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The added effect of non-pharmaceutical interventions and lifestyle behaviors on vaccine effectiveness against severe COVID-19 in Chile: A matched case-double control study

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ABSTRACT

Background: World Health Organization approved vaccines have demonstrated relatively high protection against moderate to severe COVID-19. Prospective vaccine effectiveness (VE) designs with first-hand data and population-based controls are nevertheless rare. Neighborhood compared to hospitalized controls, may differ in compliance to non-pharmacuetical interventions (NPI) compliance, which may influence VE results in real-world settings. We aimed to determine VE against COVID-19 intensive-care-unit (ICU) admission using hospital and community-matched controls in a prospective design.
Methods: We conducted a multicenter, observational study of matched cases and controls (1:3) in adults ≧18 years of age from May to July 2021. For each case, a hospital control and two community controls were matched by age, gender, and hospital admission date or neighborhood of residence. Conditional logistic regression models were built, including interaction terms between NPIs, lifestyle behaviors, and vaccination status; the model's β coefficients represent the added effect these terms had on COVID-19 VE.
Results: Cases and controls differed in several factors including education level, obesity prevalence, and behaviors such as compliance with routine vaccinations, use of facemasks, and routine handwashing. VE was 98·2% for full primary vaccination and 85·6% for partial vaccination when compared to community controls, and somewhat lower, albeit not significantly, compared to hospital controls. A significant added effect to vaccination in reducing COVID-19 ICU admission was regular facemask use and VE was higher among individuals non-compliant with the national vaccine program, and/or tonroutine medical visits during the prior year.
Conclusion: VE against COVID-19 ICU admission in this stringent prospective case-double control study reached 98% two weeks after full primary vaccination, confirming the high effectiveness provided by earlier studies. Face mask use and hand washing were independent protective factors, the former adding additional benefit to VE. VE was significantly higher in subjects with increased risk behaviors.

Abbreviations: NPI, Non-pharmaceutical intervention; VE, Vaccine Effectiveness; ICU, Intensive care unit; CMHS, Central Metropolitan Health Service; OR, Odds Ratios; CI, Confidence Interval.

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1. Introduction

Non-pharmaceutical interventions (NPIs) and mass vaccination against SARS-CoV-2 have been pivotal strategies to control the COVID-19 pandemic. By September 2022, 62% of the world's population had been fully vaccinated, although this coverage barely surpassed 20% in low-income countries [1]. In Chile, COVID-19 mass vaccination began in February 2021, with the use of four different vaccines, following a decreasing age strategy focusing initially on elders and individuals at greater risk ofor severe disease and death. As of June 1, 2021, 52% of the adult population had been fully vaccinated and by December 1, 2021, coverage reached 90% [1]. The most common vaccine used was the virus-attenuated vaccine CoronaVac (90%; Sinovac, China), followed by BNT162b2 (Pfizer-BioNTech, USA) [2]. In conjunction with the vaccination campaign, the Chilean government maintained the following policies regarding NPIs: mandatory facemask use, social distancing, geographic and area-defined quarantines, and promotion of handwashing.

Several studies had previously demonstrated the efficacy of NPIs in controlling outbreaks, especially during the early stages of the pandemic when vaccines were not available and new viral variants were emerging [3–6]. Secondly, vaccine effectiveness (VE) studies focusing on real-world vaccination campaigns supported the high protective levels reported in efficacy trials for initial variants of SARS-CoV-2 [7]. Of note is the Chilean effectiveness study on the CoronaVac vaccine, which was based on the prospective follow-up of a cohort of vaccinated and non-vaccinated individuals. This study reported effectiveness rates of 65·9% against SARS-CoV-2 infection, 90·3%, against hospitalization in the intensive care unit (ICU), and 86·3% against SARS-CoV-2 associated death [8].

Various modeling studies have evaluated attitudes toward the reduction and/or withdrawal of NPIs during the vaccination period from an ecological perspective [9–18]. For instance, a data-driven model reported that China would still need NPI despite COVID-19 vaccination [20]. Similarly, a significant interaction between NPI policies implemented by governments and VE in reducing SARS-CoV-2 transmission was recently reported [19], spotlighting that VE may differ in people/populations depending on their behaviors. While the effect of vaccination on COVID-19 prevention has been extensively evaluated, empirical studies with first-hand data evaluating VE and individual lifestyle behaviors that contribute to increased virus circulation and vaccine hesitancy [21] have not been published. Given that vaccination is voluntary and that the virus will continue to circulate, it is important to pinpoint the role of individual NPIs and lifestyle behaviors, in addition to vaccination, in the prevention of severe disease and death due to COVID-19.

The aim of our study was to determine VE in preventing ICU hospitalization associated with COVID-19, and to evaluate the isolated and combined additional protective effects of individual NPIs and lifestyle behaviors to mass vaccination, in a selected population using both hospitalized and community-matched controls. The study was conducted during the second pandemic wave in Chile, occurring from December 2020 to July 2021, when the highest RT-PCR positive SARS-CoV-2 rate at a national level reached 12.17% [1], full primary vaccination coverage was 79.5%, and Gamma followed by Lambda and Alpha were the predominant circulating variants.

2. Methods

2.1. Study design

We conducted a multicenter, matched case, double control design. For each case, a hospital control and two community controls were matched by age (±4 years), sex, and hospital admission date for hospital controls (±5 days), and neighborhood of residence for community controls (10-block radius). We included community controls as hospitalized controls may differ from the general population in their use of NPIs, lifestyle, and/or medical conditions [22].

2.2. Inclusion/exclusion criteria

The primary outcome was ICU admission due to COVID-19. Eligible COVID-19 cases were patients $\geq$ 18 years of age, admitted to the ICU with a diagnosis of COVID-19 certified by nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR), and/or chest CT imaging and/or antigen test.

