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Humoral response after a BNT162b2 heterologous third dose of COVID-19 vaccine following two doses of BBIBP-CorV among healthcare personnel in Peru

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ABSTRACT

Background: The inactivated virus vaccine, BBIBP-CorV, was principally distributed across low- and middle-income countries as primary vaccination strategy to prevent poor COVID-19 outcomes. Limited information is available regarding its effect on heterologous boosting. We aim to evaluate the immunogenicity and reactogenicity of a third booster dose of BNT162b2 following a double BBIBP-CorV regime.
Methods: We conducted a cross-sectional study among healthcare providers from several healthcare facilities of the Seguro Social de Salud del Perú - ESSALUD. We included participants two-dose BBIBP-CorV vaccinated who presented a three-dose vaccination card at least 21 days passed since the vaccinees received their third dose and were willing to provide written informed consent. Antibodies were determined using LIAISON® SARS-CoV-2 TrimericS IgG (DiaSorin Inc., Stillwater, USA). Factors potentially associated with immunogenicity, and adverse events, were considered. We used a multivariable fractional polynomial modeling approach to estimate the association between anti-SARS-CoV-2 IgG antibodies' geometric mean (GM) ratios and related predictors.
Results: We included 595 subjects receiving a third dose with a median (IQR) age of 46 [37,54], from which 40% reported previous SARS-CoV-2 infection. The overall geometric mean (IQR) of anti-SARS-CoV-2 IgG antibodies was 8,410 (5,115 – 13,000) BAU/mL. Prior SARS-CoV-2 history and full/part-time in-person working modality were significantly associated with greater GM. Conversely, time from boosting to IgG measure was associated with lower GM levels. We found 81% of reactogenicity in the study population; younger age and being a nurse were associated with a lower incidence of adverse events.
Conclusions: Among healthcare providers, a booster dose of BNT162b2 following a full BBIBP-CorV regime provided high humoral immune protection. Thus, SARS-CoV-2 previous exposure and working in person displayed as determinants that increase anti-SARS-CoV-2 IgG antibodies.

Introduction

The spread of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the Coronavirus Disease 2019 (COVID-19) have accounted for more than 619 million cases

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19, Coronavirus Disease 2019; VOC, variants of concern; mRNA, messenger ribonucleic acid; BMI, body mass index; S, spike; CLIA, chemiluminescent assay; SD, standard deviation; IQR, interquartile range; GMR, geometric means ratios; GM, geometric means.

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and 6.5 million deaths worldwide [1]. Furthermore, the continuous evolution of the COVID-19 pandemic has promoted the emergence of novel variants of concern (VOC) and the perpetuation of the disease worldwide [2–3]. Moreover, the inability to reach an acceptable long-lasting level of immune protection by natural infections [4] has encouraged the establishment of unprecedented immunization strategies.

Rapid response promoted the development of COVID-19 vaccines to prevent severe forms and fatalities [5] in late 2020. In Latin America, the most purchased vaccines included; messenger ribonucleic acids (mRNA) such as BNT162b2 (hereafter referred to as BNT, Pfizer) and mRNA-1273 (hereafter referred to as m1273, Moderna), adenoviral vectors such as ChAdOx1 nCoV-19 vaccine (hereafter referred to as Chad, AstraZeneca) and Sputnik V (Gamaleya), inactivated viruses such as CoronaVac (hereafter referred to as CV, Sinovac) and BBIBP-CorV (hereafter referred as BBIBP, Sinopharm), and protein subunits such as NVX-CoV2373 (Novavax) and ZF2001 (Zifivax) [6–8]. Due to its immediate availability, the Peruvian government acquired the BBIBP for the initial vaccination phase. As a result, healthcare workers in the COVID-19 frontline were the primary recipients of the two-dose BBIBP vaccination scheme, 21 days apart. Consequently, along with the nationwide vaccination program, prevented infections and mortality in the Peruvian population were 50.4% and 94%, respectively [9].

The immune response of inactivated vaccines drops three to five months after the two-dose regime completion [10–11], contributing to huge concerns due to the correlation between a strong immune response and lower symptomatic COVID-19. A similar relation was identified in BNT and ChAd vaccinees Xu et al., 2021; Favresse et al., 2021 Dec; Shrotri et al., 2021 Jul 31; Pilishvili et al., 2021 Dec 16;385 [11–14], and in natural infections [15]. Anti-SARS-CoV-2 antibody seronegativity was estimated at 30% after four months of complete BBIBP vaccination [16]. In Peru, natural infections triggered by the circulation of B.1.1.7 (Alpha), B.1.351 (Beta), and C.37 (Lambda) variants in early 2021 during the second wave [17], along with the extended primary vaccination that reached adult population in late 2021, did not prevent the transmission of B.1.617 (Delta) and B.1.529 (Omicron) [18]. Notably, the Omicron variant possesses better transmissibility and triggers efficient immune evasion [19]. Both VOCs contributed to the massive spread of COVID-19 in Latin America during the third wave in early 2022.

The decay of the humoral immune response and the circulation of VOCs supported the necessity of distributing a booster dose. A three-dose vaccination regime was as efficient against the Omicron variant as a two-dose was against wild SARS-CoV-2 [20]. Several studies demonstrated that complete or fractional heterologous boosters with mRNA and adenoviral vector provided a stronger humoral response than homologous regimes [20–23]. Though, these studies evaluated populations primarily vaccinated with BNT and ChAd. In Peru, a third booster dose of the BNT vaccine was authorized for health personnel at least three months after complete BBIBP vaccination. Limited reports described the humoral response of mRNA vaccines following inactivated virus formulations. Kitro *et al.* found a significant increase in antibody levels among participants who received a BNT booster dose after two doses of CV [22]. The BBIBP vaccine was widely used in Peru, and, as of today, it is mainly recognized in Latin America, Asia, and Africa [24]. Indeed, few studies describe their impact on the humoral and cellular response due to heterologous boosting. Our study attempts to determine the level of humoral response achieved after the third booster dose of BNT following the full BBIBP regime, evaluate factors associated with greater anti-SARS-CoV-2 IgG antibodies response, and report adverse events after completion of this mix boosting.

