Brazilian Journal of Microbiology (2023) 54:921–927
https://doi.org/10.1007/s42770-023-00935-1

CLINICAL MICROBIOLOGY - SHORT COMMUNICATION

IgA antibody dynamics in healthcare workers after CoronaVac® vaccination and heterologous Comirnaty® booster dose

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Received: 21 November 2022 / Accepted: 15 February 2023 / Published online: 2 March 2023

Abstract

Background This study is aimed at calculating the IgA antibody dynamic range in healthcare workers (HCWs) after immunization with CoronaVac® and Comirnaty® booster dose.

Methods A total of 118 HCW serum samples from Southern Brazil were collected the day before the first vaccine dose (day 0) and + 20, + 40, + 110, + 200 days following the vaccine's first dose, and + 15 days after a Comirnaty® booster dose. Immunoglobulin A (IgA) was quantified using immunoassays for anti-S1 (spike) protein antibodies (Euroimmun, Lübeck, Germany).

Results Seroconversion for the S1 protein occurred in 75 (63.56%) and 115 (97.47%) HCWs by day + 40 and day + 15 after the booster dose, respectively. There was an absence of IgA antibodies after the booster dose in two (1.69%) HCWs undergoing biannual rituximab administration and one (0.85%) HCW for no apparent reason.

Conclusion Complete vaccination showed a significant IgA antibody production response, and the booster dose considerably increased this response.

Keywords SARS-CoV-2 · Vaccine · Immunization · Public health · Immunoglobulin A · Pandemic

Introduction

Approximately 2 years after the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, by April 6, 2022, the number of confirmed cases was 492,189,439 people worldwide, including 6,159,474 deaths [1]. Following the discovery of this new human coronavirus in December 2019, there was a global effort to search for an effective vaccine to control the COVID-19 pandemic [2–4]. This resulted in the late 2020, in the first immunization doses being administered in the population, and by April 6, 2022, 11,242,252,352 doses of the vaccine were administered [1]. Worldwide efforts resulted in several vaccines against SARS-CoV-2 with different antigen platform systems (e.g., non-replicating viral vector, protein subunit, inactivated virus, and mRNA), with the main antigenic focus on the S protein [2, 3].

The vaccination drive in Brazil started with CoronaVac® (Sinovac Life Sciences, Beijing, China) in January 2021 with the initial administration conducted in older adults, healthcare workers, and indigenous people. The CoronaVac® (Sinovac Life Sciences, Beijing, China), which uses the inactivated SARS-CoV-2 virus as the vaccine component [2, 3], represents 24.09% (96,946,337) of the total doses administered in Brazil, being the second most administered vaccine among healthcare workers [5]. In phase I/II studies, this vaccine was safe, tolerable, presented high immunogenicity, and had uncommon adverse reactions. A similar response was observed for both tested concentrations (3 µg and 6 µg), and 97% of seroconversion occurred in the participants with 18–59 years [6]. In phase III trials conducted among healthcare workers, this vaccine presented 50.7%, 83.7%, and 100% efficacy against symptomatic cases, cases requiring medical assistance, and severe cases, respectively

Responsible Editor: Mauricio Nogueira

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[7]. Phase III also tested some serum samples against the B.1.1.28, gamma (P.1), and zeta (P.2) variants, showing great antibody response [8].

The Comirnaty® vaccine, also named BNT162b2 (BioNTech and Pfizer), consists of a nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2, encapsulated in lipid nanoparticles. It is administrated intramuscularly in two doses of 30 µg each, with a recommended dose interval of 21 days [9]. The start of Comirnaty® administration in Brazil was in May 2021 [5] after phase I/II/III clinical trial result presentation, showing 94.6% of protective efficacy in patients aged 16–85 years [9].

