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Post-vaccination seropositivity against SARS-CoV-2 in peruvian health workers vaccinated with BBIBP-CorV (Sinopharm)

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ABSTRACT

Objective: To estimate the prevalence of post-vaccination seropositivity against SARS-CoV-2 and identify its predictors in Peruvian Social Health Insurance (EsSalud) personnel in 2021.
Methods: We conducted a cross-sectional study in a representative simple stratified sample of EsSalud workers. We evaluated IgG anti-SARS-CoV-2 antibodies response (seropositivity) by passive (previous infection) and active immunization (vaccination), and epidemiological and occupational variables obtained by direct interview and a data collection form. Descriptive and inferential statistics were used with correction of sample weights adjusted for non-response rate, and crude and adjusted odds ratio (OR) and geometric mean ratio (GMR) with their respective 95% confidence intervals (95%CI) were estimated.
Results: We enrolled 1077 subjects. Seropositivity was 67.4% (95%CI: 63.4–71.1). Predictors of seropositivity were age (negative relation; $p < 0.001$), previous infection (aOR = 11.7; 95%CI: 7.81–17.5), working in COVID-19 area (aOR = 1.47; 95%CI: 1.02–2.11) and time since the second dose. In relation to antibody levels measured by geometric means, there was an association between male sex (aGMR = 0.77; 95%CI: 0.74–0.80), age (negative relation; $p < 0.001$), previous infection (aGMR = 13.1; 95%CI:4.99–34.40), non-face-to-face/licensed work modality (aGMR = 0.78; 95%CI: 0.73–0.84), being a nursing technician (aGMR = 1.30; 95%CI: 1.20–1.41), working in administrative areas (aGMR = 1.17; 95%CI: 1.10–1.25), diagnostic support (aGMR = 1.07; 95%CI: 1.01–1.15), critical care (aGMR = 0.85; 95%CI: 0.79–0.93), and in a COVID-19 area (aGMR = 1.30; 95%CI: 1.24–1.36) and time since receiving the second dose (negative relation; $p < 0.001$).
Conclusions: Seropositivity and antibody levels decrease as the time since receiving the second dose increases. Older age and no history of previous infection were associated with lower seropositivity and antibody values. These findings may be useful for sentinel antibody surveillance and the design of booster dose strategies.

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1. Introduction

The pandemic caused by the SARS-CoV-2 virus has reported figures of up to 458 million cases and 6 million deaths worldwide up to March 13, 2022 [1]. To mitigate the contagion and spread of the disease, many countries have responded with the development of vaccines.

One of the vaccines designed was BBIBP-CorV, developed by the Beijing Bio-Institute of Biological Products of the Chinese national BIOTEC group and known internationally as Sinopharm [2]. This vaccine was produced from the HB02 strain and consists of viral particles cultured in the laboratory and inactivated to lose their ability to produce disease while stimulating the host immune response [3].

Despite being one of the first countries to initiate mandatory social immobilization to reduce the spread of COVID-19, Peru has registered more than 2 million cases and has one of the highest mortality rates in the world at 9.3% [4]. These figures can be explained considering labor informality, agglomeration, precariousness of the health system and intradomiciliary overcrowding which prevail in Peruvian society [5,6].

Nonetheless, in order to address the further spread of COVID-19, one of the fundamental pillars implemented by the Peruvian government was the acquisition and administration of vaccines to immunize the population, starting with high-risk target groups such as health personnel [7]. This first group was inoculated with the BBIBP-CorV vaccine, requiring the application of 2 doses with a 21-day interval between doses [8].

Although efforts have been focused on maximizing vaccine uptake and coverage, the question of passive immunity conferred arose taking into consideration studies showing that active immunization did not necessarily lead to the generation of antibodies [9] and/or in which a drop in these antibodies was described months after completing the vaccination schedule [10]. In addition, we can introduce terms related to active immunity, such as infection-induced immunity (defined as immune protection in an unvaccinated individual after an episode of SARS-CoV-2), vaccine-induced immunity (immune protection in someone who has not previously been infected with SARS -CoV-2 but have received at least one dose of vaccine) and hydrid immunity (occurs in people who suffered at least one episode of COVID-19 and have received at least one dose of vaccine) [11]. This aspect is currently the subject of studies worldwide, focusing their attention on neutralizing antibodies as a strategy for monitoring the individual's immune response to infection and vaccination [12–15].

Studies with the BNT162b2 vaccine reported an exponential increase in neutralizing antibodies on days 11 and 21 after vaccination [16]. However, studies on vaccines with inactivated virus technologies, such as BBIBP-CorV and CoronaVac, are still scarce. A study in Chile, in health care workers who completed the 2 doses in 0–14 day schedules, reported activation of interferon gamma secreting T cells and favorable antibody levels at 14, 28 and 42 days after immunization [17].

In Peru, it was possible to vaccinate health personnel at the beginning of the second wave of COVID-19 (February to April 2021), despite various controversies regarding the efficacy and effectiveness of the BBIBP-CorV vaccine, the social and scientific scandal of "vacunagate" [18] and the deep-rooted infodemics and misinformation surrounding COVID-19 [19]. A study in health personnel vaccinated with 2 doses of BBIBP-CorV reported an effectiveness of 50.4% in preventing infection and 94% in preventing mortality due to SARS-CoV-2 [20], while a study on the CoronaVac vaccine reported an effectiveness in preventing infection of 65.9%, hospitalization of 87.5% and mortality of 86.3% [21]. These effectiveness were lower compared to efficacy reported by the World Health Organization (WHO) Phase III report for the same vaccine in relation to preventing symptomatic infection [22].

It has been shown that the BBIBP-CorV vaccine provides protection against severe forms of COVID-19 that can lead to hospitalization and death. However, to date evidence regarding the prevention of symptomatic infection is questionable. Even within the current context of the circulation of different SARS-CoV-2 variants (Omicron, Delta, and Lambda) and heterologous vaccination schemes with booster doses (BBIBP-CorV + BNT162b2, BBIBP-CorV + ChAdOx1, BNT162b2 + ChAdOx1), there is no evidence of the generation of immune response by the BBIBP-CorV vaccine and even less by the heterologous vaccination schemes. This situation highlights the importance of immunological monitoring of antibody seropositivity in vaccinees to identify specific groups of low seropositivity, as well as temporal trends of the antibodies generated. Therefore, the objective of this study was to estimate post-vaccination seropositivity against COVID-19 in Peruvian Social Health Insurance (EsSalud) personnel vaccinated with two doses of BBIBP-CorV in Lima, Peru, 2021.

