Response Letter to "Real-world Effectiveness of BNT162b2 Against Infection and Severe Diseases in Children and Adolescents: Target Trial Emulation"

Reviewer 1: This is very well done, very timely, and interesting. There are still a great many questions about COVID-19 vaccines, particularly for the different variants, so I think you hit the nail on the head here in terms of not only questions to ask, but ways to approach answering them.

- *Response: Thank you very much for your positive feedback on our work.*

Reviewer 2: This study addresses a pressing concern: assessing the real-world effectiveness of the BNT162b2 vaccine against SARS-CoV-2 among children and adolescents. As the world wrestles with the evolving COVID-19 pandemic, such investigations hold notable public health significance. The study's contribution to our understanding of the durability of vaccine protection during the Omicron period for a full year is an important fill to the existing knowledge gap.

One particularly commendable feature of this study is the innovative trial emulation approach that it introduces. This new approach allows for the estimation of the true vaccination status when it may not be accurately captured, thereby enhancing the credibility of the study's findings. Notably, the study claims to be the first to factor in the incomplete capture of vaccination status by U.S. health systems. Another strength of this research lies in its inclusion of pediatric populations across diverse U.S. health care settings. This inclusion broadens the potential for generalizing the study's findings. The pioneering use of the trial emulation design, especially in the face of misclassifications in vaccination status, amplifies the credibility of the study's results.

However, the abstract could provide more information on how the study controls for confounding variables, such as health disparities, socioeconomic status, and other influential factors that could potentially skew the vaccine's effectiveness. It was also unclear how covariates were selected for propensity score calculations.

The results are well presented in the figures and tables, and indicate that the vaccine offers durable protection for up to a year, underscoring the significance of the study's findings. Overall this is a solid and valuable contribution.

- *Response: We thank the reviewer for the positive feedback and clarification question. We revised the abstract by including "Therefore, we built the propensity score model by regressing the error-prone vaccination status using logistic regression on demographic factors including age, sex, race/ethnicity, clinical factors including obesity status, a chronic condition indicator as defined by the Pediatric Medical Complexity Algorithm (PMCA)(8), and a list of pre-existing chronic conditions, and healthcare utilization factors including the number of inpatients, outpatients, ED visits, unique mediations, and the number of*

negative COVID-19 tests prior to the cohort entry. We then stratified the patients into propensity score quintiles based on these factors."

Real-world Effectiveness of BNT162b2 Against Infection and Severe Diseases in Children and Adolescents: Target Trial Emulation

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Background

Observational studies have been conducted to investigate the effectiveness of vaccination in real-world settings(1–5). However, prior studies have had limited follow-up periods, covering the Delta variant or earlier subvariants of Omicron periods only. Studies evaluating the Omicron variant have only assessed the short-term effects of the vaccine, with only one study involving children evaluating the effect beyond 3 months(6). There is limited information on the long-term durability of vaccine protection during the Omicron period. Few existing studies on U.S. pediatric populations have covered both hospitalized patients and those with mild or asymptomatic conditions. Furthermore, while studies have acknowledged limitations due to misclassification in vaccination status in real-world effectiveness studies, none have rigorously

evaluated the impacts of such misclassification nor accounted for the potential bias it may introduce.

To address these gaps in our knowledgebase of the pediatric effectiveness of SARS-CoV-2 vaccination, we designed this study to assess the real-world effectiveness of BNT162b2 among children and adolescents during the Delta and Omicron periods using electronic health record (EHR) data from a national network of U.S. pediatric medical centers (PEDSnet). Our study used a trial emulation design and adjusted for misclassification issues in vaccination status and has several attractive features that strengthen credibility of inferences. First, the study examined the effectiveness against infection over a longer follow-up period than any previous study, enabling evaluation of the durability of vaccine protection. Second, the study included a diverse representation of U.S. pediatric populations from primary care, specialty care, emergency department, testing centers, and inpatient settings. Third, the study was the first to account for the incomplete capture of vaccination status by health systems in the U.S.

Methods

We designed and conducted emulation of three target trials(7) to investigate the effectiveness of the BNT162b2 vaccine in preventing infection with various strains of the SARS-CoV-2 virus in children and adolescents in the United States. The three target trials focused on documented SARS-CoV-2 infection and outcomes in:

- ***Target trial 1*** (Delta study in adolescents): adolescents aged 12-20 years during the period when the Delta variant was prevalent from July 1, 2021, to November 30, 2021.
- ***Target trial 2*** (Omicron study in children): children aged 5 to 11 years during the period when the Omicron variant was prevalent from January 1, 2022, to November 30, 2022.
- ***Target trial 3*** (Omicron study in adolescents): adolescents aged 12-20 years during the period when the Omicron variant was prevalent from January 1, 2022, to November 30, 2022.