Based on previous studies on vaccination strategies, the same type of vaccine (or at least the same antigen platform systems) is generally used for booster vaccination and is called homologous immunization [10]. However, for COVID-19 vaccination, some researchers have presented the sequential immunization strategy for the initial and booster heterologous immunization [11]. Heterologous vaccination is defined as using a combination of vaccines from different manufacturers or using different antigen platform systems for booster vaccination [12–15]. Studies have shown that mixed vaccination schedules for COVID-19 vaccines may lead to higher levels of antibodies and a more comprehensive immune response, exceeding even the effectiveness of standard vaccination schedules, without severe side effects compared to those caused by the vaccine's default schemes [16–18].

It has been shown that the humoral response from the IgA anti-S1-protein antibodies in patients infected with SARS-CoV-2 appears earlier and more robustly than the response from the IgM antibodies. In addition, the IgA humoral response can be detected in different fluids (saliva, breast milk, bronchial tissue, blood, and serum) for longer than IgM class antibodies [19, 20]. However, there is limited evidence on IgA dynamics after vaccination schedule and booster dose.

Due to the heterogeneity of the immune response in cases of SARS-CoV-2 infection and, as IgA is not considered a parameter for the authorization of vaccine use in humans, there is a need to understand the dynamics of IgA antibodies after vaccination. In this context, this study is aimed at identifying the IgA dynamic range after vaccination with SARS-CoV-2 (CoronaVac®) and mRNA (Comirnaty®) booster among healthcare workers (HCWs).

Methods

Participants

In total, 170 participants were recruited at the Complexo Hospital de Clínicas, UFPR, Clinical Laboratory, in Curitiba, Brazil, during the HCW vaccination period. This study was approved by the Institutional Ethics Committee (CAAE: 31687620.2.0000.0096), and all participants signed the informed consent.

The inclusion criteria were: answering the questionnaire, being vaccinated with two doses of CoronaVac® plus the Comirnaty® booster dose, and providing serum samples. Fourteen participants were excluded because they did not complete the questionnaire. In addition, seven participants received another vaccine, one participant did not have the second dose, fifteen participants did not provide a sample on day 0 (previous vaccination) or day + 40 (post-vaccination), and fifteen participants did not take booster dose or did not provide a sample on day B+15.

Serum samples of 118 healthcare workers included in this study were collected on days 0 (before the administration of the first dose), + 20, + 40, + 110, and + 200 after the first dose and + 15 days after the Comirnaty® booster dose (Booster+15/B+15). On days 0, + 40, + 110, + 200, and B+15, a total of 118 serum samples were analyzed for each collection, and on day + 20, 104 serum samples were analyzed. All samples were stored at − 20 °C until analysis was performed.

Participants were divided in two groups based on the IgA anti-spike-1 (anti-S1) results on day 0 in reactive ($n = 15$) and non-reactive ($n = 103$) and based on the presence of comorbidities in immunosuppressed ($n = 9$) or non-immunosuppressed ($n = 109$) (Table 1). The immunosuppressed group consisted of participants with compromised humoral or cellular immune response, such as HIV infection, or those who used immunosuppressive drugs, such as chemotherapy or steroids (prednisone at a dose of 20 mg/day or equivalent).

IgA seroconversion evaluation

Semi-quantitative assays were performed to detect anti-SARS-CoV-2 IgA. The serum samples from days 0, + 20, + 40, + 110, + 200, and B+15 were analyzed using the enzyme-linked immunosorbent assay (ELISA) for IgA anti-S1 spike-protein receptor-binding domain (RBD) (Euroimmun, Lübeck, Germany). Samples were tested in duplicate, following the manufacturer's instructions. Results with a variation coefficient greater than 15.0% were repeated.

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 9.0.0. The Wilcoxon and the Mann-Whitney *U* tests were used to compare intra-group or inter-group differences on IgA values in different collection periods, as appropriate. *p* values less than 0.05 were considered significant.

