

Original article

Neutralizing antibodies induced by homologous and heterologous boosters in CoronaVac vaccines in Chile

Johanna Acevedo^{1,2}, Mónica L. Acevedo^{3,4}, Aracelly Gaete-Argel^{3,4}, Rafael Araos^{1,2,5}, Cecilia Gonzalez¹, Daniela Espinoza¹, Solange Rivas¹, Pablo Pizarro⁶, Stephan Jarpa⁷, Ricardo Soto-Rifo^{3,4}, Alejandro Jara^{1,8,9,**}, Fernando Valiente-Echeverría^{3,4,*}

¹ Ministerio de Salud, Chile

² Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina, Universidad del Desarrollo, Chile

³ Laboratorio de Virología Molecular y Celular, Programa de Virología, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Chile

⁴ Millennium Institute on Immunology and Immunotherapy, Chile

⁵ Millennium Initiative for Collaborative Research in Bacterial Resistance, Chile

⁶ Servicio Nacional del Adulto Mayor, Chile

⁷ Hospital de Urgencia Asistencia Pública, Chile

⁸ Facultad de Matemáticas, Pontificia Universidad Católica de Chile, Chile

⁹ Millennium Nucleus Center for the Discovery of Structure in Complex Data, Chile

ARTICLE INFO

Article history:

Received 20 April 2022

Received in revised form

3 November 2022

Accepted 20 November 2022

Available online 25 November 2022

Editor: M. Cevik

Keywords:

Boosters

CoronaVac

COVID-19

Immunization programme

SARS-CoV-2

Vaccination

ABSTRACT

Objectives: To determine the impact of a booster dose on the humoral response in individuals inoculated with a complete schedule of any SARS-CoV-2 vaccine, we evaluated the neutralizing antibody (NAb) titres of homologous or heterologous booster doses over a 90-days period in CoronaVac vaccinees from 3 centres in Santiago, Chile.

Methods: Individuals previously inoculated with 2 doses of CoronaVac ($N = 523$) were recruited in the context of the REFUERZO clinical trial (NCT04992182) and received either placebo ($N = 129$), or a booster dose of CoronaVac ($N = 134$), BNT162b2 ($N = 133$), or ChAdOx1 ($N = 127$). Pseudovirus neutralizing antibody titres (pVNT) were determined at baseline (day 0) as well as at days 14, 30, 60, and 90 after booster dose administration.

Results: Inoculating a booster dose increases the pVNTs titres at days 14 and 30 in all groups, (13.5- and 12.0-fold increase for the CoronaVac group; 247.0- and 212.3-fold increase for the BNT162b2 group; and 89.1- and 128.1-fold increase for ChAdOx1 at each time point, respectively) with a decline observed at days 60 and 90. However, although pVNTs remained significantly higher for the BNT162b2 and ChAdOx1 groups at days 60 and 90, NAb titres reached baseline levels in the CoronaVac group at 90 days after inoculation.


Discussion: A single heterologous booster (BNT162b2 or ChAdOx1) in individuals who completed the CoronaVac primary series resulted in an important increase in NAb titres remaining significantly higher at least for 90 days. These data may directly impact middle- and low-income countries currently using CoronaVac as the main vaccination strategy. **Johanna Acevedo, Clin Microbiol Infect 2023;29:541.e1–541.e7**

© 2022 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author: Fernando Valiente-Echeverría, Laboratorio de Virología Molecular y Celular, Programa de Virología, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Independencia 1027, Independencia, Santiago, Región Metropolitana, Chile.

** Corresponding author: Alejandro Jara, Facultad de Matemáticas, Pontificia Universidad Católica de Chile, Av. Vicuña Mackenna 4860, Macul, Santiago, Región Metropolitana, Chile.

E-mail addresses: atjara@uc.cl (A. Jara), rsotorifo@uchile.cl, fvaliente@uchile.cl (F. Valiente-Echeverría).

 (F. Valiente-Echeverría)

Introduction

Waning humoral response, determined as a decline in circulating neutralizing antibodies (NABs) titres after a period, has been widely reported for individuals receiving any of the SARS-CoV-2 vaccines currently used to face the COVID-19 pandemic [1]. Some countries, including Chile, have implemented a booster dose first

<https://doi.org/10.1016/j.cmi.2022.11.017>

1198-743X/© 2022 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

focusing on the risk groups that include older adults and immunosuppressed patients, and then to the general population. This booster dose complemented the strong vaccination programme implemented in Chile, which was mainly performed with CoronaVac, an inactivated virus-based vaccine representing one of the most widely inoculated vaccines worldwide [2]. Several studies have shown that CoronaVac elicits lower levels of NAbs than other vaccine platforms with NAbs titres decreasing 3 to 6 months after inoculation [3]. However, studies in China and Chile have reported that inoculation with the third dose of CoronaVac is immunogenic indicating that a homologous booster is sufficient to recall a waned humoral response against SARS-CoV-2 [4,5].

