Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile

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Table of Contents

S1. Additional context

S1.1 Healthcare in Chile

Chile has a hybrid public-private health system, including insurance and service provisions. Healthcare coverage is high. About 98% of individuals in Chile have health insurance, with approximately 77% of the Chilean population affiliated to the Fondo Nacional de Salud (FONASA), a health insurance program that collects, manages, and distributes funds for the public healthcare system.[1] FONASA does not discriminate by age, gender, income, number of dependents, pre-existing conditions, or nationality. Access to health care is available throughout the country by a network of primary care centers and referral hospitals. A recent global comparison using an index of effective universal healthcare coverage weighted relative to its potential health gains put Chile in the 74 percentile, between other South American countries such as Argentina (61), Brazil (65), and Uruguay (69), and high-income countries such as Israel (81) and the USA (82).[2]

Testing capacity in Chile has increased significantly during the pandemic, partly as a coordinated effort from the Ministry of Science to include public and private laboratories. Processing capacity grew from a few hundred tests per day to up to 86,000 per day (cumulative of about 713 tests per 1000 population as of May 10, 2021),[3] the highest total testing rate in Latin America.[4] RT-PCR and antigen tests are freely available for FONASA affiliates. Figure S1 shows the daily number of tests conducted in Chile and the percentage positive test rates (seven-day moving average), March 2, 2020, through May 10, 2021. Figure S2 shows that SARS-CoV-2 RT-PCR positivity rates during the pandemic were relatively homogeneous across age groups except for the oldest and youngest age groups, consistently showing higher positivity rates than the rest of the population. In section S3, we show estimates of vaccine effectiveness in preventing Covid-19 among FONASA affiliates by immunization status, February 2 – May 1, 2021, including only individuals who took a RT-PCR (98.1%) or antigen test (1.9%) during the study period, in the spirit of a test-negative case-control design (Table S4).[5,6] These results address the concern that the observed vaccine

effectiveness might be affected by healthcare access, because all individuals included in the analysis had demonstrated access to the Chilean healthcare system.

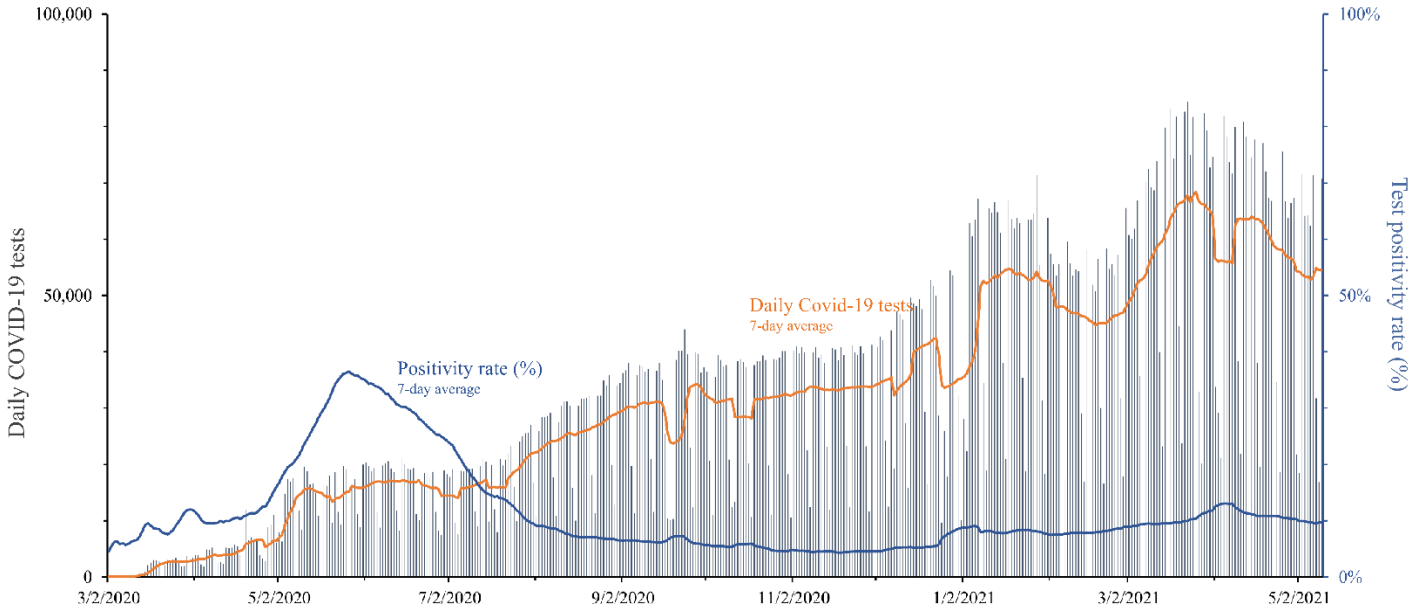

Figure S1. Daily number of Covid-19 tests conducted in Chile during the pandemic from March 2, 2020, through May 10, 2021, and the percentage positive test rates (seven-day moving average) in blue.

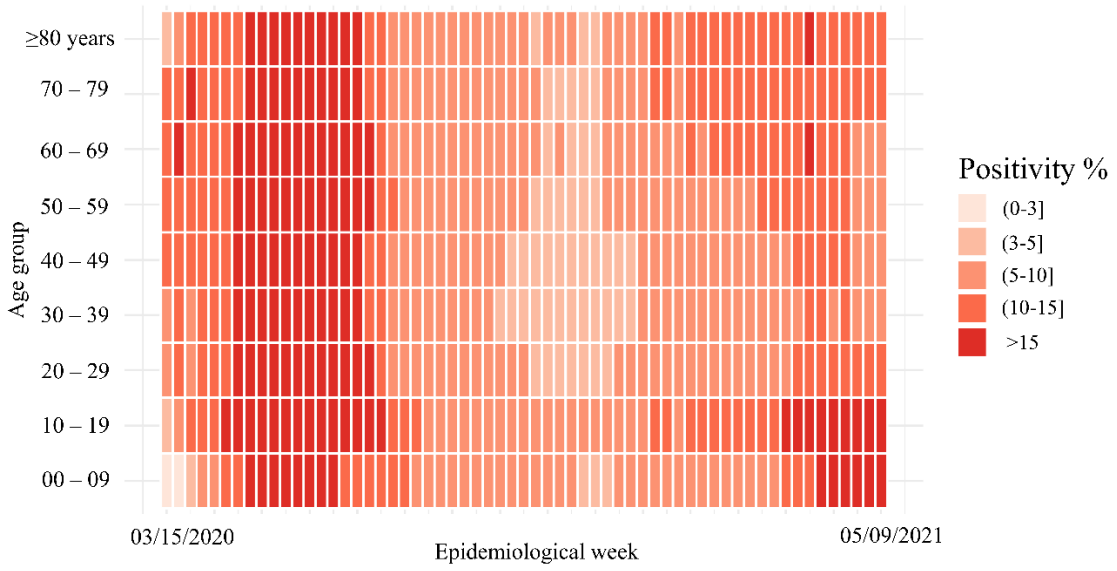

Figure S2. Percentage positive test rates by age group and epidemiological week, from March 15, 2020, through May 16, 2021. Positivity rates during the pandemic were relatively homogeneous across age groups except for the oldest and youngest age groups, which consistently showed higher positivity rates compared to the rest of the population.

S1.2 Vaccination campaign

On February 2, 2021, Chile began a mass vaccination campaign using CoronaVac.[7,8] The vaccination campaign prioritized older adults, beginning at age 90 or above, front-line health workers, and persons with underlying conditions.[8] The government relied on existing health infrastructure to roll out the vaccines to the eligible population where they live and set up more than 1400 vaccination sites in several places, including public primary healthcare clinics, universities, markets, and parks.