Children aged of 5 to 11 years or adolescents aged 12 to 20 years at the start of the study period and no previous COVID-19 vaccination or documented SARS-CoV-2 infection were eligible to the study. The intervention of interest was vaccination by BNT162b2, in comparison with no receipt of any type of COVID-19 vaccine. The four COVID-19 outcomes of interest were: documented SARS-CoV-2 infection, mild COVID-19, moderate/severe COVID-19, and ICU admission with COVID-19.

Vaccine status may be missing for individuals whose vaccine doses were administered by a site outside of the PEDSnet network care delivery sites. It is likely that patients recorded as vaccinated in the EHR are true positives, so specificity could be very high, but sensitivity would be reduced by undocumented vaccinations (false negatives). With this assumption, we proposed a new trial-emulation pipeline by pre-specifying a range of possible sensitivities. Specifically, let V denote

the true vaccination status and V^* be the observed vaccination status with error. In the first step of propensity-score stratification, under a non-differential misclassification setting,

$$P(V^* = 1|X) = sensitivity * P(V = 1|X)$$

where $P(V = 1|X)$ is the propensity score if true vaccination status was captured. Hence, even though the true propensity score cannot be estimated, the associated rank of patient propensity scores should be highly concordant with the error-prone propensity scores, such that the stratification of patients based on error-prone propensity scores is highly concordant with true propensity scores. Therefore, we built the propensity score model by regressing the error-prone vaccination status using logistic regression on demographic factors including age, sex, race/ethnicity, clinical factors including obesity status, a chronic condition indicator as defined by the Pediatric Medical Complexity Algorithm (PMCA)(8), and a list of pre-existing chronic conditions, and healthcare utilization factors including the number of inpatients, outpatients, ED visits, unique mediations, and the number of negative COVID-19 tests prior to the cohort entry. We then stratified the patients into propensity score quintiles based on these factors.

In the second step of our trial emulation pipeline, the outcome model conditional on propensity-score strata has misclassification issues in the binary exposure. Without known misclassification probabilities, we implemented the integrated likelihood approach, where the misclassification probabilities are not fixed at given values but are instead incorporated by allowing for uncertainty through integrating the likelihood(9–11). This approach reduces bias in the estimation of association by avoiding the need to fix sensitivity and specificity at particular values.

Results

Table 1 summarizes the estimated vaccine effectiveness in three target-trial emulations and Figure 1 shows the durability of protection. During the Delta period, the BNT162b2 vaccine demonstrated an overall effectiveness 98.4% (95% CI, 98.1 to 98.7) against documented infection among adolescents, with no significant waning after receipt of the first dose. During the Omicron period, the overall effectiveness was estimated to be 74.3% (95% CI, 72.2 to 76.2) in preventing documented infection among children, which was higher against moderate or severe COVID-19 (75.5%; 95% CI, 69.0 to 81.0) and ICU admission with COVID-19 (84.9%; 95% CI, 64.8 to 93.5). In the adolescent population, the overall effectiveness against documented Omicron infection was 85.5% (95% CI, 83.8 to 87.1), with effectiveness of 84.8% (95% CI, 77.3 to 89.9) against moderate or severe COVID-19, and 91.5% (95% CI, 69.5 to 97.6) against ICU admission with COVID-19. The effectiveness of the BNT162b2 vaccine against the Omicron variant declined after 4 months following the first dose and then stabilized with higher levels of uncertainty.

