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Supplementary appendix

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Supplementary Material

Effectiveness of homologous and heterologous booster shots for an inactivated SARS-CoV-2 vaccine: A large-scale observational study

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S1. Additional context

S1.1 Vaccination campaign and booster shots

We described the Chilean healthcare system in a recent article.[1] In summary, Chile has a hybrid public-private health system, including insurance and service provisions, with high healthcare coverage. About 80% of the Chilean population are affiliated with the Fondo Nacional de Salud (FONASA), a health insurance program that collects, manages, and distributes funds for the public healthcare system.[2] FONASA does not discriminate by age, gender, income, number of dependents, pre-existing conditions, or nationality. Healthcare is available through a network of primary care centers available throughout the territory and referral hospitals. Chile has the highest Covid-19 testing rate in Latin America,[3] with reverse-transcription polymerase-chain-reaction (RT-PCR) assay and antigen tests available for free to FONASA affiliates.

On February 2, 2021, Chile began a mass vaccination campaign based on four Covid-19 vaccines. The Ministry of Health organized vaccination rollout through a publicly available schedule at the national level, assigning specific dates to eligible groups through a publicly available national schedule.[4] The vaccination campaign prioritized older adults, beginning at age 90 or above, front-line health workers, essential workers, and persons with underlying conditions. On August 11, 2021, the Ministry of Health began administering a booster dose for individuals fully vaccinated with the CoronaVac Covid-19 vaccine four months earlier or two months earlier for immunocompromised patients. CoronaVac has been the campaign's backbone, with 59·0% (20·5 million) of all doses administered as of November 16, 2021. Pfizer-BioNTech's BNT162b2 represents 30·5% (10·6 million) of doses, and Oxford-AstraZeneca's AZD1222 vaccine and CanSino Biologics' Ad5-nCoV vaccine represent 8·8% (3·1M) and 1·7% of doses (0·57), respectively.[4]

By program indication, individuals aged 55 years or more received one standard dose of AZD1222, and those below 55 years old received one dose of BNT162b2. An alternative booster of CoronaVac was available for all age groups. In our analysis, we classified the cohort participants into three groups: unvaccinated individuals, vaccinated with two CoronaVac doses (≥14 days after receipt of the second vaccine dose and before the third dose), and vaccinated with three doses (≥14 days after receipt of the third vaccine dose using a homologous regimen with CoronaVac, or a heterologous booster with either AZD1222 or BNT162b2).

As described previously,[1] the vaccination campaign has relied upon existing healthcare infrastructure and vaccination experience. Chile has an electronic national immunization registry, which keeps track of 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, including the booster shots, was organized through a publicly available schedule defined by the Ministry of Health at the national level. The schedule assigns specific dates to eligible groups (Figure S1), which need to show up at any vaccination site with their national ID, with no appointments required. Figures S2 and S3 show the incidence of Covid-19 cases in Chile and in the study cohort, respectively.

