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BNT162b2 antigen dose and SARS-CoV-2 omicron infection in adolescents

COVID-19 vaccine antigen dose might affect protection against SARS-CoV-2 infection,[1,2] but direct evidence to quantify this effect is absent. We conducted a matched, retrospective, cohort study using a regression discontinuity design[3] to emulate a randomised controlled trial in Qatar between Feb 3, 2022, and Nov 8, 2022, to provide a head-to-head, controlled comparison of protection induced by two different antigen doses of the BNT162b2 (Pfizer–BioNTech) vaccine (appendix pp 4–10).

The study compared incidence of infection with the omicron (B.1.1.529) variant in the national cohort of adolescents aged 12 years who received the two-dose 30 µg BNT162b2 primary series with that in the national cohort of adolescents aged 11 years who received the two-dose pediatric 10 µg BNT162b2 primary series.

Data for SARS-CoV-2 laboratory testing, vaccination, and demographic information were extracted from Qatar's national SARS-CoV-2 databases (appendix pp 5–6). Adolescents in the 30 µg cohort were matched exactly one-to-one by sex, ten nationality groups, number of coexisting conditions, previous infection status (no previous infection, or previous infection with either pre-omicron or omicron viruses, or previous infections with both viruses) to adolescents in the 10 µg cohort, to balance observed confounders between exposure groups. Matching was also done by calendar month of the second vaccine dose to control for time since the second vaccine dose. Each matched pair was followed up from the calendar day 14 days after the adolescent in the 30 µg cohort received the second dose. Associations were estimated using Cox proportional hazard regression models.

The study population selection process is presented in the appendix (p 20). Of 4085 adolescents in the 30 µg cohort and 5323 in the 10 µg cohort, 2999 matched pairs were included. Baseline characteristics

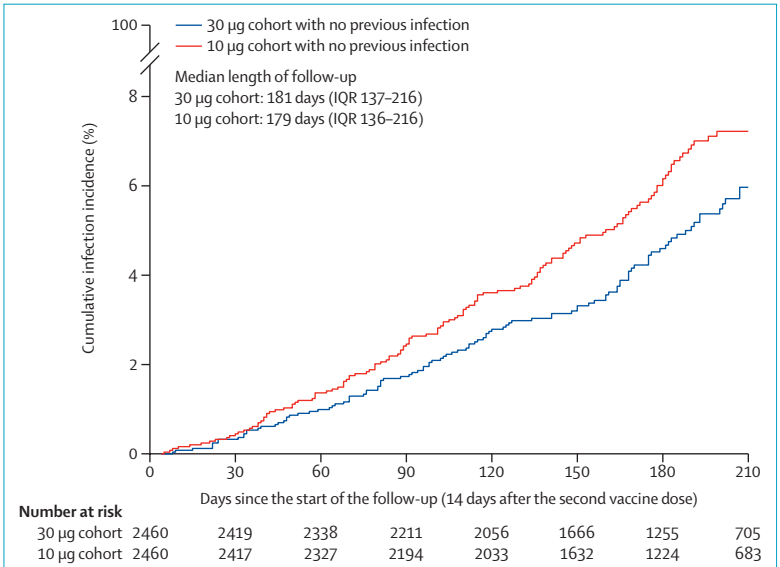

Figure: **Cumulative incidence of infection with the omicron variant of SARS-CoV-2 in adolescents vaccinated with two doses of 30 µg BNT162b2 versus two doses of 10 µg BNT162b2**

	30 µg cohort*	10 µg cohort*	HR (95% CI) for infection		Effectiveness against infection, % (95% CI)†
			Unadjusted	Adjusted†	
Matched cohorts with no previous infection			0·77 (0·60 to 0·99)	0·77 (0·60 to 0·98)	23·4% (1·6 to 40·4)
Total follow-up time, person-weeks	60 230	59 604	..	..	..
Number of incident infections	109	140	..	..	..
Incidence rate of infection, per 10 000 person-weeks (95% CI)	18·1 (15·0 to 21·8)	23·5 (19·9 to 27·7)	..	..	..
Matched cohorts with previous infection			1·50 (0·72 to 3·11)	1·50 (0·72 to 3·12)	−33·3% (−68·0 to 27·5)
Total follow-up time, person-weeks	12 212	12 222	..	..	..
Number of incident infections	18	12	..	..	..
Incidence rate of infection, per 10 000 person-weeks (95% CI)	14·7 (9·3 to 23·4)	9·8 (5·6 to 17·3)	..	..	..

HR=hazard ratio. *Each adolescent vaccinated with the 30 µg BNT162b2 vaccine was matched exactly one-to-one (by sex, ten nationality groups, number of coexisting conditions, previous infection status, and calendar month of the second vaccine dose) to the first eligible adolescent vaccinated with the pediatric 10 µg BNT162b2 vaccine who was alive and did not have a SARS-CoV-2 positive test in the 90 days before the start of the follow-up (14 days after the second vaccine dose of their match). †Vaccine effectiveness in the 30 µg cohort relative to that in the 10 µg cohort, estimated using hazard ratios derived from Cox regression analysis adjusted for sex, ten nationality groups, number of coexisting conditions, previous infection status, and calendar month of the second vaccine dose.

