ORIGINAL ARTICLE

EVALUATION OF THE HUMORAL IMMUNE RESPONSE TO PRIMARY AND BOOSTER COVID-19 VACCINATION

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Highlights: (1). Evaluation of humoral immune response to homologous and heterologous COVID-19 vaccination schemes. (2). Significant increase in anti-SARS-CoV-2 IgG after the primary vaccination scheme and booster dose. (3). Decline in antibody levels after homologous vaccination schemes, reinforcing the need for a heterologous booster dose.

PRE-PROOF
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ABSTRACT

This study aimed to evaluate the efficacy of the primary and booster vaccination response against COVID-19. This prospective cohort study was conducted in the Archipelago of Fernando de Noronha (Pernambuco, Brazil). A total of 350 adults (≥18 years), with and without previous SARS-CoV-2 infection, were included. Data collection occurred between May 2020 and May 2022. Serum levels of anti-SARS-CoV-2 IgG were evaluated before vaccination (T0), after the primary vaccination schedule with homologous vaccines (CoronaVac or ChAdOx1 – AstraZeneca/Oxford-Fiocruz), and after the heterologous booster dose with BNT162b2 (Pfizer-BioNTech). Detection of IgG antibodies was performed using a chemiluminescent immunoassay. Data were analyzed using GraphPad Prism 9.0 and SPSS 18.0 software, applying the Mann-Whitney and Sidak tests for longitudinal comparisons ($p < 0.05$). Participants were divided into two groups according to previous SARS-CoV-2 infection: infected (G1; n = 81) and not infected (G2; n = 269). In both groups, anti-SARS-CoV-2 IgG levels significantly increased after the primary vaccination scheme compared with pre-vaccination levels ($p < 0.05$). In G1, anti-SARS-CoV-2 IgG levels reduced after an interval between 14 and 30 days. After the booster dose with BNT162b2, anti-SARS-CoV-2 IgG levels increased and kept high for 233 days after vaccination. The decline in antibody levels observed after the primary vaccination with two homologous doses reinforces the need for a heterologous booster dose to maintain the humoral immune response.

Keywords: COVID-19; SARS-CoV-2; antibodies; Immunoglobulin G; COVID-19 Vaccines.

EVALUATION OF THE HUMORAL IMMUNE RESPONSE TO PRIMARY AND BOOSTER COVID-19 VACCINATION

AVALIAÇÃO DA RESPOSTA IMUNE HUMORAL DE ESQUEMA PRIMÁRIO E DOSE DE REFORÇO VACINAL CONTRA COVID-19

RESUMO

O estudo objetivou avaliar a eficácia da resposta vacinal primária e dose de reforço contra COVID-19. Trata-se de um estudo de coorte prospectiva realizado no Arquipélago de Fernando de Noronha (Pernambuco, Brasil). O estudo incluiu 350 adultos (≥18 anos), com e sem infecção prévia pelo SARS-CoV-2. As coletas foram realizadas entre maio de 2020 e maio de 2022. Foram avaliados os níveis séricos de IgG anti-SARS-CoV-2 antes da vacinação (T0), após o esquema primário com vacinas homólogas (CoronaVac ou ChAdOx1 – AstraZeneca/Oxford-Fiocruz) e após a dose de reforço heteróloga com BNT162b2 (Pfizer-BioNTech). A detecção dos anticorpos IgG foi realizada por imunoensaio de quimioluminescência. Os dados foram analisados nos programas GraphPad Prism 9.0 e SPSS 18.0, aplicando-se os testes de Mann-Whitney e Sidak para comparações longitudinais ($p < 0,05$). Os participantes foram divididos em dois grupos conforme a infecção prévia pelo SARS-CoV-2: infectados (G1; n = 81) e não infectados (G2; n = 269). Em ambos os grupos, os níveis de IgG anti-SARS-CoV-2 aumentaram significativamente após o esquema primário de vacinação em comparação com os níveis pré-vacinação ($p < 0,05$). No G1, observou-se redução dos níveis de IgG anti-SARS-CoV-2 entre 14 e 30 dias. Após a dose de reforço com BNT162b2 (Pfizer-BioNTech), os níveis de IgG anti-SARS-CoV-2 voltaram a aumentaram e permaneceram elevados por até 233 dias após a vacinação. A queda dos níveis de anticorpos observada após o esquema primário de vacinação com duas doses de vacina homóloga, reforça a necessidade da dose de reforço com vacina heteróloga.

Palavras-chave: COVID-19; SARS-CoV-2; anticorpos; Imunoglobulina G; Vacinas contra COVID-19.

1. Introduction

The severe acute respiratory syndrome coronavírus 2 (SARS-CoV-2) infection appeared in China and spread rapidly worldwide, becoming a public health emergency of international concern[1,2]. Brazil registered the first case at the end of February 2020 and by August, 2022, the country presented more than 34 million confirmed cases and more than 680,000 deaths[3].

Researchers from several countries sought epidemiological control of SARS-CoV-2. They conducted a technological acceleration in record time to develop vaccines against Coronavirus Disease 2019 **(**COVID-19)[4]. In Brazil, vaccination began in the second half of January 2021[3].

Immunogenicity against SARS-CoV-2 is provided after infection or vaccination. In COVID-19, immunity is induced after antibody production against the spike and nucleocapsid protein subunits 1 (S1) and 2 (S2)[5]. Neutralizing antibodies target the receptor binding domain (RBD) in the S1, producing IgM, IgG, and IgA[6]. Vaccines assure immunogenicity by producing specific IgG antibodies against the spike protein. Higher antibody levels provide greater protection, especially against the severe forms of the disease[7,8].

In general, more than one dose of homologous vaccine is needed for the long-term production of immunogenicity. The first dose prepares the immune system, and the second increases the effectiveness of the immune response[9]. The heterologous booster strategy (i.e., using different vaccines in the booster dose) increases the effectiveness and duration of immunity compared with the homologous scheme, especially with the emergence of new SARS-CoV-2 variants[10,11]. Although the vaccines approved and in use in Brazil promote humoral and cellular response to SARS-CoV-2 infection, the medium and long-term seroprevalence after vaccination is still being determined, especially with the vaccine scheme and platforms used in Brazil.

