovac) with 49.1% (340/693) of all those vaccinated with valid doses, whereas the most administered booster vaccine was Oxford-AstraZeneca ChAdOx1-S with 79.3% (92/116) of all those who received the first booster dose (Table 2).

A total of 79.9% (452/566) of the cases were hospitalized before the presence of the omicron variant compared to 48.4% (344/711) of the

Table 1
Distribution of eligible SARI cases across sentinel hospitals, overall and by SARS-CoV-2 test result. Ecuador, May 1, 2021 - March 31, 2022.

Sentinel hospital	SARI Cases		
	SARS-CoV-2 positive n = 683 n (%)	SARS-CoV-2 negative n = 762 n (%)	Total n = 1445 n (%)
Eugenio Espejo Specialty Hospital	256 (37.5)	112 (14.7)	368 (25.5)
Riobamba General Teaching Hospital	142 (20.8)	69 (9.1)	211 (14.6)
Enrique Garcés General Hospital	127 (18.6)	57 (7.5)	184 (12.7)
Carlos Andrade Marín Specialty Hospital (IESS)	126 (18.4)	189 (24.8)	315 (21.8)
Dr. José Daniel Maridueña Rodríguez Specialized Hospital	10 (1.5)	78 (10.2)	88 (6.1)
San Vicente de Paúl General Hospital	10 (1.5)	33 (4.3)	43 (3.0)
Verdi Cevallos General Hospital	4 (0.6)	11 (1.4)	15 (1.0)
Baca Ortiz Specialized Children's Hospital	3 (0.4)	27 (3.5)	30 (2.1)
Vicente Corral Moscoso General Hospital	2 (0.3)	26 (3.4)	28 (1.9)
Dr. Francisco Icaza Bustamante Specialized Hospital	1 (0.1)	46 (6.0)	47 (3.3)
Homero Castanier Crespo General Hospital	1 (0.1)	70 (9.2)	71 (4.9)
Roberto Gilbert Pediatric Specialized Hospital	1 (0.1)	44 (5.8)	45 (3.1)

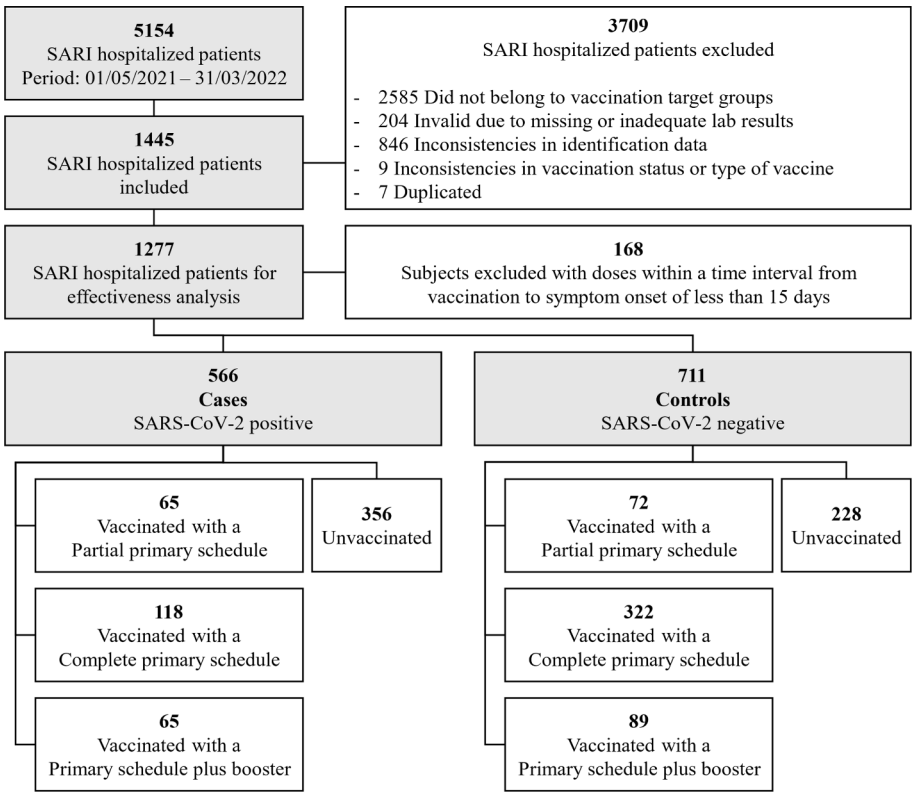

Fig. 1. Selection of severe acute respiratory infections (SARI) patients included in SARS-CoV-2 vaccine effectiveness analyses in Ecuador, May 1, 2021-March 31, 2022.

controls. Among the vaccinated cases, the median number of days from vaccination to symptom onset was 48.0, 150.5, and 40.0 for the first, second, and third doses, respectively, in the cases group. In the control group, the median number of days was 157.0, 153.0, and 53.0 for the first, second, and third doses, respectively.

