Effectiveness of CoronaVac in children 3 to 5 years during the omicron SARS-CoV-2 outbreak

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Abstract

The outbreak of the B.1.1.529 lineage of SARS-CoV-2 (omicron) has caused an unprecedented number of Covid-19 cases, including pediatric hospital admissions. Policymakers urgently need evidence of vaccine effectiveness in children to balance the costs and benefits of vaccination campaigns, but the evidence is sparse or non-existing. Leveraging a population-based cohort of 490,694 children aged 3–5 years, we estimated the effectiveness of administering a two-dose schedule, 28 days apart, of CoronaVac using inverse probability-weighted survival regression models to estimate hazard ratios of complete immunization over non-vaccination, accounting for time-varying vaccination exposure and relevant confounders. The study was conducted between December 6, 2021, and February 26, 2022, during the omicron outbreak in Chile. The estimated vaccine effectiveness was 38.2% (95%CI, 36.5–39.9) against Covid-19, 64.6% (95%CI, 49.6–75.2) against hospitalization, and 69.0% (95%CI, 18.6–88.2) to prevent intensive care unit admission. The effectiveness was modest; however, protection against severe disease remained high.

Main Text

The emergence and spread of the B.1.1.529 lineage of SARS-CoV-2, the cause of coronavirus disease 2019 (Covid-19), has caused an unprecedented number of infections worldwide in a short period.[1,2] Emerging evidence suggests that omicron causes less severe disease than previous variants of concern (VOC), probably due to lower virulence, infection-acquired immunity, and higher vaccination coverage.[3–6] However, its high transmissibility and ability to partially evade the immune response induced has been associated with a substantial increase in severe Covid-19 cases globally.[2] The absolute number of pediatric hospital admissions has also surpassed previous waves,[4,7,8] straining healthcare systems even further. The increase may be related to higher transmissibility of omicron, less use of facemasks in children, and, especially concerning, lower vaccination rates among children.

Policymakers urgently need evidence of the effectiveness of Covid-19 vaccines in preventing severe clinical presentations of Covid-19 in children to balance the costs and benefits of mass vaccination campaigns. While the risk of severe Covid-19 in healthy children is substantially lower than among adults, vaccinating children may reduce community transmission, avoid potentially life-threatening presentations such as multisystemic inflammatory syndrome (MIS-C), and prevent long-term consequences of SARS-CoV-2 infection.[9] Although numerous countries are vaccinating children, few have authorized Covid-19 vaccines for children under five, and some have restricted vaccines for children older than 12 years.[10] Evidence of the efficacy or effectiveness of Covid-19 vaccines in children is limited, primarily related to mRNA vaccines, and only one study was conducted during the omicron outbreak.[11–14] To the best of our knowledge, there is no evidence of vaccine effectiveness against Covid-19 in children under five years. Furthermore, recent research suggests that several Covid-19 vaccine platforms provide limited protection against infection and symptomatic disease caused by the omicron variant but were more effective against severe disease.[15–17] These studies have examined vaccine protection against omicron in adult

populations but are consistent with preliminary, unpublished results from a study in children 5 to 12 years.[13]

Leveraging a population-based cohort of children aged 3 to 5 years, we estimated the effectiveness of the complete primary immunization schedule (two doses, 28 days apart) of an inactivated SARS-CoV-2 vaccine, CoronaVac, to prevent laboratory-confirmed Covid-19, hospitalization, and admission to an intensive care unit (ICU). We estimated vaccine effectiveness using inverse probability-weighted survival regression models to estimate hazard ratios of complete immunization (starting 14 days after the second dose) over the unvaccinated status, accounting for time-varying vaccination exposure and available clinical, demographic, and socioeconomic confounders at baseline.