2. Methods

2.1. Study design and population

We conducted a cross-sectional study in a representative sample of health workers from five secondary and tertiary level hospitals of the Peruvian Social Health Insurance (EsSalud). The hospitals were *Hospital Nacional Edgardo Rebagliati Martins*, *Hospital Nacional Guillermo Almenara Irigoyen*, *Hospital Nacional Alberto Sabogal Sologuren* and *Villas Panamericana* and *Mongrut*. EsSalud health workers in whom there was an interval of at least 14 days since the first vaccination with the BBIBP-CorV vaccine, and who provided consent to participate in the study were enrolled. Those with contraindications for venous blood collection, active symptoms suggestive of COVID-19 and any condition related to hospitalization or quarantine hospitalization were excluded.

2.2. Sample

Based on the sampling frame defined by the list of vaccinated workers of the Health Care Centers (N = 2539), a probability, uni-stage, stratified sampling was performed with independent and representative strata corresponding to the domains represented by the occupational groups (physicians, nurses, nursing technicians, others and administrative personnel). A sample size per domain was calculated considering a nonresponse rate of 20% and a precision of 9% for each of the 24 area-occupancy strata (6 areas for each occupational group), and an estimated prevalence of seropositivity based on a previous study of post-vaccination IgG antiprotein S antibody production of 79.5% [23]. The sample size calculated was a total of 1436 participants. The sample weights were adjusted for nonresponse by the propensity score-matched class method [24]. The present analysis was restricted to health personnel who received two doses of the BBIBP-CorV vaccine in Peru as part of the vaccination campaigns promoted by the Peruvian government.

2.3. Participant recruitment, data and blood sample collection

All the participants were invited to participate by telephone and agreed on a specific date to come to the enrollment site to sign the informed consent form and to provide a blood sample. At recruitment, the participants were given a data collection form prepared by the research team to collect information on the variables of interest. All doubts or questions the participants had, were answered by a team of professionals assigned for this purpose. In addition, 5 cc of venous blood were drawn from each participant, to which EDTA was added and the sample was transported and stored in the laboratory for processing. A cold chain was maintained at all times to ensure sample stability.

In personnel who confirmed participation but were unable to do so for reasons of distance and workload, an additional period of sample collection from May to July 2021 was developed in 3 hospital sites to facilitate sample collection in these participants.

Table 1
Characteristics of the study sample including ineligible individuals.

Characteristics	Total		Seropositivity		
	Missing data	n = 1077	Negative (n = 378) n (%)	Positive (n = 687) n (%)	P value[a]
Sex	**0**				**0.200**
Female		786 (66.7%)	268 (30.2%)	514 (69.8%)	
Male		291 (33.3%)	110 (35.5%)	173 (64.5%)	
Age (years)	0				**<0.001**
Mean (SD)		45.1 (11.8)	47.6 (11.7)	43.9 (11.7)	
Median (p25-p75)	0	44.9 (35.0–55.0)	49.0 (36.0–57.7)	42.0 (35.0–52.0)	
Range (minimum-maximum)		24.0–70.0	25.0–69.0	24.0–70.0	
Age	0				**0.004**
18 to 44		500 (49.8%)	150 (25.7%)	345 (74.3%)	
45 to 59		395 (34.1%)	152 (37.0%)	237 (63.0%)	
60 or more		182 (16.1%)	76 (40.5%)	105 (59.5%)	
Nationality	0				**0.018**
Peruvian		1069 (99.6%)	377 (32.0%)	680 (68.0%)	
Foreign		8 (0.4%)	1 (4.7%)	7 (95.3%)	
Comorbidities	10				0.300
None		720 (69.6%)	250 (30.5%)	465 (69.5%)	
One		266 (24.2%)	92 (35.0%)	169 (65.0%)	
Two or more		81 (6.2%)	34 (40.8%)	45 (59.2%)	
Previous SARS-CoV-2 infection	4				**<0.001**
No		651 (58.5%)	344 (49.7%)	297 (50.3%)	
Yes		422 (41.5%)	34 (7.5%)	386 (92.5%)	
Profession	0				**<0.001**
Physician		289 (16.0%)	130 (45.4%)	151 (54.6%)	
Administrative or other		283 (45.3%)	103 (32.3%)	177 (67.7%)	
Nurse		284 (25.9%)	100 (31.7%)	183 (68.3%)	
Nursing technician		221 (12.9%)	45 (14.7%)	176 (85.3%)	
Work modality	1				**0.002**
Non-attendance		137 (11.9%)	65 (46.1%)	71 (53.9%)	
Face-to-face		866 (82.1%)	278 (29.0%)	577 (71.0%)	
Mixed		38 (3.2%)	22 (55.8%)	16 (44.2%)	
Licensed		35 (2.8%)	12 (29.0%)	23 (71.0%)	
Work area	0				0.076
Hospitalization/Surgery		226 (46.9%)	67 (29.2%)	155 (70.8%)	
Administrative or other related		151 (11.3%)	56 (32.8%)	95 (67.2%)	
Diagnostic support and other related		145 (12.3%)	54 (37.9%)	88 (62.1%)	
Outpatient, extramural and other related		191 (8.3%)	81 (45.2%)	107 (54.8%)	
Critical care		185 (6.2%)	69 (35.7%)	116 (64.3%)	
Emergency or urgent care		179 (15.0%)	51 (26.1%)	126 (73.9%)	
Main work area	66				**0.034**
ICU		167 (8.8%)	54 (26.4%)	112 (73.6%)	
Emergency		174 (16.9%)	43 (22.5%)	127 (77.5%)	
Hospitalization		212 (28.7%)	59 (27.6%)	153 (72.4%)	
Non-COVID-19 Clinic		89 (5.1%)	32 (41.5%)	55 (58.5%)	
Home care		10 (2.6%)	5 (36.3%)	5 (63.7%)	
Administrative care		61 (7.6%)	26 (37.3%)	34 (62.7%)	
Research		1 (0.0%)	1 (100.0%)	0 (0.0%)	
Remote work		86 (7.7%)	45 (52.3%)	40 (47.7%)	
Other		211 (22.6%)	85 (34.6%)	124 (65.4%)	
Works in COVID-19 area	40				**0.002**
No		527 (50.9%)	205 (36.8%)	317 (63.2%)	
Yes		510 (49.1%)	154 (24.5%)	349 (75.5%)	
EsSalud hospital of work	0				0.600
I Octavio Mongrut Muñoz Hospital		52 (4.5%)	18 (40.7%)	34 (59.3%)	
Alberto Sabogal Sologuren National Hospital		341 (23.3%)	128 (33.4%)	212 (66.6%)	
Edgardo Rebagliati Martins National Hospital		465 (42.3%)	156 (31.3%)	308 (68.7%)	
Guillermo Almenara Irigoyen National Hospital		198 (24.3%)	70 (32.5%)	118 (67.5%)	
Villa Panamericana		21 (5.5%)	6 (20.5%)	15 (79.5%)	
BBIBP-CorV doses	0				0.070
One dose		17 (2.4%)	1 (7.9%)	16 (92.1%)	
Two doses		1060 (97.6%)	377 (32.5%)	671 (67.5%)	
Additional vaccination abroad	0				0.150
No		1071 (99.6%)	378 (32.0%)	681 (68.0%)	
Yes		6 (0.4%)	0 (0.0%)	6 (100.0%)	
Time since first dose (days)	3				0.130
Median (p25-p75)		152.0 (145.0–155.0)	153.0 (145.0–155.0)	152.0 (145.0–155.0)	
Range (minimum-maximum)		13.0–163.0	95.0–163.0	13.0–163.0	
Time since second dose (days)	19				**0.033**
Median (p25-p75)		130.0 (124.0–134.0)	131.0 (124.0–134.0)	130.0 (123.0–134.0)	
Range (minimum-maximum)		14.0–142.0	14.0–142.0	14.0–142.0	

