

Original article

Effectiveness of COVID-19 vaccination schedules against severe COVID-19 in children aged 6 months to 4 years in Brazil: A population-based cohort study (2023–2024)

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ABSTRACT

Background: Although the impact of COVID-19 vaccination is widely documented in the general population, the evidence on its effectiveness in children under 5 years of age is still limited. In this context, the continuation of vaccination programs in this age group has been debated globally. Consequently, we estimated the effectiveness of the complete 3-dose series of BNT162b2 (Pfizer-BioNTech) in children aged 6 months to 4 years and the complete 2-dose series of CoronaVac (Sinovac) in children aged 3 to 4 in reducing the risk of hospitalizations due to COVID-19-attributed severe acute respiratory infection (SARI) in Brazil.

Methods: We conducted a retrospective cohort study in 24 Brazilian municipalities, using surveillance data. We evaluated vaccine effectiveness in reducing the incidence rate of COVID-19-attributed SARI hospitalizations from July 2023 to December 2024. Covariate adjustments, defined a priori based on a conceptual model, were implemented using random-effects Poisson regression models.

Results: The cohort comprised 37.7 million person-months of follow-up and 1384 COVID-19-attributed SARI hospitalizations, including 27 associated deaths. The 3-dose series of BNT162b2 vaccine had an effectiveness of 97% (Incidence rate ratio [IRR] 0.03, 95% CI 0.01–0.10) in the group aged 6 months to 4 years, with no significant differences among age-specific estimates. The effectiveness of CoronaVac was small and not statistically significant (IRR 0.96, 95% CI 0.57–1.62).

Conclusions: In this population-based cohort, completion of the 3-dose BNT162b2 primary series was associated with substantially lower rates of COVID-19-attributed SARI among children aged 6 months to 4 years.

1. Introduction

COVID-19 had numerous health impacts, including a considerable number of severe acute respiratory infection (SARI) hospitalizations. [1–5] Vaccines substantially reduced severe cases and deaths; [6–8] however, children were among the last groups to be vaccinated due to their lower perceived risk. [9,10] As adult immunity increased, severe cases and deaths became proportionally concentrated in vulnerable and under-vaccinated populations, increasing the relative contribution of children to severe cases and deaths. [11–13]

In Brazil, pediatric COVID-19 vaccination was introduced in 2022, coinciding with the circulation of the Omicron variant and its

sublineages. The Brazilian National Immunization Program (PNI) initially recommended the CoronaVac (Sinovac) vaccine for children aged 3 years and older (July 2022), followed by the BNT162b2 (Pfizer-BioNTech) vaccine for children aged 6 months to 4 years old (December 2022). [14,15] However, despite COVID-19 vaccination campaigns, vaccine coverage in these age groups remained low. [16]

Although clinical trials demonstrated safety and efficacy and there are effectiveness estimates in some countries, evidence in children under 5 years of age remains limited, especially in the context of the Omicron variant. [10,17,18] Moreover, several countries have reconsidered the COVID-19 vaccine recommendations for this age group. [19–22] Given this scenario, it is essential to understand the impact of the vaccines on

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clinically relevant outcomes to support decision-making about the continuity of these vaccines in immunization programs.

This study aimed to estimate the effectiveness of the COVID-19 vaccination series recommended for children in Brazil, including the 3-dose series of BNT162b2 for children aged 6 months to 4 years and the 2-dose series of CoronaVac for children aged 3 and 4 years, in reducing COVID-19-attributed SARI rates. Additionally, we evaluated schedules with different numbers of doses and obtained age-specific estimates of effectiveness.

2. Methods

2.1. Study design and period

This population-based retrospective cohort study used surveillance data, covering children aged 6 months to 4 years, residing in Brazilian municipalities. We aimed to avoid issues arising from sparse data, ensuring a sufficient number of exposed individuals and events for the analysis. Thus, we chose the 24 municipalities with the most events among the 200 municipalities with the highest coverage (Supplemental Table S1).

These municipalities comprised a total of 2,093,745 children aged 6 months to 4 years, representing 18.1% of the entire Brazilian pediatric population in this specific age group, according to the 2022 National Census. Because these municipalities capture the highest absolute burden of SARI events, they predominantly correspond to major, densely populated urban centers. A comparison of key demographic, socioeconomic, and healthcare indicators between the selected sample and the national total is presented in Supplemental Table S2 [23–26].

