Effectiveness of mRNA BNT162b2 and inactivated CoronaVac vaccines against severe COVID-19 outcomes among non-hospitalized children aged 1-3 years with SARS-CoV-2 Omicron infection

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Abstract

Objectives

Clinical evidence on the effectiveness of COVID-19 vaccines for children aged 1-3 years is scarce. We evaluated the effectiveness of COVID-19 vaccines among non-hospitalized children aged 1-3 years with SARS-CoV-2 Omicron infection in Hong Kong.

Methods

Our retrospective cohort of all non-hospitalized children (aged 1-3) with confirmed SARS-CoV-2 infection diagnosis between 4th August 2022 and 29th January 2023 in Hong Kong was analyzed. Vaccinated group was defined as the recipients of one or more doses of inactivated vaccine CoronaVac or mRNA vaccine BNT162b2 (original, monovalent) at least 14 days prior to the infection. Hazard ratios (HR) with 95% confidence intervals (CI) of study outcomes were estimated using Cox regression models. Effectiveness outcomes included 28-day all-cause mortality and COVID-19-related hospitalization.

Results

A total of 5,552 vaccinated patients and 5,552 propensity-score matched controls (unvaccinated patients) were included for analysis. The cumulative incidences of COVID-19-related hospitalization over 28 days were 2.3% and 2.9% in the vaccinated and control groups, respectively. No events of mortality were observed in both groups. COVID-19 vaccination was associated with a significant reduction in 28-day COVID-19-related hospitalization risk (HR=0.785, 95%CI=0.626-0.985, p=0.037), particularly for children aged 3 years, those who had received two or more vaccine doses, and received CoronaVac as the last dose.

Conclusion

COVID-19 vaccination is associated with a significantly lower risk of 28-day COVID-19-related hospitalization among infected children aged 1-3 years, especially those who had received two or more doses emphasizing the importance of completing the full two-dose or three-dose series to optimize vaccine effectiveness.

Main Text

Introduction

At the beginning of the SARS-CoV-2 Omicron wave during early 2022, rapid increases in the incidence rates of hospitalization and intensive care unit (ICU) admission of infected infants and young children aged 0-4 years (who were not yet eligible for COVID-19 vaccination at that time) were observed; and alarmingly, over 60% of them had no underlying medical conditions.[1] Furthermore, Omicron BA.2 infection in unvaccinated children (aged 0-11 years) was associated with higher risks of severe disease outcomes, neurological complications, and croup than influenza or parainfluenza viral infections.[2]

Among various vaccine platforms, mRNA vaccines have demonstrated immunogenicity and moderate vaccine efficacy against COVID-19 during the predominance of Omicron variant in children aged <5;[3,4] and both Pfizer-BioNTech and Moderna COVID-19 vaccines are now authorized for use for those aged ≥6 months. Clinical trials of inactivated vaccines have also been conducted in the pediatric population; however, only results of their immunogenicity were reported, and data on protection against infection or severe COVID-19 are lacking.[5,6] Real-world studies have estimated the effectiveness of mRNA and inactivated vaccines against infection, hospitalization and severe disease outcomes of those aged ≥3.[7-10] Recognizing the lack of clinical data of COVID-19 vaccines for infants and toddlers, this territory-wide, retrospective cohort study aims to evaluate the effectiveness of mRNA and inactivated vaccines in those aged 1-3 years with Omicron variant SARS-CoV-2 infection in Hong Kong.

Methods

Data sources, study design and population

In this retrospective cohort, non-hospitalized children aged 1-3 with confirmed SARS-CoV-2 infection diagnosis from 4th August 2022 to 29th January 2023 in Hong Kong Special Administrative Region, China were identified. Local residents can choose to be vaccinated with either the mRNA vaccine BNT162b2 (by Fosun-BioNTech) or inactivated vaccine CoronaVac (by Sinovac). The rollout of CoronaVac (0.5 mL/dose) for children aged 6 months to 3 years (3-dose series; 28 days interval between the first and second doses, 90 days interval between the second and third doses) began on 4th August 2022,[11] and that of BNT162b2 (3 mcg/dose) for those aged 6 months to 4 years (3-dose series; 56 days interval between the first and second doses, 90 days interval between the second and third doses; only the original monovalent version of BNT162b2 was available for persons aged under 12) since 9th November 2022.[12,13]

