Supplementary Appendix

Supplement to: Price AM, Olson SM, Newhams MM, et al. BNT162b2 protection against the omicron variant in children and adolescents. N Engl J Med. DOI: 10.1056/NEJMoa2202826

This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Price A.M., Olson S.M., Newhams M.M., Halasa N.B. et al. Effectiveness of BNT162b2 Vaccine Against Omicron Hospitalizations in U.S. Children

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SUPPLEMENTARY METHODS & RESULTS

Logistic regression models

VE was calculated by estimating the odds of COVID-19 vaccination among case-patients vs controls using multivariable logistic regression, where COVID-19 was the outcome and vaccination status was the exposure variable, with VE = (1 – adjusted odds ratio) × 100%.

In the primary analysis, we stratified the sample by age group (5-11 years and 12-18 years) and by delta (admitted from July 1, 2021 – December 18, 2021) vs omicron period (admitted from December 19, 2021 – February 17, 2022). We estimated VE within each stratum as:

$$logit\ (covid = 1) = \beta_0 + \beta_1(vacc) \ldots + \beta_Z Z$$

where

covid = 1 if laboratory confirmed Covid-19 case (0 otherwise)

vacc = 1 if received 2 doses of mRNA vaccine ≥14 days prior to symptom onset; (0 otherwise)

Z = vector of adjustment variables including U.S. Census region as an indicator variable (4 regions), calendar time of admission as an indicator variable (bi-week periods), continuous age, sex (female vs male), race/ethnicity as an indicator variable (non-Hispanic White, non-Hispanic Black, non-Hispanic other race, Hispanic of any race, unknown), *with VE defined as*

$$\widehat{VE} = [1 - \exp(\beta_1)] * 100\%$$

To assess VE against a gradient of disease severity, subgroup analyses were conducted among patients with and without receipt of life-supporting interventions, or in-hospital deaths. We estimated VE within each severity stratum as:

$$For\ i = 1\ to\ 2\ strata\ of\ with\ and\ without\ life - supporting\ interventions/death,$$

$$logit\ (covid = 1) = \beta_0 + \beta_1(vacc) \ldots + \beta_Z Z$$

where variables are defined as above plus life-supporting interventions was defined as receipt of non-invasive mechanical ventilation (BiPAP or CPAP), invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation during admission

Z = vector of adjustment variables including U.S. Census region as an indicator variable (4 regions), calendar time of admission as an indicator variable (bi-week periods), continuous age, sex (female vs male), race/ethnicity as an indicator variable (non-Hispanic White, non-Hispanic Black, non-Hispanic other race, Hispanic of any race, unknown), with VE defined as

$$\widehat{VE} = [1 - \exp(\beta_1)] * 100\%$$

Potential confounding variables (Z) listed above were selected *a priori* based on past vaccine effectiveness studies. Other potential confounding factors in the analytic dataset were considered. These included presence of underlying health conditions (≥1 vs 0), specific underlying conditions (respiratory, cardiovascular, neurologic/ neuromuscular, immunosuppression or autoimmune, endocrine, diabetes, or other chronic conditions), and continuous score on the Centers for Disease Control and Prevention / Agency for Toxic Substances and Disease Registry (CDC/ATSDR) Social Vulnerability Index. Using a change-in-estimate approach, we assessed confounding from these additional available factors. To derive a parsimonious fully adjusted model, we sequentially added these variables individually to the model to assess if they changed the relative odds ratio for vaccination by >5%. If a variable changed the odds ratio by >5%, we added that variable to the model, and reassessed if adding an additional variable changed our revised estimate by >5%. If another variable was added to the

model and reverted the model to the same point estimate as the a priori, the a priori model was chosen as the final model. Each model, including the primary models and the subgroups (i.e. 12-18 Overall, 12-18 Delta, 12-18 Omicron, and 5-11 Omicron) were adjusted separately. All fully adjusted models thus only included *a priori* variables because additional factors did not change the odds ratio for vaccination by more than 5% (Table S1). To account for clustering of patients by hospital, alternative models were considered using the proc surveylogistic function in SAS with site specified as a cluster variable, which yielded similar point estimates and confidence bounds as the primary model (Table S2). Measures of model fit are presented in Table S3.

TABLE S1. Model selection using change in estimate approach to evaluate for potential confounding.

