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Association of Prior BNT162b2 COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection in Children and Adolescents During Omicron Predominance

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IMPORTANCE Efficacy of 2 doses of the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech) against COVID-19 was high in pediatric trials conducted before the SARS-CoV-2 Omicron variant emerged. Among adults, estimated vaccine effectiveness (VE) of 2 BNT162b2 doses against symptomatic Omicron infection was reduced compared with prior variants, waned rapidly, and increased with a booster.

OBJECTIVE To evaluate the association of symptomatic infection with prior vaccination with BNT162b2 to estimate VE among children and adolescents during Omicron variant predominance.

DESIGN, SETTING, AND PARTICIPANTS A test-negative, case-control analysis was conducted using data from 6897 pharmacy-based, drive-through SARS-CoV-2 testing sites across the US from a single pharmacy chain in the Increasing Community Access to Testing platform. This analysis included 74 208 tests from children 5 to 11 years of age and 47 744 tests from adolescents 12 to 15 years of age with COVID-19–like illness who underwent SARS-CoV-2 nucleic acid amplification testing from December 26, 2021, to February 21, 2022.

EXPOSURES Two BNT162b2 doses 2 weeks or more before SARS-CoV-2 testing vs no vaccination for children; 2 or 3 doses 2 weeks or more before testing vs no vaccination for adolescents (who are recommended to receive a booster dose).

MAIN OUTCOMES AND MEASURES Symptomatic infection. The adjusted odds ratio (OR) for the association of prior vaccination and symptomatic SARS-CoV-2 infection was used to estimate VE: VE = (1 − OR) × 100%.

RESULTS A total of 30 999 test-positive cases and 43 209 test-negative controls were included from children 5 to 11 years of age, as well as 22 273 test-positive cases and 25 471 test-negative controls from adolescents 12 to 15 years of age. The median age among those with included tests was 10 years (IQR, 7-13); 61 189 (50.2%) were female, 75 758 (70.1%) were White, and 29 034 (25.7%) were Hispanic/Latino. At 2 to 4 weeks after dose 2, among children, the adjusted OR was 0.40 (95% CI, 0.35-0.45; estimated VE, 60.1% [95% CI, 54.7%-64.8%]) and among adolescents, the OR was 0.40 (95% CI, 0.29-0.56; estimated VE, 59.5% [95% CI, 44.3%-70.6%]). During month 2 after dose 2, among children, the OR was 0.71 (95% CI, 0.67-0.76; estimated VE, 28.9% [95% CI, 24.5%-33.1%]) and among adolescents, the OR was 0.83 (95% CI, 0.76-0.92; estimated VE, 16.6% [95% CI, 8.1%-24.3%]). Among adolescents, the booster dose OR 2 to 6.5 weeks after the dose was 0.29 (95% CI, 0.24-0.35; estimated VE, 71.1% [95% CI, 65.5%-75.7%]).

CONCLUSIONS AND RELEVANCE Among children and adolescents, estimated VE for 2 doses of BNT162b2 against symptomatic infection was modest and decreased rapidly. Among adolescents, the estimated effectiveness increased after a booster dose.

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In December 2021 and January 2022, the spread of the SARS-CoV-2 Omicron variant led to the highest rates of COVID-19 cases among children 5 to 15 years old[1] and the highest rate of pediatric hospitalizations (age ≤17 years) with COVID-19 to this point in the pandemic.[2,3] Randomized trials of the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech), the only COVID-19 vaccine authorized for use in children and adolescents 5 to 15 years of age, were conducted before the emergence of the Omicron variant and demonstrated high efficacy of 2 doses against COVID-19 (100% and 91% among those aged 12-15 and 5-11 years, respectively).[4,5] The US Food and Drug Administration issued Emergency Use Authorization for BNT162b2 (2 doses of 30 µg) for those aged 12 to 15 years on May 10, 2021,[6] and for those aged 5 to 11 years (2 doses of 10 µg) on October 29, 2021.[7] Evidence that estimated vaccine effectiveness (VE) waned over time among adults and adolescents[8] contributed to a recommendation on January 5, 2022, for a booster (30-µg dose) 5 months or more after the second dose for adolescents 12 to 15 years old.[9]

Observational studies in adults documented lower protection from mRNA vaccines against the Omicron variant compared with the Delta variant and rapid waning of protection.[10,11] However, observational estimates of VE among children 5 to 11 years old and adolescents 12 to 15 years old during Omicron variant predominance are lacking but needed to inform COVID-19 vaccine policy and use of nonpharmaceutical interventions in these age groups. The objectives of this analysis were to use the odds ratio (OR) for the association of prior vaccination and symptomatic infection to estimate BNT162b2 VE during Omicron variant predominance of (1) 2 doses among children 5 to 11 years old and adolescents 12 to 15 years old over time since the second dose and (2) 3 doses among adolescents 12 to 15 years old.

Key Points

Question Does the estimated effectiveness of 2 doses of the BNT162b2 COVID-19 vaccine against symptomatic SARS-CoV-2 Omicron variant infection (based on the odds ratio for the association of prior vaccination and infection) wane rapidly among children and adolescents, as has been observed for adults?

Findings In a test-negative, case-control study conducted from December 2021 to February 2022 during Omicron variant predominance that included 121 952 tests from sites across the US, estimated vaccine effectiveness against symptomatic infection for children 5 to 11 years of age was 60.1% 2 to 4 weeks after dose 2 and 28.9% during month 2 after dose 2. Among adolescents 12 to 15 years of age, estimated vaccine effectiveness was 59.5% 2 to 4 weeks after dose 2 and 16.6% during month 2; estimated booster dose effectiveness in adolescents 2 to 6.5 weeks after the booster was 71.1%.

