

## Supplementary Online Content

Wee LE, Tang N, Pang D, et al. Effectiveness of monovalent mRNA vaccines against omicron xbb infection in Singaporean children younger than 5 years. *JAMA Pediatr*. Published online October 16, 2023. doi:10.1001/jamapediatrics.2023.4505

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This supplementary material has been provided by the authors to give readers additional information about their work.

**Methods 1: Secondary Analysis 1- Incidence-rate-ratio (IRR) of confirmed SARS-CoV-2 infection amongst infection-naïve Singaporean children aged 1 through 4 years, by age group**

A secondary analysis was carried out by age group, with sex, ethnicity, housing type, imputed viral lineage, vaccination status, time elapsed since last vaccination dose, comorbidities and immunocompromised status as covariates in the Poisson regression model (Table S2). This analysis was restricted to the subset of the population that were infection-naïve (no previous documented SARS-CoV-2 infection). We did not perform an analysis by age group in the subset of the population with previous documented SARS-CoV-2 infection due to the very small number of re-infections in this group. The IRRs of confirmed SARS-CoV-2 infection were similar across age groups (Table S2).

**Methods 2: Secondary Analysis 2- Incidence-rate-ratio of confirmed SARS-CoV-2 infection amongst Singaporean children aged 1 through 4 years, using unvaccinated, infection-naïve children as the reference category**

Instead of stratifying our analysis by prior SARS-CoV-2 infection, we used a Poisson regression model to estimate the incidence-rate-ratio (IRR) of reported infections, adjusting for age, sex, ethnicity, housing type, imputed viral lineage, comorbidities, immunocompromised status, time elapsed since last vaccination, and vaccination combined with prior SARS-CoV-2 infection status (either unvaccinated and no prior SARS-CoV-2 infection; partially vaccinated and no prior SARS-CoV-2 infection; fully vaccinated and no prior SARS-CoV-2 infection; unvaccinated and prior SARS-CoV-2 infection; partially vaccinated and prior SARS-CoV-2 infection).(Table S3) Unvaccinated children with no prior SARS-CoV-2 infection (infection-naïve) formed the reference category; we did not estimate the IRR of SARS-CoV-2 reinfection in fully vaccinated children with prior SARS-CoV-2 infection, as there were no cases. Poisson regression was also used to analyse the IRR of infection in children with prior infection compared to infection-naïve children (the reference category), adjusting for vaccination status, age, sex, ethnicity, housing type, imputed viral lineage, comorbidities, immunocompromised status, time elapsed since last vaccination.

**Methods 3: Secondary Analysis 3- Analysis of mRNA-1273 (Moderna) vaccine effectiveness against confirmed SARS-CoV-2 infection amongst Singaporean children aged 1 through 4 years, stratified by prior SARS-CoV-2 infection and vaccination status**

A secondary analysis was carried out on the subset of the population who received mRNA-1273 (Moderna) vaccine doses, excluding individuals who received BNT162b2 (Pfizer-BioNTech) vaccine doses. Age, sex, ethnicity, housing type, imputed viral lineage, comorbidities, immunocompromised status and time elapsed since last vaccination dose were included as covariates in the Poisson regression model. We did not analyse the subset of the population who received BNT162b2 (Pfizer-BioNTech) vaccine doses due to small numbers in this group. Vaccine effectiveness was calculated as 1 minus the incidence-rate-ratio (IRR), times 100%. Results of vaccine effectiveness against confirmed SARS-CoV-2 infection (Table S4) were similar when compared against estimates derived from the complete study population (Table 2).