Because boosters with heterologous platforms might provide improved immune responses [6–8], we conducted the clinical trial REFUERZO (NCT04992182), which was intended to compare the reactogenicity, safety, and immunogenicity of homologous versus heterologous (mRNA-based or viral vector-based) booster dose in individuals with a previous two-dose CoronaVac schedule in Chile.

Here, we report results of the immunogenicity arm, which determined NAbs titres in plasma, measured at baseline as well as 14-, 30-, 60- and 90-days after booster inoculation.

Methods

Study design and participants

We conducted a phase III, randomized, double-blind, placebo-controlled clinical trial for the inoculation of a booster dose with either the mRNA vaccine BNT162b2 or the recombinant adenoviral vectored vaccine ChAdOx1, compared with a homologous boost with the inactivated virus vaccine CoronaVac, in accordance with the booster vaccine policy implemented by the Chilean National Immunization Program (PNI).

This trial had 4 intervention arms, according to the planning of possible reinforcement schemes of the Chilean Ministry of Health (MINSAL). The intervention assignment was performed through a simple randomization strategy, 1:1, double-blind. Randomization was 4 interventions stratified into 2 groups according to the age criteria of the PNI booster dose policy (55 years or older and younger than 55 years). Intervention 1: participants over 55 years received a booster dose of ChAdOx1 (AstraZeneca). Intervention 2: participants under 55 years received a booster dose of CoronaVac. Intervention 3: participants over 18 years received a booster dose of BNT162b2 (Pfizer/BioNTech). Intervention 4 (comparison group): in participants older than 18 years, a placebo of 0.9% saline solution was applied. This group was inoculated with BNT162b2 (Pfizer/BioNTech) at day 30 of follow-up.

Ethical approval was given by the Scientific Ethics Committee of Universidad del Desarrollo (N° 2021-71) and Ethics Committee of the Faculty of Medicine at Universidad de Chile (Projects N° 0361-2021 and N° 096-2020). This study was authorized by the Institute of Public Health of Chile (N° 2021-71) and was conducted in accordance with the guidelines of the International Council for the Harmonization of Good Clinical Practices.

Participants were eligible if they were 18 years or older, had received their second dose of CoronaVac before 15 April 2021, and all participants had given written informed consent. Exclusion criteria were history of laboratory-confirmed COVID-19. The three study sites were in Santiago, Chile (older residents and healthcare workers (HCWs)) from long-stay establishments for the elderly (ELEAMs); HCWs from both Public Emergency Hospital (HUAP) and the MINSAL. Regarding the sampling framework, we defined ELEAMs with a cumulative infection attack rate of COVID-19 lower than 30% between residents and HCWs. Finally, there were instances of dissemination of information and awareness in each

ELEAM to publicize the study and motivate participation. In the case of older residents, the information was also extended to their families.

Fieldwork

HCWs from the PNI conducted the fieldwork on 14 ELEAMs and MINSAL. HCWs from the quality and patient safety unit of the HUAP conducted their fieldwork. Both fieldwork teams had overseen the immunization campaign against SARS-CoV-2 of their respective study sites.

At the baseline visit (day 0), volunteers participated in the written informed consent process and answered a health survey on personal history of sociodemographic characteristics and comorbidities. The history of previous infection and immunization were obtained from the databases of MINSAL. In this visit, a 4-mL blood sample was collected with the Venojet system, and the blind vaccine was applied to the participants.

During follow-up visits (days 14, 30, 60, and 90), the participants answered a brief survey about exposures to COVID-19, and then a blood sample of 4 ml was collected as indicated above. At least 2 follow-up visits were performed for each centre to increase the possibility that participants would be available at the time of the follow-up visit because of the shift system of HCWs.

Finally, a follow-up closure visit was made after all determinations of neutralizing antibody titres were obtained. The fieldwork teams visited the participants and confidentially delivered the results.

Randomization and blinding

We made 2 randomization lists for each age group in a 1:1 ratio of the 4 interventions. An electronic randomization system in software R Study was used to define the intervention, kept in envelopes sealed in the study sites. The design was double blinded for the HCWs who administered the vaccine, the participants, and the laboratory staff. Only the team in charge of preparing the vaccine had access to the information on the type of vaccine at the time of preparation.

Procedures/intervention

Intervention 1: each 0.5 mL dose contains 5×10^{10} viral particles (not less than 2.5×10^8 infectious units) of ChAdOx1-S (Recombinant chimpanzee adenovirus expressing the surface glycoprotein spike (S) of SARS-CoV-2). Intervention 2: each 0.5 mL dose of vaccine contains 600 SU of inactivated SARS-CoV-2 virus as antigen. Intervention 3: Each 0.3 mL dose of vaccine contains 30 µg of SARS-CoV-2 spike protein nucleoside-modified mRNA encapsulated in lipid nanoparticles. Intervention 4 (comparison group): Each dose of 0.5 ml of 0.9% saline. All vaccines were administered intramuscularly.