Meaning Among children and adolescents, estimated vaccine effectiveness for 2 doses of BNT162b2 against symptomatic infection decreased rapidly, and among adolescents increased after a booster dose.

Methods

This activity was determined to be public health surveillance as defined in 45 CFR §46.102(l) (US Department of Health and Human Services [HHS], Title 45 Code of Federal Regulations, §46 Protection of Human Subjects); thus, it was not submitted for institutional review board approval and informed consent was not needed.

Data Source

Data from the Increasing Community Access to Testing (ICATT) platform were used. ICATT is an HHS program that contracts with 4 commercial pharmacy chains to facilitate drive-through SARS-CoV-2 testing nationally.[8,10,12,13] No-cost testing is available to anyone regardless of symptom or exposure status, and sites were selected to address COVID-19 health disparities by increasing access in racially and ethnically diverse communities and areas with moderate to high social vulnerability based on the Social Vulnerability Index (SVI).[14] During the analysis period, contracted pharmacy chains used different versions of the registration questionnaire and not all captured data on booster doses. This analysis was, therefore, limited to a single chain, which collected data on booster doses and provided 82% of tests platform-wide for children and adolescents aged 5 to 15 years during the analysis period.

When registering for SARS-CoV-2 testing, individuals or parents/guardians of minors answered a questionnaire (available in English or Spanish) to self-report demographic information (including race and ethnicity selected from fixed categories, shown in the **Table**), COVID-19–like illness symptoms (fever, cough, shortness of breath, recent loss of sense of smell or taste, muscle pain, fatigue, chill, headache, sore throat, congestion or runny nose, vomiting, or diarrhea; reported to HHS as asymptomatic or symptomatic with ≥1 symptom), and vaccination status.[10] Race and ethnicity were collected as part of the HHS COVID-19 laboratory reporting requirements.[15] Self-reported COVID-19 vaccination data included number of doses received up to 4, and for each dose, vaccine product and month and year received. For doses reported in the same month or the month before test registration, the registrant was asked whether the most recent dose was administered at least 2 weeks before the test date. Reporting of vaccination status was neither mandatory nor verified. Test registrants were also asked to self-report underlying health conditions, including immunocompromising conditions (defined in the questionnaire as "immunocompromising medications, solid organ or blood stem cell transplant, HIV, or other immunocompromising conditions"), and whether they had previously tested positive for SARS-CoV-2 (within 90 days and/or >90 days before test registration); answers were not verified.

Nasal swabs were self-collected at drive-through sites and tested for SARS-CoV-2 either onsite with the ID Now (Abbott Diagnostics Scarborough Inc) rapid nucleic acid amplification test (NAAT) or at contracted laboratories using laboratory-based NAAT (TaqPath COVID-19 Combo Kit [Thermo Fischer Scientific Inc] or COVID-19 RT-PCR Test [Laboratory Corporation of America]). Deidentified questionnaire data, specimen collection date, test type, test result, and testing site location

Table. Characteristics of Included Tests in Analysis of Association of BNT162b2 With Symptomatic SARS-CoV-2 Infection In Children and Adolescents Aged 5 to 15 Years, December 26, 2021-February 21, 2022