Existing primary healthcare infrastructure and experience in rapid vaccination campaigns have been the backbone of the campaign. The government keeps track of vaccination schedules through a national immunization registry, and the vaccine has had high take-up rates. Vaccination rollout was organized through a publicly available schedule, defined by the Ministry of Health at the national level, assigning specific dates to eligible groups (Figure S3). Eligible individuals need to show up at their nearest vaccination site with an ID; they did not need to make an appointment ahead of time. As of May 10, 2021, the Ministry of Health has administered 13.98 million CoronaVac doses (7.62 million first dose, 6.36 million full 2-dose schedules), and 2.4 million BNT162b2 mRNA Covid-19 vaccine doses.[9] Vaccine introduction and the scale-up of the campaign occurred during one of the highest incidence rates of Covid-19 since the beginning of the pandemic in Chile (Figure S4).

Figure S3. Illustration of the Covid-19 vaccination calendar for February 15-19, 2021.[8] Vaccination rollout was organized through a publicly available schedule (https://www.gob.cl/yomevacuno/), defined by the Ministry of Health at the national level, that assigns specific dates to eligible groups (school workers and adults between 65 and 70 years of age).

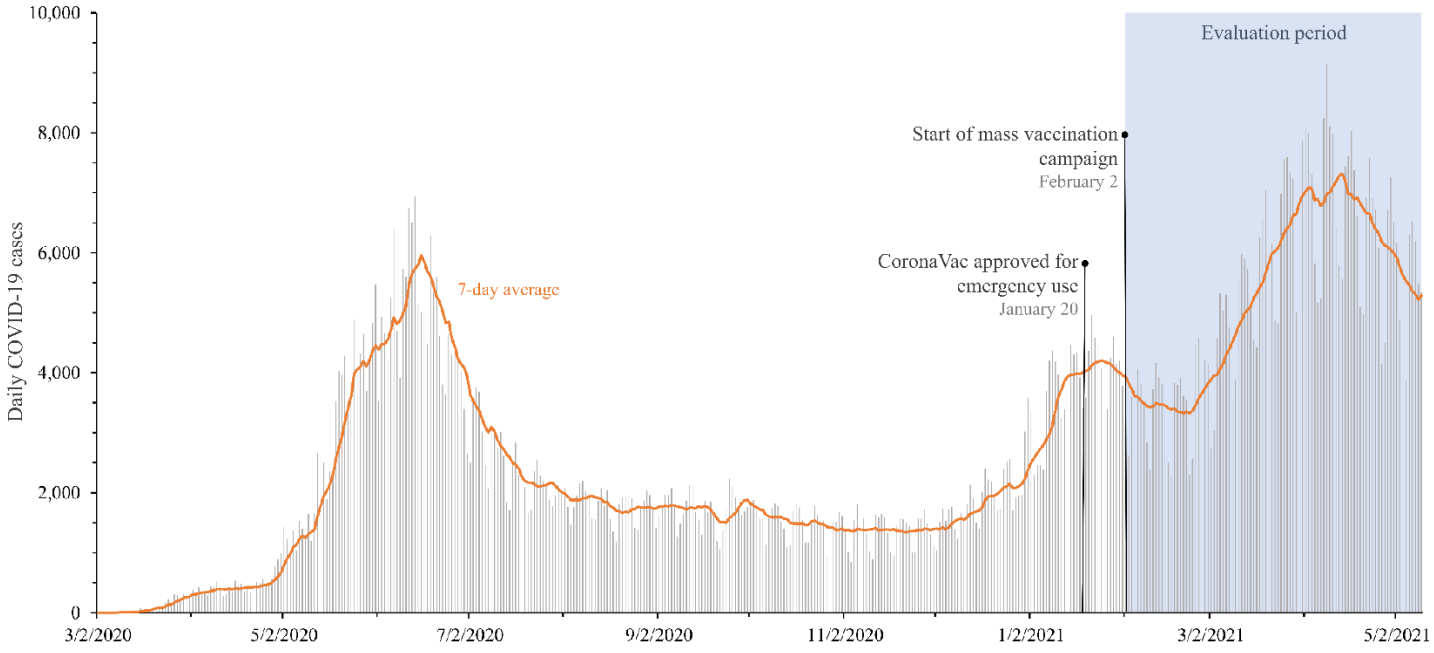

Figure S4. Incidence of Covid-19 cases in Chile, March 2, 2020, through May 10, 2021, and evaluation period for CoronaVac, February 2 through May 1, 2021. The Chilean Institute of Public Health approved the CoronaVac Covid-19 vaccine for a two-dose schedule separated by 28 days on January 20, 2021. Vaccine introduction and the scale-up of the campaign occurred with one of the highest incidence rates of Covid-19 since the beginning of the pandemic.

S1.3 Ecological vaccine effects in the Chilean population

Figures S5-S8 show the ecological effect of the vaccine introduction in Chile, January 1 through May 1, 2021, by age group. The graphs show the moving 7-day average for Covid-19 cases (Figure S5), hospitalizations (Figure S6), hospitalizations in intensive care units (ICU) (Figure S7), and Covid-19 deaths (Figure S8) (ICD-10 code U07.1 Covid-19 with laboratory virus confirmation) by date. The vertical dotted line (···) shows the initial date when the specific age group in the graph was eligible for the first vaccine dose according to the national vaccination schedule (e.g., February 2, 2021, for the group ≥80 years of age).[8] The vertical dashed line (---) shows the initial date when the age in the graph was eligible for the second vaccine dose according to the national vaccination schedule (e.g., March 2, 2021, for the group ≥80 years of age, i.e., 28 days after the group was eligible for the first dose).[8] Cases are indexed at 100 on February 2, 2021.