Model Selection - 5-11 Omicron	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.32	68
Plus Social Vulnerability Index	0.33	66
Plus underlying conditions	0.31	69
Plus respiratory	0.30	70
Plus cardiovascular	0.31	69
Plus neurologic/neuromuscular	0.34	66
Plus immunosuppression or autoimmune	0.31	69
Plus endocrine	0.31	69
Plus diabetes	0.31	69
Plus other chronic conditions	0.29	71
A priori - sex, age, race, region, calendar time + other chronic conditions	0.29	71
Plus Social Vulnerability Index	0.30	70
Plus underlying conditions	0.30	71
Plus respiratory	0.29	71
Plus cardiovascular	0.30	70
Plus neurologic/neuromuscular	0.32	68
Plus immunosuppression or autoimmune	0.30	70
Plus endocrine	0.31	69
Plus diabetes	0.29	71
A priori - sex, age, race, region, calendar time + other chronic conditions + neuromuscular	0.32	68
Plus Social Vulnerability Index	0.33	67
Plus underlying conditions	0.32	68
Plus respiratory	0.32	68
Plus cardiovascular	0.32	68
Plus immunosuppression or autoimmune	0.33	67
Plus endocrine	0.33	68
Plus diabetes	0.32	68
Model Selection - 12-18 Overall	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.18	82
Plus Social Vulnerability Index	0.18	82
Plus underlying conditions	0.17	83
Plus respiratory	0.17	83
Plus cardiovascular	0.17	83
Plus neurologic/neuromuscular	0.17	83
Plus immunosuppression or autoimmune	0.17	83
Plus endocrine	0.17	83
Plus diabetes	0.17	83
Plus other chronic conditions	0.17	83

Model Selection - 12-18 Delta	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.08	92
Plus Social Vulnerability Index	0.08	92
Plus underlying conditions	0.08	92
Plus respiratory	0.08	92
Plus cardiovascular	0.08	92
Plus neurologic/neuromuscular	0.08	92
Plus immunosuppression or autoimmune	0.08	92
Plus endocrine	0.08	92
Plus diabetes	0.08	92
Plus other chronic conditions	0.08	92
Model Selection - 12-18 Omicron	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.60	40
Plus Social Vulnerability Index	0.62	38
Plus underlying conditions	0.60	40
Plus respiratory	0.59	41
Plus cardiovascular	0.59	41
Plus neurologic/neuromuscular	0.62	38
Plus immunosuppression or autoimmune	0.60	40
Plus endocrine	0.61	39
Plus diabetes	0.61	39
Plus other chronic conditions	0.60	40

VE denotes vaccine effectiveness; OR denotes odds ratio

TABLE S2. Comparison of vaccine effectiveness using the fully adjusted logistic regression model with census region and with clustering standard errors by hospital

Age group	VE	95% LL	95% UL	OR	95% LL	95% UL
5-11 years						
Logistic Regression	68	42	82	0.68	0.42	0.822
Cluster by hospital	66	44	80	0.66	0.44	0.80
12-18 years – delta period						
Logistic Regression	92	89	95	0.92	0.89	0.95
Cluster by hospital	92	88	95	0.92	0.88	0.95
12-18 years – omicron period						
Logistic Regression	40	9	60	0.40	0.09	0.60
Cluster by hospital	39	4	61	0.39	0.04	0.61

VE denotes vaccine effectiveness; LL denotes lower confidence limits; UL denotes upper confidence limits; OR denotes odds ratio

TABLE S3. Measure of fit for the logistic regression models

Model Fit Statistics	5-11 years (omicron)	12-18 years (delta)	12-18 years (omicron)
AIC: Intercept Only	746.423	2434.052	594.744
AIC: Intercept and covariates	729.481	2107.206	574.485
SC: Intercept Only	750.709	2439.572	598.808
SC: Intercept and covariates	793.771	2234.159	635.441
-2 Log L: Intercept Only	744.423	2432.052	592.744
-2 Log L: Intercept and covariates	699.481	2061.206	544.485
Hosmer and Lemeshow Goodness-of-fit test P-value	0.2957	0.5593	0.7261
Deviance Goodness-of-Fit P-value	<.0001	<.0001	<.0001
Pearson Goodness-of-Fit P-value	0.3404	0.4447	0.3229