Materials and methods

Study design and participants

We conducted a cross-sectional study among healthcare providers from several intermediate and high-level healthcare facilities of the Seguro Social de Salud del Perú - ESSALUD in Lima, Peru, from November 2021 and January 2022. The study population included participants from a research cohort enrolled previously through random stratified sampling (n = 1,436 out of a source population composed of 2,539) to evaluate the SARS-CoV-2 humoral response after the second vaccine dose [16]. We included two-dose BBIBP-CorV vaccinated participants who presented a three-dose vaccination card at least 21 days passed since the vaccinees received their third dose schedule and provided written informed consent. Probable and suspicious COVID-19 cases were excluded. The study population achieved 595 participants.

Study procedures

The primary study population (n = 1,436) was contacted by phone calls and invited to participate in the current study. Only eligible population that agreed to participate were scheduled in appointment venues. After written informed consent was obtained, a computer-assisted personal interview was conducted. Data were collected in an online electronic survey in REDCap [25]; an automated process generated a comprehensive database after completing data entry. Blood samples were collected in vacutainer™ tubes with EDTA; the plasma was aliquoted and stored at −20 °C until laboratory processing.

Outcomes and variables

Seropositivity was defined when participants exhibited anti-SARS-CoV-2 Spike (S) protein IgG antibody levels greater or equal to 33.8 BAU/ml, in agreement with the WHO harmonization process [26]. Moreover, anti-SARS-CoV-2 IgG antibody levels were treated after logarithmic transformation as a quantitative outcome. In addition, covariates such as sex, age, occupation, working area, type of job, working in a COVID-19 area, body mass index (BMI), previous comorbidities (hypertension, diabetes mellitus, cancer, asthma, hypothyroidism, HIV, immunosuppressive condition), complete COVID-19 vaccination history and time since the third vaccine dose and the blood extraction were recorded in the research survey.

Laboratory assays

The anti-SARS-CoV-2 Spike (S) protein IgG antibodies were determined using LIAISON® SARS-CoV-2 TrimericS IgG (DiaSorin Inc., Stillwater, USA). This chemiluminescent assay (CLIA) is correlated with the microneutralization test at 100% for positive predictive value and 96.9% for negative predictive value [27–28]. The manufacturer indicated the upper (2,080 BAU/mL) and lower (4.81 BAU/mL) detection limits of the CLIA. This analytic sensitivity was previously evaluated using the dilution range of the first WHO international standard for anti-SARS-CoV-2 immunoglobulin (NIBCS 20/136) [29]. Laboratory procedures were conducted at the Clinical Pathology Service of Hospital III Suárez Angamos, ESSALUD, which met local [30] and international [31–32] criteria to assure analytical performance.

Statistical analysis

Quality control was performed to verify missing, extreme, and inconsistent values. Categorical variables were reported as absolute and relative frequencies and numerical results were described as mean and standard deviation (SD) or median and interquartile range (IQR). Bivariate analysis was conducted comparing the geometric mean levels of IgG antibodies according to the characteristics of the participants using the Student's *t*-test or ANOVA test for geometric means ratios (GMR). Additionally, we compared median antibody levels using the Mann-Whitney or Kruskal Wallis *U* test, as appropriate. Factors independently associated with antibody levels expressed in geometric means (GM) were performed using multiple linear regressions. The logarithm of the mean antibody level was included in the regression model such that the exponentiated regression coefficient represents the GMR. Two adjusted models were generated: 1) model including a set of covariates theoretically considered as explanatory for the level of antibodies (complete model), and 2) model using only variables that were selected by using a backward step-by-step selection algorithm (reduced model). We used a multivariable fractional polynomial modeling approach to model potential non-linear relationships between the numerical predictors (age, time since the second vaccine dose, time between the third vaccine dose and blood extraction, and BMI). This modeling uses a backward step-by-step selection procedure to determine the inclusion of certain functional forms for each predictor, contrasted by a closed test ($p < 0.05$). The complete model forced the inclusion of all variables; however, in the reduced model, best fitting was determined by covariates exhibiting a significant p-value. Both models included only linear forms of the numerical variables. An inspection of the partial residuals revealed an appropriate form for these variables in the data. Due to evidence of heteroskedasticity, p-values, and 95% confidence intervals were estimated from the Huber-White sandwich robust standard errors. Analysis was performed using R software, version 4.1.3 (R Foundation for Statistical Computing).

Ethics committee approval

The study procedures were approved by the Ethics and Research Institutional Committee of the Hospital Nacional Alberto Sabogal Sologuren (determination N°360-CIEI-OIyD-GRPS-ESSA LUD-2021). All participants provided written informed consent following a detailed explanation of study procedures and before recruitment. Personal data was protected, and confidentiality was assured at every step of the conducted study.

Results

Population characteristics

The study population was composed of 595 subjects, in which the median (IQR) age was 46 [37,54], 71% (n = 425) were female, and only 0.8% (n = 5) were foreigners. Eighty-four percent (n = 501) of the participants were devoted to medical and nursing activities in different working areas. Indeed, 9.4% (n = 56) requested a work leave due to risk factors for severe COVID-19 (age and comorbidities) or conducted remote work. Almost 30% (n = 184) reported at least one comorbidity. Hypertension, asthma, and immunosuppressive condition were the most frequent. The overall median (IQR) BMI was 26 (24.3 – 28.4); 64% (n = 380) of the participants presented overweight or obesity. Forty percent (n = 237) reported previous SARS-CoV-2 infection. Almost seven months (median 224 days) passed from the second to the third boosting dose. From the total recruited population (597), two persons received different vaccine types, one the m1273 and the other the BBIBP, both excluded from any analyses. Complete information is described in Table 1 and **Supplementary material 1**.

Immunogenicity

After the third dose booster, all participants were seropositive. The overall geometric mean (IQR) of anti-SARS-CoV-2 IgG antibod-

Table 1
Characteristics of healthcare workers receiving a BNT162b2 heterologous third dose.