***Table*: Risk of and vaccine effectiveness against infection with the omicron variant of SARS-CoV-2 in adolescents vaccinated with two doses of 30 µg BNT162b2 versus two doses of 10 µg BNT162b2**

of eligible and matched cohorts are presented on appendix p 22. Among adolescents with no record of previous infection, the median difference in age between matched adolescents in the two cohorts was 8·4 months (IQR 5·2–11·6). During follow-up, 109 infections were recorded in the 30 µg infection-naive cohort and 140 in the 10 µg infection-naive cohort (figure, table; appendix p 20). None progressed to severe, critical, or fatal COVID-19.

Cumulative infection incidence was 6·0% (95% CI 4·9–7·3) for the 30 µg cohort and 7·2% (6·1–8·5) for the 10 µg cohort, 210 days after the start of follow-up (figure). Incidence was dominated, consecutively, by the BA.1/BA.2, BA.4/BA.5, BA.2.75*, and XBB sublineages. The adjusted hazard ratio comparing infection incidence in the 30 µg cohort with that in the 10 µg cohort was 0·77 (95% CI 0·60–0·98; table). Corresponding vaccine effectiveness in the 30 µg cohort relative to that in the 10 µg cohort was 23·4% (95% CI 1·6–40·4).

Sensitivity analyses adjusting for differences in testing frequency or controlling for duration between the first and second doses across cohorts yielded similar results (appendix pp 9–12, 23). There was no evidence for differences in infection incidence by restricting the cohorts to participants with any previous infection, only a previous pre-omicron infection, or only a previous omicron infection (appendix p 24), but these subcohorts were small. Limitations are discussed in the appendix (pp 13–15).

To conclude, a three-fold higher BNT162b2 dose was associated with close to 25% higher protection against infection in infection-naive adolescents of similar age. This finding is consistent with observed differences in SARS-CoV-2 neutralising titres after each antigen dose.[4,5] The effect size is also similar to that observed (~30%) for protection against SARS-CoV-2 with the mRNA-1273 (Moderna) vaccine compared with the BNT162b2 vaccine,[2] with mRNA-1273 having an antigen dose three-fold higher than in BNT162b2.

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*Hiam Chemaitelly, Houssein H Ayoub, Peter Coyle, Patrick Tang, Hadi M Yassine, Asmaa A Al Thani, Hebah A Al-Khatib, Mohammad R Hasan, Zaina Al-Kanaani, Einas Al-Kuwari, Andrew Jeremijenko, Anvar Hassan Kaleeckal, Ali Nizar Latif, Riyazuddin Mohammad Shaik, Hanan F Abdul-Rahim, Gheyath K Nasrallah, Mohamed Ghaith Al-Kuwari, Hamad Eid Al-Romaihi, Adeel A Butt, Mohamed H Al-Thani, Abdullatif Al-Khal, Roberto Bertollini, *Laith J Abu-Raddad

hsc2001@qatar-med.cornell.edu; lja2002@qatar-med.cornell.edu

Infectious Disease Epidemiology Group, Weill Cornell Medicine–Qatar, Cornell University, PO Box 24144, Doha, Qatar (HC, LJA-R); Department of Mathematics, Statistics, and Physics, and Biomedical Research Center (HHA), Department of Biomedical Science (HMY, AAA-T, HAA-K, GKN), and Department of Public Health (HFA-R, LJA-R), Qatar University, Doha, Qatar; Hamad Medical Corporation, Doha, Qatar (PC, ZA-K, EA-K, AJ, AHK, ANL, RMS, AAB, AA-K); Department of Pathology, Sidra Medicine, Doha, Qatar (PT, MRH); Primary Health Care Corporation, Doha, Qatar (MGA-K); Ministry of Public Health, Doha, Qatar (HEA-R, MHA-T, RB)

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Seasonal variation in azithromycin prescription

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In *The Lancet Infectious Diseases*, Ephraim Tsalik and colleagues[1] published the results of a randomised, placebo-controlled, double-blind, non-inferiority trial on the efficacy and safety of azithromycin to treat non-pneumonia lower respiratory tract infections associated with low procalcitonin. Placebo was not non-inferior to azithromycin in terms of clinical improvement at day 5, which was the primary outcome. However, placebo was non-inferior at day 11 and day 28 in the per-protocol analysis. Most of the documented infections in this study were viral (54%), and only 1% were bacterial infections; the use of antibiotics in these patients is therefore questionable. In particular, the benefit of azithromycin in patients with non-pneumonia lower respiratory tract infections with low procalcitonin is unclear.

This question remains of particular interest. First, prescription of azithromycin increases in cold months. We identified a clear increase in azithromycin prescriptions from September to April (2018–20) in the outpatient setting in the Alsace region, France (appendix). These data were collected through the French National Health Data System. This seasonal prescription pattern could have been due to the increased prevalence of respiratory tract infections, mostly as a result of winter viral epidemics, but also due to bacterial infections. Previous studies have shown seasonal variations in inappropriate prescribing for viral infection.[2,3] This observation

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