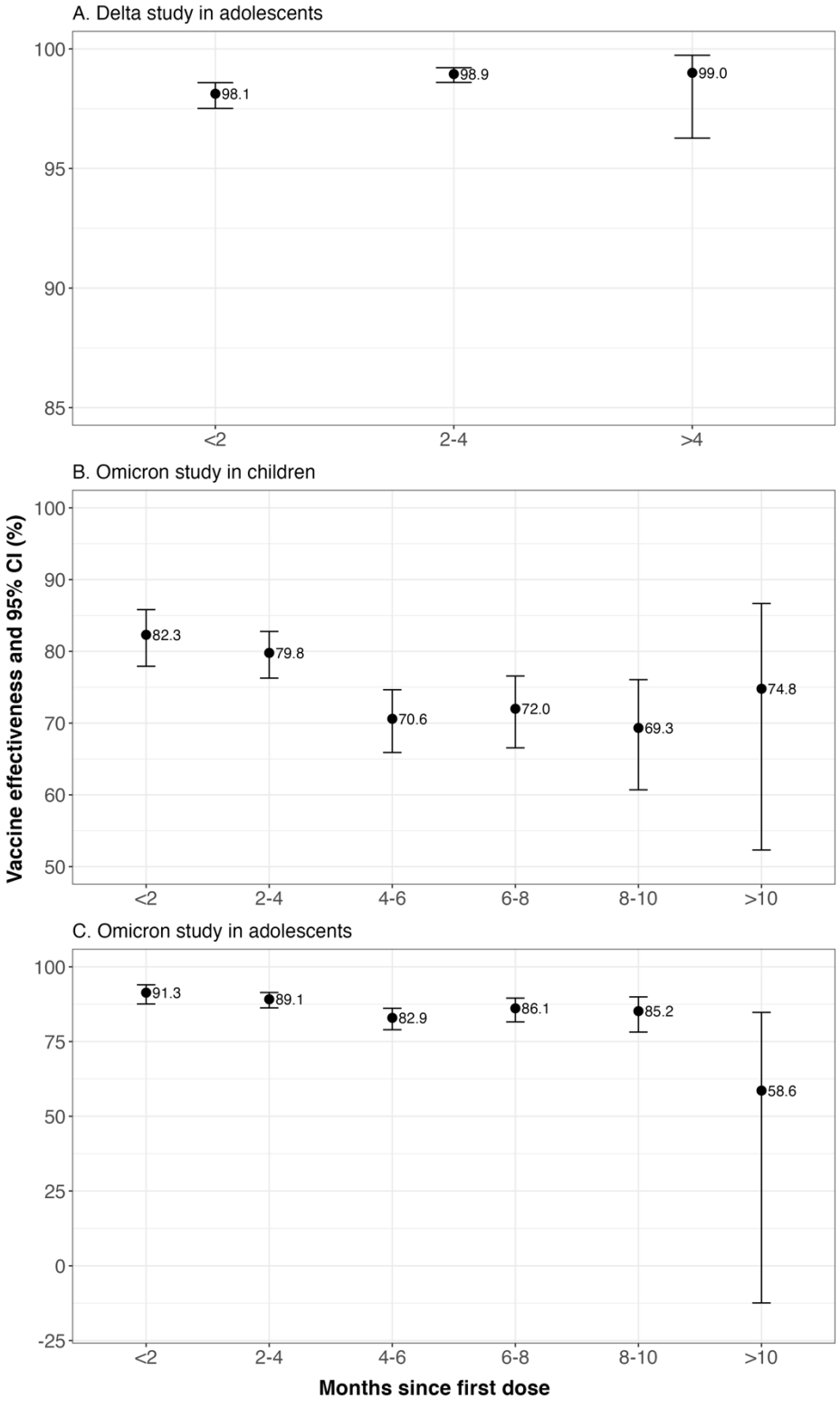
Conclusion

This study suggests BNT162b2 was effective among children and adolescents in Delta and Omicron periods for a range of COVID-19-related outcomes. The novel trial emulation pipeline also offers a new approach for assessing real-world effectiveness with incomplete vaccine records.

Table 1. Estimated effectiveness of the BNT162b2 vaccine in preventing infection and severe diseases with SARS-CoV-2 in children and adolescents.

	Vaccinated	Unvaccinated	Overall	Vaccine effectiveness (in %) and 95% CI
Delta study in adolescents				
Follow-up				
Total follow-up — no. of person-wk	644,162	398,906	1,043,068	
Median [Q1, Q3]	16 [12, 18]	13 [9, 17]	15 [10, 18]	
Incidence rate per 10,000 person-wk				
Documented infection	2.47	42.72	17.86	98.4 (98.1, 98.7)
Mild COVID-19	0.43	11.58	4.70	99.0 (98.5, 99.3)
Moderate or severe COVID-19	0.20	3.94	1.63	98.7 (97.4, 99.3)
ICU admission with COVID-19	0.02	0.43	0.17	99.0 (92.5, 99.9)
Omicron study in children				
Follow-up				
Total follow-up — no. of person-wk	1,925,686	1,911,599	3,837,285	
Median [Q1, Q3]	44 [35, 46]	36 [19, 44]	40 [25, 45]	
Incidence rate per 10,000 person-wk				
Documented infection	4.95	17.46	11.18	74.3 (72.2, 76.2)
Mild COVID-19	1.41	4.96	3.18	73.5 (69.2, 77.1)
Moderate or severe COVID-19	0.49	2.13	1.31	75.5 (69.0, 81.0)
ICU admission with COVID-19	0.04	0.26	0.15	84.9 (64.8, 93.5)
Omicron study in adolescents				
Follow-up				
Total follow-up — no. of person-wk	772,176	1,113,561	1,885,736	
Median [Q1, Q3]	42 [30, 45]	37 [22, 44]	39 [25, 45]	
Incidence rate per 10,000 person-wk				
Documented infection	4.99	25.59	17.16	85.5 (83.8, 87.1)
Mild COVID-19	1.17	6.48	4.31	87.0 (83.5, 89.8)
Moderate or severe COVID-19	0.40	2.76	1.79	84.8 (77.3, 89.9)
ICU admission with COVID-19	0.04	0.43	0.27	91.5 (69.5, 97.6)

Figure 1. Stratified effectiveness of the BNT162b2 vaccine in preventing infection with SARS-CoV-2 in children and adolescents by 2-month intervals since receipt of the first dose



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