All blood samples were collected by qualified nursing staff, through the Venojet system, in a tube without anticoagulant, transported to the Laboratory of Molecular and Cellular Virology at Universidad de Chile and stored at 4 °C. NAbs titres were measured with an HIV-1-based SARS-CoV-2 pseudotype expressing the spike protein of the Wuhan reference strain (Wuhan-Hu-1) [9]. Results are presented as the value of 50% pseudovirus neutralization titres (pVNT₅₀).

Primary outcome and sample size

The primary outcome was the humoral immune response towards the spike protein of SARS-CoV-2 Wuhan-Hu-1, measured as

the change in the half-maximal inhibitory dilution (ID50) generated by the intramuscular administration of vaccines. The sample size was determined to detect differences between the mean ID50 at baseline and 30 days after the inoculation, with a statistical power of 80%, based on a t-test for paired samples.

Statistical analysis

We considered a random intercept model [10] to account for the correlation in the ID50 measurements across time within the same subject. Specifically, we assumed a linear mixed model with Gaussian error terms and Gaussian random intercept terms for the logarithm of the ID50. We did not assume a parametric form for the evolution of the ID50 measurements across time for each treatment group by considering treatment-specific intercept coefficients and the visit-treatment-specific slope coefficients. A Bayesian version of the model was considered [11]. Independent Gaussian prior distributions were considered for the treatment-specific intercept coefficients and for the visit-treatment-specific slope coefficients. Following Gelman [12], independent uniform prior distributions were considered for the standard deviation of the random intercepts and errors. Markov chain Monte Carlo techniques were employed for exploring the posterior distributions of interest.

For the model 120,000 scans of a single Markov chain cycle were completed. The full chain was subsampled every 10 steps after a burn-in period of 20,000 samples, to give a reduced chain of length 10,000. We used the rjags package [13] for R version 4.1.1 [14]. Standard tests, as implemented in the coda R package [15], suggested convergence of the chains. Observations outside the measurement range were treated as censored observations. Both missing and censored observations were treated as random variables. We reported the posterior inferences for the marginal means of the ID50 for each treatment group and visit.

The random intercept model is employed as a tool for taking into account the correlation of repeated measurements for the same subjects across time, which is necessary to properly estimate

the means of ID50 for each time point and for the correct estimation of the associated uncertainty measures. A random intercept model for log-normal responses generates regression coefficients with subject-specific interpretations. However, their results can be employed for estimating the population-average (not subject-specific) means of ID50 for each time point, which is done in the present article.

The statistical significance was based on a Bayesian counterpart to a frequentist p value, referred to as posterior contour probability [16]. In particular, we computed simultaneous credible regions for the differences between the means of the different time points, based on the order statistics approach described by Besag et al. [17], to obtain contour posterior probabilities for the null hypothesis of no differences.

Role of the funding source

The funders of this study had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of this manuscript, or in the decision to submit the paper for publication.

Results

The clinical trial REFUERZO (NCT04992182) included 534 participants with a prior two-dose schedule of CoronaVac (90–120 days after the second dose of CoronaVac) recruited in July 2021 from 3 centres in Santiago, Chile. From these, 523 volunteers were included in the study (Fig. 1). Missing observations were treated as missing at random and imputed as part of the Bayesian analysis, implemented via Markov chain Monte Carlo simulation. Details regarding cohort demographics are shown in Table 1.

Participants were randomly assigned to the following groups: (a) ChAdOx1 ($N = 127$); (b) CoronaVac ($N = 134$); (c) BNT162b2 ($N = 133$); and (d) placebo ($N = 129$). In addition, 388 participants completed the study at day 90 as follows: ChAdOx1 ($N = 111$); CoronaVac ($N = 91$); BNT162b2 ($N = 91$); and placebo ($N = 95$). The