As this study utilized publicly available and completely anonymized surveillance data, the requirement for institutional review board approval and written informed consent was waived in accordance with national ethical guidelines.

2.2. Data sources

SARI hospitalization data were extracted from the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe), the mandatory registry for hospitalized SARI cases by any cause [27,28]. Within this system, cases are pre-classified according to the Ministry of Health's standards. Therefore, we analyzed pre-defined SARI hospitalization meeting the official clinical criteria (dyspnea, respiratory distress, hypotension, or O_2 saturation < 95%) and attributed to COVID-19 via laboratory (RT-PCR, RT-LAMP, or rapid antigen test) or clinical-epidemiological criteria. [29]

Moreover, we used the official COVID-19 campaign vaccination records from the National Health Data Network (RNDS), the mandatory national repository for all vaccination records in Brazil, including COVID-19. [27,30,31] The monthly number of unvaccinated children was calculated by subtracting cumulative vaccinated children from the total population, using single-year age estimates (monthly/annual) per municipality according to the 2022 Demographic Census projections of the Brazilian Institute of Geography and Statistics (IBGE). [32] All data are publicly available and anonymized.

2.3. Data integration and vaccine identification

Since there is no unique and universal individual identifier consistently available across the public databases, no prior individual-level vaccination linkage was performed by health authorities before data release. To overcome this, we linked numerator and denominator data using aggregated strata (municipality of residence, age in months, and calendar month). Vaccines were identified by the Ministry of Health immunobiological codes: [16,33].

BNT162b2: 87, 99, 102 and 103 (We grouped all manufacturer codes).

CoronaVac: 86 and 98.

The RNDS dataset processed in this study covers 95% of the total doses reported on the official vaccination dashboard of the Ministry of Health. Specifically for the pediatric vaccines evaluated in this study, the coverage is 100% for CoronaVac and 97% for the BNT162b2 doses. [16] Although the mRNA-1273 (Moderna) vaccine was identified, it was not evaluated as the exposure of interest due to its late introduction into the schedule, but it was considered in the statistical models as an adjustment covariate (see below).

2.4. Estimands and statistical analysis

We estimated BNT162b2 effectiveness in the population aged 6 months to 4 years, and CoronaVac effectiveness in the population aged 3 to 4 years, in reducing the incidence rate of COVID-19-attributed SARI during the study period. These age groups correspond to the approved indications for use by the Ministry of Health. [15]

The unit of analysis was defined by the combination of age group, calendar month of follow-up, municipality, and vaccination status. In each unit, the number of incident COVID-19-attributed SARI hospitalizations occurring in that stratum (numerator) and the total child-months (rate denominator) were aggregated. Children could contribute person-time to multiple consecutive months, according to their age, municipality, and vaccination status; however, each SARI episode was counted only once and attributed to the unit defined by the month and vaccination status at the time of occurrence. Doses received in the 15 days before hospitalization were disregarded when defining the vaccination status.

Child-months at risk were approximated as the stratum-specific population on the first day of each month, assuming one month of person-time per child present at that date. The first day was chosen because it lies approximately 15 days before the midpoint of the month, aligning the timing of vaccination status ascertainment with the 15-day lag applied to outcomes. This single point also approximates the monthly average population at risk, provided that vaccination coverage changes marginally within the month. Otherwise, the first-day value may deviate from the true average and bias incidence rate estimates. Within-month variation cannot be observed directly, but stable denominators across consecutive months make large within-month fluctuations unlikely. With this in mind, we noted that monthly variation in the denominators exceeded 6% during the first half of 2023 (the vaccine rollout period) and stabilized below 3% from July 2023 onward (Supplemental Table S3). We therefore restricted the analysis to July 1, 2023 – December 31, 2024, when denominator stability supports the plausibility of this approximation.

In summary, this corresponded to an as-treated analysis, in which person-time and events are classified according to the contemporaneous vaccination status. We then used random-effects Poisson regression models, aggregated by municipality, to estimate incidence rate ratios (IRR) contrasting the rate in each vaccination status category versus the unvaccinated reference. Models were adjusted for covariates suggested by a conceptual model represented by a DAG (Supplemental Fig. S1), including age, temporal trend, and use of other vaccines, as well as interaction terms between these covariates, when statistically significant. We additionally included, as a contextual covariate, the municipality-level incidence of COVID-19-attributed SARI among children under 5 years in 2022, given its plausible association with both subsequent vaccination coverage and the risk of the outcome during the study period. [34]

Each vaccine of interest was evaluated as an independent exposure, with the others included as covariates, and interactions arising from dose combinations between the vaccines were also tested in multivariable models. Next, we evaluated interaction terms between the vaccine of interest and the age and time variables, as potential effect modifiers.

