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Seroprevalence, immune response dynamics, and incidence of COVID-19 after CoronaVac vaccination in a fully vaccinated small municipality in Northeast Brazil: a population-based surveillance study

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Title: Seroprevalence, immune response dynamics, and incidence of COVID-19 after CoronaVac vaccination in a fully vaccinated small municipality in Northeast Brazil: a population-based surveillance study

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Abstract

Background: CoronaVac was the first COVID-19 vaccine deployed at scale in Brazil, yet evidence on its real-world impact and the durability of immune responses in small municipalities remains limited. Understanding vaccine performance in diverse settings is essential for informing public health strategies. This study aimed to evaluate the seroprevalence and durability of the immune response and investigate the real-world impact of the CoronaVac vaccine in adults from a small municipality in Northeast Brazil.

Methods: This is an analytical, observational, population-based study comprising a cross-sectional seroepidemiological survey and a retrospective cohort analysis conducted in Guaramiranga, Ceará, between September 2021 and August 2022. A total of 1,714 individuals who had received two doses of CoronaVac were included. Serological survey (anti-SARS-CoV-2 IgG), molecular testing (RT–PCR), and linkage of official vaccinations and notification

records were performed. The analyses included Fisher's Exact Test for categorical comparisons and Poisson regression with robust variance to estimate prevalence ratios.

Results: The seroprevalence of neutralizing IgG antibodies was 83.1% (95% CI: 79.7–86.0). Seropositivity showed a significant temporal decline, decreasing from 94.3% (≤180 days post-vaccination) to 79.4% (181–270 days post-vaccination) (p=0.0012). RT–PCR positivity was 15.3% (95% CI: 12.8–18.2%), increasing to 29.0% 270 days after the second dose (p=0.0006). In multivariable Poisson regression, time since D2 (PR=0.9987; p<0.001), age (PR=0.9924; p<0.001), and male sex (PR=0.9176; p=0.018) were associated with lower seropositivity. A total of 116 symptomatic cases and 2 severe cases (0.117%) were confirmed, corresponding to an observed incidence of severe disease of 117 per 100,000 person-years (95% CI: 14–422).

Conclusions: This population-based surveillance study demonstrates that universal CoronaVac vaccination was followed by a robust initial humoral immune response, which subsequently declined over time. The observed low incidence of severe disease in this fully vaccinated population is consistent with protection against severe outcomes. These findings reinforce the need for booster doses and ongoing epidemiological surveillance in small municipalities.

Clinical trial number: not applicable.

Keywords: COVID-19; SARS-CoV-2; Seroprevalence; Humoral immunity; Inactivated virus vaccines.

Background

The COVID-19 pandemic, caused by SARS-CoV-2, was one of the greatest health emergencies of the 21st century. With unequal impacts among countries and regions, the disease resulted in

more than 6.9 million confirmed deaths by the end of 2023, with devastating consequences for health systems, economies, and societies [1] [2].

Brazil stands out as one of the epicenters of the pandemic, ranking among the countries with the highest absolute number of cases and deaths. The country is marked by multiple waves; early circulation of variants such as Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529); and significant challenges in coordinating responses across a territory with profound regional inequalities [3] [4]. By the end of 2023, Brazil had more than 38 million confirmed cases and 708 thousand deaths, highlighting the severity and scale of the pandemic in the country [5]. Beyond confirmed deaths, studies have documented substantial excess mortality during the pandemic period, reflecting both direct COVID-19 deaths and indirect impacts on the health system and population health outcomes. For instance, an analysis of Civil Registry data estimated 39,146 excess deaths in Brazil from March to May 2020 alone, with the highest burden concentrated in the capitals of the North, Northeast, and Southeast regions [6]. Another study quantifying the burden in Disability-Adjusted Life Years (DALYs) found that COVID-19 led to 5.4 million DALYs in 2020, ranking it as the leading cause of disability that year in Brazil [7]. This excess mortality and high burden underscore the critical importance of vaccination strategies in reducing both the direct disease burden and the pandemic's collateral health consequences.

In this context, the introduction of safe and effective vaccines was essential to reduce severe cases and deaths. Multiple real-world effectiveness studies have demonstrated that COVID-19 vaccines substantially reduce severe disease and death, even as protection against infection wanes over time. For example, a large registry-based study in Brazil found that while the effectiveness of CoronaVac against severe cases waned, it remained above 25% after 19 weeks,

and protection against death remained above 50% for up to 20 weeks, with boosters significantly enhancing protection [8]. However, relevant questions remain regarding the duration of the immune response, real-world vaccine effectiveness, differences among vaccine platforms, and the impact of emerging variants on the protection conferred by vaccines available at the time [9-12].

Although serological surveys have been conducted in Brazilian capitals, most have focused on large urban contexts, with scarce data from small cities. Large-scale national household surveys such as EPICOVID-19 [13] and its successor, EPICOVID 2.0 [14], have provided valuable population-level estimates but have had limited coverage of small municipalities, as they focused on the most populous city within each of Brazil's 133 intermediate regions. A recent systematic review revealed substantial regional heterogeneity in COVID-19 seroprevalence in Brazil [15], underscoring the importance of local studies that account for cultural, demographic, and territorial differences and that can serve as models for surveillance in resource-limited settings.

CoronaVac, developed by Sinovac Biotech in partnership with the Butantan Institute, was the first vaccine used on a large scale in Brazil and played a strategic role at the start of the national immunization campaign, which was initiated in January 2021 [16]. It is an inactivated virus vaccine that is administered on a two-dose schedule with an interval of 14–28 days [17]. Although clinical trials and observational studies have demonstrated its efficacy in preventing severe forms of the disease, evidence of its effectiveness in small communities remains scarce [18] [19]. Such analyses are fundamental in a world with many regional inequalities that influence both viral exposure and the population’s response to public health measures [20] [21].

Guaramiranga, a mountainous municipality in Ceará, Northeast Brazil, was the first to fully vaccinate its adult population against COVID-19. The first dose (D1) was administered between January 20, 2021, and April 1, 2022, and the second dose (D2) was administered between February 18, 2021, and July 6, 2022, achieving 100% coverage of the registered population. Between March 2020 and February 2022, 4,663 suspected cases were reported, of which 1,565 were laboratory-confirmed, and 6 resulted in death [22] [23]. This context makes the municipality a unique setting for investigating vaccine effectiveness. In addition to high vaccine coverage, previous studies have indicated the maintenance of preventive behaviors even after vaccination [24]. Additionally, the possible influence of hybrid immunity (prior infection followed by vaccination) may have contributed to the population's immune response.

Therefore, this study aims to evaluate the seroprevalence of neutralizing IgG antibodies against SARS-CoV-2 in vaccinated adult residents of Guaramiranga, Ceará, between September 2021 and August 2022, as well as the duration of the immune response induced by vaccination. Furthermore, we sought to investigate the impact of the CoronaVac vaccine in reducing the incidence of severe COVID-19 in this same population.

Methods

Study Design and Period

This was an analytical, observational, population-based study comprising two complementary components: (1) a cross-sectional seroepidemiological survey to assess seroprevalence and

associated factors at various time points post-vaccination, and (2) a retrospective cohort analysis to calculate the incidence of symptomatic and severe COVID-19 cases in the vaccinated population. The cross-sectional serological survey was conducted among residents of the municipality of Guaramiranga, Ceará, from September 2021 to August 2022, with blood samples collected at a single time point per participant. The retrospective cohort analysis included follow-up of all fully vaccinated individuals from 14 days after the second dose (D2) through August 31, 2022.

Study Site

Guaramiranga has an estimated population of 5,193 inhabitants [25], of whom 4,002 were aged 18 years or older, with 4,219 registered in the official system of the State Health Department of Ceará (CE) at the time. The municipality is located in the Baturité massif region (4°15′01″ S, 38°55′04″ W), and borders the cities Pacoti and Palmácea to the north, Mulungu to the south, Baturité to the east, and Caridade to the west.

Following a decision by the State Health Department at the time, this Ceará municipality was the first to vaccinate 100% of its registered adult population. At the beginning of 2021, it received 5,187 COVID-19 vaccines for D1; of these, 3,328 doses were CoronaVac from Sinovac/Butantan, 1,685 doses were ChAdOx1 nCoV-19 (Vaxzevria) from AstraZeneca/Oxford/Fiocruz, and 174 doses were BNT162b2 (Comirnaty) from Pfizer-BioNTech [26].