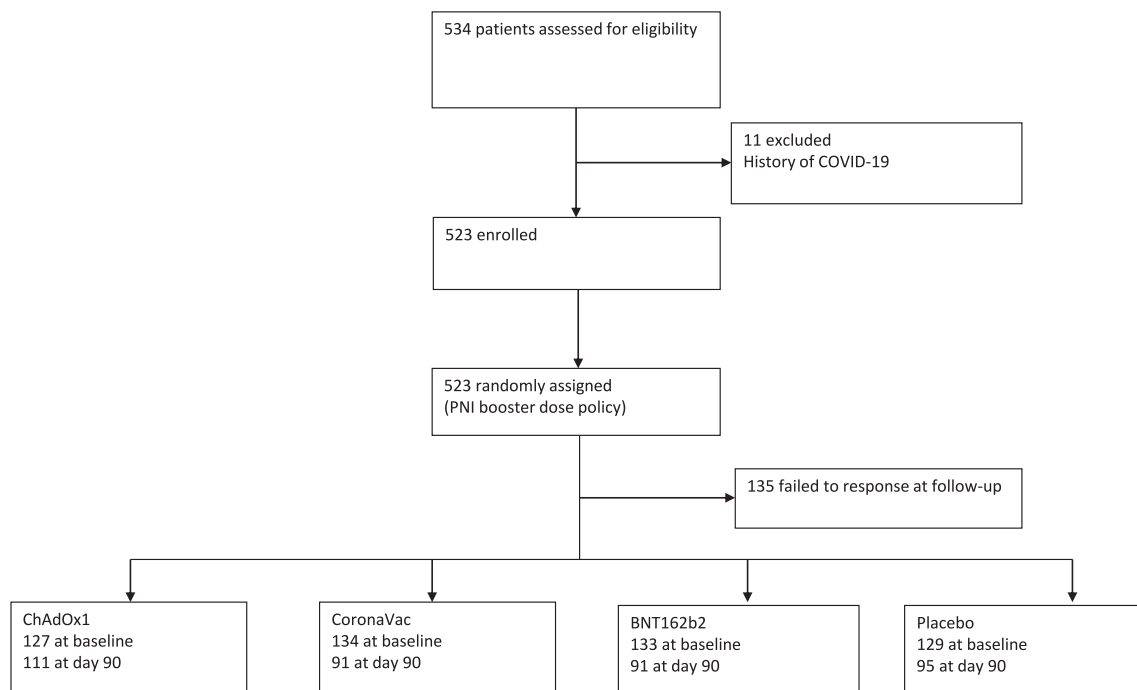
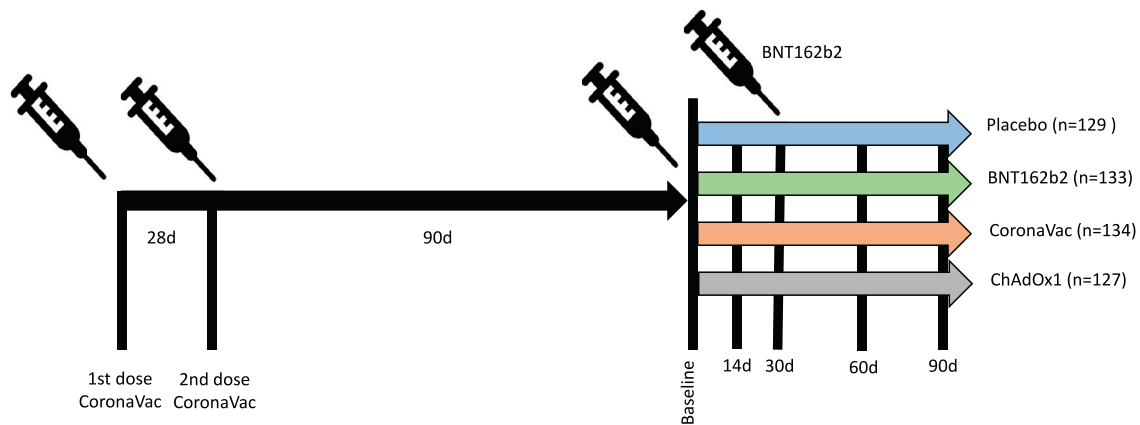


Fig. 1. Trial profile.

Table 1
Baseline characteristics of primary analysis population

	N	ChAdOx1	CoronaVac	BNT162b2	Placebo	P
Overall	523	127	134	133	129	
Study site						
ELEAM	291	115	47	67	62	
HUAP	146	8	51	46	41	
MINSAL	86	4	36	20	26	
Sex						
Female	372	67.72 %	70.15 %	75.19 %	71.32 %	0.6037
Age						
≥55 y	248	100,00 %	0,00	46,62	45,74	<0.0001
Median (SD)		77,5 (13,9)	36,6 (9,5)	52,6 (22,4)	53,6 (22,0)	
Medical history						
Heart attack	17	7.09 %	1.49 %	0.75 %	3.88 %	0.0210
Congestive heart failure	11	5.51 %	0.75 %	0.75 %	1.55 %	0.0380
Peripheral artery disease	8	1.57 %	0.00 %	1.50 %	3.10 %	0.2242
Stroke	10	3.94 %	1.49 %	1.50 %	0.78 %	0.3498
Chronic obstructive pulmonary disease	12	2.36 %	2.24 %	3.01 %	1.55 %	0.9239
Connective tissue disease	14	4.72 %	1.49 %	3.01 %	1.55 %	0.3672
Stomach ulcer	4	0.00 %	0.75 %	1.50 %	0.78 %	0.8060
Mild liver disease	10	1.58 %	1.49 %	2.56 %	2.33 %	0.9247
Moderate or severe liver disease	6	1.58 %	0.75 %	0.75 %	1.55 %	0.7757
Diabetes	50	18.11 %	2.24 %	9.02 %	9.30 %	0.0002
Diabetes mellitus	0	0.00 %	0.00 %	0.00 %	0.00 %	—
Hemiplegia	2	0.79 %	0.00 %	0.75 %	0.00 %	0.4915
Moderate or severe kidney disease	11	3.94 %	0.00 %	3.01 %	1.55 %	0.0804
Neoplasias	6	2.36 %	1.49 %	0.00 %	0.78 %	0.2850
Leukemias	1	0.00 %	0.00 %	0.00 %	0.78 %	0.4894
Lymphoma	1	0.00 %	0.00 %	0.75 %	0.00 %	0.7418
Cancer	0	0.00 %	0.00 %	0.00 %	0.00 %	—
AIDS	0	0.00 %	0.00 %	0.00 %	0.00 %	—
Hypertension	128	44.88 %	8.21 %	24.06 %	21.75 %	<0.0001
Disability	5	2.36 %	0.00 %	1.50 %	0.00 %	0.0872

