Effectiveness of an inactivated SARS-CoV-2 vaccine in children and adolescents: a large-scale observational study

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Summary

Background Policymakers urgently need evidence to adequately balance the costs and benefits of mass vaccination against COVID-19 across all age groups, including children and adolescents. In this study, we aim to assess the effectiveness of CoronaVac's primary series among children and adolescents in Chile.

Methods We used a large prospective national cohort of about two million children and adolescents 6–16 years to estimate the effectiveness of an inactivated SARS-CoV-2 vaccine (CoronaVac) in preventing laboratory-confirmed symptomatic SARS-CoV-2 infection (COVID-19), hospitalisation, and admission to an intensive care unit (ICU) associated with COVID-19. We compared the risk of individuals treated with a complete primary immunization schedule (two doses, 28 days apart) with the risk of unvaccinated individuals during the follow-up period. The study was conducted in Chile from June 27, 2021, to January 12, 2022, when the SARS-CoV-2 Delta variant was predominant but other variants of concern were co-circulating, including Omicron. We used inverse probability-weighted survival regression models to estimate hazard ratios of complete immunization over the unvaccinated status, accounting for time-varying vaccination exposure and adjusting for relevant demographic, socioeconomic, and clinical confounders.

Findings The estimated adjusted vaccine effectiveness for the inactivated SARS-CoV-2 vaccine in children aged 6–16 years was 74.5% (95% CI, 73.8–75.2), 91.0% (95% CI, 87.8–93.4), 93.8% (95% CI, 87.8–93.4) for the prevention of COVID-19, hospitalisation, and ICU admission, respectively. For the subgroup of children 6–11 years, the vaccine effectiveness was 75.8% (95% CI, 74.7–76.8) for the prevention of COVID-19 and 77.9% (95% CI, 61.5–87.3) for the prevention of hospitalisation.

Interpretation Our results suggest that a complete primary immunization schedule with the inactivated SARS-CoV-2 vaccine provides effective protection against severe COVID-19 disease for children 6–16 years.

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Research in context

Evidence before this study

We identified research articles through searches in PubMed and medRxiv, without language restrictions, using the terms ("SARS-CoV-2" OR "COVID-19" OR "2019-nCoV" OR "coronavirus") AND ("vaccine" OR "vaccination") AND ("infant" OR "newborn" OR "child" OR "adolescent"). We searched for studies published between December 1, 2020, and September 1, 2022. We also identified relevant research through the United States National Library of Medicine's website ClinicalTrials.gov. We identified at least ten ongoing phase three clinical trials including children 5–11 years; however, evidence about the efficacy and safety of COVID-19 in pediatric populations is limited, and most studies relate to mRNA vaccines.

Added value of this study

Our study estimates the effectiveness of the CoronaVac vaccine in preventing COVID-19 cases, hospitalisations, and admission to the intensive care unit (ICU), for children and adolescents aged 6–16 years. CoronaVac is among the most used vaccines globally, primarily in low- and middle-income countries. Our estimates are based on a large administrative prospective national cohort of about 2 million children and adolescents to assess the effectiveness of administering a two-dose schedule, adjusting for known demographic, socioeconomic, and clinical confounders of the association between COVID-19 vaccines and outcomes. Vaccine effectiveness estimates are essential, as they reflect real-world challenges of vaccination rollout, such as logistics, cold chains, vaccination schedules, and include more diverse populations than participants in a controlled trial.

Implications of all the available evidence

Our vaccine effectiveness estimates for CoronaVac suggest that a complete primary immunization schedule (two doses, 28 days apart) effectively protects against severe COVID-19 disease for children and adolescents 6–16 years, a finding consistent with the results from phase 2 clinical trials of the vaccine.