Study population

The study population comprised all residents of Guaramiranga aged 18 years or older who received at least one dose of a COVID-19 vaccine. Participant recruitment occurred after vaccination. The participants were invited and included voluntarily after signing the informed consent form (ICF). After the patients signed the ICF, peripheral venous blood and nasal swab samples were collected.

For the clinical outcomes analyses, only individuals who were fully vaccinated with two doses of CoronaVac and aged 18 years or older were included. Those with insufficient biological samples for laboratory testing or incomplete data were excluded.

Operational Definitions [27] [28]

1 COVID-19 case: An individual with fever and/or respiratory symptoms who tested positive for SARS-CoV-2 by RT–PCR or rapid antigen testing. Those presenting any of the following manifestations were classified as severe cases: (1) tachypnea (≥ 30 breaths per minute); (2) oxygen saturation at rest ≤ 93%; (3) ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ≤ 300 mmHg; or (4) severe disease complications (e.g., respiratory failure, need for mechanical ventilation, septic shock, or failure of nonrespiratory organs).

2 Influenza-like illness (ILI): Individuals with acute respiratory syndrome characterized by fever or reported fever accompanied by cough, sore throat, runny nose, or difficulty breathing, according to the Brazilian Ministry of Health guidelines.

3 Severe acute respiratory syndrome (SARS): ILI presenting with dyspnea/respiratory discomfort or persistent chest pressure or oxygen saturation below 95% on room air or bluish coloration of the lips or face. In children, nasal flaring, cyanosis, intercostal retractions, dehydration, and anorexia are also observed.

4 Fully vaccinated: Individuals who received two doses of a COVID-19 vaccine according to national/regional immunization recommendations

5 Vaccinated with different intervals: Individuals fully vaccinated but with an extended interval between doses compared with the vaccine label or national/regional immunization recommendations. The second-dose vaccination window was 28 days.

6 Immunized: Individuals potentially protected by vaccination from 14 days after D2.

Collection of Biological Samples

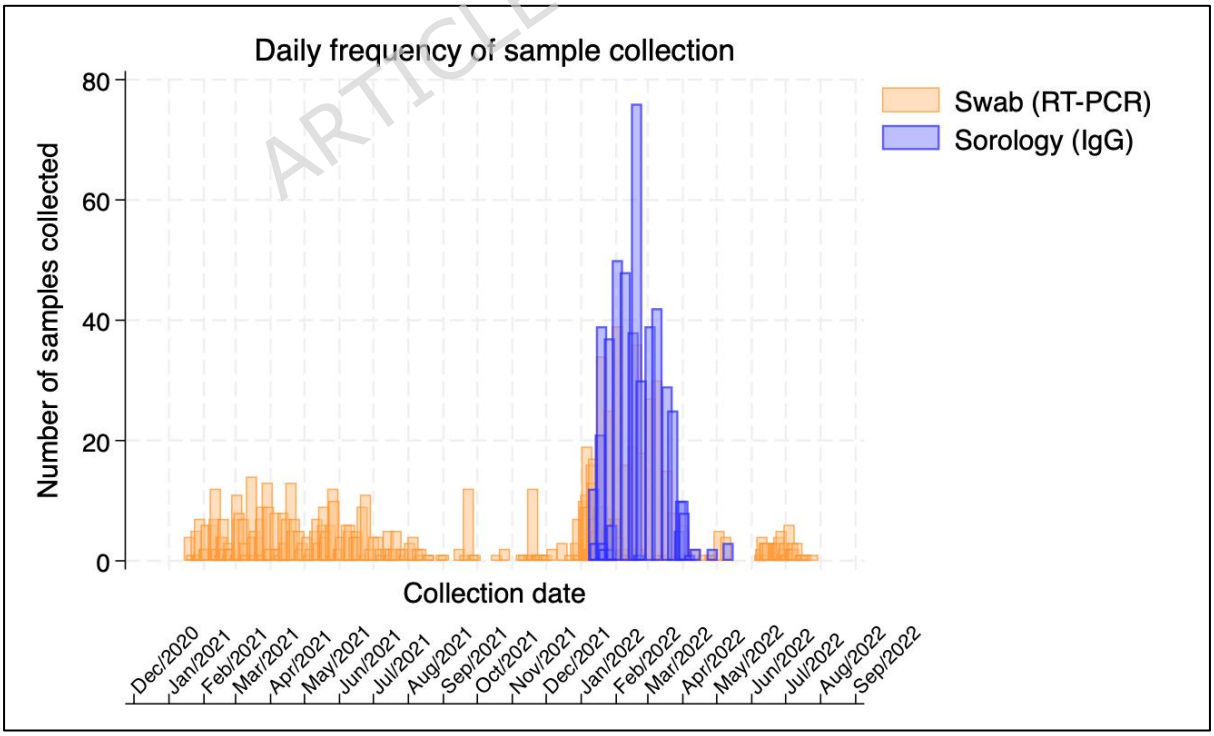
Biological samples were collected and registered in the Laboratory Environment Manager system (GAL) of the Brazilian Ministry of Health. Subsequently, aliquots were sent to the Central Public Health Laboratory (LACEN) in Fortaleza, Ceará, where they were processed and stored.

1 Blood collection for serology: For all collections, 10 mL of venous blood was obtained in tubes with a separator gel. The samples were centrifuged at 2,500 × g for 10 minutes at room

temperature, and the resulting serum was aliquoted and stored at -80 °C until serological assays were performed (Figure 1).

2 Nasal swab collection for RT–PCR: Respiratory secretion samples were obtained from the participants' nasopharynx by inserting a sterile swab into each nostril following the standard nasopharyngeal collection protocol [29]. The two swabs (one from each nostril) were placed in the same tube containing viral transport medium, constituting a single biological sample for laboratory processing. The samples were maintained at 4-8 °C until analysis. After this initial collection, new swab tests were performed on demand, generally associated with flu-like symptoms or suspected infection, and the same participant could have multiple samples collected throughout the study.

Figure 1. Period of biological sample collection.



Laboratory methods

1 Viral RNA detection by RT–PCR: Nasopharyngeal swab samples were analyzed for the presence of SARS-CoV-2 RNA using real-time reverse transcription polymerase chain reaction (RT-PCR) at the Central Public Health Laboratory of Ceará (LACEN-CE). The primary kit used was the Kit Molecular SARS-CoV-2 E/RP (Bio-Manguinhos/Fiocruz, Rio de Janeiro, Brazil), which targets the viral E gene for SARS-CoV-2 detection and the human RNase P gene as an endogenous internal control [30]. This kit accounted for the majority of tests performed (69.2%). Amplification and detection were carried out on the 7500 Real-Time PCR System (Applied Biosystems/Thermo Fisher Scientific, Waltham, USA). Additional commercial kits were used based on reagent availability at LACEN-CE during the study period. All assays were performed following the manufacturer's instructions and in accordance with the Brazilian Ministry of Health guidelines.

2 Detection of neutralizing IgG antibodies: The quantitative determination of IgG antibodies against the SARS-CoV-2 spike protein was performed using the SARS-CoV-2 IgG II Quant chemiluminescent microparticle immunoassay (CMIA) (Abbott Laboratories, Abbott Park, USA) on the Alinity i automated analyzer (Abbott Laboratories, Abbott Park, USA) [31]. This assay targets IgG antibodies against the receptor-binding domain (RBD) of the S1 subunit of the viral spike protein, a marker highly correlated with neutralizing activity in serum samples [1]. Samples with a result of 50.0 AU/mL or higher were classified as reactive (positive), and those below 50.0 AU/mL as non-reactive (negative), following the manufacturer's recommended cutoff.

Secondary data sources

1 Vaccination registry (Municipal Health Secretariat of Guaramiranga): Access was obtained to the COVID-19 vaccination database of the Secretariat. This registry is not publicly available online and does not provide a permanent URL. The records were provided upon formal request and authorization as locally generated tables (Word files) exported from the municipal immunization system. The registry included demographic data for vaccinated individuals, vaccination dates, vaccine brands, and batch numbers. The first vaccination campaign in the municipality occurred from January 20, 2021, to July 6, 2022. To organize the databases, the Brazilian Individual Taxpayer Registry number (CPF) was used as a unique identifier.

