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Factors influencing neutralizing antibody response to the original SARS-CoV-2 virus and the Omicron variant in a high vaccination coverage country, a population-based study

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ABSTRACT

Objective: The study compared immunity to the original SARS-CoV-2 virus (Wuhan) and the Omicron variant using neutralizing antibodies (NAbs), that provide a good approximation of protective immunity. The results might help determine immunization strategies. Design and methods: Unlike previous studies, we analyzed NAbs in a random sample of 110 IgG positive sera from individuals who participated in a population-based seroprevalence transversal study, carried out in May 2022 in two Chilean cities, a country with high vaccination coverage. Results: Our findings indicate that 98.2% of individuals had NAbs against Wuhan, 65.5% against Omicron, and 32.7% tested positive for Wuhan but not Omicron. Factors influencing protective immunity included a prior natural infection and the number of vaccines received. NAbs titers against the original virus were high, demonstrating vaccine effectiveness in the population. However, the level of antibodies decreased when measuring NAbs against Omicron, particularly among older individuals, indicating a decline in vaccine protection. Previous COVID-19 episodes acted as a natural booster, increasing NAbs titers against both virus strains. Conclusions: Protective immunity against the original Wuhan SARS-CoV-2 virus is reduced when compared to Omicron variant. Updating vaccine to target emerging variants and continued monitoring of effectiveness at the population level are necessary.

Introduction

In the last two and a half years, the SARS-CoV-2 pandemic has impacted the population through multiple waves of transmission, revealing a cyclical nature of the infection. It continues to have a global-scale economic and social impact [1]. These successive waves have been accompanied by the emergence of variants, such as Omicron which has been classified as a Variant of Concern (VOC) by the end of 2021 [2]. Despite their higher transmissibility, there has been a trend towards reduced clinical severity, observed in cases associated with these variants, along with immune evasion. However, it is important to emphasize the remarkable scientific effort that has facilitated the accelerated development and roll out of vaccines within a record time. With the exception of the CoronaVac vaccine (whole virus inactivated), all others SARS-CoV-2 vaccines specifically target the Spike (S) protein of the virus. Evading a portion of the humoral immune response directed at the

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original S protein [3] has been one of the characteristics of some of the VOCs. This is primarily due to SARS-CoV-2 being a virus with a high mutation rate [4], significantly reducing neutralization even in fully vaccinated individuals and amplifying the waning of humoral immunity caused by vaccination [5]. Meanwhile, other studies have suggested that gradual decline in vaccine effectiveness might be due waning immunity rather than immunological escape [6]. This highlights the importance of effective surveillance of vaccines efficacy, treatment, and control measures to mitigate the spread of this infectious disease and its consequences.

The Omicron variant currently predominates worldwide, with the BA.5 variant presenting a high resistance to vaccines that challenges the fight against COVID-19 [7]. Consequently, it is crucial to study the efficacy of vaccines against Omicron subvariants or other VOCs with epidemic potential in order to continue preventing the global spread of SARS-CoV-2 virus, especially in Chile were a CoronaVac vaccine was used as a primary scheme in over than 90% of the vaccinated population [8].

Neutralizing antibodies (NAbs) serve as highly predictive indicators of immune protection, providing evidence of both the immune response and vaccine efficacy [6]. Therefore, NAbs titers are a surrogate marker of protection. Studying immunity against the original strain and new VOCs of SARS-CoV-2, such as Omicron, is essential to ensure that new vaccines provide broad coverage against multiple virus strains, primarily based on their specificity. Additionally, the order in which vaccines are administered against different epitopes, whether designed from the original strain or all VOCs, is also a crucial molecular aspect when selecting the best population vaccination scheme [7].