Several studies at the international and national levels have evaluated the use of COVID-19 vaccines, particularly the impact of a booster (third) dose on sustaining protective immunity[11-18]. Research conducted in different populations has shown that a booster dose with BNT162b2 (Pfizer-BioNTech) significantly increases humoral and cellular responses, including higher anti-spike IgG titers and enhanced T-cell activity,

even in vulnerable groups such as older adults, immunocompromised individuals and people living with HIV[12-15]. Studies in Brazil and in collaborative analyses including Brazilian data have also demonstrated that heterologous booster strategies, such as administering an mRNA vaccine after a primary series with CoronaVac or ChAdOx1 (Astrazeneca/Oxford-Fiocruz), are both immunogenic and effective in recovering antibody levels that decline after the two-dose primary scheme and in maintaining protection against severe forms of COVID-19[17,18]. These findings support the use of booster doses as a public health strategy and highlight the need to monitor the durability of the humoral response after primary vaccination and after the first booster in real-world settings.

Evidence on the variability of humoral immunity after COVID-19 vaccination remains limited, as immune responses may differ according to vaccine platform, prior infection, and population characteristics. In Brazil, where CoronaVac and ChAdOx1 vaccines were predominantly used in the primary scheme, data on the duration and magnitude of antibody responses are still scarce, particularly in population-based cohorts. Producing local evidence is key to understanding how these regimens perform in real-world settings and to informing national and global immunization strategies. The findings of this research are expected to advance knowledge on vaccine-induced immunity and support public health decision-making aimed at sustaining population protection against severe COVID-19.

Therefore, this study aimed to evaluate the efficacy of the primary and booster vaccination response against COVID-19

2. Methods

2.1. Study design and setting

This analysis is nested within a population-based prospective cohort study conducted in the Fernando de Noronha Archipelago (Pernambuco, Brazil) a geographically isolated oceanic territory with limited health infrastructure and high dependence on tourism. The cohort entitled “Incidence and prevalence of COVID-19 in the Fernando de Noronha Archipelago" was developed by the Pernambuco State Health Department with subsidy from the Pan American Health Organization. Data collection

occurred in repeated waves from May 22, 2020, to May 31, 2022. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies.

The archipelago presented an estimated permanent population of 3,061 inhabitants and a demographic density of 154.55 inhabitants per km² in 2019[19]. The local health system is organized under the Family Health Strategy model, with primary care coverage essentially for the entire island. This setting allowed active community-based recruitment; repeated clinical, epidemiological, and laboratory assessments; and longitudinal monitoring of vaccination and humoral immune response in a real-world scenario.

For the parent cohort, the sampling frame was constructed using the Health Information System for Primary Care registries, conducted by the Archipelago Family Health Strategy team, and social assistance registries created to support families during the pandemic. A simple random sample of residents was drawn from these registries. The target sample size was defined to estimate the prevalence of SARS-CoV-2 infection in the island's population with adequate precision. We considered an expected prevalence of approximately 5%, a 95% confidence level, estimated error of 2%, and a finite population of about 3,061 residents. Under these assumptions, the minimum required sample size was approximately 750 individuals. To compensate for potential non-response and anticipated attrition in follow-up waves, we oversampled and enrolled 904 residents in the first wave.

2.2 Study population, eligibility criteria, and follow-up

The original cohort was composed of 904 residents enrolled in the first phase. All individuals were invited to participate in subsequent phases of data collection. Follow-up occurred in repeated waves, and not all initially enrolled participants were present at all phases due to temporary or permanent departure from the archipelago for work or family reasons, unavailability for in-person blood collection or interview within the scheduled fieldwork window, or refusal to continue. Some participants who missed an intermediate wave were recontacted and re-entered the study in later collections. Across the first five major waves of data collection, the number of assessed participants was 904 (phase 1 – May 2020), 815 (phase 2 -July 2020), 614 (phase 3 – septembrer 2020), 593 (phase 4 –

December 2020), 571 (phase 5 – May 2021), 375 (phase 6 – July 2021), 288 (phase 7 – Setember 2021) and 184 (phase 8 – Setember -2022).

Eligibility in the parent cohort required: (i) listing as a permanent resident of Fernando de Noronha in the Family Health Strategy registry or in the emergency social assistance registry used for pandemic response; (ii) physical presence on the island at the time of fieldwork for that phase or availability for blood sampling and interview in the predefined collection window. No exclusions were made on the basis of sex, pregnancy status, presence of symptoms suggestive of COVID-19 at the time of recruitment, or pre-existing chronic conditions. Visitors, tourists, temporary workers not classified as residents, and residents who declined participation in that collection window were not included in that phase.

The present analysis focuses on the humoral immune response to COVID-19 vaccination and is therefore restricted to adult participants (≥18 years) with complete serological information at predefined post-vaccination time points. For this immunogenicity analysis, inclusion criteria were: residence in the Fernando de Noronha Archipelago; availability of paired serum samples at the relevant time points; completion of a homologous primary vaccination scheme with two doses of CoronaVac or ChAdOx1 (AstraZeneca/Oxford–Fiocruz); and receipt of a heterologous booster dose with BNT162b2 (Pfizer–BioNTech). Individuals were excluded if they did not participate in all serological assessments of interest; if they received any vaccine dose less than 14 days before blood collection; or if essential demographic, vaccination, or serological data were missing. Both males and females were eligible. Pregnant women, individuals with suspected or confirmed COVID-19 at recruitment, and individuals with chronic comorbidities were not excluded a priori. After applying these criteria, 350 adults composed the analytic sample for the present study, considering differences in vaccination timing and availability of paired serum samples across data-collection phases.