Introduction

The global pandemic of COVID-19, caused by SARS-CoV-2, has imposed an enormous burden of disease globally. As of March 2023, more than 759 million cases and about 6.9 million deaths have been reported worldwide.[1] Several effective COVID-19 vaccines have been developed and approved since the beginning of the pandemic, and mass vaccination campaigns are now occurring in most countries.[2]

Children and adolescents can develop COVID-19, including severe illness and death. Nevertheless, the risk of severe COVID-19 in healthy children and adolescents under 18 is substantially lower than in adults and typically does not result in medical intervention.[3,4] The most common COVID-19 clinical features in this group include fever, upper respiratory symptoms, and gastrointestinal symptoms, such as diarrhoea and vomiting.[5,6] A potentially life-threatening clinical presentation of COVID-19 is the multisystemic inflammatory syndrome (MIS-C). MIS-C's clinical presentation is similar to other hyper-inflammatory diseases of children, such as Kawasaki disease, presenting most often with fever and elevated inflammatory markers.[7] MIS-C can affect multiple organ systems, including gastrointestinal, mucocutaneous, cardiovascular, and respiratory,[7,8] affecting recovery.[9] While MIS-C associated mortality is relatively low (~2%), most patients are admitted to the intensive care unit (ICU); about 40% require inotropic support, and about 15% require mechanical ventilation.[10] Another clinical presentation of concern is long COVID, i.e., persisting symptoms following SARS-CoV-2 infection,[11,12] although data on children and adolescents are still limited. A systematic review suggests that, compared to high-income countries, low and middle-income countries may have a higher burden of pediatric COVID-19 mortality.[13] As seen in adults, comorbidities are associated with a more severe clinical presentation of COVID-19 in children and adolescents.[14,15] Last, children may infect higher-risk adults in their household, although research suggests they are probably not the primary source of intra-household SARS-CoV-2 transmission.[16]

There are at least ten ongoing clinical trials for COVID-19 vaccines in children 5–11 years of age in phase 3.[17,18] Nevertheless, evidence is scarce on the efficacy of COVID-19 vaccines in paediatric populations,[19–22] and most available evidence relates to mRNA vaccines. More than 100 countries have authorised the use of mRNA vaccines in children, and about two dozen have approved inactivated-virus vaccines.[23] Two studies assessed the safety and immunogenicity of inactivated SARS-CoV-2 vaccines, Sinovac's CoronaVac and Sinopharm's BBIBP-CorV, in phase 1–2 clinical trials in children and adolescents aged 3–17 years in China.[21,22] Seven studies of real-life vaccine effectiveness in children and adolescents have been published, including the period when Delta and Omicron SARS-CoV-2 variants were predominant.[24–31] In general, mRNA vaccines have shown moderate to good protection against symptomatic COVID-19 among children but are effective in preventing severe disease.[23,24,27–31] Two studies

have examined the effectiveness of two doses of an inactivated SARS-CoV-2 vaccine in paediatric populations. One study in Chile examined the effectiveness of CoronaVac in children 3–5 years,[26] and found modest protection against symptomatic COVID-19 but high protection against severe disease during the Omicron outbreak. The other study, conducted in Argentina, found that BBIBP-CorV was highly effective against COVID-19 related hospitalisation in children 3–11 years.[25] Vaccine effectiveness estimates are essential, as they reflect real-world challenges of vaccination rollout, such as logistics, cold chains, vaccination schedules, and include more diverse populations than participants in a controlled trial. Policymakers urgently need evidence to adequately balance the costs and benefits of mass vaccination across all age groups.[32]

Several regulatory agencies have granted emergency authorisation to vaccinate children, including the US Food and Drug Administration and the European Medicines Agency, and numerous countries have begun vaccinating children.[2] On June 27, 2021, Chile began vaccinating children and adolescents, following an age-based publicly available schedule. Based on emergency use approvals by the Public Health Institute of Chile, children aged 6–11 received a two-dose schedule of CoronaVac, and children 12–16 years received two doses of CoronaVac or BNT162b2. Doses were administered 28 days apart for both vaccines. As described elsewhere, a national immunisation registry keeps track of the vaccination schedules.[33]

Using a large administrative observational dataset of about two million children and adolescents, we estimated the effectiveness of the CoronaVac vaccine in preventing laboratory-confirmed symptomatic SARS-CoV-2 infection (COVID-19), hospitalisation, and admission to an intensive care unit (ICU) associated with COVID-19, for individuals aged 6–16. We also provide vaccine effectiveness estimates among children 6–11 years and adolescents 12–16 years. We estimated the effectiveness of administering a two-dose schedule, adjusting for relevant demographic, socioeconomic, and paediatric clinical confounders of the association between COVID-19 vaccines and the outcomes. We expect these results to inform policymakers, public health officials, and funders considering COVID-19 vaccination for children and adolescents.