**Fig. 2.** Protocol of the cohort and the randomized placebo-controlled clinical trial.

placebo group received a booster dose of BNT162b2 at day 30 (Fig. 2). On the day 90 follow-up, 135 participants failed to respond. Among them, we found 4 deaths not associated with vaccine administration, 15 ELEAM residents who left the residence, 18 HCWs who changed jobs, and 98 participants who were not available at the time of the follow-up visits (off duty or outside of the institution). Of note, we made at least 2 visits to each place.

The posterior mean (95% CI) for the intraclass correlation for the natural logarithm of the ID50 was 0.4986 (0.4943; 0.5004), suggesting a significant positive correlation among the measurements of the same subjects and justifying the use of a random intercept model. For all vaccines, the contour posterior probabilities for the null hypothesis of no differences among the means across time were <0.001, indicating significant differences among them.

Analyses of NABs titres using the pseudo typed virus (pVTN) showed that the placebo group only presented an increase in NABs geometric means titres at days 60 and 90, which is consistent with the BNT162b2 booster received at day 30 (Fig. 3a). A homologous booster dose induced 13.6-fold increase in the pVNT from 243.7 (95% CI, 189.3–308.7) to 3298.5 (95% CI, 2559.9–4192.2) at day 14 after inoculation (Table 2 and Table 3). NABs titres in the CoronaVac group presented a slight decrease in the pVNT to 2935.7 (95% CI, 2284.5–3712.5) at day 30 but strongly declined to 725.2 (95% CI, 560.2–923.4) by day 60. These NABs titres further decreased to 492.8 (95% CI, 371.2–639.0) by day 90 reaching only 2.03-fold higher than the baseline (Fig. 3b). For the BNT162b2 group, we observed a 249.1-fold increase in pVNT from 207.4 (95% CI, 161.1–264.6) to 51,306.6 (95% CI, 38,818.8–66 109.9) at 14 days