Line listing of cases with SARS-CoV-2 infection diagnosis confirmed by positive reverse transcription polymerase chain reaction or rapid antigen test was obtained from the Centre for Health Protection of the Department of Health (DH). Electronic medical records of patients (including demographics, inpatient and outpatient encounters, clinical diagnoses and procedures, laboratory test results, drug prescription and dispensing records, and relevant clinical outcomes) managed under the public healthcare system were retrieved from the Hospital Authority (the statutory body managing all public healthcare services in Hong Kong), and linked COVID-19 vaccination records were extracted from the DH using unique identification numbers. Mortality events were verified from the Hong Kong Death Registry that captures both in-hospital deaths and deaths outside hospitals.

Both the symptomatic and asymptomatic cases were included. Patients who were aged under 1 or above 3, had received COVID-19 vaccines other than those locally available (i.e. other than the original monovalent BNT162b2 or CoronaVac), and those with SARS-CoV-2 infection diagnosis or symptom onset date on or after that of hospitalization or registered death were excluded. Index date of each eligible patient was denoted as that of first SARS-CoV-2 infection diagnosis or symptom onset, whichever occurred earlier. Patients were followed up from the index date until death, outcome event occurrence, 28 days after the index date, or the administrative end of the observational period (12th February 2023), whichever came first. These databases have been used collectively to evaluate the effects of novel oral antivirals for COVID-19 treatment.[14-17]

This study was approved by the institutional review board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference no. UW 20-341). Individual patient-informed consent was not required for this retrospective cohort study using anonymized data.

Exposure

COVID-19 vaccination exposure was defined as having received one or more doses of BNT162b2 or CoronaVac at least 14 days prior to the index date. Patients who were administered with the latest dose in less than 14 days from the index date would be assigned as one dose less, for instance, those who were vaccinated with the second dose would be counted as having received only one dose, and those who were vaccinated with their first dose would be considered as unvaccinated. The unvaccinated control group comprised patients who had never received any vaccine doses and those with their first dose administered in less than 14 days prior to their respective index date.

Outcomes

Primary outcomes included all-cause mortality, COVID-19-related hospitalization, and in-hospital disease progression (namely in-hospital death, invasive mechanical ventilation, and ICU admission). Secondary outcomes included multisystem inflammatory syndrome in children (MIS-C), neurological complications (namely encephalitis, encephalopathy, and seizure), and respiratory complications (namely croup and pneumonia).

Statistical analyses

Baseline covariates of patients included age, sex, date of SARS-CoV-2 confirmation, symptomatic presentation, previous SARS-CoV-2 infection, pre-existing conditions (namely asthma, cancer, cardiac disease, lung disease, mental disease, neurologic disease, obesity, diabetes mellitus, disabilities, and immunocompromised state), and healthcare utilization (any inpatient and/or outpatient encounters) in the past year. Vaccination status of the exposed group was further categorized by the number of doses received, vaccine type (BNT162b2 or CoronaVac), and days from vaccination to index date.

We used a logistic regression model conditional on baseline covariates of patients to estimate the propensity scores. One-to-one propensity-score matching between the vaccinated and unvaccinated groups was then performed using greedy nearest neighbor matching, with a caliper width of 0.05 on the logit of the propensity score. Each control was randomly matched to a patient in the vaccinated group without replacement. Standardized mean difference (SMD) of each baseline covariate between the two groups before and after propensity-score matching

were calculated, and interpreted as balanced when the SMD was below the threshold of 0.1. Hazard ratio (HR) with 95% confidence intervals (CI) of each study outcome between the two groups were estimated using Cox regression models.