Methods

Study population and design

Our study is based on a prospective paediatric observational cohort at the national level in Chile. The cohort includes children and adolescents 6–16 years of age, followed between June 27, 2021, and January 12, 2022. The anonymity of all participants was preserved during all stages of the study. We included all children and adolescents 6–16 years of age affiliated with the national public health insurance program (FONASA, Fondo Nacional de Salud). About 80% of the Chilean population are affiliated with FONASA; the remaining population has private health insurance (14%), are in the armed forces or police (3%) or have no insurance. Children or adolescents with probable or confirmed SARS-CoV-2 infection by reverse-transcription polymerase-chain-reaction (RT-PCR) or antigen test before June 27, 2021, were excluded from the study. We also excluded children who received any COVID-19 vaccine before June 27, 2021. For children that received a vaccine booster (third dose) during the study period, the follow-up was stopped at the date of the booster administration.

The Public Health Institute of Chile, the regulatory authority responsible for pharmacovigilance in Chile, approved the BNT162b2 COVID-19 vaccine for adolescents 12–16 years of age on May 31, 2021. The use of CoronaVac for children aged six years and older was authorized on September 6, 2021. By program indication, children aged 6–11 received CoronaVac, and children 12–16 received CoronaVac or BNT162b2. Both vaccines were administered in two doses, 28 days apart. Children in both age groups received the same CoronaVac dose. We did not focus on the effectiveness of the BNT162b2 vaccine, because those results have been provided elsewhere.[24] Nevertheless, we provide vaccine effectiveness estimates for BNT162b2 in adolescents in the Supplementary Material as a robustness check to our methods. The Public Health Institute authorized the use of BNT162b2 in children over 5 years in December 21, 2021; children in this age group did not have a complete primary immunisation schedule by the end of the study period and were therefore excluded. We focused on the effectiveness of the CoronaVac vaccine in children as those results are not available, and CoronaVac is among the most used vaccines globally, primarily in low- and middle-income countries.[34]

We classified participants into two groups: fully immunised, defined as those with a complete vaccination schedule starting 14 days after receiving the second dose, and unvaccinated individuals. The national vaccination campaign is described in more detail in the Supplementary material.

Outcomes and covariates

We estimated the vaccine effectiveness of CoronaVac for children aged 6–16 using three primary outcomes: laboratory-confirmed symptomatic SARS-CoV-2 infection (COVID-19), hospitalisation, and admission to the ICU associated with COVID-19. All COVID-19 cases included were laboratory-confirmed SARS-CoV-2 infections based on RT-PCR or antigen test and corresponded to ICD-10 code U07.1. RT-PCR and antigen tests are freely available for FONASA affiliates in healthcare centres throughout the country. We also provide estimates of the vaccine effectiveness of

CoronaVac for the prevention of COVID-19 and hospitalisation in the subgroup of children aged 6–11. We did not estimate vaccine effectiveness against fatal outcomes because no deaths were observed in the study cohort as of January 12, 2022. We used the time from the beginning of the follow-up, June 27, 2021, until the onset of symptoms as the endpoint for each outcome. COVID-19 is a nationally notifiable disease. The Chilean Ministry of Health requires that all suspected COVID-19 cases are notified to health authorities through an online platform and undergo laboratory confirmation, by RT-PCR or antigen test for SARS-CoV-2.

We considered relevant demographic, socioeconomic, and clinical confounders of the association between COVID-19 vaccines and the outcomes of interest. These covariates included age, sex, region of residence, health insurance category (a proxy of household income), nationality, and whether the individual had underlying conditions that have been associated with severe COVID-19 illness in children. These conditions included end-stage chronic kidney disease, diabetes mellitus types 1 and 2, cancer, congenital heart disease, human immunodeficiency virus (HIV) infection, epilepsy, haemophilia, asthma, cystic fibrosis, juvenile idiopathic arthritis, and systemic lupus erythematosus.

