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Effectiveness of primary series and booster vaccination against SARS-CoV-2 infection and hospitalisation among adolescents aged 12–17 years in Singapore: a national cohort study

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Summary
Background Singapore offered the BNT162b2 vaccine (tozinameran; Pfizer-BioNTech) to adolescents aged 12–17 years in May 18, 2021, and extended booster vaccines to this group in Jan 21, 2022. Literature on the effectiveness of primary series and booster vaccination among adolescents is scare outside of Europe and North America. We aimed to determine primary series and booster vaccine effectiveness against SARS-CoV-2 infection and hospitalisation among adolescents in Singapore.

Methods For this national cohort study, we assessed the incidence of confirmed SARS-CoV-2 infection and hospitalisation among adolescents aged 12–17 years vaccinated with BNT162b2 in Singapore from Sept 1 to Dec 15, 2021, during the delta (B.1.617.2) variant wave, and from Jan 21 to April 28, 2022, during the omicron (B.1.1.529) variant wave. Data were collected from official databases maintained by the Ministry of Health of Singapore. Individuals were classified as partly vaccinated (those who had received one dose and those who had received the second dose no more than 7 days previously), fully vaccinated (8 days after receiving a second dose), or boosted (8 days after receiving a third dose) and compared with unvaccinated individuals.

Findings 249 763 individuals aged 12–17 years were included in the study, contributing over 56·2 million person-days of observation. Compared with unvaccinated individuals, two vaccine doses achieved vaccine effectiveness of 66% (95% CI 63–69) against infection with the delta variant and 25% (21–29) against infection with the omicron variant, and 83% (74–89) against delta variant-associated hospitalisation and 75% (56–86) against omicron variant-associated hospitalisation. Booster vaccination with a third dose achieved vaccine effectiveness of 56% (53–58) against infection with the omicron variant and 94% (86–97) against omicron-associated hospitalisation, compared with unvaccinated adolescents. Vaccine effectiveness against infection for both variants after two doses waned over time, whereas vaccine effectiveness against hospitalisation for both variants remained stable; both were increased after three doses.

Interpretation Among adolescents aged 12–17 years, vaccine effectiveness against confirmed SARS-CoV-2 infection after two doses of BNT162b2 decreased over time and increased after a third dose. Boosted adolescents were also the most protected from hospitalisation compared with fully vaccinated, partly vaccinated, and unvaccinated adolescents. Therefore, the booster dose of BNT162b2 can help to reduce the burden on the health-care system and individual morbidity during an omicron wave.

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Methods

Study design and participants

For this national cohort study, we analysed the incidence of all reported SARS-CoV-2 infections confirmed by PCR or antigen rapid testing and hospitalisations for COVID-19 among adolescents aged 12–17 years in Singapore, from Sept 1 to Dec 15, 2021, and from Jan 21 to April 28, 2022, separately. The first period coincided with the time when delta was the predominant variant, while the second period covered the time when omicron was predominant. We excluded the period between Dec 16, 2021, and Jan 20, 2022, because both delta and omicron were circulating during this time. The cutoff dates and predominant variant of each infection wave were determined on the basis of whole-genome sequencing results from a representative sample of cases systematically selected under the national genomic surveillance programme for COVID-19 (appendix p 1).

Adolescents whose 12th birthday was after Sept 1, 2021, were included in the study so that unvaccinated persons days before their vaccination eligibility date could be observed. Adolescents whose 18th birthday was before Sept 1, 2021, were excluded as they were eligible to receive mRNA vaccinations other than BNT162b2.

Testing for SARS-CoV-2 infection was done on all individuals who presented with symptoms of acute respiratory infection to a health-care facility, and all positive cases were required by law to be notified to the Ministry of Health of Singapore (MOH) under the Infectious Diseases Act. Additionally, all public hospitals were required to report patient-level information on all SARS-CoV-2-related hospitalisations to the MOH. Need for hospitalisation was assessed by physicians on the basis of clinical presentation and risk factors such as comorbidities.

Data were collected from official databases maintained by the MOH including national records of all confirmed SARS-CoV-2 infections, hospitalisations, and vaccines administered. The study was done as part of national public health research under the Infectious Diseases Act, Singapore, to support policy decision making and evaluation of the public health response to COVID-19; hence, a separate ethics review by an Institutional Review Board was not required.
Outcomes
Adolescents with no previous history of SARS-CoV-2 infection and who had received one, two, or three doses of BNT162b2 were compared with those unvaccinated for the outcomes of confirmed infection and hospitalisation. Individuals were classified as partly vaccinated from the day after their first dose until 7 days after receiving their second dose, and fully vaccinated 8 days after their second dose to allow for sufficient immune response. Similarly, individuals were classified as boosted 8 days after their third dose. Classification within these groups was dynamic, with those unvaccinated becoming partly vaccinated, fully vaccinated, or boosted subsequently, similar to a published booster effectiveness analysis.