Our study cohort included 516,250 children aged 3 to 5 years affiliated to the Fondo Nacional de Salud (FONASA), the public national healthcare system. 490,694 children had received two doses of CoronaVac, 28 days apart between December 6, 2021, and February 26, 2022, or did not receive any Covid-19 vaccination. We excluded children who had probable or confirmed Covid-19 according to reverse-transcription polymerase-chain-reaction assay for SARS-CoV-2 or antigen test before December 6, 2021 (Supplementary Figure S1). The cohort characteristics are described in Supplementary Tables S1 and S2. Vaccination rollout was organized through a public schedule; children needed to show up at their nearest vaccination site with their national ID card (Supplementary Figure S2). The study period enclosed the omicron outbreak in Chile (Supplementary Tables S3 and S4, Fig.S3)

The estimated adjusted vaccine effectiveness for CoronaVac in children aged 3 to 5 years during the omicron outbreak was 38.2% (95% CI, 36.5–39.9) for the prevention of Covid-19, 64.6% (95% CI, 49.6–75.2) for the prevention of hospitalization, and 69.0% (95% CI, 18.6–88.2) for the prevention of Covid-19-related ICU admission (Table 1). We did not estimate vaccine effectiveness against fatal outcomes because only two deaths were observed in the unvaccinated group on February 26, 2022.

Table 1
Effectiveness of the CoronaVac Covid-19 vaccine in preventing Covid-19 outcomes among children 3–5 years of age in the study cohort according to immunization status, December 6, 2021, through February 26, 2022*

Immunization status		Cases		Vaccine effectiveness (95% CI)	
	Person-days	No.	Incidence rate	Weighted, standard	Weighted, stratified
			1000 person-days	adjustment †	analysis †
Covid-19					
Unvaccinated	29,404,535	7,555	0.2569	–	–
CoronaVac (3–5 year.)	18,499,492	4,562	0.2466	37.9	38.2
(≥ 14 days after 2 dose)				(36.1 ; 39.6)	(36.5 ; 39.9)
Hospitalization					
Unvaccinated	29,579,595	62	0.0021	–	–
CoronaVac (3–5 year.)	18,990,209	23	0.0012	65.2	64.6
(≥ 14 days after 2 dose)				(50.4 ; 75.6)	(49.6 ; 75.2)
Admission to ICU					
Unvaccinated	29,580,825	9	0.0003	–	–
CoronaVac (3–5 year.)	18,993,888	3	0.0002	68.8	69.0
(≥ 14 days after 2 dose)				(18.0 ; 88.1)	(18.6 ; 88.2)

* Covid-19 denotes coronavirus disease 2019, CI denotes confidence intervals, yr. denotes years. We classified participants' status into two categories during the study period: unvaccinated and fully immunized (≥ 14 days after receiving the second dose with CoronaVac). The days between the first dose vaccine administration and the full immunization were excluded from the at-risk person-time. We provide the results for the standard and stratified versions of the Cox hazards model using inverse probability of treatment weighting.

† The analyses were adjusted for 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 in children, coded as described in Table S1. The standard and stratified versions of the extended Cox proportional-hazards model were fit to test the robustness of the estimates to model assumptions.

Our estimates provide evidence of vaccination effectiveness in children aged 3 to 5 years during the omicron outbreak in Chile. These results are substantially lower than recent preliminary estimates of the effectiveness of two-dose vaccination of CoronaVac in children 6 to 16 years, in a period when B.1.617.2 (Delta) was the predominant circulating SARS-CoV-2 variant.[14] In that study, the estimated effectiveness in children 6 to 16 years was 74.5% (95% CI, 73.8–75.2) for the prevention of Covid-19, 91.0% (95% CI, 87.8–93.4) for the prevention of hospitalization, and 93.8% (95% CI, 87.8–93.4) for the prevention of Covid-19-related ICU admission. The estimates for the subgroup of children aged 6–11 were 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 hospitalization.[14] While the estimates are not directly comparable, the lower estimated vaccine effectiveness could be due to omicron or because the cohort included younger children.

Recent research suggests that vaccines may be less effective against omicron. Consistent with our results, an unpublished study in New York,[13] found that the vaccine effectiveness of BNT162b2 for the prevention of Covid-19 and hospitalization decreased from 66–51% and from 85–73% for children aged 12–17 years, respectively. The drop was more considerable among children 5 to 11 years; protection against Covid-19 fell from 68–12%, and protection against hospitalization fell from 100–48%.[13] Results among adults tell the same story. Early data from South Africa reported that BNT162b2 protection against Covid-19 related hospitalization decreased from 93–70% among adults.[15] Among adults in the United Kingdom, two doses of ChAdOx1 nCoV-19 provided no detectable protection against the omicron variant after 20 weeks, and two doses of BNT162b2 were only 8.8% effective against omicron after 25 weeks.[16] The study suggests a BNT162b2 or mRNA-1273 booster substantially increased protection against omicron.[16] Similarly, a study that evaluated serum neutralization against omicron or D614G variant among adult participants with the mRNA-1273 vaccine primary series observed neutralization titers 35 times lower for omicron.[17]