We defined the secondary outcome as severe COVID-19 according to the clinical and laboratory based National Institutes of Health criteria. This was included because not all patients admitted to the ICU had severe disease at the initial stages of the pandemic in Chile. Thus, severe COVID-19, was an ICU-admitted patient who complied with the following criteria: a positive RT-PCR for SARS-CoV-2, SpO2 < 94% on room air, and/or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300 mm Hg, and/or respiratory frequency > 30 breaths/min, and/or lung infiltrates > 50% [23], and/or individuals who died due to COVID-19 according to the treating physicians.

Eligible hospital controls were people $\geq$ 18 years of age hospitalized for causes other than COVID-19 in non-ICU services (i.e., general surgery, traumatology). Community controls were non-hospitalized individuals $\geq$ 18 years of age, who had not been previously hospitalized for COVID-19, and who lived within a ten-block radius of the paired case during the six weeks prior to the hospitalization date.

We excluded pregnant women (vaccines were not approved for this population during the study period) and individuals lacking a Chilean identification number (as government databases do not have reliable vaccine information on these individuals). Subjects who were transferred from other health services or who were not living in the jurisdiction of the selected healthcare service were excluded. Individuals hospitalized with respiratory diseases were also excluded to avoid misclassification bias in hospitalized controls. RT-PCR-positive controls were not excluded, as our main outcome was ICU admission and not SARS-CoV-2 infection; only symptomatic subjects in the community were tested for COVID-19 during the study period.

2.3. Exposures

Full primary vaccination status was defined for individuals receiving two vaccine doses 14 days or more before the date of hospitalization (except in the case of three CanSino vaccine recipients, for whom one dose was considered full vaccination). Partial primary vaccination was defined as a) a second vaccine dose received <14 days before hospitalization, or b) one vaccine dose received 14 days or more before hospitalization (except for the 3 Cansino recipients). No vaccination was defined for individuals not receiving any COVID-19 vaccines or at most one vaccine dose of a two-vaccine scheme received <14 days before hospitalization.

NPI compliance was defined as the frequency of NPI use (dichotomized as regular use or never/partially used), both outside and inside the home, during the six weeks prior to case hospitalization. We evaluated: facemask use, hand washing, and social distancing (contact with another person at <1 m). We also collected data on the type of facemasks used (cotton, surgical, or HEPA filter).

Data on lifestyle behaviors that potentially contributed to an increase in SARS-CoV-2 exposure during the six weeks prior to the date of case hospitalization were collected, including the frequency of leaving home to work, use of public transportation, and participation in gatherings of ten or more people. In addition, compliance with routine medical visits during the previous year and with the national routine vaccination program during the previous three years were recorded as proxies for healthcare use and vaccine hesitancy, respectively. We also collected information on age, sex, education level, health insurance, and pre-existing chronic medical conditions to control for confounders.

2.4. Procedures and data collection

From May to July 2021, a trained hospital-based team prospectively recruited cases and hospitalized controls from two of the three hospitals of the Central Metropolitan Health Service (CMHS) in Santiago, Chile, which is part of the public health network of Chile and serves the population of five municipalities.

Starting June 1, 2021, a second trained team recruited community controls from the five municipalities covered by the CMHS, using electronic health records of the local primary care centers (n = 19 centers). In total, the sample pool from which community controls were drawn included nearly 230,000 primary care users registered in this system. Once a case was recruited, a set of possible matched controls were identified and enrolled until the trios were completed (January 31, 2022). We used the geospatial referencing system of CMHS for neighborhood matching.

All participants were contacted by telephone and invited to participate in the study. For ICU patients, the patient provided consent if possible, and if not possible due to disease severity, a direct family member was contacted to request, through informed consent, the review of the patients clinical file and to collect primary information through questionnaires. A structured questionnaire (see Supplement) was used to collect data regarding NPIs, lifestyle behaviors, and confounders. To minimize recall bias, interviewers were trained to obtain exact hospital admission date of COVID-19 cases and determine the period of risk exposure (i.e., 6 weeks prior to hospitalization), and to interview direct relatives. Clinical and laboratory characteristics were collected from the patient's medical records and vaccination data from the National Immunization Program database.

Hospital and primary care directors approved the review of clinical records. The study protocol was revised and approved by the "Comite de Etica en Investigación en Seres Humanos of the Facultad de Medicina, Universidad de Chile.".

2.5. Statistical analysis

VE was defined as a 1-Odds Ratio (OR). ORs and their respective 95% confidence intervals (95% CI) were estimated through multivariate conditional logistic regression models, considering both types of controls separately. The primary outcome variable was ICU admission and the secondary outcome was severe COVID-19, compared to both hospital and community controls,. The independent variables added to the model were vaccination status as a categorical variable, comparing full and partially vaccinated individuals to those not vaccinated. The following potential confounders were identified by direct acyclic graphs and by WHO recommendations for COVID-19 VE evaluation: education level, pre-existing obesity, healthcare insurance, previous vaccination, hand washing and type of facemask.

For the isolated effect of NPIs and lifestyle behaviors and its combined effect with vaccination, the main outcome was ICU admission, compared only to community controls (due to larger sample size). We constructed several conditional logistic models for each NPI (type of facemask, facemask use, hand washing, and social distancing inside and outside the home) and variables related to lifestyle behaviors (regularly going out of home to work, using public transportation, attending a meeting of >10 people, attending routine medical visits and previously receiving any routine vaccine), adjusting by pre-existing obesity, education level, and health care insurance. We then included an interaction term between each NPI variable with vaccination status to estimate the added effect of a specific NPI on full or partial vaccination. Negative β coefficients indicated a synergistic effect in reducing the probability of ICU admission due to COVID-19. Similarly, an interaction term between each lifestyle behavior variable and vaccination status was tested to identify influences of behaviors in VE or to determine if high-risk groups could benefit more from vaccination. For example, an isolated OR > 1 indicated a high-risk behavior for ICU admission, but the magnitude of a negative β value for the interaction term, indicated the magnitude of added benefit of vaccination in reducing the baseline risk due to the specific behavior; on the contrary, a positive β indicated that VE would decrease due to specific behaviors in real-world settings.