Blood collection for anti–SARS-CoV-2 IgG measurement was performed at predefined intervals that corresponded to key milestones of the local COVID-19 vaccination campaign. We defined the pre-vaccination baseline as T0. After completion of the homologous primary vaccination scheme (two doses of CoronaVac or ChAdOx1), post-vaccination samples were grouped by the interval between the second dose and blood draw: 14–30 days, 31–45 days, 46–60 days, and 61–125 days. Following

administration of the heterologous booster dose with BNT162b2, antibody levels were assessed in additional windows: 84–115 days, 116–147 days, 148–177 days, and 178–233 days after the second dose. These windows were defined a priori based on three elements: (i) operational feasibility of repeated community-based collections in a geographically isolated island; (ii) alignment with the municipal/state vaccination rollout, which began on January 19, 2021, prioritizing adult residents; and (iii) previously described kinetics of post-vaccination IgG responses.

2.3. Vaccination and laboratory procedures

From the beginning of the COVID-19 vaccination campaign in Brazil, vaccine allocation in Fernando de Noronha followed national guidelines and Ministry of Health availability under the National Plan for the Operationalization of Vaccination against COVID-19[20]. All included individuals received a homologous two-dose primary vaccination scheme with either CoronaVac or ChAdOx1 and, subsequently, a heterologous booster dose with BNT162b2 (Pfizer–BioNTech), in accordance with public health recommendations in force at the time.

Venous blood was collected in tubes without anticoagulant for assessment of humoral response, with all samples collected in person at the primary health care units. Samples were centrifuged at 3,000 rpm for 5 minutes in a refrigerated centrifuge to obtain serum. Serum aliquots were then used to measure anti–SARS-CoV-2 IgG levels before and after vaccination using the SARS-CoV-2 IgG II Quant kit (Code 6S60B; ARCHITECT i System/Abbott), a chemiluminescent microparticle immunoassay (CMIA).

The SARS-CoV-2 IgG II Quant assay is designed to detect IgG antibodies, including neutralizing antibodies directed to the receptor-binding domain (RBD) of the S1 subunit of the spike protein. Results for anti-spike/RBD IgG were expressed in arbitrary units per mL (AU/mL). According to the manufacturer, values ≥50.0 AU/mL were interpreted as reactive. The analytical range of the assay was 7 to 40,000 AU/mL[21].

2.4 Sociodemographic and clinical data

Along with biological sampling, participants answered a structured questionnaire administered by trained field staff at each data-collection wave. This instrument collected: (i) sociodemographic information (age, sex, self-reported race/color, marital status, educational level, and socioeconomic status according to the Brazilian Economic

Classification Criteria); (ii) clinical and epidemiological history (previous SARS-CoV-2 infection confirmed by laboratory tests, presence of COVID-19–compatible symptoms, comorbidities, health service use, and self-reported isolation practices); and (iii) vaccination-related information during the immunization period (vaccine product received and date of each dose).

These variables were used to describe the study population and to stratify analyses according to previous SARS-CoV-2 infection. For this purpose, participants were classified at baseline (T0) into two groups: previously infected (G1) and not previously infected (G2), based on documented infection by SARS-CoV-2 or detection of anti–SARS-CoV-2 antibodies prior to vaccination. Given limitations in real-time internet connectivity on the island, questionnaires were initially completed on paper and subsequently entered into a secure electronic database for analysis.

2.5 Statistical Analysis

Data were analyzed using GraphPad Prism (version 9.0) and Statistical Package for the Social Sciences - SPSS (version 18.0). Categorical variables were expressed as absolute and relative numbers, while continuous variables were presented as median with interquartile range (IQ). The Shapiro-Wilk test verified data normality. The Mann-Whitney test compared non-parametric variables. Sidak's multiple comparisons test with adjusted P value was used for longitudinal analysis between pre-vaccinal (T0) and post-vaccinal in days. Statistical significance was set at $p< 0.05$.

2.6. Ethics

The study was approved by the human research ethics committee of Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) (number 31291620.8.0000.5201) and followed resolution 466/2012 of the National Health Council and Declaration of Helsinki. All participants signed an informed consent form.

3. Results

A total of 350 individuals were included. They were divided according to SARS-CoV-2 infection before vaccination: not infected (G1; n = 269) and infected (G2; n = 81) and. Table 1 shows the individuals divided by age group, sex, previous infection by SARS-CoV-2, and primary vaccination scheme. About 23% and 21% of individuals were

previously infected by SARS-CoV-2 before the first dose of the ChAdOx1 and CoronaVac, respectively.

Table 1. Demographic and clinical data of the individuals. Fernando de Noronha - PE, Brazil. 2021.

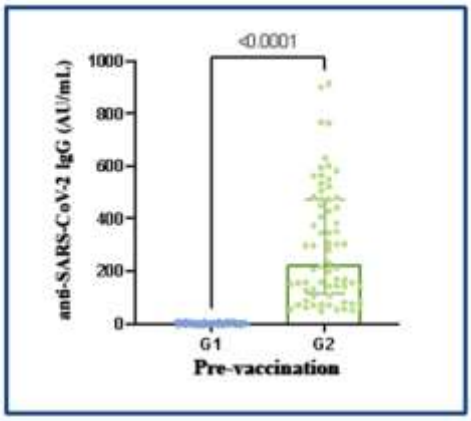
Variables	CoronaVac n = 93 (26.6%)		ChAdOx1 n = 257 (73.4%)		Total n = 350	
	n	%	n	%	n	%
Age						
18 to 59 years old	80	86.0	218	84.8	298	85.1
≥ 60 years old	13	14.0	39	15.2	52	14.9
Sex						
Women	64	68.8	140	54.5	204	58.3
Men	29	31.2	117	45.5	146	41.7
Previous infection by SARS-CoV-2*						
No (G1)	73	78.5	196	76.3	269	76.9
Yes (G2)	20	21.5	61	23.7	81	23.1