Table 1 Demographics characteristics of participants included in the study for each respective group

	IgA Anti-S1 (day 0)			Immunosuppressive comorbidities*		
	Reactive	Non-reactive	*p* value	With	Without	*p* value
	n	*n*		*n*	*n*	
Total	15	103		9	109	
Female (%)	13 (86.67)	81 (78.64)	0.7328	6 (66.67)	87 (79.82)	0.3974
Median age (IQR)	43 (24.00–49.00)	50 (40.00–53.00)	0.0874	51 (45.50–54.50)	54 (39.50–53.50)	0.1896

*Comorbidities (immunosuppressive) included: immunosuppressive drugs use, Crohn's disease, bariatric surgery, HIV+, and diabetes. The patient with myasthenia gravis is not included here because the treatment used was non-immunosuppressive

Information on the handling of special cases: two immunosuppressed (rituximab 1400 mg/biannually), one myasthenia gravis (pyridostigmine 120 mg/day), one Crohn's disease (azathioprine 100 mg/day), two bariatric surgery, and one HIV+

Results

Compared to IgA reactive serum ($p = 0.0353$) (Fig. 1A) and IgA non-reactive serum both on day 0 ($p < 0.0001$) (Fig. 1B), in the analysis on day + 40, 75 (63.56%) showed a statistically significant positive result for IgA antibodies.

However, 15 days after the booster dose (B+15), 115 (97.47%) samples had positive results for IgA antibodies, and the statistical significance was observed on both groups (reactive and non-reactive).

Comparing the values found between the IgA reagent and non-reagent groups on the same collection date, all results showed a statistically significant difference (all $p < 0.05$).

The most common comorbidities reported by the HCWs were Crohn's disease, prior bariatric surgery, HIV+, and diabetes. The participant's response to the vaccine was similar regardless of having comorbidities (Fig. 1C). However, two participants in the immunosuppressed group did not undergo seroconversion, and one participant (in the non-immunosuppressed group) did not seroconvert by day B+15, for no apparent cause (Fig. 2C).

Sixteen participants reported previous detectable RT-PCR for SARS-CoV-2; therefore, it was not possible to observe any statistically significant difference between the results obtained before the second dose of the vaccine (days 0 and 20) ($p = 0.0730$) and the sample collected on day 20 after the first dose in comparison to the samples obtained on days 110 ($p = 0.1205$) and 200 ($p = 0.1514$) (Fig. 2A).

Six participants (5.1%) had positive molecular diagnosis for SARS-CoV-2 after two vaccine doses (Fig. 2B). None of them had severe disease, four (66.7%) participants reported fever or headache, three reported (50%) anosmia, two reported (33%) rhinorrhea or myalgia, and one reported (16.7%) cough, diarrhea, fatigue, dysgeusia, and runny nose. The SARS-CoV-2 infection occurred between 121 and 219 days after the second vaccine dose. Most ($n = 5$, 83%) infections occurred more than 5 months after complete vaccination.

Discussion

As previously reported by Padoan et al. [19], IgM and IgG antibody response against SARS-CoV-2 infection presents a similar dynamic. In contrast, IgA class antibodies are detected earlier, more intensely, and remain for a longer period of time than IgM class antibodies. In addition, similar studies by Pozzetto et al. [16], Costa Clemens et al. [17], and Liu et al. [18] showed similar effect to that found in this study with anti-S1-protein IgA class antibodies, but their analyses focused on antibodies of the anti-S1-protein IgG class instead.

Among the reported results, no statistical difference was observed in the analysis of anti-S1-protein IgA antibodies from participants who had COVID-19 previously, suggesting that only one dose of vaccine was not capable of modifying the humoral response in these cases. In addition, humoral response after the antibodies' peak decreased as expected and this finding has been reported in other studies [21–24]. However, the response remained higher and significantly different from the results before the first dose, including the comparison between days 0 and 200. Therefore, it is safe to assure that vaccination should be administered even among people who were previously infected with the SARS-CoV-2.

It is important to note that all participants who had positive serology for anti-S1-protein IgA in the sample collected on day 0 had persistent positive serology in all other scheduled collection times, even those with probably asymptomatic infection.