Characteristic	N = 595[1]
Age (years)	46 [37–54]
Age group	
20–44	269 (45)
45–59	235 (39)
60+	91 (15)
Sex	
Male	170 (29)
Female	425 (71)
Profession	
Administrative and others[2]	94 (16)
Technical nurses	146 (25)
Nurses	168 (28)
Pyshicians	187 (31)
Hospital	
Hospital Nacional E. Rebagliati Martins	258 (43)
Hospital Nacional A. Sabogal Sologuren	186 (31)
Hospital Nacional G. Almenara Irigoyen	118 (20)
Other healthcare facillities	33 (5.5)
Unknown	1
Working area	
Administration and diagnosis assistance	141 (24)
External consultation	69 (12)
Emergency	118 (20)
In-hospital	162 (27)
ICU	104 (18)
Unknown	1
Working modality	
Work leave/remote	56 (9.4)
Full/part-time in-person	539 (91)
Height (cm)	160 [155 – 166]
Weight (kg)	67 [60 – 78]
Unknown	1
Number of comorbidities	
0	411 (69)
1	146 (25)
2	31 (5.2)
3–5	7 (1.2)
Body mass index (kg/m2)	26.0 [24.3 – 28.4]
Unknown	1
Body mass index group	
Normal interval	215 (36)
Overweight	283 (48)
Obesity	97 (16)
Unknown	1
Hypertension	64 (11)
Diabetes mellitus	27 (4.5)
Cancer	12 (2.0)
Asthma	45 (7.6)
Hypothyroidism	41 (6.9)
HIV	1 (0.2)
Immunosuppressive condition[3]	518 (87)
Previous SARS-CoV-2 infection	237 (40)
Time from 1st dose to boosting	246 [240 – 248]
Time from 2nd dose to boosting	224 [219 – 227]
Time from boosting to IgG measure	38 [32–48]
Antibodies anti-SARS-CoV-2 levels (BAU/mL)	8,410 [5,115 – 13,000]
Seropositivity	
Negative	0 (0)
Positive	595 (100)
Reactogenicity	483 (81)

[1]Median [IQR]; n (%)
[2]Medical technologists, biochemists and other laboratory professionals
[3]Any participant reported chronic lung disease, organ transplantation, nor undernourishment

ies was 8,410 (5,115 – 13,000) BAU/mL. Previous SARS-CoV-2 history and working modality were significantly associated with greater GM. However, no significant differences in GM were identified when considering age, sex, profession, working area, number of comorbidities, and BMI. Data is described in Table 2, and the distribution of covariates is observed in Fig. 1.

Moreover, adjusted models showed that time from boosting to anti-SARS-CoV-2 IgG antibody level measurement displayed as the best-associated covariate. An 86% lower GM was identified for each additional day in the corresponding period. The GM of participants with previous SARS-CoV-2 infection was 18% greater than non-exposed, and full/part-time in-person work entailed 29% greater risk. Likewise, participants with diabetes had 34% less GM than healthy ones. Estimations between models (full and reduced) are concordant despite overfitting in the full model. Non-adjusted and adjusted analyses are described in Table 3.

Additionally, time from boosting to IgG measure represents a negative correlation, in which the smaller the time frame, the greater the antibody level. A positive correlation was presumed for the time from the second dose to boosting; however, no statistical association was identified. A similar lack of association was found for age and body mass index (Fig. 2).

Reactogenicity

Eighty-one percent of reactogenicity was reported (See Tables 1 and 2); pain in the application site (71%), general discomfort (25%), headache (18%), and fever (12%) were the most frequent reports. No severe adverse events were identified. The characteristics of participants expressing reactogenicity to the vaccine is described in Table 4. The complete adverse events report is described in Fig. 3 (and **Supplementary material 2**). In multivariable models, younger age and being a nurse were factors associated with a lower incidence of reactogenicity (Table 5). The effect of age within modeling is depicted in Fig. 4.

Discussion

High immunogenicity was identified among healthcare workers receiving a third booster dose of BNT after complete BBIBP vaccination. All participants were IgG seropositive to SARS-CoV-2 even though in a pre-booster measurement, a significant percentage of seronegativity was estimated [16]. Besides, participants reported a high occurrence of reactogenicity related to pain in the application site; however, no serious adverse events were identified. The

Table 2
Anti-SARS-CoV-2 IgG antibody levels following a BNT162b2 heterologous third dose in healthcare practitioners.

Variable	Geometric Mean (GSD)[1]	P-value[2]	Median (Percentiles 25th; 75th)	P-value[3]
Age group				
20–44	8221.5 ± 2	0.167	8410 (5230; 13600)	0.150
45–59	8168.3 ± 2.3		8950 (5290; 12950)	
60+	6914.1 ± 2.3		6680 (4620; 11050)	
Sex				
Male	8026.2 ± 2.1	0.919	8375 (5370; 12375)	0.989
Female	7970.1 ± 2.2		8440 (5000; 13100)	
Profession				
Administrative and others	9447.8 ± 2.1	0.105	8655 (5742.5; 17125)	0.218
Technical nurses	7358.7 ± 2.1		8270 (4642.5; 12375)	
Nurses	8072.1 ± 2.3		9005 (5085; 14050)	
Pyshicians	7748.2 ± 2.2		8150 (5220; 12000)	
Hospital				
Hospital Nacional E. Rebagliati Martins	7960.9 ± 2	0.040	8305 (5180; 12675)	0.070
Hospital Nacional A. Sabogal Sologuren	7542 ± 2.3		8610 (4820; 12300)	
Hospital Nacional G. Almenara Irigoyen	9434 ± 2.1		9490 (6290; 15950)	
Others	6649.1 ± 2.6		7500 (4870; 10800)	
Working area				
Administration and diagnosis assistance	7870 ± 2.3	0.247	8170 (5110; 12300)	0.070
External consultation	7588.5 ± 2.2		8190 (4630; 10800)	
Emergency	9030 ± 1.9		9385 (6367.5; 14025)	
In-hospital	8073.6 ± 2.4		8790 (5507.5; 14750)	
ICU	7121.9 ± 2		7300 (4657.5; 10375)	
Working modality				
Work leave/remote	6055.3 ± 2.8	0.033	7350 (3470; 10850)	0.035
Full/part-time in-person	8219 ± 2.1		8570 (5260; 13200)	
Number of comorbidities				
0	8118.2 ± 2.1	0.481	8370 (5120; 13450)	0.936
≥1	7698.7 ± 2.4		8615 (5000; 12225)	
Body mass index group				
Normal interval	7968.7 ± 2.1	0.960	8330 (4975; 12600)	0.841
Overweight	7943 ± 2.2		8530 (5105; 13000)	
Obesity	8152.4 ± 2.5		8360 (5550; 13800)	
Immunosuppressive condition				
No	6713.2 ± 2.5	0.072	8290 (4920; 10700)	0.213
Yes	8194.8 ± 2.2		8425 (5172.5; 13475)	
Previous infection				
No	7437.9 ± 2.3	0.005	8060 (5010; 11925)	0.025
Yes	8891.7 ± 2		9060 (5210; 14200)	
Reactogenicity				
No	8194.9 ± 2.2	0.106	8530 (5270; 13450)	0.102
Yes	7144.9 ± 2.2		7820 (4742.5; 11525)	