Age-specific estimates were also obtained. In strata with no events recorded in the vaccinated group, we presented crude estimates, with

confidence intervals calculated by the exact Poisson method. When the vaccine was associated with a statistically significant reduction in the COVID-19-attributed SARI rate, we reported the vaccine effectiveness (VE), calculated as:

$$VE = (1 - IRR) \times 100\%$$

Two sensitivity analyses were conducted to evaluate the data robustness. The first was the analysis excluding the São Paulo municipality from the study, due to the potential selection bias from the migration of the local information system (Vacivida) to the RNDS [35]. (Supplemental Table S4) Additionally, the denominator validation, comparing the 2022 Census with the live birth records (SINASC 2019–2024), resulted in a difference of 2%, indicating high agreement between the datasets [36] (Supplemental Table S5).

3. Results

The analyzed cohort accumulated 37,687,410 person-months of

observation across the 24 selected municipalities (Fig. 1). There were 1384 COVID-19-attributed SARI hospitalization events, resulting in an overall incidence of 3.67 cases per 100,000 person-months, including 27 associated deaths. The distribution of person-months across vaccine and dose categories varied substantially over the study period (Supplemental Fig. S2). Follow-up time accrued progressively in higher-dose strata as children completed their schedules. The composition of vaccine categories also shifted gradually from CoronaVac to BNT162b2, reflecting changes in the Brazilian pediatric immunization schedule. Total person-time declined markedly in late 2024, driven by children aging out of the cohort.

For BNT162b2 vaccine, the unvaccinated category accounted for most of the follow-up time (28 million person-months), 84.9% of hospitalizations (1175), and 23 of the 27 deaths. No deaths were recorded in children who completed the primary series (3 doses). Of the 4 deaths among the vaccinated children, 2 occurred in the 1-dose and 2 in the 2-dose categories (Table 1).