Chile grants a unique case for understanding the relationship between immunization and predominant variants due to its high incidence during the initial waves and extensive immunization coverage. During the study period, the vaccination coverage in Chile with the primary schedule reached approximately 90%. Besides, over 60% of the population had received a first and/or a second booster dose [8]. Seroprevalence studies conducted by the same researchers showed that the prevalence of IgG antibodies against the original SARS-CoV-2 strain reached 98% six months after vaccine roll out, the seropositivity among participants who did not receive any booster after the full baseline scheme dropped to 75% after 6 months of the last dose. However, it was significantly lower in those who received only one dose of vaccine or the basic vaccination scheme, and seroprevalence varied depending on the type of vaccine administered [8]. Seroprevalence was also high in Chilean children, who were early vaccinated in the country [9]. Despite this, all vaccine formulas used until the time of the research contained the original virus (Wuhan), while the circulating virus was predominantly the Omicron variant, according to the genomic surveillance conducted by the Chilean Ministry of Health [10]. In this study, the purpose was to compare the levels of NAbs titer against both original Wuhan and Omicron variants of SARS-CoV-2 in a population-based sample of Chilean individuals vaccinated with heterologous schemes or not vaccinated. Additionally, we aimed to explore variables related to a hypothetical lower humoral immunity against the Omicron variant.

Methods

Participants in this investigation were randomly selected from a population-based seroprevalence study of SARS-CoV-2 conducted in two cities of Chile (La Serena-Coquimbo and Talca). In April and May 2022, a total of 853 participants aged 7 years and older were invited to participate [8]. For the measurement of NAbs, only seropositive samples for IgG against SARS-Cov-2 were selected, which corresponded to 839 people (98.4% seroprevalence in the sample). The ELISA test against the Wuhan variant, used for all analyzed samples, has been previously described by Amanat et al. [11]. Our laboratory standardized and used the same test, using pre-pandemic patient sera as negative controls and sera from confirmed PCR-positive patients with symptoms of COVID-19 as positive controls [12,13]. Among the IgG seropositive serum, we included all samples from non-vaccinated individuals (n = 10) and 100 individuals selected randomly. Half of these randomly selected individuals (50%) had completed the full primary vaccination scheme and received one booster, while the remaining 50% had received the full primary scheme and two boosters.

The objective of including unvaccinated individuals was to assess the degree of protective humoral immunity left by natural infection, considering that they were unvaccinated but tested seropositive for ELISA.

Serum neutralization capacity against the original Wuhan strain was measured using a pseudotyped vesicular stomatitis virus, plus coding the enhanced green fluorescent protein (eGFP) as a reporter gene (VSV-GFP-Spike SARS-CoV-2 original Wuhan strain) [14,15]. To measure NAbs against the Omicron variant, we used a VSV Pseudotyped ΔG-GFP rVSV decorated with Omicron spike protein of SARS-CoV-2, which has been generated according to a modified protocol from the manufacturer (Kerafast) [16]. Briefly, serially diluted serum previously incubated with pseudovirus VSV-GFP-Spike SARS-CoV-2 was transferred into a HeK293-T ACE2-TMPRSS2 cell monolayer at a final multiplicity of infection of 0.5 and incubated at 37 °C 5% CO2 for 18 to 20 h. The infection was measured in each well by determining GFP + cells from 16 acquired images using a Cytation3 plate reader and counting in an automated manner using Fiji software. In the NAbs assay, the degree of infection or neutralization is evidenced by the expression of the GFP protein incorporated into the genome of pseudo virus. A 100% infection corresponds to more than 50% of the infected cells in a well, resulting in fluorescence intensity values greater than 4000 for Wuhan. In the case of Omicron, a number above 3500 GFP-positive cells correspond to 100% infection. Sera from pre-pandemic patients who do not show any neutralization against the pseudo viruses were used as negative controls. Additionally, Anti-VSV-G protein antibody (AMBF2321-Merck, USA) was used as a quality control, and wells with non-infected cells were used as a background signal control. The NAbs unit used is the reciprocal of the IC50 (1/IC50). IC50 (half-maximal inhibitory concentration) is defined as the dilution of an antibody required to inhibit 50% of viral infection. The IC50 was calculated by nonlinear regression analysis in Graphpad prism V9 software, and all measurements were made with technical replicates by triplicate.