**Methods 4: Secondary Analysis 4- Incidence-rate-ratio of confirmed SARS-CoV-2 re-infection amongst Singaporean children aged 1 through 4 years with prior SARS-CoV-2 infection, controlling for time elapsed since last infection**

A secondary analysis was carried out with time elapsed since last infection as an additional covariate, together with age, sex, ethnicity, housing type, comorbidities, immunocompromised status and time elapsed since last vaccination dose as other covariates in the Poisson regression model. This analysis was restricted to the subset of the population that had prior SARS-CoV-2 infection. Time elapsed since last infection was stratified into  $\leq 6$  months, 7-8 months, 9-10 months, and  $\geq 11$  months. Incidence-rate-ratios of confirmed SARS-CoV-2 re-infection (Table S5) were similar to that reported without the inclusion of time elapsed since last infection as a covariate (Table 2).

**eTable 1: COVID-19 vaccine combinations received by individuals in the vaccinated cohort (N=11,705)**

<b>Vaccine combinations</b>	<b>N (%)</b>
Total	11,705 (100.0)
Single dose of mRNA-1273 (Moderna)	6,505 (55.6)
Two doses of mRNA-1273 (Moderna)	4,789 (40.9)
Single dose of BNT162b2 (Pfizer-BioNTech)	330 (2.8)
Two doses of BNT162b2 (Pfizer-BioNTech)	81 (0.7)
Three doses of BNT162b2 (Pfizer-BioNTech)	0 (0.0)

**eTable 2: Incidence-rate-ratio (IRR) of confirmed SARS-CoV-2 infection amongst infection-naïve Singaporean children aged 1 through 4 years, stratified by age group (N= 75,935)**

Vaccination status	Adjusted IRR <sup>§</sup> for confirmed SARS-CoV-2 infection during study period (95% CI), stratified by age			
	1 year	2 years	3 years	4 years
Unvaccinated	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Partially vaccinated <sup>†</sup>	0.38 (0.15-0.94)	0.43 (0.21-0.90)	0.65 (0.39-1.11)	0.62 (0.36-1.10)
Fully vaccinated <sup>‡</sup>	0.35 (0.10-1.22)	0.35 (0.12-0.98)	0.47 (0.21-1.06)	0.26 (0.10-0.68)

IRR=incidence rate ratio. <sup>†</sup>Partial vaccination was defined as having received at least one dose of mRNA vaccines, but not having completed a full vaccination regimen. <sup>‡</sup>Full vaccination was defined as having a primary vaccination series of 2 doses of mRNA-1273 (Moderna), or 3 doses of BNT162b2 (Pfizer-BioNTech) vaccine, at a recommended interval of 8 weeks apart, with  $\geq 7$  days having elapsed since the final dose. <sup>§</sup>Adjusted for sex, ethnicity, housing type, imputed viral lineage, comorbidity, immunocompromised status and time elapsed since last vaccination dose with Poisson regression.

**eTable 3: Incidence-rate-ratio of confirmed SARS-CoV-2 infection amongst Singaporean children aged 1 through 4 years, using unvaccinated, infection-naïve children as the reference category (N= 121,628)**

	Vaccination status	Total person-days at risk	Number of cases	Incidence, per million person-days	Adjusted IRR§ (95% CI)
<b>No prior SARS-CoV-2 infection</b>	Unvaccinated	12,532,687	3,261	260.2	1.00 (reference)
	Partially vaccinated†	519,177	69	132.9	0.57 (0.41-0.77)
	Fully vaccinated‡	308,180	21	68.1	0.38 (0.23-0.61)
<b>Prior SARS-CoV-2 infection<sup>†</sup></b>	Unvaccinated	7,208,375	532	73.8	0.27 (0.25-0.30)
	Partially vaccinated†	446,247	5	11.2	0.05 (0.02-0.12)
	Fully vaccinated‡	1290	0	0.0	N.A <sup>‡</sup>

IRR=incidence rate ratio. †Partial vaccination was defined as having received at least one dose of mRNA vaccines, but not having completed a full vaccination regimen. ‡Full vaccination was defined as having a primary vaccination series of 2 doses of mRNA-1273 (Moderna), or 3 doses of BNT162b2 (Pfizer-BioNTech) vaccine, with a recommended interval of 8 weeks apart, with ≥7 days having elapsed since the final dose. §Adjusted for age, sex, ethnicity, housing type, imputed viral lineage, comorbidity, immunocompromised status and time elapsed since last vaccination dose with Poisson regression. †Prior SARS-CoV-2 infection was defined as either positive polymerase-chain-reaction, PCR, or rapid-antigen-test, RAT, in national records. ‡Not computed due to an absence of cases.