2 Laboratory results (LACEN-CE): The COVID-19 test results database of Guaramiranga, recorded in the GAL System of LACEN-CE, was used for the period from June 4, 2020, to July 31, 2022. From the start of the vaccination campaign until July 2022, 5,613 biological samples were analyzed: 1,693 serum samples for IgG detection and 3,920 nasal swab samples for RT–PCR.

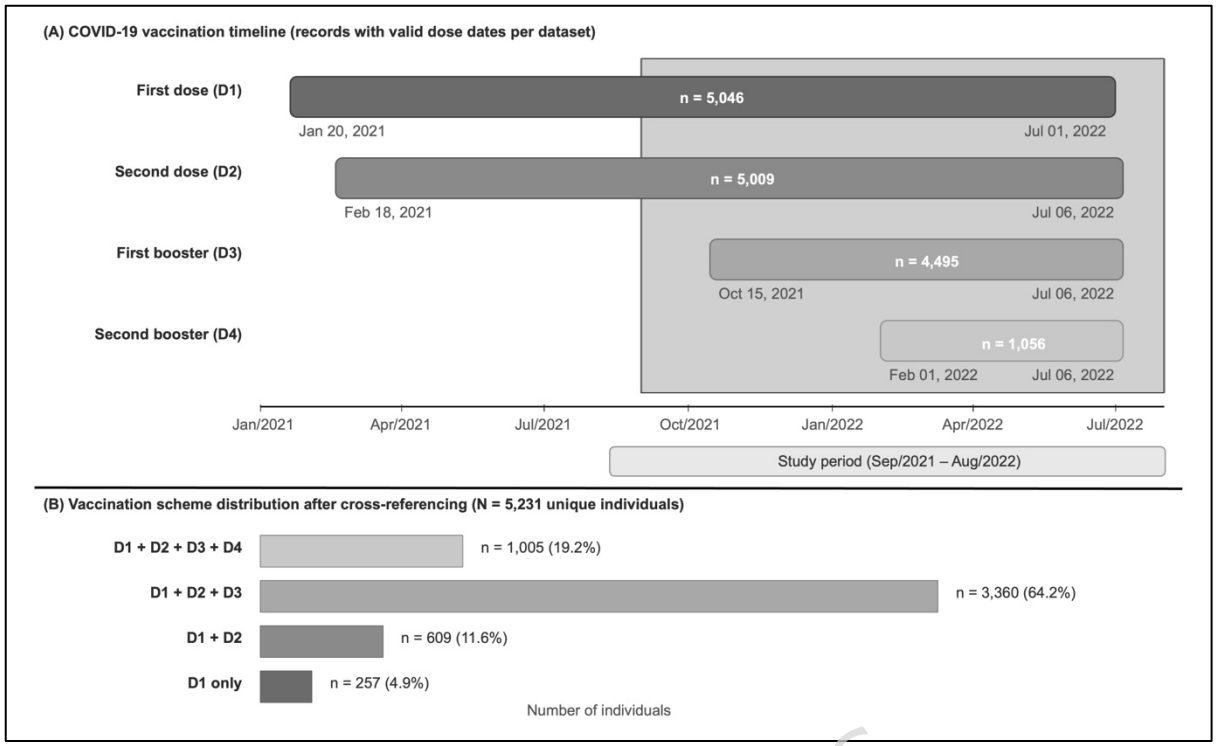
3 Case notification (e-SUS Notifica): The e-SUS Notifica system, a national epidemiological surveillance platform, was used for recording suspected cases of influenza-like illness (ILI) and severe acute respiratory syndrome (SARS) [32]. The system contains demographic data, dates of symptom onset, confirmatory test results, and clinical outcomes. Records of residents of Guaramiranga notified between January 1, 2022, and August 31, 2022, corresponding to the postvaccination follow-up phase, were extracted. These records were linked to the vaccination database by CPF to identify symptomatic cases in vaccinated individuals.

Database processing

Deterministic database linkage was performed using CPF as the unique identifier. The process included excluding records with invalid, missing, or symbol-only CPFs; removing duplicates; standardizing names and dates; and merging with the vaccination databases of Guaramiranga, laboratory results (LACEN), and notifications (e-SUS).

Initially, four databases from the Guaramiranga Municipal Health Secretariat were used, referring to COVID-19 vaccine administrations: first dose (D1), second dose (D2), first booster (D3), and second booster (D4), totaling 5,231 unique records. Cross-referencing the databases revealed the following vaccination schemes: 257 individuals received only D1; 609 received only D1 and D2; 3,360 received up to the first booster (D3); and 1,005 completed the scheme with the second booster (D4). The observed dates in the organized database indicate that D1 was administered between January 20, 2021 and July 1, 2022; D2, between February 18, 2021 (28 days after D1) and July 6, 2022; D3, between October 15, 2021 and July 6, 2022; and D4, between February 1, 2022 and July 6, 2022 (Figure 2). After the vaccination data were consolidated, linkage with the LACEN and e-SUS Notifica databases was also performed via CPF.

Figure 2. COVID-19 vaccination timeline and vaccination scheme distribution in Guaramiranga, Ceará, Brazil.



(A) Timeline of COVID-19 vaccine dose administration dates (D1–D4) as recorded in the four dose-specific datasets provided by the Guaramiranga Municipal Health Secretariat. Numbers within bars indicate the number of valid records (after removal of missing, invalid, or duplicate CPF entries) in each dose-specific dataset. The shaded area and dashed lines indicate the study observation period (September 2021 to August 2022). Note: individual-level counts per dataset differ from the total number of unique individuals (N = 5,231) because each dataset was independently cleaned prior to cross-referencing, and some individuals appeared in later dose datasets (e.g., D2) without a corresponding record in D1, reflecting administrative reclassifications during the vaccination campaign.
(B) Distribution of final vaccination schemes identified after cross-referencing all four dose-specific datasets using the individual taxpayer identification number (CPF) as a unique identifier (N = 5,231 unique individuals). Percentages are calculated relative to the total number of unique individuals.
Abbreviations: D1, first dose; D2, second dose; D3, first booster; D4, second booster; CPF, Cadastro de Pessoas Físicas (Brazilian individual taxpayer registration number).

Following deterministic database linkage using CPF as the unique identifier, the process included excluding records with invalid, missing, or symbol-only CPFs; removing duplicates; standardizing names and dates; and merging with the vaccination databases of Guaramiranga, laboratory results (LACEN), and notifications (e-SUS). The detailed flow of records through each step of data processing and cohort construction is presented in Figure 3.

