FEATURES

SARS-CoV-2 humoral immune response in patients with cardiovascular risk factors: The COmmunity Cohort Study

Vivienne C. Bachelet* , Ignacio Silva-Ayarza , María S. Navarrete

ᵃEscuela de Medicina, Universidad de Santiago de Chile, Santiago, Chile

ABSTRACT

In response to the Vaccine Advisory Committee and the National Immunization Program recommendations, Chile implemented an early vaccination campaign for the population with vaccines from different laboratories. Studying neutralizing antibody levels in different population subgroups contributes to the establishment of correlates of protection against SARS-CoV-2 infection. In 2022 and 2023, we set up a community cohort of 914 adults with cardiovascular risk factors. In this cohort we are measuring the humoral immune response to SARS-CoV-2 antigen exposure, either by vaccination or infection, as well as the incidence of COVID-19 and other adverse events. This cohort, which we call The COmmunity Cohort, is providing us with valuable information on the levels of neutralizing antibodies and the degree of protection against COVID-19 among these individuals.

KEYWORDS COVID-19, Cohort studies, vaccines, SARS-CoV-2

INTRODUCTION

In response to the Vaccine Advisory Committee's recommendations and the National Immunization Program, Chile implemented an early vaccination campaign for the population with vaccines from different laboratories, different presentation platforms, and different SARS-CoV-2 antigens. By December 2022, 94.28% of the Chilean population had received the complete primary vaccination schedule. On the other hand, Chile also reports excess mortality during pandemic years that can be attributed to COVID-19 directly, or indirectly due to less control and treatment of acute and chronic diseases during that period [1]. This excess mortality is still present in 2023, despite high vaccination rates and very significant decreases in disease lethality.

The evolution of the COVID-19 pandemic in Chile and in the world raises several important questions, among which the following can be mentioned:

1. In view of the vaccination campaigns carried out in the country and with the current immunization levels in the population, would the inclusion of booster doses of the anti-SARS-CoV-2 vaccine in the National Immunization Plan be justified or not?
2. With what administration schedule?
3. What should be the prioritized population subgroups, or, rather, should there be a population-wide immunization approach?
4. Should we integrate the SARS-CoV-2 vaccine with influenza vaccines?
5. Are the antigens with which people in Chile have been vaccinated the most adequate to generate protection against future variants?
6. What will be the impact of the bivalent vaccine, and will it be associated with a clinically significant gain over immunity already achieved with previous vaccines, infections, or both?

These knowledge gaps are directly related to the effectiveness (protection of the population) and social acceptability (or its opposite, vaccine hesitancy) of preventive interventions deployed at the primary healthcare level.

Throughout the SARS-CoV-2 pandemic, vaccines have been developed using different platforms and different virus antigenic components, or the whole virus. The challenge now is to develop a pan-sarbecovirus vaccine that can prevent morbidity and mortality caused by any known or future variants of this virus, as well as infection by other sarbecoviruses that have not yet emerged [2]. The efficacy of such a vaccine (protecting against any coronavirus) cannot be established in

MAIN MESSAGES

- The study of neutralizing antibody levels in different population subgroups is important because it contributes to establishing correlates of protection against SARS-CoV-2 infection.
- Studies that evaluate the strength and duration of the immune response in relation to booster doses or their scheduling are scarce.
- This cohort will contribute to the scientific knowledge of SARS-CoV-2 vaccines and the humoral immune response of a rarely studied Chilean population with prevalent comorbidities.

phase 3 clinical trials against placebo but will have to use one or more correlates of protection that take into account the complexity of the immune response [3]. A correlate of protection is an immunological function causally or correlatively associated with vaccine-induced clinical efficacy [4].

The study of neutralizing antibody levels in different population subgroups is important because it contributes to establishing the correlates of protection against SARS-CoV-2 infection (mild, moderate, or severe). Both in Chile and worldwide, the presence and strength of neutralizing antibodies after exposure to vaccines or natural SARS-CoV-2 infection have been studied and quantified [5] only in descriptive investigations, with no long-term follow-up and often only with small sample sizes. However, unlike what happens with influenza [6], the search continues for a marker that is easily identified in the serum of individuals and correlates with protection. This marker is usually an antibody that expresses a correlate of protection against infection, symptomatic disease, severe illness, or death [7].