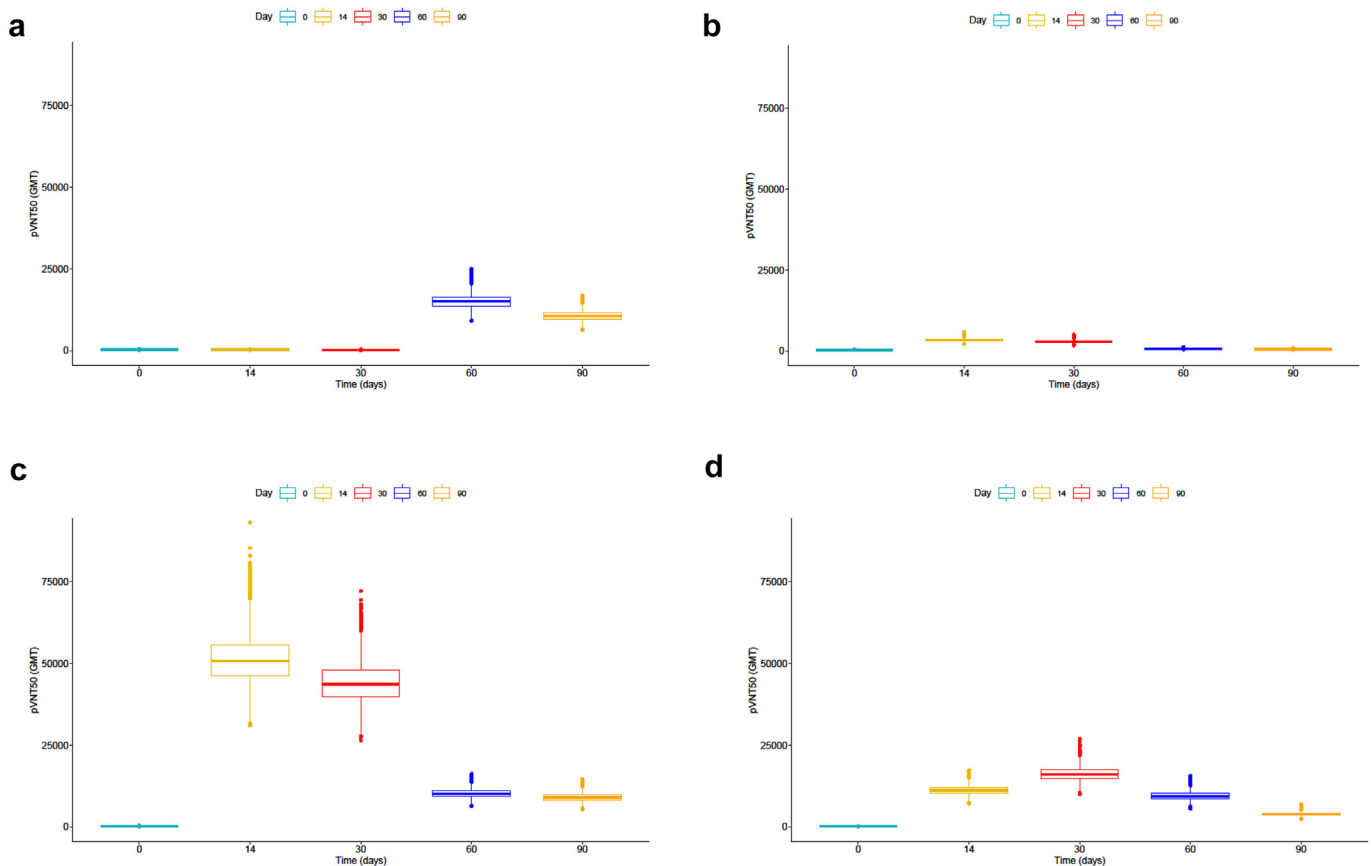


Fig. 3. Pseudovirus neutralization before and 14, 30, 60 and 90 days after vaccination by booster vaccine allocation. (a) Placebo; (b) CoronaVac; (c) BNT162b2; and (d) ChAdOx1. Boxplots summarizing the posterior distribution of the pVNT50 (Geometric means titres - GMT) at the different time points (0 Baseline, 14, 30, 60 and 90 days). See [Tables 2 and 3](#) for summary statistics and comparisons.

after inoculation of the booster dose ([Fig. 3c](#)). NAb titres were maintained at day 30 with a pVNT of 44,035.7 (95% CI, 33,457.8–56,968.8) but decreased by 4.3-fold to 10,185.7 (95% CI, 7779.6–13,104.8) at day 60. Interestingly, NAb titres were maintained at day 90 after inoculation with a pVNT of 9032.3 (95% CI, 6830–11,761.1) remaining 43.8-fold higher than that of the baseline ([Fig. 3c](#)). Similar to what we observed with the mRNA vaccine booster, inoculation of the viral vector vaccine ChAdOx1 resulted in an 89.9-fold increase in the pVNT from 126.8 (95% CI, 97.4–161.2) to 11,292.2 (95% CI, 8681.3–14,452.1) at day 14 after inoculation ([Fig. 3d](#)). The pVNT was slightly increased to 16,242.3 (95% CI, 12,473.9–20,855.7) at day 30 and then decreased to 9440.3 (95% CI, 7266.1–12,159.8) at day 60 and to 3882.8 (95% CI, 2973.5–4994.6) at day 90 ([Fig. 3d](#)). Despite this waning, NAb titres in the ChAdOx1 group remained 30.9-fold higher than that at baseline ([Fig. 3d](#)).

Discussion

CoronaVac was one of the most widely inoculated COVID-19 vaccine as an initial protocol but also as a booster in some countries. However, previous studies have raised concerns about the ability of this inactivated virus vaccine to trigger a potent humoral response as it elicits lower NAb titres than mRNA vaccines [18]. Moreover, these low NAb titres were shown to decrease 3 to 6 months after completion of the initial two-dose schedule raising the necessity of booster doses, particularly for high-risk groups. Despite these apparent low levels of NAb elicited by CoronaVac, a nation-wide study conducted in Chile for the two-dose schedule

showed an effectiveness of 65.9% (IC 95%, 65.2–66.6) in preventing infections; 87.5% (IC 95%, 86.7–88.2) in preventing hospitalizations and 86.3% (IC 95%, 84.5–87.9) in preventing COVID-19-related deaths [19]. This effectiveness was achieved under a predominant circulation of the variant of concern Gamma and the variant of interest Lambda, which were characterized by the presence of mutations allowing escape to NAb [19,20]. A more recent nationwide study from Chile evaluating the effectiveness of the CoronaVac booster dose revealed a 78.8% (IC 95%, 76.8–80.6) in preventing symptomatic infections, whereas it was 96.5% (IC 95%, 96.2–96.7) for the BNT162b2 booster and 93.2% (IC 95%, 92.9–93.6) for ChAdOx1 [21]. The vaccine effectiveness against hospitalization, intensive care unit admission, and COVID-19 related deaths was 86.3%, 92.2%, and 86.7%, respectively, for a three-dose schedule with CoronaVac; 96.1%, 96.2%, and 96.8% for BNT162b2 booster; and 97.7%, 98.9%, and 98.1% for ChAdOx1 booster [21]. Because the booster dose in Chile has been mostly administered with BNT162b2 (<55 years old) and to a lesser extent with ChAdOx1 (>55 years old), our data of NAb titres may provide an explanation to the success of the booster dose programme, which occurred when the Delta variant was predominant. The differences in the effectiveness of the booster schemes followed in Chile combined with the analysis of NAb titres described in this work provide further evidence for the use of NAb titres as a correlate of protection against the development of symptomatic infection, hospitalization, and death.