Statistical analysis

We determined the vaccine effectiveness by estimating the hazard ratio between the treated (complete vaccination schedule) and non-treated unvaccinated status, using the observed time-to-onset of symptoms, from June 27, 2021, through January 12, 2022. We estimated hazard ratios based on the Cox hazards model, allowing for the time-varying vaccination status of children in the cohort.[33,35] We adjusted for differences in observed individual characteristics by inverse probability of treatment weighting as in marginal structural models,[36] estimating the weights non-parametrically based on observed characteristics.[37] To show that our results do not hinge on model specification, we present the hazard ratio estimates using the standard and stratified versions of the Cox hazards model (Supplementary Material, section S4), adjusting by individual's age, sex, region of residence, nationality, health insurance category, and underlying health conditions. Under the stratified Cox model, each combination of predictors has a specific hazard function that can evolve independently. We defined vaccine effectiveness as one minus the corresponding hazard ratio. The comparison of the risk of an event for fully vaccinated and unvaccinated children is made at the same calendar time and the baseline hazard is defined in 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. Inference was based on a partial likelihood approach. Statistical analyses were conducted using the survival package of R version 4.0.5.

Ethics statement

The research protocol was approved by the Comité Ético Científico Clínica Alemana Universidad del Desarrollo. The study was considered exempt from informed consent, no human health risks were identified. Research analysts belong to the Chilean Ministry of Health; our use of data follows Chilean law 19.628 on personal data protection.

Role of the funding source

The funders of this study had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of this manuscript or in the decision to submit the paper for publication.

Results

Study population

Fig. 1 shows the flow diagram of the study cohort. The cohort included 2,086,108 children and adolescents between six and 16 years of age affiliated to FONASA. Of these, 1,976,344 were included in the study as they did not have a COVID-19 history and had not been vaccinated against COVID-19 before June 27, 2021. The descriptive statistics for the study cohort are presented in Table 1. Additional descriptive statistics, including the region of residence and underlying conditions, are provided in Tables S1 and S2.

Vaccine effectiveness

The total follow-up period included approximately 120 million person-days in the CoronaVac group (children 6–16 years) and 230 million person-days in the unvaccinated group (Table 2). A total of 274,042 children (196,769 under 12 years) contributed 299,696,288 person-days, and 1,564,261 children (815,079 under 12 years) contributed 119,679,580 person-days by the end of the follow-up period. The overall study cohort had 12,735 events of COVID-19 disease, 207 hospitalisations, and 30 ICU admissions associated with SARS-CoV-2 confirmed infection among unvaccinated children and children with a complete primary immunization schedule (Table 2 and Table S5).

The estimated adjusted vaccine effectiveness for CoronaVac in children aged 6–16 years, with a complete primary immunization was 74.5% (95% CI, 73.8–75.2) for the prevention of symptomatic COVID-19, 91.0% (95% CI, 87.8–93.4) for the prevention of hospitalisation, and 93.8% (95% CI, 87.8–93.4) for the prevention of COVID-19-related ICU admission (Table 2). For the subgroup of children 6–11 years, the estimated adjusted vaccine effectiveness for CoronaVac with a complete primary immunization was 75.8% (95% CI, 74.7–76.8) for the prevention of COVID-19 and 77.9% (95% CI, 61.5–87.3) for the prevention of