A p-value < 0.05 was considered significant. We used the Bonferroni correction to adjust the p-values for multiple testing for all the analyses. Data analysis was done with STATA SE/V17© (StataCorp LLC, College Station).

3. Results

3.1. Participants

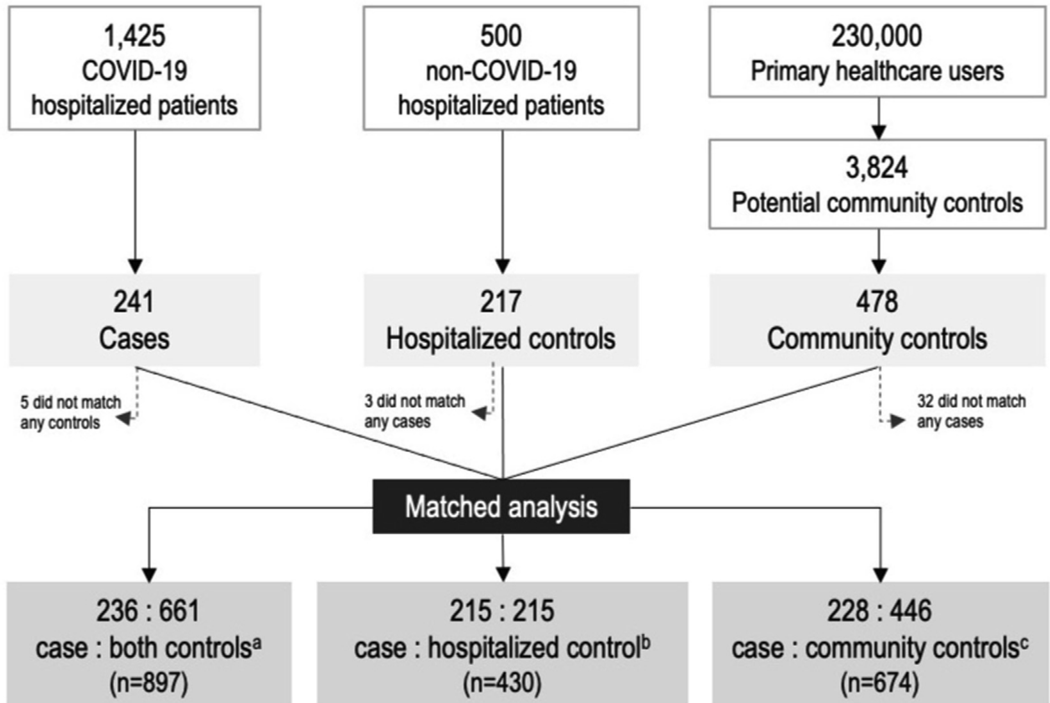
A total of 1,425 COVID-19 patients were hospitalized from May to July 2021 in the two participating hospitals. Of these, 241 (17%) met the inclusion criteria and agreed (personally or family member) to participate in the study. We screened nearly 500 patients hospitalized for reasons other than COVID-19 and 3,824 potential community controls, resulting in a final analytical sample of 936 participants: 241 cases, 217 hospitalized controls, and 478 community controls. The study acceptance rate was 67.8% for COVID-19 patients, 73% for hospitalized controls, and 60% for community controls.

The matched trios included in our analysis are detailed in Fig. 1. The sample size of matched controls appears slightly unbalanced due to the matching procedure, study acceptance rate, and the fact that not every COVID-19 case (n = 5) could be matched to a defined control.

3.2. Descriptive data

The mean age of cases was 54 years and 61·7% were male, with no differences between cases and controls (p = 1·00). Superior educational levels were more common in community controls than in cases and hospital controls (44·6% vs. 34·2% and 20·8% respectively, p < 0·05), and reported obesity was higher for cases compared to hospitalized and community controls (36·3% vs. 16·6% and 14.3% respectively, p < 0·001). In contrast, chronic kidney disease was more common in hospitalized controls as compared to cases (14·5% vs. 5%, p = 0·003) and community controls (14·5% vs 2·8%, p < 0.001). Pre-existing immunosuppressive treatment or a diagnosed autoimmune disease was more common in cases than in community controls (13·5% vs. 7·4%, p = 0·031), but not significantly different from hospitalized controls (p = 0.113) (Table 1).

Attending regular medical visits over the past year was reported more frequently in community controls compared to cases (50·9% vs. 38·5%, p = 0·006). Receiving any vaccinations during the previous three years was significantly lower among cases compared to hospitalized (41·0% vs. 60·2%, p < 0·001) and community controls (57·5%, p < 0·001). Full COVID-19 vaccination was as follows, cases:



Matched sets Case : Hospitalized control : Community control						Matched sets enrolled				
1	:	1	:	3	=	1	:	1	:	3
1	:	1	:	2	=	196	:	196	:	392
1	:	1	:	1	=	10	:	10	:	10
1	:	1	:	0	=	8	:	8	:	0
1	:	0	:	1	=	1	:	0	:	1
1	:	0	:	2	=	20	:	0	:	40
					total	236		215		446

Fig. 1. Flowchart of study population recruitment and matched sets.

30·7%; hospital controls: 61·3%; community controls: 68·6 % ($p < 0·001$ cases vs. both controls) (Table 1).

Hospitalized and community controls differed in education level, health insurance, chronic disease (hypertension, kidney disease, and cancer), type of facemasks used, and compliance with some NPIs (Table 1).

3.3. Main results

For the primary outcome ICU admission related to COVID, comparing cases to matched hospitalized controls, adjusted VE for full primary vaccination versus not-vaccinated was 87·7% (95%CI: 67.5-95·3%, $p < 0.001$). For partial primary vaccination compared to not-vaccinates, VE was 4·7% and not statistically significant ($p = 1.000$). Considering the community controls, for full primary vaccination the VE was 98·2% (95%CI: 92.5-99·9, $p = 0.013$) and 85.6% for partial vaccination (95%CI: 46.9-96·0%, $p = 0.003$). Crude and adjusted VE estimates were similar (Table 2).

