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Vaccine effectiveness in reducing COVID-19-related hospitalization after a risk-age-based mass vaccination program in a Chilean municipality: A comparison of observational study designs

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ABSTRACT

Background: Case–control studies involving test-negative (TN) and syndrome-negative (SN) controls are reliable for evaluating influenza and rotavirus vaccine effectiveness (VE) during a random vaccination process. However, there is no empirical evidence regarding the impact in real-world mass vaccination campaigns against SARS-CoV-2 using TN and SN controls.

Objective: To compare in the same population the effectiveness of SARS-CoV-2 vaccination on COVID-19-related hospitalization rates across a cohort design, TN and SN designs.

Method: We conducted an unmatched population-based cohort, TN and SN case–control designs linking data from four data sources (public primary healthcare system, hospitalization registers, epidemiological surveillance systems and the national immunization program) in a Chilean municipality (Rancagua) between March 1, 2021 and August 31, 2021. The outcome was COVID-19-related hospitalization. To ensure sufficient sample size in the unexposed group, completion of follow-up in the cohort design, and sufficient time between vaccination and hospitalization in the case–control design, VE was estimated comparing 8-week periods for each individual.

Results: Among the 191,505 individuals registered in the primary healthcare system of Rancagua in Chile on March 1, 2021; 116,453 met the cohort study's inclusion criteria. Of the 9,471 hospitalizations registered during the study period in the same place, 526 were COVID-19 cases, 108 were TN controls, and 1,628 were SN controls. For any vaccine product, the age- and sex-adjusted vaccine effectiveness comparing fully and nonvaccinated individuals was 67.2 (55.7–76.3) in the cohort design, whereas it was 67.8 (44.1–81.4) and 77.9 (70.2–83.8) in the TN and SN control designs, respectively.

Conclusion: The VE of a COVID-19 vaccination program based on age and risk groups tended to differ across the three observational study designs. The SN case-control design may be an efficient option for evaluating COVID-19 VE in real-world settings.

1. Introduction

To determine vaccine efficacy, disease reduction attributable to immunization alone must be demonstrated while excluding other confounding factors. Randomized clinical trials assess vaccination efficacy under controlled conditions, whereas vaccine effectiveness is evaluated under real-world settings; however, randomization is not always feasible. Population-based observational cohort studies are the

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primary reference design for effectiveness evaluation [1]; but, a sizable population and comprehensive follow-up are required, especially when the incidence of the disease is low.

An alternative approach involves employing retrospective test-negative (TN) and syndrome-negative (SN) case–control designs. These designs contribute to vaccine effectiveness estimates without being confounded by healthcare-seeking behavior [2]. TN controls are similar to patients with symptomatic acute respiratory infection. Conversely, SN controls are acute respiratory infection free, which minimizes the misclassification between case and control patients because of the absence of overlap of symptoms. Despite its retrospective approach, previous studies support the reliability of TN and SN in evaluating influenza and rotavirus vaccine effectiveness [3–7] under a random vaccination process [8–9].

During the COVID-19 pandemic, only a few countries could utilize cohort designs to assess vaccine effectiveness by integrating national surveillance systems with testing and vaccination data [12–16]. Without these advantages, most countries adopted the TN design because of the availability of hospital records and its rapid roll-out [16–18]. However, COVID-19 mass vaccination campaigns were sequentially implemented in high-risk groups in most countries. On the other hand, SN and hospitalized TN controls lack of representativeness, which may impact vaccine effectiveness estimation. Only theoretical [10] and partial comparisons have been conducted between SN and TN patients receiving COVID-19 vaccination [11], leaving a caveat in the evidence regarding the performance of TN and SN designs in real-world settings.

This study aimed to estimate vaccine effectiveness in reducing COVID-19-related hospitalization by comparing a population-based cohort, a TN and an SN case–control design in the same population during the second COVID-19 pandemic wave in Chile from March to August 2021, when the predominant variant was Gamma SARS-CoV-2 [12] and the average COVID-19 mass vaccination program coverage was $>$ 70 % [13]. Thus, this study contributes methodological recommendations in a health emergency when cohort designs are not feasible or secondary data availability is limited.

2. Methods

2.1. Overall study design, study population, and data sources

We linked available secondary data from the public primary healthcare system, hospitalization registers, epidemiological surveillance systems and the national immunization program to conduct the following unmatched designs: a retrospective population-based cohort, a TN and a SN case–control design with the same population base and period. The study period was from March 1, 2021, to August 31, 2021. Previously, we had developed the case–control designs as part of the Pan-American Health Organization vaccine effectiveness study [14]; thus, in the present study, we focused on assembling a cohort with the same population base.

