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Short communication

Duration of vaccine protection against breakthrough infections during five COVID-19 waves among healthcare workers primarily vaccinated with CoronaVac

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ABSTRACT

We aimed to characterise vaccine-induced protection against COVID-19 during five waves caused by Variants of Concern (VOCs). This is a nested case-control study of 3,972 HCW primarily vaccinated with CoronaVac (98%) that evaluated symptomatic SARS-CoV-2 breakthrough infections (BI) in almost two-years follow-up until the 3rd Omicron wave. Predictors of protection against SARS-CoV-2 BI were analysed using conditional logistic regression models. We included 1,491 SARS-CoV-2 breakthrough cases, mostly mild, and 2,962 controls. Most participants (90%) had received at least one booster before the onset of the Omicron waves, mainly BNT162b2. A multivariate logistic regression showed that vaccine-induced protection against BI wanes after six months regardless of the number of monovalent booster doses. Additionally, booster dose with BNT162b2 showed a trend for higher protection compared to CoronaVac during the Omicron waves. In conclusion, immunity of monovalent booster doses against SARS-CoV-2 is short-lasting. Individuals previously vaccinated with an inactivated vaccine should receive a BNT162B2 booster dose.

1. Introduction

As of January 23rd, 2023, Brazil has confirmed almost 37 million cumulative COVID-19 cases with approximately 700,000 deaths [1]. Immunisation has played a crucial role in reducing COVID-19 morbidity and case-fatality; however, a notable number of SARS-CoV-2 breakthrough infections (BI) have been reported [2]. Vaccine-induced protection has been described to wane progressively but can be enhanced by booster doses [3,4]. Nevertheless, the effect of booster doses on the risk of BI remains not fully understood.

We aimed to characterise vaccine-induced protection against COVID-19 during five waves caused by Variants of Concern (VOCs) in healthcare workers (HCW).

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2. Methods

2.1. Setting

Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (HC) is a tertiary-care teaching hospital that has been a reference for severe COVID-19 cases in São Paulo, Brazil. Nearly 30,000 HCWs work at the HC hospital complex. HCWs with suspected COVID-19 symptoms are evaluated by the HCW Health Service, tested by real-time polymerase chain reaction (RT-PCR) or rapid antigen test (RAT) for SARS-CoV-2 on respiratory samples, and receive paid leave for seven days from the onset of symptoms if COVID-19 is confirmed. COVID-19 vaccination at HC started with an inactivated vaccine (CoronaVac, produced by Sinovac/Instituto Butantan), on January 18, 2021, and the second dose was first administered on February 17, 2021. Other vaccines (AZD1222, by AstraZeneca/BioManguinhos; Ad26.COV2.S by Jansen; or mRNA BNT162b2, by Pfizer) became available in the following months. The first and second booster doses were released in October 2021 and July 2022, respectively. A small number of HCW (n = 28) initiated vaccination in 2020, participating in vaccine clinical trials.

2.2. Study design and population

This was a nested case-control study within a prospective cohort of HCWs from HC, that had been immunised with at least two doses of COVID-19 vaccines. All HCW were followed-up from the administration of the second dose (02/17/2021) until the end of the third Omicron wave (01/20/2023) or discontinuation of work at HC, whichever came first. The outcome was SARS-CoV-2 symptomatic BI. For each of the five waves, cases of BI were matched with controls at a 1:2 ratio using a propensity score controlling for sex and age. Controls were defined as HCWs with no SARS-CoV-2 BI during the wave of the matched case. Each HCW could be selected as a case or control in each wave. Cases and controls from each wave were included in a combined dataset for analysis.

COVID-19 waves time span was delimited based on whole genome sequencing (WGS) genotyping from cases on regional SARS-CoV-2 monitoring platforms: FioCruz/Global Initiative on Sharing All Influenza Data (GISAID)[5] and "Instituto Todos pela Saúde" (ITpS)[6], and from cases of our cohort and others hospital units from the University of São Paulo [7]. A representative number of respiratory samples positive for SARS-CoV-2 (n = 2,043) were evaluated using WGS for sublineage identification.

The predominant variant was determined based on its presence in at least 75 % of the isolates. However, Omicron cases unfolded into three distinct waves composed by different sublineages that co-circulated, each one representing less than 75 %. Thus, COVID-19 waves were classified as follows: Gamma wave (March 5 – August 5, 2021), Delta wave (August 20 – December 18, 2021), 1st Omicron wave (December 25, 2021 – March 19, 2022), 2nd Omicron wave (April 9 – August 30, 2022), and 3rd Omicron wave (October 22, 2022 – January 22, 2023) (Fig. 1).

