THE LANCET
Child & Adolescent Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Yung CF, Pang D, Kam KQ, et al. BNT162b2 vaccine protection against omicron and effect of previous infection variant and vaccination sequence among children and adolescents in Singapore: a population-based cohort study. *Lancet Child Adolesc Health* 2023; published online May 15. https://doi.org/10.1016/S2352-4642(23)00101-3.

Supplementary Appendix

Figure S1: Study population

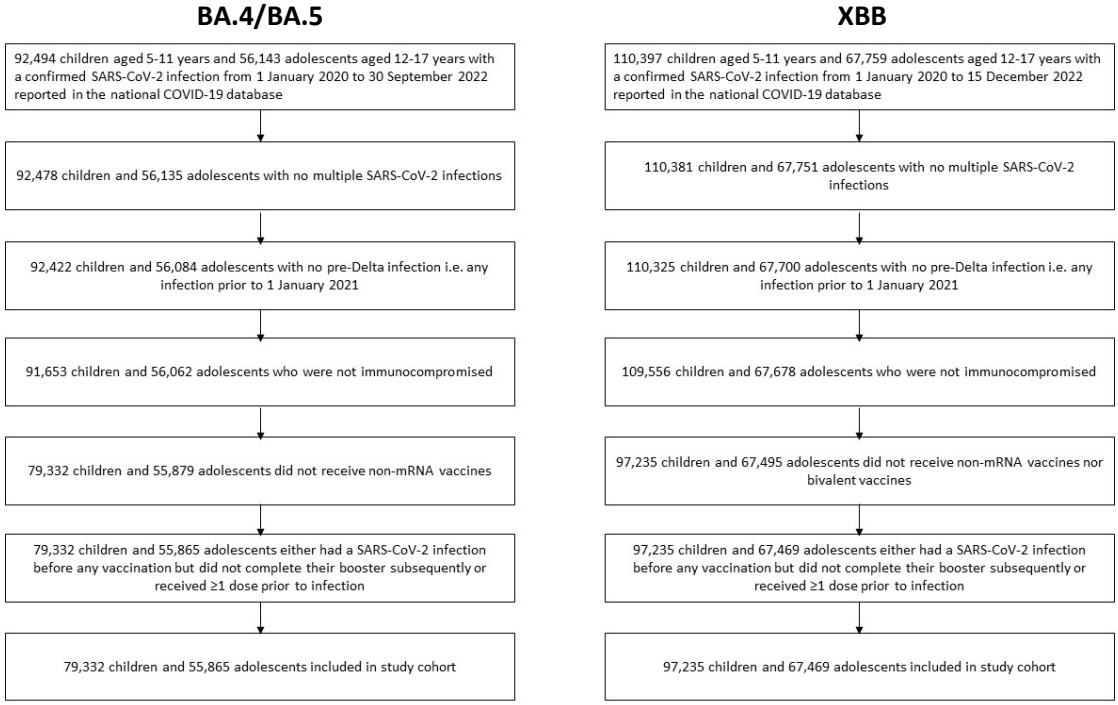

Table S2: Crude incidence and adjusted VE against Omicron BA.4/BA.5 infection by days since last vaccination dose in fully vaccinated previously infected children and adolescents.

Vaccination dose(s)	Days since last vaccine dose	5-11 years old		12-17 years old	
		Crude incidence, No. of BA.4/BA.5 Infections Per 100,000 Person-Days	Adjusted vaccine effectiveness, % (95%CI)*	Crude incidence, No. of BA.4/BA.5 Infections Per 100,000 Person-Days	Adjusted vaccine effectiveness, % (95%CI)*
0		26.2	Reference	47.4	Reference
2	<120 days	10.2	67.9 (58.5,75.2)	NA	NA
	120-<150 days	3.7	78.6 (65.2,86.8)	NA	NA
	150-<180 days	8.5	79.9 (71.4,85.9)	NA	NA
	≥180 days	5.0	78.7 (70.4,84.7)	NA	NA
3	<90 days	NA	NA	9.5	84.6 (78.7,88.9)
	90-<120 days	NA	NA	9.8	93.0 (77.3,97.8)
	120-<150 days	NA	NA	11.5	96.0 (89.4,98.5)
	150-<180 days	NA	NA	9.4	96.1 (89.6,98.5)
	≥180 days	NA	NA	4.4	92.6 (82.1,96.9)