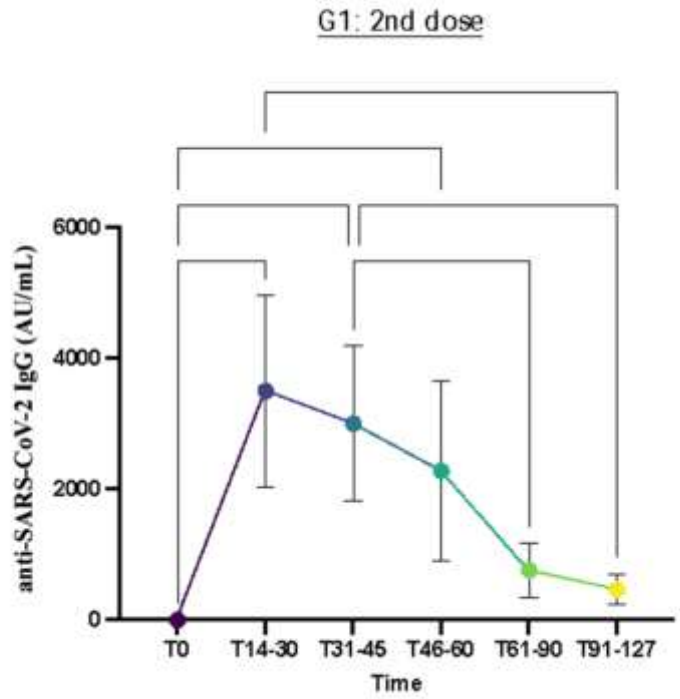
*Confirmed by serological detection of anti-SARS-CoV-2 IgG or IgM.
Source: elaborated by the authors.

Anti-SARS-CoV-2 IgG levels were higher in G2 than in G1 at T0 ($p < 0.0001$) (Fig. 1 and 2). The anti-SARS-CoV-2 IgG levels were quantified in T0 and after the second dose (T2nd) of CoronaVac or ChAdOx1 evaluated by intervals (days) between the application and blood collection in G1 (Fig. 1) and G2 (Fig. 2). In G1, antibody levels increased between T0 vs. T14-30 and T46-60 days. Moreover, anti-SARS-CoV-2 IgG levels were significantly different from T14-30 onwards (Fig. 1). In the G2, anti-SARS-CoV-2 IgG levels increased from T0 onwards. From T14-30, anti-SARS-CoV-2 IgG levels were reduced over time but were not significant (Fig. 2).

The anti-SARS-CoV-2 IgG levels between the second dose and booster dose with a 30-day interval (from 83 to 233 days) are presented in Fig. 3. After the booster dose, anti-SARS-CoV-2 IgG levels increased. Moreover, anti-SARS-CoV-2 IgG levels did not significantly reduce the second and booster dose (Fig. 3).