SARS-CoV-2 infections data were obtained from two different sources: HCWs that visited the HCW Health Service and had a positive RT-PCR or RAT at the HC laboratory; and HCWs with confirmed COVID-19 based on external assays notified to the Human Resources Department. COVID-19 vaccination data was verified using the VaciVida, an online database of the Epidemiological Surveillance Centre (CVE) of the Health Department of São Paulo state that records all COVID vaccines administered doses. For HCW who were vaccinated in other Brazilian states, vaccination data was obtained from the National Immunisation

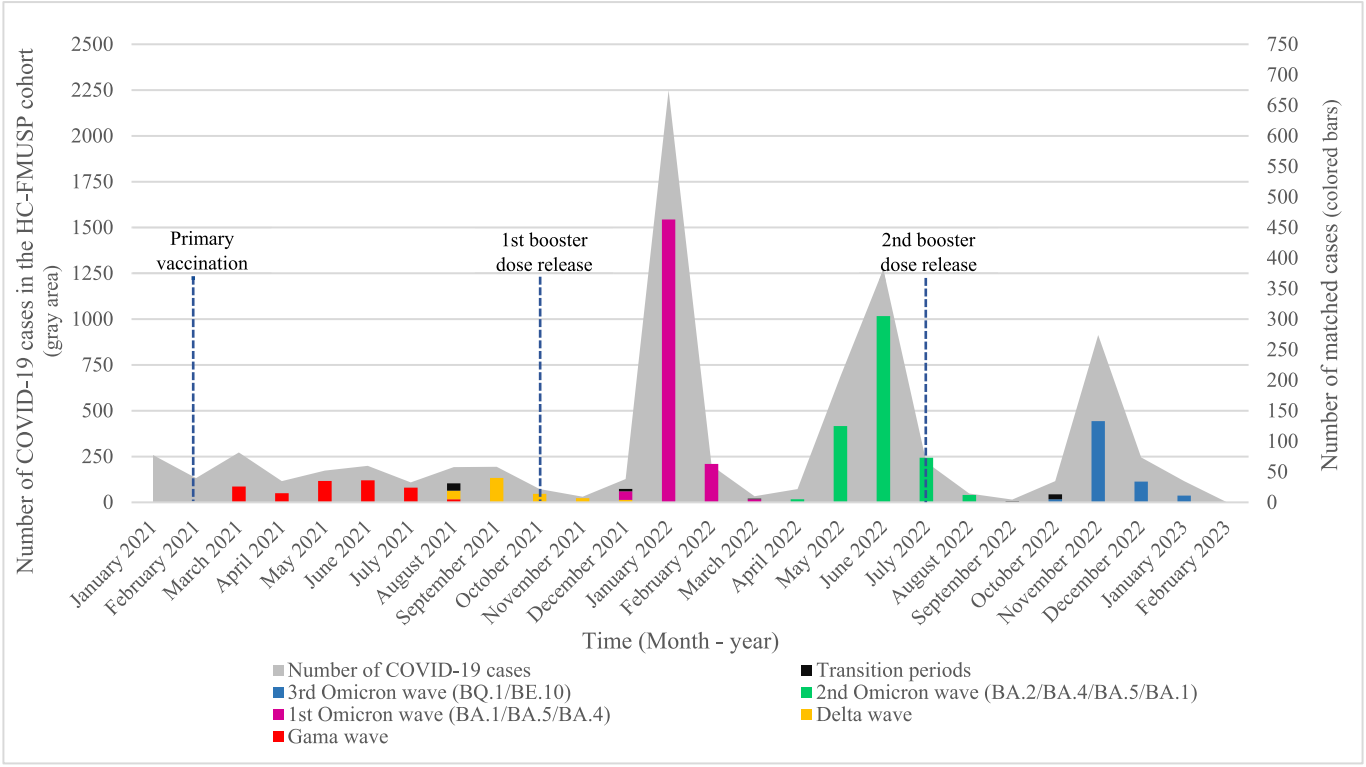

Fig. 1. Distribution of SARS-CoV-2 breakthrough infections during the five waves of Variants of Concern (VOCs) in a cohort of healthcare workers from Hospital das Clinicas da Faculdade de Medicina Universidade de Sao Paulo, Brazil, between February 2021 and January 2023. Left axis shows the number of SARS-CoV-2 infections in the cohort (gray area). Right axis shows the number of matched cases in our nested case-control study (colored bars) with gamma wave cases in red, delta wave cases in yellow, 1st Omicron wave cases in magenta, 2nd Omicron wave cases in green, and the 3rd Omicron wave cases are in blue. Transition periods between waves were grouped in black (n = 27). The first Omicron wave was caused mainly by BA.1 and fewer cases of BA.5 and BA.4. The second Omicron wave included BA.2, BA.4, BA.5 and a smaller number of BA.1 cases. The 3rd Omicron wave was caused mainly by the sublineages BQ.1 and BE.10.

Program. Demographic and clinical data were obtained through structured data forms.

2.3. SARS-CoV-2 whole genome sequencing

Respiratory samples were aliquoted and stored at −80 °C. RNA was extracted using Extracta 96 kit (*Loccus*). Library preparation and sequencing were conducted using *Illumina* COVIDseq according to manufacturer's recommendations. SARS-CoV-2 genomes were assembled, and lineages were identified using the *Pangolin* version (https://pangolin.cog-uk.io/) and *NextClade* version (https://clades.nextstrain.org) softwares.

2.4. Statistical analysis

Clinical and demographic data were reported as proportions and medians because continuous variables showed non-normal distribution. To evaluate the predictors of protection against BI, we evaluated data from five COVID-19 waves separately and aggregated. Bivariate analyses were performed using chi-squared test or Mann Whitney-*U* test comparing cases and controls. Predictors of protection against SARS-CoV-2 BI were analysed using conditional logistic regression models. The following independent variables were included in the models: number of vaccine doses, vaccine used on last dose, time elapsed since the last dose, and time elapsed since the last SARS-CoV-2 infection. The number of previous