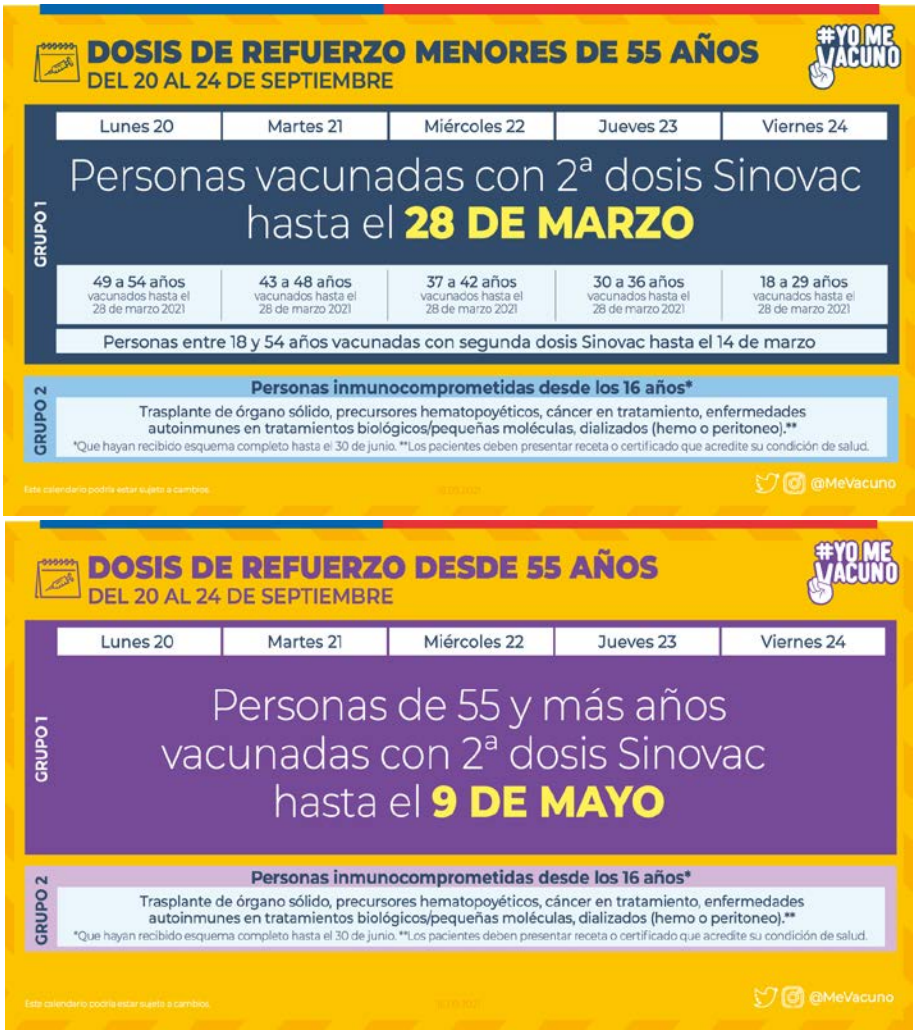

Figure S1. Illustration of the Covid-19 vaccination calendar for booster shots on the week of September 20-24, 2021.[4] Vaccination rollout, including third-dose booster shots, was organized through a publicly available schedule (https://www.gob.cl/yomevacuno/), defined by the Ministry of Health at the national level.

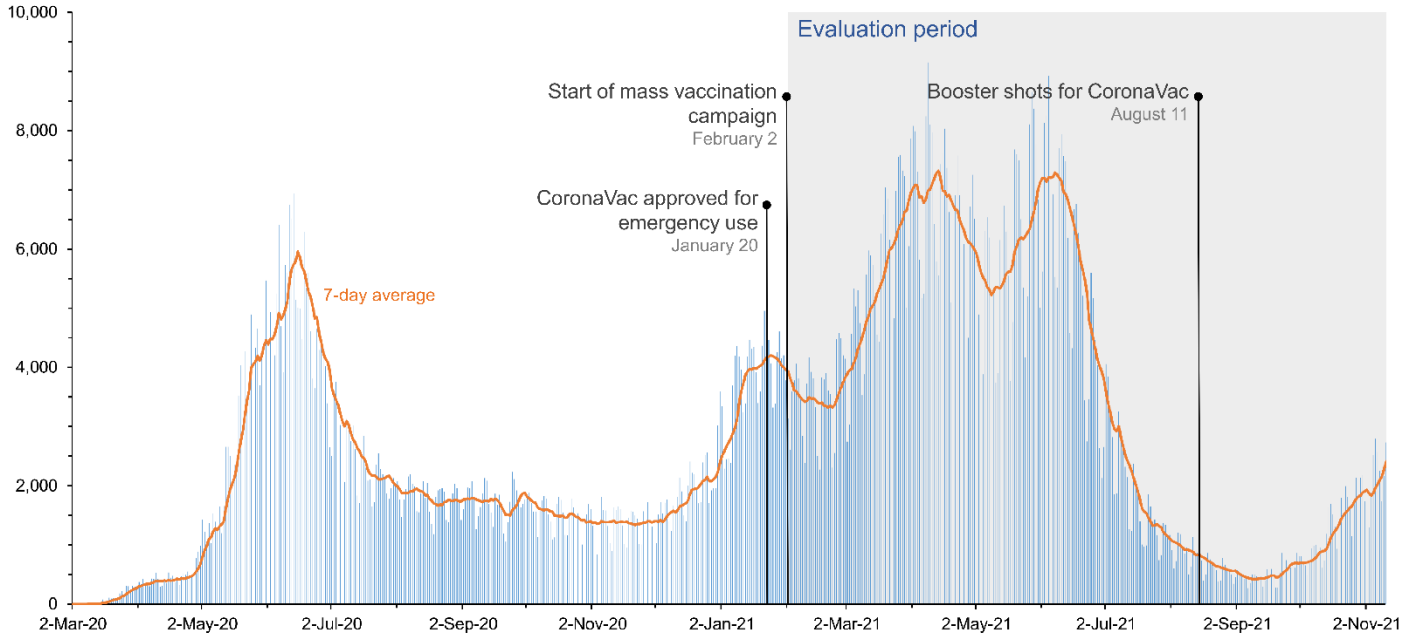

Figure S2. Incidence of Covid-19 cases in Chile, March 2, 2020, through November 10, 2021, and evaluation period for CoronaVac, February 2 through November 10, 2021. Vaccine introduction and the scale-up of the campaign occurred with one of the highest incidence rates of Covid-19 in the pandemic. On August 11, 2021, the Ministry of Health began administering a booster dose using CoronaVac, AZD1222, or BNT162b2 based on a publicly available national vaccination schedule, as shown in Figure S1.