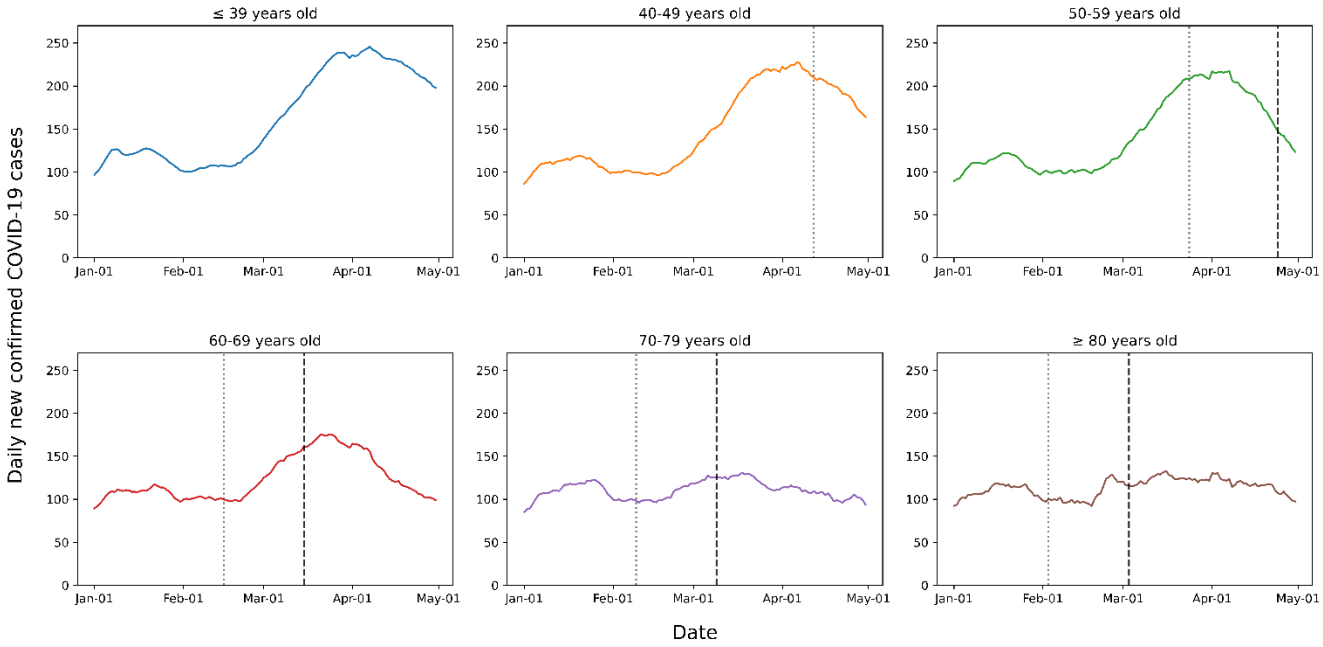

Figure S5. Daily laboratory-confirmed Covid-19 cases in Chile by age group, January 1 through May 1, 2021. Cases are indexed at 100 on February 2, 2021. The vertical dotted line (···) shows the initial date when the specific age group in the graph was eligible for the first vaccine dose according to the national vaccination schedule. The vertical dashed line (---) shows the initial data when the age in the graph was eligible for the second vaccine dose.[8]

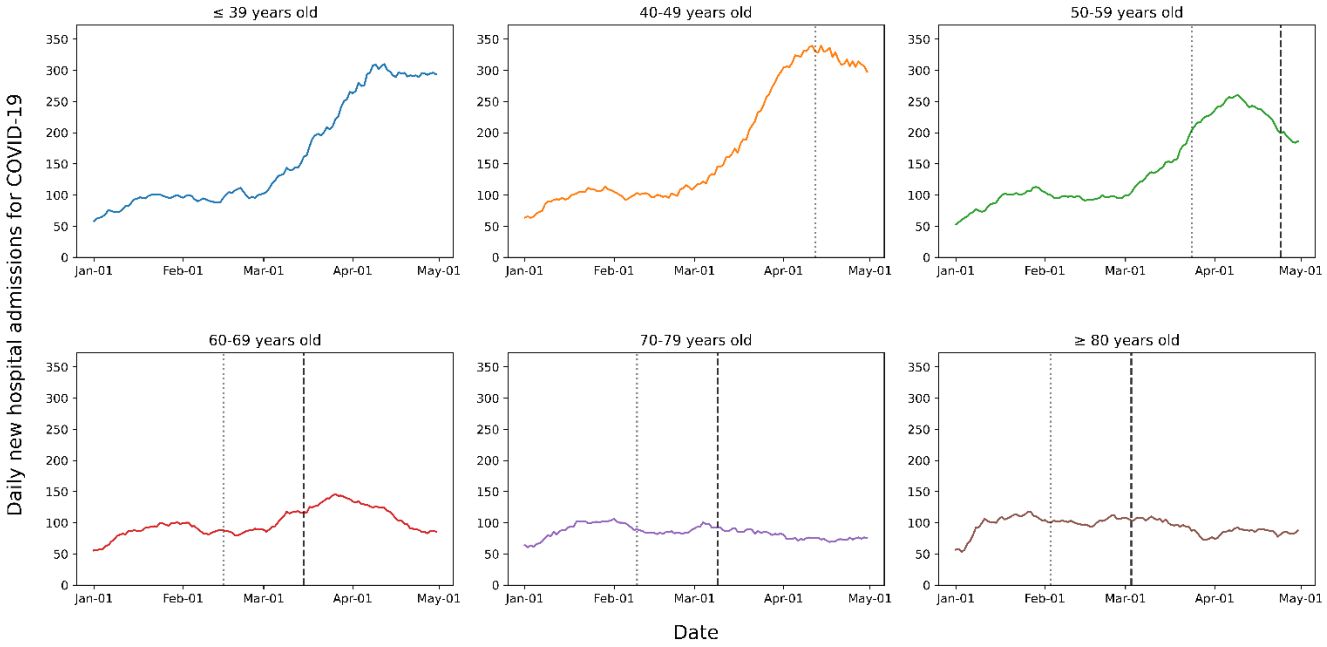

Figure S6. Daily new confirmed Covid-19 hospitalizations in Chile by age group, January 1 through May 1, 2021. Cases are indexed at 100 on February 2, 2021. The vertical dotted line (···) shows the initial date when the specific age group in the graph was eligible for the first vaccine dose according to the national vaccination schedule. The vertical dashed line (---) shows the initial data when the age in the graph was eligible for the second vaccine dose.[8]

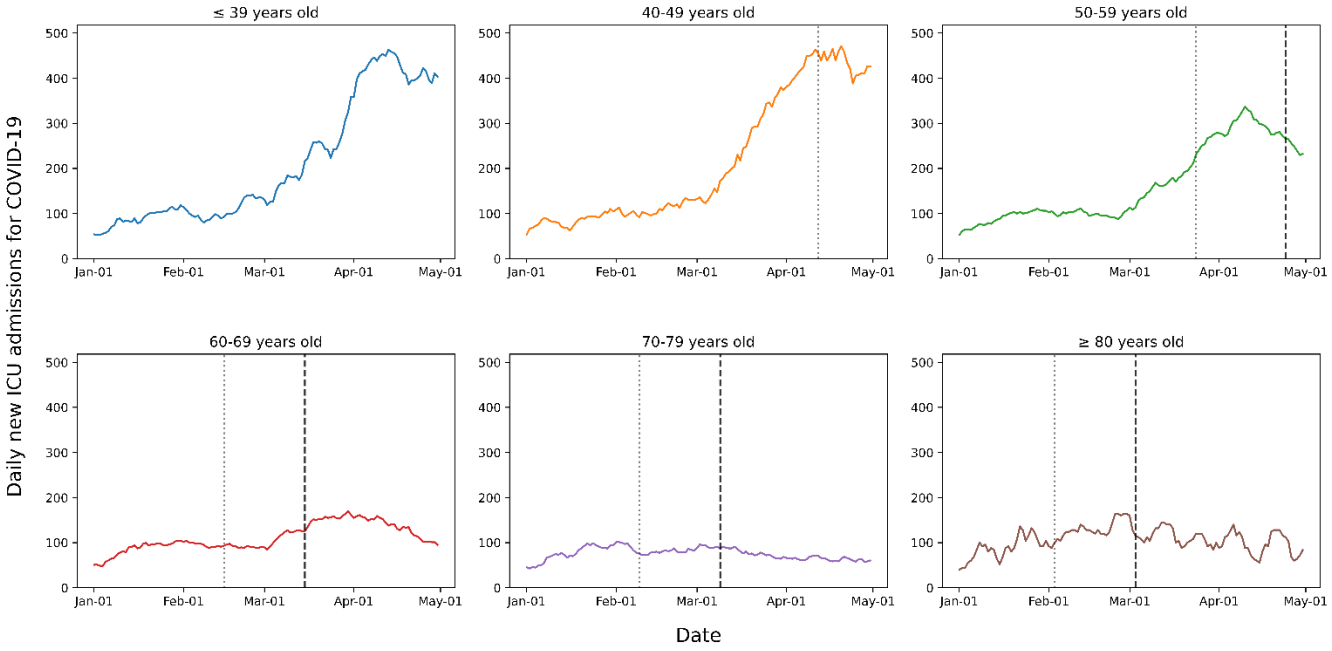

Figure S7. Daily new confirmed Covid-19 hospitalizations in intensive care units (ICU) in Chile by age group, January 1 through May 1, 2021. Cases are indexed at 100 on February 2, 2021. The vertical dotted line (···) shows the initial date when the specific age group in the graph was eligible for the first vaccine dose according to the national vaccination schedule. The vertical dashed line (---) shows the initial data when the age in the graph was eligible for the second vaccine dose.[8]