n: unweighted absolute frequency; %: weighted percentage; ICU: intensive care unit; SD: standard deviation.
*Ineligible individuals were those who had only one dose of vaccine, were vaccinated with a vaccine other than BBIBP-CorV and/or were vaccinated abroad. Likewise. we also excluded those who did not have complete data on the response variable.
[a] Squared chi-square test with Rao and Scott second-order correction; Wilcoxon rank sum test for complex samples.

2.4. Laboratory methods

Blood samples were processed at the Clinical Pathology Service Laboratory of the *Hospital Nivel II Suárez Angamos* following standardized protocols and the manufacturer's recommendations.

IgG anti-SARS-CoV-2 antibodies were measured using the LIAISON® SARS-CoV-2 TrimericS IgG test (DiaSorin Inc., Stillwater, USA), Stillwater, USA). This chemiluminescence immunoassay has a positive and negative concordance greater than 96% with the microneutralization plate test and has proven to be an excellent substitute for the Plate Reduction Neutralization Test - PRNT (gold standard) [25,26]. Likewise, the equipment complied with the verification method recommended by the National Institute of Quality - INACAL [27] and the Clinical & Laboratory Standards Institute - CLSI, under the EP06-A, EP12-A2 and EP15A3 evaluation protocols [28–30].

3. Variables

3.1. Outcomes and covariates

A participant was defined as seropositive with antibody levels greater than or equal to 33.8 BAU/ml, which is the cut-off value recommended by the WHO harmonization process [31]. Antibody levels were also analyzed as a quantitative variable after transformation as a

Table 2
Predictors of seropositivity 14 to 142 days after receiving the second dose in health personnel vaccinated with BBIBP-CorV.

Characteristics	14–142 days post second dose			Crude analysis			Adjusted analysis		
	Negative (n = 377) n (%)	Positive (n = 665) n (%)	P value[a]	cOR[b]	95%CI[c]	P value	aOR[d]	95%CI[c]	P value
Sex			0.200						
Female	267 (31.0%)	495 (69.0%)		–	–		–	–	
Male	110 (36.0%)	170 (64.0%)		0.80	0.61–1.04	0.091	0.82	0.58–1.17	0.300
Age (years)			**0.001**			**<0.001**			**<0.001**
Mean (SD)	47.5 (11.6)	44.0 (11.6)							
Median (p25-p75)	49.0 (36.0–57.3)	43.0 (35.0–52.0)							
Range (minimum-maximum)	25.0–69.0	24.0–70.0							
Comorbidities			0.200						
None	252 (31.1%)	460 (68.9%)		–	–		–	–	
One or more	125 (36.4%)	205 (63.6%)		0.79	0.60–1.03	0.086	0.96	0.68–1.35	0.800
Previous SARS-CoV-2 infection			**<0.001**						
No	343 (49.9%)	292 (50.1%)		–	–		–	–	
Yes	34 (7.8%)	373 (92.2%)		11.7	8.00–17.2	**<0.001**	11.7	7.81–17.5	**<0.001**
Profession			**<0.001**						
Physician	130 (46.3%)	147 (53.7%)		–	–		–	–	
Administrative or other	102 (32.9%)	172 (67.1%)		1.76	1.25–2.49	**0.001**	1.24	0.77–2.02	0.400
Nurse	100 (32.2%)	178 (67.8%)		1.82	1.24–2.66	**0.002**	1.53	0.91–2.58	0.110
Nursing technician	45 (15.6%)	168 (84.4%)		4.67	2.73–8.00	**<0.001**	2.24	1.14–4.37	**0.019**
Work modality			**0.017**						
Face-to-face/Mixed	300 (30.7%)	576 (69.3%)		–	–		–	–	
Non-attendance/Licensed	77 (43.9%)	89 (56.1%)		0.57	0.40–0.80	**0.001**	0.94	0.58–1.51	0.800
Work area			0.089						
Hospitalization/Surgery	66 (30.3%)	146 (69.7%)		–	–		–	–	
Administrative or other related	56 (32.8%)	94 (67.2%)		0.89	0.58–1.35	0.600	0.61	0.36–1.03	0.065
Diagnostic support or other related	54 (38.4%)	86 (61.6%)		0.70	0.47–1.04	0.078	0.77	0.46–1.28	0.300
Outpatient. extramural and other related	81 (45.9%)	102 (54.1%)		0.51	0.32–0.81	**0.005**	0.83	0.48–1.42	0.500
Critical care	69 (36.1%)	113 (63.9%)		0.77	0.45–1.31	0.300	0.53	0.28–1.02	0.058
Emergency or urgent care	51 (26.2%)	124 (73.8%)		1.22	0.82–1.82	0.300	0.77	0.47–1.27	0.300
Works in COVID-19 area			**<0.001**						
No	220 (39.0%)	318 (61.0%)		–	–		–	–	
Yes	157 (25.6%)	347 (74.4%)		1.86	1.44–2.40	**<0.001**	1.47	1.02–2.11	**0.040**
EsSalud hospital of work			>0.900						
Edgardo Rebagliati Martins National Hospital	155 (31.6%)	298 (68.4%)		–	–		–	–	
Guillermo Almenara Irigoyen National Hospital	70 (33.2%)	114 (66.8%)		0.93	0.67–1.29	0.700	0.87	0.57–1.32	0.500
I Octavio Mongrut Muñoz Hospital/Villa Panamericana	24 (33.9%)	45 (66.1%)		0.90	0.57–1.42	0.600	0.27	0.14–0.53	**<0.001**
Alberto Sabogal Sologuren National Hospital	128 (33.5%)	208 (66.5%)		0.92	0.66–1.26	0.600	0.61	0.40–0.94	**0.024**
Time since second dose (days)			**0.030**			**<0.001**			**<0.001**
Median (p25-p75)	131.0 (124.0–134.0)	130.0 (123.0–134.0)							
Range (minimum-maximum)	14.0–142.0	14.0–142.0							