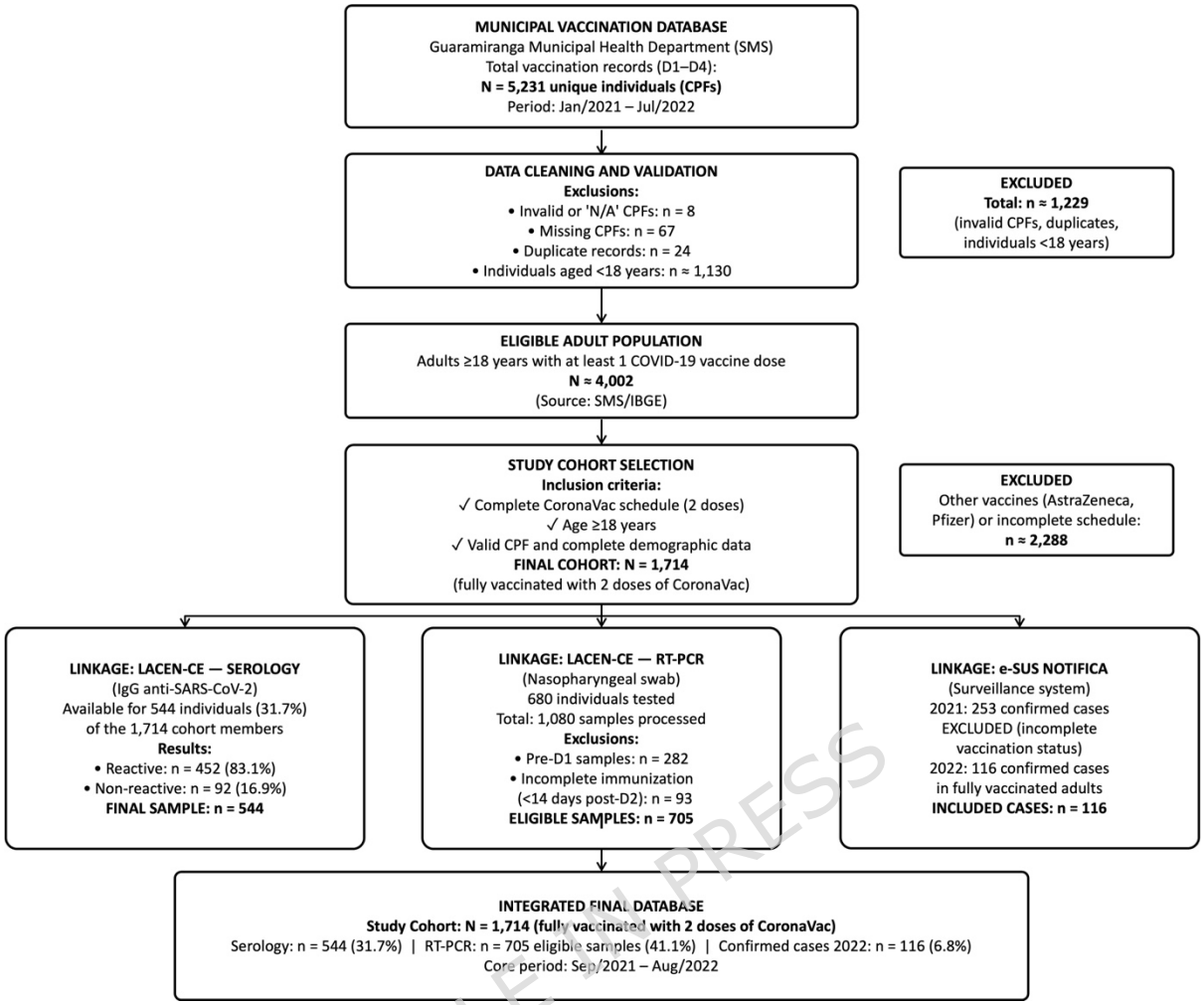
The final study database consisted of a cohort of 1,714 fully vaccinated adult residents of Guaramiranga (two doses of CoronaVac). For integrated analysis, the vaccination data were linked to three additional information sources: serological data, RT–PCR results, and symptomatic case notifications:

1. Serological data were available for 544 individuals (31.7%), corresponding to serum samples analyzed for anti-SARS-CoV-2 IgG antibodies.

2. RT–PCR data: Among vaccinated individuals, 680 underwent molecular testing, resulting in the processing of 1,080 nasal swab samples. For analysis of infections occurring after complete immunization, 282 samples collected before the first dose (pre-D1) and 93 samples from incompletely immunized individuals (collected before D2, on the same day as D1, or less than 14 days after D2) were excluded. This process resulted in a final set of 705 samples (65.3%) eligible for analysis.

3. Case notification data: Records of COVID-19 patients notified in the e-SUS notification system between January 2021 and December 2022 were analyzed. In 2021, 253 confirmed cases (no SARS) were identified but were not eligible for this analysis due to a lack of vaccination status data. For the analysis, 116 confirmed COVID-19 cases among fully vaccinated adults in 2022 were identified.

Figure 3. Flowchart of data linkage, cleaning, and participant selection process. Guaramiranga, Ceará, Brazil, 2021–2022.



Abbreviations: SMS, Secretaria Municipal de Saúde (Municipal Health Department); IBGE, Instituto Brasileiro de Geografia e Estatística (Brazilian Institute of Geography and Statistics); CPF, Cadastro de Pessoas Físicas (Brazilian individual taxpayer registry number, used as unique identifier for record linkage); D1–D4, first through fourth vaccine doses; LACEN-CE, Laboratório Central de Saúde Pública do Ceará (Ceará State Central Public Health Laboratory); IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; e-SUS Notifica, Brazilian national surveillance notification system for COVID-19.

Data analysis

1 Seroprevalence assessment

Seroprevalence was calculated as the proportion of individuals with a "reactive" result, with 95% confidence intervals (95% CI) calculated using the exact binomial method (Clopper-

Pearson). For incidence rates (events per person-time), 95% CIs were computed using exact Poisson limits. Continuous variables are described by medians and interquartile ranges (IQRs), and categorical variables are described by absolute and relative frequencies. Group comparisons were performed via Pearson's chi-square test for qualitative variables and the Mann–Whitney test for quantitative variables.

2 Evaluation of the immune response and associated factors

For descriptive purposes, seroprevalence was analyzed cross-sectionally in temporal strata defined by the interval between the second dose (D2) and the collection date (0–90, 91–180, 181–270, and >270 days). It is important to note that this temporal analysis is cross-sectional in nature: different individuals were sampled at different times post-vaccination, and the observed differences in seropositivity across time strata reflect differences between groups of individuals sampled at different intervals, not changes within the same individuals over time. This distinction is critical for interpreting the apparent "waning" pattern. To identify factors associated with seropositivity, a predictive model was constructed via Poisson regression with robust variance. This approach was chosen to directly estimate the prevalence ratio (PR), as the outcome was common in the sample (>10% prevalence), as it avoids the bias inherent in odds ratios for common outcomes and provides more interpretable effect measures. The multivariate model included time since the second dose (D2), age, and sex as independent variables. Adjusted PRs with their respective 95% confidence intervals (95% CIs) were calculated.

3 Evaluation of post-vaccination clinical outcomes

Owing to the absence of an unvaccinated control group in the municipality, which precludes direct calculation of vaccine effectiveness, the epidemiological analysis focused on describing two impact metrics. First, the cumulative incidence of symptomatic infection was calculated, defined as the proportion of individuals who developed the disease during the study period. Additionally, the incidence rate of severe disease was calculated, expressed as the number of events per 100,000 person-years of follow-up, with its 95% confidence interval. For the incidence rate calculation, the follow-up time (person-time) was calculated for each individual from 14 days after the second dose (D2) until the date of SARS diagnosis or the study end date (August 31, 2022), whichever occurred first. Individuals who did not present the outcome were censored at the study end date.

4 Statistical Analysis

Analyses were performed via Stata BE 19.0 (StataCorp LP, College Station, TX, USA). A significance level of 95% was adopted for all the statistical tests. The complete analysis code, including data cleaning, descriptive analyses, and regression modeling, is provided in Supplementary Material 1.

Ethics

This study was approved by the Research Ethics Committee of the Faculty of Medicine of the Unichristus University Center (CAAE 51252221.3.0000.5049). Written informed consent was obtained from all participants. All procedures involving human subjects complied with the ethical standards of the Declaration of Helsinki (1964/2013). Portions of the text were revised for language clarity and English translation using an AI-assisted writing tool, under full author supervision. The tool was not used for data analysis or interpretation.

Results

Vaccination coverage

A total of 1,714 individuals fully vaccinated with two doses of the CoronaVac vaccine were registered, corresponding to 42.8% of the adult population of Guaramiranga. The median age was 36 years (IQR: 26–52), with a predominance of females (58.3%). The age group distribution showed the highest concentration between 18–30 years (32.4%), followed by 31–40 years (22.1%), 41–50 years (18.7%), 51–60 years (14.2%), and >60 years (12.6%). Regarding the vaccination priority category, most vaccinated individuals belonged to the "General Population" group (68.5%), followed by "Elderly" (18.3%), "Health Professionals" (8.7%), and other categories (4.5%).

The median interval between D1 and D2 was 27 days (IQR: 24–89). Half of the vaccinated individuals (50.1%) received D2 at intervals < 28 days, whereas 49.9% received D2 at intervals ≥ 28 days. A wide variation in the interval was observed, ranging from 17–287 days, reflecting changes in the recommendations of the National Immunization Program (PNI) during the campaign (Table 1).

Table 1 – Demographic and vaccination characteristics of the population vaccinated with CoronaVac (n=1,714), Guaramiranga, CE, 2021–2022.