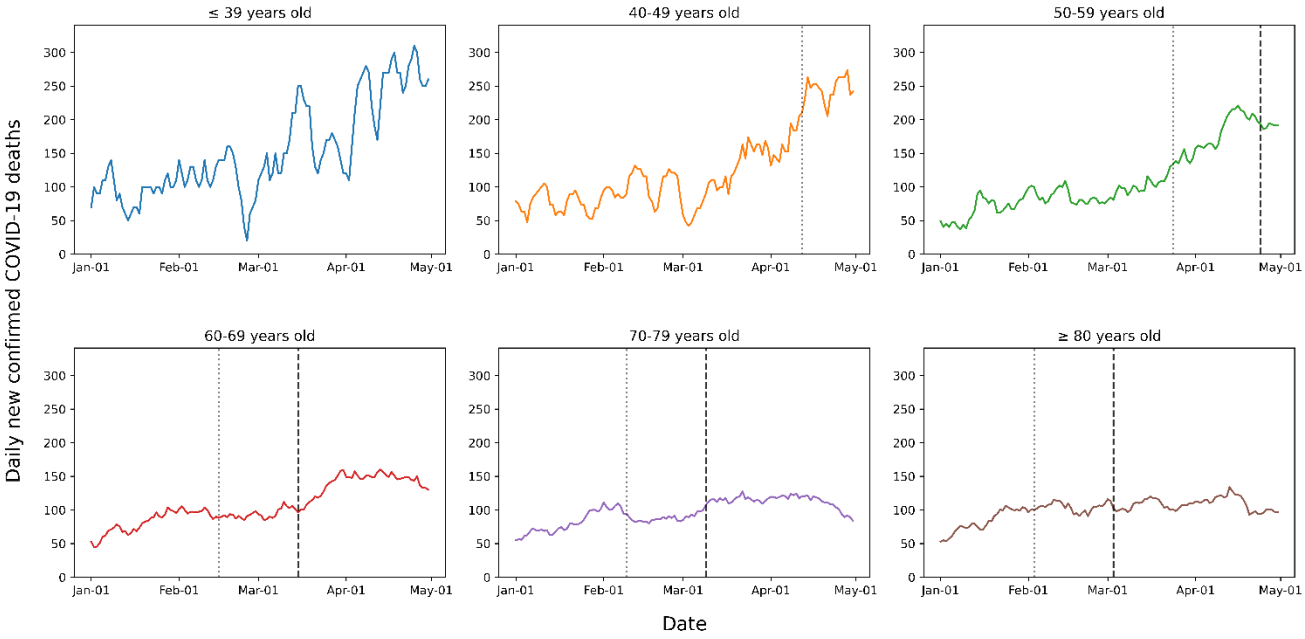

Figure S8. Daily new confirmed Covid-19 deaths (ICD-10 codes U07.1 Covid-19 with laboratory virus confirmation) in Chile by age group, January 1 through May 1, 2021. Deaths are indexed at 100 on February 2, 2021. The vertical dotted line (···) shows the initial date when the specific age group in the graph was eligible for the first vaccine dose according to the national vaccination schedule. The vertical dashed line (---) shows the initial data when the age in the graph was eligible for the second vaccine dose.[8]

S1.4 Characteristics of FONASA affiliates cohort with laboratory-confirmed Covid-19

Table S1. Characteristics of FONASA affiliates cohort with laboratory-confirmed Covid-19 and the percentage receiving one or more doses of CoronaVac Covid-19 vaccine, February 2 – May 1, 2021[†]

			COVID-19			Unvaccinated		Vaccinated 1 dose		Vaccinated 2 doses		
Characteristic	No.	Col.%	No.	Row%	p-value	No.	Row%	No.	Row%	No.	Row%	p-value
Total	10,187,720	100	248,645	2.4	-	5,471,728	53.7	542,418	5.3	4,173,574	41.0	-
Cohort location												
Arica	124,916	1.2	3,032	2.4	<0.001	80,111	64.1	6,858	5.5	37,947	30.4	<0.001
Tarapacá	171,531	1.7	4,929	2.9		106,584	62.1	13,518	7.9	51,429	30.0	
Antofagasta	289,597	2.8	5,919	2.0		182,159	62.9	10,392	3.6	97,046	33.5	
Atacama	167,776	1.6	2,543	1.5		101,648	60.6	7,772	4.6	58,356	34.8	
Coquimbo	474,231	4.7	8,125	1.7		265,227	55.7	33,568	7.1	175,436	37.0	
Valparaíso	1,118,795	11.0	23,000	2.1		570,383	51.0	65,852	5.9	482,560	43.1	
Metropolitana	3,756,887	37.0	80,871	2.2		2,018,505	53.7	183,974	4.9	1,554,408	41.4	
LB O'Higgins	573,335	5.6	12,149	2.1		303,168	52.9	25,235	4.4	244,932	42.7	
Maule	696,091	6.8	19,901	2.9		366,098	52.6	36,306	5.2	293,687	42.2	
Ñuble	317,086	3.1	7,694	2.4		150,580	47.5	19,575	6.2	146,931	46.3	
Biobío	955,607	9.4	31,577	3.3		479,183	50.1	54,088	5.7	422,336	44.2	
Araucanía	629,329	6.2	24,023	3.8		338,909	53.9	38,734	6.2	251,686	40.0	
Los Ríos	245,812	2.4	8,919	3.6		134,842	54.9	13,265	5.4	97,705	39.8	
Los Lagos	527,219	5.2	13,065	2.5		302,866	57.5	23,267	4.4	201,086	38.1	
Aysén	54,613	0.5	666	1.2		31,818	58.3	3,767	6.9	19,028	34.8	
Magallanes	84,895	0.8	2,232	2.6		39,647	46.7	6,247	7.4	39,001	45.9	
Sex												
Female	5,469,202	54.0	135,311	2.5	<0.001	2,775,436	50.8	272,044	5.0	2,421,722	44.3	<0.001
Male	4,718,518	46.0	113,334	2.4		2,696,292	57.1	270,374	5.7	1,751,852	37.1	
Age group												
16-19	708,676	7.0	14,871	2.1	<0.001	670,451	94.6	8,192	1.2	30,033	4.2	<0.001
20-29	2,017,676	20.0	59,645	3.0		1,655,595	82.1	55,854	2.8	306,227	15.2	

30-39	1,867,491	18.0	54,480	2.9		1,446,544	77.5	59,166	3.1	361,781	19.4	
40-49	1,423,770	14.0	39,993	2.8		851,622	59.8	165,487	11.6	406,661	28.6	
50-59	1,457,564	14.0	37,539	2.6		434,694	29.8	184,268	12.6	838,602	57.5	
60-69	1,365,940	13.0	23,669	1.7		221,738	16.2	41,693	3.1	1,102,509	80.7	
70-79	870,082	8.5	11,778	1.4		111,592	12.8	16,412	1.9	742,078	85.3	
80-more	476,521	4.7	6,670	1.4		79,492	16.7	11,346	2.4	385,683	80.9	
Comorbidities*												
None	6,880,426	68.0	168,401	2.4	0.040	4,447,684	64.6	394,030	5.7	2,038,712	29.6	<0.001
≥ 1	3,307,294	32.0	80,244	2.4		1,024,044	31.0	148,388	4.5	2,134,862	64.6	
Nationality												
Chilean	9,497,058	93.2	233,572	2.5	<0.001	4,913,208	51.7	513,604	5.4	4,070,246	42.9	<0.001
Non-Chilean	690,662	6.8	15,073	2.2		558,520	80.9	28,814	4.2	103,328		

Notes. Col.: column, No.: number † FONASA: Fondo Nacional de Salud is a health insurance program that collects, manages, and distributes funds for the public healthcare system. The model also included individual-level income. *Comorbidities included chronic kidney disease, diabetes, cardiovascular disease (hypertension, myocardial infarction), stroke, chronic obstructive pulmonary disease, hematological disease (lymphoma, leukemia, myeloma), autoimmune disease (rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus), HIV, and Alzheimer's and other dementias.

