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Effectiveness of Bivalent mRNA COVID-19 Vaccines in Preventing SARS-CoV-2 Infection in Children and Adolescents Aged 5 to 17 Years

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IMPORTANCE Bivalent mRNA COVID-19 vaccines were recommended in the US for children and adolescents aged 12 years or older on September 1, 2022, and for children aged 5 to 11 years on October 12, 2022; however, data demonstrating the effectiveness of bivalent COVID-19 vaccines are limited.

OBJECTIVE To assess the effectiveness of bivalent COVID-19 vaccines against SARS-CoV-2 infection and symptomatic COVID-19 among children and adolescents.

DESIGN, SETTING, AND PARTICIPANTS Data for the period September 4, 2022, to January 31, 2023, were combined from 3 prospective US cohort studies (6 sites total) and used to estimate COVID-19 vaccine effectiveness among children and adolescents aged 5 to 17 years. A total of 2959 participants completed periodic surveys (demographics, household characteristics, chronic medical conditions, and COVID-19 symptoms) and submitted weekly self-collected nasal swabs (irrespective of symptoms); participants submitted additional nasal swabs at the onset of any symptoms.

EXPOSURE Vaccination status was captured from the periodic surveys and supplemented with data from state immunization information systems and electronic medical records.

MAIN OUTCOME AND MEASURES Respiratory swabs were tested for the presence of the SARS-CoV-2 virus using reverse transcriptase–polymerase chain reaction. SARS-CoV-2 infection was defined as a positive test regardless of symptoms. Symptomatic COVID-19 was defined as a positive test and 2 or more COVID-19 symptoms within 7 days of specimen collection. Cox proportional hazards models were used to estimate hazard ratios for SARS-CoV-2 infection and symptomatic COVID-19 among participants who received a bivalent COVID-19 vaccine dose vs participants who received no vaccine or monovalent vaccine doses only. Models were adjusted for age, sex, race, ethnicity, underlying health conditions, prior SARS-CoV-2 infection status, geographic site, proportion of circulating variants by site, and local virus prevalence.

RESULTS Of the 2959 participants (47.8% were female; median age, 10.6 years [IQR, 8.0-13.2 years]; 64.6% were non-Hispanic White) included in this analysis, 25.4% received a bivalent COVID-19 vaccine dose. During the study period, 426 participants (14.4%) had laboratory-confirmed SARS-CoV-2 infection. Among these 426 participants, 184 (43.2%) had symptomatic COVID-19, 383 (89.9%) were not vaccinated or had received only monovalent COVID-19 vaccine doses (1.38 SARS-CoV-2 infections per 1000 person-days), and 43 (10.1%) had received a bivalent COVID-19 vaccine dose (0.84 SARS-CoV-2 infections per 1000 person-days). Bivalent vaccine effectiveness against SARS-CoV-2 infection was 54.0% (95% CI, 36.6%-69.1%) and vaccine effectiveness against symptomatic COVID-19 was 49.4% (95% CI, 22.2%-70.7%). The median observation time after vaccination was 276 days (IQR, 142-350 days) for participants who received only monovalent COVID-19 vaccine doses vs 50 days (IQR, 27-74 days) for those who received a bivalent COVID-19 vaccine dose.

CONCLUSION AND RELEVANCE The bivalent COVID-19 vaccines protected children and adolescents against SARS-CoV-2 infection and symptomatic COVID-19. These data demonstrate the benefit of COVID-19 vaccine in children and adolescents. All eligible children and adolescents should remain up to date with recommended COVID-19 vaccinations.

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Although rates of SARS-CoV-2–related hospitalizations and death among children and adolescents are lower than rates in adults,[1] severe disease can still occur and lead to hospitalization, life-threatening complications (such as multisystem inflammatory syndrome in children),[2-5] and postinfection sequelae.[6-8] As of December 31, 2023, there have been at least 911 COVID-19–associated deaths among individuals aged 5 to 17 years in the US.[9]

The Omicron variant was more transmissible and included lineages with greater potential to evade vaccine-induced immunity than previous variants.[10-12] To provide protection against the Omicron variant, the US Food and Drug Administration authorized use of the bivalent mRNA COVID-19 vaccine, which was composed of ancestral and Omicron BA.4/5 strains.[13] On September 1, 2022, the bivalent mRNA COVID-19 vaccine was recommended for persons aged 12 years or older (to be administered ≥2 months after completion of any monovalent primary series or monovalent booster dose authorized by the Food and Drug Administration), and on October 12, 2022, the bivalent COVID-19 vaccine was recommended for children aged 5 to 11 years.[14,15]

Although data have shown that bivalent mRNA COVID-19 vaccination among adults is effective at reducing the risk of COVID-19,[16-20] including severe outcomes, limited data exist on the effectiveness of bivalent COVID-19 vaccine doses among children and adolescents. Available studies are limited by small sample size and a short duration of follow-up and reliance on voluntary testing.[21,22] Understanding how well children and adolescents are protected by a bivalent COVID-19 vaccine dose is important for informing public health strategies, especially in the context of updated vaccine formulations and emergence of new variants.