For severe diseases o including death due to COVID-19, the secondary outcome, the adjusted VE for full primary vaccinations was 85·2% (95%CI 62·9-94·1) comparing cases to matched hospital controls, and 97· 1% (95%CI 91·1-99·0) to community controls. VE for partial vaccination was only statistically significant when comparing cases to matched community controls (74·3%, 95%CI 33·2-90·1). These findings were similar to crude VE estimates (Table 2).

Supplementary Table 1 shows the clinical characteristics of cases, type of vaccine received, and distribution by age group, and Supplementary Table 2 includes the overall VE for matched pairs combining the two types of controls according to type of vaccine product and age groups. In brief, not all COVID-19 patients admitted to ICU had complete clinical and laboratory data in their clinical records for severe disease definition. The point VE estimates tended to be higher for Pfizer® than CoronaVac® vaccine, and lower for individuals 60 years of age or older, however 95% confidence intervals overlapped.

Increased risk for ICU admission due to COVID-19, independent of vaccination status, was significant for individuals declaring not having received routine vaccines during the previous three years (OR:1·59, $p = 0·048$), and among those reporting commonly moving out of home to work (OR: 1·68, $p = 0·006$). In contrast, regular hand washing both within and outside the home (OR: 0·40, $p < 0.001$), surgical facemask use (OR: 0·38. $p < 0·001$), and N95 facemask use (OR:0·34, $p < 0·001$) were associated with reduced ICU admissions due to COVID-19 (Table 3).

The added effects of NPIs and lifestyle behaviors on vaccination (β interaction coefficients) are shown in Table 3 and Fig. 2. For

Table 1
Differences between COVID-19 cases, hospitalized controls, and community controls.

	COVID-19 Cases (n = 241)	Hospitalized controls (n = 217)	Community controls (n = 478)	p-value[1]	p-value[2]	p-value[3]
Sociodemographic						
Age, mean *years* (SD)	53·8 (16·4)	54·4 (15·8)	54·1 (16·7)	1·000	1·000	1·000
Sex						
male	152 (63·1)	133 (61·6)	291 (61·0)	1·000	1·000	1·000
female	89 (36·9)	83 (38·4)	186 (38·3)			
Education level						
none	6 (2·5)	12 (5·6)	6 (1·3)	0·005	0·023	<0·001
basic	60 (25·0)	71 (32·9)	74 (15·6)			
secondary	92 (38·3)	88 (40·7)	182 (38·5)			
superior	82 (34·2)	45 (20·8)	211 (44·6)			
Healthcare insurance						
public	226 (94·6)	213 (98·2)	437 (94·8)	0·160	1·000	0·040
private or none	13 (5·4)	4 (1·8)	31 (6·6)			
Healthcare worker	6 (2·5)	6 (2·8)	23 (4·8)	1·000	0·423	0·646
Pre-existing chronic conditions						
Diabetes	41 (17·3)	49 (23·0)	81 (17·2)	0·379	1·000	0·222
Obesity	86 (36·3)	36 (16·6)	66 (14·3)	<0·001	<0·001	1·000
Hypertension	90 (37·7)	99 (46·3)	165 (34·7)	0·192	1·000	0·012
Chronic kidney disease	12 (5·0)	31 (14·4)	13 (2·8)	0·003	0·392	<0·001
Cancer	12 (5·0)	22 (10·2)	15 (3·2)	0·117	0·745	0·001
Asthma	18 (7·5)	11 (5·1)	25 (5·4)	0·855	0·772	1·000
Immunosuppressive treatment or disease	32 (13·5)	16 (7·4)	35 (7·4)	0·113	0·031	1·000
Healthcare use/vaccine hesitancy						
Attended medical visits regularly in the last year	92 (38·5)	104 (47·9)	240 (50·9)	0·127	0·006	1·000
Received vaccination(s) during the previous three years	96 (41·0)	130 (60·2)	269 (57·5)	<0·001	<0·001	1·000
Exposure to SARS-CoV-2 in the last 6 weeks						
regular out of home work	118 (49·2)	91 (41·9)	199 (42·0)	0·365	0·205	1·000
Use of public transportation	93 (39·1)	105 (48·6)	196 (41·4)	0·123	1·000	0·225
Attendance of a meeting of more than > 10 people	17 (7·2)	17 (7·8)	52 (11·0)	1·000	0·334	0·620
Compliance with NPI						
Type of facemask regularly used						
cotton	30 (12·5)	31 (14·3)	67 (14·0)	1·000	1·000	1·000
surgical	138 (57·3)	170 (78·3)	345 (72·2)	<0·001	<0·001	0·259
HEPA filter (N95)	33 (13·7)	50 (23·0)	169 (35·4)	0·031	<0·001	0·004
Regular facemask use	160 (86·5)	189 (91·3)	448 (96·1)	1·000	0·334	0·620
Regular hand washing	103 (59·4)	121 (58·7)	387 (83·4)	1·000	<0·001	<0·001
Common social distancing (>1 m)	99 (56·6)	144 (69·6)	294 (63·6)	0·026	0·306	0·410
Facemask use within the home	7 (3·7)	6 (2·9)	22 (4·7)	0·488	0·543	1·000
Hand washing within the home	103 (55·7)	117 (56·3)	101 (21·6)	0·056	<0·001	<0·001
Social distancing (>1 m) within the home	34 (17·9)	39 (18·8)	44 (9·5)	1·000	0·009	0·003
COVID-19 vaccination status						
Full (2 doses + 14 days)	74 (30·7)	133 (61·3)	328 (68·6)	<0·001	<0·001	0·177
Partial (1 dose + 14 days)	24 (12·5)	24 (11·1)	53 (11·1)	0·166	0·002	0·875
Not vaccinated	60 (58·9)	60 (27·7)	97 (20·29)	<0·001	<0·001	0·097