EVALUATION OF THE HUMORAL IMMUNE RESPONSE
TO PRIMARY AND BOOSTER COVID-19 VACCINATION

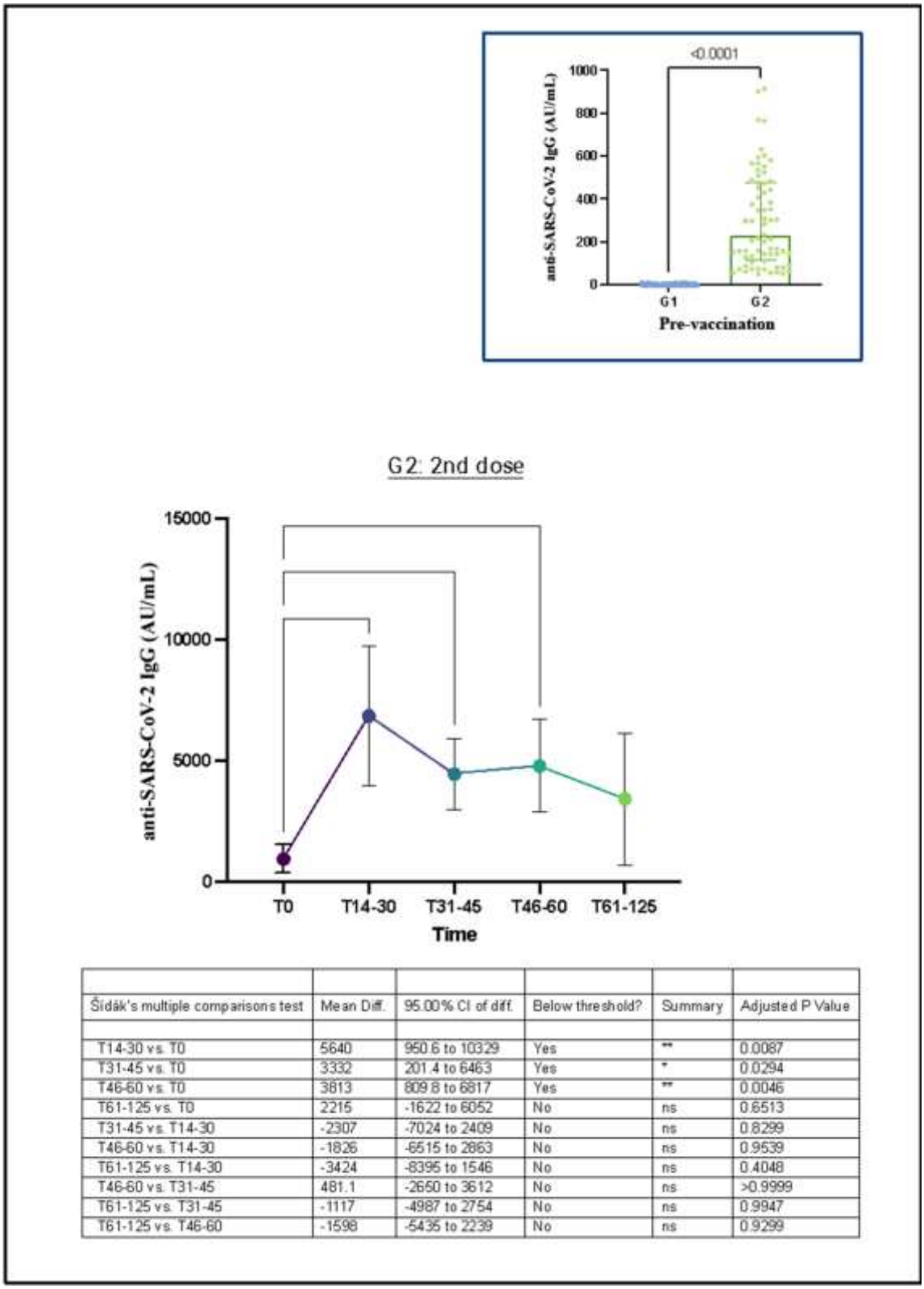




Šidák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
T14-30 vs. T0	2874	373.9 to 5374	Yes	*	0.0119
T31-45 vs. T0	2973	1026 to 4919	Yes	***	0.0002
T46-60 vs. T0	2278	373.0 to 4183	Yes	**	0.0074
T61-90 vs. T0	-42.56	-2752 to 2667	No	ns	>0.9999
T91-127 vs. T0	-246.1	-2824 to 2331	No	ns	>0.9999
T31-45 vs. T14-30	98.64	-2412 to 2610	No	ns	>0.9999
T46-60 vs. T14-30	-596.4	-3097 to 1904	No	ns	>0.9999
T61-90 vs. T14-30	-2917	-5854 to 20.66	No	ns	0.0532
T91-127 vs. T14-30	-3120	-5936 to -304.5	Yes	*	0.0181
T46-60 vs. T31-45	-695.0	-2641 to 1251	No	ns	0.9942
T61-90 vs. T31-45	-3015	-5735 to -295.7	Yes	*	0.0180
T91-127 vs. T31-45	-3219	-5807 to -631.0	Yes	**	0.0045
T61-90 vs. T46-60	-2320	-5030 to 389.5	No	ns	0.1643
T91-127 vs. T46-60	-2524	-5101 to 53.65	No	ns	0.0601
T91-127 vs. T61-90	-203.5	-3181 to 2774	No	ns	>0.9999

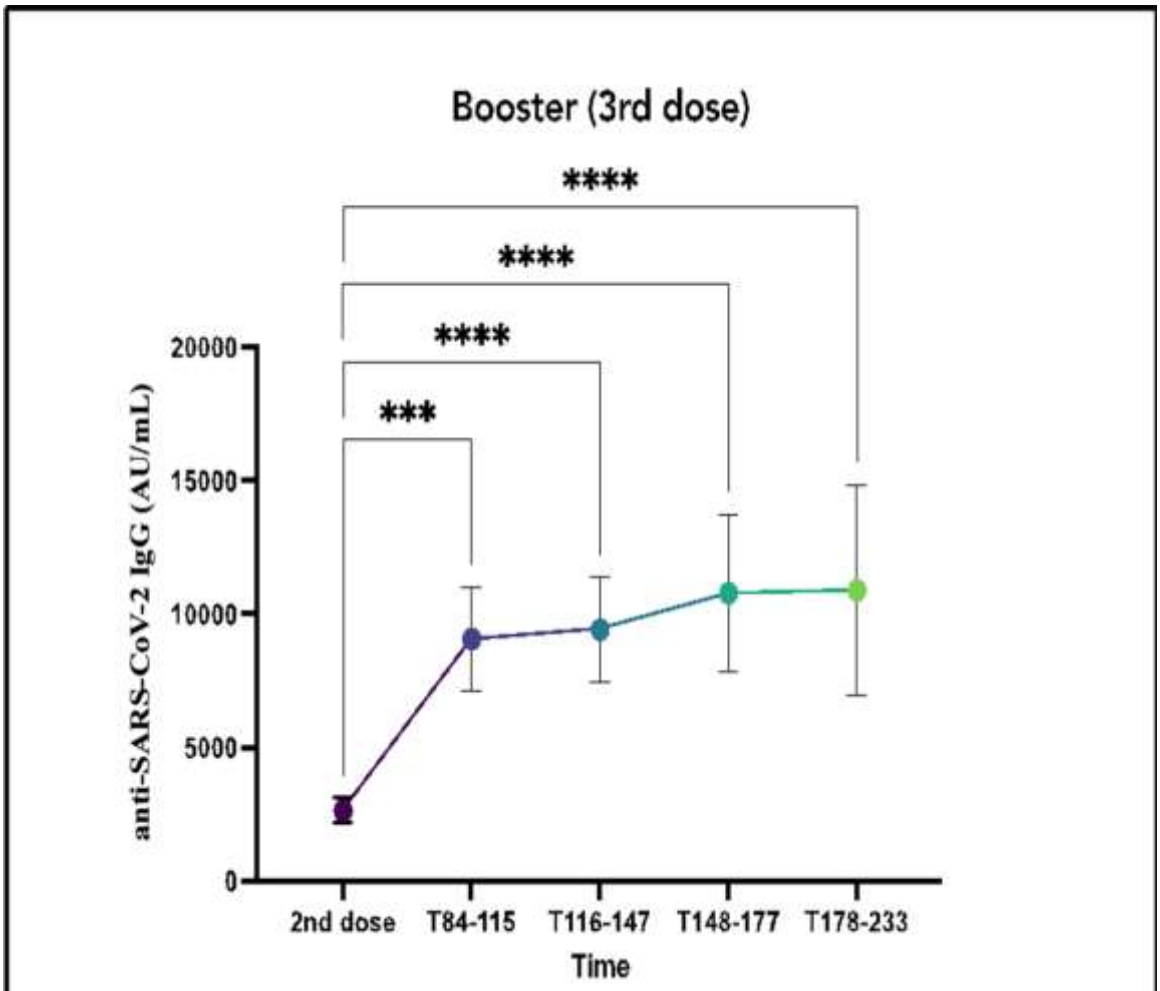
Figure 1. Anti-SARS-CoV-2 IgG levels between the pre-vaccination phase (T0) and after the second dose of the CoronaVac or ChAdOx1 (AstraZeneca) in individuals not previously infected by SARS-CoV-2 (G1) before vaccination. They were grouped by time intervals (days) after the second dose.
Source: elaborated by the authors.