S1.5 Adverse events

The Chilean Institute of Public Health is the regulatory authority responsible for pharmacovigilance in Chile, including passive surveillance of adverse events potentially associated with the use of SARS-CoV-2 vaccines. The Institute has published four reports with data collected from December 20, 2020, through March 10, 2021. The Ministry of Health administered 5,350,038 doses of CoronaVac in this period, and 2.584 adverse events were notified to the Institute (48.3 notifications per 100,000 doses). Of these events, 122 were classified as serious adverse events (2.3 notifications per 100,000 doses). The most frequent clinical manifestations were headache (988), reactions at the site of injection (914), itching (333), nausea (307), fatigue (283), myalgias (278), general malaise (271), diarrhea (258), fever (200), dizziness (178), vomiting (161), urticarial reactions (144), unspecified rash (122), odynophagia (121), dyspnea (121), arthralgias (94), chills (91), erythema (84), anaphylaxis (69), and abdominal pain (56). According to the Brighton Collaboration definition, anaphylactic symptoms could have been reported separately or as a group. Fifteen deaths were notified in this period, with a mean age of 75 years old. Two deaths occurred in subjects aged 39 and 36 years, respectively. The Institute did not find any pattern among these deaths that could suggest a security issue for CoronaVac. Two cases were ruled out as a vaccine-related adverse event due to the lack of temporal relationship with immunization. Ten cases were classified as not consistent because there were alternative conditions that explained the events, and three cases are still under investigation.

S1.6 Variants

The Ministry of Health has focused its genomic surveillance efforts by incorporating SARS-CoV-2 infection into an already existing network of sentinel centers that monitor respiratory viruses. The strategy has focused on detecting variants of concern[10] among travelers entering the country through the main international airport (Aeropuerto Internacional Arturo Merino Benitez). 1,369 SARS-CoV-2 genomes were sequenced from December 22, 2020 through May 10, 2021.[11] Of these, 391 (28.6%), 203 (14.8%), and 2 (0.1%) corresponded to P.1, B.1.1.7, and B.1.351, respectively. In April 2021, the proportion of P.1 and B.1.1.7 variants detected represented 37.5% (228) and 11% (67) of the lineages identified, respectively (Table S2). Both variants circulate in the community, although the sampling method does not allow us to estimate the true prevalence of these variants during the study period.

Table S2. Main SARS-CoV-2 variants and lineages detected in Chile through genomic surveillance, December 22, 2020, through May 10, 2021

Variant	Community	Travelers	Total (%)
Variants of concern			
B.1.1.7	120	83	203 (14.8%)
P.1	311	80	391 (28.6%)
B.1.351	0	2	2 (0.1%)
Variants of interest			
B.1.427/429	11	3	14 (1.0%)
B.1.525	0	2	2 (0.1%)
B.1.526	2	1	3 (0.2%)
P.2	15	25	40 (2.9%)
Other variants			
C.37	317	0	317 (27.0%)
B.1.1.348	187	0	187 (15.9%)
B.1.1.1	25	0	25 (2.1%)
Others	185	0	185 (13.5%)
Total	**1173**	196	1369

Notes. Travelers include secondary cases associated with travelers.

S2. Methods

S2.1 Outcomes

All suspected Covid-19 cases are notified to health authorities through an online platform and undergo confirmatory laboratory testing. Covid-19 cases and deaths were laboratory-confirmed infections (98.1% RT-PCR and 1.9% antigen test) and correspond to ICD-10 code U07.1. We are modeling the following outcomes:

i) The time-to-the-onset of symptoms from the beginning of the follow-up (February 2, 2021) for symptomatic cases.
ii) The time-to-the-onset of symptoms from the beginning of the follow-up (February 2, 2021) for symptomatic cases that required hospitalization.
iii) The time-to-the-onset of symptoms from the beginning of the follow-up (February 2, 2021) for symptomatic cases that required ICU hospitalization.
iv) The time-to-the-onset of symptoms from the beginning of the follow-up (February 2, 2021) for symptomatic cases that died because of Covid19.

For ii)-iv), the classification of the event as failure can occur after the onset of symptoms. We focused on the case and used the onset of symptoms as a proxy for the time of infection.

S2.2 Model description

We estimated the effectiveness by estimating the hazard ratio between the treated and non-treated individuals. We estimated hazard ratios using the extension of the Cox proportional hazards model,[12] accounting for the time-varying vaccination status. Let T_i be the time-to-event of interest, from February 2, 2021, for the i-th individual in the cohort, $i = 1, \dots, n$. Let $x_i, i = 1, \dots, n$, be a p-dimensional vector of individual-specific characteristics, such as age and sex, and $z_i(t)$ be the time-dependent treatment indicator. The model assumes that the time-to-events are independent and with probability distribution given by

$$T_i \mid \boldsymbol{x}_i, z_i \overset{ind.}{\sim} f(t \mid \boldsymbol{x}_i, z_i), \quad \imath = 1, \dots, n,$$

where

$$f(t \mid \boldsymbol{x}_i, z_i) = \lambda_0(t) \exp\left\{\boldsymbol{x}_i'\boldsymbol{\gamma} + z_i(t)\beta\right\} \exp\left\{-\exp\left\{\boldsymbol{x}_i'\boldsymbol{\gamma} + z_i(t)\beta\right\} \int_0^t \lambda_0(u)du\right\},$$

with $\gamma \in \mathbb{R}^p$ being a vector of regression coefficients, $\beta \in \mathbb{R}$ being the regression coefficient measuring the effectiveness of the vaccine, and λ_0 being the baseline hazard function

$$\lambda_0(t) = \lim_{h \to 0} \left\{ \frac{P_0\left(t \leq T \leq t + h \mid T \geq t\right)}{h} \right\},$$

were P_0 is the baseline probability distribution. A Cox model with time-dependent covariates compares the risk of the event of interest between immunized and non-immunized subjects at each event time, but re-evaluates which risk group each person belonged in, based on whether they had been immunized by that time.

To evaluate the robustness of the inferences to the model assumptions, we fit a stratified version of the model,[13] where the time-to-event distribution is given by

$$f(t \mid \boldsymbol{x}_i, z_i) = \lambda_{\boldsymbol{x}_i,0}(t) \exp\{z_i(t)\beta\} \exp\left\{-\exp\{z_i(t)\beta\} \int_0^t \lambda_{\boldsymbol{x}_i,0}(u)du\right\},$$

with $\beta \in \mathbb{R}$ being the regression coefficient measuring the effectiveness of the vaccine, and $\lambda_{x,0}$ is the predictor-specific baseline hazard function. We fit a stratified version of the extended Cox proportional hazards model to test the robustness of our estimates to model assumptions. Under the stratified Cox model, each combination of predictors has a specific hazard function that can evolve independently.

We calculated hazard ratios of unvaccinated person-days to partial immunization person-days (≥14 days after the first dose and before the second dose) and to full immunization person-days (≥14 days after the second dose) separately. Because immunity status induced by CoronaVac is unknown during the 13 days between vaccine administration and partial or complete immunization, those periods were excluded from the at-risk person-time in our analyses.[14]

We estimated the vaccine effectiveness as $100\% \cdot (1 - exp\{\beta\})$. We show the adjusted vaccine effectiveness results, including covariates as controls (age, gender, region, nationality, income, and comorbidities).