infections was not included in the model due to collinearity with the variable "time elapsed since last SARS-CoV-2 infection". The number of doses were categorised as two doses, three doses, and four or more doses. The time elapsed since the last dose of vaccine was classified as vaccinated within six months, between six to 12 months, and more than 12 months. Time elapsed since the last SARS-CoV-2 infection was categorised as follows: no previous infection, infection in the last six months, between six to twelve months, and more than 12 months. The last dose of vaccine was classified as BNT162b2, CoronaVac, AZD1222 and Ad26.COV2.S. For controls, the number of infections, number of doses, and time elapsed since the last dose of vaccine and since the last SARS-CoV-2 infection were calculated using the date of SARS-CoV-2 BI of the respective matched case. Since age and sex were used for matching cases and controls, these variables were disregarded for inferential analyses. Since current WHO recommended COVID-19 vaccination schedule for immunocompetent adults comprises administration of one booster dose, we also evaluated risk factors for BI among HCW with at least one booster dose in a separate multivariate regression model during the Omicron era. All statistical analyses were two-tailed with an alpha error of 0.05. The software SPSS (version 20.0) was used for the analyses.

Ethical approval

All study participants signed written informed consent before enrollment in the cohort. This study was approved by the HC Ethics Committee (CAAE: 42708721.0.0000.0068).

3. Results

Among the 3,972 HCWs included in the cohort, 79 % were female, and median age was 44 years (Table 1). Primary vaccination was predominantly with CoronaVac (n = 3,890 [98%]) and 90% (n = 3,574/3,972) had received at least one booster dose prior to the onset of the Omicron waves, mainly with BNT162b2 (n = 3,409/3,574 [95%]) (Table 1). A total of 757 (19%) HCWs had a SARS-CoV-2 infection before primary vaccination. There were 1,504 BI, of which 146 (10%) cases were during the Gamma wave; 79 (5%) during the Delta wave; 547 (36%) during the 1st Omicron wave; 522 (35%) during the 2nd Omicron wave; 183 (12%) during the 3rd Omicron wave; and 27 (2%) during the transition periods between waves. Nearly all BI cases were mild. Only one patient required hospitalisation, during the Delta wave, complicated by a ventilator associated pneumonia, with a fatal outcome. This patient was a 48-year-old female with multiple comorbidities (hypertension, diabetes, obesity, and asthma), who was primarily vaccinated with CoronaVac, without any booster.

Table 1
Clinical and demographic characteristics of the vaccinated healthcare workers' cohort participants (n = 3,972) and of the cases and controls. (Hospital das Clinicas, Universidade de Sao Paulo, Brazil).