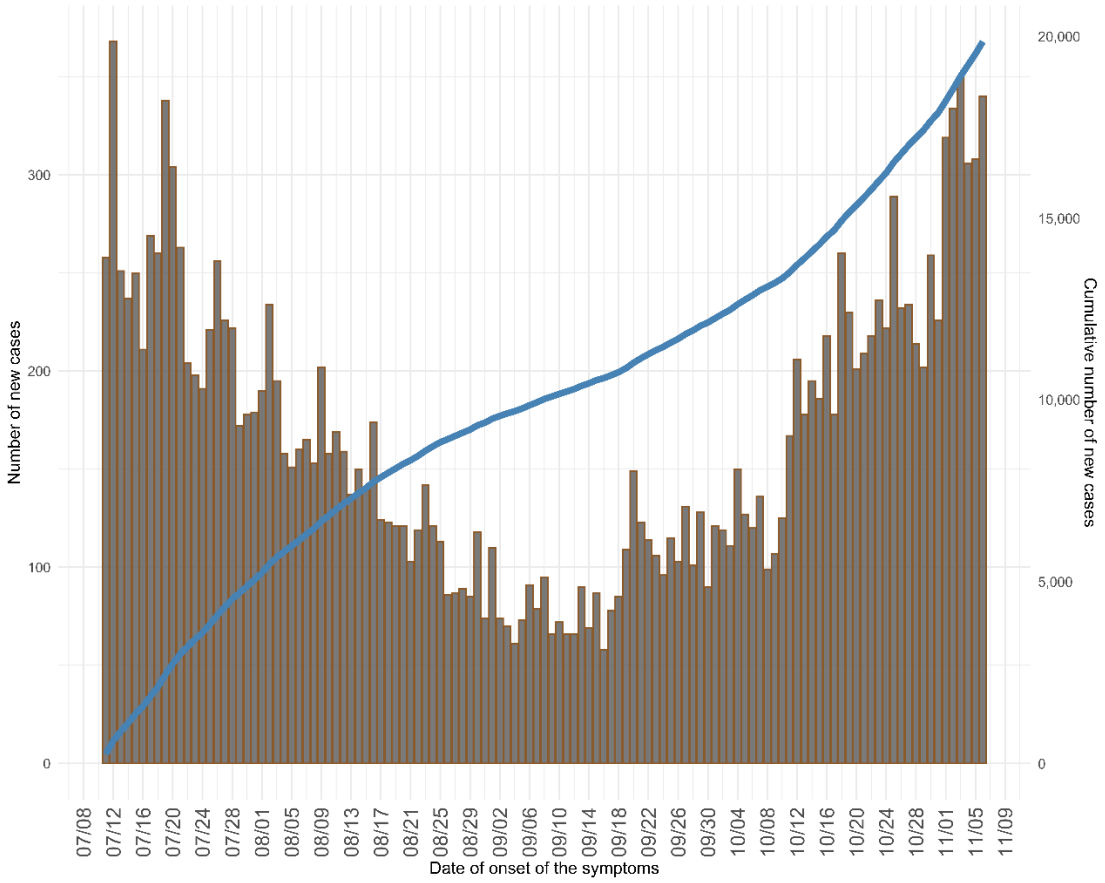

Figure S3. Incidence of Covid-19 cases in the study cohort, August 11 through November 10, 2021. Participants were ≥16 years of age, affiliated to the Fondo Nacional de Salud (FONASA), the public national healthcare system, and vaccinated with CoronaVac, BNT162b2, AZD1222, or Ad5-nCoV Covid-19 vaccines between February 2 and November 10, 2021, or not receiving any Covid-19 vaccination.