The population source comprised individuals enrolled in the public healthcare system of the commune (municipality) of Rancagua in Chile. Rancagua is the principal commune of the O'Higgins region of Chile and has a population of 215,296 inhabitants (official census 2017), with $>$ 70 % of the population accessing the public healthcare system. We conducted the study only in Rancagua and not in the entire country to ensure that the same population base was utilized in the three designs to facilitate comparisons. Moreover, unlike other communes, Rancagua has a single tertiary-level public hospital of reference. The referral rate of patients to other regions or hospitals was minimal during the pandemic in Chile. This facilitated the traceability of hospitalizations in the cohort design group.

From the four data sources, the variables analyzed were demographic characteristics (age as a discrete variable and sex as a dichotomous variable), COVID-19-related symptoms, prior SARS-CoV-2 testing history on RT-PCR testing, hospitalization due to COVID-19 diagnosed according to the International Classification of Diseases 10th Revision guidelines (ICD-10) U07.1, U07.2, or U10.9, and COVID-19 vaccine information. Comorbidity history was considered a dichotomous variable (any recorded diagnosis of diabetes, hypertension, stroke, acute myocardial infarction, cancer, or immunosuppressed diseases) within the year prior to the pandemic. This information was only available in hospitalization records for the case–control design group.

2.2. Cohort design

The cohort consisted of individuals aged $\geq$ 18 years utilizing the public healthcare system of Rancagua, a network of six primary healthcare centers, until March 1, 2021. We restricted the cohort to this age group because the Chilean vaccination program excluded younger individuals in the initial stages. We excluded data with invalid identification numbers as it was not feasible to correlate vaccination status, hospitalization, and testing records. We also excluded those who were vaccinated for SARS-CoV-2, had been hospitalized, and tested positive for SARS-CoV-2 within 90 days prior to the cohort's assembly date (March 1, 2021) to ensure a cohort without any prior outcomes and with the same vaccination period as the case–control designs. The outcome was COVID-19-related hospitalization at the Hospital Regional de Rancagua using the U07.1, U07.2, or U10.9 ICD-10 codes.

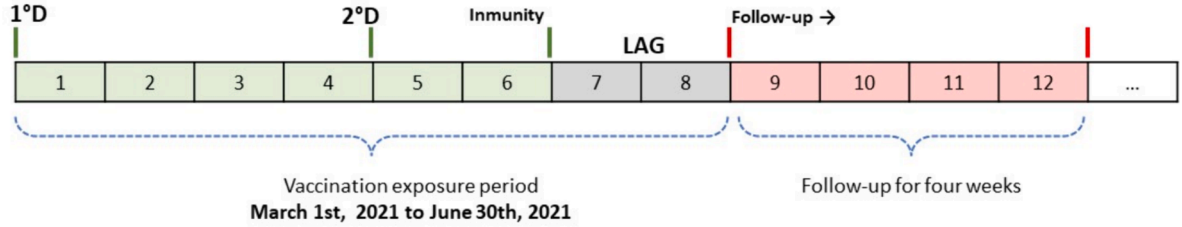
2.3. Vaccination and follow-up period

Because the mass vaccination program was staggered according to priority groups and a weekly age-based calendar in Chile, we constructed sequential vaccination and follow-up periods based on a stepped-wedge design [15] and the natural history of the disease. Thus, according to the Chilean COVID-19 vaccine schedule, the second dose was administered 4 weeks after the first dose, and complete immunity was achieved after 14 days of the second dose. We set a lag period of 2 additional weeks to account for the minimum time required for a person to be exposed to the virus and get diagnosed using RT-PCR, which typically takes 3–5 days if infected. This 2-weeks lag period additionally incorporates 5–9 days from diagnosis until COVID-19-related hospitalization to account for the delay in hospitalization and in the individual's vaccination process.

Consequently, we defined 8-week vaccine exposure periods for each individual, from March 1 to June 30, 2021. Follow-up was commenced after the lag period for each individual and concluded either 4 weeks later or when the outcome occurred. The follow-up ended on August 31 for individuals who received the second dose on June 30, 2021 (Scheme 1). We decided not to extend the follow-up period beyond 4 weeks because the nonvaccinated group (unexposed) became partially vaccinated due to the rapid roll-out of vaccination in Chile. Thus, we ensured the inclusion of a sufficient number of individuals in the nonvaccinated group, an equal and sufficiently long follow-up time for the exposed and unexposed groups, and a design that was comparable to the case–control designs.