Characteristic	Symptomatic, No. (%)								
	Children aged 5-11 y (n = 74 208)				Adolescents aged 12-15 y (n = 47 744)				
	SARS-CoV-2 status				SARS-CoV-2 status			Vaccinated[a]	
	Negative controls	Positive cases	Unvaccinated	Vaccinated with 2 doses[a]	Negative controls	Positive cases	Unvaccinated	With 2 doses	With 3 doses
Total	43 209	30 999	58 430	15 778	25 471	22 273	24 767	22 072	905
Age, median (IQR), y	8 (6-10)	8 (6-10)	8 (6-10)	9 (7-10)	14 (13-15)	14 (13-15)	13 (12-14)	14 (13-15)	14 (13-15)
Sex[b]									
No.	43 190	30 988	58 410	15 768	25 398	22 224	24 728	22 001	893
Female	21 433 (49.6)	15 171 (49.0)	28 958 (49.6)	7646 (48.5)	13 079 (51.5)	11 506 (51.8)	12 662 (51.2)	11 463 (52.1)	460 (51.5)
Male	21 757 (50.4)	15 817 (51.0)	29 452 (50.4)	8122 (51.5)	12 319 (48.5)	10 718 (48.2)	12 066 (48.8)	10 538 (47.9)	433 (48.5)
Race[c]									
No.	38 603	27 327	51 576	14 354	22 615	19 454	21 934	19 289	846
American Indian or Alaska Native	465 (1.2)	340 (1.2)	650 (1.3)	155 (1.1)	268 (1.2)	253 (1.3)	257 (1.2)	256 (1.3)	8 (0.9)
Asian	2840 (7.4)	2399 (8.8)	3017 (5.8)	2222 (15.5)	1323 (5.9)	1551 (8.0)	627 (2.9)	2144 (11.1)	103 (12.2)
Black or African American	7855 (20.3)	5584 (20.4)	12 037 (23.3)	1402 (9.8)	4670 (20.7)	3818 (19.6)	5077 (23.1)	3345 (17.3)	66 (7.8)
Native Hawaiian or Other Pacific Islander	314 (0.8)	234 (0.9)	491 (1.0)	57 (0.4)	186 (0.8)	141 (0.7)	183 (0.8)	142 (0.7)	2 (0.2)
White	27 129 (70.3)	18 770 (68.7)	35 381 (68.6)	10 518 (73.3)	16 168 (71.5)	13 691 (70.4)	15 790 (72.0)	13 402 (69.5)	667 (78.8)
Hispanic/Latino ethnicity[c]									
No.	40 112	28 661	53 899	14 874	23 585	20 581	22 753	20 544	869
Hispanic/Latino	9869 (24.6)	7469 (26.1)	14 324 (26.6)	3014 (20.3)	6103 (25.9)	5593 (27.2)	5844 (25.7)	5703 (27.8)	149 (17.1)
Testing site region[d]									
East North Central	10 422 (24.1)	5850 (18.9)	11 960 (20.5)	4312 (27.3)	5492 (21.6)	4088 (18.4)	4771 (19.3)	4535 (20.5)	274 (30.3)
South Atlantic	9618 (22.3)	8553 (27.6)	14 938 (25.6)	3233 (20.5)	6027 (23.7)	6209 (27.9)	6569 (26.5)	5492 (24.9)	175 (19.3)
West South Central	7263 (16.8)	4985 (16.1)	10 138 (17.4)	2110 (13.4)	4543 (17.8)	3692 (16.6)	4437 (17.9)	3697 (16.7)	101 (11.2)
Mountain	3474 (8.0)	2283 (7.4)	4567 (7.8)	1190 (7.5)	2034 (8.0)	1745 (7.8)	1905 (7.7)	1815 (8.2)	59 (6.5)
East South Central	3344 (7.7)	2891 (9.3)	5323 (9.1)	912 (5.8)	2355 (9.2)	2101 (9.4)	2688 (10.9)	1713 (7.8)	55 (6.1)
West North Central	3096 (7.2)	1896 (6.1)	3758 (6.4)	1234 (7.8)	1848 (7.3)	1387 (6.2)	1755 (7.1)	1408 (6.4)	72 (8.0)
Mid Atlantic	2579 (6.0)	1544 (5.0)	2994 (5.1)	1129 (7.2)	1386 (5.4)	1085 (4.9)	1080 (4.4)	1315 (6.0)	76 (8.4)
Pacific	2294 (5.3)	2087 (6.7)	3514 (6.0)	867 (5.5)	1129 (4.4)	1318 (5.9)	1121 (4.5)	1273 (5.8)	53 (5.9)
New England	923 (2.1)	751 (2.4)	1060 (1.8)	614 (3.9)	520 (2.0)	541 (2.4)	388 (1.6)	648 (2.9)	25 (2.8)
Puerto Rico	196 (0.5)	159 (0.5)	178 (0.3)	177 (1.1)	137 (0.5)	107 (0.5)	53 (0.2)	176 (0.8)	15 (1.7)
Social Vulnerability Index[e]									
No.	43 175	30 981	58 389	15 767	25 462	22 258	24 753	22 062	905
Mean (SD)	0.51 (0.28)	0.52 (0.29)	0.54 (0.28)	0.43 (0.28)	0.53 (0.28)	0.53 (0.29)	0.56 (0.28)	0.49 (0.29)	0.40 (0.27)
History of SARS-CoV-2 positive test result[f]									
None[g]	32 735 (75.8)	22 587 (72.9)	42 963 (73.5)	12 359 (78.3)	18 041 (70.8)	16 071 (72.2)	17 007 (68.7)	16 346 (74.1)	759 (83.9)
Positive within 90 d of test date	5603 (13.0)	6835 (22.0)	9949 (17.0)	2489 (15.8)	3958 (15.5)	4710 (21.1)	4194 (16.9)	4365 (19.8)	109 (12.0)
Positive >90 d prior to test date	4794 (11.1)	1523 (4.9)	5399 (9.2)	918 (5.8)	3420 (13.4)	1449 (6.5)	3498 (14.1)	1334 (6.0)	37 (4.1)
Prior positive both within 90 d and >90 d prior to test date	77 (0.2)	54 (0.2)	119 (0.2)	12 (0.1)	52 (0.2)	43 (0.2)	68 (0.3)	27 (0.1)	0
SARS-CoV-2 test type									
NAAT									
Rapid[h]	30 463 (70.5)	18 660 (60.2)	40 082 (68.6)	9041 (57.3)	18 211 (71.5)	13 543 (60.8)	17 759 (71.7)	13 515 (61.2)	480 (53.0)
Laboratory-based[i]	12 746 (29.5)	12 339 (39.8)	18 348 (31.4)	6737 (42.7)	7260 (28.5)	8730 (39.2)	7008 (28.3)	8557 (38.8)	425 (47.0)

(continued)

Table. Characteristics of Included Tests in Analysis of Association of BNT162b2 With Symptomatic SARS-CoV-2 Infection In Children and Adolescents Aged 5 to 15 Years, December 26, 2021-February 21, 2022 (continued)

Characteristic	Symptomatic, No. (%)								
	Children aged 5-11 y (n = 74 208)				Adolescents aged 12-15 y (n = 47 744)				
	SARS-CoV-2 status				SARS-CoV-2 status			Vaccinated[a]	
	Negative controls	Positive cases	Unvaccinated	Vaccinated with 2 doses[a]	Negative controls	Positive cases	Unvaccinated	With 2 doses	With 3 doses
Vaccination status[f]									
Unvaccinated	33 169 (76.8)	25 261 (81.5)	58 430	NA	13 303 (52.2)	11 464 (51.5)	24 767	NA	NA
2 BNT162b2 doses (≥2 wk prior to test date)[a]	10 040 (23.2)	5738 (18.5)	NA	15 778	11 435 (44.9)	10 637 (47.8)	NA	22 072	NA
3 BNT162b2 doses (≥2 wk prior to test date)[a]	NA	NA	NA	NA	733 (2.9)	172 (0.8)	NA	NA	905
SARS-CoV-2 status									
Positive case	NA	30 999	25 261 (43.2)	5738 (36.4)	NA	22 273	11 464 (46.3)	10 637 (48.2)	172 (19.0)
Negative control	43 209	NA	33 169 (56.8)	10 040 (63.6)	25 471	NA	13 303 (53.7)	11 435 (51.8)	733 (81.0)

Abbreviations: ICATT, Increasing Community Access to Testing; NA, not applicable; NAAT, nucleic acid amplification test; SVI, Social Vulnerability Index.