Categorical variables were described using proportions. To assess differences between variables and the Omicron and Wuhan neutralizing antibodies, either chi-square or Pearson's test was used. Bivariate analysis was conducted to compare the variables of interest with the reciprocal of the half maximal inhibitory concentration (IC50) of NAbs titers against the Omicron and Wuhan strains, using Mann-Whitney and Kruskal-Wallis tests, depending on the variable categories. A multivariate linear regression model was applied for the reciprocal of the IC50 of the NAbs titers against the original version of the virus (Wuhan) and the Omicron variant, as well as their logarithm, given their non-normal distribution. The variables introduced in the regression model were those that resulted statistically significant in the bivariate analysis or were relevant in previous literature. Those were age, sex, history of COVID-19, number of vaccine boosters and time elapse since the last vaccine dose. Statistical significance was defined as $p < 0.05$. All analyses were conducted using Stata V15 software.

Results

All participants included in the study had previously tested positive for IgG antibodies against SARS-CoV-2 virus using ELISA tests. Among the 110 selected sera, 52.7% were from the Coquimbo-La Serena. Of the participants, 64.5% were women, and 70.9% were over 40 years of age (Table 1). Furthermore, 83.3% were affiliated to the public health system and 25.2% had completed higher education. The majority of participants (71.3%) were overweight or obese according to their BMI. There were no significant differences in seropositivity for the Wuhan

Table 1
Characteristics of the individuals who were analyzed for neutralizing antibodies against the original strain (Wuhan) and Omicron variant. Two Chilean cities, May 2022.

Variable		n	%
Total sample		110	
City	Coquimbo-La Serena	58	52,7
	Talca	52	47,3
Sex	Male	39	35,5
	Female	71	64,5
Age	7–19 years	4	3,6
	20–49 years	43	39,1
	50–69 years	40	36,4
	70 or more	23	20,9
Country of birth	Chilean	109	99,1
	Foreigner	1	0,9
Ethnic background	Yes	7	6,4
	No	103	93,6
Medical Insurance	Public insurance (FONASA)	92	83,3
	Private insurance (ISAPRE)	11	10,7
Education (Individuals older than 7 years, n = 107)	Elementary education and lower	20	18,7
	High school education	60	56,1
	Technical education	7	6,5
	University	20	18,7
Nutritional status based on BMI (n = 101)	Malnourished	6	5,9
	Normal	23	22,8
	Overweight	37	36,6
	Obese	35	34,7
Comorbidities	Yes	68	61,8
Smoking habits	Smoker	29	26,4
On-site worker	Yes	54	49,1
Health worker (n = 54)	Yes	8	14,8

strain among age groups, although there were significant differences observed for the Omicron variant (data in supplementary material). The seropositivity in the 7–19 age group was 75% for both the original Wuhan strain and the Omicron variant (note that this age group only had 4 individuals). However, for the other age groups, seropositivity for the Wuhan strain was over 97%, while for the Omicron variant, remained around 70%, except for the over 70 age group, where it dropped to 39.1% (p = 0.033).

Table 2 shows that around 21.8% reported a previous diagnosis of COVID-19, and 8.3% of these experienced the disease twice. Ten of the participants had not received any vaccines. Among those who received one booster, the predominant vaccination scheme was Sinovac-Sinovac-Pfizer (S-S-P; 42%), followed by P-P-P (36%). On the other hand, among those who received two boosters, the Sinovac-Sinovac-AstraZeneca-Pfizer (S-S-A-P) scheme was more prevalent (46%).