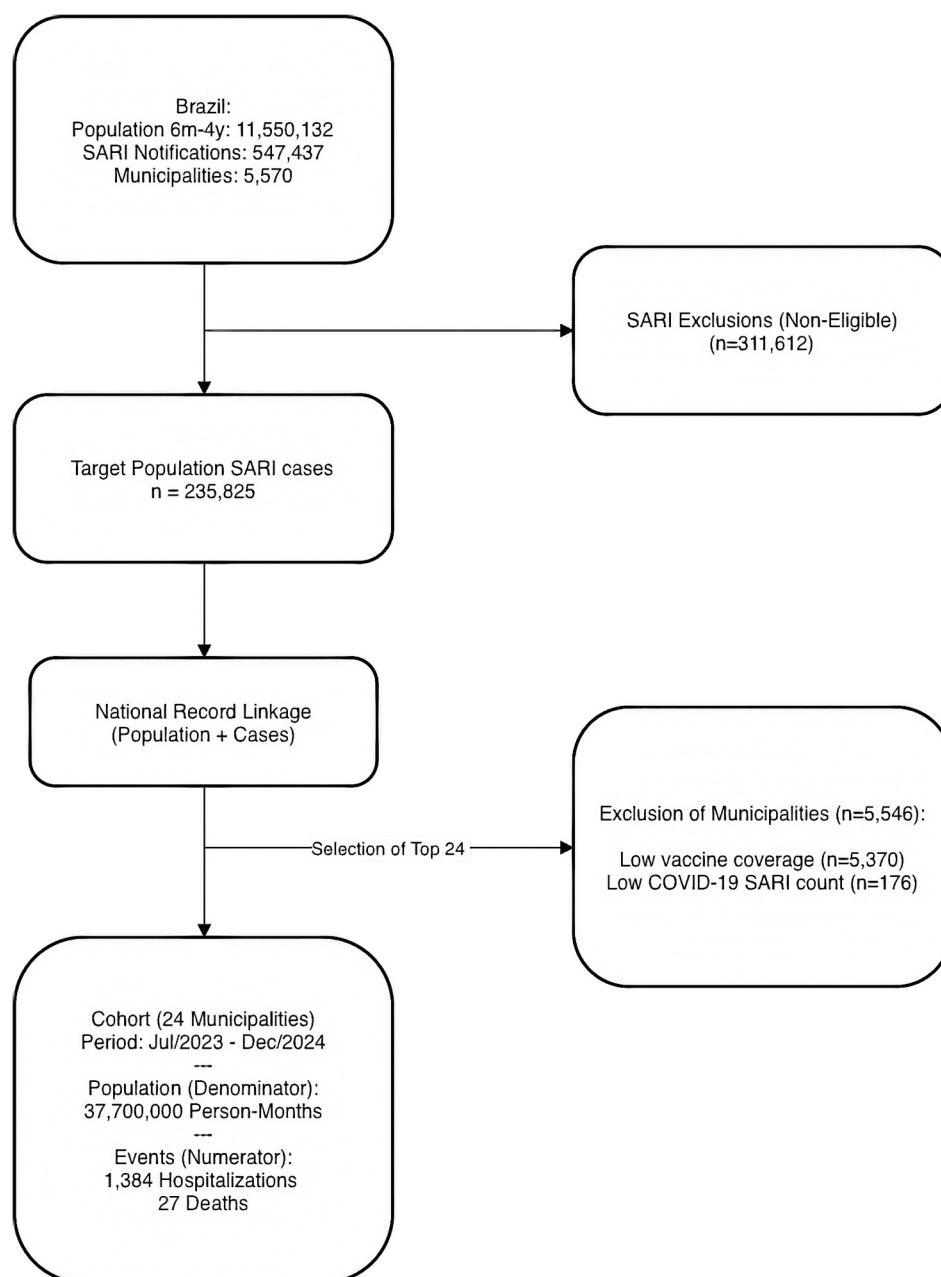


Fig. 1. Flowchart for the database used in the study.

Table 1

Observation time and events by age group and BNT162b2 vaccination status (July 2023–December 2024).

Age group and vaccination status	Person-months	COVID-19-attributed SARI	Incidence (per 100,000 person-months)	Deaths
<i>6–11 months</i>				
Unvaccinated	3,427,416	560	16.33	13
BNT162b2, 1 dose	210,621	16	7.60	0
BNT162b2, 2 doses	122,606	7	5.71	0
BNT162b2, 3 doses	28,233	0	0	0
Subtotal	3,788,876	583	15.38	13
<i>1 year</i>				
Unvaccinated	5,572,891	331	5.94	9
BNT162b2, 1 dose	695,314	34	4.89	0
BNT162b2, 2 doses	622,766	48	7.71	0
BNT162b2, 3 doses	585,566	1	0.17	0
Subtotal	7,476,537	414	5.54	9
<i>2 years</i>				
Unvaccinated	5,976,247	110	1.84	1
BNT162b2, 1 dose	881,863	12	1.36	0
BNT162b2, 2 doses	737,556	30	4.07	1
BNT162b2, 3 doses	781,783	2	0.25	0
Subtotal	8,377,449	154	1.84	2
<i>3 years</i>				
Unvaccinated	6,285,258	85	1.35	0
BNT162b2, 1 dose	1,059,433	10	0.94	1
BNT162b2, 2 doses	793,259	28	3.53	1
BNT162b2, 3 doses	748,124	0	0	0
Subtotal	8,886,074	123	1.39	2
<i>4 years</i>				
Unvaccinated	6,778,621	89	1.31	0
BNT162b2, 1 dose	1,299,644	12	0.92	1
BNT162b2, 2 doses	622,184	9	1.45	0
BNT162b2, 3 doses	453,392	0	0	0
Subtotal	9,153,841	110	1.20	1
<i>6 months–4 years</i>				
Unvaccinated	28,040,433	1175	4.19	23
BNT162b2, 1 dose	4,146,875	84	2.02	2
BNT162b2, 2 doses	2,898,371	122	4.21	2
BNT162b2, 3 doses	2,597,098	3	0.12	0
Total analyzed	37,682,777	1384	3.67	27

For CoronaVac, 92% of the children who completed the primary series were 4 years old. Although this vaccine was indicated for children aged 3 years and older, it was administered to a small proportion of children aged 6 months to 2 years. There were no deaths in any of the vaccinated strata (Table 2).