[a] Cases and controls considered vaccinated with 2 or 3 doses if tests were from children and adolescents who reported receiving the second or third dose 2 weeks or more before their SARS-CoV-2 test date.

[b] Tests with missing sex (n = 30 for 5-11 years, n = 122 for 12-15 years) were not included in adjusted analyses.

[c] Race and ethnicity were self-reported from fixed categories provided at test registration. The question regarding race was required on the questionnaire, and registrants were only able to select 1 category or select "Decline to answer," which was coded as unknown race. Unknown race (n = 8278 for 5-11 years, n = 5675 for 12-15 years) and ethnicity (n = 5435 for 5-11 years, n = 3578 for 12-15 years) were coded as categorical levels within each variable to retain those tests in regression models.

[d] Regions defined as: East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin), South Atlantic (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington, DC, and West Virginia), West South Central (Arkansas, Louisiana, Oklahoma, and Texas), Mountain (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming), East South Central (Alabama, Kentucky, Mississippi, and Tennessee), West North Central (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota), Mid-Atlantic (New Jersey, New York, and Pennsylvania), Pacific (Alaska, California, Hawaii, Oregon, and Washington), New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont), and Puerto Rico.

[e] Testing site census tract SVI was an available variable in ICATT data. SVI is assigned on a scale of 0 to 1 for all US census tracts by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry based on US Census data.[14] Higher SVI indicates greater social vulnerability. Tests with missing SVI data (n = 52 for 5-11 years, n = 24 for 12-15 years) were not included in adjusted analyses.

[f] Self-reported on questionnaire at SARS-CoV-2 test registration.

[g] Persons who answered "yes" to the question: "Have you tested positive for COVID-19 in the past?" but "no" to both "Did you receive this positive test within the last 90 days?" and "Did you receive this positive test prior to the last 90 days?" were counted as having no history of a SARS-CoV-2–positive test (n = 1).

[h] Rapid NAAT was performed on-site on self-collected nasal swabs using ID Now (Abbott Diagnostics Scarborough Inc).

[i] Laboratory-based NAAT was performed on self-collected nasal swabs at contracted laboratories using either TaqPath COVID-19 Combo Kit (Thermo Fischer Scientific Inc) or COVID-19 RT-PCR Test (Laboratory Corporation of America).

and census tract SVI[14] were reported to HHS with an approximate 3-day lag.

Study Design

A test-negative, case-control analysis[16] was conducted to estimate BNT162b2 VE against symptomatic infection. This analysis used rapid and laboratory-based NAATs from children and adolescents aged 5 to 15 years reporting 1 or more symptoms tested at the pharmacy chain from December 26, 2021, to February 21, 2022 (data downloaded February 22, 2022). The unit of analysis was tests, because unique identifiers for individuals were not available. Cases were defined as those with positive SARS-CoV-2 NAAT results, and controls were those with negative NAAT results. Tests from children and adolescents meeting any of the following criteria were excluded: indeterminate test results, missing assay type, reported an immunocompromising condition (because COVID-19 vaccine recommendations differ for these individuals),[9] unknown vaccination status, vaccine product other than BNT162b2, receipt of 1 vaccine dose or receipt of the second or third dose within 2 weeks of the test date, vaccination before the month of the recommendation by the Advisory Committee on Immunization Practices (for children 5-11 years, November 2021; for adolescents 12-15 years, May 2021 for the primary series and January 2022 for the booster dose),[9,17,18] receipt of more than the authorized number of doses for nonimmunocompromised individuals (>2 for children 5-11 years, >3 for adolescents 12-15 years), receipt of a third dose less than 4 months after the second dose (for adolescents 12-15 years),[9] or inconsistent vaccination information (eg, reported vaccine receipt but missing dose dates, reported no vaccine receipt but doses reported).

Exposure

The exposures of interest were 2 BNT162b2 doses for children 5 to 11 years old and 2 or 3 BNT162b2 doses for adolescents 12 to 15 years old. Cases and controls were considered unvaccinated if tests were from children and adolescents who

received no COVID-19 vaccine before the SARS-CoV-2 test. Cases and controls were considered vaccinated with 2 or 3 doses if tests were from children and adolescents who reported receiving the second or third dose 2 weeks or more before their SARS-CoV-2 test.

Outcome

The outcome measure was symptomatic SARS-CoV-2 infection determined by positive NAAT result in a person reporting COVID-19–like illness.

Statistical Analysis

Associations between symptomatic SARS-CoV-2 infection and BNT162b2 vaccination were estimated by comparing the odds of prior vaccination with 2 or 3 doses (exposed) vs no vaccination (unexposed) in cases vs controls using multivariable logistic regression. The OR was used to estimate VE, where VE = (1 − OR) × 100%. Logistic regression models were adjusted for calendar day of test (continuous variable), race, ethnicity, sex, testing site region, and testing site census tract SVI (continuous variable).[14] Tests with missing sex and site census tract SVI were not included in adjusted analyses. Unknown race and ethnicity were coded as categorical levels within each variable to retain those tests in regression models.

Adjusted OR and corresponding VE of 2 doses were estimated by age group (5-11 years and 12-15 years) and month since the second dose. Because only vaccination month and year but not exact calendar dates of each dose were reported, month since the second dose was calculated as the difference between the month and year of testing and the month and year of the second vaccine dose (at least 2 weeks after the second dose). The range of possible days after the second dose for month 0 was 14 to 30 days; month 1, 14 to 60 days; month 2, 30 to 90 days; month 3, 60 to 120 days, and so on (assuming 30 days per month). Because of potential imprecision of month since vaccination based on calendar month of vaccination and testing rather than exact dates, a simulation analysis (of scenarios with rapid vs slow vaccine uptake and varying date of vaccine introduction) and an analysis of previously published data from this platform[8] were conducted to compare VE estimates using this approach with those with exact number of days since the second dose (eAppendix in the Supplement).