Values are numbers (%) unless stated otherwise. Chi-squared test and ANOVA with Bonferroni correction for multiple comparisons. SD: Standard Deviation. NPI: non-pharmaceutical intervention. HEPA: High-Efficiency Particulate Air. *Always versus not always or never.
[1] Cases versus hospitalized controls. [2] Cases versus community controls. [3] Hospitalized versus community controls.

example, the protective effect of complete COVID-19 vaccination status on reducing ICU admission increased significantly in subjects who regularly used facemasks, specifically HEPA or surgical masks (β = -1.66, p = 0.023). A significant difference in the vaccine effect was observed only in those that regularly used facemasks, as illustrated by the divergent slopes seen in Fig. 2A. In contrast, compliance with the other NPIs did not significantly interact with COVID-19 vaccination (Table 3), as illustrated by the parallel slopes for hand washing in Fig. 2B. Among people who went out of home to work, or who did not receive any routine vaccination during the previous three years, VE was significantly greater than their counterparts (see β coefficients in Table 3, and Fig. 2 C and D). Similar results were found for those individuals who did not regularly attend routine medical visits during the year prior to the study period (β = -1.27, p = 0.005).

3.4. Sensitivity analysis

VE point estimated by unconditional logistic models tended to be lower; nevertheless, this was not significantly different when compared to conditional models. (Supplementary Table 2). Community controls significantly differed from hospitalized controls in pre-existing chronic disease and compliance with some NPIs (Table 1). Conditional models on the combined effect of vaccination and NPIs and lifestyle behaviors compared to community controls did not change the study's conclusion.

4. Discussion

Overall, VE against ICU admission and severe disease, including death, due to COVID-19 approached 90% in this Chilean population at least two weeks (and up to 25 weeks) after a full primary vaccination schedule, at a time when vaccination coverage had reached 79·5% in the adult population. Not surprisingly, the effectiveness of partial vaccine coverage was significantly lower, with wide confidence intervals. This data, provided by a robust prospective case-control design that controlled for important confounders, confirms the high effectiveness observed by earlier real-world observational studies [24]. Importantly, while effectiveness results were some-

Table 2
Vaccine effectiveness in preventing ICU admission related to COVID-19 and severe COVID-19 or death.

	Matched sets		Crude analysis			Adjusted analysis		
	Cases	Controls	OR (95%CI)	VE% (95%CI)	p-value*	OR (95%CI)	VE% (95%CI)	p-value*
ICU Admission								
Cases and Hospitalized controls[2] (n = 430)								
Not vaccinated	119 (55·6)	59 (27·6)	Ref	–	–	Ref	–	–
Partial vaccination	27 (12·6)	24 (11·2)	0·477 (0·220- 1·04)	52·3 (-9·3-78·1)	0·183	0·953 (0·353-2·57)	4·7 (-15·7-64·7)	1·000
Full vaccination	69 (32·1)	132 (61·4)	0·143 (0·076-0·269)	85·7 (73·1-92·4)	<0·001	0·123 (0·047-0·325)	87·7 (67·5-95·3)	<0·001
Cases and Community controls[3] (n = 674)								
Not vaccinated	128 (56·1)	88 (19·8)	Ref	–	–	Ref	–	–
Partial vaccination	28 (12·3)	48 (10·3)	0·311 (0·150-0·588)	68·9 (38·1-84·3)	0·001	0·144 (0·040-0·531)	85·6 (46·9-96·0)	0·003
Full vaccination	72 (31·6)	310 (69·5)	0·055 (0·028-0·107)	94·5 (89·3-97·2)	<0·001	0·018 (0·001-0·075)	98·2 (92·5-99·9)	0·013
Severe COVID-19 including death								
Cases and Hospitalized controls[2] (n = 371)								
Not vaccinated	90 (57·7)	59 (27·4)	Ref	–	–	Ref	–	–
Partial vaccination	19 (12·2)	24 (11·2)	0·764 (0·297-1·96)	23·6 (-9·3-70·3)	1·000	0·898 (0·296-2·72)	10·2 (-1·72-70·4)	1·000
Full vaccination	47 (30·1)	132 (61·4)	0·149 (0·072-0·306)	85·1 (69·4-92·8)	<0·001	0·148 (0·059-0·371)	85·2 (62·9-94·1)	<0·001
Cases and Community controls[3] (n = 490)								
Not vaccinated	104 (59·4)	68 (21·6)	Ref	–	–	Ref	–	–
Partial vaccination	21 (12·0)	34 (10·9)	0·300 (0·134-0·704)	70·0 (29·6-86·6)	0·016	0·257 (0·099-0·668)	74·3 (33·2-90·1)	0·016
Full vaccination	50 (28·6)	213 (67·6)	0·043 (0·019-0·100)	94·5 (89·3-97·2)	<0·001	0·029 (0·010-0·089)	97·1 (91·1-99·0)	<0·001

Conditional logistic regression models. OR: Odds ratio. VE: Vaccine Effectiveness. CI: Confidence Interval. ICU: Intensive care unit.
[1] Adjusted for education level, pre-existing obesity, healthcare insurance, previous vaccination, and type of facemask (n = 837). Both controls mean that one case matched a minimum of one hospitalized or ≥ 1 community control. *including Bonferroni correction.

Table 3
Isolated effects of compliance with NPIs and lifestyle behaviors and their added effects on the COVID-19 vaccination campaign in preventing ICU admission.