3.1. Effectiveness estimates

Incidence in the BNT162b2-unvaccinated reference group was 4.19 cases per 100,000 person-months, dropping to 0.12 cases per 100,000 person-months with the complete primary series. Consequently, the complete 3-dose series of BNT162b2 was associated with a 97% reduction in the incidence rate of COVID-19-attributed SARI (IRR 0.03, 95% CI 0.01–0.10). In more than 2.5 million person-months corresponding to this series, there were only 3 recorded events. This effectiveness was not modified by time, age, or the administration of other vaccines ($p > 0.60$ for all interaction terms), remaining consistent across all ages (Table 3).

When evaluating incomplete series, the incidence-rate was 2.02 per 100,000 person-months for the 1-dose series, which was significantly associated with an overall risk reduction of 38% (IRR 0.62, 95% CI 0.50–0.77). For the 2-dose series, the incidence was 4.21 per 100,000 person-months, and this schedule was not statistically associated with the outcome (IRR 1.15, 95% CI 0.95–1.39). The effectiveness of these incomplete series was significantly modified by the child's age

Table 2

Observation time and events by age group and CoronaVac vaccination status (July 2023–December 2024).

Age group and vaccination status	Person-months	COVID-19-attributed SARI	Incidence (per 100,000 person-months)	Deaths
<i>6–11 months</i>				
Unvaccinated	3,788,734	583	15.39	13
CoronaVac, 1 dose	153	0	0	0
CoronaVac, 2 doses	19	0	0	0
CoronaVac, 3 doses	4	0	0	0
Subtotal	3,788,910	583	15.39	13
<i>1 year</i>				
Unvaccinated	7,476,114	410	5.48	9
CoronaVac, 1 dose	1247	4	320.77	0
CoronaVac, 2 doses	145	0	0	0
CoronaVac, 3 doses	0	0	0	0
Subtotal	7,477,506	414	5.54	9
<i>2 years</i>				
Unvaccinated	8,375,836	154	1.84	2
CoronaVac, 1 dose	2297	0	0	0
CoronaVac, 2 doses	712	0	0	0
CoronaVac, 3 doses	11	0	0	0
Subtotal	8,378,856	154	1.84	2
<i>3 years</i>				
Unvaccinated	8,694,435	116	1.33	2
CoronaVac, 1 dose	103,491	2	1.93	0
CoronaVac, 2 doses	88,888	5	5.62	0
CoronaVac, 3 doses	470	0	0	0
Subtotal	8,887,284	123	1.38	2
<i>4 years</i>				
Unvaccinated	7,329,864	87	1.19	1
CoronaVac, 1 dose	801,273	12	1.50	0
CoronaVac, 2 doses	1,017,357	11	1.18	0
CoronaVac, 3 doses	6360	0	0	0
Subtotal	9,154,854	110	1.20	1
<i>3–4 years</i>				
Unvaccinated	16,024,299	203	1.27	3
CoronaVac, 1 dose	904,764	14	1.55	0
CoronaVac, 2 doses	1,106,245	16	1.45	0
CoronaVac, 3 doses	6830	0	0	0
Total 3–4 years	18,042,138	233	1.29	3
Total	37,687,410	1384	3.67	27

(Supplemental Table S6), and we observed a significant benefit from the 1-dose and 2-dose series only in children under 1 year of age (IRR 0.43, 95% CI 0.26–0.71, and IRR 0.30, 95% CI 0.14–0.63, respectively; Table 3).

The 1- and 2-dose series of CoronaVac were associated with non-statistically significant reductions in the rate of COVID-19-attributed SARI in the 3–4-year age group compared with unvaccinated children (Table 4). Although no cases were identified among children who received a third dose of CoronaVac, this estimate was imprecise and not statistically significant (IRR 0; exact Poisson 95% CI 0–41.8). In age-

Table 3

Incidence Rate Ratios of the BNT162b2 vaccine against COVID-19-attributed SARI: overall and age-specific estimates.