The maximum difference between calendar month of SARS-CoV-2 test and calendar month of the second dose was 3 months for children 5 to 11 years old (tested during February 2022 and second dose received in November 2021) and 9 months for adolescents 12 to 15 years old (tested during February 2022 and second dose received in May 2021). However, VE was not calculated for the last month since the second dose (month 3 for children and month 9 for adolescents) because the number of possible days since the second dose was limited in the last month. This was a result of both the timing of vaccine authorization (children became eligible for second doses in late November 2021[18] and adolescents in late May 2021[17]) and by the timing of the end of the study period (test dates were only included through February 21, 2022) (eAppendix in the Supplement). For adolescents 12 to 15 years of age, the maximum possible time after a booster was 6.5 weeks (tested February 21, 2022, and booster dose received after recommendation by the Advisory Committee on Immunization Practices on January 5, 2022).[9]

To assess the effect of reported prior SARS-CoV-2 infection on estimated 2-dose VE (by age group and month since the second dose), 3 sensitivity analyses were conducted. The first analysis included only tests from individuals without any reported prior SARS-CoV-2–positive test result. The second analysis included only tests from individuals without reported prior SARS-CoV-2–positive test result within 90 days, because a recent prior positive test result could have been due to prolonged NAAT positivity,[19] multiple tests within the same illness episode (eg, confirming an at-home test), or reinfection with a different variant in the setting of Omicron variant emergence. The third analysis included only tests from individuals without reported prior SARS-CoV-2–positive test result more than 90 days prior to the test date, because prior SARS-CoV-2 infection provides infection-induced immunity in both vaccinated and unvaccinated individuals.[20]

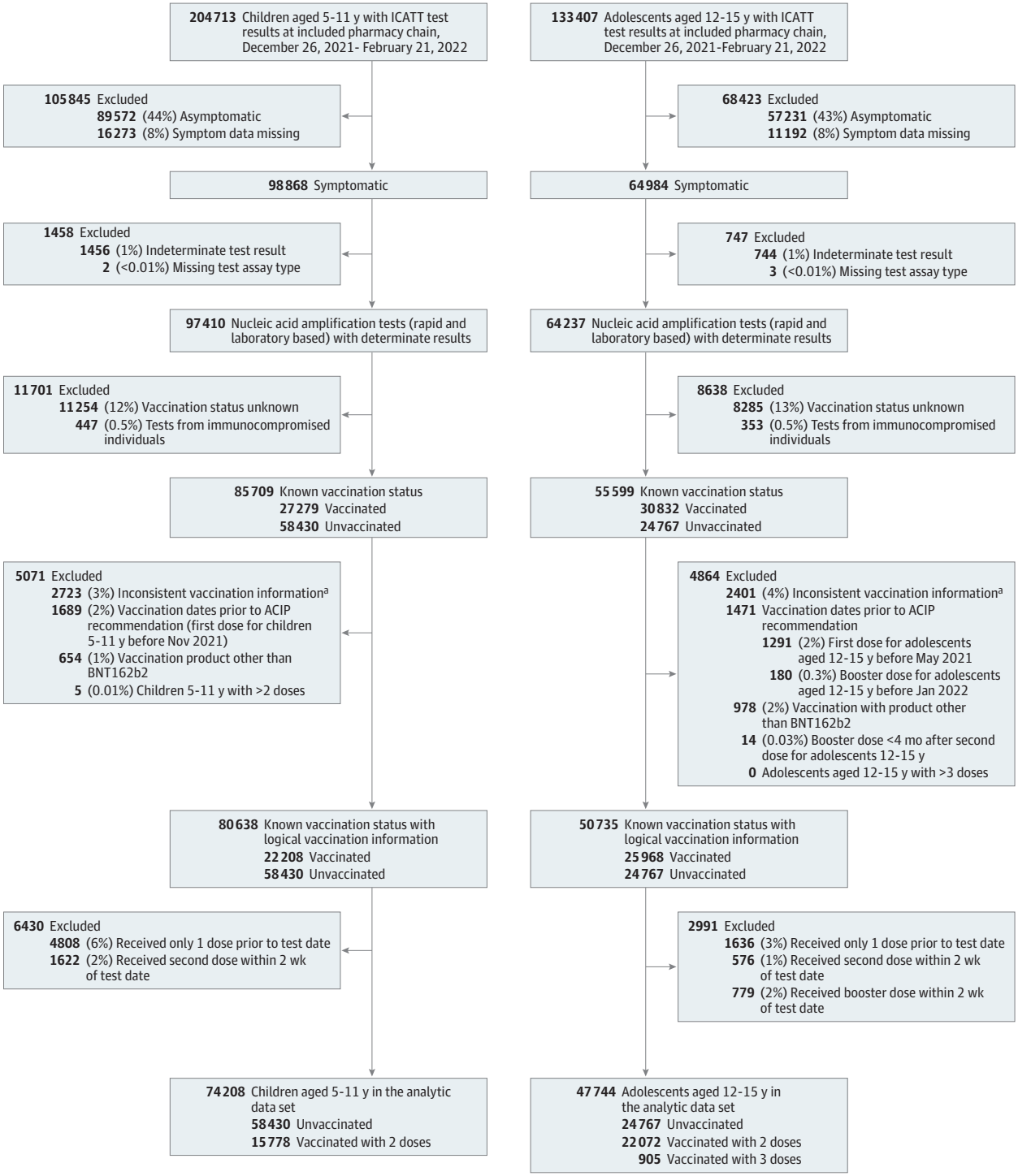
The adjusted OR and corresponding VE of 3 doses among adolescents 12 to 15 years old were estimated overall (ie, not by month since the second dose) due to the short timeframe (6.5 weeks) since booster recommendation.