EVALUATION OF THE HUMORAL IMMUNE RESPONSE TO PRIMARY AND BOOSTER COVID-19 VACCINATION



Šídák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
T14-30 vs. T0	5640	950.6 to 10329	Yes	**	0.0087
T31-45 vs. T0	3332	201.4 to 6463	Yes	*	0.0294
T46-60 vs. T0	3813	809.8 to 6817	Yes	**	0.0046
T61-125 vs. T0	2215	-1622 to 6052	No	ns	0.6513
T31-45 vs. T14-30	-2307	-7024 to 2409	No	ns	0.8299
T46-60 vs. T14-30	-1826	-6515 to 2863	No	ns	0.9539
T61-125 vs. T14-30	-3424	-8395 to 1546	No	ns	0.4048
T46-60 vs. T31-45	481.1	-2650 to 3612	No	ns	>0.9999
T61-125 vs. T31-45	-1117	-4987 to 2754	No	ns	0.9947
T61-125 vs. T46-60	-1598	-5436 to 2239	No	ns	0.9299

Figure 2. Anti-SARS-CoV-2 IgG antibody levels between the pre-vaccination phase (T0) and after the second dose of CoronaVac or ChAdOx1 (AstraZeneca) in individuals previously infected by SARS-CoV-2 (G2) confirmed by serological quantification of IgG/IgM anti-SARS-CoV-2 in T0. They were grouped by time intervals (days) after the second dose.
Source: elaborated by the authors.



Šidák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
T84-115 vs. 2nd dose	6856	2111 to 11601	Yes	***	0.0006
T116-147 vs. 2nd dose	5713	2470 to 8956	Yes	****	<0.0001
T148-177 vs. 2nd dose	7776	3466 to 12086	Yes	****	<0.0001
T178-233 vs. 2nd dose	8573	3556 to 13589	Yes	****	<0.0001
T116-147 vs. T84-115	-1143	-5888 to 3602	No	ns	0.9989
T148-177 vs. T84-115	919.8	-4219 to 6059	No	ns	>0.9999
T178-233 vs. T84-115	1717	-3759 to 7192	No	ns	0.9909
T148-177 vs. T116-147	2063	-2247 to 6373	No	ns	0.8563
T178-233 vs. T116-147	2860	-2157 to 7876	No	ns	0.6800
T178-233 vs. T148-177	796.8	-4607 to 6200	No	ns	>0.9999

Figure 3. Anti-SARS-CoV-2 IgG antibody levels in individuals with the primary vaccination scheme with CoronaVac or ChAdOx1(AstraZeneca). They were grouped by time intervals (days after the booster dose with BNT162b2 (Pfizer-BioNTech).
Source: elaborated by the authors.

4. Discussion

The present study found that the vaccines used in Brazil produce immunogenicity by inducing the humoral response; however, antibody levels were reduced after the second dose in both groups (G1 and G2). Also, the booster dose with a heterologous vaccine increased the immunogenicity in both groups, corroborating Munro et al. results, which concluded that all vaccines increased antibody responses after booster dose without safety concerns[12,13].

G2 presented more anti-SARS-CoV-2 IgG than the G1 at T0. Also, the anti-SARS-CoV-2 IgG levels in the G2 were significantly higher in the T14-30. Then, they reduced but maintained acceptable levels for 125 days; however, the same did not happen with G1. Lo Sasso et al. observed changes in antibody levels over the days after vaccination, and Yalçın et al. and Mak et al. detected higher antibody levels and a more robust humoral response in individuals previously infected by SARS-CoV-2, corroborating our findings [22-24].

The antibody levels of G2 did not significantly reduce over time, suggesting that these levels remained stable after four months of the second dose compared with the previous two months. This finding must be interpreted cautiously since many variables and aspects still need further research through a phase four study. Therefore, applying a booster dose (heterologous vaccine) after four months of the primary vaccination scheme was an adequate strategy in Brazil.

The antibody levels after the booster dose (BNT162b2) doubled the values (10000 AU/mL) of seroconversion compared with the primary vaccination scheme, corroborating Lustig et al. and Franzese et al. results. They stated that the BNT162b2 vaccine induced a rapid, robust, and lasting response [14,15].

The present study observed that the antibody levels among individuals who received the ChAdOx1 were significantly higher than the individuals who received CoronaVac, suggesting that individuals who received CoronaVac need a booster dose with a heterologous vaccine (Data not shown). Voysey et al. observed that individuals vaccinated with ChAdOx1 presented higher immunogenicity[16].

Additionally, a Brazilian study identified that patients who received homologous doses of CoronaVac presented low antibody levels before administration of the booster

dose[14]. The IgG antibody levels increased from baseline to day 28 after the booster dose: 77 (95%CI: 67 to 88) for Ad26.COV2-S, 152 (95%CI: 134 to 173) for BNT162b2, 90 (95%CI: 77 to 104) for ChAdOx1, and 12 (95%CI: 11 to 14) for CoronaVac. This study also showed that a booster dose of the four vaccines tested increased antibody levels after two doses of CoronaVac; the booster dose was applied six months after the second dose. Moreover, individuals vaccinated with CoronaVac (two doses) presented very low antibody levels after six months[17].