One of the limitations of this study is that we have not evaluated the impact of booster doses on cellular immune responses, which

Table 2
Mean (95% CI) of the geometric mean of the ID50, according to day and vaccination group

	Baseline	14d	30 d	60 d	90 d
ChAdOx1	126.8 (97.4; 161.2)	11,292.2 (8681.3;14,452.1)	16,242.3 (12,473.9; 20,855.7)	9440.3 (7266.1; 12,159.8)	3882.8 (2973.5; 4994.6)
CoronaVac	243.7 (189.3; 308.7)	3298.5 (2559.9; 4192.2)	2935.7 (2284.5; 3712.5)	725.2 (560.2; 923.4)	492.8 (371.2; 639.0)
BNT162b2	207.4 (161.1; 264.6)	51,306.6 (38,818.8; 66,109.9)	44,035.7 (33,457.8; 56,968.8)	10,185.7 (7779.6; 13,104.8)	9032.3 (6830.0; 11,761.1)
Placebo	248.7 (192.7; 316.2)	236.6 (183.2; 303.6)	202.8 (155.3; 259.9)	15,066.5 (11,421.1; 19,444.9)	10,625.4 (7989.0; 13,862.4)

ID50, half-maximal inhibitory dilution.

Table 3
Mean (95% CI) of the fold increase, with respect to the baseline value, of the geometric mean of ID50 for different days and vaccination groups

Group	Day			
	14	30	60	90
ChAdOx1	89.9521 (69.4405; 114.8099)	129.4050 (98.9828; 166.4937)	75.3126 (57.9771; 96.7833)	30.9045 (23.5561; 39.8468)
CoronaVac	13.6291 (10.6190; 17.2913)	12.1218 (9.4187; 15.4561)	3.0035 (2.2970; 3.8591)	2.0361 (1.5333; 2.6519)
BNT162b2	249.1058 (186.6250; 325.5506)	214.2830 (160.7243; 280.5830)	49.3832 (37.3716; 64.4371)	43.8427 (32.7607; 57.7167)
Placebo	0.9579 (0.7326; 1.2345)	0.8225 (0.6207; 1.0611)	61.0175 (45.8376; 79.9135)	43.0150 (32.1751; 56.7965)

ID50, half-maximal inhibitory dilution.

has been recently shown in recipients of 2 or 3 doses of CoronaVac [3,22]. Moreover, we have not investigated the impact of any of the subvariants of Omicron on the neutralizing capacity of antibodies elicited by the homologous and heterologous booster doses analysed in our cohort. In this sense, 2 recent reports suggested that antibodies elicited by the two-dose schedule of CoronaVac did not provide neutralizing ability against the Omicron BA.1 subvariant and that a heterologous booster with mRNA vaccines should be preferred over an homologous booster [23–25]. Our data are in line with these observations as we showed that a heterologous booster in CoronaVac vaccines provided a stronger and lasting humoral response. Our data may have direct implications for those middle- and low-income countries currently using CoronaVac as the main vaccination strategy.

Author contributions

J.A., A.J., R.A., C.G., P.P., S.J., R.S-R. and F.V-E. designed the study. D.E., S.R., P.P. and S.J. provided clinical samples. M.L.A. and A.G.A. performed experiments with pseudotyped viruses. A.J., A.G-A., and F.V-E. performed statistical analysis. A.J., F.V-E., J.A. and R.S.R wrote the manuscript. F.V-E, J.A. and RSR acquired funding. All authors approved the final version of the manuscript.

Transparency declaration

The authors declare that they have no conflicts of interest.

Funding

This research was supported by the Agencia Nacional de Investigación y Desarrollo, Chile through Fondecyt grants N° 1190156 (R.S-R.), 1211547 (F.V.-E.), 1180640 (A.J.), 1211643 (A.J.), and Millennium Science Initiative Program - Millennium Nucleus Center for the Discovery of Structures in Complex Data (MiDaS) grant N° NCN17_059 (A.J) and ANID - ICM, ICN2021_045 (R.S-R).

Acknowledgements

The authors thank all the volunteers for participating in this study. The authors also thank Joseline Catrileo (Universidad de Chile), Dina Silva (Universidad de Chile), and HCWs from PNI and HUAP for technical support and sample collection.