* Vaccine effectiveness (VE) was calculated by taking one minus the incidence rate ratios x 100. Poisson regression was used to estimate incidence rate ratios of SARS-CoV-2 reinfection with Omicron BA.4/BA.5 adjusted for age, gender, ethnicity, housing type (as a proxy for socioeconomic status) and calendar week (to account for varying force of infection across time), variant of previous infection and time from previous infection.

NA: Not Applicable

Table S3: Adjusted VE against Omicron BA.4/BA.5 and XBB infection in previously infected children and adolescents without comorbidities based on ICD coding

Vaccination dose(s)	Adjusted vaccine effectiveness, % against BA.4/BA.5 (95%CI)*		Adjusted vaccine effectiveness, % against XBB (95%CI)*	
	5-11 years old	12-17 years old	5-11 years old	12-17 years old
0	Reference	Reference	Reference	Reference
1	44.2 (32.2,53.8)	70.5 (53.4,81.1)	58.8 (35.3,73.8)	54.4 (21.9,73.4)
2	74.1 (67.6,79.1)	84.8 (77.1,90.1)	62.6 (42.1,75.9)	57.9 (33.5,73.3)
3	NA	85.6 (80.1,89.6)		48.1 (20.4,66.2)

* Vaccine effectiveness (VE) was calculated by taking one minus the incidence rate ratios x 100. Poisson regression was used to estimate incidence rate ratios of SARS-CoV-2 infection with Omicron BA.4/BA.5 adjusted for age, gender, ethnicity, housing type (as a proxy for socioeconomic status), calendar week (to account for varying force of infection across time), vaccination status and time from last vaccine dose, variant of previous infection and time from previous infection.

Genomic Surveillance of COVID-19 in Singapore

Under the Ministry of Health's COVID-19 genomic surveillance programme to monitor the prevalence and distribution of circulating SARS-CoV-2 variants, whole genome sequencing (WGS) is done systematically for 3 groups: imported cases, general community cases, and severe cases. For imported cases, individuals who test positive on antigen rapid test (ART) and have a travel history within 5 days from positive test date are randomly selected to receive an additional PCR test. For general community cases, a sample of individuals presenting with acute respiratory symptoms at sentinel primary care sites undergo dual testing with ART and PCR. PCR samples from all cases with severe COVID-19 (required oxygen supplementation, admission to intensive care unit or died) are also sent for sequencing. SARS-CoV-2 positive specimens are screened for S-gene target failure (SGTF) with the TaqPath COVID-19 Combo Kit (ThermoFisher Scientific) and selected for WGS based on their viral load, SGTF results and case categories.

Methodology for imputation of Omicron sublineage

During time periods where 75% or more of cases systematically sequenced under the national genomic surveillance program for COVID-19 belonged to a particular predominant variant, imputation would follow the predominant variant. In time periods when there was no predominant variant, regression imputation was performed using a logistic regression model based on calendar date of reporting and additional demographic variables (age, gender, ethnicity and housing type) as predictors. Between 1 December 2021 and 17 October 2022, 82 of the total 336 days did not have a predominant variant accounting for ≥75% of cases sequenced systematically under the national COVID-19 genomic surveillance programme. Imputation of Omicron sub-lineage was conducted for cases without WGS or SGTF results notified on those days.