During a period in which the Omicron BA.4/5 sublineages and subsequent Omicron lineages were predominant, this analysis used merged data from 3 prospective cohort studies to estimate vaccine effectiveness of authorized COVID-19 bivalent vaccines against laboratory-confirmed SARS-CoV-2 infection and symptomatic COVID-19 among children and adolescents aged 5 to 17 years.

Key Points

Question What is the effectiveness of the bivalent COVID-19 vaccines among children and adolescents aged 5 to 17 years?

Findings In this prospective cohort study including 2959 participants aged 5 to 17 years, vaccine effectiveness against laboratory-confirmed SARS-CoV-2 infection was 54.0% and vaccine effectiveness against symptomatic COVID-19 was 49.4%.

Meaning During a period when the Omicron BA.4/5 sublineages were the predominant circulating variants, children and adolescents received protection against SARS-CoV-2 infection and symptomatic COVID-19 from the bivalent COVID-19 vaccines compared with those who were unvaccinated or received only the monovalent COVID-19 vaccine.

Methods

Study Population

From September 4, 2022, to January 31, 2023, we conducted an analysis across 6 sites in the US to estimate COVID-19 vaccine effectiveness among children and adolescents aged 5 to 17 years by combining data from 3 prospective cohort studies (Pediatric Research Observing Trends and Exposures in COVID-19 Timelines [PROTECT], CASCADIA, and Community Vaccine Effectiveness [CoVE], which is an expansion of the Household Influenza Vaccine Evaluation [HIVE] cohort).[23-25] Children and adolescents living in Arizona, Michigan, Oregon, Texas, Utah, and Washington, including individuals from the same household, were eligible for inclusion.

Written informed consent was obtained from the parents or guardians of the enrolled children and assent was obtained from children and adolescents aged 7 to 17 years. This study was reviewed by the US Centers for Disease Control and Prevention and approved by the institutional review boards at participating sites, or under a reliance agreement with the Abt Associates institutional review board, and was conducted in a manner consistent with applicable federal law and policy of the Centers for Disease Control and Prevention.[26-30]

Data and Specimen Collection

Each participant or a parent or legal guardian (on behalf of the participant) completed an enrollment survey regarding demographics, household characteristics, chronic medical conditions, COVID-19 vaccination history, and prior SARS-CoV-2 infection. Participants were resurveyed at regular intervals to capture up-to-date demographic information.

As part of the demographic information, race and ethnicity were collected because vaccine uptake and risk of SARS-CoV-2 infection may vary by race and ethnicity. This information was reported by each participant or a parent or legal guardian using predefined race and ethnicity categories.

Blood specimens were collected from participants who consented to phlebotomy. Weekly surveillance was conducted for COVID-19 symptoms. Participants were asked to self-collect (performed by the parent, legal guardian, child, or adolescent) upper respiratory specimens weekly, irrespective of symptoms. To optimally capture all infections, participants were instructed to collect an additional respiratory specimen upon onset of symptoms if outside the timing of their regular weekly specimen collection (swab).

Laboratory Testing

All respiratory specimens were tested for the presence of the SARS-CoV-2 virus using multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) (eTable 1 in Supplement 1). Specimens that failed molecular testing due to contamination or that were misidentified or had a cycle threshold value in the inconclusive range were considered negative. Whole-genome sequencing was attempted on all SARS-CoV-2 infection–positive specimens with an adequate viral quantity in the CASCADIA and CoVE studies and on a representative subset in the PROTECT study.[31-34]

Available serum specimens were tested for the presence of antinucleocapsid IgG using a qualitative IgG enzyme-linked immunosorbent assay or quantitative Meso Scale Dis-

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covery VPLEX assays (eTable 1 in Supplement 1). For the Meso Scale Discovery assay, antinucleocapsid IgG titers were compared with a standard curve provided by the manufacturer to determine titer quantity. Specimens below the lower limit of quantitation per assay insert were set to a value of half the lower limit. Per the assay insert, specimens were determined to have detectable antinucleocapsid IgG if they had a titer equal to or greater than 5000 AU/mL.