For the outcome of COVID-19-related hospitalization, sensitivity analyses were performed by varying the determination of vaccination status by (i) excluding patients receiving 1 dose, (ii) using a 7-day lag prior to the index date, and (iii) using a 21-day lag, instead of a 14-day lag in the primary analysis. Also, subgroup analyses were conducted by (i) age (1-2 versus 3 years old) and (ii) vaccine type (BNT162b2 or CoronaVac as the last dose).

All statistical analyses were performed using Stata/MP (version 17). All significance tests were two-tailed, and p-value <0.05 was considered statistically significant.

Results

During the study period, 22,911 COVID-19 patients aged 1-3 years were eligible for inclusion (Figure 1). After matching, baseline characteristics were balanced between 5,552 vaccinated and 5,552 unvaccinated patients (Table 1), and the distribution of their propensity scores were highly overlapping (eFigure 1). At baseline, 65.9% of the cohort were 3 years old, and over 60% had symptomatic presentation. Pre-existing medical conditions were minimal in both groups. Among vaccinated patients, 33.2%, 59.9%, and 6.9% had received one, two, and three doses, respectively; and the majority were vaccinated with CoronaVac. The latest vaccine dose was administered at a median of 82.8 (standard deviation=62.2) days prior to the index date. The distribution of COVID-19 cases over the study period is illustrated in eFigure 2.

Over 28 days of follow-up, no events of mortality were recorded (Table 2). The cumulative incidences of COVID-19-related hospitalization were 2.3% and 2.9% among vaccinated patients and unvaccinated controls, respectively (Figure 2). COVID-19 vaccination was associated with a significantly lower risk of COVID-19-related hospitalization (HR=0.785, 95%CI=0.626-0.985, p=0.037). Similar findings were obtained using 7-day or 21-day lag to determine the vaccination status, including those who had received ≥2 doses in sensitivity analyses (eTable 1). The association between COVID-19 vaccination and reduced risk of COVID-19-related hospitalization was generally consistent across subgroups, notably for patients aged 3 years (eTable 2). No significant differences in the risk of ICU admission, seizure, or croup (all cumulative incidences <1%) were observed between the two groups.

Discussion

In this retrospective cohort of children aged 1-3 years with SARS-CoV-2 Omicron infection, COVID-19 vaccination was associated with a significantly lower risk of 28-day COVID-19-related hospitalization by approximately 22%. Notably, our vaccinated cohort had mainly received 1-2 doses of the inactivated vaccine CoronaVac. Apart from an observational study of 27 children aged 7 months to 5 years who had been inadvertently vaccinated with a single dose of CoronaVac and demonstrated potential humoral responses to the immunization,[18] our study is likely the first to estimate the association between COVID-19 vaccination and various clinical outcomes among infected children aged 1-3. Compared to unvaccinated controls, a cohort study in Chile during the Omicron outbreak has reported vaccine effectiveness of 64.6% against hospitalization in children aged 3-5 after completing the 2-dose series of CoronaVac.[8] Differences in the age group and number of doses received might have contributed to the

smaller effect size of our results. Meanwhile, a case-control study in Hong Kong amid the Omicron wave suggested no significant protection against 28-day COVID-19-related hospitalization with two doses of CoronaVac in children aged 3-17, and a dose-response relationship was indicated with vaccine effectiveness of 51.7% among those receiving three doses.[10] The reduced risk of COVID-19-related hospitalization associated with ≥2 vaccine doses observed in our cohort is in line with the current literature recognizing such dose-dependent protection against infection, hospitalization, and severe COVID-19.[9,10,19] This also applies to mRNA vaccines for the pediatric population, hence the importance of completing the full 3-dose series to optimize vaccine effectiveness.[7,10]