2.4. Case–control designs

COVID-19 cases were defined as individuals aged $\geq$ 18 years who presented with fever and cough or three or more COVID-19-like symptoms, as defined by the World Health Organization, and were admitted to the Hospital Regional de Rancagua within 14 days of symptom onset, with a positive SARS-CoV-2 RT-PCR test result obtained within 10 days of symptom onset. We excluded those with a positive SARS-CoV-2 RT-PCR test result or a history of SARS-CoV-2 infection in the previous 90 days. The criteria for the TN controls were the same as those for the COVID-19 cases described above, except that they had to have a negative SARS-CoV-2 RT-PCR test result within 10 days of symptom onset. SN controls were defined as patients hospitalized for any non-COVID-19 cause with a negative RT-PCR test for SARS-CoV-2 at admission. We



Scheme 1. Vaccination exposure and follow-up period for each individual in the cohort design.

applied the date of the initial hospitalization to the subsequent hospitalizations that occurred within 7 days of each other. We excluded controls who had previously been diagnosed with COVID-19, but cases could serve as controls prior to hospitalization.

2.5. SARS-CoV-2 vaccine exposure

For the three designs employed in our study, the classification of SARS-CoV-2 vaccination status was as follows: *fully vaccinated*—those who received two doses of a two-dose primary series product (i.e., Sinovac, Pfizer/BioNTech, or AstraZeneca) and had completed at least 14 days since the second dose during the vaccination period; *partially vaccinated*—those who received only one dose of a two-dose primary series or two doses during the vaccination period; and *nonvaccinated*—those who did not receive any vaccine during the vaccination period. Those who received an additional dose during the vaccination and follow-up period were considered to have received boosters and excluded from the primary analysis. We also excluded individuals with incomplete or inconsistent vaccination data (e.g., only a date for a second dose was recorded or inconsistent dose registries). Individuals who had availed of one-dose vaccination schemes and international vaccination were also excluded from the analysis. In the case–control designs, similar to the cohort design, fully vaccinated, partially vaccinated, and nonvaccinated individuals met the criteria, but 2 additional weeks (the lag period) before hospitalization were considered to avoid misclassification bias.

2.6. Statistical analysis

We described the characteristics of the overall eligible population from which they were drawn using counts with percentages for categorical variables (sex, vaccination state, and comorbidity history) and mean and standard deviation (SD) for age. We compared TN with SN controls using Student's *t*-test for age because of their symmetric distribution in the dataset and Fisher's exact test for categorical variables.

We estimated the odds ratio (OR) and 95 % confidence interval (CI) using multivariate logistic models for the three designs as follows:

Cohort

$$logit\,Pr(Y) = \alpha_0 + \beta_1 v + \beta_2 t + \beta' c$$

TN and SN

$$logit\,Pr(Y) = \alpha_0 + \beta_1 v + \beta' c$$

where Y is the outcome status of the patients as a dichotomous variable (irrespective of COVID-19-related hospitalization), α is the parameter for the intercept, β_1 is the parameter for vaccination, v is the vaccination status as a categorical variable (fully, partially, and nonvaccinated as the reference group), β_2 is the parameter for time, and t is an indicator variable of the 12-week period required for vaccination and follow-up (6-week vaccination period, 2-week lag, and 4-week follow-up) according to the stepped-wedge design employed in the cohort design. For adjusted OR, β' is the vector for parameter confounders, and c is the vector for covariate confounders (age and sex). Crude and adjusted ORs based on age and sex with 95 % CIs are reported. We calculated vaccine effectiveness as 1 minus OR. Vaccine effectiveness was calculated for different vaccine products and by type, focusing only on Sinovac and Pfizer/BioNTech due to the small sample size available for AstraZeneca. P-value of < 0.05 was considered statistically significant, and all analyses were performed using R Studio.

The PAHO WHO funded data collection under the Multicenter Regional Study of COVID-19 VE in Latin America [14]. The Universidad de Chile and the Rancagua Health Service Scientific Ethics Committee approved the study protocol and anonymized data collection. Additionally, the study was authorized by each primary healthcare center and the Hospital Regional de Rancagua.