Variables of Interest

COVID-19 vaccination status was captured from enrollment, weekly, and monthly surveys (self-report); vaccine cards provided by the participant; and from queries of the state immunization information systems and electronic medical records when available. Vaccination data included vaccination dates, number of doses, and manufacturer. If discrepant information was recorded across multiple data sources, information from the electronic medical record and state immunization information systems was used preferentially over self-reported information.

SARS-CoV-2 infection was defined as a positive RT-PCR test regardless of symptoms. Symptomatic COVID-19 was defined as a positive RT-PCR test and 2 or more COVID-19 symptoms reported within 7 days before or after the specimen collection date. The surveyed list of COVID-19 symptoms varied by study cohort (eTable 2 in Supplement 1).

Prior SARS-CoV-2 infection was defined as a positive RT-PCR test from a specimen collected during study enrollment but before the start of the study period, self-report of infection prior to enrollment or start of the study period (whichever occurred later), or a positive antinucleocapsid SARS-CoV-2 antibody. Time since prior SARS-CoV-2 infection was defined as less than 4 months, 4 months to less than 6 months, 6 months to less than 12 months, 12 months or longer, and no prior infection. Dates of prior SARS-CoV-2 infection were imputed for 146 participants (4.9%) who only had serological results and, therefore, did not have dates associated with prior SARS-CoV-2 infection. Imputation was done using results from linear regression models, in which the baseline nucleocapsid blood draw date and the numeric nucleocapsid values served as the predictors for the date of prior infection among study participants with known prior infection dates (eMethods in Supplement 1).

Statistical Analysis

Descriptive statistics comparing participants who had SARS-CoV-2 infection during the study period vs participants who remained uninfected included frequency (proportion) for categorical variables and median (IQR) for continuous variables. The *P* values were calculated using χ^2 tests for categorical variables and Wilcoxon tests for continuous variables at the .01 level. The Andersen-Gill extension of the Cox proportional hazards model with time-varying vaccination status was used to estimate the hazard ratios for first occurrence of SARS-CoV-2 infection in each participant, comparing participants who received a bivalent COVID-19 vaccine dose (>7 days after receipt) vs those who did not receive a bivalent COVID-19 vaccine dose (either unvaccinated or received monovalent COVID-19 vaccine doses only).[35]

Multivariable models used L2 regularization to adjust for potential confounders,[36] specifically age, sex, race, ethnicity, underlying health conditions, time since prior SARS-CoV-2 infection, geographic site, 7-day average of COVID-19 cases per 100 000 by site (local incidence was modeled as a continuous linear variable), and proportion of circulating variants by site (categorized by those containing the spike substitution R346T).[37] The L2-regularized models used bootstrap resampling by household to estimate the 95% CIs and account for household clustering because 30.6% of households had 2 or more children and adolescents included in the analysis.[38]

Person-time was calculated as the total number of days under surveillance for a given vaccination status during the study period. The study period started on September 4, 2022, for children and adolescents aged 12 to 17 years and on October 16, 2022, for children aged 5 to 11 years. Surveillance ended on the date of a participant's first positive RT-PCR test result for SARS-CoV-2 infection, the participant's study withdrawal date, 18th birthday, or at the end of the study period (January 31, 2023). For the participants who enrolled in 1 of the cohorts after the start of the study period, time at risk started at their enrollment or at 6 weeks after SARS-CoV-2 infection if recently infected prior to enrollment.

Surveillance weeks were not censored for missing specimen result (eg, participant skipped a weekly swab) or if there were problems with specimen testing. The 2 weeks after a monovalent COVID-19 primary vaccine dose and the week after bivalent and monovalent COVID-19 booster vaccine doses were excluded from person-time. COVID-19 vaccine effectiveness was calculated as vaccine effectiveness = (1 − hazard ratio) × 100.

In the primary analysis, the effectiveness of a dose of bivalent COVID-19 vaccine compared with no vaccine or monovalent only doses was estimated against laboratory-confirmed SARS-CoV-2 infection (inclusive of asymptomatic and symptomatic infections) and symptomatic COVID-19. For the outcome of laboratory-confirmed SARS-CoV-2 infection, the estimates were also stratified by age group (5-11 years and 12-17 years) and prior SARS-CoV-2 infection status. In a secondary analysis, the effectiveness of bivalent COVID-19 vaccine was estimated stratified by time since bivalent vaccination (7-60 days or 61-150 days) compared with no vaccine or monovalent doses received 180 or more days ago.

Two sensitivity analyses for vaccine effectiveness were conducted. The first analysis restricted the reference category to only participants who received a monovalent COVID-19 vaccine dose. The second analysis restricted to only participants from the Arizona study sites because they constituted 52% of the study population and had low coverage for the bivalent COVID-19 vaccine.