Among the analyzed sample, 98.2% were positive for neutralizing antibodies (NAbs) against the Wuhan strain, while the NAbs seropositivity against the Omicron variant was 65.5%. All individuals who tested positive for Omicron also tested positive for the Wuhan strain. A 32.7% tested positive for the Wuhan strain but not for Omicron, and only 1.8% were seronegative for both variants. Seropositivity for the original Wuhan strain was similar among individuals with and without a history of COVID-19 (diagnosed by PCR). In contrast, for the Omicron variant, those who had the disease had higher seropositivity (p = 0.029). Significant differences were observed in seropositivity for the Wuhan strain based on vaccination status, with 100% NAbs seropositivity in vaccinated individuals compared to 80% in those unvaccinated (p = 0.008). However, this difference was not observed for the Omicron variant. Additionally, significant differences were observed for both neutralizing antibodies based on the number of vaccine doses administered. Seropositivity for the Wuhan strain was 100% in individuals who received the complete primary vaccination scheme plus 1 or 2 booster doses. In contrast, for the Omicron variant, unvaccinated participants had similar seropositivity to those who received the complete basal scheme with 1 booster (50% and 54%, respectively). Higher seropositivity (82%) was observed in the group that received the complete basal scheme with 2 boosters (p = 0.013).

Table 3 shows that only 7 out of 24 (30%) individuals experienced the disease prior to December 2021, which was the time when Omicron was identified as circulating in the community [17]. The distribution of NAbs positivity did not show any variation between the original strain and Omicron when the history of having had the disease was after December. However, before that date, 100% of the sera tested positive for NAbs against the original strain, and only 57% presented NAbs against Omicron.

We also conducted an analysis of NAbs titers by comparing their half maximal inhibitory concentration (IC50) measurement between Wuhan and Omicron for the same individual. We observed that NAbs titers were

Table 2
Comparison of clinical and vaccination characteristics of the individuals who were analyzed for neutralizing antibodies against the original strain (Wuhan) and Omicron variant. Two Chilean cities, May 2022.

		Wuhan (n = 110)			Omicron (n = 110)		
Variable		Positive cases	%	p-value	Positive cases	%	p-value
Previous diagnoses of COVID-19	No	85	98,8	0,39	52	60,5	0,029
	Yes	23	95,8		20	83,3	
Two episodes of COVID-19 (n = 24)	No	21	95,5	0,917	18	81,8	0,688
	Yes	2	100		2	100	
At least one vaccine	No	8	80	0,008	5	50	0,229
	Yes	100	100		67	67	
Vaccine Scheme	No vaccine	8	80	0,008	5	50	0,013
	Full scheme + booster	50	100		27	54	
	Full scheme + 2 boosters	50	100		40	80	
Full scheme + booster	P -P - P	18	100		10	55,6	0,281
	S - S - P	21	100		13	61,9	
	S - S - A	6	100		1	16,7	
	Other	5	100		3	60	
Full scheme + 2 boosters	P - P - P -P	7	100		6	85,7	0,245
	S- S - P -P	13	100		12	92,3	
	S - S - A -P	23	100		15	65,2	
	P - P - P - M	2	100		2	100	
	Other	5	100		5	100	
Time elapsed since the last vaccine	Less than 15 days	13	100		12	92,3	0,066
	15 to 179 days	75	100		49	65,3	
	180 or more days	12	100		59	50	

P = Pfizer/ S = CoronaVac/A = AstraZeneca/M = Moderna. P-value refers to Chi Square Test.

Table 3
Distribution of NAbs results against Wuhan strain and the Omicron variant, according to history of having COVID-19 and the period of the Omicron variant circulation in Chile (December 2021).

History of COVID-19 diagnose	Neutralizing antibodies against Wuhan (n = 24)		Neutralizing antibodies against Omicron (n = 24)	
	Positive n (%)	Negative n (%)	Positive n (%)	Negative n (%)
Before December 2021	7 (100%)	0	4 (57,1%)	3 (42,9%)
From December 2021 onwards	16 (94,1%)	1 (5,9%)	16 (94,1%)	1 (5,9%)
p value (Chi square test)	0,512		0,027	

lower against Omicron compared to Wuhan (Fig. 1). Correlation of IgG and neutralising antibody titres for the original version of the virus (Wuhan) and the Omicron variant is presented in supplementary material.