Characteristic	n (%)

Age group (years)	
18-30	556 (32.4%)
31-40	379 (22.1%)
41-50	320 (18.7%)
51-60	243 (14.2%)
>60	216 (12.6%)
Sex	
Female	999 (58.3%)
Male	715 (41.7%)
Vaccination category	
General Population	1174 (68.5%)
Elderly	314 (18.3%)
Healthcare Professionals	149 (8.7%)
Others	77 (4.5%)
D1-D2 interval (days)	27 (24-89)
<28 days	859 (50.1%)
≥28 days	855 (49.9%)

Seroprevalence of neutralizing anti-SARS-CoV-2 IgG antibodies

Considering only the 1,714 individuals vaccinated with CoronaVac, 544 serum samples were analyzed. The samples mostly originated from males (n = 324; 59.6%), the "general population" category (n = 407; 74.8%), individuals of mixed race (pardo) (n = 339; 62.3%), individuals with a median age of 34 years (18–76; IQR 18), and individuals considered immunized (more than 14 days after D2) (n = 540; 99.3%). The overall seroprevalence of neutralizing anti-SARS-CoV-2 IgG antibodies was 83.1% (95% CI: 79.7%–86.0%), with 452

individuals presenting a "reactive" result. Only 16.9% remained seronegative (92/544; 95% CI: 13.9%–20.3%). The median interval between D2 and serum collection was 210 days (IQR: 175–223), indicating that most samples were collected between 6 and 8 months after vaccination.

The binomial test indicated that the observed seroprevalence (83.1%) was significantly greater than the null hypothesis of 50% ($p<0.001$), confirming a robust immune response in the vaccinated population.

Cross-sectional association between time since vaccination and seropositivity

To evaluate the association between postvaccination time and seropositivity, Fisher's Exact Test was used to compare the proportions of reactive and nonreactive individuals among the four temporal strata. Due to very small sample sizes in the earliest period (0–90 days, n=7), this stratum was combined with the 91–180 days stratum for the primary analysis, resulting in three temporal categories: ≤180 days (n=141), 181–270 days (n=399), and >270 days (n=4). It is important to emphasize that these strata represent different individuals sampled at different times post-vaccination, not longitudinal follow-up of the same individuals. The analysis revealed a progressive decline in seropositivity across these strata (Fisher's Exact Test p=0.0012). The main decline was observed between the ≤180 days period and the 181–270 days period (6–9 months), an absolute reduction of 14.9 percentage points. Although data for periods longer than 270 days are limited (n=4), they suggest that this downward trend continues (Table 2). Importantly, the estimate for the >270-day stratum should be interpreted with caution due to the small sample size in this period, which yields unstable estimates and wide confidence intervals. The primary inferential analysis of the temporal association between time since

vaccination and seropositivity is therefore based on the adjusted Poisson regression model (Table 3), which treats time as a continuous variable and provides more stable estimates.

Table 2 – Seropositivity of anti-SARS-CoV-2 IgG antibodies according to the time elapsed since the second dose of the CoronaVac vaccine.

Post-D2 period (days)	n	Reactive n (%)	95% CI	Non-Reactive n (%)	95% CI
≤180	141	133 (94.3%)	89.4–97.5%	8 (5.7%)	2.5–10.6%
181–270	399	317 (79.4%)	75.1–83.3%	82 (20.6%)	16.7–24.9%
>270	4	2 (50.0%)	6.8–93.2%	2 (50.0%)	6.8–93.2%
Total	544	452 (83.1%)	79.7–86.0%	92 (16.9%)	14.0–20.3%

The Poisson regression model with robust variance revealed that time since D2, age, and sex were independently associated with lower antibody prevalence (Table 3). After mutual adjustment, for each additional day since the second dose, the prevalence of seropositivity decreased by 0.13% (PR = 0.9987; 95% CI: 0.9981–0.9994; p<0.001). Similarly, each additional year of age was associated with a 0.76% reduction in seroprevalence (PR = 0.9924; 95% CI: 0.9891–0.9958; p<0.001). Additionally, male sex was associated with an 8.2% lower prevalence of seropositivity than female sex was (PR = 0.9176; 95% CI: 0.8543–0.9856; p = 0.018). The predicted decline in seropositivity based on this model is illustrated in Figure 4.

Figure 4. Predicted seropositivity decline by time since second dose of CoronaVac vaccination, estimated using Poisson regression with robust variance (adjusted for age and sex), Guaramiranga, CE, 2022.

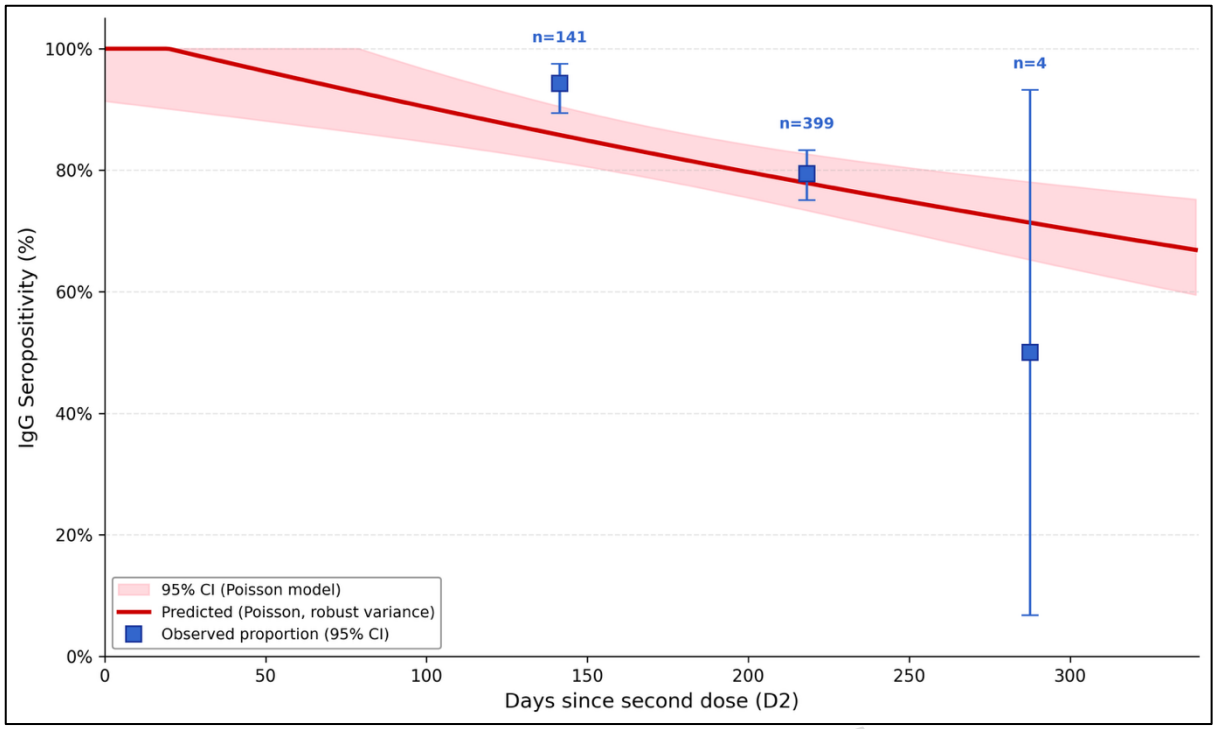


Table 3 – Factors associated with seropositivity: Adjusted Poisson regression model with robust variance.

Variable	Adjusted PR	95% CI	p value
Time since D2 (days)	0.9987	0.9981 - 0.9994	<0.001
Age (years)	0.9924	0.9891 - 0.9958	<0.001
Sex (Male vs. Female)	0.9176	0.8543 - 0.9856	0.018