Effectiveness in preventing hospitalization by the type of vaccination schedule

When evaluating the VE of all vaccine types combined, by number of doses, adjusting the result considering the variables of sex, age group, comorbidity, and predominance of the Omicron variant, a slight decrease in the aVE of the complete schedule and the schedule with booster was observed. The aVE of the partial primary schedule (one dose) was 44.5% (95% CI: 15.8 – 63.5), of the complete primary schedule (two doses) 74.7% (95% CI: 65.4 – 81.5), and 79.9% (95% CI: 65.3 – 88.4) for the complete schedule with a booster dose (Table 3).

Effectiveness in preventing hospitalization by vaccine type

The CoronaVac (Sinovac) vaccine showed aVE for the partial primary schedule, with 44.5% (95% CI: 15.8 – 63.5), being the most administered vaccine in the country for the primary series (Table 3).

The complete primary schedule was homologous in 99.3% (437/440) of all vaccinees with two valid doses. 57.0% (251/440) received CoronaVac (Sinovac), 32.3% (142/440) Pfizer-BioNTech BNT162b2, 8.4% (37/440) Oxford-AstraZeneca ChAdOx1-S, and 1.6% (7/440) CanSino. Irrespective of whether administered as a homologous or heterologous completed primary schedule, Pfizer-BioNTech BNT162b2 exhibited the highest aVE with a rate of 83.1% (95% CI: 73.3 – 89.3), followed by CoronaVac (Sinovac) with 80.1% (95% CI: 71.5 – 86.1), and finally, the recombinant Oxford-AstraZeneca ChAdOx1-S vaccine with 55.7% (95% CI: 10.0 – 78.2). (Table 3). Upon evaluating all vaccines included in this assessment, it is evident that the aVE improves with an increasing number of doses received.. The aVE for the completed primary schedule was not calculated for CanSino since there were only seven patients in this sample.

In the cases group, 7% (27/383) had a complete primary plus booster schedule, while in the control group, the proportion was higher at 28.1% (89/317). Among the cases, 3.0% (11/367) received a heterologous booster consisting of CoronaVac (Sinovac) as the complete primary schedule, along with either Pfizer-BioNTech BNT162b2 or Oxford-AstraZeneca ChAdOx1-S. In the control group, the percentage was higher at 16.5% (45/273). The aVE for this schedule was 93.1% (95% CI: 85.7 – 96.7), as shown in Table 3.

Table 4 displays the adjusted vaccine effectiveness (aVE) among different age groups. It is observed that as the number of vaccine doses administered increases, there is a corresponding improvement in the aVE in all groups. It was not possible to evaluate the aVE in children under 16 years of age due to the small number of cases.

Effectiveness in preventing admission in the ICUs and death

Table 5 shows an aVE of 77.0% (95% CI: 61.8 – 86.1) and 78.4% (95% CI: 54.8 – 89.7) in avoiding admission to ICU for both the complete primary schedule and the complete schedule plus booster, respectively. The aVE in avoiding COVID-19 deaths was 89.1% (95% CI: 80.0 – 94.2) with the complete schedule and reached 98.2% (95% CI: 92.0 – 99.6) with the primary plus booster schedule.

Discussion

The analysis performed in this study shows a significant effectiveness of COVID-19 vaccinations in the prevention of SARI hospitalization due to SARS-CoV-2, from May 1, 2021 to March 31, 2022. The combined result of all vaccines evaluated with the complete primary schedule

Table 2
Demographic and clinical characteristics of enrolled patients SARS-CoV-2 associated with severe acute respiratory infections (SARI), by case status and vaccination status (n = 1277).