[1]GSD = geometric standard deviation
[2]Student T or F test for geometric mean ratio
[3]Wilcoxon or Kruskall-wallis test

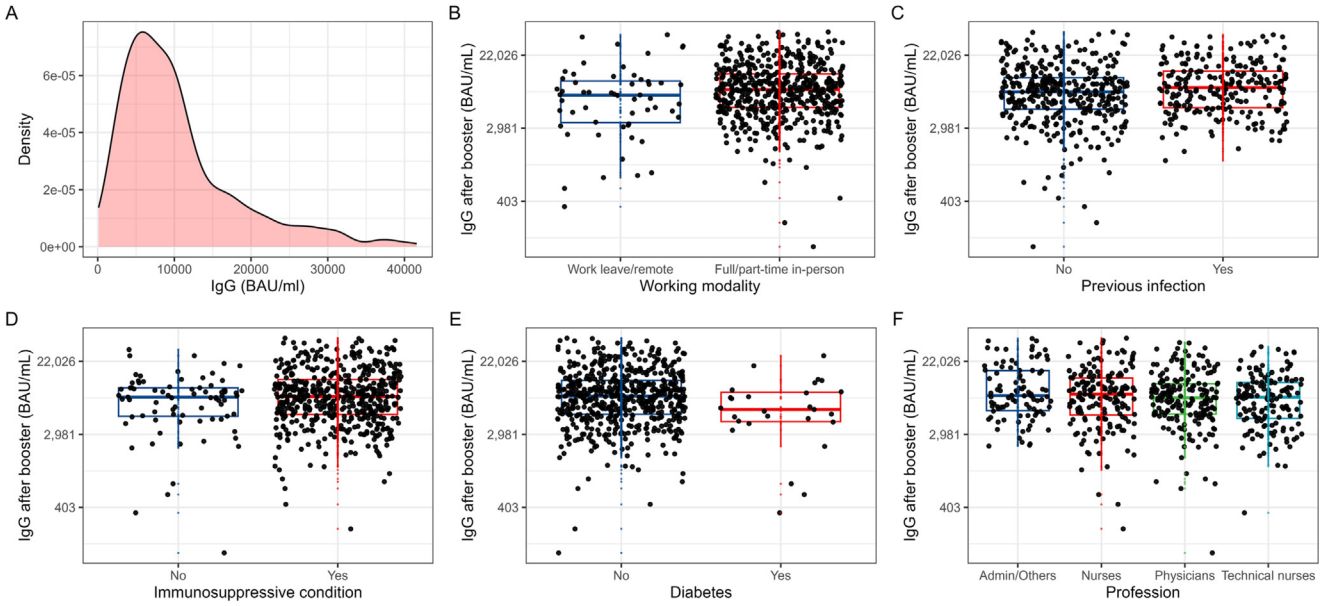

Fig. 1. Distribution of SARS-CoV-2 IgG antibody level and factors associated. Anti-SARS-CoV-2 IgG density, representing an overall geometric mean (IQR) estimated in 8,410 (5,115 – 13,000) BAU/mL (A). We identified an increased amount of anti-SARS-CoV-2 IgG antibodies in full/part-time in-person work modality (B), previous COVID-19 infection (C), reporting immunosuppressive condition (D), and not having diabetes (E). Diverse IgG antibody response according to the profession is observed (F).

Table 3
Independent association of factors with anti-SARS-CoV-2 IgG antibody levels following a BNT162b2 heterologous third dose.

Variable	Crude Models		Full Model		Reduced Model	
	cGMR (95% CI)[1]	P-value[3]	aGMR (95% CI)[2]	P-value[3]	aGMR (95% CI)[2]	P-value[3]
Time from boosting to IgG measure						
Time from boosting to IgG measure	0.98 (0.98; 0.99)	**<0.001**	0.15 (0.09; 0.25)	**<0.001**	0.14 (0.09; 0.23)	**<0.001**
Time from dosis 2 to boosting						
Time from dosis 2 to boosting	1.01 (1; 1.01)	0.061	1.31 (0.79; 2.15)	0.291		
Age (years)						
Age (years)	1 (0.99; 1)	0.08	0.77 (0.42; 1.4)	0.388		
Sex						
Male	Reference		Reference			
Female	0.99 (0.87; 1.14)	0.909	1.02 (0.88; 1.19)	0.755		
Profession						
Administrative and others	Reference		Reference		Reference	
Technical nurses	0.77 (0.63; 0.93)	**0.046**	0.76 (0.62; 0.94)	0.098	0.78 (0.65; 0.94)	0.087
Nurses	0.84 (0.69; 1.02)		0.84 (0.69; 1.04)		0.86 (0.71; 1.04)	
Pyshicians	0.8 (0.66; 0.97)		0.85 (0.69; 1.05)		0.87 (0.73; 1.04)	
Working area						
Administration and diagnosis assistance	Reference		Reference			
External consultation	0.96 (0.76; 1.21)	0.135	1 (0.79; 1.27)	0.579		
Emergency	1.14 (0.95; 1.37)		1.07 (0.86; 1.32)			
In-hospital	1.02 (0.84; 1.24)		1 (0.8; 1.24)			
ICU	0.9 (0.74; 1.1)		0.92 (0.73; 1.15)			
Work modality						
Work leave/remote	Reference		Reference		Reference	
Full/part-time in-person	1.36 (1.03; 1.79)	**0.031**	1.24 (0.93; 1.66)	0.141	1.29 (1.01; 1.64)	**0.038**
Number of comorbidities						
0	Reference		Reference			
≥1	0.96 (0.82; 1.11)	0.550	1.05 (0.9; 1.21)	0.541		
Body mass index (kg/m2)						
Body mass index (kg/m2)	1 (0.98; 1.02)	0.877	1.01 (0.84; 1.21)	0.909		
Diabetes						
No	Reference		Reference		Reference	
Yes	0.65 (0.44; 0.95)	**0.028**	0.72 (0.48; 1.07)	0.105	0.66 (0.46; 0.95)	**0.026**

(*continued on next page*)

Table 3 (*continued*)

Variable	Crude Models		Full Model		Reduced Model	
	cGMR (95% CI)[1]	P-value[3]	aGMR (95% CI)[2]	P-value[3]	aGMR (95% CI)[2]	P-value[3]
Immunosuppressive condition						
No	Reference					
Yes	1.22 (0.98; 1.52)	0.070				
Previous infection						
No	Reference		Reference		Reference	
Yes	1.19 (1.05; 1.35)	**0.005**	1.18 (1.03; 1.34)	**0.013**	1.18 (1.04; 1.34)	**0.011**

[1]cGMR = Crude Geometric Mean Ratio (95% confidence interval)
[2]aGMR = Adjusted Geometric Mean Ratio (95% confidence interval)
[3]All p-values was obtained using a robust standard error estimator for heteroskedasticity.