S1.2 Characteristics of FONASA affiliates cohort with laboratory-confirmed Covid-19

Table S1. Characteristics of the national study cohort of FONASA affiliates, overall, with laboratory-confirmed Covid-19, and proportion receiving one or more doses of Covid-19 vaccines, February 2 – November 10, 2021*

							Vaccinated					
			COVID-19		Unvaccinated		one dose		two doses		three doses	
Characteristic	No.	Col.%	No.	Row%	No.	Row%	No.	Row%	No.	Row%	No.	Row%
Total	11,174,257	100·0	534,314	4·8	1,071,988	9·6	678,341	6·1	4,754,198	42·6	4,669,390	41·8
Cohort location												
Arica	142,891	1·3	7,148	5·0	17,437	12·2	10,325	7·2	68,012	47·6	47,117	33·0
Tarapacá	200,784	1·8	9,449	4·7	26,400	13·1	14,210	7·1	96,762	48·2	63,412	31·6
Antofagasta	326,840	2·9	11,460	3·5	35,576	10·9	21,932	6·7	153,451	46·9	115,881	35·5
Atacama	189,563	1·7	6,388	3·4	18,496	9·8	11,753	6·2	90,316	47·6	68,998	36·4
Coquimbo	525,697	4·7	18,646	3·5	47,706	9·1	31,870	6·1	242,323	46·1	203,798	38·8
Valparaíso	1,212,248	11·0	47,637	3·9	126,184	10·4	67,511	5·6	489,390	40·4	529,163	43·7
Metropolitana	4,097,759	37·0	202,116	4·9	420,146	10·2	250,787	6·1	1,626,579	39·7	1,800,247	43·9
LB O'Higgins	623,115	5·6	25,372	4·1	46,752	7·5	31,979	5·1	273,685	43·9	270,699	43·4
Maule	762,358	6·8	40,867	5·4	57,384	7·5	41,417	5·4	321,341	42·1	342,216	44·9
Ñuble	344,017	3·1	14,629	4·3	24,771	7·2	16,124	4·7	149,437	43·4	153,685	44·7
Biobío	1,053,354	9·4	56,481	5·4	80,238	7·6	57,905	5·5	456,679	43·3	458,532	43·5
Araucanía	682,943	6·1	42,375	6·2	68,645	10·0	41,571	6·1	321,411	47·1	251,316	36·8
Los Ríos	273,092	2·4	18,019	6·6	25,989	9·5	16,934	6·2	128,341	47·0	101,828	37·3
Los Lagos	584,761	5·2	27,117	4·6	61,123	10·4	46,026	7·9	278,749	47·7	198,863	34·0
Aysén	60,162	0·5	2,406	4·0	5,898	9·8	7,354	12·2	25,923	43·1	20,987	34·9
Magallanes	94,673	0·8	4,204	4·4	9,243	9·8	10,643	11·2	32,139	33·9	42,648	45·0
Sex												
Female	5,993,736	54·0	292,040	4·9	505,607	8·4	298,962	5·0	2,432,234	40·6	2,756,933	46·0
Male	5,180,521	46·0	242,274	4·7	566,381	10·9	379,379	7·3	2,322,304	44·8	1,912,457	36·9
Age group												
16-19	736,905	6·6	32,034	4·3	62,457	8·5	127,731	17·3	514,370	69·8	32,347	4·4

20-29	2,121,616	19·0	127,418	6·0	241,502	11·4	238,566	11·2	1,318,987	62·2	322,561	15·2
30-39	2,001,611	18·0	116,321	5·8	243,211	12·2	144,776	7·2	1,059,332	52·9	554,292	27·7
40-49	1,735,067	16·0	88,973	5·1	165,463	9·5	84,411	4·9	769,601	44·4	715,592	41·2
50-59	1,795,580	16·0	79,308	4·4	136,770	7·6	51,346	2·9	548,956	30·6	1,058,508	59·0
60-69	1,421,931	13·0	49,711	3·5	97·548	6·9	15,666	1·1	289,219	20·3	1,019,498	71·7
70-79	881,220	7·9	26,116	3·0	65,071	7·4	8,657	1·0	148,063	16·8	659,429	74·8
80-more	480,327	4·3	14,433	3·0	59,966	7·2	7,188	1·5	106,010	22·1	307,163	64·0
Comorbidities†												
None	7,586,853	68·0	361,575	4·8	839,456	11·0	558,203	7·4	3,611,727	47·6	2,584,467	34·1
≥ 1	3,587,404	32·0	172,739	4·8	239,532	6·7	120,138	3·4	1,142,811	31·9	2,084,923	58·1
Nationality												
Chilean	10,427,613	93·3	501,394	4·8	895,370	8·6	616,986	5·9	4,417,917	42·4	4,497,340	43·1
Non-Chilean	746,644	6·7	32,920	4·4	176,618	23·7	61,355	8·2	336,621	45·1	172,050	23·0
Income (Chilean pesos)												
<250,000	5,950,957	53·0	258,665	4·3	711,966	12·0	419,695	7·1	2,599,724	43·7	2,219,572	37·3
250,001-500,000	2,813,220	25·0	146,701	5·2	230,977	8·2	164,417	5·8	1,215,177	43·2	1,202,649	42·8
500,001-750,000	1,279,325	11·0	72,281	5·6	77,032	6·0	59,201	4·6	528,235	41·3	614,857	48·1
750,001-1,000,000	569,995	5·1	30,692	5·4	27,697	4·9	20,266	3·6	219,466	39·0	302,566	53·1
1,000,001-1,250,000	275,932	2·5	13,596	4·9	12,037	4·4	8,274	3·0	100,814	36·5	154,807	66·1
1,250,001-1,500,000	133,102	1·2	6,122	4·6	5,758	4·3	3,313	2·5	44,936	33·8	79,095	59·4
>1,500,000	151,726	1·4	6,257	4·1	6,521	4·3	3,175	2·1	46,186	30·4	95,844	63·2