	Adjusted IRR (95 CI%) ^a	VE-% (95 CI%) ^c	p-value
Overall estimate (6 months–4 years)			
1 dose	0.62 (0.49–0.77)	38 (23–51)	<0.001
2 doses	1.15 (0.95–1.38)	–	0.15
3 doses	0.03 (0.01–0.10)	97 (90–99)	<0.001
Age-specific estimate 6–11 months			
1 dose	0.43 (0.26–0.71)	57 (29–74)	<0.001
2 doses	0.30 (0.14–0.63)	70 (37–86)	<0.001
3 doses	0.00 ^d (0.00–0.80)	100 (20–100) ^d	0.01
1 year			
1 dose	0.83 (0.59–1.19)	–	0.32
2 doses	1.26 (0.93–1.71)	–	0.13
3 doses	0.03 (0.00–0.19)	97 (81–100)	<0.001
2 years			
1 dose	0.75 (0.41–1.37)	–	0.35
2 doses	2.26 (1.51–3.40)	–	<0.001
3 doses	0.15 (0.04–0.60)	85 (40–96)	0.008
3 years			
1 dose	0.69 (0.36–1.34)	–	0.27
2 doses	2.74 (1.77–4.22)	–	<0.001
3 doses	0.00 ^d (0.00–0.37)	100 (63–100) ^d	< 0.001
4 years			
1 dose	0.79 (0.44–1.50)	–	0.47
2 doses	1.36 (0.68–2.74)	–	0.39
3 doses	0.00 ^d (0.00–0.63)	100 (37–100) ^d	0.003

Notes a) Adjusted for age, time and other vaccines.

b) Adjusted for time and other vaccines.

c) VE = (1 – IRR) × 100. Effectiveness is reported only when the IRR was significantly less than 1.

d) Due to the absence of recorded events among 3-dose vaccinated children in these strata, the IRR was equal to zero, making it impossible to obtain adjusted estimates using the multivariable model. Therefore, we present the crude estimates restricted to these age strata and the 95% confidence intervals calculated using the exact Poisson method.

Table 4

Incidence Rate Ratios of the CoronaVac vaccine against COVID-19-attributed SARI: overall and age-specific estimates for 3- and 4-year-old children.

	Adjusted IRR (95 CI%) ^a	p-value
Overall estimate (3–4 years)		
1 dose	0.93 (0.54–1.62)	0.81
2 doses	0.96 (0.57–1.62)	0.87
3 doses	0.00 (0.00–41.78) ^b	0.91
Age-specific estimate		
3 years		
1 dose	1.07 (0.26–4.41)	0.92
2 doses	3.31 (1.31–8.37)	0.01
4 years		
1 dose	0.97 (0.52–1.80)	0.93
2 doses	0.71 (0.37–1.36)	0.30

Notes a) Adjusted for time and other vaccines (given the restriction to children aged 3–4 years, age was not included in the multivariable model).

b) Due to the absence of recorded events among 3-dose vaccinated children in this group, the IRR was equal to zero, making it impossible to obtain an adjusted estimate using the multivariable model. Therefore, we present the crude estimate restricted to this age group and the 95% confidence interval calculated using the exact Poisson method.

specific analyses, the 2-dose schedule was associated with a higher rate of COVID-19-attributed SARI in the 3-year age group and with a non-statistically significant reduction in risk in the 4-year age group.

Finally, when testing for interactions, we observed a positive and

statistically significant interaction for the combination of one dose of CoronaVac and one dose of BNT162b2 (Supplemental Table S6). The sensitivity analysis excluding the São Paulo municipality showed similar effectiveness estimates to the primary analysis, suggesting that the overall findings were not dependent on this single municipality (Supplemental Table S4).

4. Discussion

In this population-based cohort study, we evaluated the first pediatric COVID-19 vaccines introduced in Brazil. Our results indicated that the complete 3-dose BNT162b2 primary series was associated with a marked reduction in the COVID-19-attributed SARI rate in children aged 6 months to 4 years. However, fewer doses did not consistently yield benefits, with effects being significantly modified by age.

The phase 2–3 clinical trial showed an efficacy of 73.2% (95% CI 43.8–87.6) for the 3-dose series of the BNT162b2 against symptomatic COVID-19 in this age group. [10] However, as the authors noted, the trial did not have the power to assess efficacy against severe disease. Although the outcomes and study designs are not directly comparable, our findings are compatible with the broader evidence that COVID-19 vaccines tend to provide greater and more durable protection against severe outcomes, including hospitalization, than against mild symptomatic infection. [6,7] Furthermore, our estimate in this age group also exceeded the effectiveness observed with other mRNA vaccines. Specifically, a 2023 study in children aged 1 to 4 years reported that a complete 2-dose primary series (predominantly of mRNA-1273) exhibited a 63.3% (95% CI 40.6–77.3) effectiveness against omicron infection. [37]