n: unweighted absolute frequency; %: weighted percentage.
The associations of seropositivity with age and time since second vaccination are shown in Figs. 1 and 2.
[a] Squared chi-square test with Rao and Scott second-order correction; Wilcoxon rank sum test for complex samples.
[b] cOR: crude odds ratio.
[c] CI: confidence interval.
[d] aOR: adjusted odds ratio; SD: standard deviation.

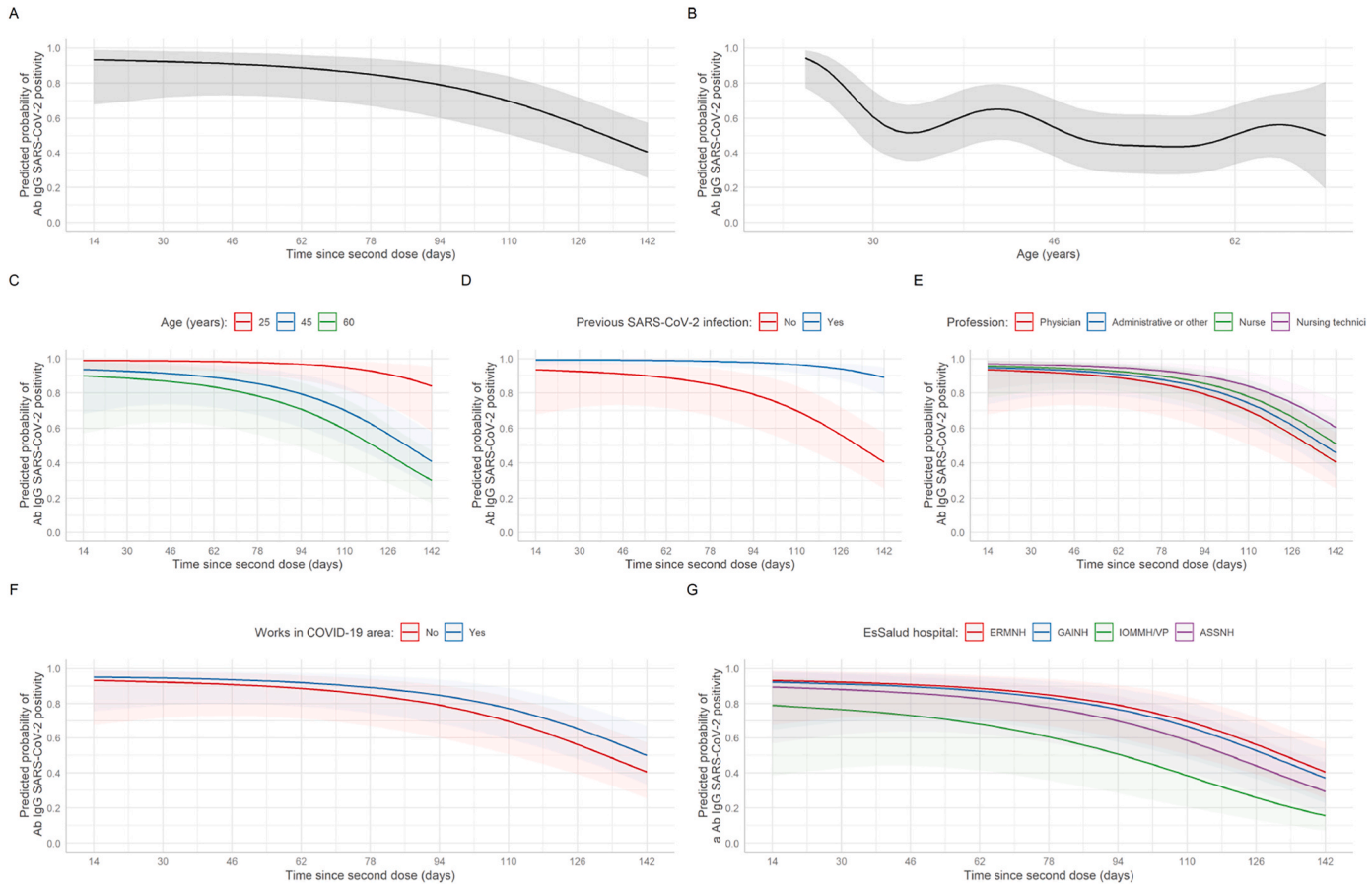

Fig. 1. Association between SARS-CoV-2 IgG antibody positivity and time since receiving the second vaccination dose (days) (A), age (B), according to age group (C), history of previous SARS-CoV-2 infection (D), profession (E), work in COVID-19 area (F) and EsSalud hospital (G).

logarithm. Variables related to sex, age, occupation, work area, work modality (referring to the participants main work and classified as non-attendance, face-to-face or mixed), work in COVID-19 area, comorbidities, full dose of BBIBP-CorV vaccine, and time from the first/second dose to sampling were measured. In addition, we collected history of previous SARS-CoV-2 infection through self-report.

3.2. Statistical analysis

All analyses were performed with the R statistical program [32]. The data were entered into the REDCap® capture platform [33] and were subjected to a quality control process that checked for missing, extreme and/or inconsistent values. Missing data were completed by simple multivariate imputation processing by random Forest [34].

Numerical variables were described as means (standard deviation [SD]) or medians (25th and 75th percentiles), as appropriate. Categorical variables were described as absolute and relative frequencies. Bivariate analyses were performed using the Wald or Mann-Whitney *U* test (both adjusted for the sample design) to compare numerical variables between groups; and the Chi-2 test with Rao-Scott second-order correction for association of categorical variables. Prevalences of seropositivity were reported together with 95% confidence intervals (95% CI) obtained by the logit method.