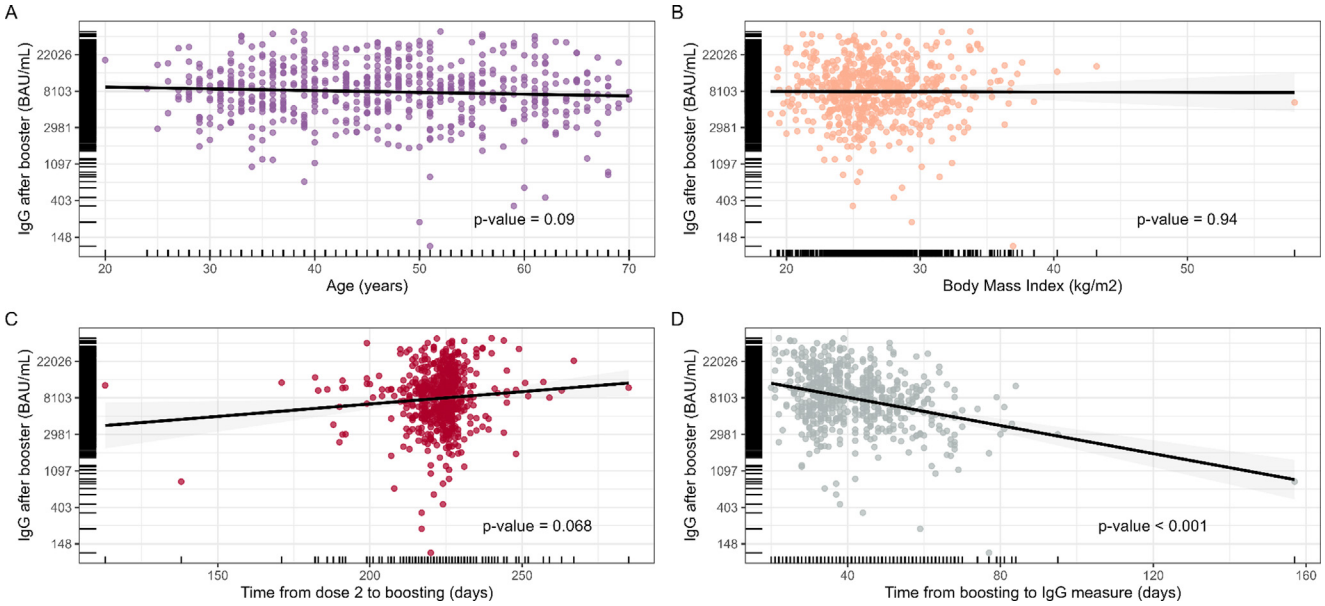

Fig. 2. Correlation between SARS-CoV-2 IgG antibody level and numerical predictors. A lack of correlation was found for age and body mass index, although no statistical association was identified (A and B). Time from boosting to IgG measure represents a negative correlation (C); a positive correlation was presumed for the time from the second dose to boosting (D). Natural cubic splines estimated the predicted probability of anti-SARS-CoV-2 S IgG antibody positivity for all variables presented in this Figure.

heterologous boosting mix of mRNA following a full viral inactivated regime provides an adequate humoral immune response, as seen in other vaccine-matching strategies. Our study enlightens the landscape of the impact of the BBIBP [20–21] application, deployed primarily in low- and middle-income countries. It should be noted that high COVID-19 transmission rates in these regions were reported and could have contributed to a better immunological response.

Heterologous boosting regimes provide stronger and more sustained immune responses for mRNA and adenoviral vector vaccines [20–21], similarly occurring among heterologous viral inactivated vaccine boosters, as reported for CV and BBIBP [33–37]. However, most studies are focused on the effect of boosting mRNA and adenoviral vector vaccines [20–21]. Limited reports describe the impact of a third dose of mRNA, adenoviral vector, or protein subunit vaccines following a full BBIBP regime, a prevalent match in Latin America and Asia. Reports conducted among small-sized populations show that boosting two-dose BBIBP vaccinees with mRNA (BNT or m1273) elicited better humoral response than adenoviral vector vaccines (Chad and Sputnik V) [38–39]. Additionally, protein subunit (NVX-CoV2373) boosting after a two-dose BBIBP showed no differences in humoral immunity with prior Chad and BNT vaccination [40]. In Peru, studies that explore this effect found GM between 486.6 and 2,312.0 AU/mL of anti-SARS-CoV-2 S [17,41] 14 days after boosting (conversion factor to BAU/mL = AU/mL*1.0288 [26]. The humoral response elicited in our study was found to be 8,410 BAU/mL (GM), like in previous studies [35,38]. Other studies evaluating mRNA/inactivated virus vaccine match presented lower measurements than ours. Chad booster following full CV regimes after two weeks reached 873.9–2037.1 BAU/mL [33,42–43]. A greater immune response was also observed compared to two-dose CV vaccinees boosted with BNT [4,22,44–45].

Inactivated viral particles induce an immune response leading to low longevity [4]. However, the homologous BNT regime elicited a greater humoral response and protection than the BBIBP booster following complete BNT vaccination [46–47]. Although this finding remains controversial, studies have identified lower humoral response within homologous BNT-boosted participants [17,35]. Therefore, heterologous regimes activate different immune pathways, conducting to stronger and longer-lasting T and B-cell responses [48–49], contributing to better protection against SARS-CoV-2. Previous studies reported that 3–4 weeks after boosting, two-dose BBIBP subjects receiving mRNA or adenoviral vaccines achieve the highest levels of IgG antibodies. However, after three months, antibody waning accounted for 41.7%, 36.6%, and 30.9% of loss for AZ, BNT, and m1730, respectively [39]. However still higher than homologous BBIBBP boosting observed in naive COVID-19 population [36].

Table 4
Reactogenicity after a after a BNT162b2 heterologous third dose according to the characteristics of healthcare workers recruited.