Viral RNA detection by RT–PCR

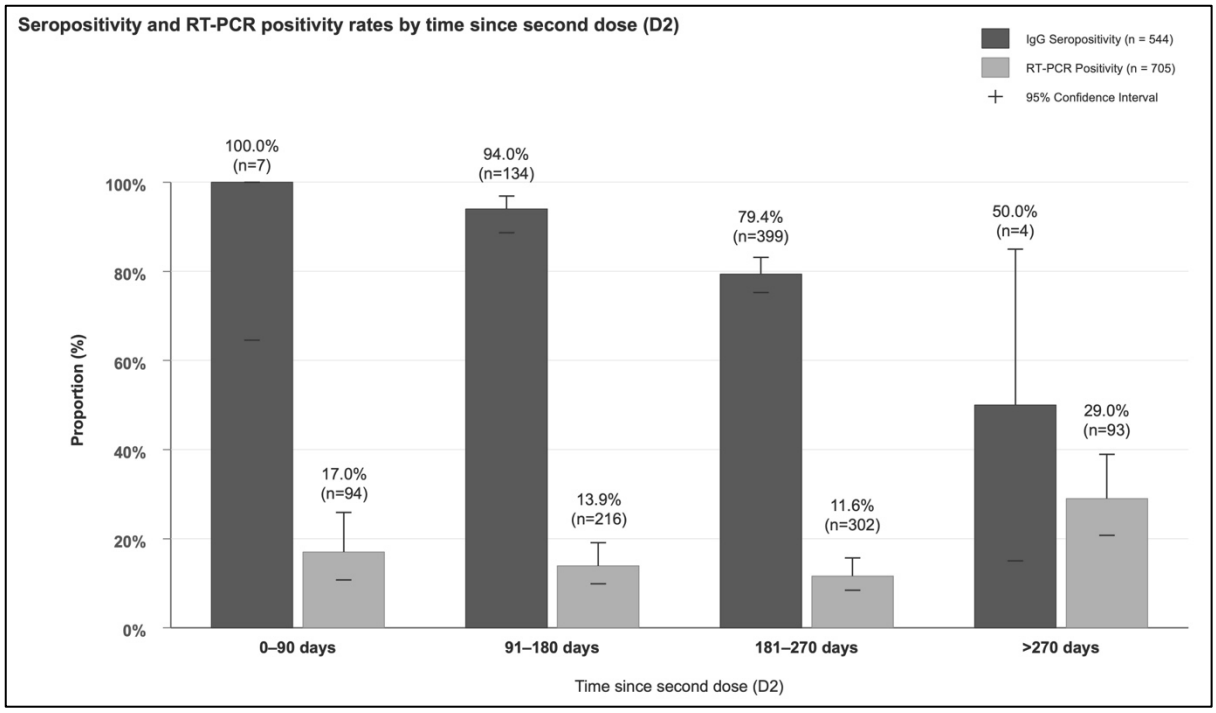
Among the 705 analyzed samples, 108 (15.3%; 95% CI: 12.8%–18.2%) yielded a "detectable" result, and 597 (84.7%; 95% CI: 81.8%–87.3%) yielded a "not detectable" result. This observed positivity rate (15.3%) was significantly lower than the null hypothesis of 50% (binomial test: $p<0.001$), indicating partial protection against infection detectable by RT–PCR.

A significant increase in the RT–PCR positivity rate over time was observed, with a pattern inverse to that of seropositivity (Figure 5). The chi-square test demonstrated a statistically significant association between time since D2 and RT–PCR positivity (χ^2=17.27; p=0.0006). Notably, there was an abrupt increase in positivity after 270 days (29.0%), nearly double the rates observed in earlier periods (11–17%), which coincided with the decline in seropositivity during the same period (Table 4).

Table 4 – RT–PCR positivity rate according to the time elapsed since the second dose of the CoronaVac vaccine.

Post-D2 period (days)	**n**	**Detectable n (%)**	**Not Detectable n (%)**	**χ^2**	**p value**
0-90	94	16 (17.0%)	78 (83.0%)	17.27	0.0006
91-180	216	30 (13.9%)	186 (86.1%)		
181-270	302	35 (11.6%)	267 (88.4%)		
>270	93	27 (29.0%)	66 (71.0%)		
Total	**705**	**108 (15.3%)**	**597 (84.7%)**		

Figure 5. Temporal trends in IgG seropositivity and RT-PCR positivity rates according to time elapsed since the second dose of the CoronaVac vaccine, Guaramiranga, Ceará, 2021–2022.



Dark gray bars represent the proportion of individuals with reactive anti-SARS-CoV-2 IgG antibodies (seropositivity; n = 544 samples), and light gray bars represent the proportion of nasal swab samples with detectable SARS-CoV-2 RNA by RT-PCR (positivity; n = 705 samples). Error bars indicate 95% confidence intervals calculated using the exact binomial method (Clopper-Pearson). Numbers above bars indicate the observed proportion and sample size for each stratum. The inverse temporal pattern illustrates the decline in humoral immunity accompanied by an increase in viral RNA detection over time since vaccination. Statistical significance was assessed using Fisher's Exact Test for seropositivity ($p = 0.0012$) and Pearson's chi-square test for RT-PCR positivity ($\chi^2 = 17.27$, $p = 0.0006$).

The analysis of factors associated with seropositivity for anti-SARS-CoV-2 IgG antibodies revealed significant differences in demographic characteristics. Compared with men, women exhibited significantly greater seropositivity, with 88.2% (95% CI: 84.8–91.0%) versus 79.6% (95% CI: 74.7–83.9%), respectively (χ^2=6.23; p=0.0126). Age-stratified analysis revealed a statistically significant association (χ^2=23.55; p=0.0001), revealing a progressive decline in seropositivity with increasing age: 91.0% in individuals aged 18–30 years (162/178), 86.0% in those aged 31–40 years (104/121), 80.4% in those aged 41–50 years (82/102), 78.2% in those aged 51–60 years (61/78), and 66.2% in those aged over 60 years (43/65). Conversely, no statistically significant associations were detected between the vaccination priority category and seropositivity (χ^2=1.13; p=0.5680), with similar seropositivity rates among the general population (83.3%; 310/372), the elderly population (80.8%; 80/99), and healthcare professionals (84.9%; 62/73).

Post-vaccination symptomatic cases and severe outcomes

Among the 1,714 individuals in the cohort, 116 cases of COVID-19 were identified in 2022 and confirmed after completion of the vaccination schedule, resulting in an attack rate of 6.77% (95% CI: 5.67--8.06%). The profile of the 116 infected individuals was predominantly female (n=62; 53.4%), with a median age of 34 years (IQR: 28--43). Diagnostic confirmation was performed via rapid antigen testing (n=97; 83.6%) or RT–PCR (n=19; 16.4%). At the time of diagnosis, 43 (37.1%) individuals had already received one booster dose (D3), and 12 (10.3%) had received a second booster dose (D4). Analysis of the temporal distribution of cases revealed a pattern of increasing incidence over the period since vaccination. Most cases (n=85; 73.3%) occurred more than 180 days (6 months) after the second dose, with 43 cases (37.1%) occurring after 270 days (9 months), suggesting an association between the time postvaccination and the risk of breakthrough infection (Table 5).

Table 5 – Temporal distribution of confirmed COVID-19 cases after the second dose of the CoronaVac vaccine (n = 116).

Post-D2 period	**n**	**Frequency (%)**	**Cumulative Frequency (%)**
0-90 days	8	6.9%	6.9%
91-180 days	23	19.8%	26.7%
181-270 days	42	36.2%	62.9%
>270 days	43	37.1%	100.0%
Total	**116**	**100.0%**	-

The combination of cough, fever, and sore throat was the most prevalent symptomatic presentation (n = 14; 12.1%). Only 2 patients (1.7% of symptomatic individuals) presented with dyspnea and were classified as having severe acute respiratory syndrome (SARS). These events occurred in a 21-year-old woman and a 38-year-old man, who were diagnosed by rapid antigen tests 205 and 210 days after the second dose, respectively. The SARS rate in the entire cohort was 0.117% (2/1,714; 95% CI: 0.014%-0.421%), corresponding to an incidence rate of severe disease of 117 cases per 100,000 person-years (95% CI: 14-422 per 100,000). The wide confidence interval reflects substantial uncertainty around this estimate due to the very small number of events (n=2), and no meaningful statistical inference about vaccine protection against severe disease is possible with this sample size.

Discussion

This study investigated the seroprevalence, immune response, clinical outcomes associated with CoronaVac vaccination under real-world conditions in the first small municipality in Northeast Brazil to achieve universal vaccination coverage. These results indicate that although the vaccine induced a robust initial serological response, humoral immunity declined over time, accompanied by increased susceptibility to symptomatic infections. Notably, the incidence of severe disease remained very low throughout the study period, despite declining antibody levels, consistent with sustained protection against severe outcomes in this vaccinated population.

An important factor to consider in interpreting the serological response is the potential influence of hybrid immunity. Given that the municipality recorded confirmed COVID-19 cases in 2021, before the start of serological sampling, some members of the population were

likely exposed to SARS-CoV-2 before vaccination. Studies have shown that individuals with prior infection followed by vaccination (hybrid immunity) tend to exhibit higher and more durable antibody titers than those with vaccine-induced immunity alone [33]. Although our study did not differentiate antibody origins, the high observed seroprevalence may partly reflect this synergistic effect, which does not diminish but rather underscores the robustness of the immune response in the community.