Of note, the standard Cox argument can be used to show that the overall partial likelihood is a product of partial likelihoods, one for each type of failure, and each identical to the partial likelihood one would obtain by treating all other causes of failures as censored cases.

Inference was based on a partial likelihood approach. We conducted the analysis with the survival package[15] of R, version 4.0.5.[16]

S2.3 Summary of the main model assumptions

The Cox proportional hazards model can be used to study the effect of various predictors on the instantaneous hazard experienced by experimental units. The extension of the Cox model allowing for time-dependent predictors can also be used to study the effect of predictors on the instantaneous hazard experienced by experimental units and, in addition to standard assumptions for the Cox model, assumes the following:

- All units in the set experience the same baseline hazard rate, where the study period goes from February 2 through May 1, 2021.
- The coefficients for all covariates in Table S1 (cohort location, sex, age group, comorbidities, nationality, income) in the model do not change with time.
- The vaccination status is allowed to change with time. This implies that the model is not a proportional hazards model over time because, for example, the hazard ratios of individuals with different predictors depend on their vaccination status, which is time dependent. However, the proportional hazards assumption applies for each time point. The model assumes that vaccine effectiveness is constant throughout the study period.

The stratified version of the Cox model, allowing for time-dependent predictors, makes the following assumptions:

- The units in the set experience a different baseline hazard rate, which depends on the values of the predictors listed in Table S1 (cohort location, sex, age group, comorbidities, nationality, income). The study period goes from February 2 through May 1, 2021.
- The vaccination status is allowed to change with time. The model assumes that vaccine effectiveness is constant throughout the study period.

The assumption that the vaccine effectiveness is constant throughout the study period, common to both models, is formally tested using the data (see section S3.4).

In addition to the conditional model assumptions, the following assumptions are needed to provide valid causal inferences:

- The censoring mechanism is not informative. We argue that this is a valid assumption for our analysis because, with the exception of non-Covid-19 related deaths (treated as independent competing risks), the censoring arises due to the defined end of the follow-up period.
- The chance to get the vaccine is the same for everyone in the time-predictor-dependent risk set is the same. We think this is also a valid assumption for our analysis because the vaccination scheme was primarily based on individual's age.
- There are no time-dependent confounders that were themselves affected by vaccination or infection status. We could not think of time-dependent confounders; this could theoretically be a study limitation.
- The model assumes that, conditional on all other predictors, individuals at risk are not more likely to get the vaccine. That is, the change in the vaccination status does not depend on future events. It is theoretically possible that the causality assumption for the time-dependent covariate could be violated in our data, particularly the assumption that individuals at high risk were not more likely to get the vaccine.

S3. Additional results and sensitivity analysis

Here we show four important complementary results. First, we show estimates for the vaccine effectiveness in preventing Covid-19 among FONASA affiliates aged 16 to 59 years old by immunization status, February 2 - May 1, 2021. Table S3 shows the estimated adjusted vaccine effectiveness for the fully immunized group of individuals aged 16 to 59 years (two doses, ≥14 days after the second dose) of 63.5% (95%CI: 62.4-64.6) for Covid-19, 91.9% (95%CI: 90.2-93.2) for hospitalization, 94.6% (95%CI: 92.2-96.3) for ICU hospitalization, and 85.8% (95%CI: 69.6-93.4) for death.

Second, we show estimates of vaccine effectiveness in preventing Covid-19 among FONASA affiliates by immunization status, February 2-May 1, 2021, including only individuals who took an RT-PCR (98.1%) or antigen test (1.9%) during the study period, in the spirit of a test-negative case-control design (Table S4).[5,6] These results address the concern that the observed vaccine effectiveness might be affected by healthcare access because all individuals included in the analysis had demonstrated access to the Chilean healthcare system. To clarify, in this subgroup analysis, we included only individuals who had been tested for SARS-CoV-2 during the study period and fit the same models. Several potential disadvantages offset the ability to avoid potential biases related to healthcare access (please also see the "vaccination campaign" section), as discussed in detail by Lipstich et al.[5] The results, conditional on testing, show larger effects for vaccination than when including the complete cohort. The estimated adjusted vaccine effectiveness for the fully immunized group of individuals aged 60 years and older (two doses, ≥14 days after the second dose) of 72.9% (95%CI: 72-74) for COVID-19, 85% (95%CI: 82-87) for hospitalization, 88% (95%CI: 84-91) for ICU hospitalization, and 79% (95%CI: 71-85) for death. Overall, these results were qualitatively similar to those obtained by considering the complete cohort, which provides empirical evidence that the results are unaffected by a potential differential health care access.

Third, we evaluate the robustness of CoronaVac Covid-19 vaccine effectiveness in preventing Covid-19 among FONASA affiliates by immunization status, February 2 – May 1, 2021, to the definition of time 0. Specifically, we considered the date on which individuals became eligible for the vaccine as time 0 (Table S5). The definition of time 0 may be important when vaccination is not available to all the cohort. Young individuals had a positive (but small) probability of being vaccinated along with the vaccine rollout (Table 1), because the vaccination calendar included healthcare workers, education workers, and individuals with underlying conditions, in addition to adults of older age. The time-dependent risk set also depends on predictors, including age. The vaccine effectiveness estimates in Table S5 are qualitatively equivalent to the vaccine effectiveness estimates. Choosing time 0 as the date on which individuals become eligible for the vaccine would unnecessarily reduce the number of person-days for the non-treated period.

Fourth, we used the same approach as for CoronaVac, to estimate the BNT162b2 mRNA Covid-19 vaccine effectiveness in preventing COVID-19 among FONASA affiliates for fully immunized individuals. Between February 2 and May 1, 2021, 490,760 individuals received two doses of the BNT162b2 mRNA Covid-19 vaccine, and 420,174 received one dose. The estimated effectiveness for the BNT162b2 mRNA Covid-19 vaccine was 92.6% (91.5-93.5%) for Covid-19, 95.1% (92.3-96.2) for hospitalization, 96.2% (91.4-98.3%) for ICU admission, and 91.0% (64.0-97.8%) for preventing deaths. These vaccine effectiveness estimates are consistent with vaccine efficacy estimates for fully immunized participants of 95.0% (95%CI: 90.3-97.6%) to prevent Covid-19 found in the BNT162b2 clinical trial.[17] They are also consistent with vaccine effectiveness estimates using real-world data in Israel,[18] of 94% (87-98%) for Covid-19, 87% (55-100%) for hospitalization, and 92% (75-100%) for severe disease (Dagan et al.[18] do not report vaccine effectiveness against Covid-19 deaths for fully immunized patients). These analyses provide an additional robustness check to support our analysis approach used.

S3.1 Subgroup analysis: individuals 16 – 59 years of age

Table S3. CoronaVac Covid-19 vaccine effectiveness in preventing Covid-19 among FONASA affiliates from 16 to 59 years old by immunization status, February 2 - May 1, 2021