*****Covid-19 denotes coronavirus disease 2019. The stud**y** cohort included eligible persons affiliated with the Fondo Nacional de Salud (FONASA), the national public health insurance program which collects, manages, and distributes funds for the public healthcare system in Chile. The model also included individual-level income and location (16 regions). We found statistically significant differences ($p<0·001$) both in the incidence of Covid-19 and according to vaccination status (unvaccinated, vaccinated with one dose, two doses, or vaccinated with a booster) by sex, age group, comorbidities, nationality, region of residence, and income.. Covid-19 vaccines include AZD1222, Ad5-nCov, BNT162b2, and CoronaVac (Table 2).

†Coexisting conditions 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.

Table S2. Age and sex of cohort participants who received a booster shot, August 11 – November 10, 2021

Booster	Sex	Number	Age		
			Mean	Median	St. deviation
CoronaVac	Female	113,135	69·7	69·1	11·9
	Male	73,811	69·5	69·1	10·6
BNT162b2	Female	1,246,703	44·8	43·5	14·5
	Male	772,557	45·8	45·2	14·7
AZD1222	Female	1,076,741	68·4	67·0	9·36
	Male	844,599	67·5	66·3	8·71

Table S3. Time between vaccine doses by age group

			Time between doses 1 and 2		Time between doses 2 and 3	
Booster	Age group	No.	Days	St. Deviation	Days	St. Deviation
CoronaVac	<20	98	28·2	3·50	171	28·0
	20-29	1,091	29·0	3·26	180	25·8
	30-39	1,789	28·9	3·43	175	26·9
	40-49	2,757	29·0	3·60	175	22·8
	50-59	27,275	28·9	4·07	167	21·0
	60-69	66,791	28·7	3·71	170	19·5
	70-79	53,117	28·6	3·79	171	20·0
	80 or more	34,028	28·7	3·83	174	21·7
BNT162b2	<20	22,273	28·9	4·21	178	22·0
	20-29	280,640	29·0	4·39	176	28·1
	30-39	482,812	29·0	4·13	167	27·9
	40-49	556,904	29·0	3·93	170	23·4
	50-59	392,470	29·1	4·42	178	20·1
	60-69	137,093	29·1	5·44	185	29·9
	70-79	94,254	28·7	4·59	180	30·1
	80 or more	52,814	28·7	4·22	178	29·6
AZD1222	<20	1	28·0	NA	172	NA
	20-29	29	30·3	6·23	151	54·1
	30-39	51	30·7	6·32	166	39·0
	40-49	1,602	28·7	3·86	173	18·8
	50-59	414,496	28·9	3·87	163	20·8
	60-69	780,427	28·7	3·50	168	18·8
	70-79	505,995	28·4	2·97	166	16·3
	80 or more	218,739	28·4	2·73	164	15·9

S1.3 Adverse events

The Chilean Institute of Public Health is the regulatory authority responsible for pharmacovigilance in Chile. Pharmacovigilance is based on passive surveillance and includes the mandatory notification of all adverse events potentially associated with using Covid-19 vaccines by all healthcare facilities and treating healthcare providers. Priority cases classified as serious, unexpected, and of clinical interest are evaluated by an expert committee, including specialists from the National Pharmacovigilance Center, the Immunization Department, and external clinicians. In addition to mandatory reporting of all adverse events, in the context of the Covid-19 vaccination campaign, surveillance included a postvaccination observation period of 30 minutes and an online follow-up survey sent by email for people who received Covid-19 vaccines with a follow-up for suspected adverse events.