References

- [1] Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;27:1205–11. <https://doi.org/10.1038/s41591-021-01377-8>.
- [2] Mallapaty S. China's COVID vaccines have been crucial – now immunity is waning. *Nature* 2021;598:398–9. <https://doi.org/10.1038/d41586-021-02796-w>.
- [3] Schultz BM, Melo-González F, Duarte LF, Gálvez NMS, Pacheco GA, Soto JA, et al. A booster dose of coronavac increases neutralizing antibodies and T cells that recognize Delta and Omicron variants of concern. *mBio* 2022;13:e0142322. <https://doi.org/10.1128/mbio.01423-22>.
- [4] Cao Y, Hao X, Wang X, Wu Q, Song R, Zhao D, et al. Humoral immunogenicity and reactogenicity of CoronaVac or ZF2001 booster after two doses of inactivated vaccine. *Cell Res* 2022;32:107–9. <https://doi.org/10.1038/s41422-021-00596-5>.
- [5] Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. *Lancet Infect Dis* 2022;22:483–95. [https://doi.org/10.1016/S1473-3099\(21\)00681-2](https://doi.org/10.1016/S1473-3099(21)00681-2).
- [6] Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. *N Engl J Med* 2022;386:1046–57. <https://doi.org/10.1056/NEJMoa2116414>.
- [7] Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, Flores-Ortiz R, Júnior JB, Paixão ES, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. *Nat Med* 2022;28:838–43.
- [8] Mayr FB, Talisa VB, Shaikh O, Yende S, Butt AA. Butt, effectiveness of homologous or heterologous Covid-19 boosters in veterans. *N Engl J Med* 2022;386:1375–7.
- [9] Beltrán-Pavez C, Riquelme-Barrios S, Oyarzún-Arrau A, Gaete-Argel A, González-Stegmaier R, Cereceda-Solis K, et al. Insights into neutralizing antibody responses in individuals exposed to SARS-CoV-2 in Chile. *Sci Adv* 2021;7. <https://doi.org/10.1126/sciadv.abe6855>.
- [10] Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data*. New York: Springer; 2000.
- [11] Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. *Bayesian data analysis*. 3rd ed. Chapman & Hall/CRC; 2013.
- [12] Gelman A. Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). *Bayesian Anal* 2006;1:515–34. <https://doi.org/10.1214/06-BA117A>.

- [13] Plummer M. rjags: bayesian graphical models using MCMC. 2019 (Version 4–10) [Software].
- [14] Team RCR. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021 [software], version 4.0.5.
- [15] Plummer M, Best N, Cowles K, Vines K. CODA: convergence diagnosis and output analysis for MCMC. 2006.
- [16] Lesaffre E, Lawson A. Bayesian biostatistics. Chichester, West Sussex: Wiley; 2012.
- [17] Besag J, Green P, Higdon D, Mengersen K. Bayesian computation and stochastic systems. *Stat Sci* 1995;10:3–41. <http://www.jstor.org/stable/2246224>.
- [18] Lim WW, Mak L, Leung GM, Cowling BJ, Peiris M. Comparative immunogenicity of mRNA and inactivated vaccines against COVID-19. *Lancet Microbe* 2021;9:e423. [https://doi.org/10.1016/s2666-5247\(21\)00177-4](https://doi.org/10.1016/s2666-5247(21)00177-4).
- [19] Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med* 2021;385:875–84. <https://doi.org/10.1056/NEJMoa2107715>.
- [20] Acevedo ML, Gaete-Argel A, Alonso-Palomares L, de Oca MM, Bustamante A, Gaggero A, et al. Differential neutralizing antibody responses elicited by CoronaVac and BNT162b2 against SARS-CoV-2 Lambda in Chile. *Nat Microbiol* 2022;7:524–9. <https://doi.org/10.1038/s41564-022-01092-1>.
- [21] Jara A, Undurraga EA, Zubizarreta JR, González C, Pizarro A, Acevedo J, et al. Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study. *Lancet Glob Health* 2022;10:e798–806. [https://doi.org/10.1016/S2214-109X\(22\)00112-7](https://doi.org/10.1016/S2214-109X(22)00112-7).
- [22] Bueno SM, Abarca K, Gonzalez PA, Galvez NMS, Soto JA, Duarte LF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in a subgroup of healthy adults in Chile. *Clin Infect Dis* 2021;75:e792–804. <https://doi.org/10.1093/cid/ciab823>.
- [23] Cheng SMS, Mok CKP, Leung YWY, Ng SS, Chan KCK, Ko FW, et al. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med* 2022;28:486–9. <https://doi.org/10.1038/s41591-022-01704-7>.
- [24] Costa Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silveira MBV, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. *Lancet* 2022;399:521–9. [https://doi.org/10.1016/S0140-6736\(22\)00094-0](https://doi.org/10.1016/S0140-6736(22)00094-0).
- [25] Pérez-Then E, Lucas C, Monteiro VS, Miric M, Brache V, Cochon L, et al. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. *Nat Med* 2022;28:481–5. <https://doi.org/10.1038/s41591-022-01705-6>.