Variable	Cases n = 566 n (%)	Controls n = 711 n (%)	*p* value	Vaccinated Partial primary schedule n = 137 n (%)	Vaccinated Complete primary schedule n = 440 n (%)	Vaccinated Primary schedule + booster n = 116 n (%)	Unvaccinated n = 584 n (%)	*p* value
Gender								
Female	270 (47.7)	311 (43.7)	0.158	56 (40.9)	205 (46.6)	52 (44.8)	268 (45.9)	0.694
Male	296 (52.3)	400 (56.3)		81 (59.1)	235 (53.4)	64 (55.2)	316 (54.1)	
Age								
Median (Q1-Q2)	56.0 (43.0 – 72.0)	48.5 (19.0 – 72.0)	<0.0001	50.0 (28.0 – 67.0)	55.0 (26.0 – 74.0)	74.0 (57.0 – 82.5)	49.0 (32.5 – 67.0)	<0.0001
Age groups								
<16 years	6 (1.1)	173 (24.3)	<0.0001	18 (13.1)	72 (16.4)	0 (0.0)	86 (14.7)	<0.0001
16–39 years	105 (18.6)	130 (18.3)		31 (22.6)	58 (13.2)	22 (19.0)	102 (17.5)	
40–59 years	204 (36.0)	125 (17.6)		36 (26.3)	58 (13.2)	10 (8.6)	196 (33.6)	
60–74 years	140 (24.7)	124 (17.4)		33 (24.1)	58 (13.2)	30 (25.9)	112 (19.2)	
≥75 years	111 (19.6)	159 (22.4)		19 (13.9)	76 (17.3)	54 (46.5)	88 (15.1)	
≥one comorbidity*	256 (45.2)	435 (61.2)	<0.0001	71 (51.8)	277 (21.7)	77 (66.4)	266 (45.5)	<0.0001
Asthma	7 (1.2)	51 (7.2)	0.000	7 (5.1)	26 (5.9)	2 (1.7)	23 (3.9)	0.202
Chronic Heart Disease	124 (21.9)	151 (21.2)	0.772	27 (19.7)	100 (22.7)	47 (40.5)	101 (17.3)	<0.0001
Chronic Kidney Disease	27 (4.8)	55 (7.7)	0.032	8 (5.8)	37 (8.4)	19 (16.4)	18 (3.1)	<0.0001
Chronic Liver Disease	8 (1.4)	8 (1.1)	0.645	4 (2.9)	7 (1.6)	1(0.9)	4 (0.7)	0.161
Chronic Lung Disease	17 (3.0)	83 (11.7)	<0.0001	7 (5.1)	53 (12.0)	12 (10.3)	28 (4.8)	<0.0001
Diabetes Mellitus	69 (12.2)	87 (12.2)	0.980	18 (13.1)	60 (13.6)	24 (20.7)	54 (9.2)	0.004
Down's Syndrome	0 (0.0)	1 (0.1)	0.372	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0.593
Immune Disease	24 (4.2)	58 (8.2)	0.005	12 (8.8)	29 (6.6)	5 (4.3)	36 (6.2)	0.534
Neurological Disease	19 (3.4)	51 (7.2)	0.003	5 (3.6)	28 (6.4)	8 (6.9)	29 (5.0)	0.513
Obesity	30 (5.3)	22 (3.1)	0.127	7 (5.1)	21 (4.8)	0 (0.0)	24 (4.1)	0.400
ICU admission	133 (23.5)	150 (21.1)	0.554	36 (26.3)	97 (22.0)	36 (31.0)	114 (19.5)	0.029
Deaths	113 (20.0)	103 (14.5)	0.018	23 (16.8)	66 (15.0)	9 (7.8)	118 (20.2)	0.029
Vaccine type								
Pfizer-BioNTech BNT162b2	53 (9.4)	136 (19.1)	<0.0001	26 (19.0)	143 (32.5)	20 (17.2)	–	
Oxford-AstraZeneca ChAdOx1-S	48 (8.5)	109 (15.3)		28 (20.4)	37 (8.4)	92 (79.3)	–	
CoronaVac (Sinovac)	108 (19.1)	232 (32.6)		83 (60.6)	253 (57.5)	4 (3.4)	–	
CanSino	1 (0.2)	6 (0.8)	0.012	–	7 (1.6)	0 (0.0)	–	
Virus variant period								
Pre-Omicron	452 (79.9)	344 (48.4)	<0.0001	93 (67.9)	213 (48.4)	12 (10.3)	478 (81.8)	<0.0001
Omicron	114 (20.1)	367 (51.6)		44 (32.1)	227 (51.6)	104 (89.7)	106 (18.2)	

*Presence of one or more comorbidities.

showed an aVE of about 75%, and with a booster dose close to 80%. Additionally, the complete schedule, and the schedule with the first booster showed an aVE of around 78% in avoiding ICU admissions; moreover, an aVE in preventing death of about 89% for the complete primary schedule, and 98 % for the complete schedule with a booster dose.