All analyses were conducted using SAS software version 9.4 (SAS Institute Inc) or R software version 4.1.2 (R Foundation for Statistical Computing).

Results

Between September 4, 2022, and January 31, 2023, a total of 2959 participants were included in the analyses (**Table 1**). The median adherence to weekly upper respiratory specimen col-

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Table 1. Characteristics of Participants Aged 5 to 17 Years by COVID-19 Vaccination Status, September 4, 2022, Through January 31, 2023

	Participants, No. (%)[a]			
	Total[b]	Unvaccinated or received monovalent vaccine	Received bivalent vaccine	*P* value
All participants	2959	2207 (74.6)[c]	752 (25.4)[d]	
Cohort site				
PROTECT study[23]				
Arizona	1528 (51.6)	1366 (89.4)	162 (10.6)	
Texas	124 (4.2)	121 (97.6)	3 (2.4)	
Utah	207 (7.0)	161 (77.8)	46 (22.2)	
CASCADIA study[25]				<.001
Oregon	438 (14.8)	192 (43.8)	246 (56.2)	
Washington	543 (18.4)	270 (49.7)	273 (50.3)	
CoVE study[24]				
Michigan	119 (4.0)	97 (81.5)	22 (18.5)	
Sex				
Female	1415 (47.8)	1044 (73.8)	371 (26.2)	.34
Male	1544 (52.2)	1163 (75.3)	381 (24.7)	
Age, median (IQR), y	10.6 (8-13.2)	10.6 (8-13.2)	10.5 (8-13)	.22
Age group, y				
5-11	1848 (62.5)	1390 (75.2)	458 (24.8)	.31
12-17	1111 (37.5)	817 (73.5)	294 (26.5)	
Race and ethnicity				
Hispanic	509 (17.2)	422 (82.9)	87 (17.1)	
Non-Hispanic				
White	1912 (64.6)	1396 (73.0)	516 (27.0)	<.001
Multiple races	278 (9.4)	190 (68.3)	88 (31.7)	
Other[e]	260 (8.8)	199 (76.5)	61 (23.5)	
Chronic conditions[f]				
0	2512 (84.9)	1914 (76.2)	598 (23.8)	<.001
≥1	447 (15.1)	293 (65.5)	154 (34.5)	
No. of individuals living in household				
2	95 (3.2)	71 (74.7)	24 (25.3)	
3	447 (15.1)	307 (68.7)	140 (31.3)	.01
≥4	2417 (81.7)	1829 (75.7)	588 (24.3)	
One child living in the household	469 (15.8)	331 (70.6)	138 (29.4)	.03
Weekly upper respiratory specimen collection (swab) adherence, median (IQR), %	93.8 (84-100)	94.1 (84-100)	93.3 (85-100)	.86
Prior SARS-CoV-2 infection[g]	1825 (61.7)	1413 (64.0)	412 (54.8)	<.001
Time since prior SARS-CoV-2 infection, mo[h]				
<4	104 (3.5)	81 (77.9)	23 (22.1)	
4-<6	363 (12.3)	263 (72.5)	100 (27.5)	<.001
6-<12	1073 (36.3)	832 (77.5)	241 (22.5)	
≥12	285 (9.6)	237 (83.2)	48 (16.8)	
Had symptomatic COVID-19[i]	184 (43.2)	164 (89.1)	20 (10.9)	.64

Abbreviations: CoVE, Community Vaccine Effectiveness; PROTECT, Pediatric Research Observing Trends and Exposures in COVID-19 Timelines.

[a] Two characteristics are expressed as median (IQR) as indicated.

[b] This column contains the denominators for columns 3 and 4.

[c] Of the 2207 participants, 535 (24.2%) were unvaccinated.

[d] Contributed exposure time to the unvaccinated or received monovalent vaccine reference group before they received the bivalent dose.

[e] Includes participants who identified as American Indian or Alaska Native, Asian, Black or African American, and Native Hawaiian or Pacific Islander.

[f] For the PROTECT study, included asthma, chronic lung disease, cancer, diabetes, obesity, heart disease, hypertension, kidney disease, immunosuppression, liver disease, neurological or neuromuscular disease, and autoimmune disease. For the CASCADIA and CoVE studies, included asthma, heart disease, sleep apnea, Down syndrome, diabetes, cancer, autoimmune disease, liver disease, kidney disease, hematological disease, neurological or neuromuscular disease, stroke, deep vein thrombosis or pulmonary embolism, anxiety, depression, immunosuppression, hypertension, and thyroid disease.