THE COMMUNITY COHORT STUDY

Studies evaluating the strength and duration of the immune response following booster doses or their timing are scarce. There is also scarce evidence on the immune response (humoral or cellular) in specific subpopulations characterized by greater vulnerability, such as adults with cardiovascular risk factors in an outpatient or community setting. Accordingly, during 2022 and early 2023, we established a cohort of 914 adults enrolled in the Cardiovascular Health Program of three community healthcare centers in Chile to evaluate this high risk group. The methods of this study, including sample size calculation, enrollment and follow-up strategies, were published in the study protocol [8]. In this cohort we are measuring the humoral immune response to SARS-CoV-2 antigen exposure, either by vaccines or infection, as well as the incidence of COVID-19 and other adverse events. This cohort, which we call The COmmunity Cohort, is giving us valuable information on neutralizing antibody response in these more susceptible individuals and their degree of protection against COVID-19.

We chose this population because, since the beginning of the pandemic, numerous publications have concluded that a higher cardiovascular risk is associated with higher morbidity and mortality due to COVID-19 [9,10]. In Chile, there is a Cardio-vascular Health Program that treats adults with atherosclerotic cardiovascular diseases, hypertension, type-2 diabetes mellitus, dyslipidemia, and smoking. It was, therefore, of interest to focus on this population. So far, all we know about the humoral immune response to SARS-CoV-2 is in populations not characterized by risk but by data accessibility or convenience.

Figure 1 shows the eligible population, those enrolled per primary healthcare center, and the main results of enrollment and follow-up. Preliminary baseline analysis of 682 participants showed that female sex was predominant (76%), 46% were between 50 and 70 years of age, 81% were overweight or obese, 55% had only one cardiovascular risk factor, 31% had two associated risk factors, and 14% had three or four risk factors. The most frequent risk factor was hypertension (75%), followed by diabetes mellitus (40%) and dyslipidemia (36%). Smoking is the least frequent cardiovascular risk factor, being found in only 5% of the participants. The vaccination coverage profile of the cohort mirrors the well-known national coverage. Only 2% had not been vaccinated; although small, this group can contribute valuable data. Regarding history of COVID-19 prior to cohort entry, 64% had no history of COVID-19, 29% had mild (as defined by the World Health Organization) or no symptoms, and 7% had moderate or severe COVID-19. On the other hand, to date, 10% of the cohort has had mild COVID-19 during follow-up. Losses or withdrawals have been low, only 3%.

Neutralizing antibody levels are being measured with a quantitative chemiluminescence detection assay. The analysis considered the time elapsed between the last vaccine received and the date of sample collection. Figure 2 shows that the drop in levels has been rather discrete, considering that finding changes on a logarithmic scale is usual.

CONCLUSIONS

Longitudinal studies are an essential tool for COVID-19 epidemiological surveillance and pandemic response preparations. Prospective cohort studies are essential for probing questions of harm (or protection, their complement). They are also the best design for establishing associations between risk factors and exposures of interest, such as different types of SARS-CoV-2 vaccines.

The cohort of 914 adults with cardiovascular risk factors is currently constituted and under follow-up. The study is called the COmmunity Cohort Study, and more information can be accessed at www.communitystudy.cl. This cohort will contribute to the scientific knowledge of SARS-CoV-2 vaccines and the