Statistical analyses were performed in R (version 4.1.2; R Foundation) and SAS (version 9.4; SAS Institute Inc). OR and VE estimates were presented with 95% CIs. To compare the waning pattern for estimated VE since the second dose between children and adolescents, an interaction term between age group (5-11 vs 12-15 years) and month after the second dose (for months 0, 1, and 2) was added to the model; a likelihood ratio test comparing the models with and without the interaction term was used to evaluate the interaction. Two-sided *P* values comparing the magnitude of the association of vaccination and infection between the 2 age groups and across study months were estimated; a *P* value less than .05 was considered significant. Because of the potential for type I error due to multiple comparisons, findings should be interpreted as exploratory.

Results

A total of 121 952 tests from children and adolescents aged 5 to 15 years at 6897 sites across 49 states (all states except North Dakota), Washington, DC, and Puerto Rico, met inclusion criteria (**Figure 1**), including 53 272 cases (43.7%) and 68 680 controls (56.3%). The median age among individuals with included tests was 10 years (IQR, 7-13); 61 189 (50.2%) were female, 75 758 (70.1%) were White, and 29 034 (25.7%) were Hispanic/Latino. Among 74 208 included tests from children 5 to 11 years old, 58 430 (78.4%) were from unvaccinated children and 15 778 (21.3%) from those vaccinated with 2 doses. Among 47 744 included tests from adolescents 12 to 15 years old, 24 767 (51.9%) were from unvaccinated adolescents, 22 072 (46.2%) from those vaccinated with 2 doses, and 905 (1.9%) from those with booster doses.

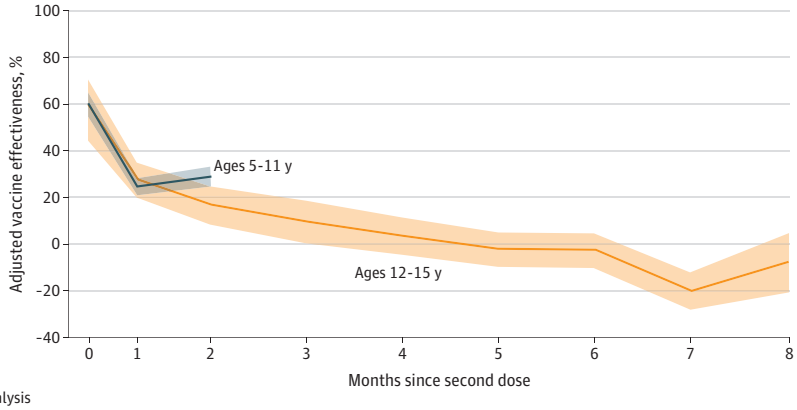
Figure 1. Inclusion Criteria for Analysis of Association of BNT162b2 With Symptomatic SARS-CoV-2 Infection in Children and Adolescents



Data from the Increasing Community Access to Testing (ICATT) platform were used from children and adolescents tested from December 26, 2021, to February 21, 2022, ie, during predominance of the SARS-CoV-2 Omicron variant. During the analysis period, ICATT contracted 4 pharmacy chains, which used different versions of the registration questionnaire and not all captured data on booster doses. This analysis was limited to a single chain that collected data on booster doses and provided 82% of tests platform-wide for children and adolescents aged 5 to 15 years during the analysis period. Nasal swabs were self-collected at drive-through sites and tested for SARS-CoV-2 either onsite with the ID Now (Abbott Diagnostics Scarborough Inc) rapid nucleic acid amplification test (NAAT) or at contracted laboratories using laboratory-based NAAT (TaqPath COVID-19 Combo Kit [Thermo Fischer Scientific Inc] or COVID-19 RT-PCR Test [Laboratory Corporation of America]).

[a] For example, reported vaccine receipt but no doses or reported no vaccine receipt but reported doses.

Figure 2. BNT162b2 2-Dose Adjusted Estimated Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection In Children and Adolescents



Children aged 5-11 y included in the analysis									
No. of cases	363	3134	1955						
No. of controls	909	4786	3758						
Adolescents aged 12-15 y included in the analysis									
No. of cases	53	638	767	759	1341	1848	1907	2670	604
No. of controls	144	1022	1131	908	1428	1892	1877	2266	700
Range of possible days after second dose[a]									
No. of days	14-30	14-60	30-90	60-120	90-150	120-180	150-210	180-240	210-270

The graph shows BNT162b2 2-dose adjusted estimated vaccine effectiveness (VE = [1 − odds ratio] × 100%) with 95% CI against symptomatic SARS-CoV-2 infection for children aged 5 to 11 years (shown in blue) and adolescents aged 12 to 15 years (shown in orange), from December 26, 2021, to February 21, 2022. Adolescents who received booster doses are not included in this figure. Estimated VE (2 doses vs no vaccination) with 95% CI by month since second dose was adjusted for calendar day of test (continuous variable), race, ethnicity, sex, testing site region, and testing site census tract Social Vulnerability Index (SVI; continuous variable). Tests with missing sex (n = 30 for 5-11 years, n = 122 for 12-15 years) and missing SVI (n = 52 for 5-11 years, n = 24 for 12-15 years) were not included in adjusted analyses. Unknown race (n = 8278 for 5-11 years, n = 5675 for 12-15 years) and ethnicity (n = 5435 for 5-11 years, n = 3578 for 12-15 years) were coded as categorical levels within each variable to retain those tests in regression models. Sample size for estimates for each age group and month are shown in the table at the bottom of the figure. A likelihood ratio test comparing models with and without an interaction term between age group (5-11 and 12-15 years) and month (0, 1, 2) was used to evaluate the difference between the waning patterns (*P* value for month 0: .99; month 1: .40; month 2: .01, and for months 0-2 combined: .06). Among children aged 5 to 11 years who did not receive the vaccine, 25 241 tested positive and 33 128 tested negative for SARS-CoV-2; among adolescents aged 12 to 15 years who did not receive the vaccine, 11 436 tested positive and 13 278 tested negative for SARS-CoV-2.