	ISOLATED		ADDED			
	OR (95%IC)	p-value	Full vaccination β[†] (95%CI)	p-value*	Partial vaccination β[†] (95%CI)	p-value*
Compliance with NPIs						
Facemask use outside the house	0.58 (0.28 to1.21)	0.146	−1.66 (-3.1 to −0.23)	0.023	0.51 (-2.43 to 1.32)	0.733
surgical	0.38 (0.25 to 0.56)	<0.001	−0.16 (-0.99 to 0.67)	0.699	0.14 (-1.11 to 1.38)	0.831
HEPA filter (N95)	0.34 (0.20 to 0.56)	<0.001	−0.03 (-1.13 to 1.08)	0.960	0.67 (-0.73 to 2.07)	0.351
Hand washing outside the home	0.40 (0.24 to 0.66)	<0.001	−0.87 (-1.88 to 0.14)	0.090	−0.34 (-1.79 to 1.11)	0.646
Hand washing within the home	0.61 (0.39 to 0.95)	0.030	−0.36 (-1.32 to 0.61)	0.466	−0.73 (-2.03 to 0.61)	0.276
Healthcare access and vaccine hesitancy						
Did not attend medical controls regularly in the last year	1.09 (0.72 to 1.63)	0.681	−1.27 (-2.15 to −0.38)	0.005	−0.24 (-1.59 to 1.1)	0.720
Did not receive vaccination(s) during the previous three years	1.59 (1.01 to 2.5)	0.048	−1.63 (-2.64 to 0.62)	0.002	0.31 (-1.20 to 1.82)	0.689
Exposure to SARS-CoV-2 in the last 6 weeks						
Regularly moving out of home to work	1.68 (1.08–2.63)	0.022	−1.24 (-2.13 to −0.35)	0.006	− 0.81 (-2.0 to 0.41)	0.193

Multivariate conditional logistic models adjusted for pre-existing obesity, education level, and healthcare insurance. NPIs: Non-pharmaceutical interventions. OR: Odds ratio. VE: Vaccine Effectiveness. CI: Confidence Interval. ICU: Intensive care unit.
*Including Bonferroni correction.

what higher when considering community compared to hospital controls, VE remained high when compared to both groups. The observed differences are likely explained by the fact that, despite a rigorous matching process, hospital controls differed substantially from community controls on important factors related to COVID-19, an observation that was previously reported [24,25].

Inclusion of additional population-based controls and the application of a questionnaire to all participants [26], uncovered interesting and significant results related to the role of risk factors during the vaccination period, when SARS-CoV-2 circulation was high. Working outside the home and non-compliance with routine vaccinations during the previous three years were independently associated with an increased risk for ICU admission, while high compliance with NPIs was protective, especially facemask usage and hand washing. Cases were less likely to use both surgical and HEPA filter masks than hospitalized and community controls and HEPA filter masks were more commonly used by community controls. Furthermore, among community controls, a larger proportion reported frequent hand washing. Thus, this case-control design confirms the conclusions of a series of quasi-experimental design studies, which demonstrated the positive effect of NPI measures on pandemic control. In one study, mortality was up to 10 times higher in places with low adherence to NPIs, namely facemask use, compared to countries with high adherence [27]. Another study in the United States concluded that the use of facemasks was associated with a decrease in the daily COVID-19 case rate, resulting in an estimated reduction of over 200,000 COVID-19 cases over thirty-seven days [28].

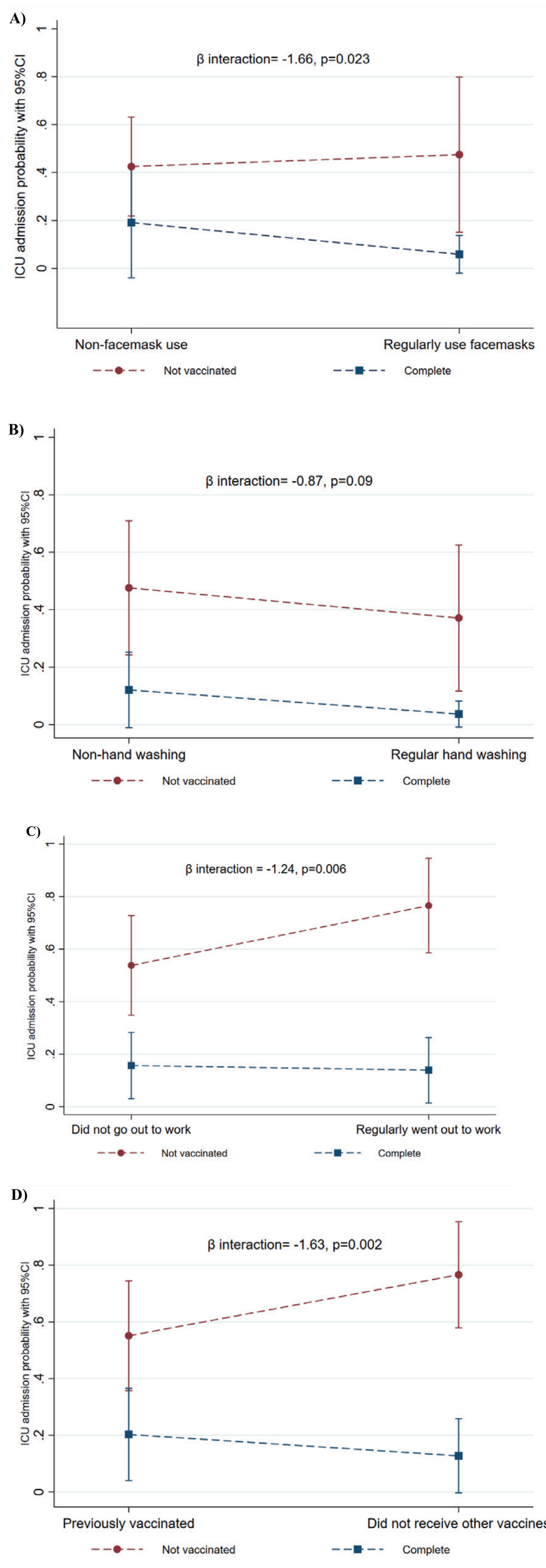


Fig. 2. Combined effects of the Covid-19 vaccination campaign with facemasks use (A), hand washing (B), regularly moving out of home out to work (C), and previously receiving routine vaccinations, in preventing ICU admission.