Figure 1. Constitution and follow-up of the cohort.
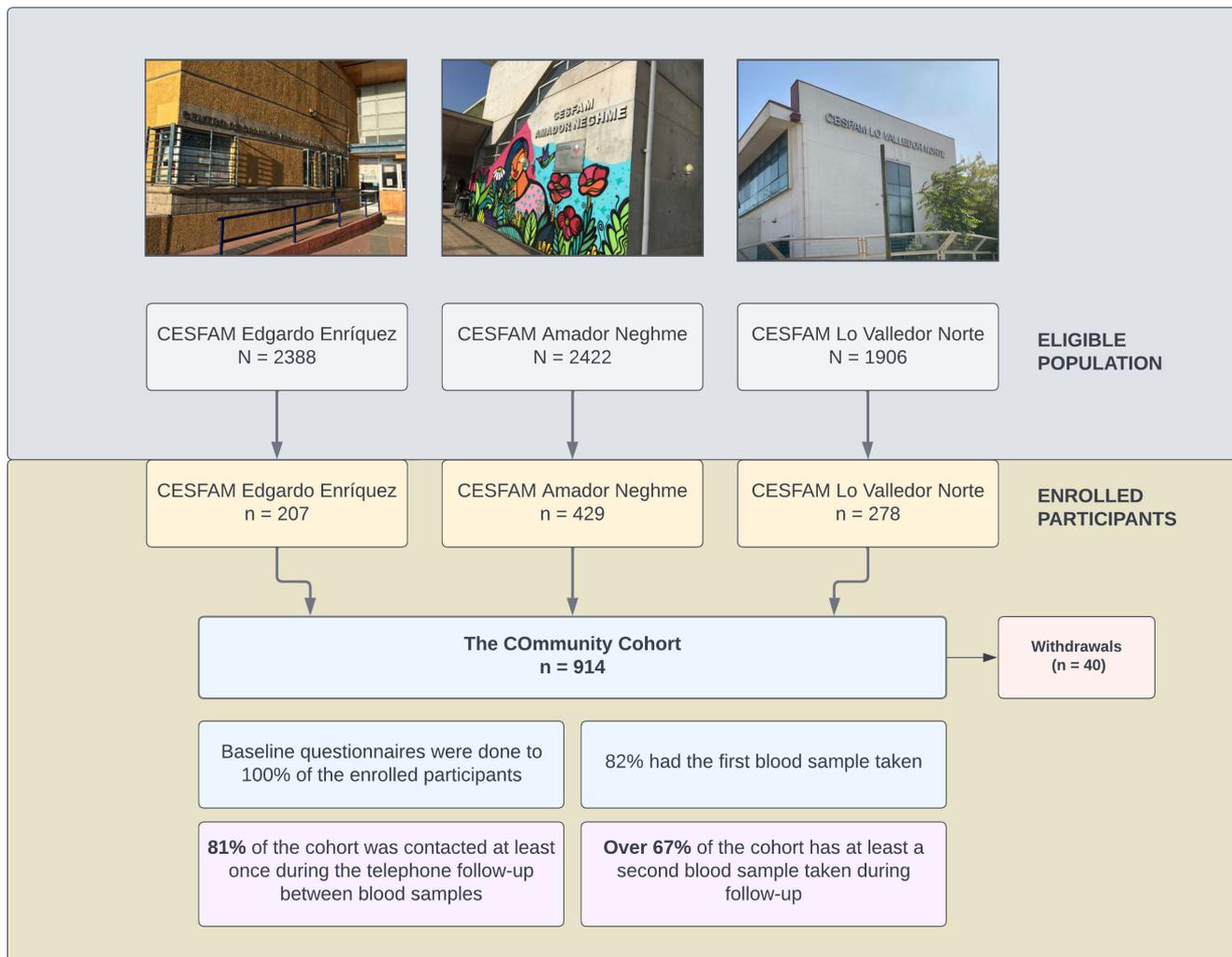
CESFAM: primary healthcare center.
Source: Prepared by the authors based on the results of the study.

humoral immune response of a rarely studied Chilean population with highly prevalent comorbidities that make it more vulnerable to exposures such as COVID-19.

The results obtained annually are relevant input for decision-making on using COVID-19 vaccines in Chile, a key healthcare policy. Likewise, other lines of research can be opened from the stored serum and blood samples of the cohort.

REFERENCES

1. Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet. 2022;399: 1513–1536. https://doi.org/10.1016/S0140-6736(21)02796-3

Figure 2. Neutralizing antibody levels expressed in index units/ml, measured by the sCOVG assay (n = 469).
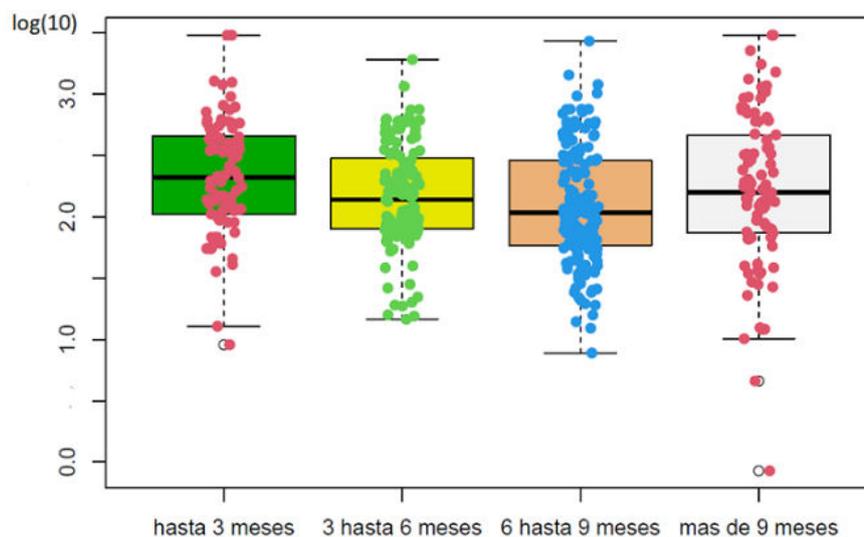
Source: Prepared by the authors based on the results of the study.