Characteristic	Yes, N = 483[1]	No, N = 112[1]	p-value[2]
Age (years)	46 [37–54]	46 [36–56]	0.970
Age group			0.390
20–44	217 (81)	52 (19)	
45–59	196 (83)	39 (17)	
60+	70 (77)	21 (23)	
Sex			0.820
Male	139 (82)	31 (18)	
Female	344 (81)	81 (19)	
Profession			**<0.001**
Administration and diagnosis assistance	74 (79)	20 (21)	
Technical nurses	99 (68)	47 (32)	
Nurses	151 (90)	17 (10)	
Pyshicians	159 (85)	28 (15)	
Hospital			0.370
Hospital Nacional E. Rebagliati Martins	147 (79)	39 (21)	
Hospital Nacional A. Sabogal Sologuren	217 (84)	40 (16)	
Hospital Nacional G. Almenara Irigoyen	92 (78)	26 (22)	
Others	25 (81)	6 (19)	
Unknown	2	1	
Working area			0.210
Administration and diagnosis assistance	116 (82)	25 (18)	
External consultation	51 (74)	18 (26)	
Emergency	103 (87)	15 (13)	
In-hospital	130 (80)	32 (20)	
ICU	82 (79)	22 (21)	
Unknown	1	0	
Working modality			0.600
Work leave/remote	44 (79)	12 (21)	
Full/part-time in-person	439 (81)	100 (19)	
Height (cm)	160 [155 – 166]	160 [155 – 165]	0.950
Weight (kg)	67 [59 – 78]	68 [61 – 78]	0.730
Unknown	1	0	
Number of comorbidities			0.610
0	330 (80)	81 (20)	
1	121 (83)	25 (17)	
2	27 (87)	4 (13)	
3–5	5 (71)	2 (29)	
Body mass index (kg/m2)	26.1 [24.2 – 28.5]	25.8 [24.7 – 28.4]	0.750
Body mass index group			0.360
Normal interval	180 (84)	35 (16)	
Overweight	223 (79)	60 (21)	
Obesity	80 (82)	17 (18)	
Hypertension	51 (80)	13 (20)	0.750
Diabetes	23 (85)	4 (15)	0.590
Cancer	9 (75)	3 (25)	0.480
Asthma	36 (80)	9 (20)	0.830
Hypothyroidism	34 (83)	7 (17)	0.770
HIV	1 (100)	0 (0)	>0.999
Immunosuppressive condition	421 (81)	97 (19)	0.870
Previous infection	194 (82)	43 (18)	0.730
Time from 1st dose to boosting	246 [240 – 248]	246 [240 – 249]	0.730
Time from 2nd dose to boosting	224 [219 – 227]	224 [219 – 227]	0.910
Time from boosting to IgG measure	38 [32–48]	40 [33–50]	0.470
Antibodies Anti-SARS-CoV-2 levels (BAU/mL)	8,530 [5,270 – 13,450]	7,820 [4,742 – 11,525]	0.100

[1]Median [IQR]; n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Although vaccination induces a more robust humoral response than natural infection [4], previous COVID-19 history contributed as an associated factor leading to higher anti-SARS-CoV-2 IgG antibody levels [17,41,44] as described in our study. Furthermore, T-cell response seems to be better among persons previously COVID-19 infected and vaccinated, although another study described the humoral response as more intense in uninfected subjects [46]. The population assessed was placed in the frontline and was supposed to have one of the highest seroprevalences reported due to natural infection. Interestingly, one study comparing naive, alpha/delta/omicron infected, and BNT boosted among two-dose BBIBP demonstrated that a previous infection with any strain provided humoral immune protection as good as BNT booter [35,50]. Additionally, longer intervals (seven to eight months) between the second and booster dose were associated with high anti-SARS-CoV-2 IgG antibody levels [17,22,34], consistent with our results. Moreover, high antibody levels before boosting contributed to higher anti-SARS-CoV-2 IgG levels after the booster shot [17,22].

Our findings identified no association with sex, despite estrogens' potential role; which might contribute to stronger cellular and humoral responses, according to previous reports [22,34]. Moreover, other studies have described lower antibody levels among older participants and smokers [34,44], which was inconsistent with our results. Non-differential immune protection among young and adult populations was identified when receiving ZF2001 boosting after full BBIBIP vaccination [37]. Moreover, a study that estimated the relative vaccine effectiveness prevented death by COVID-19 in people $\geq$ 60 this finding was similar in BNT homologous (86.1%) and BBIBP/BNT heterologous (86.1%) boosted vaccinees, showing that both vaccine matches were suitable to protect highly vulnerable older population [47].

Moreover, in our study, having a full/part-time in-person working modality was associated with an increased humoral response. This group was greatly exposed to COVID-19 patients at healthcare centers, who are constantly ejecting high viral loads via fomites. Passive exposure is a direct consequence of being on the frontline of the COVID-19 pandemic [51], which could define a stronger immune response among healthcare workers regardless of vaccination. Although, even after multivariable adjustments, work modality remained explanatory with the increased level of IgG antibodies. Also, not having diabetes was associated with greater IgG levels, as previously reported [52]. This result was expected due to the immunosuppressive condition that could entail diabetes treatment. Complementary, higher odds of hospitalization and mortality were identified among people living with diabetes [53], possibly because of weak protective immune mechanisms at the humoral and cellular response levels.

High reactogenicity was described in our study (81%). However, this is similar to other reports of heterologous regimes using BNT boosters following inactivated virus vaccines, between 88.3 and 94% of adverse events [22,44]. Heterologous regimes produced more local and systemic reactogenicity after a booster dose than homologous [22]. Moreover, the efficiency of S protein amplification within the host through mRNA vaccines allows for triggering diverse inflammatory pathways [54] that might produce more adverse events. Previous reports show that application site reaction was the most frequent event [17,22,44]. However, BBIBP and CV homologous boosters reported fewer local and systemic adverse events than inactivated virus/mRNA heterologous boosters [36,55]. In two-dose BBIBP subjects, the pain site reported was similar across BNT, m1730, and Chad boosted (90–94%). However, fever was four times more incident in Chad than in BNT or m1730 boosted [39]. Possibly because m1730 contains 100ug, more than three times the amount of mRNA than BNT (30ug) [56–57]. Nevertheless, adverse symptoms were primarily transient.