Fig. 2 presents a separate comparison of NAbs titers for the original variant of the SARS-CoV-2 virus and the Omicron variant based on the received vaccination scheme. We observed significant differences of NAbs levels related to the number of doses administered for both strains. For the Wuhan original virus, administering one booster increased the median of neutralizing antibodies by 24 times compared to having no vaccine (a natural infection), and doubled it compared if 2 boosters were administered (Fig. 2 left panel). In contrast, for the Omicron variant, having one booster only increased the median by a factor of two compared to having no vaccine, and in turn, increased it by 2.8 compared to having one vaccine booster (Fig. 2 right panel).

Finally, we performed a multivariate linear regression to model the variables associated with the level of NAbs, measured by the reciprocal of the IC50 and its logarithm (Table 4). We found that the variables

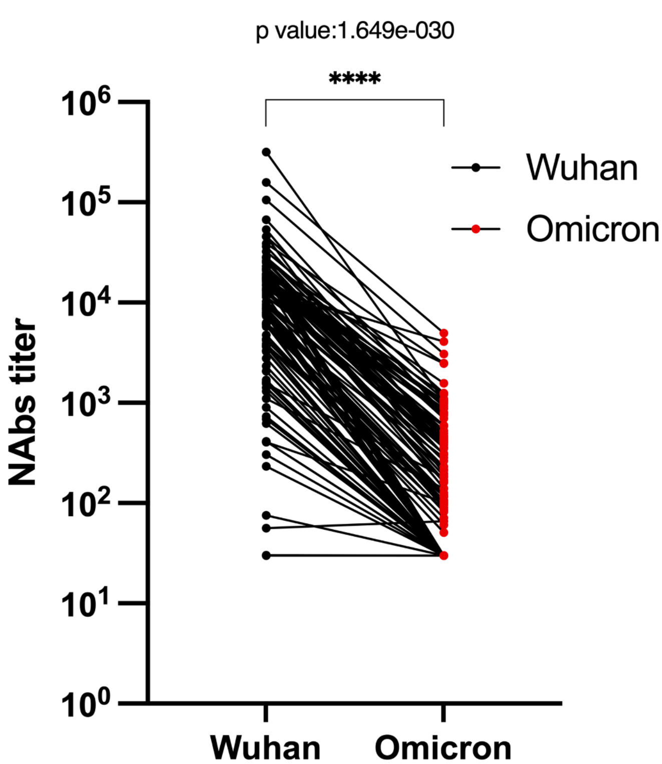

Fig. 1. NAbs titers for Omicron Spike variant in comparison to Wuhan original strain in the same individual from a representative sample of Chilean population. The graph shows the differences of the reciprocal IC50 values of NAbs against Wuhan and Omicron strains in a log scale, for each of the sera sample. Mann-Whitney test, P value <0.0001(****).

influencing the level of NAbs against the original version of the virus (Wuhan) were a recent history of having the disease and receiving the basic scheme plus two boosters. Additionally, for NAbs against Omicron, individuals over 70 years showed lower protective humoral immunity against the Omicron variant only.

Discussion

The main findings of the study shows that the level of NAbs against SARS-CoV-2 Omicron variant is significantly lower compared to the level of NAbs against its original Wuhan strain of the virus within the same group of individuals, who previously tested seropositive for IgG antibodies through ELISA testing.

Consistent with previous studies, the variables that influence humoral protective immunity are related to the history of prior infection (naturally acquired immunity) and the number of vaccine doses received (passively acquired immunity) [18]. The results regarding NAbs against the original Wuhan strain show that the vaccine boosters effectively increase antibody levels in individuals. However, when evaluating the administration of one or two booster, this increase was significant only for individuals without a history of infection. On the other hand, for individuals who had previously contracted COVID-19, the natural infection acted as a natural booster, narrowing the differences in Nabs levels compared to those who received one or two vaccination boosters. Notably, previous studies have shown that SARS-CoV-2 induces long-lived B plasma cells that produce stable but low concentrations of antibodies up to a year later [19]. Vaccination in convalescent individuals is suggested to restore pre-existing memory B cells against SARS-CoV-2, leading to an increase in the maturation and affinity of NAbs [20], which may explain the observed differences between the groups. Notably, this effect is strain-in dependent when comparing Wuhan and Omicron, consistent with previous reports [18].