**eTable 4: Vaccine effectiveness of mRNA-1273 (Moderna) against confirmed SARS-CoV-2 infection amongst Singaporean children aged 1 through 4 years, stratified by prior SARS-CoV-2 infection and vaccination status (N= 121,027)**

No prior SARS-CoV-2 infection (N=75,544)		Confirmed SARS-CoV-2 infection during study period			
Vaccination status	Total person-days at risk	Number of cases	Incidence, per million person-days	Adjusted IRR§ (95% CI)	Vaccine efficacy (1-IRR)*100%, (95%CI)
Unvaccinated	12,476,420	3,239	259.6	1.00 (reference)	-
Partially vaccinated†	507,842	66	130.0	0.55 (0.40-0.75)	45.3% (24.7%-60.2%)
Fully vaccinated‡	308,180	21	68.1	0.38 (0.23-0.61)	62.2% (38.8%-76.6%)
Prior SARS-CoV-2 infection† (N=45,483)		Confirmed SARS-CoV-2 re-infection during study period			
Vaccination status	Total person-days at risk	Number of cases	Incidence, per million person-days	Adjusted IRR§ (95% CI)	Vaccine efficacy (1-IRR)*100%, (95%CI)
Unvaccinated	7,182,624	526	73.2	1.00 (reference)	-
Partially vaccinated†	438,329	5	11.4	0.26 (0.11-0.62)	74.2% (37.7%-89.3%)
Fully vaccinated‡	1290	0	0.0	N.A.‡	-

IRR=incidence rate ratio. †Partial vaccination was defined as having received at least one dose of mRNA-1273 vaccine, but not having completed a full vaccination regimen. ‡Full vaccination was defined as having a primary vaccination series of 2 doses of mRNA-1273 (Moderna), at a recommended interval of 8 weeks apart, with ≥7 days having elapsed since the final dose. §Adjusted for age, sex, ethnicity, housing type, imputed viral lineage, comorbidity, immunocompromised status and time elapsed since last vaccination dose with Poisson regression. †Prior SARS-CoV-2 infection was defined as either positive polymerase-chain-reaction, PCR, or rapid-antigen-test, RAT, in national records. ‡Not computed due to an absence of cases.

**eTable 5: Incidence-rate-ratio (IRR) of confirmed SARS-CoV-2 re-infection amongst Singaporean children aged 1 through 4 years with prior SARS-CoV-2 infection, controlled for time elapsed since last infection (N= 45,693)**

Prior SARS-CoV-2 infection <sup>†</sup> (N=45,693)	Total person-days at risk	Confirmed SARS-CoV-2 re-infection during study period, adjusted IRR <sup>§</sup> (95% CI)
<b>Vaccination status</b>		
Unvaccinated	7,208,375	1.00 (reference)
Partially vaccinated <sup>‡</sup>	446,247	0.27 (0.11-0.64)
Fully vaccinated <sup>‡</sup>	1,290	N.A <sup>‡</sup>
<b>Time elapsed since last infection</b>		
≥11 months	2,020,822	1.00 (reference)
9-10 months	1,685,628	1.05 (0.80-1.39)
7-8 months	1,962,636	1.72 (1.35-2.20)
≤6 months	1,986,826	0.96 (0.73-1.27)

IRR=incidence rate ratio. <sup>†</sup>Partial vaccination was defined as having received at least one dose of mRNA vaccines, but not having completed a full vaccination regimen. <sup>‡</sup>Full vaccination was defined as having a primary vaccination series of 2 doses of mRNA-1273 (Moderna), or 3 doses of BNT162b2 (Pfizer-BioNTech) vaccine, at a recommended interval of 8 weeks apart, with ≥7 days having elapsed since the final dose. <sup>§</sup>Additionally adjusted for age, sex, ethnicity, housing type, imputed viral lineage, comorbidity, immunocompromised status and time elapsed since last vaccination dose with Poisson regression. <sup>†</sup>Prior SARS-CoV-2 infection was defined as either positive polymerase-chain-reaction, PCR, or rapid-antigen-test, RAT, in national records. <sup>‡</sup>Not computed due to an absence of cases.