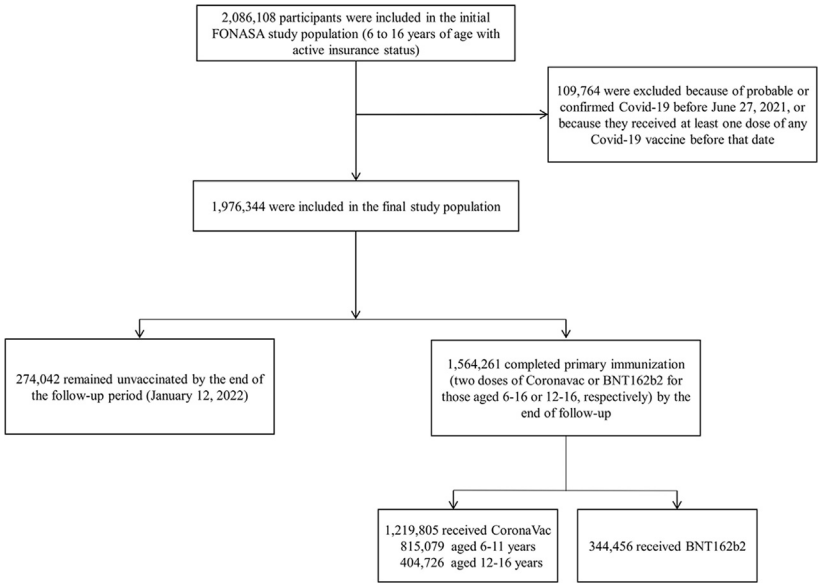

***Fig. 1:* Study participants and cohort eligibility, June 27, 2021, to January 12, 2022.** Participants were between 6 and 16 years of age, affiliated to the Fondo Nacional de Salud (FONASA), the public national healthcare system, and vaccinated with a complete primary immunization (2 doses 28 days apart) with CoronaVac (6–16 years) or BNT162b2 (12–16 years) Covid-19 vaccines between June 27, 2021, and January 12, 2022, or not receiving any Covid-19 vaccination. We excluded individuals who had probable or confirmed coronavirus disease 2019 (Covid-19) according to reverse-transcription polymerase-chain-reaction assay for SARS-Cov-2 or antigen test before June 27, 2021.

hospitalisation. Only six children 6–11 years old were admitted to the ICU in the unvaccinated group and none among those who received CoronaVac (Table 3).

Last, the estimated adjusted vaccine effectiveness for BNT162b2 in adolescents aged 12–16 years, with a complete primary immunization, was 84.4% (95% CI, 83.7–85.0) for the prevention of COVID-19, 93.5% (95% CI, 90.4–95.6) for the prevention of hospitalisation, and 98.0% (95% CI, 89.9–99.6) for the prevention of ICU admission (Table S5).

Discussion

This study provides estimates of the effectiveness of an inactivated SARS-CoV-2 vaccine (CoronaVac) in children and adolescents 6–16 years of age in a countrywide mass vaccination campaign to prevent laboratory-confirmed COVID-19, hospitalisation, and COVID-19-related ICU admission. For children and adolescents with a complete primary immunization with CoronaVac, the adjusted vaccine effectiveness was 74.5%, 91.0%, and 93.8% for COVID-19, hospitalisation, and ICU admission. The subgroup of children 6–11 years had an adjusted vaccine effectiveness of 75.8% against COVID-19 and 77.9% to prevent hospitalisation. Six cases were admitted to the ICU in the unvaccinated group, resulting in an estimated 100% vaccine effectiveness for preventing COVID-19-related ICU admission, but additional data would likely result in a lower estimate.

Our results are consistent with estimates of the effectiveness of the CoronaVac vaccine in preventing COVID-19 in an adult cohort 16 years and older in Chile in early 2021.[33] The study found and adjusted vaccine effectiveness of 65.9% (95% CI, 65.2–66.6) for the prevention of COVID-19, 87.5% (95% CI, 86.7 to 88.2) for the prevention of hospitalisation, and 90.3% (95% CI, 89.1 to 91.4) for the prevention of ICU admission in adults. For children 6–11 years with a complete primary immunization with CoronaVac, the adjusted vaccine effectiveness was 75.8% for preventing COVID-19 and 77.9% for hospitalisation. The low baseline risk for presenting severe disease among unvaccinated children and few hospitalisation events during the study period may explain the lower effectiveness estimated for this group, but younger children could respond to the vaccine differently. Similar to previous vaccine effectiveness estimates for adults,[33] our estimates for children and adolescents 6–16 years also show higher protection against severe disease than against COVID-19. A recent study found substantially lower effectiveness of a primary immunization schedule with CoronaVac in children 3–5 years during the Omicron outbreak.[26] The adjusted vaccine effectiveness was 38.2% (95%CI, 36.5–39.9) against symptomatic COVID-19, 64.6% (95% CI, 49.6–75.2) against hospitalisation, and 69.0% (95% CI, 18.6–88.2) against ICU admission. The lower vaccine effectiveness could be explained by a younger cohort or because of the predominance of Omicron in that study.