Specifically, for NAbs titers against the Omicron variant, age also influences the individual levels. This finding could be attributed to older people having lower exposure to the virus due to their avoidance of risky situations and their adherence to protection measures such as the mask usage. A second explanation could be a decline in the neutralizing capacity of the immune response over time among individuals of this age group. This aligns with other studies that have found that lower NAbs titers against RBD-Domain in mRNA vaccines platforms among elderly [21]. Conversely, there are also studies describing higher NAbs titers in older patients who have recovered from COVID-19 [22]. It should be noted that significant differences in NAbs titers among age groups were only observed in relation to the Omicron variant. In a population with high vaccination coverage, like the Chilean population, the overall seroprevalence found is also high, making it challenging to identify factors that discriminate between risk groups. However, this effect is not evident when evaluating NAbs against Omicron. Since the initially used vaccines were formulated based on the original variant of the virus, they appear to be less protective against this emerging variant, particularly for older people, as previously discussed.

Regarding the relationship between the presence of NAbs and the history of COVID-19, out of the study group, 24 individuals had experienced the disease. Among them, 7 had the disease before Omicron was identified as a circulating variant of concern (VOC) in the country. It is worth to note that 57% of these individuals exhibited the presence of NAbs against Omicron. This could be attributed to two possibilities. Firstly, it is possible that this variant began circulating before it was detected by the variant surveillance system. Secondly, individuals may have had the disease asymptomatically or not confirmed by PCR (which was the reporting method in our survey). The first explanation is related to the rapid expansion speed associated with this variant [2] which would affect the timely detection of the existing surveillance system. The second explanation for the presence of NAbs against Omicron in individuals who had the disease before is related to the methodology employed in our study, which favors diagnostic certainty (high