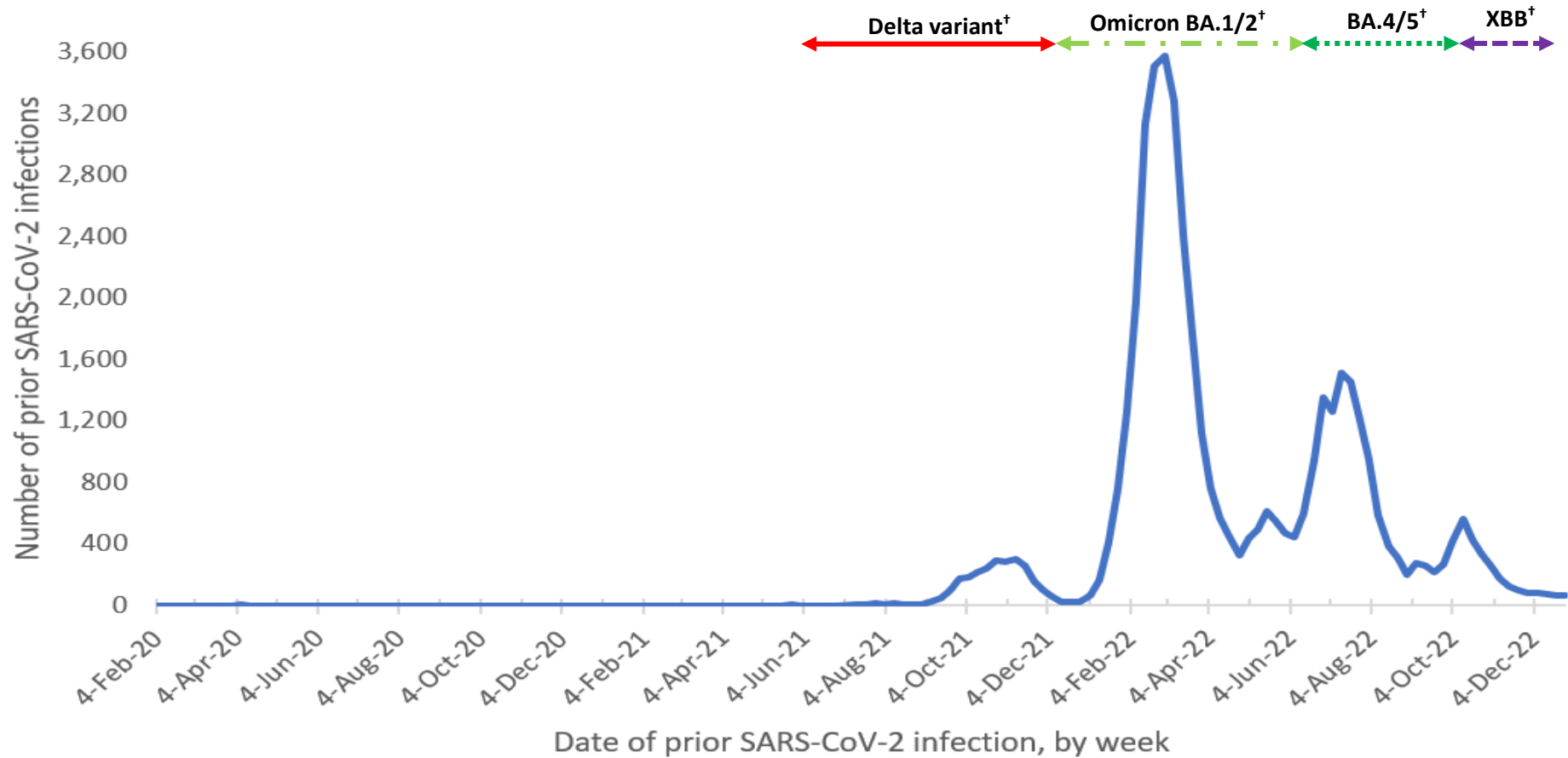


**eTable 6: Vaccine effectiveness against confirmed SARS-CoV-2 infection and hospitalization amongst Singaporean children aged 1 through 4 years, stratified by prior SARS-CoV-2 infection and vaccination status, using interval of 14 days post-receipt of vaccination (N= 121,628)**

<b>No prior SARS-CoV-2 infection (N=75,935)</b>		<b>Hospitalization for COVID-19 during study period</b>		<b>Confirmed SARS-CoV-2 infection during study period</b>			
Vaccination status	Total person-days at risk	Number of cases	Incidence, per million person-days	Number of cases	Incidence, per million person-days	Adjusted IRR§ (95% CI)	Vaccine efficacy (1-IRR)*100%, (95%CI)
Unvaccinated	12,584,770	122	10.1	3,271	259.9	1.00 (reference)	-
Partially vaccinated†	500,120	5	10.4	59	118.0	0.51 (0.37-0.71)	48.5% (28.5%-62.9%)
Fully vaccinated‡	275,154	0	0.0	21	76.3	0.44 (0.28-0.71)	55.6% (29.0%-72.2%)
<b>Prior SARS-CoV-2 infection† (N=45,693)</b>		<b>Hospitalization for COVID-19 during study period</b>		<b>Confirmed SARS-CoV-2 re-infection during study period</b>			
Vaccination status	Total person-days at risk	Number of cases	Incidence, per million person-days	Number of cases	Incidence, per million person-days	Adjusted IRR§ (95% CI)	Vaccine efficacy (1-IRR)*100, (95%CI)
Unvaccinated	7,237,563	11	1.6	532	73.5	1.00 (reference)	-
Partially vaccinated†	417,186	0	0.0	5	12.0	0.25 (0.11-0.62)	74.5% (38.5%-89.5%)
Fully vaccinated‡	1,163	0	0.0	0	0.0	N.A.	-