Reactogenicity was more frequent in older (60–70yearsold) and younger (20–30 years old) participants. In other studies, senior people reported fewer adverse events [21,58]. The older population was a significant number of people receiving work leave or con-

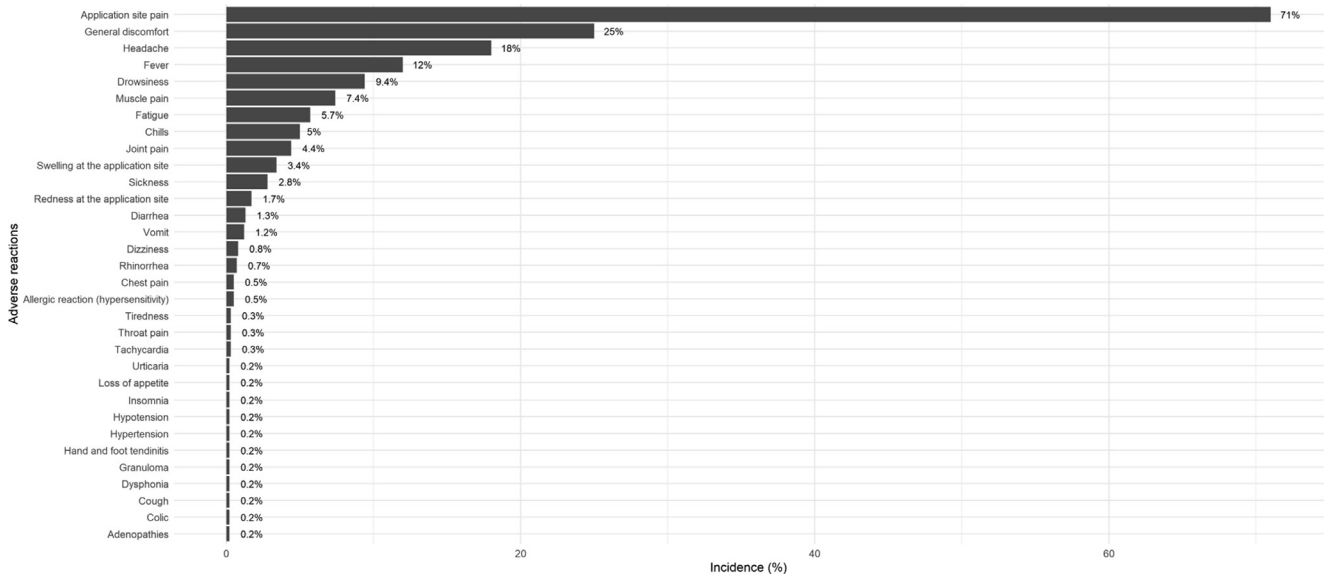

Fig. 3. Relative frequencies of adverse events reported after the third dose of BNT162b2. Self-reporting of adverse events resulted in a predominance of local rather than systemic events. No severe adverse events were identified.

Table 5
Multivariable analysis of factors associated with reactogenicity after a BNT162b2 heterologous third dose.

Characteristic	Crude models			Full model		Reduced model	
	N	OR[1] (95% CI[1])	p-value	OR[1] (95% CI[1])	p-value	OR[1] (95% CI[1])	p-value
Time from boosting to IgG measure							
Time from boosting to IgG measure	595	1 (0.99; 1.02)	0.540	1.33 (0.24; 6.78)	0.740		
Age (years)							
Age (years)	595	1 (0.98; 1.02)	0.860				
Age (non-linear terms)							
Age (non-linear terms)					**0.002**		**0.002**
Sex	595						
Male		Reference		Reference			
Female		1.06 (0.67; 1.69)	0.820	0.81 (0.47; 1.41)	0.450		
Profession	595						
Administration and diagnosis assistance		Reference		Reference		Reference	
Technical nurses		1.76 (0.97; 3.26)	**<0.001**	2.13 (1.05; 4.47)	**<0.001**	1.9 (0.96; 3.84)	**<0.001**
Nurses		0.42 80.20; 0.84)		0.41 (0.19; 0.89)		0.4 (0.19; 0.85)	
Pyshicians		0.65 (0.35; 1.24)		0.54 (0.26; 1.11)		0.6 (0.30; 1.20)	
Working area	594						
Administration and diagnosis assistance		Reference		Reference		Reference	
External consultation		1.64 (0.81; 3.25)	0.200	1.66 (0.77; 3.58)	0.160	1.65 (0.77; 3.50)	0.180
Emergency		0.68 (0.33; 1.34)		0.62 (0.27; 1.38)		0.64 (0.29; 1.39)	
In-hospital		1.14 (0.64; 2.05)		1.16 (0.59; 2.29)		1.17 (0.61; 2.28)	
ICU		1.24 (0.65; 2.36)		1.17 (0.54; 2.54)		1.2 (0.57; 2.54)	
Working modality	595						
Work leave/remote		Reference		Reference			
Full/part-time in-person		0.84 (0.44; 1.71)	0.610	1.13 (0.48; 2.80)	0.780		
Number of comorbidities	595						
0		Reference		Reference			
≥1		0.83 (0.52; 1.29)	0.410	1 (0.57; 1.72)	>0.999		
Body mass index (kg/m2)							
Body mass index (kg/m2)	595	1 (0.95; 1.05)	0.980	1.04 (0.55; 1.87)	0.910		
Diabetes	595						
No		Reference		Reference			
Yes		0.74 (0.21; 1.97)	0.570	0.48 (0.12; 1.50)	0.220		
Immunosuppressive condition	595						
No		Reference					
Yes		0.95 (0.53; 1.80)	0.870				
Previous infection	595						
No		Reference		Reference			
Yes		0.93 (0.61; 1.41)	0.730	0.73 (0.45; 1.19)	0.210		
Time from dosis 2 to boosting	595	1 (0.98; 1.01)		1.27 (0.18 to 10.9)	0.820		