The positive interaction between full primary vaccination and regular facemask use in our study, confirms the added effect of facemasks on VE for preventing severe disease during periods of high circulation, which is consistent with conclusions from several simulation studies at a population level [9–12,16–19,29–31]. For example, using a stochastic network based on the SEIR framework (susceptible, exposed, infected, and recovered), any type of vaccination coverage together with NPIs significantly further decreased the risk for SARS-CoV-2 infection compared to vaccinated individuals in the absence of NPIs [31]. Conversely, the significant interaction between COVID-19 vaccination and going out of home to work and non-compliance with routine health controls and compliance to routine vaccinations suggests that the protective effect of a full vaccination schedule is higher in subjects who are at increased risk for severe COVID-19.

This is, to our knowledge, the first prospective matched case-control study examining VE that collected primary information on individual behaviors. Although test-negative designs are broadly used to monitor VE, test-positive cases and test-negative controls tend to share similar daily behaviors and exposure to the virus (*e.g.*, mask use) [25,26]. Population-based controls, in contrast, represent people who may be symptomatic or asymptomatic, who do not necessarily undergo testing, and who have followed more common practices. Stringent matching by the neighborhood of residence for community controls, allowed our study to comply with the assumption of a similar selection of cases and controls, controlling for the influence of socio-environmental factors [32]. Unlike studies that are retrospective and/or based on secondary data, the prospective nature of our study allowed us to match and collect new data related to individual behaviors and potential confounders, which can be common in observational studies [33]. Also, of note is that the vaccination records of all study participants were extracted from official government sources and are therefore highly reliable. It is worth mentioning that the SARS-CoV-2 variants circulating during the study period, May-July 2021, included mostly Gamma, followed by Lambda, which were also present during previous observational effectiveness trials [34].

5. Limitations

At the time of study design, in a rapidly evolving pandemic, we aimed to prospectively enroll participants in real-time. However, this was not possible for all subjects, thus some controls were enrolled beyond the initial 2-week target period following case hospitalization, leading to the possibility of some recall bias. Due to the difficulty in matching, our initial age criteria and requirements for geographical matching were broadened; nevertheless, the broadened criteria were still strict (protocol amended August 10, 2022), allowing for relatively stringent matching. Difficulty in obtaining fully matched controls resulted in a smaller number of individuals recruited than originally planned; a decision was made to end recruitment in January 2022 in order to begin study analysis within a feasible timeline, thus avoiding possible changes in pandemic behavior. The decrease in sample size was relatively small, reaching 80%, 72%, and 80% of the expected cases, hospital and community controls, respectively. Nevertheless, the *post-hoc* statistical power for our main results was nearly 99%. For some variables, the sample size reached was not sufficient to address specific questions.

6. Conclusion

In a prospective Chilean, case-double control design, overall VE against ICU admission and severe disease or death due to COVID-19 reached 98% two weeks after a full vaccination schedule, somewhat higher when compared to community than hospitalized controls matched by age, sex, time of admission and neighborhood of residence (for community controls). This high effectiveness, which supports results from a previous large observational study [8], was observed during May-July 2021, at a time when vaccination coverage reached 79.5%, and when Gamma and Lambda variants were predominant. Adherence to NPIs, especially mask usage and hand washing, was a significant preventive factor during the study period. Our study design allowed the identification of interactions between vaccination, NPI use, and individual behaviors. We confirmed an added effect of facemasks on VE for preventing severe disease and increased protective effectiveness among people going out of home to work and among individuals non-compliant with routine health visits and/or routine vaccinations , suggesting that the protective effect of a full vaccination schedule is higher in subjects who are at increased risk for severe COVID-19 due to individual behaviors. Importantly, our study should encourage future research on the selection and evaluation of control groups for VE determination in Covid-19.

7. Competing interests

None of the authors declares a conflict of interest.

Data availability

Data will be made available upon request.

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.

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Data sharing statement

The study database is available from the authors upon reasonable request and with the permission of Cinthya Urquidi, the first author of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.03.060.