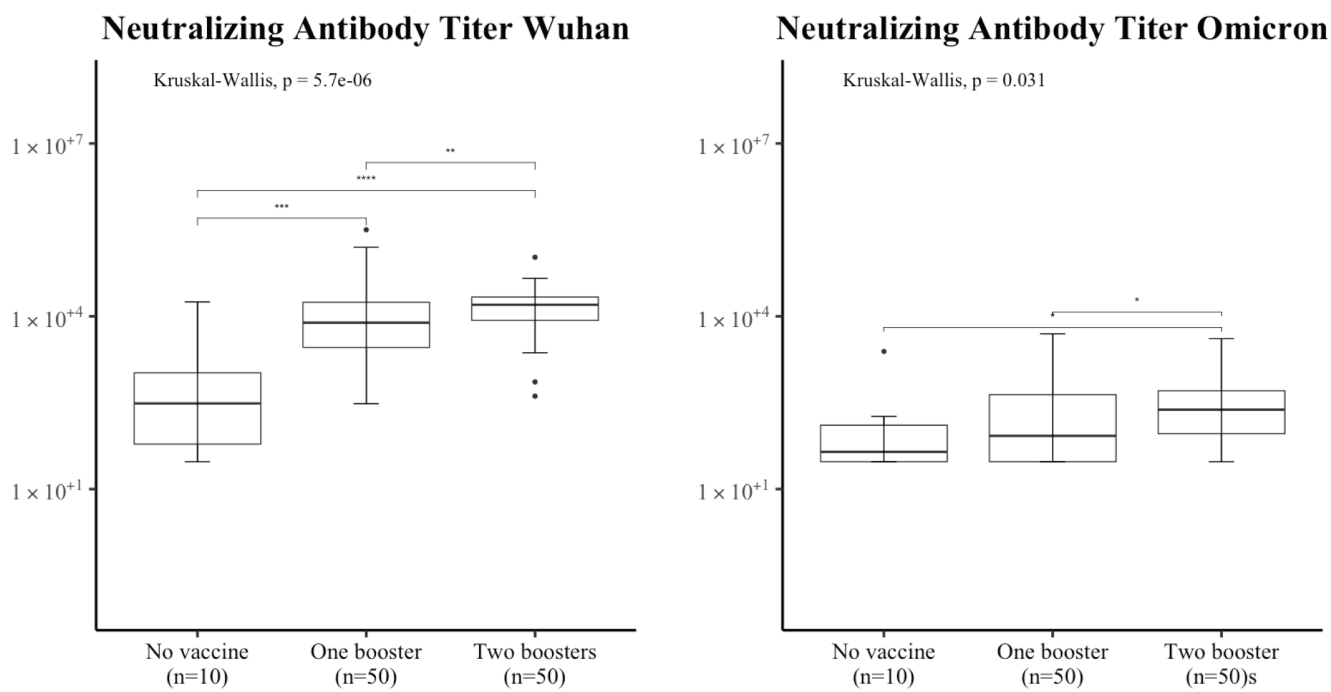

Fig. 2. NAbs titers against the original SARS-CoV-2 virus (Wuhan) and the Omicron variant, according to the vaccination scheme received. Kruskal-Wallis test *p≤0.05; **≤p 0.01; ***p≤0.001 and **** p≤0.0001.

specificity); as opposed to relying on self-report symptoms.

The rapid rise of the Omicron variant as a dominant worldwide VOC [23] can be attributed to specific mutations in the viral genome, mainly in the region that codes for the Spike protein (one of the most immunogenic proteins). These mutations enable the variant to evade parts of the immune response, as evidenced in this study and previous investigations [24,25]. The humoral immune response, in part represented by NAbs measurements, shows a significant decrease in neutralization values when comparing the IC50 values against the original Wuhan strain and the Omicron variant within the same serum sample from the study participants. Based on these results, it is possible to suggest that there is a loss of protective immunity against emerging variants, thereby indicating the persistence of reinfections and their consequences, as already demonstrated by Omicron [3]. Notably, extrapolating the mathematical model of the Influenza framework to SARS-CoV-2, NAbs titers could serve as a predictor of immunity protection, the severity of the condition and even in relation to the efficacy of vaccines against various variants [26]. Meanwhile, the immune system and adaptive memory response also plays a decisive role in the clearing of the infection [21]. In addition, B and T cells are critical in recognizing and eliminating virus-infected cells in the body. Some studies suggest that cellular immunity may play a more prominent role than neutralizing antibodies in clearing SARS-CoV-2 and individuals who have recovered from COVID-19 may still have low levels of neutralizing antibodies but maintain a robust T cell response [27]. Therefore, it is essential to continue studying the role of cellular immunity in the clearance of SARS-CoV-2 to develop more effective treatments and preventive measures against COVID-19, including evaluating vaccines effectiveness.

To fully understand the relationship between NAbs levels over time and immunological protection against emerging VOC, further research into the evolution of the immune response to SARS-CoV-2 is pivotal. This will provide a deeper insight of the population's ability to respond to novel variants. Notably, the Chilean health authorities have recognized the importance of incorporating a bivalent format in their booster vaccination programs, which has been incorporated since October 2022 [28].

The main strength of this research lies in studying a random sample drawn from a territorially representative population sample of two cities in Chile. This enhances the generalizability of the results to the wider population. This territorial representativeness has not been used in other Chilean studies on the same topic [29]. Additionally, this study gathers information from a country with one of the highest vaccination rates for the basic vaccine regimen and booster shots worldwide. This valuable data can contribute to a better understanding of the disease's future progression in other countries that achieve similar vaccination coverage, as well as the evolution of new virus variants. From a laboratory analysis perspective, the use of pseudo virus simplifies the assay without compromising the strong correlation between the tested NAbs with the presence of protective immunity [26]. The authors acknowledge certain limitations of the study. Firstly, we report results of a relatively small number of sera (n = 110) and only from people who received one or two vaccine boosters, excluding those who received only the basic vaccination scheme. Secondly, the study focused on assessing NAbs against the spike protein of the virus, neglecting antibodies targeting other viral antigens. Lastly, the evaluation of cellular immunity was not including due to financial constraints.