[1]OR = Odds Ratio, CI = Confidence Interval

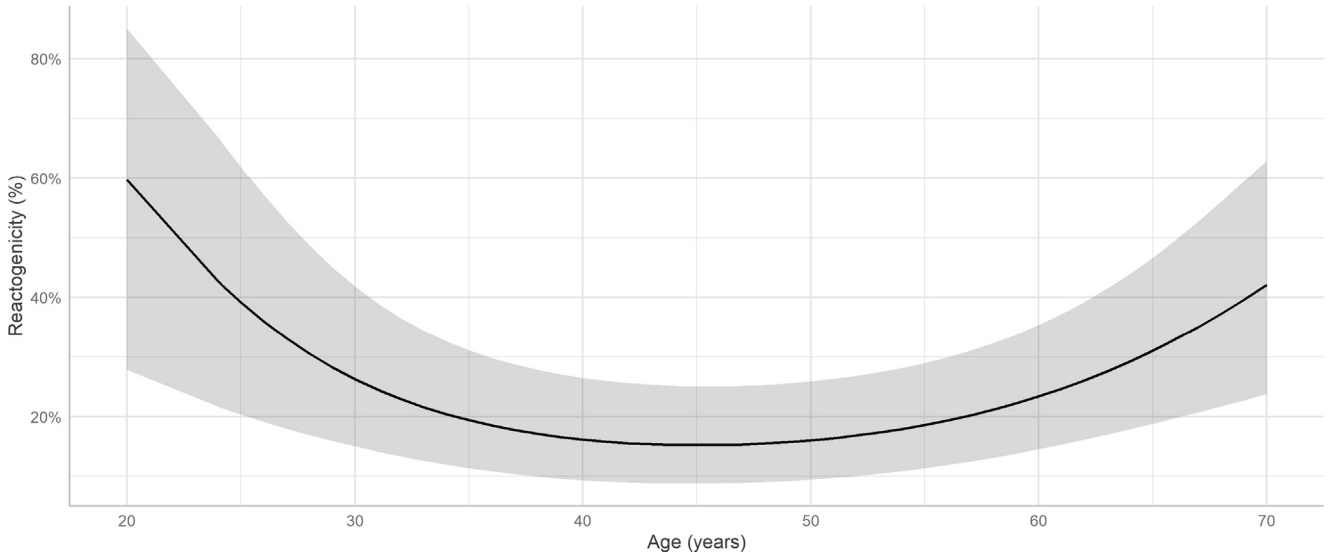

Fig. 4. The effect of age for a multivariable model explaining reactogenicity. Lower reactogenicity was identified among participants between 40 and 50 years, and higher adverse events were reported in younger and older subjects from the study population. Natural cubic splines estimated the predicted reactogenicity for age after a third-dose BNT162b2 boosted two-dose BBIBP-CorV subjects.

ducting remote activities due to their higher risk of poor outcomes. Also, comorbidities and related treatments present in late life could influence a higher reactogenicity compared with 30–60-year-old participants. Besides, we prefer not to discard the presence of unmeasured immunological determinants that might interact with the findings herein identified. Younger people self-reporting reactogenicity might be led by prior introduction into hospital routine and possibly over-sensitized to discomfort. Another possibility is that self-reporting was confounded by concomitant activities between 30 and 60-year-old participants that prevent remembering discomfort, especially considering local adverse events were more frequent, but less disabling than systemic. Similar could have occurred with nurses, who were less affected by reactogenicity than other workers. Also, stronger resistance to adverse events among nurses could occur due to passive exposure to a broad range of infections. However, both interpretations should be carefully taken because technical nurses, who overlapped healthcare activities with nurses, expressed an inverse relation to reactogenicity.

Limitations

There are specific limitations identified in our study. The lack of antibody measurement before the booster shot is the most critical limitation; a 17-fold increase has already been described [17], and similar results are reported in different studies. Also, the variable interval between the second and third dose could have misestimated the anti-SARS-CoV-2 IgG antibody level; adjusted models have been used herein to address this variability. Determining anti-SARS-CoV-2 antibodies with CLIA is another potential limitation, although not a gold standard method; concordance between binding antibody determination was previously estimated to approach viral neutralization results [59]. Unfortunately, the lack of cell-culture capacity, reagent shortage, infrastructure, unavailability of trained personnel, and non-suitable characteristics of neutralization tests [60], encouraged the research team to conduct CLIA. Also, we believe that previous COVID-19 infection is underestimated due to limited-availability diagnosis and differential misclassification due to the use of 1) real-time PCR detecting viral RNA, 2) rapid antigenic serologic tests, and primarily 3) rapid IgG/IgM antibody tests; not suited for the detection of acute infections. Although this issue, previous COVID-19 infection resulted as a determinant of increased anti-SARS-CoV-2 IgG. The amount of population recruitment was also a concern, considering that the primary study enrolled 1,436 healthcare workers, and we only achieved 595 subjects. This significant reduction of the sample was probably influenced by the need to meet the selection criteria (having received the third dose) and the loss of interest in participating in the current study. The current study is not a follow-up of the primary study; they were both independent protocols. Generalizability should be extended to populations entailing a high risk of exposure, such as healthcare personnel, which does not include underage and younger people. Furthermore, information regarding the cellular response would allow us to understand this topic more comprehensively.

Despite these limitations, current reports that depict the landscape of cellular and humoral response after boosting are mainly conducted among naive or exposed to wild SARS-CoV-2 populations. However, the role of previous COVID-19 infections seems substantial in developing middle-term immune responses. Therefore, high-exposed populations, such as our cohort, provide insight into the immunogenicity and reactogenicity of all vaccination regimes in the real world. A booster vaccination is vital to maintaining herd immunity by building enough protection that eventually decays after a full primary regime. Despite the worldwide distribution of booster doses, it is unclear how rapidly the protection from a third dose booster wanes over time [20]. Likewise, the role of cellular response driven by memory lymphocytes is unknown across different mixed boosting strategies. The impact of both approaches is even more limiting for primary BBIBP recipients, given that they were mostly distributed in low- and middle-income countries. Furthermore, fractional dosing reduces inflammation and adverse events and increases the global vaccine supply [20–21]. Research in multicomponent vaccines with more conserved antigens across VOC or IgA formulations is essential to mitigate poor COVID-19 outcomes due to SARS-CoV-2 permanent circulation worldwide.

Conclusions

A booster dose of BNT following a full BBIBP regime provided immune protection among healthcare providers due to high levels of anti-SARS-CoV-2 IgG antibodies. Determinants significantly

associated with higher levels of anti-SARS-CoV-2 IgG antibodies were; a smaller time frame from boosting to anti-SARS-CoV-2 IgG measurement, not reporting diabetes, prior COVID-19 infection, and full/part-time in-person working modality. High local but low systemic adverse events were identified. Additionally, younger participants and nurses were less associated with reactogenicity post-BNT boosting.

Author's contribution

JM, AC, and PS designed the study. AC, MG, AS, RC, SA, and EC coordinated the project administration. AC, SM, and MG conducted the data curation. LF processed and validated laboratory results. PS designed and conducted the formal analysis. SM and PS interpreted the results. SM drafted the manuscript. LF, AC, and MG commented on the final draft. JM, PS, DU, MA, and CD provided critical review and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

Data will be made available on request. The information generated during the current study will be made available from the corresponding author upon reasonable request.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2023.100311.

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