Between August 11 and October 18, the Ministry of Health administered 4,364,923 booster doses of the SARS-CoV-2 vaccines from Pfizer-BioNTech's mRNA vaccine BNT162b2, Oxford-AstraZeneca's ChAdOx1 nCov-19 AZD1222 vaccine, and Sinovac's CoronaVac inactivated SARS-CoV-2.[5] During this period, the Chilean Institute of Public Health received 1,302 notifications of postvaccination adverse events;[6] about 29·8 notifications per 100,000 vaccine doses administered. Of these events, 142 were classified as serious, equivalent to 3·3 events per 100,000 doses administered. The majority of reported events (75·4%) were associated with the AZD1222 booster vaccine shot, with 4·8 events per 100,000 doses administered. The rate of reported serious events for BNT162b2 and CoronaVac were 1·7 and 0·9 per 100,000, respectively.

Potential postvaccination adverse events reported may include more than one manifestation. The most frequent clinical manifestations were local manifestations (1055), headache (529), general malaise (309), fever (257), myalgia (164), nausea (154), arthralgia (134), pruritus (123), and fatigue (116), with no statistically significant differences for each symptom by vaccine type. The most frequently reported events were cerebrovascular accident (21), anaphylaxis (18), deep vein thrombosis (13), pulmonary embolism (12). These events rarely occurred, and their association with the vaccine is still under investigation by the Chilean Institute of Public Health. 74·2% of reported adverse occurred in female vaccinees. Eighteen deaths were notified in this period, with a mean age of 76 years. One case was considered inconsistent because there were alternative causes that explained the event. Two cases were considered unclassifiable, and more information is begin collected to reach a final evaluation. The remaining cases are still under investigation.

S1.4 Variants

The Ministry of Health has incorporated SARS-CoV-2 infection into an already existing network of sentinel centers that monitor respiratory viruses using genomic surveillance.[7] The strategy has focused on detecting variants of concern (VOC)[8] through traveler and community surveillance, using non-probabilistic sampling. Traveler surveillance includes testing individuals entering the country through the main international airport (Aeropuerto Internacional Arturo Merino Benitez), other land and sea entry points. Community surveillance includes public and private laboratories, sentinel hospitals, and other organizations.

Between December 22, 2020 and November 15, 2021, 42,297 SARS-CoV-2 samples have been analyzed. Of these, 31·3% (n=13,224) were sequenced and 68·7% (n=29,073) assessed by detection of variant-associated mutations (VAM) using RT-PCR. Of these analyzed samples, 80·4% (n=34,009) correspond to VOC and 8·4% (n=3,573) to variants of interest (VOI).[8] Table S4 shows the variants and main lineages of SARS-CoV-2 by detection method during the study period, December 22, 2020 to November 15, 2021, and Figure S4 shows the evolution of the predominant SARS-CoV-2 lineages.

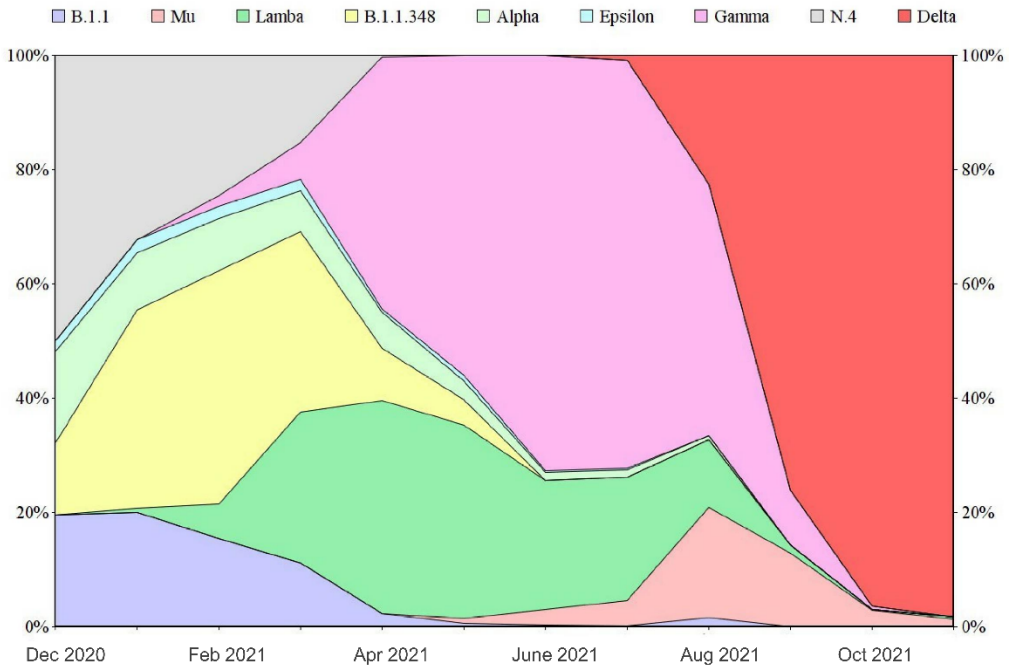

Figure S4. Evolution of the predominant SARS-CoV-2 lineages in Chile, December 22, 2020, to November 15, 2021