Clear data on the duration of immunity and the level of protection of booster doses are scarce. Furthermore, the vaccine amount needed to ensure adequate antibody levels is unclear. Previous studies did not assess the long-term prevalence of antibodies against SARS-CoV-2 in the vaccinated population[25]; this information was partially evaluated in the present study. However, Hayashi et al. showed that the reduced immunity after 75 days or more after the vaccination scheme with homologous doses of CoronaVac or ChAdOx1 (AstraZeneca) could be recovered by a booster dose of BNT162b2 (Pfizer-BioNTech)[18].

Despite the several studies with different vaccines, most are related to humoral immunity, and few are about the cellular response, limiting the conclusions regarding the sufficiency of a single dose in previously infected individuals and the need for a booster dose[26,27]. Future studies should identify the immunological marker most closely associated with the effectiveness of the vaccine[26], detailing the cellular response of T and B lymphocytes[28].

The data of sex (52.3% women) and age (mean 44.70 ± 11.64 years) of the individuals of this study were similar to the 3,381 individuals of the cohort [29]; however, the number of individuals evaluated was above that described by IBGE, which informed a population of 3,061 individuals in 2019 [30]. Also, the tourist population is almost twice the resident population [29], why may have influenced the change in the total number. Still, this traffic was partially controlled between March and October 2020, when entry and exit from the archipelago were restricted due to the lockdown.

Vaccines that promote immunogenicity are essential for preventing morbidity and mortality caused by SARS-CoV-2 infection [31]. In the present study, we analyzed the IgG anti-SARS-CoV-2 levels in adults before and after a homologous vaccination scheme (CoronaVac or ChAdOx1) and after the booster dose with a heterologous vaccine

(BNT162b3). Data on antibody levels after a complete vaccination scheme using different vaccines are scarce [32]. Additionally, understanding vaccine-induced and virus-induced immunogenicity will help adjust dosage strategies and accelerate vaccination efforts [33], an important aspect in Brazil.

Among the limitations of this study are: (i) the absence of cellular immunity assessment; and (ii) the low prevalence of chronic comorbidities such as hypertension and diabetes, which prevented stratified analyses of the humoral immune response among individuals presenting these conditions.

5. Conclusions

The findings of this study showed that antibody levels increased after the primary vaccination with both CoronaVac and ChAdOx1 but declined shortly afterward, especially among non-infected individuals. Previously infected participants presented higher baseline antibody levels and a more sustained humoral response over time. After the booster dose with a heterologous BNT162b2 vaccine, antibody levels significantly increased, reinforcing the benefit of heterologous boosting for enhancing and maintaining immune protection.

The results highlight the importance of continuous monitoring of humoral immunity to guide vaccination strategies and support decisions on booster timing and combinations.

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REFERENCES

1. World Health Organization (WHO). Timeline of WHO's response to COVID-19. Geneva: WHO; 2020 [Accessed 2023 Nov 22]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline

2. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 – 21 December 2020. Geneva: WHO; 2020 [Accessed 2023 Nov 22]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---21-december-2020

3. World Health Organization (WHO). WHO COVID-19 dashboard. Geneva: WHO; 2023 [Accessed 2023 Nov 22]. Available from: https://covid19.who.int/region/amro/country/br

4. Bonanni P, Cantón R, Gill D, Halfon P, Liebert UG, Crespo KA, et al. The role of serology testing to strengthen vaccination initiatives and policies for COVID-19 in Europe. COVID. 2021;1(1):20–38. https://doi.org/10.3390/covid1010004

5. Min L, Sun Q. Antibodies and vaccines target RBD of SARS-CoV-2. Front Mol Biosci. 2021;8:671633. https://doi.org/10.3389/fmolb.2021.671633

6. World Health Organization (WHO). Update 34 – What we know about the COVID-19 immune response: the latest on COVID-19 immunity & the current global situation. Geneva: WHO; 2020 [Accessed 2023 Nov 22]. Available from: https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-34-immunity-2nd.pdf?sfvrsn=8a488cb6_2

7. Decru B, Van Elslande J, Steels S, Van Pottelbergh G, Godderis L, Van Holm B, et al. IgG anti-spike antibodies and surrogate neutralizing antibody levels decline faster 3 to 10 months after BNT162b2 vaccination than after SARS-CoV-2 infection in healthcare workers. Front Immunol. 2022;13:909910. https://doi.org/10.3389/fimmu.2022.909910

8. Havervall S, Jernbom Falk A, Klingström J, Ng H, Greilert-Norin N, Gabrielsson L, et al. SARS-CoV-2 induces a durable and antigen-specific humoral immunity after asymptomatic to mild COVID-19 infection. PLoS One. 2022;17(1):e0262169. https://doi.org/10.1371/journal.pone.0262169

9. Mahase E. COVID-19: vaccine brands can be mixed in "extremely rare occasions," says Public Health England. BMJ. 2021;372:n12. https://doi.org/10.1136/bmj.n12

10. Lu S. Heterologous prime–boost vaccination. Curr Opin Immunol. 2009;21:346–51. https://doi.org/10.1016/j.coi.2009.05.016

11. Yue L, Zhou J, Zhou Y, Yang X, Xie T, Yang M, et al. Antibody response elicited by a third boost dose of inactivated SARS-CoV-2 vaccine can neutralize SARS-CoV-2 variants of concern. Emerg Microbes Infect. 2021;10:2125–7. https://doi.org/10.1080/22221751.2021.1996210

12. Munro AP, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021;398(10318):2258–76. https://doi.org/10.1016/S0140-6736(21)02717-3

13. Munro AP, Feng S, Janani L, Cornelius V, Aley PK, Babbage G, et al. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial. Lancet Infect Dis. 2022;22(8):1131–41. https://doi.org/10.1016/S1473-3099(22)00271-7

14. Lustig Y, Sapir E, Regev-Yochay G, Cohen C, Fluss R, Olmer L, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in healthcare workers. Lancet Respir Med. 2021;9(9):999–1009. https://doi.org/10.1016/S2213-2600(21)00220-4