As a robustness check to support our approach and analysis, we estimated an adjusted vaccine effectiveness

Characteristic	No.	Col.%	COVID-19		Unvaccinated		Vaccinated					
							One dose		Two doses		Three doses	
			No.	Row%	No.	Row%	No.	Row%	No.	Row%	No.	Row%
Total	1,976,344	100	14,282	0.7	274,042	13.9	138,041	7.0	1,430,124	72.4	134,137	6.8
Sex												
Female	967,074	49.0	7291	0.75	128,067	13.0	64,903	6.7	703,542	72.7	70,562	7.3
Male	1,009,270	51.0	6991	0.69	145,975	14.0	73,138	7.2	726,582	72.0	63,575	6.3
Age group												
6	185,179	9.4	992	0.5	43,852	24.0	20,757	11.0	120,569	65.1	1	0.0
7	183,622	9.3	1025	0.6	36,650	20.0	17,694	9.6	129,277	70.4	1	0.0
8	181,165	9.2	1138	0.6	32,877	18.0	16,139	8.9	132,148	72.9	1	0.0
9	185,022	9.4	1256	0.7	30,802	17.0	16,143	8.7	138,077	74.6	0	0.0
10	188,996	9.6	1428	0.7	28,676	15.0	15,856	8.4	144,464	76.4	0	0.0
11	187,941	9.5	1514	0.8	23,912	13.0	13,488	7.2	150,260	79.9	281	0.1
12	185,790	9.4	1489	0.8	19,591	11.0	10,229	5.5	150,447	81.0	5523	3.0
13	179,140	9.1	1519	0.8	16,299	9.1	8752	4.9	147,117	82.0	6972	3.9
14	173,105	8.8	1385	0.8	15,146	8.7	7288	4.2	125,450	72.5	25,221	14.6
15	168,202	8.5	1266	0.7	13,752	8.2	6226	3.7	104,537	62.1	43,687	26.0
16	158,182	8.0	1270	0.8	12,485	7.9	5469	3.5	87,778	55.5	52,450	33.2
Comorbidities[b]												
None	1,726,075	87.0	12,146	0.7	244,342	14.0	121,003	7.0	1,244,602	72.1	116,128	6.7
≥1	250,269	13.0	2136	0.8	29,700	12.0	17,038	6.8	185,522	74.1	18,009	7.2
Nationality												
Chilean	1,917,024	97.0	14,044	0.7	260,369	14.0	134,454	7.0	1,391,052	72.6	131,149	6.8
Non-Chilean	59,320	3.0	238	0.4	13,673	23.0	3587	6.0	39,072	65.9	2988	5.0

Notes. [a]COVID-19 denotes coronavirus disease 2019. The study cohort included children and adolescents 6–16 years of age 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. We excluded children or adolescents with probable or confirmed SARS-CoV-2 infection before June 27, 2021, or if they had received any COVID-19 vaccine before June 27, 2021. The model also included health insurance category (a proxy of family income), and location (16 regions). We found statistically significant differences ($p < 0.001$) between COVID-19 patients and the vaccinated and unvaccinated groups by sex, age group, comorbidities, nationality, region of residence, and category of health insurance. Additional details are shown in Table S1. COVID-19 vaccines include CoronaVac and BNT162b2 (Table 2 and Table S5, respectively). [b]Coexisting conditions included chronic kidney disease, diabetes mellitus types 1 and 2, cancer, congenital heart disease, HIV, epilepsy, hemophilia, asthma, cystic fibrosis, juvenile idiopathic arthritis, and systemic lupus erythematosus.

Table 1: **Characteristics of the study cohort of children and adolescents affiliated to FONASA, overall, with laboratory-confirmed COVID-19, and the proportion receiving one or more doses of COVID-19 vaccines, June 27, 2021 through January 12, 2022.**[a]

for adolescents with a complete primary immunization using BNT162b2 of 84.4%, 93.5%, and 98.0% for COVID-19, hospitalisation, and COVID-19 related ICU admission associated with SARS-CoV-2 infection. Our BNT162b2 vaccine effectiveness estimates for adolescents are consistent with the results of a multicenter case–control study of fully immunised adolescents 12–18 years old in June through October 2021 in the United States.[24] The study reported vaccine effectiveness of 94% (95%CI 90 to 96) to prevent COVID-19 related hospitalisations and 98% (95%CI 93 to 99) against ICU admission. The study estimated vaccine effectiveness in a period when B.1.617.2 (Delta) was the predominant circulating SARS-CoV-2 variant. Delta was also the predominant variant during the study period in Chile (Fig. S1). Furthermore, a recent study reported a vaccine efficacy against COVID-19 of 90.7% (95% CI 67.7–98.3) for BNT162BT in 5-to-11-year-old children.[20] Our vaccine effectiveness estimate for protection against COVID-19 in 12-to-16-year-old children was a slightly lower, 84.4% (95% CI 83.7–85.0), but within their estimated confidence intervals. Our estimates are also consistent with as study from Singapore, when the Omicron variant was rapidly spreading.[29] Those researchers found that BNT162b2 had a vaccine effectiveness of 82 7% (95%CI, 74 8 to 88 2) against COVID-19 related hospitalisation among children aged 5–11 years. Other studies conducted during the Omicron outbreak found substantially lower vaccine effectiveness estimates for BNT162BT.[30,31]