[a] Vaccination dose dates were collected as month and year. Month since second dose was calculated as the difference between the month and year of testing and the month and year of the second vaccine dose (at least 2 weeks after the second dose). The range of possible days after second dose assumes 30 days per month. The maximum difference between calendar month of SARS-CoV-2 test and calendar month of the second dose was 3 months for children aged 5 to 11 years (tested during February 2022 and second dose received in November 2021) and 9 months for adolescents aged 12 to 15 years (tested during February 2022 and second dose received in May 2021). Estimated VE for children 5 to 11 years of age during month 3 was not calculated (vaccinated children during month 3 since second dose: n = 852) or for adolescents 12 to 15 years of age during month 9 (vaccinated adolescents during month 9 since second dose: n = 36) because the number of possible days since the second dose was limited in the last month. This was a result of timing of vaccine authorization (children became eligible for second doses in late November 2021 and adolescents in late May 2021) and by the end of the study period (test dates were only included through February 21, 2022).

Included tests were more frequently rapid NAAT (66.3%) than laboratory-based NAAT (33.7%), and controls were more often tested by rapid NAAT than cases (70.5% vs 60.2% for children; 71.5% vs 60.8% for adolescents) (Table). Cases vs controls were more often tests from persons from the South Atlantic region (27.6% vs 22.3% for children; 27.9% vs 23.7% for adolescents). Report of prior positive SARS-CoV-2 test result within 90 days of the test date was more common among cases than controls (22.0% vs 13.0% for children; 21.1% vs 15.5% for adolescents), while report of a positive test result more than 90 days before the test date was less common among cases than controls (4.9% vs 11.1% for children; 6.5% vs 13.4% for adolescents).

Among children 5 to 11 years old, the adjusted OR for symptomatic infection for tests performed during month 0 after the second dose was 0.40 (95% CI, 0.35-0.45; estimated VE, 60.1% [95% CI, 54.7%-64.8%]) and during month 2 after the second dose was 0.71 (95% CI, 0.67-0.76; estimated VE, 28.9% [95% CI, 24.5%-33.1%]) (**Figure 2**). For adolescents 12 to 15 years old, the adjusted OR during month 0 after the second dose was 0.40 (95% CI, 0.29-0.56; estimated VE, 59.5% [95% CI, 44.3%-70.6%]), during month 2 after the second dose was 0.83 (95% CI, 0.76-0.92; estimated VE, 16.6% [95% CI, 8.1%-24.3%]), and was no longer significantly different from 0 during month 3 after the second dose (OR, 0.90 [95% CI, 0.82-1.00]; estimated VE, 9.6% [95% CI, −0.1% to 18.3%]). Estimated VE was not significantly different between children and adolescents during months 0 and 1 after the second dose, but estimated VE in children was significantly higher than in adolescents during month 2 (*P* value for month 0: .99; month 1: .40; month 2: .01; and for months 0-2 combined: .06).

The simulation analysis showed that estimated VE waning curves that used either the exact number of days or calculated months since the second dose were in close agreement in scenarios with rapid and slow vaccine uptake and vaccine introduction on day 1 and day 16 of month 0 (eFigures 1-2 in the Supplement). The analysis of previously published data from this platform showed estimated monthly VE

waning curves aligned well with daily VE waning curves (eFigures 3-4 in the Supplement).

Sensitivity analyses limited to those without any prior SARS-CoV-2-positive test result (eFigure 5 in the Supplement), without prior SARS-CoV-2-positive test result within 90 days of test date (eFigure 6 in the Supplement), and without prior SARS-CoV-2-positive test result more than 90 days prior to test date (eFigure 7 in the Supplement) yielded estimated VE at month 0 of 60.4% to 66.4% among children 5 to 11 years old and 58.3% to 64.3% among adolescents 12 to 15 years old. These were similar to the main analysis results that did not take prior infection into account. However, estimated VE in the sensitivity analyses was somewhat more sustained over time relative to the main analysis, particularly for the model limited to tests from individuals without any reported prior infection (estimated VE among children was 39.8% during month 2; among adolescents, estimated VE was significantly different from 0 until month 7) and the model limited to tests from those without infection within 90 days (estimated VE among children was 39.8% at month 2; among adolescents, estimated VE was significantly different from 0 until month 5).

Among adolescents, the adjusted OR for a booster dose 2 to 6.5 weeks after the dose was 0.29 (95% CI, 0.24-0.35; estimated VE, 71.1% [95% CI, 65.5%-75.7%]).

Discussion

This analysis estimated BNT162b2 VE among children 5 to 11 years old and adolescents 12 to 15 years old with COVID-19-like illness tested for SARS-CoV-2 using NAAT at drive-through US pharmacy sites from December 26, 2021, to February 21, 2022. It found the estimated VE of the BNT162b2 2-dose primary series against symptomatic infection with the Omicron variant was modest and decreased over time since vaccination in both age groups, similar to the pattern observed in adults during Omicron variant predominance.[10] A booster dose was associated with increased protection against symptomatic infection in adolescents.