Characteristics	Cohort (n = 3,972) N (%) or Med (IQR[§])	Cases[*] (n = 1,491) N (%) or Med (IQR[§])	Controls[*] (n = 2,962) N (%) or Med (IQR[§])	*p* value (cases *vs.* controls) [†]
Female	3,137 (79)	1,227 (82)	2,443 (83)	0.88
Age (years)	44 (34–55)	44 (35–54)	44 (35–54)	0.98
Primary vaccination				
CoronaVac	3,879 (98)	1,455 (98)	2,903 (98)	0.36
AZD1222	82 (2)	32 (2)	53 (2)	0.41
BNT162b2	9 (0)	3 (0)	4 (0)	0.69
Ad26.COV2.S	2 (0)	1 (0)	2 (0)	1.00
Number of previous doses of vaccine				
2 doses	NA [‡]	307 (21)	540 (18)	0.058
2 doses + 1 booster	NA [‡]	954 (64)	1,960 (66)	0.15
2 doses + ≥ 2 boosters	NA [‡]	230 (15)	462 (16)	0.88
Time elapsed since last vaccine dose				
≤ 6 months	NA[‡]	860 (58)	1,770 (60)	0.18
6 to 12 months	NA[‡]	556 (37)	1,055 (36)	0.27
> 12 months	NA[‡]	75 (5)	137 (5)	0.55
Last dose of vaccine				
BNT162b2[¶]	NA[‡]	949 (64)	1,968 (67)	0.06
CoronaVac	NA[‡]	362 (24)	626 (21)	0.02
Ad26.COV2.S	NA[‡]	92 (6)	202 (7)	0.41
AZD1222	NA[‡]	88 (6)	166 (6)	0.69
SARS-CoV-2 infection before primary vaccination	757 (19)	231 (16)	586 (20)	<0.001
Number of previous SARS-CoV-2 infections				
No previous infection	NA[‡]	1,123 (75)	1,943 (66)	<0.001
One infection	NA[‡]	341 (23)	943 (32)	<0.001
≥ 2 infections	NA[‡]	27 (2)	76 (2)	0.11
Time elapsed since previous SARS-CoV-2 infection				
No previous infection	NA[‡]	1,123 (75)	1,943 (66)	<0.001
≤ 6 months	NA[‡]	40 (3)	274 (9)	<0.001
6 to 12 months	NA[‡]	85 (6)	190 (6)	0.35
> 12 months	NA[‡]	243 (16)	555 (19)	0.045

[*] The cohort participants were categorised as both cases and controls during the different periods of evaluated waves.
[§] Interquartile range.
[†] Comparison between cases and controls using univariate logistic regression.
[‡] Not applicable. The result depends on the wave that is being evaluated.
[¶] Only one HCW received the bivalent COVID-19 vaccine.

In this study, 1,491 BI cases and 2,962 controls were analysed. Overall, cases and controls had similar distribution of primary vaccination immunizer, number of vaccine doses, and time elapsed since last vaccine dose (Table 1). However, the control group had a lower proportion of HCW who had received CoronaVac as the last dose (21% *vs.* 24%, p = 0.02). Additionally, there were more previous SARS-CoV-2 infections among controls compared to cases (34% *vs.* 25%, p < 0.001). Furthermore, there was a higher number of persons with less than six months since previous SARS-CoV-2 infection among controls (9% *vs.* 3%, p < 0.001) (Table 1).

The comparison of cases and controls within the Gamma, Delta, and Omicron waves showed comparable results for the distribution of

primary vaccination schedule. Previous SARS-CoV-2 infections were more common among controls in all waves. During the Gamma wave, most participants (99 %) had received only two doses and there were no differences regarding time elapsed since last vaccine dose among cases and controls. During the Delta wave and the Omicron waves, controls had received a booster more often when compared with cases. There was also a higher proportion of controls who had received the last dose less than six months before (Table S1-S3). In addition, fewer controls had received CoronaVac as their last dose (8% *vs.*11%, p = 0.002) compared with cases during the Omicron waves (Table S2 and S3).