The association between the probability of seropositivity with predictors of interest was assessed using a logistic generalized additive model (GAM). Odds ratios (OR) were estimated with their respective 95%CI. On the other hand, the relationship between antibody level and predictors of interest was evaluated by tobit GAM, with identity link function and censoring on both sides corresponding to the lower (3.81 BAU/mL) and upper (2080 BAU/mL) limit of the test. Considering evidence that the response to vaccination would vary differentially according to age, time since vaccination, and the existence of previous infection [35], we constructed models that evaluated the interaction between these three variables. The interactions were evaluated by specifying a tensor product of B-splines that allowed modeling the nonlinearity among these variables. To reduce the risk of overfitting we performed a smoothing penalty by restricted maximum likelihood. We assessed collinearity using generalized variance inflation factor and concurvity, a generalization of collinearity that can make estimates unstable, as previously described [36]. We selected variables a priori based on an epidemiological approach, considering previous studies [13,20].

3.3. Ethical issues

The study was approved by the Institutional Research Ethics Committee of the National Heart Institute (INCOR) (12/2021-CEI). Participants provided informed consent prior to enrollment in the study. The information was anonymized and coded to avoid any subsequent identification of the participant.

4. Results

4.1. General characteristics according to seropositivity

A total of 1077 subjects were enrolled. Seventeen participants were excluded for only having received one dose and 18 because they did not have the variables of interest. The prevalence of seropositivity was 67.4% (95%CI: 63.4–71.1) with a coefficient of variation of 2.9%. Among the main characteristics of the sample, we found that 66.7% (n

Table 3
Predictors of anti-SARS-CoV-2 antibody levels 14 to 142 days after receiving the second dose in health personnel vaccinated with BBIBP-CorV.

Characteristics	Crude analysis			Adjusted analysis		
	cGMR[a]	95%CI[2]	P value	aGMR[3]	95%CI[2]	P value
Sex						
Female	–	–		–	–	
Male	0.88	0.83–0.93	**<0.001**	0.77	0.74–0.80	**<0.001**
Age (years)			**<0.001**			**<0.001**
Comorbidities						
None	–	–		–	–	
More than one	0.87	0.83–0.92	**<0.001**	1.00	0.96–1.05	0.900
Previous SARS-CoV-2 infection						
No	–	–		–	–	
Yes	7.7	7.40–8.02	**<0.001**	13.1	4.99–34.40	**<0.001**
Profession						
Physician	–	–		–	–	
Administrative or other	1.57	1.46–1.69	**<0.001**	0.98	0.92–1.05	0.600
Nurse	1.41	1.30–1.52	**<0.001**	1.01	0.94–1.08	0.800
Nursing technician	3.18	2.90–3.50	**<0.001**	1.30	1.20–1.41	**<0.001**
Work modality						
Face-to-face/Mixed	–	–		–	–	
Non-attendance/Licensed	0.48	0.45–0.51	**<0.001**	0.78	0.73–0.84	**<0.001**
Work area						
Hospitalization/Surgery	–	–		–	–	
Administrative or other related	1.39	1.28–1.51	**<0.001**	1.17	1.10–1.25	**<0.001**
Diagnostic support or other related	0.92	0.85–1.00	0.053	1.07	1.01–1.15	**0.045**
Outpatient. extramural and other related	0.65	0.59–0.72	**<0.001**	1.04	0.97–1.12	0.300
Critical care	0.98	0.88–1.08	0.600	0.85	0.79–0.93	**<0.001**
Emergency or urgent care	1.52	1.41–1.63	**<0.001**	1.06	1.00–1.13	0.057
Works in COVID-19 area						
No	–	–		–	–	
Yes	1.71	1.62–1.80	**<0.001**	1.30	1.24–1.36	**<0.001**
EsSalud hospital of work						
Edgardo Rebagliati Martins National Hospital	–	–		–	–	
Guillermo Almenara Irigoyen National Hospital	1.01	0.95–1.08	0.700	1.02	0.97–1.07	0.500
I Octavio Mongrut Muñoz Hospital/Villa Panamericana	1.09	0.99–1.20	0.067	0.62	0.58–0.68	**<0.001**
Alberto Sabogal Sologuren National Hospital	0.99	0.93–1.05	0.700	0.84	0.80–0.89	**<0.001**
Time since second dose (days)			**<0.001**			**<0.001**
Interaction (Time since second dose (days) * Previous SARS-CoV-2 infection)						**<0.001**

[a] cGMR: crude geometric mean ratio; [2]CI: confidence interval; [3]aGMR: adjusted geometric mean ratio.

= 786) were female, the median age was 44.9 years (IQR: 35.0–55.0), 69.6% (n = 720) had no comorbidities, 58.5% (n = 651) had no previous SARS-CoV-2 infection, 82.1% (n = 866) worked in an office and 50.9% (n = 527) worked in an area with COVID-19 patients. In addition, the median time since receipt of the second dose was 130 days (interquartile range: 124 to 134). There were no statistically significant differences between groups according to seropositivity and sex, reported comorbidities, area of work, work setting, number of BBIBP-CorV doses received, additional vaccination abroad, and time in days since receiving the first and second doses (Table 1).

4.2. Seropositivity predictors

In the adjusted analysis, we found a negative association between seropositivity and age ($p < 0.001$). In addition, belonging to the occupational group of nursing technicians (aOR = 2.24; 95%CI: 1.14–4.37), belonging to the *Villa Mongrut* or *Panamericana* group (aOR = 0.27; 95% CI: 0.14–0.53) and *Sabogal* Hospital (aOR = 0.60; 95%CI: 0.40–0.94), time since second vaccination ($p < 0.001$), previous SARS-CoV-2 infection (aOR = 11.7; 95%CI: 7.81–17.5) and working in a COVID-19 area (aOR = 1.47; 95%CI: 1.02–2.11) were associated with presenting seropositivity (see Table 2).

The associations of seropositivity and time since the second vaccination are shown in the graphs in Fig. 1. Fig. 1A shows the trend to a decrease in the predicted probability of seropositivity to Ac IgG SARS-CoV-2 with a longer time since the second vaccination dose, showing a notable reduction after day 110. In addition, in Fig. 1B we describe a slightly negative association between SARS-CoV-2 IgG antibody positivity and age. This is also shown in Fig. 1C in individuals aged 25, 45 and 60 years, with a sustained reduction in individuals aged 60 years after day 110. The predicted probability of seropositivity remained high over time in individuals who reported having had a previous infection compared to those who did not. Fig. 1E, F and 1G show the predicted probability of seropositivity according to occupational groups, working in a COVID-19 area and the hospital work site.