Another different point in this study, regarding the IgG serology in this same cohort [25], there was a difference between the response presented by the participants with detectable IgA in the sample since day 0. In these subjects, the serum level of IgA remained higher than in those with negative serology, despite following the same dynamics, suggesting that vaccination induces a more intense IgA response, but not an IgG response in previously infected people.

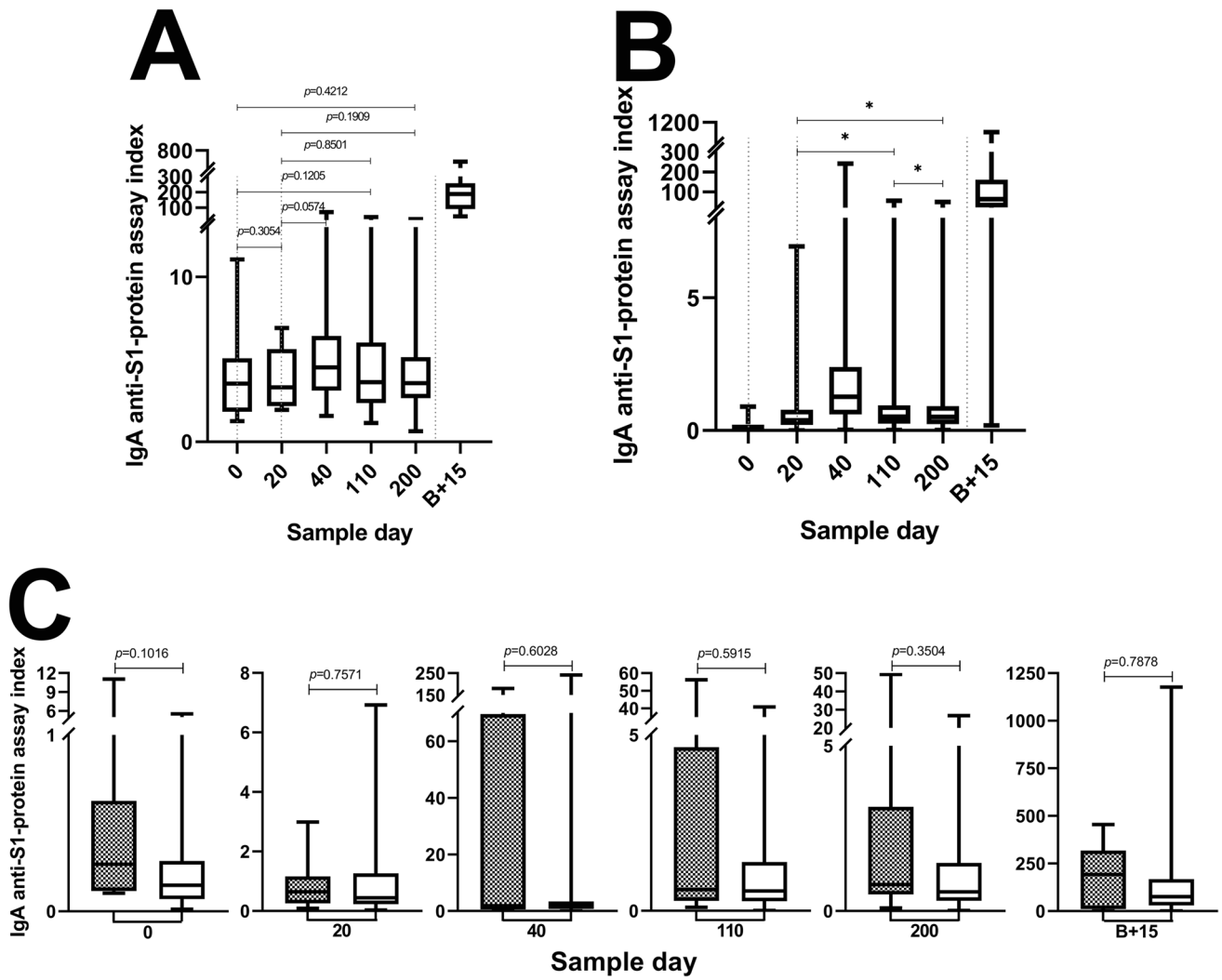

Fig. 1 IgA anti-S1-protein index dynamic range. **A** Evaluation of participants with IgA reagent in sample on day 0. Only non-significant *p* values are shown. All other comparisons reached statistical significance (Suppl. Table 1). **B** Evaluation of participants with IgA non-reactive in samples on day 0. *Statistically significant *p* values different from 0.0001 (Suppl. Table 1). **C** Comparison between IgA anti-S1-protein index in immunosuppressed and non-immunosuppressed. Checkered boxes represent the immunosuppressed group, and white boxes represent the non-immunosuppressed group. The dotted line represents the vaccine administration

No statistical difference was observed between IgA immune response and the presence of immunosuppressive comorbidities. However, two out of the three cases who did not seroconverted after all three vaccine doses were immunosuppressed participants from Rituximab® use, corroborating the findings from Felten et al. [26]. In this situation, as described by Kado et al. [27], there is a significant decrease in B lymphocyte levels, leading to a cease in antibody production until B lymphocyte recovery occurs in 6 to 24 months. In such cases, the response must be evaluated after the repletion time, and re-vaccination considered under medical and clinical endorsement. Two other participants did not seroconvert on day + 40. One of these had late-response seroconversion on day + 60. No explanation was found for the other case, and more studies are needed to understand factors that can potentially interfere with the immune response.

As shown in a cohort study [25], one participant did not present IgG seroconversion after two CoronaVac® doses for no apparent reason, but the participant did for IgA antibody. This case requires a deeper analysis of cellular activity and individual antibody production, as there was no production of anti-S1-protein IgA antibodies. By contrast, a previous study of anti-S1-protein IgG antibodies showed seroconversion after the two doses of CoronaVac® and after a booster dose [25]. In patients with B lymphocyte depletion, the booster dose remained without humoral IgA response induction.

This study has limitations, which include a small sample size and a low prevalence of immunosuppressed