Our results are lower than those obtained by Liu et al. [21] who analyzed 32 studies that evaluated the effectiveness of complete primary schedules during 2021, which found an effectiveness of 93% (95% CI: 89 – 96) for hospitalization, 96% (95% CI: 93 – 98) for ICU, and 95% (95% CI: 92 – 98) for avoiding death. Our study's lower VE results may be attributed to several factors. Firstly, the variation in study design between our test-negative design and Liu et al.'s systematic review, which included cohort and case-control studies, can introduce methodological differences and potential biases that influence estimated VE [22,23]. Additionally, the emergence of the Omicron variant is a critical consideration. Our study was conducted during a period when the Omicron variant was present in the study population, allowing us to capture its potential impact on VE. In contrast, Liu et al.'s study was conducted prior to the emergence of the Omicron variant and therefore did not include cases associated with this particular variant. The unique characteristics of the Omicron variant, such as potential immune escape and increased transmissibility [24–26], may have influenced the VE in our study population, leading to divergent results compared to Liu et al.'s findings. To obtain a comprehensive understanding of vaccine performance against different SARS-CoV-2 variants, future studies should aim to incorporate data on variant-specific effectiveness. This will enable a more accurate assessment of VE in the context of evolving viral variants and provide valuable insights for public health interventions.

Table 3
Evaluation of the effectiveness of COVID-19 vaccines in preventing hospitalization for SARI.

	Cases n (%)	Controls n (%)	VE % (95% CI)	aVE* % (95% CI)
	Vaccinated	Vaccinated		
Partial primary schedule	**65 (15.4)**	**72 (24.0)**	**42.2 (15.9 – 60.2)**	**44.5 (15.8 – 63.5)**
Pfizer-BioNTech BNT162b2	11 (2.6)	15 (5.0)	53.1 (NE)	NE
Oxford-AstraZeneca ChAdOx1-S	13 (3.1)	15 (5.0)	44.4 (NE)	NE
CoronaVac (Sinovac)	41 (9.7)	42 (14.0)	37.5 (1.0 – 60.6)	42.6 (5.0 – 65.3)
Complete primary schedule	**118 (24.9)**	**322 (58.5)**	**76.5 (69.3 – 82.1)**	**74.7 (65.4 – 81.5)**
Pfizer-BioNTech BNT162b2	36 (7.6)	107 (19.4)	78.5 (67.4 – 85.7)	83.1 (73.3 – 89.3)
Oxford-AstraZeneca ChAdOx1-S	15 (3.2)	22 (4.0)	56.3 (14.1 – 77.8)	55.7 (10.0 – 78.2)
CoronaVac (Sinovac)	66 (13.9)	187 (34.0)	77.4 (68.7 – 83.7)	80.1 (71.5 – 86.1)
CanSino	1 (0.2)	6 (1.1)	89.3 (10.7 – 98.7)	NE
Primary schedule plus booster**	**27 (7.0)**	**89 (28.1)**	**80.6 (69.2 – 87.8)**	**79.9 (65.3 – 88.4)**
Pfizer-BioNTech BNT162b2	6 (1.5)	14 (4.4)	72.7 (27.5 – 89.6)	83 (52.5 – 93.9)
Oxford-AstraZeneca ChAdOx1-S	20 (5.2)	72 (22.7)	82.2 (70.0 – 89.5)	90.4 (82.9 – 94.6)
CoronaVac (Sinovac)	1 (0.3)	3 (1.0)	78.6 (NE)	NE
Heterologous booster***	**11 (3.0)**	**45 (16.5)**	**84.3 (69.1 – 92.1)**	**93.1 (85.7 – 96.7)**

VE: Vaccine effectiveness, **aVE:** Vaccine effectiveness adjusted for variables: sex, age group, comorbidity, and period of predominance of the omicron variant, **NE:** Not estimated, not significant.
*For the logistic regression, unvaccinated patients were used as the reference category.
**Primary schedule with both homologous and heterologous boosters.
***Sinovac complete primary schedule + booster with either Oxford-AstraZeneca ChAdOx1-S or Pfizer-BioNTech BNT162b2.