In the multivariate analysis encompassing the entire study period, having received the most recent vaccine dose within the last six months was protective in comparison with six to twelve months (OR = 1.14 [CI 1.02 – 1.28; p = 0.026]), and more than twelve months (OR = 1.23 [CI 0.95 – 1.58; p = 0.12]). There was no protective effect of the number of vaccine doses nor of the immunizer used as the last dose (Table 2). This time-restricted vaccine protection was similar when analyzing the Delta and the Omicron periods separately (Table 3). Additionally, in the multivariate analysis of the Omicron period, booster with CoronaVac exhibited a trend for higher risk of BI (OR = 1.30 [CI 0.98 – 1.73; p = 0.07]) when compared to booster with BNT162b2 (Table 3). Prior SARS-CoV-2 infections elicited protection as compared with no previous infection: infection in the previous six months (OR = 0.30 [CI 0.22 – 0.42; p < 0.001]); six to twelve months (OR = 0.81 [CI 0.64 – 1.02; p = 0.08); and more than twelve months (OR = 0.80 [CI 0.68 – 0.93; p = 0.003]) (Table 2).

4. Discussion

This study analysed the duration of vaccine-induced protection against symptomatic SARS-CoV-2 BI over five waves caused by VOCs (from Gamma to the third Omicron wave). We observed that immunity evoked by monovalent vaccines wanes after six months. In addition, booster doses with BNT162b2 showed a trend for higher protection against BI compared with CoronaVac.

Vaccine effectiveness (VE) against SARS-CoV-2 has already been shown to decrease over time [3,4,8,9]. In our study, vaccine protection against BI lasted six months during Delta and the Omicron period. A recent *meta*-analysis found that VE against Omicron symptomatic BI decreased from 53% one month after primary vaccination to lower than 20% (14%) at six months and to 9 % at nine months. Similarly, VE of booster doses against symptomatic BI decreases from 60% at one month to 13% at nine months [3]. However, different from our investigation, previous studies with monovalent vaccines [2,3,8–12] did not evaluate Omicron waves caused by the BA.5-derived sublineages BQ.1 and BE.10. Thus, we demonstrated that these vaccines have similar duration of protection against these different Omicron sublineages. Although VE against hospitalisations and deaths due to COVID-19 also decreases over time, it has been shown to wane more slowly [2,4,8,12].

There is little evidence about inactivated vaccines as boosters against COVID-19. We found that homologous booster in persons primarily immunised with an inactivated vaccine displayed lower protection against symptomatic BI during the Omicron waves compared to BNT162b2, agreeing with previously described data [8,12–14]. A Brazilian population-based study evaluating persons primarily vaccinated with CoronaVac showed that VE against BI up to two months after homologous and heterologous (with BNT162b2) booster was 5% and 53%, respectively, compared to not receiving a booster dose six months after primary series[10]. The different effect of these booster might be due to improved protection conferred by heterologous booster compared to homologous booster [4,13–17] or to superiority of mRNA vaccines compared inactivated vaccines for booster doses [4,16].

This study has some limitations. It is a unicentric study. There was no data available about comorbidities of participants, and we could not evaluate vaccine effect on COVID-19 severity. However, we managed to implement a thorough surveillance for the prospective follow up for almost two years.

In conclusion, we demonstrated that monovalent vaccine-induced

Table 2
Factors associated with SARS-CoV-2 breakthrough infections during the five waves caused by VOCs in vaccinated healthcare workers (n = 4,453). (Hospital das Clinicas, Universidade de Sao Paulo, Brazil).

Variables	OR*	95 % CI§	*p* value
Number of previous doses of vaccine			
2 doses	Ref		
3 doses	1.12	0.83 – 1.51	0.46
≥ 4 doses	1.22	0.88 – 1.69	0.24
Time elapsed since last vaccine dose			
≤ 6 months	Ref		
6 to 12 months	1.14	1.02 – 1.28	0.026
> 12 months	1.23	0.95 – 1.58	0.12
Last dose of vaccine			
BNT162b2	Ref		
CoronaVac	1.21	0.92 – 1.60	0.17
AZD1222	1.13	0.82 – 1.55	0.46
Ad26.COV2.S	0.96	0.69 – 1.32	0.79
Time elapsed since previous SARS-CoV-2 infection			
No previous infection	Ref		
≤ 6 months	0.30	0.22 – 0.42	<0.001
6 to 12 months	0.81	0.64 – 1.02	0.08
> 12 months	0.80	0.68 – 0.93	0.003

* Odds ratio.
§ Confidence interval.

Table 3
Factors associated with SARS-CoV-2 breakthrough infections during the Omicron waves in healthcare workers vaccinated with at least one booster dose (n = 3,565). (Hospital das Clinicas, Universidade de Sao Paulo, Brazil).