15. Franzese M, Coppola L, Silva R, Santini SA, Cinquanta L, Ottomano C, et al. SARS-CoV-2 antibody responses before and after a third dose of the BNT162b2 vaccine in Italian healthcare workers aged ≤60 years: one year of surveillance. Front Immunol. 2022;13:947187. https://doi.org/10.3389/fimmu.2022.947187

16. Voysey M, Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397:881–91. https://doi.org/10.1016/S0140-6736(21)00432-3

17. Clemens SA, Weckx L, Clemens R, Mendes AV, Souza AR, Silveira MB, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single-blind, randomised study. Lancet. 2022;399:521–9. https://doi.org/10.1016/S0140-6736(22)00094-0

18. Hayashi JY, Simizo A, Miyamoto JG, Costa LV, Souza OF, Chiarelli T, et al. Humoral and cellular responses to vaccination with homologous CoronaVac or ChAdOx1 and heterologous third dose with BNT162b2. J Infect. 2022;84(6):834–72. https://doi.org/10.1016/j.jinf.2022.02.026

19. Instituto Brasileiro de Geografia e Estatística (IBGE). Estimativas da população 2020. Rio de Janeiro: IBGE; 2020 [Accessed 2023 Apr 26]. Available from: https://ftp.ibge.gov.br/Estimativas_de_Populacao/Estimativas_2020/estimativa_dou_2020.pdf

20. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Imunização e Doenças Transmissíveis. Coordenação-Geral do Programa Nacional de Imunizações. Plano nacional de operacionalização da vacinação contra a COVID-19. 2ª ed. Brasília: Ministério da Saúde; 2021 [Accessed 2023 Nov 22]. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/svsa/coronavirus/plano-nacional-de-operacionalizacao-da-vacinacao-contra-a-covid-19-pno-2a-edicao-com-isbn/view

21. Abbott Laboratories. Abbott ARCHITECT SARS-CoV-2 IgG II Quant reagent instructions for use. Abbott Park (IL): Abbott; 2022 [Accessed 2023 Nov 26]. Available from: https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2.html

22. Lo Sasso B, Giglio RV, Vidali M, Scazzone C, Bivona G, Gambino CM, et al. Evaluation of anti–SARS-CoV-2 S-RBD IgG antibodies after COVID-19 mRNA BNT162b2 vaccine. Diagnostics. 2021;11(7):1135. https://doi.org/10.3390/diagnostics11071135

23. Yalçın TY, Topçu Dİ, Doğan Ö, Aydın S, Sarı N, Erol Ç, et al. Immunogenicity after two doses of inactivated virus vaccine in healthcare workers with and without previous COVID-19 infection: prospective observational study. J Med Virol. 2022;94:279–86. https://doi.org/10.1002/jmv.27316

24. Mak WA, Koeleman JG, van der Vliet M, Keuren F, Ong DS. SARS-CoV-2 antibody and T cell responses one year after COVID-19 and the booster effect of vaccination: a prospective cohort study. J Infect. 2022;84(2):171–8. https://doi.org/10.1016/j.jinf.2021.12.003

25. Sharif N, Alzahrani KJ, Ahmed SN, Dey SK. Efficacy, immunogenicity and safety of COVID-19 vaccines: a systematic review and meta-analysis. Front Immunol. 2021;12:714170. https://doi.org/10.3389/fimmu.2021.714170

26. Santos-Filho A, Vieira L, Lima A. COVID-19: imunidade natural e vacinal. In: Secretaria de Saúde de Goiás, editor. Síntese de evidências CONECTA-SUS. Goiânia: Gerência de Informações Estratégicas em Saúde; 2022 [Accessed 2023 Nov 22]. Available from: https://www.saude.go.gov.br/files/banner_coronavirus/protocolos-notas/S%C3%ADnteses%20de%20Evid%C3%AAncias/2021/Imunidade%20Natural%20e%20Vacinal.pdf

27. Callaway E. COVID vaccine boosters: the most important questions. Nature. 2021;596:178–80. https://doi.org/10.1038/d41586-021-02158-6

28. Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to two doses. JAMA. 2021;326:1063–5. https://doi.org/10.1001/jama.2021.12339

29. Sales MJ, Kerr LR, Brizolara RV, Barreto IC, de Almeida RL, Angeiras PS, et al. Fernando de Noronha: how an island controlled the community transmission of COVID-19 in Brazil. medRxiv. 2020;2020-10. https://doi.org/10.1101/2020.10.22.20216010

30. Instituto Brasileiro de Geografia e Estatística (IBGE). Estatísticas das cidades: Fernando de Noronha, PE. Rio de Janeiro: IBGE; 2019 [Accessed 2023 Feb 22]. Available from: https://cidades.ibge.gov.br/brasil/pe/fernando-de-noronha/panorama

31. Costa PR, Correia CA, Marmorato MP, de Carvalho Dias JZ, Thomazella MV, da Silva AC, et al. Humoral and cellular immune responses to CoronaVac assessed up to one year after vaccination. medRxiv. 2022. https://doi.org/10.1101/2022.03.16.22272513

32. Michos A, Tatsi EB, Filippatos F, Dellis C, Koukou D, Efthymiou V, et al. Association of total and neutralizing SARS-CoV-2 spike-receptor binding domain antibodies with epidemiological and clinical characteristics after immunization with the 1st and 2nd doses of the BNT162b2 vaccine. Vaccine. 2021;39:5963–7. https://doi.org/10.1016/j.vaccine.2021.07.067

33. Trougakos IP, Terpos E, Zirou C, Sklirou AD, Apostolakou F, Gumeni S, et al. Comparative kinetics of SARS-CoV-2 anti-spike protein RBD IgGs and neutralizing antibodies in convalescent and naïve recipients of the BNT162b2 mRNA vaccine versus COVID-19 patients. BMC Med. 2021;19:90. https://doi.org/10.1186/s12916-021-02090-6

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EVALUATION OF THE HUMORAL IMMUNE RESPONSE TO PRIMARY AND BOOSTER COVID-19 VACCINATION

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