Research on COVID-19 vaccine effectiveness against hospitalization and severe disease outcomes are lacking for children aged <4, thus our findings are preliminary and may not be directly comparable to results of immunogenicity or vaccine efficacy against infection as illustrated in the clinical trial for BNT162b2 in children aged <5.[4] Besides, only 3% of our vaccinated patients had received BNT162b2; and among them, most had only been vaccinated with a single dose. This might be attributed to the late introduction of mRNA vaccine for infants and toddlers in Hong Kong, or children vaccinated with BNT162b2 were less likely to be infected and hence not included in the current analysis. Unfortunately, estimation of vaccine effectiveness against infection was not feasible from our data sources of infected patients; and further studies with larger sample sizes of toddlers vaccinated with mRNA vaccines are needed to delineate their clinical significance in preventing hospitalization and complications of COVID-19. Nevertheless, our results demonstrating amelioration of disease in breakthrough infections is of public health importance. Moreover, assessments of the immune responses of infants and toddlers to inactivated vaccines are necessary to inform the optimal dosing schedule

and maximize vaccine protection against various clinical outcomes of SARS-CoV-2 infection, especially for those aged ≤2.

Several limitations of our study should be acknowledged. Our data sources are restricted to identifying patients engaged with the public healthcare system, and fails to capture treatment exposure and outcomes in the private healthcare sector. Therefore, misclassification bias could not be eliminated. Despite propensity-score matching on various baseline covariates, our study remains susceptible to selection bias by comparing vaccinated patients with unvaccinated controls, as potential differences in their healthcare seeking behavior, access to healthcare, and other unmeasured or residual confounding could have an impact on the interpretation of our results. Finally, the sample sizes of BNT162b2 recipients or those fully vaccinated with three doses were relatively small, limiting the interpretation and generalizability of effectiveness, especially for mRNA vaccines. Further studies on the real-world effectiveness of mRNA vaccines among younger children with COVID-19 are needed to confirm our findings and explore the protective effects of mRNA vaccines against hospitalization and severe clinical outcomes.

Conclusion

In conclusion, COVID-19 vaccination (mainly the inactivated vaccine CoronaVac) is associated with a reduced risk of 28-day COVID-19-related hospitalization among infected children aged 1-3 years, especially among those who had received ≥2 doses. Our study findings emphasize the importance of completing the full two-dose or three-dose series to optimize vaccine effectiveness. Further research will give insight into the durability of such vaccine protection and effectiveness of mRNA vaccines in younger children.

Authors' contributions

C.K.H.W. designed the study, contributed to the interpretation of the analysis, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. C.K.H.W. and K.T.K.L. reviewed the literature and wrote the manuscript. I.C.H.A. conducted analysis and revised the manuscript. I.C.H.A., E.H.Y.L. and C.K.H.W. accessed and verified the underlying data. E.H.Y.L. and B.J.C. reviewed and revised the manuscript. C.K.H.W., K.T.K.L. and I.C.H.A. contributed equally to the current study.

Ethics approval

This study was approved by the institutional review board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference no. UW 20-341). Individual patient-informed consent was not required for this retrospective cohort study using anonymized data.

Funding

This work was supported by AIR@InnoHK administered by Innovation and Technology Commission of The Government of the Hong Kong Special Administrative Region, China. BJC is supported by the RGC Senior Research Fellow Scheme grant (HKU SRFS2021-7S03) from the Research Grants Council of the Hong Kong Special Administrative Region, China; and the Health and Medical Research Fund (HMRF) (grant number: CID-HKU2-13) from the Health Bureau, Hong Kong Special Administrative Region, China. The funding sources had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Data sharing statement

The data custodians (the Hospital Authority and the Department of Health) provided the underlying individual patient data to The University of Hong Kong for the purpose of performing scientific research for the study. Restrictions apply to the availability of these data, which were used under license of the Hospital Authority and the Department of Health for this study. The authors cannot transmit or release the data, in whole or in part in whatever form or media, or to any other parties or place outside Hong Kong; and the authors fully comply with the duties under the laws of Hong Kong relating to the protection of personal data including those under the Personal Data (Privacy) Ordinance and its principles in all aspects.

Declaration of interests

C.K.H.W. reports the receipt of General Research Fund, Research Grant Council, Government of Hong Kong SAR, China; EuroQol Research Foundation; AstraZeneca; and Boehringer Ingelheim, all outside the submitted work. B.J.C. consults for AstraZeneca, Fosun Pharma, GlaxoSmithKline, Haleon, Moderna, Pfizer, Roche and Sanofi Pasteur. All other authors declare no competing interests.