There were multiple variants but no predominant variant in the following time periods: (i) 13 December 2021 to 26 December 2021 when Delta and BA.1 variants were present, (ii) 19 February 2022 to 28 February 2022 when BA.1 and BA.2 were present, (iii) 12 June 2022 to 10 July 2022 when BA.2 and BA.4/BA.5 were present and (iv) 19 September 2022 to 17 October 2022 when BA.4/BA.5 and XBB were present. A logistic regression model with reporting date and additional demographic variables (age, sex, ethnicity, housing type and residency status) as predictors was fitted for each of the above time periods to impute the Omicron sublineage for cases without WGS nor SGTF results.

Variable selection was determined through stepwise regressions, starting with only age in the base model, subsequently adding one variable at a time to the model and keeping it only if the area under the ROC curve increased by at least 1% from the previous iteration.

Validation of imputation models

Variables included in the final models are presented in Table S1. The area under the receiver operating curve (ROC) of the final models ranged from 66.3% to 70.4%.

5-fold cross-validation was conducted on cases with known WGS or SGTF screening results to validate the accuracy of imputation. The absolute percentage deviation in the variant predicted by our imputation models ranged from 0.7% to 6.6% (Table S1).

Table S4. Validation results of imputation models.

Time Period	Main SARS-CoV-2 variants circulating during time period	Variant used as outcome variable in logistic regression model	Variables included in final model	Area under ROC of final model	Actual no. of cases with variant set as the outcome variable	Predicted no. of cases with variant set as the outcome variable	Absolute percentage deviation in predicted variant
13 December 2021 to 26 December 2021	Delta BA.1	BA.1	Age and housing type	70.4%	91	85	6.6%
19 February 2022 to 28 February 2022	BA.1 BA.2	BA.2	Age and reporting date	66.3%	416	438	5.3%
12 June 2022 to 10 July 2022	BA.2 BA.4/BA.5	BA.4/BA.5	Age and reporting date	67.6%	1,285	1,294	0.7%
19 September 2022 to 17 October 2022	BA.4/BA.5 XBB	XBB	Age, sex, and reporting date	68.5%	4,557	4,399	3.5%

Table S5: Adjusted VE against Omicron BA.4/BA.5 infection stratified by previous SARs-CoV-2 infection variant.

Previous SARS-CoV-2 variant infection	Vaccination dose(s)	5-11 years old		12-17 years old	
		Crude incidence, No. of BA.4/BA.5 Infections Per 100,000 Person-Days	Adjusted VE against BA.4/BA.5 reinfection (95% CI)*	Crude incidence, No. of BA.4/BA.5 Infections Per 100,000 Person-Days	Adjusted VE against BA.4/BA.5 reinfection (95% CI)*
Delta	0	65.5	Reference	116.8	Reference
	1	68.0	32.3 (13.8,46.8)	79.8	60.1 (29.4,77.5)
	2	44.5	51.9 (5.3,75.6)	48.8	75.4 (57.2,85.9)
	3	NA	NA	39.4	77.5 (63.9,86.0)
BA.1	0	29.7	26.4 (7.2,41.5)	48.9	43.7 (-7.5,70.5)
	1	21.5	63.8 (52.6,72.4)	35.9	75.4 (37.2,90.4)
	2	11.3	81.9 (75.9,86.4)	7.7	94.8 (90.5,97.1)
	3	NA	NA	6.8	95.0 (91.6,97.0)
BA.2	0	10.0	63.2 (48.2,73.8)	25.6	62.6 (23.4,81.7)
	1	5.4	86.6 (77.9,91.9)	0	NA
	2	3.3	92.3 (88.9,94.7)	4.5	96.4 (93.0,98.2)
	3	NA	NA	4.3	96.4 (93.5,98.0)

* Vaccine effectiveness (VE) was calculated by taking one minus the incidence rate ratios x 100. Poisson regression was used to estimate incidence rate ratios of SARS-CoV-2 reinfection with Omicron BA.4/BA.5 adjusted for age, gender, ethnicity, housing type (as a proxy for socioeconomic status), calendar week (to account for varying force of infection across time), vaccination status of the naive group, time from last vaccine dose and time from previous infection.

NA: Not Applicable