The calculated aVE of Pfizer-BioNTech BNT162b2 vaccine for the complete primary schedule was 83% in preventing hospitalizations due to SARI caused by COVID-19, a result that is consistent with information published in other studies, which have shown a VE of 84% to 86% for hospitalization due to COVID-19 [21,27,28]. Zeng et al. [29] reported a high effectiveness of the booster dose in preventing hospitalization; however, the study found that the effectiveness of all vaccines decreases against new variants, especially omicron, but also against new variants. We found a booster dose effectiveness of 83% in preventing hospitalization, our data coincide with the aforementioned study, which also showed that the effectiveness of all vaccines decreased against the new variants, especially omicron. We believe that this result is because since January 2022, there has been a predominance of the omicron variant in the country; however, given the limited sample size, it was not possible to make a precise estimate for the period of greatest circulation of this variant.

The effectiveness of the Oxford-AstraZeneca ChAdOx1-S vaccine with the complete primary schedule to prevent hospitalizations due to COVID-19 was 55.7%, lower than that reported by Bouillon et al. [30], that indicates an effectiveness of around 91%. This is probably due to the small number of subjects who received the primary homologous schedule with this vaccine in Ecuador. Nevertheless, it was the vaccine that was most frequently administered as a booster dose, demonstrating greater effectiveness, comparable to that described by Zeng et al. [29].

The effectiveness found for the CoronaVac (Sinovac) vaccine in preventing hospitalizations due to SARI by COVID-19 was 43% for the partial primary schedule and 80% for the complete primary schedule. Our results are comparable to those of a study conducted in Chile [31], of 37% and 90% respectively. However, the results of that study came before the appearance of the omicron variant, and therefore, the effectiveness of the complete schedule could have been different. Although this vaccine was not used as a first booster dose in Ecuador, at the time of the data cut-off, the administration of a heterologous booster dose increased the effectiveness in preventing hospitalization to 93%.

Table 4
Evaluation of the effectiveness of COVID-19 vaccines in preventing hospitalization for SARI by age group.

	Cases n (%)	Controls n (%)	VE % (95% CI)	aVE* % (95% CI)
	Vaccinated	Vaccinated		
<16 years of age (n = 179)				
Partial primary schedule	0 (0)	18 (10.4)	NE	NE
Complete primary schedule	3 (50.0)	72 (41.6)	14.9 (NE)	14.9 (NE)
16–39 years of age (n = 235)				
Partial primary schedule	12 (11.3)	19 (14.6)	64.0 (18.0 – 84.3)	61.9 (14.4 – 83.6)
Complete primary schedule	22 (21.0)	58 (44.6)	78.4 (59.2 – 88.6))	78.2 (58.3 – 88.6)
Primary schedule plus booster	6 (5.7)	16 (12.3)	78.6 (40.8 – 92.3)	78.9 (40.4 – 92.5)
40–59 years of age (n = 329)				
Partial primary schedule	22 (10.8)	14 (11.2)	51.9 (NE)	51.5 (NE)
Complete primary schedule	29 (14.2)	58 (46.4)	81.9 (73.2 – 91.2)	81.5 (67.1 – 89.6)
Primary schedule plus booster	3 (1.5)	7 (5.6)	86.9 (47.1 – 96.7)	88.2 (51.6 – 97.1)
60–74 years of age (n = 264)				
Partial primary schedule	21 (15.0)	12 (9.7)	32.9 (NE)	29.3 (NE)
Complete primary schedule	31 (22.1)	58 (46.8)	79.6 (62.7 – 88.8)	80.0 (62.8 – 89.2)
Primary schedule plus booster	7 (5.0)	23 (18.5)	88.4 (70.1 – 95.5)	87.3 (67.3 – 95.1)
>75 years of age (n = 270)				
Partial primary schedule	10 (9.0)	9 (5.7)	39.4 (NE)	47.8 (NE)
Complete primary schedule	33 (29.7)	76 (47.8)	76.4 (57.1 – 87.0)	74.9 (53.6 – 86.4)
Primary schedule plus booster	11 (9.9)	43 (27.0)	86.1 (69.2 – 93.7)	85.4 (67.3 – 93.5)

VE: Vaccine effectiveness, **aVE:** Vaccine effectiveness adjusted for variables: sex, comorbidity, and period of predominance of the omicron variant, **NE:** Not estimated, not significant.
*For the logistic regression, unvaccinated patients were used as the reference category.

Table 5
Evaluation of the effectiveness of COVID-19 vaccines in preventing ICU admission and deaths for SARI.