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Figure Legend

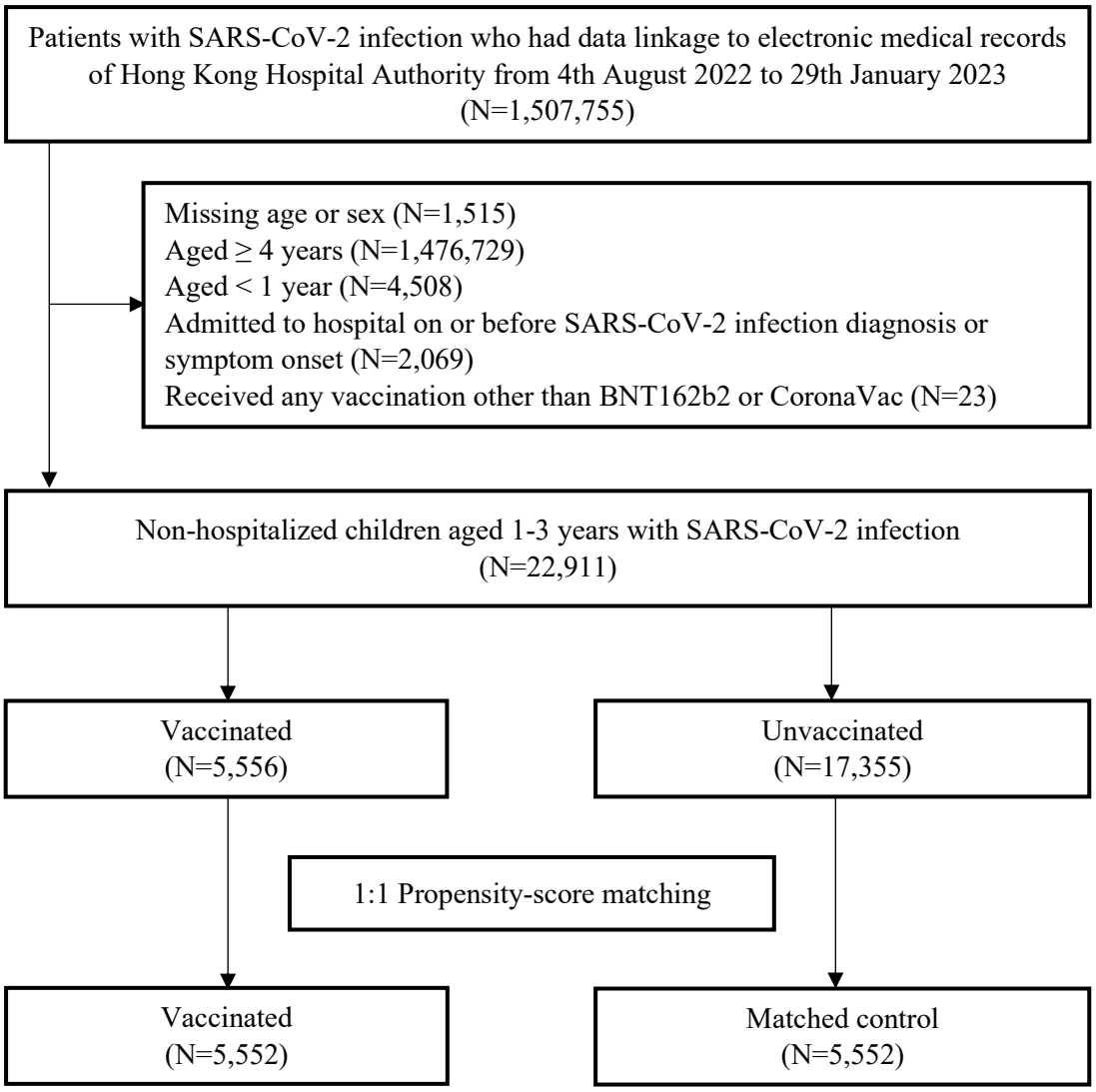
Figure 1. Flowchart of identifying eligible patients with SARS-CoV-2 infection from 4th August 2022 to 29th January 2023 in Hong Kong SAR, China

During the study inclusion period, a total of 22,911 non-hospitalized children aged 1-3 years with confirmed SARS-CoV-2 infection diagnosis were eligible for inclusion in the current study. Stratified by vaccination status and following one-to-one propensity-score matching, 5,552 vaccinated and 5,552 unvaccinated (control) patients were analyzed.