Statistical analysis
Using a Poisson regression model, we estimated the incidence rate ratio (IRR) of confirmed SARS-CoV-2 infection and hospitalisation, controlling for age, gender, ethnicity, housing type (a marker of socioeconomic status), and varying force of infection (exposure risk) across time (by including daily calendar date dummy variables in the model). In counting person-time, we accounted for the time-varying nature of vaccination status: the same individual could contribute person-time to unvaccinated, partly vaccinated, fully vaccinated, and boosted groups depending on time. Vaccine effectiveness was calculated by taking 1 minus the relative risk in relation to the unvaccinated group, with the lower bound set at 0%. We calculated 95% CIs on the basis of Wald statistics, assuming that the over-dispersion parameter was one. We report estimates of vaccine effectiveness during the delta wave and the omicron wave separately. Estimates of booster effectiveness were only available for the omicron wave.

We also present estimates from a modified Poisson regression with robust error variance using a sandwich estimator and estimates from a cluster variance estimator using unique individuals as the cluster variable in the appendix (p 2). We evaluated model fit by comparing modelled incidences of infections with empirically observed ones. The analysis was done with Stata, version 17.

Role of the funding source
There was no funding source for this study.

Results
249763 individuals aged 12–17 years were included in the study cohort (appendix p 4); of these, 127 379 (51–0%) were boys and 122 384 (49–0%) were girls, and median age was 15 years (IQR 13–16). These adolescents contributed over 56·2 million person-days of observation, of which about 9·4 million (16·7%) were boosted, 42·8 million (76·1%) were fully vaccinated, 1·1 million (2·0%) were partly vaccinated, and 2·9 million (5·2%) were unvaccinated (table 1). Median time interval was 35 days (28–42) between the first and second dose, and 211 days (201–224) between the second and third dose. 49 921 adolescents developed SARS-CoV-2 infection over the study period, of whom 372 (0·7%) were hospitalised for COVID-19. None of the adolescents had a reinfection within the study period. There was one severe case of a 16-year-old female individual requiring intubation in an intensive care unit, and one case of multisystem inflammatory syndrome in a 12-year-old male individual. Both were vaccinated with two doses and were infected during the omicron wave.

After adjusting for age, gender, ethnicity, socioeconomic status, and daily infection rate, two doses of vaccination achieved vaccine effectiveness of 66% (95% CI 63–69) against delta infection and 25% (21–29) against omicron infection, and 83% (74–89) against delta hospitalisation and 75% (56–86) against omicron hospitalisation (table 2). Booster vaccination with a third dose achieved a vaccine effectiveness of 56% (53–58) against omicron infection.

### Table 1: Demographic characteristics of the study cohort by vaccination status

| Ethnicity | Unvaccinated, person-days at risk | Partly vaccinated*, person-days at risk | Fully vaccinated†, person-days at risk | Boosted, person-days at risk |
|-----------|----------------------------------|----------------------------------------|----------------------------------------|----------------------------|
| Chinese   | 2 032 024 (69.7%)                | 747 042 (67.9%)                         | 28 790 570 (62.2%)                     | 6 493 360 (68.9%)          |
| Malay     | 349 395 (12.0%)                  | 128 544 (12.6%)                         | 5 206 046 (12.4%)                      | 1 118 044 (11.9%)          |
| Indian    | 395 418 (13.6%)                  | 127 286 (15.7%)                         | 6 954 905 (16.2%)                      | 1 395 842 (14.8%)          |
| Others‡  | 140 032 (4.8%)                   | 42 081 (3.8%)                           | 1 790 256 (4.2%)                       | 418 352 (4.4%)            |

Housing type

| 1–2-room public housing | Unvaccinated, person-days at risk | Partly vaccinated*, person-days at risk | Fully vaccinated†, person-days at risk | Boosted, person-days at risk |
|-------------------------|----------------------------------|----------------------------------------|----------------------------------------|----------------------------|
| Chinese                 | 0.675 (2.7%)                     | 39 686 (3.6%)                          | 1 295 819 (3.0%)                       | 240 468 (2.6%)            |
| Malay                   | 466 347 (16.0%)                  | 196 454 (15.4%)                        | 7 395 470 (12.7%)                      | 1 241 808 (13.2%)        |
| Indian                  | 910 565 (31.2%)                  | 340 384 (30.9%)                        | 1 038 812 (30.6%)                      | 2 809 701 (29.8%)        |
| Others                  | 829 121 (28.4%)                  | 319 141 (29.0%)                        | 1 250 335 (29.2%)                      | 2 756 023 (29.2%)        |