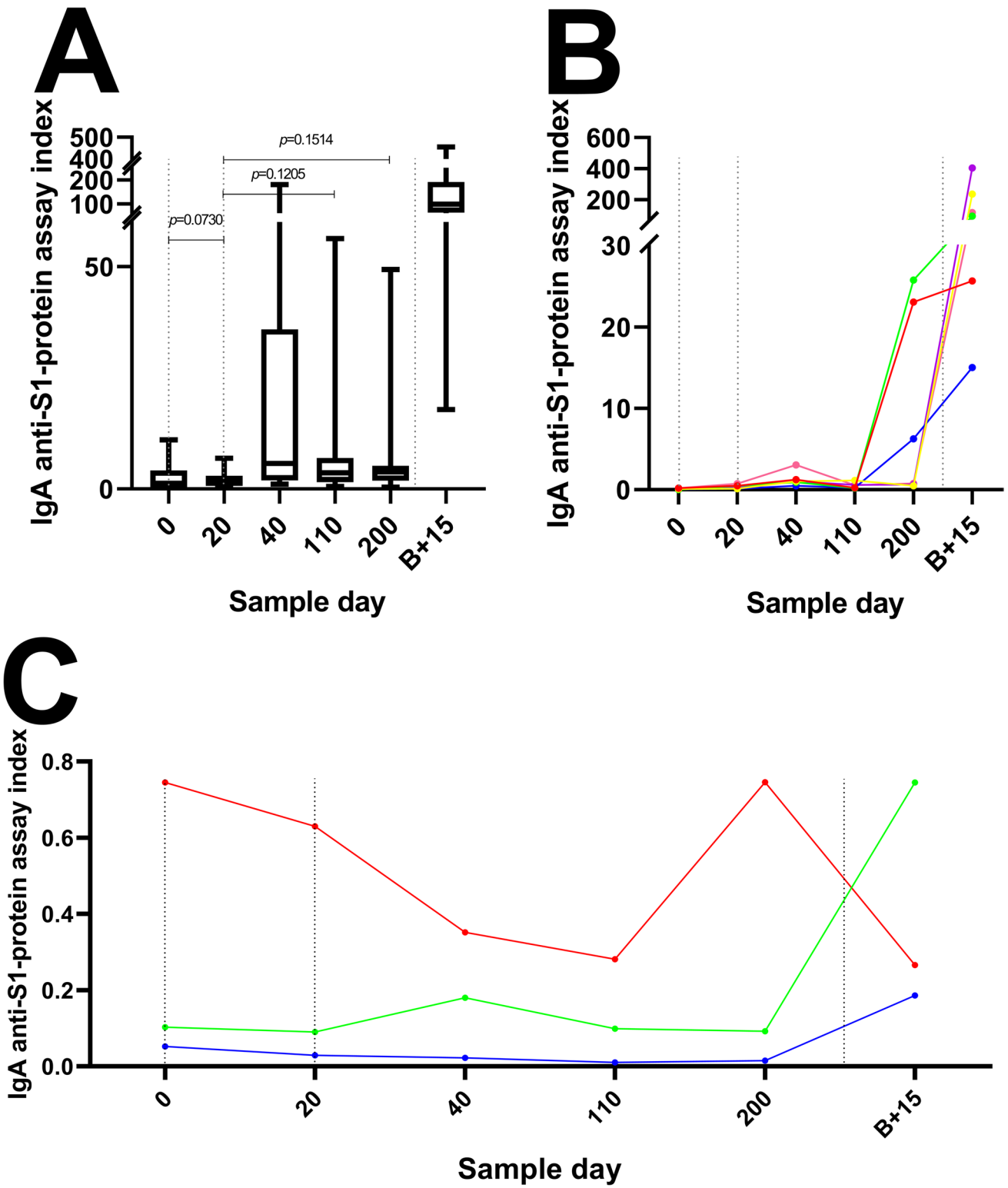

Fig. 2 IgA anti-S1-protein dynamic range for participants with detectable RT-PCR for SARS-CoV-2 or with no seroconversion. **A** Participants who had molecular diagnostic previous to vaccination. Only non-significant *p* values are shown (Suppl. Table 1). **B** Participants who had molecular diagnostic after vaccination. **C** Dynamics of the anti-S1 protein IgA index for each participant who did not present a reactive result during the analysis. The dotted line represents the administration of the vaccine. Each color line represents a different participant (online version only)

comorbidities. There is a need to expand the knowledge about anti-S1-protein IgA antibodies. Although its high concentration in secretion fluids such as breast milk [28] and saliva [29] results in additional protection for newborns, this age group still does not have vaccine available against SARS-CoV-2.

In conclusion, vaccination with CoronaVac® induces an IgA antibody response, a critical antibody class for protection against infections, with a robust antibody response found after the Comirnaty® booster dose administration. In addition, most comorbidities assessed in this study did not interfere with the humoral response.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s42770-023-00935-1.

Acknowledgements The authors would like to thank all participants who agreed to participate in this study, those involved in the collection and storage of samples, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Author contribution L.B.B.: data collection, analysis, interpretation, and article drafting. L.H.F.: data collection and article drafting. G.G.: data collection and article drafting. M.B.N.: data analysis and interpretation, article drafting, critical revision, and funding acquisition. S.M.R: conception, data analysis and interpretation, article drafting, and critical revision. All authors approved the final version of the manuscript.

Funding This research project was supported by the PROPLAN/Federal University of Paraná, Curitiba-Paraná, Brazil, and FINEP, Funder of Studies and Projects, Ministry of Science, Technology and Innovation, Brazil Institutional Network, Project: Laboratories for Diagnostic Tests for COVID-19 (0494/20).

Declarations

Conflict of interest The authors declare no competing interests.

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