Figure 2. Cumulative incidence plot for the study outcome of COVID-19-related hospitalization

The cumulative incidences of COVID-19-related hospitalization over 28 days were 2.3% and 2.9% in the vaccinated and control groups, respectively. COVID-19 vaccination was associated with a significant reduction in 28-day COVID-19-related hospitalization risk (HR=0.785, 95%CI=0.626-0.985, p=0.037).

Figure 1. Flowchart of identifying eligible patients with SARS-CoV-2 infection from 4th August 2022 to 29th January 2023 in Hong Kong SAR, China



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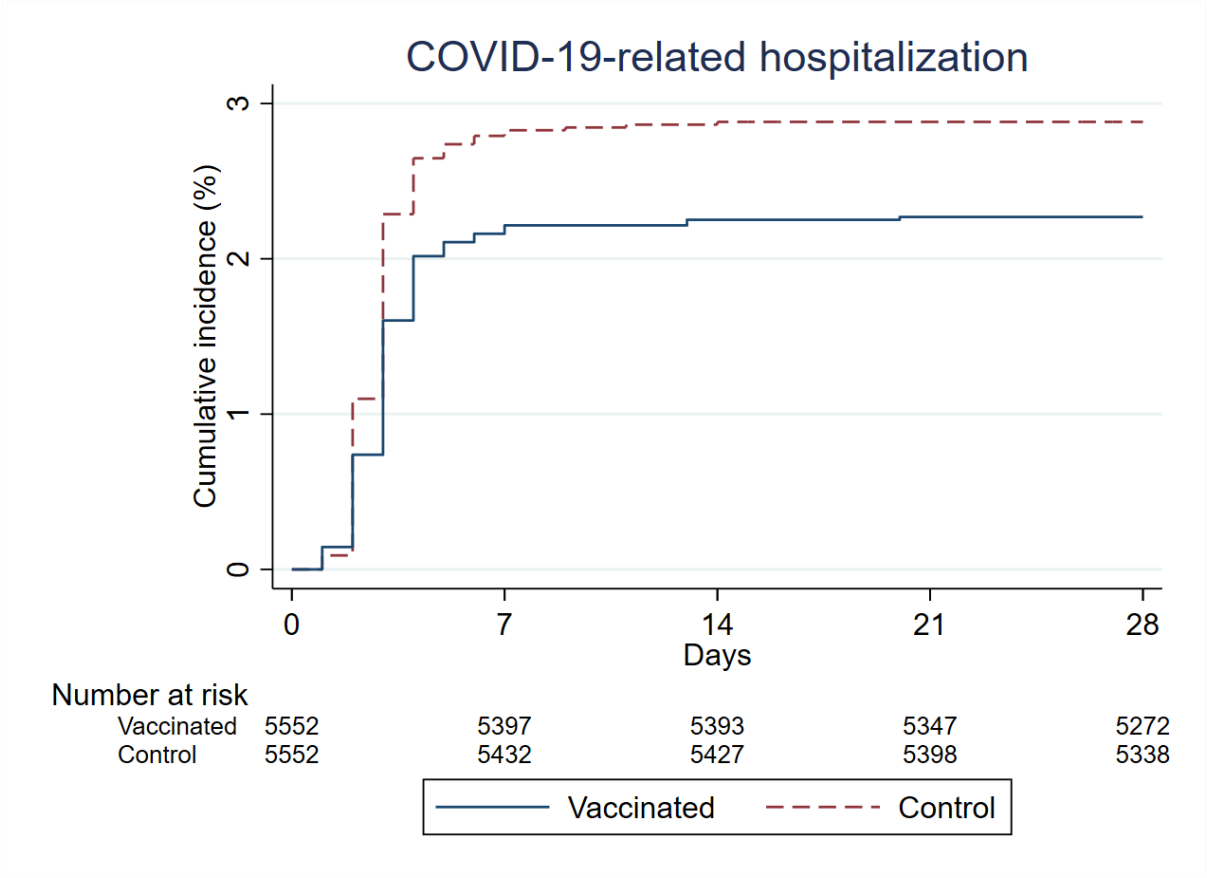