Private housing

| 5-room public housing | Unvaccinated, person-days at risk | Partly vaccinated*, person-days at risk | Fully vaccinated†, person-days at risk | Boosted, person-days at risk |
|-----------------------|----------------------------------|----------------------------------------|----------------------------------------|----------------------------|
| Chinese               | 564 652 (19.4%)                  | 199 370 (18.1%)                        | 8 369 597 (20.1%)                      | 2 048 150 (21.7%)        |
| Malay                 | 66 009 (2.3%)                    | 31 736 (2.9%)                          | 1 443 740 (3.4%)                       | 329 439 (3.5%)           |

Data are n or n (%). *Partial vaccination was defined as having received one dose of BNT162b2 or two doses with 7 days or fewer after the second dose. †Full vaccination was defined as having received two doses of BNT162b2 with 8 days elapsed after the second dose to allow for sufficient immune response. ‡Boosted was defined as having received a third dose of BNT162b2 at least 5 months after the second dose, and 8 days after the third dose. §Includes individuals of other ethnicities or mixed ethnicities.
and 94% (86–97) against omicron hospitalisation, compared with unvaccinated adolescents. Estimates using a sandwich and cluster variance estimators yield similar point estimates and 95% CIs (appendix p 2).

Table 2: Primary series and booster vaccine effectiveness against SARS-CoV-2 infection and hospitalisation among adolescents, stratified by time period

|                          | Confirmed SARS-CoV-2 infection, delta-variant wave | Confirmed SARS-CoV-2 infection, omicron-variant wave | Hospitalisation, delta-variant wave | Hospitalisation, omicron-variant wave |
|--------------------------|---------------------------------------------------|-----------------------------------------------------|-------------------------------------|----------------------------------------|
|                          | Unvaccinated                                      | Partly vaccinated*                                   | Fully vaccinated†                    | Boosted‡                               |
| Number of cases          | 997                                               | 163                                                 | 3884                                | NA                                     |
| Incidence, per million person-days | 449                                              | 204                                                 | 169                                 | NA                                     |
| Adjusted IRR (95% CI)    | 1 (ref)                                           | 0·41 (0·35–0·49)                                    | 0·34 (0·31–0·37)                    | NA                                     |
| Adjusted VE (95% CI)     | (ref)                                             | 0·59 (0·51–0·65)                                    | 0·66 (0·63–0·69)                    | NA                                     |
| Number of cases          | 1254                                              | 388                                                 | 30 866                               | 11 226                                 |
| Incidence, per million person-days | 3159                                              | 2768                                                | 2721                                 | 1198                                   |
| Adjusted IRR (95% CI)    | 1 (ref)                                           | 0·78 (0·69–0·87)                                    | 0·75 (0·71–0·79)                    | 0·44 (0·42–0·47)                       |
| Adjusted VE (95% CI)     | (ref)                                             | 0·22 (0·13–0·31)                                    | 0·25 (0·21–0·29)                    | 0·56 (0·53–0·58)                       |
| Number of cases          | 70                                                | 7                                                   | 112                                 | NA                                     |
| Incidence, per million person-days | 31                                                 | 9                                                    | 5                                    | NA                                     |
| Adjusted IRR (95% CI)    | 1 (ref)                                           | 0·28 (0·13–0·61)                                    | 0·17 (0·11–0·26)                    | NA                                     |
| Adjusted VE (95% CI)     | (ref)                                             | 0·72 (0·39–0·87)                                    | 0·83 (0·74–0·89)                    | NA                                     |
| Number of cases          | 15                                                | 5                                                   | 131                                 | 12                                     |
| Incidence, per million person-days | 40                                                 | 37                                                  | 12                                   | 1                                      |
| Adjusted IRR (95% CI)    | 1 (ref)                                           | 0·67 (0·24–1·87)                                    | 0·25 (0·14–0·44)                    | 0·06 (0·03–0·14)                       |
| Adjusted VE (95% CI)     | (ref)                                             | 0·33 (0·00–0·76)                                    | 0·75 (0·56–0·86)                    | 0·94 (0·86–0·97)                       |

The delta-variant wave occurred between September and December, 2021. The omicron-variant wave occurred between January and April, 2022. IRR=incidence rate ratio. NA=not applicable. VE=vaccine effectiveness. *Partial vaccination was defined as having received one dose of BNT162b2 or two doses with 7 days or fewer after the second dose. †Full vaccination was defined as having received two doses of BNT162b2 with 8 days elapsed after the second dose to allow for sufficient immune response. ‡Boosted was defined as having received a third dose of BNT162b2 at least 5 months after the second dose, and 8 days after the third dose. §Adjusted for age, gender, ethnicity, housing type, and date of reporting (to control for daily infection rate) with Poisson regression.