2. Zhou J, Liu Z, Zhang G, Xu W, Xing L, Lu L, et al. Development of variant-proof severe acute respiratory syndrome coronavirus 2, pan-sarbecovirus, and pan-β-coronavirus vaccines. J Med Virol. 2023;95. https://doi.org/10.1002/jmv.28172

3. Tan C-W, Chia W-N, Young BE, Zhu F, Lim B-L, Sia W-R, et al. Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors. N Engl J Med. 2021;385: 1401–1406. https://doi.org/10.1056/NEJMoa2108453

4. Plotkin SA. Recent updates on correlates of vaccine-induced protection. Front Immunol. 2022;13. https://doi.org/10.3389/fimmu.2022.1081107

5. Chen X, Chen Z, Azman AS, Sun R, Lu W, Zheng N, et al. Neutralizing Antibodies Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants Induced by Natural Infection or Vaccination: A Systematic Review and Pooled Analysis. Clin Infect Dis. 2022;74: 734–742. https://doi.org/10.1093/cid/ciab646

6. Krammer F, Weir JP, Engelhardt O, Katz JM, Cox RJ. Meeting report and review: Immunological assays and correlates of protection for next-generation influenza vaccines. Influenza Other Respir Viruses. 2020;14: 237–243. https://doi.org/10.1111/irv.12706

7. Krammer F. A correlate of protection for SARS-CoV-2 vaccines is urgently needed. Nat Med. 2021;27: 1147–1148. https://doi.org/10.1038/s41591-021-01432-4

8. Bachelet VC, Silva-Ayarza I, Lizana FJ, Gomolán P, Silva-Villalobos D, Navarrete MS. SARS-CoV-2 humoral immune response in patients with cardiovascular risk factors: the COmmunity Cohort Study protocol. BMJ Open. 2022;12. https://doi.org/10.1136/bmjopen-2022-061345

9. Chidambaram V, Tun NL, Haque WZ, Majella MG, Sivakumar RK, Kumar A, et al. Factors associated with disease severity and mortality among patients with COVID-19: A systematic review and meta-analysis. PLOS ONE. 2020;15. https://doi.org/10.1371/journal.pone.0241541

10. Long J, Luo Y, Wei Y, Xie C, Yuan J. The effect of cardiovascular disease and acute cardiac injury on fatal COVID-19: a meta-analysis. Am J Emerg Med. 2021;48: 128–139. https://doi.org/10.1016/j.ajem.2021.04.013

Respuesta inmune humoral por exposición a antígenos de SARS-CoV-2 en adultos con riesgo cardiovascular: *The COmmunity Cohort*

RESUMEN

A partir de las recomendaciones emanadas del Comité Asesor en Vacunas y el Programa Nacional de Inmunizaciones, Chile implementó precozmente un proceso de vacunación de la población con vacunas provenientes de diferentes laboratorios. El estudio de los niveles de anticuerpos neutralizantes en diferentes subgrupos poblacionales, contribuye al establecimiento de los correlatos de protección frente a infección por SARS-CoV-2. En 2022 y 2023 establecimos una cohorte comunitaria de 914 adultos con factores de riesgo cardiovascular. En esta cohorte estamos midiendo la respuesta inmune humoral frente a exposición a antígenos de SARS-CoV-2, ya sea por vacunas o por infección, así como la incidencia de COVID-19 y otros eventos adversos. Esta cohorte, que llamamos *The COmmunity Cohort*, nos está entregando valiosa información sobre los niveles de anticuerpos neutralizantes en estas personas y su grado de protección frente al COVID-19.