Table 1. Baseline characteristics of children aged 1-3 years with SARS-CoV-2 infection in vaccinated and control (unvaccinated) groups before and after propensity-score matching

Baseline characteristics	Before matching					After matching				
	Vaccinated (N=5,556)		Control (N=17,355)		SMD	Vaccinated (N=5,552)		Control (N=5,552)		SMD
	N / Mean	% / SD	N / Mean	% / SD		N / Mean	% / SD	N / Mean	% / SD	
Age, years	2.5	0.7	2.0	0.8	0.74	2.5	0.7	2.5	0.7	0.00
1	618	11.1%	5,968	34.4%		618	11.1%	620	11.2%	
2	1,277	23.0%	5,969	34.4%	0.78	1,277	23.0%	1,275	23.0%	0.00
3	3,661	65.9%	5,418	31.2%		3,657	65.9%	3,657	65.9%	
Sex										
Male	2,863	51.5%	8,928	51.4%	0.00	2,859	51.5%	2,881	51.9%	0.01
Female	2,693	48.5%	8,427	48.6%		2,693	48.5%	2,671	48.1%	
SARS-CoV-2 infection period										
August 2022 - November 2022	2,871	51.7%	10,017	57.7%	0.12	2,868	51.7%	2,850	51.3%	0.01
December 2022 - January 2023	2,685	48.3%	7,338	42.3%		2,684	48.3%	2,702	48.7%	
Symptomatic presentation	3,632	65.4%	12,264	70.7%	0.11	3,629	65.4%	3,652	65.8%	0.01
Prior SARS-CoV-2 infection	5	0.1%	14	0.1%	0.00	5	0.1%	3	0.1%	0.01
Pre-existing conditions										
Asthma	0	0.0%	2	0.0%	0.02	0	0.0%	1	0.0%	0.02
Cancer	1	0.0%	1	0.0%	0.01	1	0.0%	1	0.0%	0.00
Cardiac disease	2	0.0%	6	0.0%	0.00	2	0.0%	3	0.1%	0.01
Lung disease	33	0.6%	80	0.5%	0.02	29	0.5%	27	0.5%	0.01
Mental disease	1	0.0%	0	0.0%	0.02	1	0.0%	0	0.0%	0.02
Neurologic disease	3	0.1%	29	0.2%	0.03	3	0.1%	1	0.0%	0.02
Obesity	0	0.0%	0	0.0%	NA	0	0.0%	0	0.0%	NA
Diabetes mellitus	0	0.0%	4	0.0%	0.02	0	0.0%	0	0.0%	NA
Type 1 diabetes	0	0.0%	0	0.0%	NA	0	0.0%	0	0.0%	NA

Type 2 diabetes	0	0.0%	4	0.0%	0.02	0	0.0%	0	0.0%	NA
Disabilities	8	0.1%	77	0.4%	0.06	8	0.1%	13	0.2%	0.02
ADHD	0	0.0%	0	0.0%	NA	0	0.0%	0	0.0%	NA
Autism	0	0.0%	0	0.0%	NA	0	0.0%	0	0.0%	NA
Immunocompromised	16	0.3%	72	0.4%	0.02	16	0.3%	18	0.3%	0.01
Healthcare utilization in the past year	402	7.2%	1,141	6.6%	0.03	400	7.2%	396	7.1%	0.00
Number of doses										
0	0	0.0%	17,355	100.0%		0	0.0%	5,552	100.0%	
1	1,845	33.2%	0	0.0%	NA	1,844	33.2%	0	0.0%	NA
2	3,329	59.9%	0	0.0%		3,327	59.9%	0	0.0%	
3	382	6.9%	0	0.0%		381	6.9%	0	0.0%	
Sequence of vaccinations received*										
B	147	2.7%	NA	NA		147	2.7%	NA	NA	
BB	4	0.1%	NA	NA		4	0.1%	NA	NA	
BBB	11	0.2%	NA	NA		11	0.2%	NA	NA	
BC	1	0.0%	NA	NA	NA	1	0.0%	NA	NA	NA
C	1,698	30.6%	NA	NA		1,697	30.6%	NA	NA	
CC	3,324	59.8%	NA	NA		3,322	59.8%	NA	NA	
CCB	4	0.1%	NA	NA		4	0.1%	NA	NA	
CCC	367	6.6%	NA	NA		366	6.6%	NA	NA	
Last dose										
BNT162b2	166	3.0%	NA	NA	NA	166	3.0%	NA	NA	NA
CoronaVac	5,390	97.0%	NA	NA		5,386	97.0%	NA	NA	