The study was initially designed as a longitudinal study to evaluate the dynamics of the immune response to vaccination. The original protocol included a schedule of seven blood collections: a baseline collection (D0), immediately before the second vaccine dose (D2), and six follow-up collections at defined intervals (D14 ± 3, D44 ± 3, D104 ± 3, D194 ± 3, D284 ± 3, and D379 ± 3). However, owing to operational challenges, the implemented design was cross-sectional. Most participants had only one blood sample collected at a significantly late time point. Thus, analyses of serological decline should be interpreted as cross-sectional comparisons stratified by time since vaccination, not as longitudinal risk measures. Nevertheless, the temporal distribution of serologies allowed consistent characterization of the community pattern of humoral immunity decline. The median interval between the second dose (D2) and serum collection was 210 days (IQR: 175–223), indicating that the analysis reflects the serological response between 6 and 8 months post-vaccination.

The observed seroprevalence is consistent with Brazilian and international studies evaluating the response to CoronaVac, which reported seroconversion rates between 80% and 90% after two doses [34-36]. Although mRNA vaccines induce higher and more durable antibody titers [37, 38], CoronaVac has the capacity to generate a significant immune response, possibly complemented by cellular immunity, as described in other contexts [39, 40].

The phenomenon of waning immunity was evident, with a progressive reduction in seropositivity in the months following vaccination, which is consistent with studies conducted in Chile and Brazil documenting declines in neutralizing antibodies between three and six months [35, 41, 42]. Similar findings were reported in a Brazilian multicenter study conducted with blood donors, which reported a marked decline in seropositivity across multiple capitals between three and six months after infection or vaccination [41]. This pattern has also been described for mRNA vaccines, albeit with slower kinetics [37, 38].

Importantly, the decrease in circulating antibodies does not imply complete loss of protection, since memory T and B cells confer durable immunity against severe outcomes [39]. Indeed, a Brazilian study following individuals vaccinated with CoronaVac for one year demonstrated that although IgG antibody levels decreased, the cellular immune response mediated by virus-specific T cells remained robust and detectable for more than 12 months [42]. These findings support the hypothesis that despite declining antibody titers, memory cell-mediated mechanisms contribute to sustained protection against severe COVID-19. The increase in RT–PCR positivity after 9 months from the second dose coincided with the predominance of the Omicron variant in Brazil, characterized by a high degree of immune escape, which likely explains the greater susceptibility to infections during this period [10, 11].

The observed low incidence of severe disease in this fully vaccinated population is noteworthy. However, with only two severe cases identified, meaningful statistical inference about vaccine protection against severe outcomes is not possible. The wide confidence interval (14–422 per 100,000 person-years) reflects the substantial uncertainty inherent in estimating rare outcomes with very small numbers of events. While the observed incidence is consistent with findings

from larger comparative studies conducted in other settings, we cannot definitively attribute the low incidence in our population to vaccine protection based on this study design alone. Rather, the low incidence observed in this fully vaccinated population aligns with reports from other vaccinated populations, suggesting that vaccination likely contributes to protection against severe disease. In Chile, a national cohort estimated effectiveness of 65.9% against symptomatic COVID-19, 87.5% against hospitalization, and 86.3% against death [35]; in Uruguay, population analyses indicated protection of 75% against severe forms and 92% against deaths [43]; and in Brazil, the multicenter VEBRA-COVID study confirmed similar results, although with reduced protection in elderly individuals and individuals with comorbidities [44]. These findings align with a global meta-analysis comparing the effectiveness of different vaccine platforms, which reported sustained performance of inactivated virus vaccines against severe outcomes [45], confirming the robustness of protection conferred by CoronaVac even in the face of more transmissible variants.

Our findings align directly with recent national literature. A cohort of 75.9 million vaccinated Brazilians estimated effectiveness above 70% against hospitalizations and deaths [46]. In specific subgroups, such as elderly and pregnant women, protection against severe outcomes also remained consistent, albeit with expected variations. Ranzani et al. (2021) [34] reported 55.5% effectiveness against hospitalization in individuals ≥70 years during circulation of the Gamma variant, whereas Paixão et al. (2022) [47] reported 85% effectiveness against severe COVID-19 in pregnant women. More recently, Luna et al. (2024) [48] reported 95.6% effectiveness against hospitalization among healthcare professionals during the Gamma–Delta transition. Our findings are also consistent with the real-world effectiveness study of Project S in the city of Serrana, a small municipality in the state of São Paulo, southeastern Brazil, which also achieved high vaccination coverage and reported a 95% reduction in COVID-19 deaths [44].

The convergence between this large-scale evidence and the results of the present study reinforces its external validity and highlights the contribution of CoronaVac to pandemic mitigation in Brazil by maintaining sustained protection against the most severe disease manifestations.

Evidence from other settings in Ceará supports the findings observed in Guaramiranga. In Fortaleza, the state capital and a large urban center, Monteiro et al. (2023) [49] demonstrated, through a target-trial emulation, that CoronaVac substantially reduced hospitalizations and deaths from COVID-19 among elderly individuals, even amid intense community transmission and marked social inequalities. The convergence between results from a large urban center and those observed in a small, tourist-profile municipality suggests that the benefit of CoronaVac in preventing severe outcomes is maintained across different epidemiological and sociostructural contexts. Considering that Guaramiranga achieved high vaccination coverage early in the campaign, it is plausible that this extended protection contributed to the lower number of severe cases recorded in the municipality. In both contexts, the conferred protection appears to have been modulated by advanced age, comorbidities, and the time elapsed since the last dose, factors that influence the persistence of the immune response and reinforce the need for timely booster strategies.

Despite this prolonged protection against severe outcomes, our data indicated a progressive decline in protection against symptomatic infections over time. The increase in case incidence, which was concentrated in more than 70% of infections occurring 180 days after the second dose, directly reflects the observed serological decline. This behavior supports the hypothesis

that a reduction in humoral immunity is associated with increased infection risk, thereby justifying the periodic administration of booster doses to restore and prolong protection.

The high vaccination adherence of the Guaramiranga population was a determinant of the observed results. As described in a previous study conducted in the municipality, preventive behaviors remained frequent even after vaccination, which may have contributed to reducing viral exposure and enhancing the protective impact of immunization [24]. This finding illustrates the interaction between biological and sociocultural factors in determining vaccine impact.

Serological analysis also confirmed patterns observed in other contexts, such as a greater humoral response in younger individuals and females, possibly associated with hormonal and immunological factors [50-52]. Conversely, elderly individuals exhibited lower seropositivity, reflecting the impact of immunosenescence and reinforcing the need for specific vaccination strategies for this group, such as shorter intervals between booster doses and, potentially, heterologous schemes [54, 54].

Another relevant point was the integration of multiple data sources, including municipal records, official notifications, and laboratory results, which increased accuracy in case and outcome identification, reducing the impact of underreporting—a recurrent problem in COVID-19 surveillance in Brazil [20]. This integrated approach constitutes a methodological strength of the study and may serve as a model for evaluations in small municipalities, contributing to improving vaccine and epidemiological surveillance in the country.

Limitations

This study has important limitations. The absence of an unvaccinated control group, owing to high local vaccination coverage or comparisons with neighboring municipalities, precluded a direct comparison, and effectiveness was estimated indirectly via literature data [55, 56]. The unequal distribution of sample collections over time, concentrated in a single period, limits the precision of estimates and statistical power in some strata. RT–PCR testing is not random and is primarily performed in symptomatic individuals, potentially overestimating positivity rates or introducing selection bias. Our objective was not to distinguish vaccine-induced antibodies from those due to prior infection, which may overestimate the seroprevalence attributed exclusively to vaccination, or to perform systematic genomic characterization for variant-specific analyses. The reliance on e-SUS Notifica records leads to underreporting of oligosymptomatic cases, and the small number of severe outcomes limits robust analyses of its impact against SARS. The findings should be generalized to large urban contexts with caution, given the specific characteristics of the studied municipality.

The original protocol envisioned a longitudinal design with multiple blood collections per participant at defined intervals (baseline, pre-D2, and six follow-up collections at specified intervals). However, due to operational constraints, the implemented design was cross-sectional, with most participants providing a single blood sample at a variable time post-vaccination. Consequently, the temporal analysis of antibody decline should be interpreted as a cross-sectional comparison among groups sampled at different times, rather than as a measure of within-individual decline. This approach is subject to potential confounding by factors that may differ between individuals vaccinated earlier and those vaccinated later, such as priority group status, age distribution, or prior infection prevalence. Nevertheless, the temporal

distribution of serologies allowed characterization of the community-level pattern of humoral immunity decline across the post-vaccination period, providing useful descriptive evidence for surveillance purposes.