	Cases n (%) Vaccinated	Controls n (%) Vaccinated	VE % (95 %CI)	aVE* % (95% CI)
ICU admission				
Partial primary schedule	17 (12.8)	53 (9.4)	20.0 (NE)	NE
Complete primary schedule	29 (21.8)	254 (45.3)	71.6 (54.5 – 82.1)	77.0 (61.8 – 86.1)
Primary schedule plus booster	11 (8.3)	64 (11.4)	57.0 (14.1 – 78.5)	78.4 (54.8 – 89.7)
Death				
Partial primary schedule	11 (9.7)	58 (9.9)	57.3 (14.2 – 78.7)	64.7 (23.8 – 83.6)
Complete primary schedule	21 (18.6)	270 (46.2)	82.5 (70.6 – 89.6)	89.1 (80.0 – 94.0)
Primary schedule plus booster	2 (1.8)	79 (13.5)	94.3 (76.2 – 98.6)	98.2 (92.0 – 99.6)

VE: Vaccine effectiveness, **aVE:** Vaccine effectiveness adjusted for variables: sex, age group, comorbidity, and period of predominance of the omicron variant, **NE:** Not estimated,
*For the logistic regression, unvaccinated patients were used as the reference category.

The vaccines showed a similar effectiveness among the age groups 16 to 75 years for the complete primary schedule of approximately 80% but decreased to 75% in those older than 75 years. This might be because at the later ages of life, the immune response is less intense to vaccination, and therefore, lower VE in preventing COVID-19 is expected [32–35]. However, the booster dose increased the VE, reaching more than 85%.

To our knowledge, this is the first study that reports the effectiveness of vaccines against COVID-19 in Ecuador. One study strength is that all sentinel hospitals collected information using national surveillance guidelines, systematically looking for SARI cases, allowing similar data to be obtained between institutions. We adopted a methodology formally accepted to evaluate VE, the "test-negative design", in which the same clinical case definition is used for enrolling both cases and controls, and laboratory testing is subsequently used to distinguish which patients were cases and which were controls, being convenient and efficient. This approach increases the similarity between cases and controls, thus minimizing selection bias.

However, our study has some limitations: first, it was based on an existing sentinel surveillance system that was not designed to generate VE estimates for SARS-CoV-2. Second, due to the observational nature of the data, our study could have been affected by some confounding factors due to differences between cases and controls, especially in terms of health care-seeking behavior or risk of infection, which could have been affected by changes in virus transmission dynamics during the study data collection period. Third, the evaluation was performed on a retrospective dataset obtained from secondary sources, SARI sentinel surveillance records, vaccination records and records of RT-qPCR and viral genotyping results. The databases were analyzed separately and then consolidated into a single database. Erroneous information was found due to inadequate recording of the unique linkage code between the databases; therefore, there is a risk of data loss. Finally, despite the advantage of the sentinel surveillance system of being able to pool data from several institutions and cities in the country, we were unable to obtain large sample sizes, which limited our ability to make more precise estimates at the disaggregated level for variables such as SARS-CoV-2 variant type. Furthermore, VE evaluation in groups under 17 years of age was not possible due to the small prevalence of SARI cases associated with COVID-19 in this group.

Conclusion

Vaccination against SARS-CoV-2 is effective in protecting against severe forms of COVID-19, to prevent hospitalization, ICU hospitalization, and deaths from this disease. All vaccines analyzed in this study were effective when a complete primary plus booster series was used.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

[1] Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. Nature 2022 613:7942 [Internet]. 2022 Dec 14 [cited 2023 Jan 29];613(7942):130–7. Available from: https://www.nature.com/articles/s41586-022-05522-2.
[2] Xin H, Wu P, Wong JY, Cheung JK, Lau EHY, Leung GM, et al. Hospitalizations and mortality during the first year of the COVID-19 pandemic in Hong Kong, China: An observational study. Jan 1 [cited 2023 Jan 29];30. Available from: Lancet Reg Health West Pac [Internet] 2023. http://www.thelancet.com/article/S2666606522002607/fulltext.
[3] Rajkumar RP. COVID-19 and mental health: A review of the existing literature. Asian J Psychiatr 2020;52. 102066, Aug 1.
[4] Middleton J, Adongo PB, Low WY, Magaña L. Global network for academic public health statement on the World Health Organization's response to the COVID-19 pandemic. Int J Public Health [Internet] 2020. Dec 1 [cited 2023 Jan 29];65(9):1523. Available from: /pmc/articles/PMC7518398/.
[5] Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons, and prospects. Aug 10 [cited 2023 Jan 29, Available from: Immunity [Internet] 2021;54(8):1636–51. http://www.cell.com/article/S1074761321003034/fulltext.
[6] Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Sep 1 [cited 2023 Jan 29, Available from: Lancet Infect Dis [Internet] 2022;22(9):1293–302. http://www.thelancet.com/article/S1473309922003206/fulltext.
[7] Schwalb A, Armyra E, Méndez-Aranda M, Ugarte-Gil C. COVID-19 in Latin America and the Caribbean: Two years of the pandemic. Sep 1 [cited 2023 Jan 29, Available from: J Intern Med [Internet] 2022;292(3):409–27. https://pubmed.ncbi.nlm.nih.gov/35411985/.
[8] Alarcón-Braga EA, Hernandez-Bustamante EA, Salazar-Valdivia FE, Valdez-Cornejo VA, Mosquera-Rojas MD, Ulloque-Badaracco JR, et al. Acceptance towards COVID-19 vaccination in Latin America and the Caribbean: A systematic review and meta-analysis. Travel Med Infect Dis [Internet]. 2022 Sep 1 [cited 2023 Jan 29];49. Available from: https://pubmed.ncbi.nlm.nih.gov/35680058/.