4.3. Predictors of anti-SARS-CoV-2 antibody levels

In the adjusted analysis, a statistically significant association was found for male sex (aGMR = 0.77; 95%CI: 0.74–0.80), non-face-to-face/licensed work modality (aGMR = 0.78; 95%CI: 0.73–0.84), type of administrative or other related service (aGMR = 1.17; 95%CI: 1.10–1.25), work in critical care (aGMR = 0.85; 95%CI: 0.79–0.93), the nursing technician occupational group (aGMR = 1.30; 95%CI: 1.20–1.41), having worked at Villa Mongrut/Panamericana (aGMR = 0.62; 95%CI: 0.58–0.68) and Sabogal Hospital (aGMR = 0.84; 95%CI: 0.80–0.89), having reported a previous SARS-CoV-2 infection (aGMR = 13.1; 95%CI: 4.99–34.3), having worked in a COVID-19 area (aGMR = 1.30; 95%CI: 1.24–1.36), age ($p < 0.001$) and time since second vaccination ($p < 0.001$) (Table 3). The association between the geometric mean of SARS-CoV-2 IgG antibody levels and time since second vaccination is shown in Fig. 2. Fig. 2A shows the trend to a reduction in the geometric mean of antibody levels in individuals 62 years of age or older. In addition, Fig. 2B presents a negative relation between antibody levels and time since second dose. Likewise, Fig. 2D and E presents the geometric mean of antibody levels and time since second vaccination comparing previous SARS-CoV-2 infection and disease presentation in individuals 25, 45 and 60 years old. In all these cases there was a reduction in the time of the geometric mean which was especially notable in those without previous infection and 60 years of age. Graphs

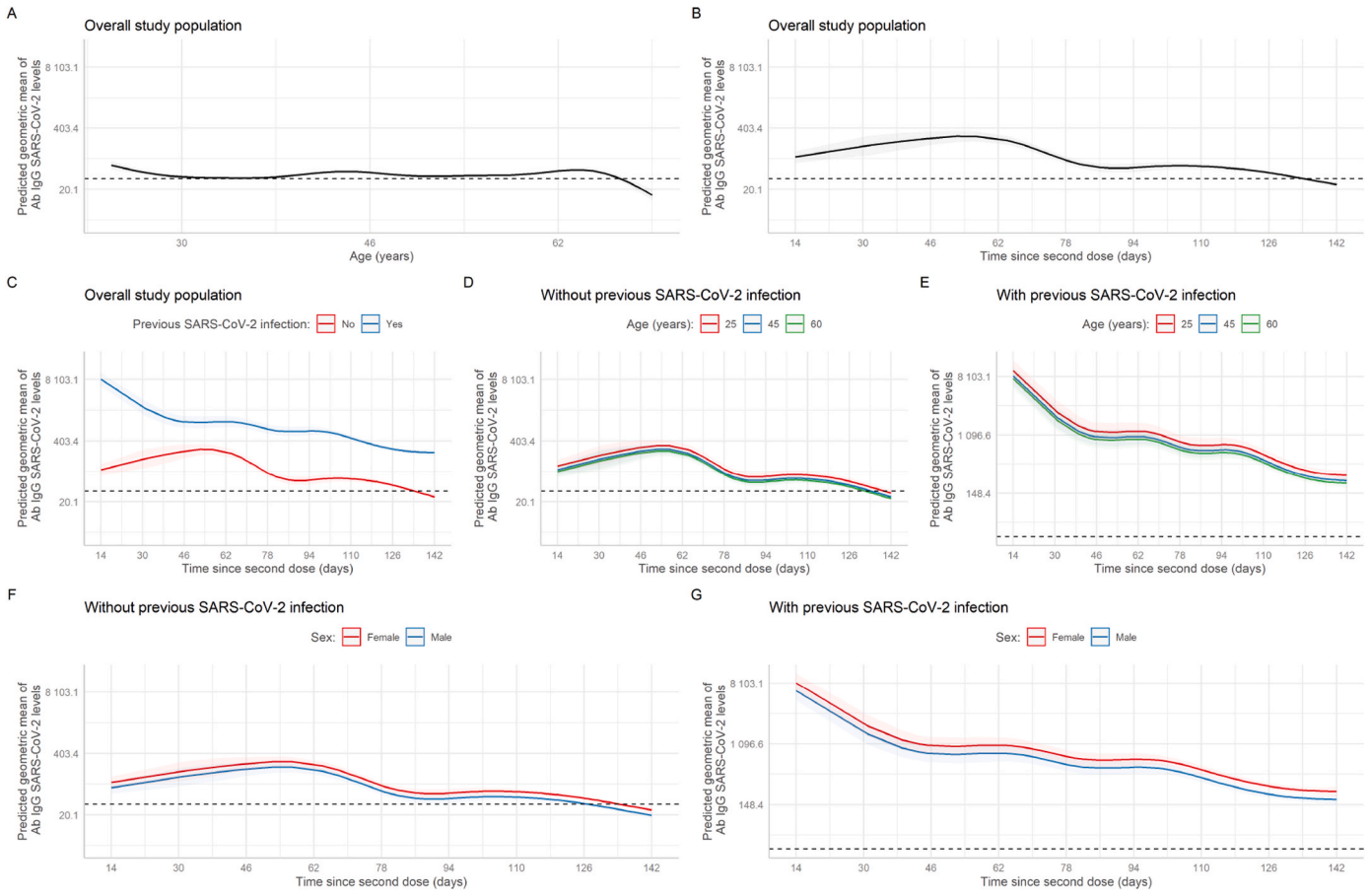

Fig. 2. Association between the SARS-CoV-2 IgG antibodies (BAU/mL) levels and age (A), time (days) since receipt of the second vaccination dose (B) according to: age groups with no history of previous SARS-CoV-2 infection (C), age groups with this history (D), previous SARS-CoV-2 infection (E), groups according to sex and no history of previous SARS-CoV-2 infection (F), groups by sex with this history (G).

2F and 2G show the behavior of the curve according to previous infection and by sex. In Fig. 3, it is important to highlight that the occupational group of nursing technicians and those who worked in the on-site modality had a higher predicted geometric mean of IgG SARS-CoV-2 antibodies. In addition, we showed in supplementary material the behavior of the curve according to groups by EsSalud hospital of work and working areas (by previous SARS-CoV-2 infection).