Table S4. Main SARS-CoV-2 variants and lineages detected in Chile through genomic surveillance, by detection method, December 22, 2020, through November 15, 2021

Variant	Genomic sequencing	MAV	Total	Proportion (%)	Sub Total	Proportion (%)
Variants of concern VOC						
Alfa (B.1.1.7)	293	127	420	1·0		
Beta (B.1.135)	4	1	5	0·0	34,009	80·4
Gamma (P.1)	4,328	2,618	6,946	16·4		
Delta (B.1.617.2)	5,078	21,556	26,638	63·0		
Variants of interest VOI						
Lambda (C37)	1,684	25	1,709	4·0	3,573	8·4
Mu (B.1.621)	837	1,027	1,864	4·4		
Variants under monitoring VUM						
B.1.525	2	1	3	0·0		
B.1.526	4	0	4	0·0	8	0·0
B.1.617.1	1	0	1	0·0		
Lineages and other variants						
Other lineages*	989	29	1,018	2·4	1,018	2·4
Indeterminate	0	3,689	3,689	8·7	3,689	8·7
Total	13,224	29,073	42,297	100	42,297	100

Notes. MAV denotes mutation associated with variant according to reverse-transcriptase–polymerase-chain-reaction assay for severe acute respiratory syndrome coronavirus 2.
* Corresponds to other low-frequency lineages and unspecified variants. Preliminary data in process of validation.
Source: Department of Epidemiology, Ministry of Health, Chile[7]

S2. Methods

S2.1 Outcomes

Suspected Covid-19 cases notifiable to health authorities through an online platform and require laboratory testing with reverse-transcription polymerase-chain-reaction assay or antigen tests. We estimated the vaccine effectiveness of booster shots using four primary outcomes of interest: laboratory-confirmed Covid-19 cases, hospitalization, admission to the intensive care unit (ICU), and death (ICD-10 code U07.1)[9]. We considered the time from the beginning of the follow-up, on February 2, 2021, to the onset of symptoms as the endpoint for all outcomes. Vaccine effectiveness estimates to Covid-19 cases include the more severe outcomes that follow it. For hospitalization, ICU admission, and death, the classification of the event of interest as failure could have occurred after the onset of symptoms. We focused on the case and used the onset of symptoms as a proxy for the time of infection.

In our main analysis, we classified the cohort participants into two groups: unvaccinated individuals and vaccinated with three doses (≥14 days after receipt of the third vaccine dose using a three-dose schedule with CoronaVac, or mix and match with a booster shot from AZD1222 or BNT162b2).

S2.2 Model description

To estimate hazard ratios, we used an extension of the Cox hazards model that allowed accounting for the time-varying vaccination status of participants.[1,10] We adjusted for differences in observed individual characteristics by inverse probability of treatment weighting as in marginal structural models,[11] estimating the weights non-parametrically based on observed characteristics.[12] . Only time-independent covariates were available in our analyses: cohort location (16 levels), sex (female and male), age group at baseline (8 groups), comorbidities (presence or absence), nationality (Chilean and non-Chilean), and income group (9 groups). The large sample size allowed us to implement a fully non-parametric estimation of the treatment weights based on the empirical frequency (i) of receiving the third dose and second dose, for the existing product combinations, and (ii) of being unvaccinated in the study period, for each combination of the available time-independent predictors.

To account for the time-varying vaccination status and show that our results do not hinge on model specification, we report estimates of the hazard ratios adjusted for age, sex, region of residence, nationality, income, and underlying conditions under both standard and stratified versions of the Cox hazards model, stratifying by all variables in Table

S1. Our analysis strategy and model assumptions for the standard and stratified versions of the Cox hazards model are described in detail the Supplementary Appendix of our recent publication on the effectiveness of CoronaVac.[1]

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,[10] 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 the immunized status (≥14 days after the third dose) over the unvaccinated status. Because immunity status is unknown during the first 13 days between vaccine administration, those periods were excluded from the at-risk person-time in our analyses.[1,14,15]

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).