[9] Ministerio de Salud Pública. Plan Nacional de Vacunación e Inmunización contra el COVID – 19 "PLAN VACUNARSE" Ecuador 2021 [Internet]. 2021 [cited 2023 May 6]. Available from: https://www.salud.gob.ec/wp-content/uploads/2021/05/01-Plan-nacional-de-vacunacion-e-inmuniczacion-contra-el-COVID-19-Ecuador-2021-1.pdf.

[10] Ministerio de Salud Pública del Ecuador. Vacunómetro COVID-19 [Internet]. 2023 [cited 2023 Jan 29]. Available from: https://app.powerbi.com/view?r=eyJrIjoiYTkzNTFkMmUtZmUzNi00NDcwLTg0MDEtNjFkNzhhZTg5ZWYyIiwidCI6IjcwNjIyMGRiLTliMjktNGU5MS1hODI1LTI1NmIwNmQyNjlmMyJ9&pageName=ReportSection.

[11] Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol 2021 21:10 [Internet]. 2021 Aug 9 [cited 2023 Jan 29];21(10):626–36. Available from: https://www.nature.com/articles/s41577-021-00592-1.

[12] Organización Panamericana de la Salud / Organización Mundial de la Salud. Protocolo genérico REVELAC-COVID-19 [Internet]. [cited 2023 Jan 31]. Available from: https://www.paho.org/es/documentos/protocolo-generico-revelac-covid-19.

[13] Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. Aug 20 [cited 2023 Jan 29];374. Available from: BMJ [Internet] 2021. https://pubmed.ncbi.nlm.nih.gov/34417165/.

[14] Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. May 13 [cited 2023 Jan 29];373. Available from: BMJ [Internet] 2021. https://pubmed.ncbi.nlm.nih.gov/33985964/.

[15] Reynolds MW, Secora A, Joules A, Albert L, Brinkley E, Kwon T, et al. Evaluating real-world COVID-19 vaccine effectiveness using a test-negative case-control design. Nov 1 [cited 2023 Jan 29, Available from: J Comp Eff Res [Internet] 2022;11(16):1161–72. https://pubmed.ncbi.nlm.nih.gov/36148919/.

[16] Ministerio de Salud Pública. Información – Infecciones Respiratorias Agudas Graves [Internet]. [cited 2023 Jul 6]. Available from: https://www.salud.gob.ec/influenza/.

[17] Ministerio de Salud Pública. Ministerio de Salud Pública. Sistema de Vigilancia de Infecciones Respiratorias Agudas Graves [Internet]. 2023 [cited 2023 Jul 6]. Available from: https://aplicaciones.msp.gob.ec/IRAG/php/users/index.php.

[18] Instituto Nacional de Investigación en Salud Pública. Instituto Nacional de Investigación en Salud Pública - INSPI [Internet]. [cited 2023 Jul 6]. Available from: http://www.investigacionsalud.gob.ec/.

[19] World Health Organization (WHO). WHO surveillance case definitions for ILI and SARI [Internet]. 2014 [cited 2023 Jul 6]. Available from: https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari#:~:text=SARI%20case%20definition,within%20the%20last%2010%20days.

[20] Ministerio de Salud Pública. Cuatro meses es el intervalo para la aplicación del refuerzo COVID-19 [Internet]. 2022 [cited 2023 Feb 1]. Available from: https://www.salud.gob.ec/cuatro-meses-es-el-intervalo-para-la-aplicacion-del-refuerzo-covid-19/.