3. Results

In the cohort design, 116,453 from 191,505 individuals who were registered with the public health system of Rancagua on March 1, 2021, were included. Of these, 29,273 fully vaccinated (2 doses plus 14 days), 18,911 partially vaccinated (1 or 2 doses), and 68,269 nonvaccinated (or those who had received one dose but within 14 days when the follow-up began) individuals were surveyed following the stepped-wedge design of the study until June 30, 2021. The most frequently used 2-dose vaccine product was Sinovac (73.2 %), followed by Pfizer/BioNTech (26.4 %) and AstraZeneca (0.3 %) (Fig. 1).

Table 1 shows the sex distribution and mean age of the vaccination status groups as of the cohort assembly date (March 1, 2021). Fully vaccinated, partially vaccinated, and nonvaccinated individuals had a mean age of 45.1 (SD 18.6), 46.0 (SD 18.0), and 44.7 (SD 17.9) years, respectively. Regarding sex distribution, women comprised 56.9%, 57.6 %, and 56.6 % of the fully vaccinated, partially vaccinated, and nonvaccinated groups, respectively.

In the case–control designs, among 9,471 hospitalizations recorded during the study period, 526 COVID-19 cases, 108 TN controls, and 1,628 SN controls complied with the inclusion and exclusion criteria. The mean age of the cases, TN controls, and SN controls was 50.7 (SD 15.6), 58.3 (SD 19.5), and 53.2 (SD 17.2) years, respectively. Furthermore, men comprised 53.4 % (281/526), 52.8 % (57/108), and 51.8 % (844/1,628) of the cases, TN controls and SN controls, respectively (Table 1).

When comparing both types of controls in the case–control designs, TN controls were older than SN controls (58.3 years vs. 53.2 years, P=0.0031). Additionally, the mean age of the case–control design group tended to be higher than that of the cohort design group, and women were predominantly more frequent in the cohort design group than in the case–control design group. The most frequently used two-dose vaccine product in the cohort and case–control design was Sinovac, followed by Pfizer/BioNTech (Table 1).

Fig. 2 and Table 2 show the main results of the vaccine effectiveness according to each study design. The estimated crude vaccine effectiveness of the cohort design group was 66.9 (95 % CI, 55.3–76.1), 75.6 (61.0–84.8) in the TN group and 74.6 (66.7–80.8) in the SN group. After adjustment for sex and age and stratification according to vaccine product, the VE was 67.2 (55.7–76.3), 67.8 (44.1–81.4), and 77.9 (70.2–83.8) in the cohort, TN, and SN control design groups,