Notes: ADHD = attention deficit hyperactivity disorder; NA = not applicable; SD = standard deviation; SMD = standardized mean difference
* Sequence of vaccinations received was presented in the order of first, second, and third doses, with B = BNT162b2 and C = CoronaVac
Table 2. All-cause mortality, COVID-related hospitalization, in-hospital progression, and secondary outcomes among children aged 1-3 years with SARS-CoV-2 infection in vaccinated and control (unvaccinated) groups

Outcomes	Vaccinated (N=5,552)					Control (N=5,552)					Vaccinated vs Control		
	Cumulative incidence		Crude incidence rate (Events / 100,000 person-days)			Cumulative incidence		Crude incidence rate (Events / 100,000 person-days)			HR†	95% CI	P-value
	New events	Rate	Estimate	95% CI	Person-days	New events	Rate	Estimate	95% CI	Person-days			
Primary outcomes													
All-cause mortality	0	0.0%	0.0	NA	154,934	0	0.0%	0.0	NA	154,715	NA	NA	NA
COVID-related hospitalization	126	2.3%	83.0	(69.1, 98.8)	151,834	160	2.9%	106.1	(90.3, 123.9)	150,742	0.785	(0.626, 0.985)	0.037
In-hospital disease progression	2	0.0%	1.3	(0.2, 4.7)	154,896	3	0.1%	1.9	(0.4, 5.7)	154,637	0.666	(0.111, 3.989)	0.657
In-hospital death	0	0.0%	0.0	NA	154,934	0	0.0%	0.0	NA	154,715	NA	NA	NA
Invasive mechanical ventilation	0	0.0%	0.0	NA	154,934	1	0.0%	0.6	(0.0, 3.6)	154,691	NA	NA	NA
Intensive care unit admission	2	0.0%	1.3	(0.2, 4.7)	154,896	3	0.1%	1.9	(0.4, 5.7)	154,637	0.666	(0.111, 3.989)	0.657
Secondary outcomes													
Multisystem inflammatory syndrome in children (MIS-C)	0	0.0%	0.0	NA	154,878	0	0.0%	0.0	NA	154,715	NA	NA	NA
Encephalitis	0	0.0%	0.0	NA	154,934	0	0.0%	0.0	NA	154,687	NA	NA	NA
Encephalopathy	0	0.0%	0.0	NA	154,934	0	0.0%	0.0	NA	154,715	NA	NA	NA
Seizure	11	0.2%	7.1	(3.6, 12.7)	154,617	14	0.3%	9.1	(5.0, 15.2)	154,341	0.786	(0.356, 1.732)	0.550
Croup	41	0.7%	26.6	(19.1, 36.1)	153,899	32	0.6%	20.8	(14.2, 29.3)	153,945	1.282	(0.817, 2.012)	0.279
Pneumonia	0	0.0%	0.0	NA	154,855	0	0.0%	0.0	NA	154,575	NA	NA	NA

Note: CI = confidence interval; NA = not applicable

† HR >1 (or <1) indicates vaccinated patients had a higher (lower) risk of outcome compared to the matched control group.

HR was estimated only when the number of events in both groups were more than or equal to two.