Children's age could also potentially affect vaccine effectiveness estimates for severe disease, as suggested by older children in recent unpublished studies in New York[13] and Chile.[14] Furthermore, clinical trials for Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2 in children six months to under five years old are being conducted. Preliminary results for two 3 µg dose schedule, 21 days apart, of the BNT162b2 in children 2 to < 5 years old found disappointing results, although the immune response of children between six months and two years was comparable to that of young adults.[18] Data from the mRNA-1273 vaccine in children have not yet been released.

Observational studies have limitations. Selection bias could affect vaccine effectiveness estimates if the vaccinated and unvaccinated groups are systematically different. We partially addressed this issue by adjusting our estimates with observable confounders that may affect vaccination and the risk of Covid-19. However, we do not have data to assess whether vaccinated and unvaccinated children or their caregivers differ in some unobservable characteristics, such as compliance with Covid-19 protocols. Another limitation in our study relates to genomic surveillance capabilities. The Ministry of Health's

strategy has focused on detecting variants of concern through traveler and community surveillance but uses non-probabilistic sampling (Supplementary Fig.S3, Tables S3 and S4).

To our advantage, data were collected during the omicron outbreak, with the highest transmission rates since the beginning of the pandemic. Vaccination rollout was quick and had high uptake (Supplementary Figure S2). Our estimated vaccine effectiveness reflects a “real-life” situation by including the challenges public health officials face in the field, such as a more diverse set of participants (e.g., with underlying conditions), schedule compliance, logistics, and cold chains. These estimates may be essential for decision making as a complement to controlled clinical trials.

Our results show that the effectiveness of CoronaVac in children 3 to 5 years against Covid-19 during the omicron was modest, although protection against severe disease remained high.

Online Methods

Outcomes

The Ministry of Health in Chile requires that all suspected Covid-19 cases are notified to health authorities through an online platform. Suspected Covid-19 cases require laboratory testing with reverse-transcription polymerase-chain-reaction assay or antigen tests. We estimated the vaccine effectiveness of CoronaVac for children aged 3 to 5 years using three primary outcomes: laboratory-confirmed Covid-19, hospitalization, and admission to the ICU associated with SARS-CoV-2 infection. We considered the time to the onset of symptoms from the beginning of the follow-up, December 6, 2021, as the endpoint of each outcome. We used the onset of symptoms as a proxy for the time of infection. We classified participants status into two categories along the study period: unvaccinated and fully immunized (≥ 14 days after receipt of the second dose with CoronaVac). The period between the first dose administration and 13 days after the second dose was excluded from the at-risk person-time in our analyses.

Model description

To estimate hazard ratios, we used extensions of the Cox hazards model that allowed us to account for the time-varying vaccination status of participants.[19,20] We adjusted for differences in observed individual characteristics by inverse probability of treatment weighting as in marginal structural models,[21] estimating the weights non-parametrically.[22] Vaccine effectiveness was estimated as hazard ratio between the treated and non-treated status. We reported hazard ratios estimates adjusted for age, sex, region of residence, nationality, health insurance category (a proxy of household income), and underlying conditions (Supplementary Tables S1 and S2) under the standard and stratified versions of the Cox hazards model.

Let T_i be the time-to-event of interest, from December 6, 2021, for the *i*-th individual in the cohort,

$i = 1, \ldots, n$. Let x_i, $i = 1, \ldots, n$, 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

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

where

$$\begin{aligned} f(t \mid \boldsymbol{x}_i, z_i) &= \lambda_0(t) \exp\left\{\boldsymbol{x}_i'\gamma + \beta_{z_i(t)}\right\} \times \\ &\quad \exp\left\{-\exp\left\{\boldsymbol{x}_i'\gamma + \beta_{z_i(t)}\right\} \int_0^t \lambda_0(u)du\right\}, \end{aligned}$$

with $\gamma \in \mathrm{R}^p$ being a vector of regression coefficients, $\beta_k \in \mathrm{R}$ being the regression coefficient measuring the effectiveness of the k^{th} 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 participants at each event time but re-evaluates which risk group each person belonged to, based on whether they had been immunized by that time.