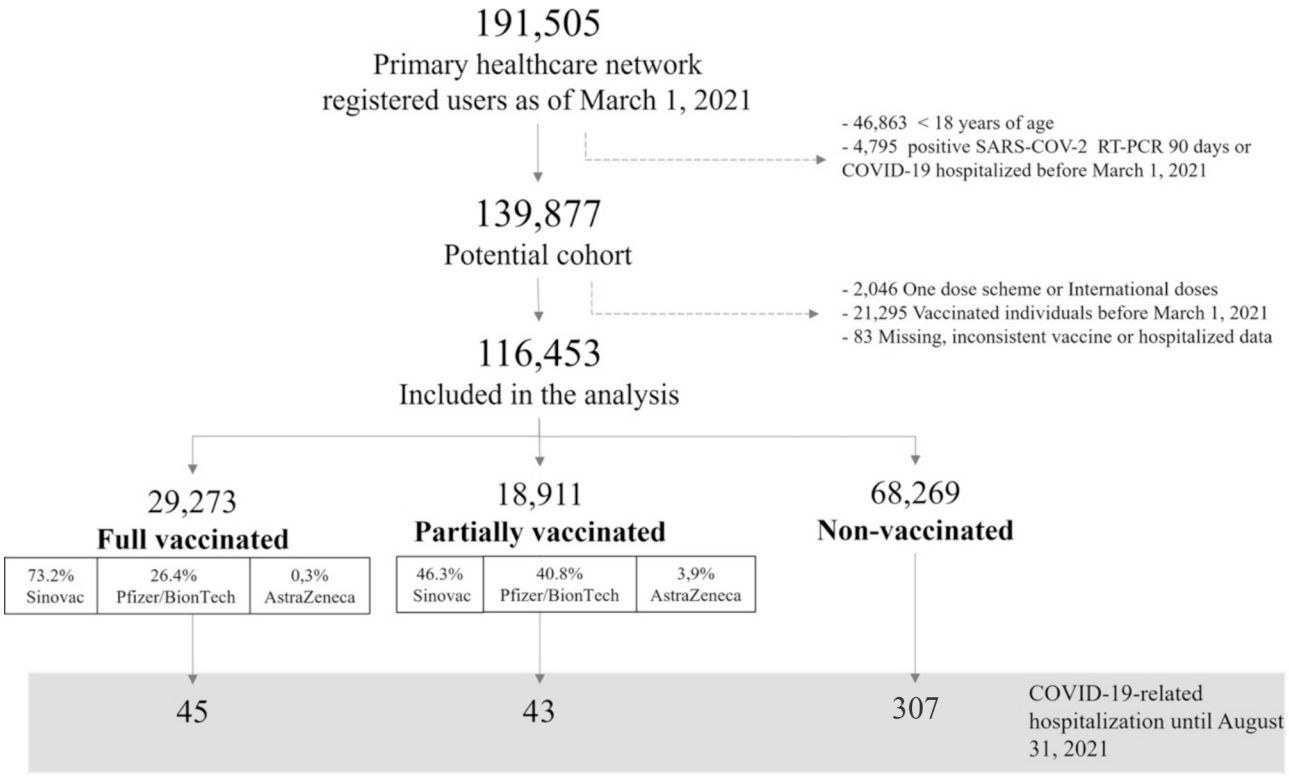


Fig. 1. Patients evaluated and included in the analysis during study period, according to the status of vaccination.

respectively.

4. Discussion

This study demonstrates that the vaccine effectiveness for COVID-19 vaccines obtained simultaneously from three observational designs applied to the same population yield different results. The effectiveness point estimates from the TN and SN designs were higher than those from the cohort design. The TN estimates exhibited wider CIs, especially in the adjusted analysis. In contrast, crude and adjusted estimates had better precision when using the SN control design than the cohort and TN designs. Although our study did not account for essential confounders due to the lack of available data, controlling for the same covariates, adjusted and crude estimates were similar, except in the TN design. After adjusting for age differences, the TN data were closer to the cohort results.

It is well known that OR overestimates risk ratios (RRs) as the disease frequency increases. However, in our study, the incidence of COVID-19-related hospitalization in the population-based cohort design was minimal (3.4 per 100,000 inhabitants); thus, practically, the OR was equal to the RR (RR: 0.33 vs. OR: 0.33). If the vaccine effectiveness estimated in the cohort design is as anticipated (crude: 66.9 %), methodological factors and vaccination in real-world settings may explain the variations in effectiveness from case–control designs in similar settings.

The assembled cohort study represents the population registered in the public health system in Rancagua municipality, Chile, which is approximately 70 % of the total population. We prospectively identified almost 400 (n = 395) COVID-19-related hospitalizations through the records, whereas more than 500 (n = 526) hospitalizations were recorded in the retrospective case–control design group, revealing a mismatch between the types of studies. Theoretically, the number of cases in the case–control design group should be the same as that in the cohort design group, as they have the same population base. Even though the referral rate in Rancagua was minimal during the pandemic, it cannot be ruled out that people from the cohort were hospitalized in other regions. The large number of cases in the case–control design group suggests that some of them may have originated from other populations despite efforts to adhere to the inclusion criteria [14].

The mass vaccination program in Chile was not random. High-risk groups, such as individuals aged > 60 years, those with comorbidities, and healthcare personnel were vaccinated first. Moreover, vaccination roll-out and high coverage rates were rapidly reached in Chile (70 % coverage) and Rancagua halfway through the study period. Assuming that the cases in the case–control design group were equivalent to those in the cohort design group and considering the observed frequency distribution of fully vaccinated individuals in our case–control study (15 %), we discovered through secondary analysis that the vaccine effectiveness obtained from the TN and SN designs exceeded that obtained from the cohort design as vaccine coverage increased.

Theoretically, controls from the case–control design group may mirror the vaccination distribution in the general population. Despite TN controls addressing healthcare bias in VE evaluation, its representativeness remains debatable. For example, in our study, the percentage of fully vaccinated TN controls was 49 %, which was greater than that of the SN controls (39 %). Additionally, TN controls were older than SN controls, suggesting that SN controls exhibited a distribution similar to that of the population. Conversely, SN controls could also have a higher probability of having received vaccination as they belonged to the high-risk groups in the national COVID-19 vaccination schedule. For example, for SN controls, we previously demonstrated that controls without acute respiratory infection were hospitalized for chronic conditions [16].