There is an ongoing scientific debate about the convenience of vaccinating children against COVID-19.[32,38] The cost-benefit analysis is not straightforward, particularly when considering global COVID-19 vaccination targets and inequities in vaccine access.[38] Vaccinating children and adolescents against SARS-CoV-2 has several potential benefits.[32] First, it prevents COVID-19 cases, particularly severe illness and potential deaths among children with underlying health conditions. Second, it may prevent long-term consequences of

Immunization status	Person-days	Cases		Vaccine effectiveness (95% CI)	
		No.	Incidence rate	Weighted, standard adjustment[b]	Weighted, stratified analysis[c]
			1000 person-days		
COVID-19					
Unvaccinated	229,123,227	8648	0.0377	–	–
CoronaVac (6–16 yr) (≥14 days after 2 dose)	118,833,107	2998	0.0252	74.8 (74.1–75.5)	74.5 (73.8–75.2)
Hospitalisation					
Unvaccinated	229,684,717	181	0.0008	–	–
CoronaVac (6–16 yr) (≥14 days after 2 dose)	119,666,696	16	0.0001	91.3 (88.1–93.6)	91.0 (87.8–93.4)
Admission to ICU					
Unvaccinated	229,696,288	28	0.0001	–	–
CoronaVac (6–16 yr) (≥14 days after 2 dose)	119,679,580	1	0.00001	93.8 (85.7–97.3)	93.8 (85.7–97.3)

[a]Participants were classified into two groups: those who were unvaccinated and those who were fully immunized (≥14 days after receipt of the second dose) with CoronaVac. The 13 days between vaccine administration and 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. COVID-19 denotes coronavirus disease 2019, CI denotes confidence intervals. [b]The analysis was adjusted for age, sex, 16 regions of residence, health insurance category, nationality, and whether the patient had underlying conditions that have been associated with severe COVID-19 in children. [c]A stratified version of the Cox proportional-hazards model was fit to test the robustness of the estimates to model assumptions, stratifying by age, sex, region of residence, health insurance category (a proxy of household income), nationality, and whether the patient had underlying conditions that have been associated with severe COVID-19, and coded as described in Table 1.

Table 2: **Effectiveness of the CoronaVac vaccine in preventing COVID-19 outcomes among children 6–16 years of age in the study cohort according to immunization status, June 27, 2021, through January 12, 2022.[a]**

SARS-CoV-2 infection, including MIS-C and long COVID.[39] Third, vaccination may reduce transmission to other children and adults[16] and, by mitigating community transmission, may help reduce the need for non-pharmaceutical interventions such as lockdowns, school exclusions and closures, and quarantines. COVID-19, regardless of clinical severity, and also non-pharmaceutical interventions to mitigate transmission have already affected children's educational attainment, mental health, school services, and have increased inequalities.[38,40] There is increasing evidence that vaccinating children and adolescents may significantly reduce the disease burden of COVID-19. Longer follow-up will allow responding whether vaccines can help prevent long-term complications, such as MIS-C and persistent symptoms following severe SARS-CoV-2

Immunization status	Person-days	Cases		Vaccine effectiveness (95% CI)	
		No.	Incidence rate	Weighted, standard adjustment[b]	Weighted, stratified analysis[c]
			1000 person-days		
COVID-19					
Unvaccinated	155,092,218	5021	0.0324	–	–
CoronaVac (6–11 yr) (≥14 days after 2 dose)	78,449,194	1502	0.0191	75.8 (74.8–76.8)	75.8 (74.7–76.8)
Hospitalisation					
Unvaccinated	155,434,360	61	0.0004	–	–
CoronaVac (6–11 yr) (≥14 days after 2 dose)	78,940,292	8	0.0001	78.5 (62.8–87.6)	77.9 (61.5–87.3)