Previous analyses among adults have shown lower estimated VE against the Omicron variant than against the Delta variant and waning of mRNA vaccine protection against symptomatic infection, regardless of predominant variant.[8,10,11] A recent analysis from the same testing platform as this analysis demonstrated the estimated VE of the 2-dose BNT162b2 primary series against symptomatic Omicron infection among adults 18 years or older was 42% at 2 to 4 weeks after the second dose. This decreased to not significantly different from 0 by 3 months after the second dose.[10] In this analysis, the estimated VE against symptomatic infection among adolescents 12 to 15 years old also was not significantly different from 0 during month 3 after the second dose. Among children 5 to 11 years old, the duration of protection could only be assessed up through month 2 since the second dose, and continued monitoring will be important.

Among adolescents 12 to 15 years old, the estimated VE against symptomatic infection increased after a booster dose. This finding is consistent with data on adults from this platform and from other studies among adults and adolescents during Omicron variant predominance, which provide evidence of increased protection following mRNA vaccine booster dose.[10,21,22] Given the well-established pattern of waning mRNA VE after 2 doses and early evidence of waning of booster dose protection in adults,[22] monitoring the duration of protection from booster doses in adolescents will be important. Booster doses may be needed to optimize protection against symptomatic infection with the Omicron variant in children 5 to 11 years old as well.

Children aged 5 to 11 years receive a lower-dose formulation (10 µg) of BNT162b2 than adolescents and adults (30 µg), and limited observational data are available on VE with the 10-µg dose. In this analysis, the similar starting VE among children and adolescents and slower waning seen in children than adolescents suggest the 10-µg dose performed as well or better in children than the 30-µg dose in adolescents. These findings are consistent with the phase 2-3 trial in which immunogenicity of the 10-µg dose among children 5 to 11 years old, as measured by geometric mean titers of neutralizing antibodies 1 month after the second dose, was not significantly different from that generated by 30 µg in persons 16 to 25 years old.[4] Furthermore, recent studies indicate estimated 2-dose BNT162b2 VE is similar among children 5 to 11 years old and adolescents 12 to 15 years old against any Omicron infection with or without symptoms (31% and 59%, respectively, with overlapping CIs)[23] and against emergency department and urgent care visits due to COVID-19 (51% among children 5-11 years vs 45% among adolescents 12-15 years, with overlapping CIs).[21]

Prior SARS-CoV-2 infection may influence estimated VE in various ways. Unvaccinated persons with prior infection may have infection-induced immunity, which could bias VE estimates toward the null, whereas vaccinated persons with prior infection may have higher levels of protection than those with vaccination alone.[20] Additionally, the proportion of the population with prior infection and how protective prior infection from a previous variant is against currently circulating variants can also influence estimated VE. The sensitivity analysis including only children and adolescents without any reported prior infection showed that waning of estimated VE was less pronounced than in the main analysis, which may provide the clearest picture of protection provided by vaccination. However, prior SARS-CoV-2 infection is increasingly common; the estimated SARS-CoV-2 infection–induced antibody seroprevalence among US children 0 to 17 years old who had blood specimens tested at commercial laboratories (for reasons unrelated to COVID-19) was 45% in December 2021.[24] Although history of SARS-CoV-2 infection was self-reported in this analysis and is an imperfect measure, 27% of tests were from persons reporting prior infection. Thus, inclusion of tests from persons with prior infection may more accurately reflect vaccine performance under current conditions in the US.

Although estimated VE against symptomatic infection waned quickly in this analysis, vaccine protection against symptomatic infection is harder to achieve than protection against severe disease. For mRNA vaccines including BNT162b2,

estimated VE against severe disease and hospitalization has been higher and waned more slowly than estimated VE against infection among adolescents and adults during Delta predominance[25] and Omicron predominance.[21,22] While estimated VE against symptomatic infection is an important end point to inform nonpharmaceutical intervention policy decisions and can provide an early warning signal of declining VE, estimated VE against severe disease is needed for children and adolescents during Omicron variant predominance.

Limitations

This analysis is subject to several limitations. First, vaccination status was self-reported, which may lead to misclassification. Second, approximately 12% of tests were from people who did not report vaccination status, and 8% had missing symptom data. Exclusion of these tests may have biased results. Third, vaccination dose dates were provided as month and year rather than exact calendar date, which could affect the estimated VE over time through imprecise classification of months since vaccination. A simulation analysis and an analysis of previously published data from this platform[8] (eAppendix in the Supplement) suggested that the magnitude and patterns of estimated VE over time would be similar when estimated by day or month since second dose and additionally would be robust to different speeds of vaccine uptake and timing of vaccine authorization.

Fourth, person-level identifiers were not available; therefore, the unit of analysis was tests, not individuals. The analysis was restricted to symptomatic children and adolescents tested within a 2-month timeframe, likely reducing the number of individuals contributing multiple tests. Fifth, these data are from children and adolescents who sought testing at ICATT sites and may not be generalizable to the US population. Nonetheless, these data represent a large sample of children and adolescents 5 to 15 years old tested at 6897 sites nationally. Sixth, primary series vaccine coverage among children 5 to 11 years old and booster coverage among adolescents 12 to 15 years old remained low in the US during the time of this study.[26] Children who received the primary series and boosted adolescents may differ in meaningful and unmeasured ways from unvaccinated children and unboosted adolescents.

Seventh, due to the short time (6.5 weeks) since adolescents 12 to 15 years old were recommended for a booster dose, this analysis was unable to estimate booster VE over time in adolescents. Eighth, this analysis includes both rapid and laboratory-based NAAT. While there may be slight variation in the sensitivity of assays performed at different laboratories, NAAT, including rapid NAAT, is the most sensitive method available for detection of SARS-CoV-2 infection.[27] Simulations of the effect of test sensitivity on influenza VE estimates using the test-negative design suggest that estimated VE remains relatively stable over a range of test sensitivity from 80% to 100%.[28]

Conclusions

Among children and adolescents, estimated VE for 2 doses of BNT162b2 against symptomatic infection was modest and decreased rapidly. Among adolescents, the estimated effectiveness increased after a booster dose.

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