Interestingly, after adjusting for age differences, VE estimates derived from the TN design group were the closest to those derived from the cohort design group, but with wider CIs. The strict criteria to define controls based on respiratory symptoms could have limited the achievement of adequate sample sizes during the COVID-19 VE evaluation or similar infectious diseases. Conversely, VE estimations using control with acute respiratory infections and negative laboratory tests weaken the representativeness of asymptomatic individuals or those

Table 1
Characteristics comparison in the A) cohort and the B) case-control designs during March 1, 2021 and August 31, 2021, in the Municipality of Rancagua, Chile.

A) COHORT			
	Fully vaccinated (n = 29,273)	Partially vaccinated (n = 18,911)	Non-vaccinated (n = 68,269)
Age, mean (SD)	45.1 (18.6)	46.0 (18.0)	44.7 (17.9)
Sex, % (n)			
Male	43.1 (12,617)	42.4 (8,018)	43.4 (29,629)
Female	56.9 (16,656)	57.6 (10,893)	56.6 (38,640)
COVID-19-related hospitalization, % (n)	0.15 (45)	0.23 (43)	0.45 (307)

B) CASE-CONTROL				
	COVID-19 cases (n = 526)	Test-Negative controls (n = 108)	Syndrome-Negative controls (n = 1,628)	*P* TN vs. SN controls
Age, mean (SD)	50.7 (15.6)	58.3 (19.5)	53.2 (17.2)	0.0031
Sex, % (n)				
Male	53.4 (281)	52.8 (57)	51.8 (844)	0.8404
Female	46.6 (245)	47.2 (51)	48.2 (784)	
2-doses vaccinated by vaccine product, % (n)				
Sinovac	13.3 (70)	10.5 (37)	32.5 (529)	<0.001
Pfizer/BionTech	0.4 (2)	2.0 (7)	4.7 (77)	0.194
AstraZeneca	0.4 (2)	0.0 (0)	0.06 (1)	0.799
Non-vaccinated	68.5 (360)	15.6 (55)	47.4 (772)	<0.001

[1]Student-t and Fisher exact test for test-negative versus syndrome-negative controls
*Do not include heterologous vaccination. SD: Standard Deviation

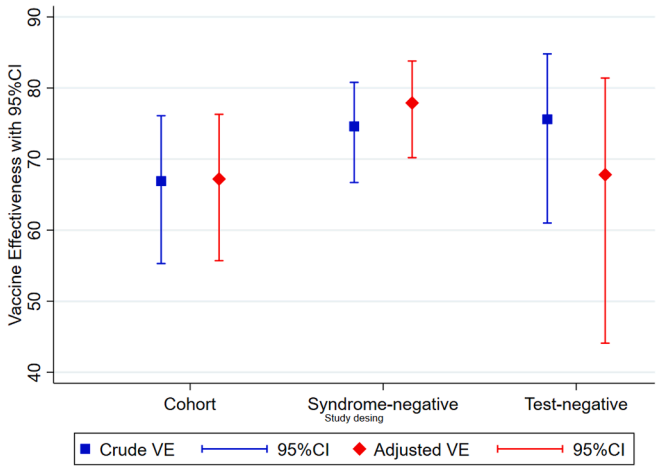


Fig. 2. Vaccine effectiveness against COVID-19-related hospitalization during March 1, 2021 and August 31, 2021 in the Chilean Municipality of Rancagua, Chile, according to the study designs.

with less specific symptoms who were not tested, which was very frequent during the COVID-19 pandemic, depending on the circulating variant.

Enrollment of hospitalized TN controls with COVID-19-like symptoms was challenging in our study, resulting in a low sample size and wide CIs. When the primary outcome is hospitalization, SN controls would be a better option given the feasibility under real-world settings

Table 2
Vaccine effectiveness comparing fully vaccinated versus non-vaccinated against COVID-19-related hospitalization during March 1, 2021 and August 31, 2021, in the Municipality of Rancagua, Chile.