[a]Participants were classified into two groups: those who were unvaccinated and those who were fully immunized (≥14 days after receipt of the second dose) with CoronaVac. The 13 days between vaccine administration and 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. COVID-19 denotes coronavirus disease 2019, CI denotes confidence intervals. There were only six children 6–11 years admitted to the ICU in the unvaccinated group and none among those who received CoronaVac. This results in an estimated 100.0% vaccine effectiveness for the prevention of COVID-19-related ICU admission, but more data would most likely result in a lower estimate. [b]The analysis was adjusted for age, sex, 16 regions of residence, health insurance category, nationality, and whether the patient had underlying conditions that have been associated with severe COVID-19 in children. [c]A stratified version of the Cox proportional-hazards model was fit to test the robustness of the estimates to model assumptions, stratifying by age, sex, region of residence, health insurance category (a proxy of household income), nationality, and whether the patient had underlying conditions that have been associated with severe COVID-19, and coded as described in Table 1.

Table 3: **Effectiveness of the CoronaVac COVID-19 vaccine in preventing COVID-19 outcomes among children 6–11 years of age in the study cohort according to immunization status, June 27, 2021, through January 12, 2022.[a]**

infection, such as headaches, fatigue, and sleep disturbances.[11] We hope our estimates will help inform this ongoing debate and support global decision-making in the COVID-19 response.

The main strengths of this study include the use of a large cohort of about two million children, aged six to 16 years, combining administrative and healthcare data that represents about 80% of the Chilean population. This large sample size allowed us to non-parametrically estimate the inverse probability of treatment weights and fit a stratified Cox proportional hazards model for the different outcomes of interest (each combination of predictors has a specific hazard function), adding robustness to our statistical approach. Our real-world estimates examine one of the most widely used COVID-19 vaccines globally and are an essential complement to efficacy estimates from randomized controlled trials.

The main limitations in our study include potential selection and misclassification biases, as in all observational studies. We adjusted for known and observable demographic, socioeconomic, and clinical confounders that could affect vaccine effectiveness estimates, but there may be residual confounding. We cannot completely rule out the existence of systematic unobservable differences between the treated and unvaccinated children or their caregivers, such as health-seeking behaviour or personal beliefs, that could affect their risk of infection and their propensity to be vaccinated. We cannot be sure in which direction, if any, these unmeasured confounders could potentially affect our estimates. Misclassification bias is unlikely, as Chile has a centralized electronic immunization and laboratory registry and testing for SARS-CoV-2 infection is free and widely available. A second limitation is that Chile lacks representative genomic surveillance data to estimate the true prevalence of variants of concern (Alfa, Beta, Gamma, Delta, and Omicron) that may affect vaccine effectiveness estimates. Genomic surveillance reports by the Ministry of Health suggest that the predominant variant during the study period was Delta, although Omicron became predominant during the final weeks of the study (Tables S3 and S4, and Fig. S1). We lack representative data to estimate vaccine effectiveness against specific variants of concern.

Overall, our vaccine effectiveness estimates suggest that a complete primary immunization schedule (two doses, 28 days apart) provides an effective protection against severe COVID-19 disease for children 6–16 years.

Contributors

The study team was entirely responsible for study design, data collection, and analysis. The authors vouch for the accuracy and completeness of the data and accept responsibility for publication. AJ, FL, HGE, and RA directly accessed and verified the underlying data reported. AJ, HE, and RA had access to raw data. Drs. A. Jara, E. Undurraga, and R. Araos wrote the first draft of the manuscript and contributed equally to this article. RA is responsible for the decision to submit the manuscript for publication.

Data sharing statement

Owing to data privacy regulations, this study's individual-level data used in this study cannot be shared (Law N19.628). Aggregate data on vaccination and COVID-19 incidence are publicly available at https://github.com/MinCiencia/Datos-COVID19/.

Declaration of interests

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J.C. Flores is a non-paid member of the Servicio de Salud Metropolitano Sur Oriente's Ethics Committee, Santiago, Chile.

The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100487.

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