We show the results for the standard and stratified versions of the Cox hazards model using inverse probability of treatment weighting and also without weighting as a robustness check. Inference was based on a partial likelihood approach.[14]

It is important to underscore that the effectiveness estimate for the booster shot in the Cox model with time-dependent vaccination status compares the risk of an event for individuals who received a booster shot and those who were unvaccinated at each event time. Their risk group is determined by whether they had received or not the booster shot in a specific calendar time. The comparison of the risk of an event is made at the same calendar time. Each term in the partial likelihood of the effectiveness regression coefficient corresponds to the conditional probability of an individual to express the outcome of interest from the risk set at a given calendar time. Under the standard Cox model, all individuals at risk are included in the risk set, and their contribution is weighted based on their covariates (Table S1). Under the stratified version of the Cox model, each stratum has a different risk set determined by the covariates (Table S1).

We conducted the analysis with the survival package[16] of R, version 4.0.5.[17]

S3. Additional results

Table S5. Effectiveness of Covid-19 vaccine CoronaVac, BNT162b2, and AZD1222 boosters in preventing Covid-19 outcomes among cohort participants compared to recipients with primary two-dose vaccination schedule, August 11–November 10, 2021

Immunization status		Cases		Vaccine effectiveness (95% CI)	
	Person-days	No.	Incidence rate 1000 person-days	Weighted, adjusted for all covariates†	Weighted, stratified analysis‡
Covid-19					
CoronaVac (2-doses)	84,878,845	24,910	0·0647	–	–
CoronaVac booster (≥14 days after 3 dose)	8,795,237	323	0·0367	65·6 (62·4 – 68·6)	63·8 (60·4 – 67·0)
BNT162b2 booster (≥14 days after 3 dose)	34,755,396	334	0·0096	93·0 (92·6 – 93·4)	93·5 (93·1 – 93·9)
AZD1222 booster (≥14 days after 3 dose)	96,601,030	969	0·0100	88·9 (88·4 – 89·5)	88·4 (87·8 – 89·0)
Hospitalization					
CoronaVac (2-doses)	403,152,635	1,978	0·0049	–	–
CoronaVac booster (≥14 days after 3 dose)	8,999,341	89	0·0099	60·4 (52·8 – 66·7)	59·3 (51·5 – 65·9)
BNT162b2 booster (≥14 days after 3 dose)	35,941,136	55	0·0015	86·2 (83·1 – 88·7)	86·6 (83·6 – 89·1)
AZD1222 booster (≥14 days after 3 dose)	98,599,509	139	0·0014	93·0 (92·0 – 94·0)	93·0 (91·9 – 93·9)
Admission to ICU					
CoronaVac (2-doses)	404,591,261	610	0·0015	–	–
CoronaVac booster (≥14 days after 3 dose)	9,046,214	21	0·0023	72·3 (59·8 – 81·0)	71·2 (58·1 – 80·2)
BNT162b2 booster (≥14 days after 3 dose)	36,034,118	16	0·0004	82·4 (75·2 – 87·5)	84·1 (77·4 – 88·8)
AZD1222 booster (≥14 days after 3 dose)	98,801,374	26	0·0003	95·9 (94·4 – 97·0)	95·9 (94·3 – 97·0)
Confirmed death					
CoronaVac (2-doses)	404,868,970	316	0·0008	–	–
CoronaVac booster (≥14 days after 3 dose)	9,059,669	18	0·0020	63·5 (46·2 – 75·2)	62·7 (44·9 – 74·7)
BNT162b2 booster (≥14 days after 3 dose)	36,060,324	6	0·0002	90·5 (81·9 – 95·0)	90·7 (82·2 – 95·1)
AZD1222 booster (≥14 days after 3 dose)	98,845,182	22	0·0002	94·7 (92·5 – 96·3)	94·7 (92·5 – 96·3)

*****Participants were classified into two groups: those who were fully immunized with a complete primary immunization schedule (≥14 days after receipt of the second dose), and those who were vaccinated with CoronaVac and received a booster shot. The 13 days between vaccine administration and partial or full immunization were excluded from the at-risk person-time. We show the results for the standard and stratified versions of the Cox hazards model using inverse probability of treatment weighting and also without weighting as a robustness check. Covid-19 denotes coronavirus disease 2019, CI denotes confidence intervals.

† The analysis was adjusted for age, sex, 16 regions of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19.

‡ A stratified version of the extended Cox proportional-hazards model was fit to test the robustness of the estimates to model assumptions, stratifying by age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19, and coded as described in Table 1.

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