Immunization status	Person-days	COVID-19		Vaccine effectiveness (%)		
		No.	Incidence rate 1000 person-days	Adj. sex, age† (95% CI)	Adj. all cov.* (95% CI)	Stratified ‡ (95% CI)
Symptomatic COVID-19						
Unvaccinated	539,160,335	170,036	0.3154	-	-	-
Partially immunized (≥14 days after 1 dose)	34,112,748	12,532	0.3674	8.57 (6.82 ; 10.28)	17.11 (15.52 ; 18.68)	18.77 (17.13 ; 20.38)
Fully immunized (≥14 days after 2 dose)	25,108,525	4,776	0.1902	55.79 (54.47 ; 57.08)	63.50 (62.39 ; 64.57)	60.96 (59.72 ; 62.16)
Hospitalization						
Unvaccinated	544,847,066	12,730	0.0234	-	-	-
Partially immunized (≥14 days after 1 dose)	34,729,203	1,202	0.0346	35.40 (31.26 ; 39.28)	42.58 (38.88 ; 46.06)	42.16 (38.25 ; 45.81)
Fully immunized (≥14 days after 2 dose)	25,458,474	118	0.0046	90.33 (88.39 ; 91.95)	91.86 (90.22 ; 93.23)	91.22 (89.41 ; 92.73)
Hospitalization in ICU						
Unvaccinated	545,121,633	4,712	0.0086	-	-	-
Partially immunized (≥14 days after 1 dose)	34,774,516	482	0.0139	35.33 (28.64 ; 41.40)	44.63 (38.85 ; 49.87)	43.64 (37.48 ; 49.20)
Fully immunized (≥14 days after 2 dose)	25,466,417	29	0.0011	93.47 (90.57 ; 95.48)	94.59 (92.18 ; 96.26)	94.07 (91.39 ; 95.92)
Death						
Unvaccinated	545,257,091	787	0.0014	-	-	-
Partially immunized (≥14 days after 1 dose)	34,800,381	79	0.0023	30.56 (11.24 ; 45.68)	42.01 (25.60 ; 54.80)	46.10 (40.48 ; 51.19)
Fully immunized (≥14 days after 2 dose)	25,468,641	7	0.0003	84.61 (67.22 ; 92.77)	85.79 (69.61 ; 93.36)	82.28 (61.70 ; 91.80)

Notes. Adj: adjusted**.** CI: confidence intervals. Cov: covariates. ICU: Intensive Care Units. † Estimates adjusted for age and sex. *Adjusted for age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19 illness. ‡ We fit a stratified version of the extended Cox proportional hazards model to test the robustness to model assumptions, stratifying by the variables in Table 1, including income, and coded as described in the Table.

S3.2 Sensitivity analysis: access to healthcare

Table S4. CoronaVac Covid-19 vaccine effectiveness in preventing Covid-19 among FONASA affiliates by immunization status, February 2 – May 1, 2021, including only individuals who took an RT-PCR (98.1%) or antigen test (1.9%) during the study period.

Immunization status	Person-days	COVID-19		Vaccine effectiveness (%)		
		No.	Incidence rate 1000 person-days	Adj. sex, age† (95% CI)	Adj. all cov.* (95% CI)	Stratified ‡ (95% CI)
Symptomatic COVID-19						
Unvaccinated	142,011,772	185,633	1.3072	-	-	-
Partially immunized (≥14 days after 1 dose)	16,300,236	20,865	1.2800	30.15 (29.06 ; 31.22)	29.04 (27.93 ; 30.13)	32.55 (31.40 ; 33.67)
Fully immunized (≥14 days after 2 dose)	19,357,683	12,286	0.6347	73.80 (73.25 ; 74.35)	72.86 (72.29 ; 73.43)	73.37 (72.72 ; 74.00)
Hospitalization						
Unvaccinated	148,038,238	18,034	0.1218	-	-	-
Partially immunized (≥14 days after 1 dose)	17,202,680	3,370	0.1959	47.70 (45.59 ; 49.74)	47.94 (45.82 ; 49.97)	50.85 (48.66 ; 52.94)
Fully immunized (≥14 days after 2 dose)	20,131,219	1,462	0.0726	89.46 (88.81 ; 90.07)	89.16 (88.49 ; 89.79)	88.82 (88.05 ; 89.54)
Hospitalization in ICU						
Unvaccinated	148,459,813	6,523	0.0439	-	-	-
Partially immunized (≥14 days after 1 dose)	17,348,481	1,154	0.0665	51.44 (48.07 ; 54.59)	52.91 (49.62 ; 55.98)	54.22 (50.75 ; 57.45)
Fully immunized (≥14 days after 2 dose)	20,204,072	360	0.0178	91.67 (90.65 ; 92.58)	91.56 (90.52 ; 92.49)	91.56 (90.43 ; 92.57)
Death						
Unvaccinated	148,570,009	2,786	0.0188	-	-	-
Partially immunized (≥14 days after 1 dose)	17,366,071	847	0.0488	54.82 (50.85 ; 58.47)	54.77 (50.79 ; 58.44)	56.02 (51.85 ; 59.84)
Fully immunized (≥14 days after 2 dose)	20,200,147	409	0.0202	88.05 (86.53 ; 89.41)	87.78 (86.20 ; 89.17)	88.17 (86.53 ; 89.61)

Notes. Adj: adjusted**.** CI: confidence intervals. Cov: covariates. ICU: Intensive Care Units. † Estimates adjusted for age and sex. *Adjusted for age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe COVID-19 illness. ‡ We fit a stratified version of the extended Cox proportional hazards model to test the robustness to model assumptions, stratifying by the variables in Table 1, including income, and coded as described in the Table.

S3.3 Sensitivity analysis: date of vaccine eligibility as time 0

Table S5. CoronaVac Covid-19 vaccine effectiveness in preventing Covid-19 among FONASA affiliates by immunization status, February 2 – May 1, 2021, considering the date on which individuals became eligible for the vaccine as time 0

Immunization status	Person-days	Covid-19		Vaccine effectiveness (%)	
		No.	Incidence rate 1000 person-days	Adj. sex, age[†] (95% CI)	Adj. all cov.* (95% CI)
Covid-19					
Unvaccinated	57,053,175	17,926	0.3142	-	-
Fully immunized (≥14 days after 2 dose)	86,886,460	11,464	0.1319	63.10 (61.87 ; 64.28)	67.24 (66.13 ; 68.31)
Hospitalization					
Unvaccinated	57,332,821	5,470	0.095408	-	-
Fully immunized (≥14 days after 2 dose)	87,468,360	1,430	0.016349	83.78 (82.63 ; 84.85)	85.93 (84.92 ; 86.87)
Confirmed death					
Unvaccinated	57,422,257	1,641	0.028578	-	-
Fully immunized (≥14 days after 2 dose)	87,525,080	405	0.004627	84.71 (82.65 ; 86.52)	86.88 (85.09 ; 88.45)

Notes. Adj: adjusted**.** CI: confidence intervals. Cov: covariates. ICU: Intensive Care Units. [†] Estimates adjusted for age and sex. *Adjusted for age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19 illness.

S3.4 Sensitivity analysis: evaluation of the vaccine effectiveness proportionality assumption

A fundamental assumption for the vaccine effectiveness estimation is the proportionality along the study period. We formally assessed this assumption by performing a test based on Schoenfeld residuals.[19] We considered the test implemented in the function cox.zph of R's survival package.[20] Table S6 shows the statistic and corresponding p-value for the test evaluating the proportionality VE assumption in the study period. The results show no significant deviations from the proportionality assumption for any of the outcomes of interest.

Table S6. Test for the proportional assumption of the vaccine effect

Immunization status	Non-stratified model		Stratified model	
	Statistic	p-value	Statistic	p-value
Covid-19				
Partially immunized	0.579	0.4468	0.986	0.3200
Fully immunized	0.378	0.5390	2.790	0.0950
Hospitalization				
Partially immunized	2.430	0.1200	1.130	0.2900
Fully immunized	1.858	0.1729	2.800	0.0940
Hospitalization in ICU				
Partially immunized	0.730	0.3928	0.408	0.5200
Fully immunized	0.467	0.4940	0.433	0.5100
Death				
Partially immunized	2.230	0.1356	2.320	0.1300
Fully immunized	0.096	0.7564	0.268	0.6000

The graphical analyses of the residuals confirm the results in Table S6. Figures S9 and S10 show the scaled Schoenfeld residuals against time for the primary outcomes for the partially immunized and fully immunized stages. These results show no major systematic departures from a horizontal line, which are indicative of non-proportional hazards.