[21] Liu Q, Qin C, Liu M, Liu J. Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: a systematic review and meta-analysis. Dec 1 [cited 2023 Jan 30, Available from: Infect Dis Poverty [Internet] 2021;10(1):1–15. https://idpjournal.biomedcentral.com/articles/10.1186/s40249-021-00915-3.

[22] Dean NE, Hogan JW, Schnitzer ME. Covid-19 vaccine effectiveness and the test-negative design. Oct 7 N Engl J Med 2021;385(15):1431–3.

[23] Lewnard JA, Patel MM, Jewell NP, Verani JR, Kobayashi M, Tenforde MW, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. Jul 13 Epidemiology 2021;32(4):508–17.

[24] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. Apr 21 N Engl J Med 2022;386(16):1532–46.

[25] Medigeshi GR, Batra G, Rathna Murugesan D, Thiruvengadam R, Chattopadhyay S, Das B, et al. Sub-optimal neutralisation of omicron (B.1.1.529) variant by antibodies induced by vaccine alone or SARS-CoV-2 Infection plus vaccine (hybrid immunity) post 6-months. EBioMedicine [Internet]. 2022 [cited 2023 Jul 17];78:103938. Available from: https://doi.org/10.1016/j.

[26] Willett BJ, Grove J, Maclean OA, Wilkie C, De Lorenzo G, Furnon W, et al. SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway. [cited 2023 Jul 17]; Available from: https://doi.org/10.1038/s41564-022-01143-7.

[27] Talic S, Shah S, Wild H, Gasevic D, Maharaj A, Ademi Z, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. Nov 18 [cited 2023 Feb 13];375. Available from: BMJ [Internet] 2021. https://www.bmj.com/content/375/bmj-2021-068302.

[28] Higdon MM, Wahl B, Jones CB, Rosen JG, Truelove SA, Baidya A, et al. A systematic review of coronavirus disease 2019 vaccine efficacy and effectiveness against severe acute respiratory syndrome coronavirus 2 infection and disease. Open Forum Infect Dis [Internet]. 2022 Jun 1 [cited 2023 Feb 13];9(6). Available from: /pmc/articles/PMC9047227/.

[29] Zeng B, Gao L, Zhou Q, Yu K, Sun F. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. BMC Med [Internet]. 2022 Dec 1 [cited 2023 Jan 30];20(1). Available from: https://pubmed.ncbi.nlm.nih.gov/35606843/.

[30] Bouillon K, Baricault B, Botton J, Jabagi MJ, Bertrand M, Semenzato L, et al. Effectiveness of BNT162b2, mRNA-1273, and ChAdOx1-S vaccines against severe covid-19 outcomes in a nationwide mass vaccination setting: cohort study. BMJ Medicine [Internet]. 2022 Jun 1 [cited 2023 Jan 30];1(1):e000104. Available from: https://bmjmedicine.bmj.com/content/1/1/e000104.

[31] Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. Sep 2 [cited 2023 Jan 30, Available from: New Engl J Med [Internet] 2021;385(10):875–84. https://www.nejm.org/doi/10.1056/NEJMoa2107715.

[32] Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med [Internet]. 2021 Dec 9 [cited 2023 Jan 30];385(24):e85. Available from: https://pubmed.ncbi.nlm.nih.gov/34706170/.

[33] Britton A, Fleming-Dutra KE, Shang N, Smith ZR, Dorji T, Derado G, et al. Association of COVID-19 vaccination with symptomatic SARS-CoV-2 infection by time since vaccination and delta variant predominance. Mar 15 [cited 2023 Jan 30, Available from: JAMA [Internet] 2022;327(11):1032–41. https://pubmed.ncbi.nlm.nih.gov/35157002/.

[34] Tartof SY, Slezak JM, Puzniak L, Hong V, Frankland TB, Ackerson BK, et al. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: A retrospective cohort study. May 1 [cited 2023 Jan 30];9. Available from: Lancet regional health Americas [Internet] 2022. https://pubmed.ncbi.nlm.nih.gov/35187521/.

[35] Kshirsagar M, Nasir M, Mukherjee S, Becker N, Dodhia R, Weeks WB, et al. The risk of hospitalization and mortality after breakthrough SARS-CoV-2 infection by vaccine type: observational study of medical claims data. JMIR Public Health Surveill [Internet]. 2022 Nov 8 [cited 2023 Jan 30];8(11):e38898. Available from: https://pubmed.ncbi.nlm.nih.gov/36265135/.