Conclusions

The study provides valuable insights into the effectiveness of the vaccine against the original variant of the SARS-CoV-2 virus, highlighting the importance of the number of administered doses and the need for boosters. This protection given by the high vaccination coverage, however, is reduced when new VOCs circulate, as is the case of Omicron. The study also confirms that having previously contracted the disease provides humoral protection, acting as a natural immunity booster. Moreover, it reveals that older people exhibit less protective immunity, particularly against new virus variants. Furthermore, since the effectiveness of vaccines is specific to the variants they target, the study supports the decision of the Chilean authorities to use the bivalent vaccine. This decision was justified even when having a high vaccination coverage. Therefore, the ongoing challenge lies in the surveillance of emerging variants with high circulation, along with the development of vaccines tailored to these variants, to sustain protective immunity

Table 4
Multivariate linear regression model with variables that influence the level of NAbs against the original SARS-CoV-2 virus and its Omicron variant, measured through the reciprocal of the IC50 and its logarithm.

Variables	Categories	Reciprocal IC50			
		Wuhan Coeff. (p-value)	Omicron Coeff. (p-value)	Log Wuhan Coeff. (p-value)	Log Omicron Coeff. (p-value)
Age (baseline: 7–19)	20–49	6690.4	−432.0	−0.373	−1.095
		(0.769)	(0.347)	(0.602)	(0.165)
	50–69	1750.0	−234.9	−0.983	−1.405
		(0.940)	(0.617)	(0.182)	(0.083)
	70+	2744.0	−493.1	−0.953	−2.203*
		(0.911)	(0.320)	(0.218)	(0.011)
Sex (base: Male)	Female	5318.4	110.4	0.210	0.103
		(0.510)	(0.496)	(0.406)	(0.710)
COVID-19 History (Self-reported)	COVID-19	−12752.8	−238.7	−0.498	−0.677
		(0.398)	(0.431)	(0.293)	(0.193)
	COVID-19 (from December 2121 onwards)	26600.3	741.3*	1.446*	2.054**
		(0.144)	(0.044)	(0.012)	(0.001)
Scheme (base: one booster)	Two boosters	−2343.6	162.9	0.835**	0.969**
		(0.816)	(0.421)	(0.009)	(0.006)
Time elapse since last vaccine dose (base: 0–14 days)	2 weeks – 6 months	−8773.9	−39.08	0.0394	0.0162
		(0.504)	(0.882)	(0.923)	(0.971)
	More than 6 months	−7288.8	231.5	−0.109	0.103
		(0.690)	(0.529)	(0.849)	(0.869)
Constant		19517.4	603.1	9.185***	5.777***
		(0.435)	(0.230)	(0.000)	(0.000)
Observations		100	100	100	100
R-squared		0.045	0.130	0.192	0.290
AIC		2400.0	1618.4	325.8	344.2
BIC		2426.1	1644.4	351.8	370.3

IC50 = Half maximal inhibitory concentration; AIC = Akaike's information criterion; BIC = Bayesian information criterion; *p ≤ 0.05; **≤p 0.01; ***p ≤ 0.001.

among populations, especially those at higher risk of severe disease.

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Institutional Review Board Statement

This research was approved by the Ethics Committees of the Universidad de Talca and the Facultad de Medicina of the Universidad Católica del Norte, Statement numbers 50-2021 and 38-2021, respectively.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study, including informed assent and consent of guardians in the case of minors.

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.

Data availability

Data will be made available on request.

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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.2023.100372.

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