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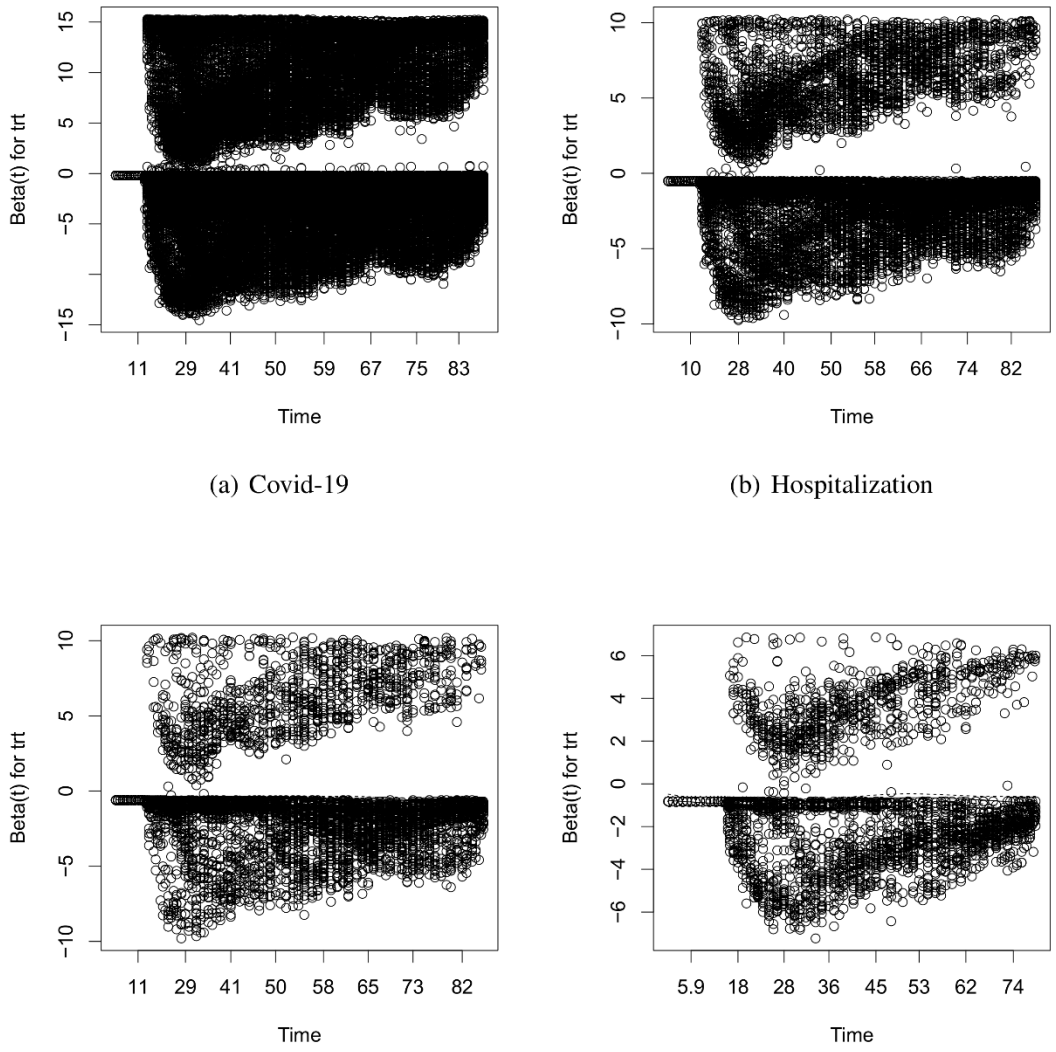
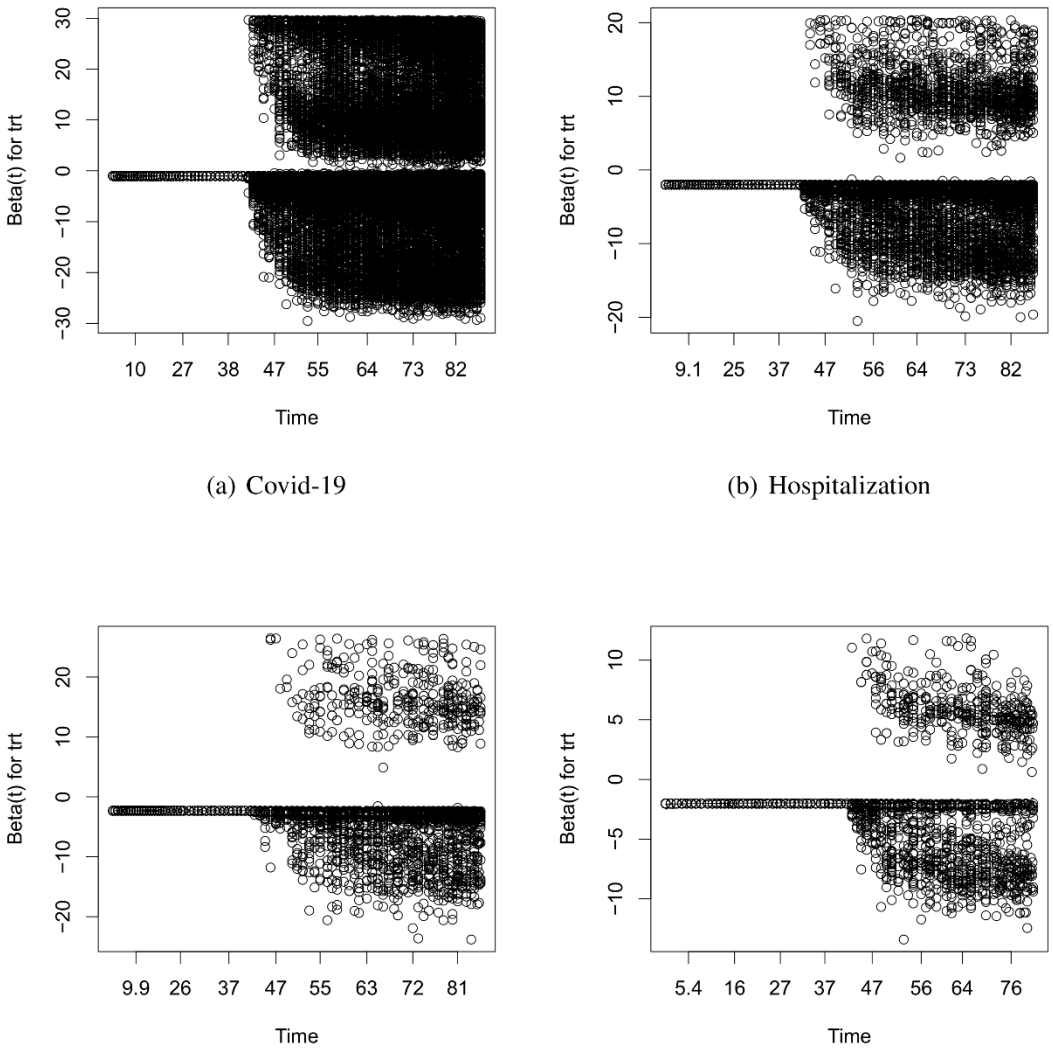


(a) Covid-19 (b) Hospitalization

(c) ICU Hospitalization (d) Confirmed death

Figure S9. Scaled Schoenfeld residuals as a function of time for the analyses of the partially immunized stage. The results are presented under the stratified version of the Cox model with time-dependent vaccination status.



(a) Covid-19 (b) Hospitalization

(c) ICU Hospitalization (d) Confirmed death

Figure S10. Scaled Schoenfeld residuals as a function of time for the analyses of the fully immunized stage. The results are presented under the stratified version of the Cox model with time-dependent vaccination status.

S4. References for the supplementary material

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