5. Discussion

Our study estimated the prevalence of post-vaccination seropositivity against SARS-CoV-2 and identified the predictors in Peruvian health personnel during 2021. Approximately 70% of the participants were seropositive, with younger age, having a history of COVID-19, and working in a COVID-19 area being associated with higher seropositivity. In addition, being male, younger age, having previous COVID-19 infection, working in a non-face-to-face modality, as well as in a COVID-19 area were predictors of higher antibody levels. We also found that antibody levels progressively decreased from day 110 after receiving the second vaccine dose.

About seven out of ten participants presented seropositivity for anti-SARS-CoV-2 IgG anti-SARS-CoV-2 protein S antibodies generated from vaccination. There was a negative significant association with age and in subcategories of age group, highlighting a marked difference in seropositivity between the groups of 18–44, 45 to 59, and greater than or equal to 60 years of age. Some studies have reported similar findings on the relationship of age and antibody quantification. One study, by Ferenci et al. evaluated the levels of neutralizing antibodies after receiving a second dose of the BBIBP-CorV vaccine, and reported that 90% of participants younger than 50 had detectable antibodies, while 50% of those older than 80 had no detectable antibodies [37]. Likewise, a cohort study evaluating antibody response in participants after receiving the ChAdOx1 and BNT162b2 vaccines identified a group of non-responders, mainly composed of those over 75 years of age, males and individuals with chronic health problems [35]. The decrease in antibody levels with increasing age could be explained by immunosenescence [38], which would produce a reduced adaptive immune response and a decline in humoral and cellular immune response [39,40], indicating a greater need for booster doses in this age group.

We found that being female was predictive of higher antibody levels compared to males. However, we observed a similar sustained reduction in antibody levels from day 110 onwards regardless of having had previous infection or not. Our finding is consistent with that described by Wei et al. who reported that being male was a predictor of lower antibody positivity [35]. Likewise, sex differences have been described after natural infection with COVID-19 [41]. This finding could be explained by the fact that biological sex affects the response of the innate and adaptive immune system, inducing different responses to a pathogen or vaccines [42,43]. In addition, males are at higher risk for diseases caused by X-linked alleles [44,45] and epigenetic expression in this group would determine exposure to sex steroids that would have a direct effect on immune function [46–48].

Our results showed that working in an area with patients with COVID-19 infection was a predictor of seropositivity and higher antibody levels and working in the non-face-to-face modality was a predictor of lower antibody levels. These findings could be explained in that the participants who worked in a face-to-face setting as well as in COVID-19 areas had an additional risk of becoming infected. These two

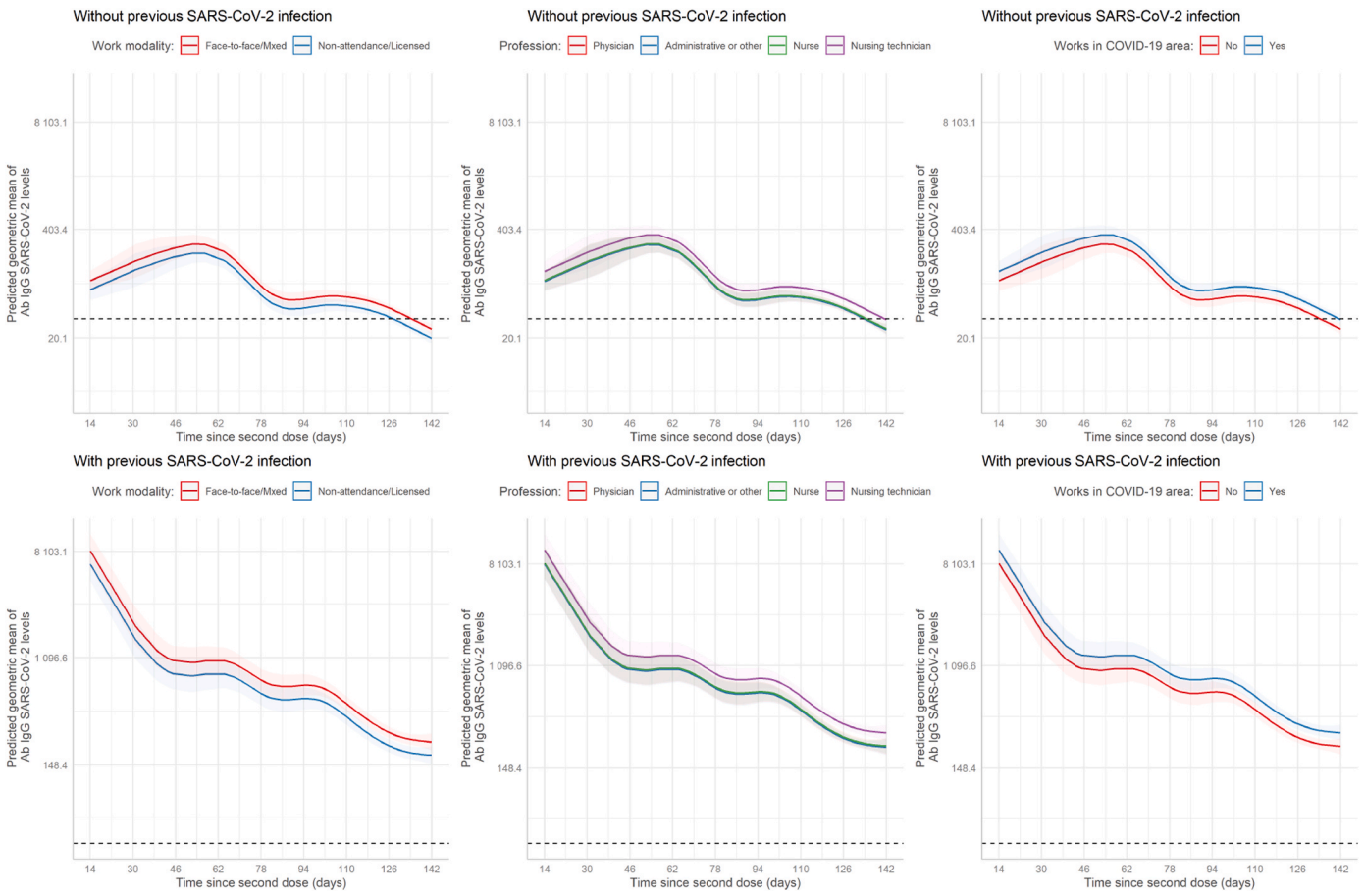

Fig. 3. Association between the SARS-CoV-2 IgG antibodies (BAU/mL) levels and time since receipt of the second vaccination dose (days) according to: groups by work modality according to previous SARS-CoV-2 infection, groups by profession according to previous SARS-CoV-2 infection, groups according to work in COVID-19 area and -CoV-2 infection and groups by working area according to previous SARS-CoV-2 infection.

characteristics are important because they could be associated with having a history of COVID-19. Thus, passive re-exposure would cause the immune system to produce a greater proportion of antibodies [49] compared to individuals without these occupational characteristics.