The small number of severe outcomes (n=2) substantially limits the ability to draw conclusions about vaccine impact on severe disease. The study was not powered to evaluate this outcome, and the wide confidence interval around the incidence estimate reflects considerable uncertainty. Statements about protection against severe disease should therefore be interpreted with substantial caution, and these findings should be considered descriptive rather than inferential.

Public health implications

The findings of high seroprevalence associated with a low incidence of severe cases suggest protection conferred by vaccination and contribute to understanding the vaccine response in real community settings. The experience of Guaramiranga demonstrates that small municipalities can serve as “natural laboratories” for postvaccination immunity surveillance, reinforcing the importance of booster campaigns, serological monitoring, and local epidemiological surveillance, essential elements to guide public policies aimed at protecting vulnerable populations.

The decline in the humoral immune response after six to nine months indicates the need for booster doses, especially in elderly, immunocompromised, and healthcare professionals. Owing to the slightly lower response to CoronaVac than to mRNA vaccines, heterologous

schemes have emerged as effective alternatives, with evidence of higher antibody titers when boosting is performed with mRNA vaccines.

Although protection against severe cases remains high, protection against infection has declined over time, making it advisable to maintain nonpharmacological measures during periods of high transmission. Furthermore, continuous monitoring of vaccine effectiveness, coupled with genomic surveillance for emerging variants, is indispensable for enabling rapid adjustments to immunization strategies.

Conclusion

Guaramiranga provided a unique setting to evaluate the impact of CoronaVac vaccination in an adult population with high adherence to the vaccination schedule. The study demonstrated that the vaccine induces a robust immune response that gradually declines over time. The observed low incidence of severe disease in this fully vaccinated population is consistent with protection against severe outcomes, though causality cannot be definitively established without a comparator group. It was also observed that demographic factors, such as age and sex, influenced seropositivity.

These findings reinforce the need for booster doses to maintain immunity at protective levels, especially in vulnerable groups, and are consistent with the positive impact of CoronaVac in real-world conditions across small municipalities. Additionally, they underscore the importance of regular serological surveys as a tool for postvaccination surveillance. Experiences such as that of Guaramiranga provide valuable evidence for improving

immunization policies and strengthening the national response to COVID-19. The Guaramiranga experience demonstrates that small municipalities can provide relevant platforms for vaccine effectiveness studies under real-world conditions, particularly in contexts of broad coverage and strong integration with surveillance databases.

List of Abbreviations

CDC: Centers for Disease Control and Prevention

CI: Confidence Interval

CLIA: Chemiluminescence Immunoassay

COVID-19: Coronavirus Disease 2019

CPF: Brazilian Individual Taxpayer Registry (Cadastro de Pessoas Físicas)

D1: First Dose

D2: Second Dose

D3: Third Dose (First Booster)

D4: Fourth Dose (Second Booster)

GAL: Laboratory Environment Manager (Gerenciador de Ambiente Laboratorial)

ICF: Informed Consent Form

ILI: Influenza-like Illness

IQR: Interquartile Range

IgG: Immunoglobulin G

IgM: Immunoglobulin M

LACEN: Central Public Health Laboratory (Laboratório Central de Saúde Pública)

PR: Prevalence Ratio

RT-PCR: Reverse Transcription Polymerase Chain Reaction

SARS: Severe Acute Respiratory Syndrome

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SD: Standard Deviation

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

The research was approved by the Ethics Committee of the Christus University Center (opinion nº. 4,997,175). All participants provided written informed consent to participate in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study contain individual-level health information derived from laboratory surveillance systems and official epidemiological records. Due to Brazilian data protection legislation and confidentiality agreements, these datasets cannot be publicly shared. However, de-identified data can be made available to the corresponding author upon reasonable request, provided permission is obtained from the relevant health authorities.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LBC contributed to the study conception, design, data analysis, and manuscript drafting, critical review, and approved the final version of the manuscript. FKAB, ALSB, SSS, ACBMM, DBS, and RWJFF contributed to data collection and validation. MMA provided supervision and critical revision of the study design. PPLB participated in data analysis and interpretation, as well as manuscript writing and review. LPGC and CHA provided overall supervision, contributed to the study conception, methodology, and critical review, and approved the final version of the manuscript. All authors have read and agreed to the published version of this article.

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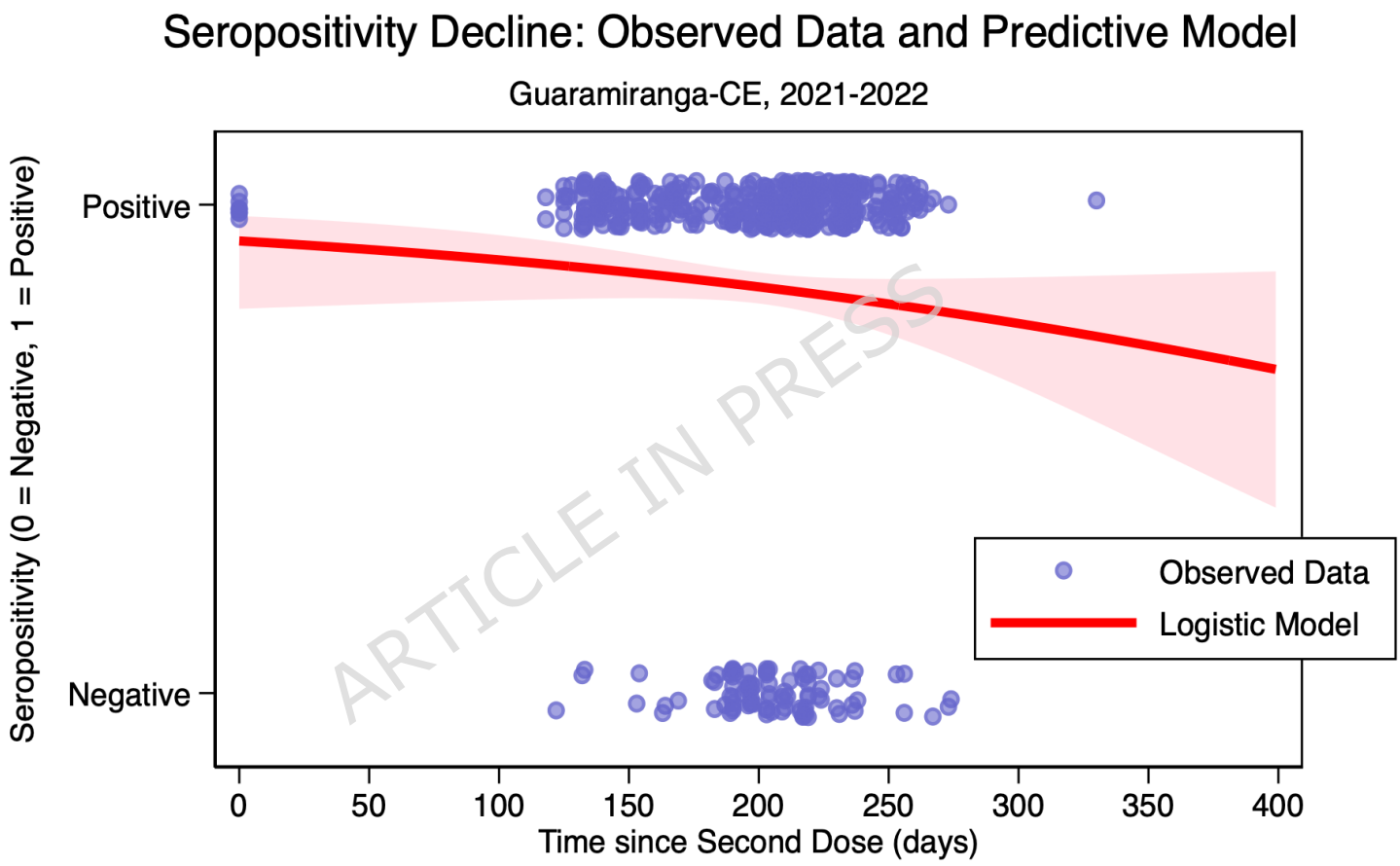

Red curve: probability predicted by logistic regression. Shaded area: 95% CI.