Direct comparisons with real-world studies are limited because, to our knowledge, no previous study has estimated the effectiveness of the complete 3-dose BNT162b2 primary series exclusively in children younger than 5 years. Existing systematic reviews predominantly include older pediatric groups (mean ages between 7 and 8 years) and evaluate 1- or 2-dose series. [8] In our age-specific analysis, 1- or 2-dose BNT162b2 schedules were associated with lower SARI rates only among children aged 6–11 months, with no benefit in those older than 1 year. This pattern aligns with clinical trial immunogenicity data showing that two doses elicited an insufficient immune response in children aged 2–4 years, supporting the need for a third dose. [10]

In our interpretation, the higher incidence rates observed with incomplete BNT162b2 schedules, particularly two doses among children older than 1 year, are unlikely to represent vaccine-associated harm. Rather, they may reflect residual confounding and selection processes inherent to this population-level design. For example, children at higher baseline risk of severe disease may have been preferentially vaccinated early in the campaign and may have remained in incomplete-schedule strata [14,15]. Moreover, incomplete immune protection and waning after partial vaccination may also have contributed. However, the available data cannot disentangle these explanations from other potential biases, including healthy vaccinee effects, differential healthcare-seeking, and factors associated with completion of a multidose schedule. Accordingly, the direction and magnitude of the net residual bias cannot be quantified.

With CoronaVac, the reduction in COVID-19-attributed SARI risk in the 3–4-year age group was small and not statistically significant. The absence of deaths among children who received any dose of CoronaVac is reassuring but should be interpreted descriptively, given the limited number of severe outcomes and the study's limited power for mortality. The coverage of a third CoronaVac dose was insufficient to estimate its association with SARI risk with adequate precision; therefore, our findings do not exclude a benefit from schedules with additional doses.

These results contrast with estimates from other populations, such as those reported in Chile, where a study conducted in children aged 3 to 5 years estimated that a 2-dose CoronaVac series had an effectiveness of 64.6% (95% CI: 49.6–75.2) against COVID-19-associated

hospitalizations (December 2021–February 2022). [17] Differences between the estimates may reflect, in part, the timing of follow-up: the Chilean study evaluated protection shortly after vaccination, whereas our analysis covered a later and longer period (July 2023–December 2024). Differences in outcome definitions (COVID-19-associated hospitalization in Chile versus COVID-19-attributed SARI under stricter criteria in our study) may also have contributed to the observed divergences.

Residual unmeasured confounding may be a central limitation of this observational study. Individual-level information on comorbidities, prior SARS-CoV-2 infection, clinical vulnerability, healthcare utilization, and socioeconomic characteristics was unavailable. Consequently, vaccinated and unvaccinated children may have differed in ways that were not adequately controlled by the analysis. The resulting bias could operate in either direction. Vaccinated children may have had more health-seeking caregivers or better access to care, whereas children at higher baseline risk may also have been preferentially vaccinated, especially early in the campaign. Our data suggest that the latter mechanism was present: 1-year-old children who received a single dose of CoronaVac, a vaccine not indicated for this age group, exhibited a higher hospitalization incidence than unvaccinated children (Table 2). Adjustment for age, calendar time, other vaccines, and municipality-level contextual indicators may have reduced some imbalance, but these variables are imperfect proxies for individual-level confounders.

Another potential limitation is the exclusive use of the campaign information system to identify the vaccinated cohort. At the end of the observation period, vaccinations were also recorded in a separate routine database, which was not linked by us due to the inability to identify and exclude duplicates. The high agreement with the official Ministry of Health dashboard (see Methods) suggests minimal under-reporting. If present, the magnitude of misclassification cannot be quantified; however, unrecorded vaccinations would have shifted vaccinated person-time to the unvaccinated denominator, attenuating the contrast in incidence rates and biasing effectiveness estimates toward the null.

The linkage between vaccination and SARI data was made by stratifying the population by municipality, age (in months) and calendar month. Deterministic individual-level linkage, the ideal standard, was not feasible because unique individual identifiers are not consistently available across the national databases. Nevertheless, this aggregate-level approach is used in epidemiological surveillance, such as in the Morbidity and Mortality Weekly Report published by the United States Centers for Disease Control and Prevention [38,39], to calculate Incidence Rate Ratios and estimate vaccine effectiveness. We also restricted our analysis to the period of greater denominator stability, expecting to minimize potential errors in the linkage. Furthermore, SIVEP-Gripe is the official mandatory reporting system for SARI hospitalizations. Although incomplete reporting cannot be ruled out, the use of this established surveillance system supports the capture of severe hospitalized outcomes, particularly in the major urban centers included in the cohort.