	UNADJUSTED		ADJUSTED*	
Any Vaccine	VE (95% CI)	*P*	VE (95% CI)	*P*
Cohort	66.9 (55.3–76.1)	<0.001	67.2 (55.7–76.3)	<0.001
Test-negative	75.6 (61.0–84.8)	<0.001	67.8 (44.1–81.4)	<0.001
Syndrome-negative	74.6 (66.7–80.8)	<0.001	77.9 (70.2–83.8)	<0.001
Sinovac				
Cohort	64.8 (50.8–75.6)	<0.001	64.9 (51.1–75.7)	<0.001
Test-negative	71.9 (54.1–82.9)	<0.001	61.1 (30.9–78.9)	0.027
Syndrome-negative	71.6 (62.5–78.5)	<0.001	74.3 (64.8–81.2)	<0.001
Pfizer/BionTech				
Cohort	72.1 (51.8–86.1)	<0.001	72.9 (51.8–86.1)	<0.001
Test-negative	95.7 (76.7–99.5)	<0.001	95.5 (76.7–99.3)	0.019
Syndrome-negative	94.4 (77.2–98.6)	<0.001	94.9 (79.0–98.8)	<0.001

VE: Vaccine Effectiveness. CI: Confidence Interval
*Adjusted for age and sex

during the COVID-19 pandemic and the more similar results of VE in comparison to the cohort design. Moreover, SN controls would not overlap with cases because they do not exhibit acute respiratory infection symptoms; thus, the representativeness of controls may improve. The high sensitivity and specificity of RT-PCR in confirming SARS-CoV-2 infection in the three designs of our study reduced the possibility of misclassification of the cases and confounding bias in healthcare-seeking behaviors. Nevertheless, other relevant confounders were not analyzed for VE estimation due to inconsistency or missing data, especially in the cohort design.

Because mass vaccination programs differ, comparing VE with other countries may be misleading. However, our findings regarding effectiveness differ from those of other reports in Chile [14,16–18]. Regarding the cohort design, in a prospective national cohort based on secondary data in Chile, the effectiveness in reducing hospitalization was 87.5 % (95 % CI, 86.7–88.2), with an unclear interpretation of the incidence of hospitalization in the partial and nonvaccinated groups [18]. To avoid statistical artifacts, we accounted for the time-varying vaccination status in the study design rather than adjusting for it during the analysis. Adapting the stepped-wedge design in our cohort study allowed each vaccinated cohort to have a sufficient number of non-vaccinated individuals and short but plausible and similar follow-up periods. Therefore, we compared vaccination status at multiple periods, resulting in a gradient and coherent trend in the incidence of hospitalization (0.15 % fully vaccinated, 0.23 % partially vaccinated and 0.44 % nonvaccinated). Conversely, our estimates were similar to those of another TN design study conducted in Chile with a larger sample size, our previous work involving other hospitals in Chile [17], and another case–control study of VE in Latin America [14].

The main limitation of our study is that the results represent a specific region of the country and cannot be generalized to other settings or conditions, such as outpatients in case–control designs. VE estimates in this study need to be interpreted cautiously, as we excluded important confounders. Finally, the small sample size of TN controls precluded us from drawing better conclusions about this design.

5. Key message

The VE of a COVID-19 vaccination program based on age and risk groups tended to differ across the three observational study designs. The SN case–control design may help efficiently to evaluate COVID-19 VE in real-world settings or rapidly monitor effectiveness.

Ethics approval

The data for this study come from the Multicenter Regional Study of

COVID-19 VE in Latin America (14), which had approval from the Scientific Ethics Committee of the Universidad de Chile and the Rancagua Health Service. This approval means any secondary analysis and its publication. Data were anonymously collected from secondary sources per the Declaration of Helsinki and with the authorization of the primary healthcare centers and the Hospital involved in this study.

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CRediT authorship contribution statement

Cinthya Urquidi: Writing – original draft, Methodology, Investigation, Conceptualization. **Alejandro Sepúlveda-Peñaloza:** Formal analysis, Data curation, Conceptualization. **María T. Valenzuela:** Writing – original draft, Methodology, Conceptualization. **Alexander Ponce:** Software, Formal analysis, Data curation. **Verónica Menares:** Project administration, Methodology, Conceptualization. **Claudia P. Cortes:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Rosana Benítez:** Writing – original draft, Project administration, Conceptualization. **Emilio Santelices:** Writing – original draft, Supervision, Conceptualization. **Renato Anfossi:** Writing – original draft, Validation, Project administration. **Andrea Moller:** Validation, Project administration. **María E. Santolaya:** Writing – review & editing, Project administration, Methodology, Conceptualization.

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

The data that has been used is confidential.

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