We also fitted a stratified version of the model,[23] where the time-to-event distribution is given by

$$\begin{aligned} f(t \mid \boldsymbol{x}_i, z_i) &= \lambda_{\boldsymbol{x}_i,0}(t) \exp\left\{\beta_{z_i(t)}\right\} \times \\ &\quad \exp\left\{-\exp\left\{\beta_{z_i(t)}\right\} \int_0^t \lambda_{\boldsymbol{x}_i,0}(u)du\right\}, \end{aligned}$$

with $\beta_k \in \mathrm{R}$ being the regression coefficient measuring the effectiveness of the kth vaccine, and $\lambda_{x,0}$ is the predictor-specific baseline hazard function. We fitted 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 estimated the vaccine effectiveness as $100\% \bullet \left(1 - exp\left\{\beta_k\right\}\right)$. We show the adjusted vaccine effectiveness results, including covariates as controls (age, gender, region, nationality, health insurance category, and comorbidities). We show the results for the standard and stratified versions of the Cox hazards model using inverse probability of treatment weighting. Inference was based on a partial likelihood approach.[24] Please recall that the effectiveness estimate for the Covid-19 vaccines in the Cox model with time-dependent vaccination status compares the risk of an event for children who received the vaccine and those who were unvaccinated at each event time. The risk group is determined by whether the child had received or not the vaccine shot in a specific calendar time, and 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 (as shown in Supplementary Table S1). Under the stratified version of the Cox model, each stratum has a different risk set determined by the covariates.

We conducted the analysis with the survival package[25] of R, version 4.0.5.[26]

Declarations

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

References

1. Tracking SARS-CoV-2 variants. WHO, 2022. (Accessed March 2, 2022, at https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/)
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20:P533-P4.
3. Madhi SA, Kwatra G, Myers JE, et al. Population Immunity and Covid-19 Severity with Omicron Variant in South Africa. N Engl J Med 2022.
4. Cloete J, Kruger A, Masha M, et al. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. Lancet Child Adolesc Health 2022.
5. Altarawneh HN, Chemaitelly H, Hasan MR, et al. Protection against the Omicron Variant from Previous SARS-CoV-2 Infection. N Engl J Med 2022.
6. Hoffmann M, Krüger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. Cell 2022;185:447 –

56.e11.

7. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. medRxiv 2022.
8. Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in disease severity and health care utilization during the early omicron variant period compared with previous SARS-CoV-2 high transmission periods — United States, December 2020–January 2022. Morb Mortal Wkly Rep 2022;71:146–52.
9. Zimmermann P, Pittet LF, Finn A, Pollard AJ, Curtis N. Should children be vaccinated against COVID-19? Arch Dis Child 2021;107:e1.
10. Coronavirus Vaccine Tracker. The New York Times, 2022. (Accessed March 1, 2022, at https://nyti.ms/3nvAEc4)
11. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med 2022;386:35–46.
12. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. N Engl J Med 2022;386:713–23.
13. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Effectiveness of the BNT162b2 vaccine among children 5–11 and 12–17 years in New York after the Emergence of the Omicron Variant. medRxiv 2022.
14. Jara A, Undurraga EA, Flores JC, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Children and Adolescents: A Large-Scale Observational Study. SSRN Preprint:http://dx.doi.org/10.2139/ssrn.4035405.
15. Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. N Engl J Med 2022;386.
16. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. N Engl J Med 2022.
17. Pajon R, Doria-Rose NA, Shen X, et al. SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination. N Engl J Med 2022.
18. Pfizer and BioNTech Provide Update on Ongoing Studies of COVID-19 Vaccine. 2022. (Accessed March 1, 2022, at https://bit.ly/3J3GZHc)
19. Jara A, Undurraga EA, González C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021;385:875–84.
20. Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34:187–202.
21. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.
22. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656–64.
23. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model: Springer; 2000.

24. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med 2021;385:320–9.
25. Therneau TM. A Package for Survival Analysis in R. R package version 3.1–12. Computer software] Rochester, MN: Mayo Clinic Retrieved from https://CRAN R-project org/package = survival 2020.
26. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2019.

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