Self-reported previous COVID-19 infection was a predictor of seropositivity and higher antibody levels. In addition, this group of participants recorded a lower reduction in antibody levels during the time after receiving the second dose compared to those who had no history of COVID-19. Previous studies have reported similar findings, describing higher antibody levels in vaccinated persons with a history of COVID-19 [50,51] independently of the age group [35]. Thus, it was proposed that, in a scenario of vaccine shortage, a dose of mRNA-type BNT162b2 vaccine could generate a robust immune response in persons who have had a COVID-19 infection three to six months prior to vaccination [35, 52]. Immune response following inoculation with a COVID-19 vaccine involves two processes; the first is related to cellular response involving the production of different T-cell lineages, interleukins and interferons, while the second process is triggered by the first and involves the production of IgG immunoglobulins against viral antigens, such as protein S [53]. This process must be understood as a whole for the correct study of the immune response of a particular individual. These antibodies usually persist for up to six months [54–56] and then decline by 5 to 10-fold [57, 58]. However, B and T cells can be detected even longer and are essential for protection against possible reinfections [56–59], highlighting the role of cellular immunity [56,60]. Thus, our finding on the reduction of antibody levels 110 days after receiving the second vaccination dose indicate the need to administer a booster dose in the event of the circulation of new variants.

Previous studies have highlighted the reduction in antibody levels generated after passive immunization over time. One study showed a decrease in antibody levels three months after receiving the second dose of the BNT162b2 vaccine (mRNA type vaccine produced by the Pfizer laboratory) [61]. On the other hand, another report indicated that between days 21–70 after receiving the second dose of ChAdOx1 (viral vector vaccine produced by the University of Oxford and the AstraZeneca laboratory) and BNT162b2 there was a 5-fold and 2-fold reduction in antibody levels, respectively [62]. Similarly, a study evaluating antibody levels in two groups after receiving a type of inactivated virus vaccine produced by the Sinopharm laboratory described a significant reduction in antibody levels after the third- or fourth week following receipt of the second dose. However, after receiving a third dose, the humoral immune response was very high [63]. The evidence is consistent in showing a decrease in the level of antibodies three months after receiving the second dose, a finding that is consistent with our results. This evidence supports the need for a booster dose after this period to increase antibody levels.

Although low antibody values would not imply greater vulnerability and decreased protection against the virus, the need for a booster dose should be considered due to the adaptive mutability of the virus. This characteristic has generated different variants that can compromise the protection of vaccines against severe forms of the disease, hospitalization, admission to the intensive care unit and death [64,65]. By compromising vaccine protection, new waves, collapse of health systems and greater impact on the population could be generated [6,66], all of which are preventable scenarios.

Our results elucidate the need for follow-up and immunologic

surveillance (at humoral and cellular levels) in the risk group of health personnel. This surveillance would generate information for evidence-based decision making to identify the times at which a booster dose is necessary to maintain elevated antibody levels and provide better protection against SARS-CoV-2 and its variants [67].

Our study has limitations. Since antibody levels tend to decline over time, some of the seronegative measurements could previously have been seropositive. Despite having considered non-response and loss rates, we were unable to reach the estimated sample size for the study due to the high workload of the participants, limiting their availability for sample collection. To deal with this drawback, we went to the hospitals in which the health personnel worked to try to extract samples and increase the recruitment of participants. Another limitation is that memory bias could affect the validity of the information obtained in some questions such as the date of vaccination, self-report of previous SARS-CoV-2 infection, and a history of a positive diagnostic test for COVID-19. However, to reduce this bias, we provided support for filling out the survey and obtaining the vaccination date from the official portal of the Peruvian Ministry of Health. In addition, although previous studies have evaluated seropositivity and antibody production after receiving different vaccines worldwide, information related to the BBIBP-CorV vaccine is still scarce, thereby limiting comparison with other vaccines. Finally, this study only evaluated the humoral response of the immune system but not the cellular response. Studies on cellular immunity are needed for better evidence-based decision making. To our knowledge, this study is one of the first reports of active surveillance of SARS-CoV-2 anti-SARS-CoV-2 IgG antiprotein S antibody levels and post-vaccination seropositivity in a high-risk group, such as health care workers.

6. Conclusions

Two out of three participants achieved seropositivity after receiving both doses of the inactivated BBIBP-CorV vaccine produced by the Sinopharm laboratory. We found predictors of seropositivity to be male sex, younger age, self-reported COVID-19 and working in an area with COVID-19 patients. In addition, a longer time after receiving the second dose was a predictor of lower antibody levels. We described a sustained drop in antibody levels after day 110, elucidating the need for a booster dose three months after the second dose.

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CRediT authorship contribution statement

Aleksandar Cvetkovic-Vega: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Diego Urrunaga-Pastor:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Percy Soto-Becerra:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Luis E. Figueroa-Montes:** Conceptualization, Investigation, Writing – review & editing. **Lizette Fernandez-Bolivar:** Conceptualization, Investigation, Writing – review & editing. **Sergio Alvizuri-Pastor:** Conceptualization, Investigation, Writing – review & editing. **Martin Oyanguren-Miranda:** Conceptualization, Investigation, Writing – review & editing. **Ibeth Neyra-Vera:** Conceptualization, Investigation, Writing – review & editing. **Elizabeth Carrillo-Ramos:** Conceptualization, Investigation, Writing – review & editing. **Arturo Sagástegui:** Conceptualization, Investigation, Writing – review & editing. **Roxana Contreras-Macazana:** Conceptualization, Investigation, Writing – review & editing. **Diana Lecca-Rengifo:** Conceptualization, Investigation, Writing – review & editing. **Nikolai Grande-Castro:** Conceptualization, Investigation, Writing – review & editing. **Moises Apolaya-Segura:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Jorge L. Maguina:** Conceptualization, Investigation, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2022.102514.

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