Modelled incidences of infections among unvaccinated, fully vaccinated, and boosted adolescents were similar to empirically observed incidences (appendix pp 6–7).

For both variants, vaccine effectiveness against infection among fully vaccinated individuals waned over time, from an initial 75% after completion of the second dose to 57% after 150–179 days for delta, and from 47% to 16% over a similar duration for omicron (figure). However, among those boosted, vaccine effectiveness against omicron infection increased to 60% 14–29 days after the third dose, before declining to 40% after 60 days. Vaccine effectiveness against hospitalisation among fully vaccinated individuals remained stable, ranging between 76% and 89% from 8 days up to 149 days after the second dose for delta, and fluctuating between 59% and 89% from 8 days up to 239 days after the second dose for omicron. This effectiveness against hospitalisation was further increased among those boosted to 84–96% up to 60 days after the third dose for omicron.

**Discussion**

Our study found that the two-dose vaccine effectiveness against SARS-CoV-2 infection among adolescents was lower for omicron than for delta, corroborating existing studies comparing the efficacy of numerous vaccines against these two variants in adults. This finding is probably due to greater immune evasion by omicron and...
is supported by higher incidence of infections observed during the omicron wave in Singapore compared with the delta wave (appendix p 5).

We also showed that a booster dose provided the greatest protection against SARS-CoV-2 infection and hospitalisation. Among boosted adolescents, our observed vaccine effectiveness of 56% against omicron infection was lower than the 71.1% vaccine effectiveness reported by a US study involving adolescents aged 12–15 years during omicron predominance. Our observed vaccine effectiveness of 66% against delta infection among fully vaccinated adolescents was also lower than the 90% vaccine effectiveness against delta reported by a study in Israel involving similar-age adolescents. Another study in the USA found a vaccine effectiveness of 93% against SARS-CoV-2 hospitalisation for fully vaccinated adolescents during delta predominance, higher than our observed vaccine effectiveness of 83% against delta hospitalisation. The lower vaccine effectiveness against SARS-CoV-2 infection and hospitalisation in our study could be a result of vaccination-differentiated social distancing measures implemented in Singapore from Aug 10 2021, which restricted the access of unvaccinated individuals to settings with potentially higher risk of SARS-CoV-2 transmission such as eateries, shopping malls, and religious and recreational facilities. This could have reduced the exposure risk of unvaccinated individuals.

Our findings also suggest a gradual waning of immunity over 5 months from completion of the second dose for both variants, which supports the need for a booster dose. A study of individuals aged older than 12 years in the USA similarly showed that vaccine effectiveness against delta infections declined from 93% during the first month after full vaccination to 53% after 4 months. Another US study showed that vaccine effectiveness against omicron infections rapidly declined from 59.5% during the first month after full vaccination to 16.6% after 2 months. A slight waning of vaccine effectiveness over 2 months after the third dose was also observed in our study, and should be evaluated over a longer term in further studies.

Despite waning immunity against infection over time, vaccine effectiveness against hospitalisation remained stable among those fully vaccinated up to 4 months after the second dose for delta. Protection against hospitalisation was slightly lower against omicron compared with delta after two doses but increased to similar levels after the booster dose. This aligns with a US study that found that three doses were required to achieve similar protection against omicron hospitalisation compared with two doses against delta hospitalisation, highlighting the benefit of a booster dose in reducing stress on the health-care system and maintaining individual protection against severe disease in an omicron wave.

Our study is based on comprehensive national data on paediatric COVID-19 vaccinations and infections. However, there are a few limitations. First, despite our adjustments for demographic, socioeconomic, and time variables that might affect exposure risk, there might be residual confounding from comorbidities and other unknown factors that influence an adolescent’s vaccination status or health-care-seeking behaviour. Second, admission to hospital is a clinical decision, and thus a subjective measure of disease severity. Lastly, as genomic sequencing was not routinely done on all confirmed cases of SARS-CoV-2 infection, variant type was assumed on the basis of case-reporting date and predominant variant of each infection wave in Singapore. As both delta and omicron were codominant between Dec 16, 2021, and Jan 20, 2022, cases reported during this period were omitted from the analysis.

Among adolescents aged 12–17 years, vaccine effectiveness against confirmed SARS-CoV-2 infection after two doses of BNT162b2 decreased over time and increased after a third dose. Boosted adolescents were also most protected from hospitalisation, compared with fully vaccinated, partly vaccinated, and unvaccinated adolescents.
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