References

[1] Our World in Data. https://ourworldindata.org/covid-vaccinations (accessed 18 September 2022).
[2] Gobierno de Chile. Cifras Oficiales COVID-19. https://www.gob.cl/coronavirus/cifrasoficiales/ (accessed 18 March 2022).
[3] Iezadi S, Gholipour K, Azami-Aghdash S, Ghiasi A, Rezapour A, Pourasghari H, et al. Effectiveness of non-pharmaceutical public health interventions against COVID-19: A systematic review and meta-analysis. PLoS One. 2021;16: e0260371.
[4] Bo Y, Guo C, Lin C, Zeng Y, Li HB, Zhang Y, et al. Effectiveness of non-pharmaceutical interventions on COVID-19 transmission in 190 countries from 23 January to 13 April 2020. Int J Infect Dis 2021;102:247–53.
[5] Ge Y, Zhang W-B, Liu H, Ruktanonchai CW, Hu M, Wu X, et al. Impacts of worldwide individual non-pharmaceutical interventions on COVID-19 transmission across waves and space. International Journal of Applied Earth Observation and Geoinformation. 2022;106:102649.
[6] Stokes J, Turner AJ, Anselmi L, Morciano M, Hone T. The relative effects of non-pharmaceutical interventions on wave one Covid-19 mortality: natural experiment in 130 countries. BMC Public Health. 2022;22:1113.
[7] International Vaccine Access Center (IVAC). Johns Hopkins Bloomberg School of Public Health. VIEW-hub. http://www.view-hub.org (accessed July 26, 2022).
[8] Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. New England Journal of Medicine Massachusetts Medical Society 2021;385:875–84.
[9] Zhou F, Hu T-J, Zhang X-Y, Lai K, Chen J-H, Zhou X-H. The association of intensity and duration of non-pharmacological interventions and implementation of vaccination with COVID-19 infection, death, and excess mortality: Natural experiment in 22 European countries. J Infect Public Health 2022;15(5):499–507.
[10] Sonabend R, Whittles LK, Imai N, Perez-Guzman PN, Knock ES, Rawson T, et al. Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study. Lancet 2021;398 (10313):1825–35.
[11] Li H, Wang L, Zhang M, Lu Y, Wang W. Effects of vaccination and non-pharmaceutical interventions and their lag times on the COVID-19 pandemic: Comparison of eight countries. PLOS Neglected Tropical Diseases. Public Library of Science; 2022;16:e0010101.
[12] Diarra M, Kebir A, Talla C, Barry A, Faye J, Louati D, et al. Non-pharmaceutical interventions and COVID-19 vaccination strategies in Senegal: a modelling study. BMJ Global Health BMJ Specialist Journals 2022;7(2):e007236.
[13] Zhu H, Liu S, Zheng W, Belay H, Zhang W, Qian Y, et al. Assessing the dynamic impacts of non-pharmaceutical and pharmaceutical intervention measures on the containment results against COVID-19 in Ethiopia. PLOS ONE. Public Library of Science; 2022;17:e0271231.
[14] Moore S, Hill EM, Tildesley MJ, Dyson L, Keeling MJ. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. Lancet Infect Dis 2021;21(6):793–802.
[15] Yang J, Marziano V, Deng X, Guzzetta G, Zhang J, Trentini F, et al. Despite vaccination, China needs non-pharmaceutical interventions to prevent widespread outbreaks of COVID-19 in 2021. Nat Hum Behav Nature Publishing Group 2021;5:1009–20.
[16] Shattock AJ, Le Rutte EA, Dünner RP, Sen S, Kelly SL, Chitnis N, et al. Impact of vaccination and non-pharmaceutical interventions on SARS-CoV-2 dynamics in Switzerland. Epidemics 2022;38:100535.
[17] Vilches TN, Abdollahi E, Cipriano LE, Haworth-Brockman M, Keynan Y, Sheffield H, et al. Impact of non-pharmaceutical interventions and vaccination on COVID-19 outbreaks in Nunavut, Canada: a Canadian Immunization Research Network (CIRN) study. BMC Public Health 2022;22(1).
[18] Bohloli H, Jamshidi HR, Ebraze A, Rabbani KaF. Combining government, non-pharmaceutical interventions and vaccination in optimal control COVID-19. International Journal of Healthcare Management Taylor & Francis 2022:1–9.
[19] Ge Y, Zhang W-B, Wu X, Ruktanonchai CW, Liu H, Wang J, et al. Untangling the changing impact of non-pharmaceutical interventions and vaccination on European COVID-19 trajectories. Nat Commun. Nature Publishing Group; 2022;13:3106.
[20] Wafula ST, Mugume IB, Sensasi B, Okware S, Chimbaru A, Nanyunja M, et al. Intention to vaccinate against COVID-19 and adherence to non-pharmaceutical interventions against COVID-19 prior to the second wave of the pandemic in Uganda: a cross-sectional study. BMJ Open 2022;12(6): e057322.
[21] Olivera Mesa D, Hogan AB, Watson OJ, Charles GD, Hauck K, Ghani AC, et al. Modelling the impact of vaccine hesitancy in prolonging the need for Non-Pharmaceutical Interventions to control the COVID-19 pandemic. Commun Med Nature Publishing Group 2022;2:1–8.
[22] Schnitzer ME, Harel D, Ho V, Koushik A, Merckx J. Identifiability and Estimation Under the Test-negative Design With Population Controls With the Goal of Identifying Risk and Preventive Factors for SARS-CoV-2 Infection. Epidemiology 2021;32:690–7.
[23] National Institutes of Health. Clinical Spectrum of SARS-CoV-2 Infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (accessed July 26, 2022).
[24] Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of Effectiveness of vaccines against SARS-CoV-2 infection and COVID-

19 disease: results of a systematic review and meta-regression. The Lancet Elsevier 2022;399:924–44.

[25] Dean NE, Hogan JW, Schnitzer ME. Covid-19 Vaccine Effectiveness and the Test-Negative Design. New England Journal of Medicine Massachusetts Medical Society 2021;385:1431–3.

[26] Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls CMJE, Pearce N. A Test-Negative Design with Additional Population Controls Can Be Used to Rapidly Study Causes of the SARS-CoV-2 Epidemic. Epidemiology 2020;31:836–43.

[27] Margraf J, Brailovskaia J, Schneider S. Adherence to behavioral Covid-19 mitigation measures strongly predicts mortality. PLoS One. 2021;16: e0249392.

[28] Lyu W, Wehby GL. Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US. Health Aff (Millwood) 2020;39(8):1419–25.

[29] Niu Z, Scarciotti G. Ranking the Effectiveness of non-pharmaceutical interventions to counter COVID-19 in UK universities with vaccinated population. Sci Rep. Nature Publishing Group; 2022;12:13039.

[30] Jentsch PC, Anand M, Bauch CT. Prioritising COVID-19 vaccination in changing social and epidemiological landscapes: a mathematical modelling study. The Lancet Infectious Diseases Elsevier 2021;21:1097–106.

[31] Patel MD, Rosenstrom E, Ivy JS, Mayorga ME, Keskinocak P, Boyce RM, et al. Association of Simulated COVID-19 Vaccination and Nonpharmaceutical Interventions With Infections, Hospitalizations, and Mortality. JAMA Network Open. 2021;4:e2110782.

[32] Verani JR, Baqui AH, Broome CV, Cherian T, Cohen C, Farrar JL, et al. Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls. Vaccine. 2017;35:3295-302.

[33] Schulz KF, Grimes DA. Case-control studies: research in reverse. The Lancet Elsevier 2002;359:431–4.

[34] Sección Gestión de la Información - ANDID, Instituto de Salud Pública: Ministerio de Salud, Gobierno de Chile. Vigilancia Genómica SARS-Cov2 ISP. https://vigilancia.ispch.gob.cl/app/varcovid (accessed July 26 2022).