Variables	OR*	95 % CI§	*p* value
Number of previous doses of vaccine			
3 doses	Ref		
≥ 4 doses	1.08	0.82 – 1.41	0.60
Time elapsed since last dose of vaccine			
≤ 6 months	Ref		
6 to 12 months	1.14	1.00 – 1.31	0.047
> 12 meses	1.14	0.80 – 1.62	0.47
Last dose of vaccine			
BNT162b2	Ref		
CoronaVac	1.30	0.98 – 1.73	0.07
AZD1222	1.14	0.81 – 1.60	0.46
Ad26.COV2.S	0.91	0.65 – 1.28	0.59
Time elapsed since previous SARS-CoV-2 infection			
No previous infection	Ref		
≤ 6 months	0.30	0.21 – 0.42	<0.001
6 to 12 months	0.79	0.61 – 1.04	0.09
> 12 months	0.79	0.68 – 0.93	0.005

* Odds ratio.
§ Confidence interval.

protection against BI caused by different VOCs, including various Omicron sublineages, wanes after six months regardless of booster vaccination. Furthermore, booster vaccination with BNT162b2 provided higher protection against BI compared to an inactivated vaccine. Our findings contribute to the discussion of the benefit of additional booster doses by further characterizing the durability of protection provided by monovalent vaccines against symptomatic BI.

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Author contributions

SFC, ECS, ASL, EGK and ACS contributed to project conceptualisation and methodology. SFC contributed to the acquisition of the financial support for the project leading to this publication. ALM, ASB and RBS contributed to the inclusion of the participants. ALM, ASB, EF and APBB contributed to data collection. Respiratory samples collection and RT-PCR analyses were supervised by MN and CSL. MFC, BCS, CAMS, ECR, FMO, VRS, RHAE, ACM, and AMH contributed to the whole genome sequencing and analysis. ALM, ICB and VS performed the statistical analyses. ALM, ICB, MF, VGBP, MS and AMCS contributed to data interpretation. ALM and ICB wrote the first draft. All authors revised the manuscript and approved the final version of the manuscript.

All authors attest they meet the ICMJE criteria for authorship.

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CRediT authorship contribution statement

Alessandra Luna-Muschi: Writing – original draft, Resources, Project administration, Investigation, Formal analysis, Data curation. **Igor Carmo Borges:** Writing – original draft, Investigation, Formal analysis. **Antonio dos Santos Barboza:** Writing – review & editing, Supervision, Resources. **Elizabeth de Faria:** Writing – review & editing, Supervision, Resources. **Marina Farrel Cortês:** Writing – review & editing, Resources, Methodology. **Roseli B. Santos:** Writing – review & editing, Resources, Investigation. **Bianca Costa Silva:** Writing – review & editing, Resources, Methodology. **Camila Alves Maia da Silva:** Writing – review & editing, Resources, Methodology, Conceptualization. **Esmenia Coelho Rocha:** Writing – review & editing, Resources, Methodology. **Valquíria Reis de Souza:** Writing – review & editing, Resources, Methodology. **Raissa H. de Araujo Eliodoro:** Writing – review & editing, Resources, Methodology. **Franciane Mendes de Oliveira:** Writing – review & editing, Resources, Methodology. **Ana Carolina Mamana:** Writing – review & editing, Resources, Methodology. **Amanda Miyuki Hidifira:** Writing – review & editing, Resources, Methodology. **Marli Nishikawara:** Writing – review & editing, Supervision, Resources. **Victor Bertollo Gomes Porto:** Writing – review & editing, Visualization, Validation. **Ana Paula B. Barboza:** Writing – review & editing, Investigation, Data curation. **Vanderson Sampaio:** Writing – review & editing, Formal analysis, Conceptualization. **Mariângela Simão:** . **Carolina S. Lazari:** Writing – review & editing, Supervision, Resources. **Aluisio C. Segurado:** Writing – review & editing, Methodology, Conceptualization. **Esper G. Kallas:** Writing – review & editing, Methodology, Conceptualization. **Ana Marli C. Sartori:** Writing – review & editing, Visualization, Validation. **Anna S. Levin:** Writing – review & editing, Validation, Methodology, Conceptualization. **Ester Cerdeira Sabino:** Writing – review & editing, Validation, Methodology. **Silvia Figueiredo Costa:** Writing – review & editing, Validation, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [AMCS received a grant from Instituto Butantan (2021-2022) as Principal Investigator of a study that evaluated the immunogenicity and safety of CoronaVac in immunocompromised patients].

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.07.015.

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