Another relevant consideration is the natural immunity due to widespread viral circulation. [40–42] In Brazil, the EPICOVID 2.0 study reported that 28.4% of the general population had experienced at least one COVID-19 infection by March to June 2024, whereas a study conducted in India in June–July 2021 found a SARS-CoV-2 antibody prevalence of 68.3% among unvaccinated children. [42,43] Thus, infection-acquired immunity among unvaccinated children may have reduced the contrast in incidence rates and attenuated the estimated effectiveness for some schedules. However, prior infection was not measured in this study, and the magnitude of this effect cannot be determined.

This phenomenon may also explain differences between epidemiological contexts. In Hong Kong, first dose BNT162b2 effectiveness among children aged 3 to 11 years was estimated at 65.6% (95% CI: 38.2–82.5), higher than our single-dose estimate (38%). [18] That study was conducted in early 2022 in a population with relatively low prior

exposure to SARS-CoV-2. In contrast, our analysis took place later, when a higher prevalence of infection-acquired immunity would be expected, potentially reducing the relative benefit of vaccination.

Regarding the generalizability of our findings, we restricted our analysis to 24 major municipalities to prioritize methodological robustness and mitigate potential biases associated with sparse data in areas with low case counts. These urban centers present distinct socio-demographic and healthcare infrastructure characteristics compared to the national average. These 24 municipalities encompass the areas with the highest burden of COVID-19 in the country, making them the most epidemiologically relevant setting for evaluating vaccine impact. However, any extrapolation of our effectiveness estimates to other populations would require assuming that the contextual differences between our study municipalities and other settings do not act as effect modifiers of vaccine effectiveness.

Despite the limitations inherent to this population-level observational design, the association observed for the complete 3-dose BNT162b2 series was large, consistent across age strata, and coherent with the trial immunogenicity data in this age group. [10] Although residual confounding, exposure misclassification, and aggregate-level linkage may have affected the magnitude of the estimate, we consider it plausible that some of the biases operating in this setting (particularly preferential early vaccination of children at higher clinical risk and infection-acquired immunity among unvaccinated children) would tend to attenuate rather than create a strong protective association. This interpretation cannot be verified with the available data, and alternative sources of bias, including healthy vaccinee effects, may operate in the opposite direction. Nevertheless, the overall pattern of findings provides supportive population-based evidence that completion of the BNT162b2 primary series was associated with lower rates of COVID-19-attributed SARI in this population.

These findings should not be interpreted as a stand-alone basis for pediatric vaccination policy or as a definitive causal estimate of vaccine effectiveness. Rather, they are consistent with a clinically meaningful benefit of the complete 3-dose BNT162b2 schedule against severe COVID-19 in children aged 6 months to 4 years. This evidence is particularly relevant as several countries have reassessed universal COVID-19 vaccination recommendations for young children in the context of changing disease severity, population immunity, and cost-effectiveness. [19–21] Further individual-level studies incorporating comorbidities, prior infection, healthcare utilization, and socioeconomic characteristics are needed to better quantify the magnitude and durability of protection and to clarify the role of residual confounding.

5. Conclusion

Among the COVID-19 vaccination schedules evaluated in this population-based cohort, completion of the 3-dose BNT162b2 primary series was consistently associated with substantially lower rates of COVID-19-attributed SARI among children aged 6 months to 4 years. Although residual bias cannot be excluded, the magnitude of the association and its biological coherence support a benefit of completing the BNT162b2 primary series and provide evidence relevant to discussions on maintaining access to this schedule in routine pediatric immunization programs. Further studies with more detailed individual-level information could help refine estimates of the impact of COVID-19 vaccination in children.

Author contribution

INS participated in the conceptualization of the study, data curation, data analysis execution, and result interpretation, and wrote the original draft. FADQ participated in the conceptualization of the study, planned and reviewed the data analyses, interpreted the results, and reviewed and edited the original draft and subsequent versions of the manuscript.

AI tools declaration

The authors used AI tools, such as ChatGPT (OpenAI) and Apple Intelligence for English proofreading and grammatical refinement. All suggestions generated by the tools were carefully reviewed and only those considered appropriate were incorporated by the authors, who are fully responsible for the manuscript.

All authors attest they meet the ICMJE criteria for authorship.

CRedit authorship contribution statement

Isaac Negretto Schrartzhaupt: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Fredi Alexander Diaz-Quijano:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2026.129096>.

Data availability

Data will be made available on request.

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