IRR=incidence rate ratio. †Partial vaccination was defined as having received at least one dose of mRNA vaccines, but not having completed a full vaccination regimen. ‡Full vaccination was defined as having a primary vaccination series of 2 doses of mRNA-1273 (Moderna), or 3 doses of BNT162b2 (Pfizer-BioNTech) vaccine, at a recommended interval of 8 weeks apart, with ≥14 days having elapsed since the final dose. §Adjusted for age, sex, ethnicity, housing type, imputed viral lineage, time elapsed since last vaccination dose, comorbidities and immunocompromised status, with Poisson regression. †Prior SARS-CoV-2 infection was defined as either positive polymerase-chain-reaction, PCR, or rapid-antigen-test, RAT, in national records. ‡Not computed due to an absence of cases.

eFigure: Date of prior recorded SARS-CoV-2 infections in study cohort (N=45,693)



<sup>†</sup>Based on publicly released genomic surveillance information from the Ministry of Health, Singapore; Omicron BA.1 replaced Delta as the predominant strain ( $\geq 50\%$  of circulating strains on genomic surveillance) in January 2022; subsequently from February 2022 onwards, Omicron BA.2 predominated. This was followed by a surge of cases driven by Omicron BA.4/5 predominance in July 2022, and subsequently predominance of the Omicron XBB variant from October 2022 onwards. As individuals were continuously introduced throughout the study period into the study population for prior SARS-CoV-2 infection 90 days after the reported date of prior infection, the last date of prior SARS-CoV-2 infection was 31st December 2022.