[g] Defined as laboratory confirmation of infection by reverse transcriptase–polymerase chain reaction (RT-PCR) from a study-collected specimen prior to the study period, positive antinucleocapsid SARS-CoV-2 antibody, or self-report of infection prior to enrollment or study period start (whichever occurred later).

[h] Calculated as the date of the prior infection to the first week each participant was included in the analysis.

[i] A positive RT-PCR test result and at least 2 COVID-19 symptoms (see eTable 2 in Supplement 1) reported within 7 days of the specimen collection date. The denominator for column 2 is 426 (participants who had SARS-CoV-2 infection).

lection (swabbing) throughout the study period was 93.8% (IQR, 84%-100%). Overall, 47.8% of the participants were female, the median age was 10.6 years (IQR, 8.0-13.2 years), the majority were non-Hispanic White (64.6%), 25.4% had received a bivalent COVID-19 vaccine dose, and 61.7% had self-reported or confirmed SARS-CoV-2 infection prior to the study period (Table 1).

During the study period, 426 participants (14.4%) had a laboratory-confirmed SARS-CoV-2 infection (eTable 3 in Supplement 1); of those with SARS-CoV-2 infection, 184 (43.2%) had symptomatic COVID-19 (Table 1). Participants living in Michigan (20.2%; 24/119) and those without documented prior SARS-CoV-2 infection (22.5%; 255/1134) had the highest proportion of in-study SARS-CoV-2 infection. Of the 426 partici-

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pants with SARS-CoV-2 infection, 238 (56.0%) had genetic sequencing results. Of the 238 participants with genetic sequencing results, the most prevalent lineages were BA.4 or BA.5 (50.0%), BQ.1.1 (36.5%), XBB (5.9%), and BA.2 (3.8%) (eFigure in Supplement 1).

Participants living in Oregon had the highest uptake of bivalent COVID-19 vaccine (56.2%; 246/438), whereas those living in Texas had the lowest (2.4%; 3/124). Participants reporting Hispanic ethnicity had lower bivalent COVID-19 vaccine uptake (17.1%; 87/509) compared with non-Hispanic participants of all races (27.1%; 665/2450). Participants with 1 or more chronic medical conditions had higher uptake of bivalent COVID-19 vaccine (34.5%; 154/447) compared with those without a chronic medical condition (23.8%; 598/2512). Of the 2207 participants who did not receive a bivalent COVID-19 vaccine dose, 535 (24.2%) were unvaccinated and 1672 (75.8%) received at least 1 monovalent COVID-19 vaccine dose.

Of the 426 participants with SARS-CoV-2 infection, 383 (89.9%) were either unvaccinated or received monovalent COVID-19 vaccine doses only (1.38 infections per 1000 person-days) and 43 (10.1%) received a bivalent COVID-19 vaccine dose (0.84 infections per 1000 person-days) (**Table 2**). Compared with being unvaccinated or receiving only monovalent COVID-19 vaccine doses, the adjusted vaccine effectiveness of a bivalent COVID-19 vaccine dose was 54.0% (95% CI, 36.6%-69.1%) against laboratory-confirmed SARS-CoV-2 infection (Table 2). The median number of observation days after COVID-19 vaccination was 276 (IQR, 142-350 days) for those who received any monovalent COVID-19 vaccine doses and 50 (IQR, 27-74 days) for those who received a bivalent COVID-19 vaccine dose.

When stratified by age, the adjusted bivalent COVID-19 vaccine effectiveness was 58.3% (95% CI, 34.0%-76.5%) for children aged 5 to 11 years and 47.5% (95% CI, 18.2%-71.9%) for children and adolescents aged 12 to 17 years (**Table 3**). Among children aged 5 to 11 years, the median number of observation days after COVID-19 vaccination was 221 (IQR, 140-349 days) for those who received any monovalent COVID-19 vaccine doses and 44 (IQR, 24-66 days) for those who received a bivalent COVID-19 vaccine dose. Among children and adolescents aged 12 to 17 years, the median number of observation days after COVID-19 vaccination was 313 (IQR, 241-404 days) for those who received any monovalent COVID-19 vaccine doses and 59 (IQR, 32-87 days) for those who received a bivalent COVID-19 vaccine dose.

Of the 184 participants with symptomatic COVID-19, 164 (89.1%) were either unvaccinated or received monovalent COVID-19 vaccine doses only (0.59 infections per 1000 person-days) and 20 (10.9%) received a bivalent COVID-19 vaccine dose (0.39 infections per 1000 person-days) (Table 2). The adjusted vaccine effectiveness of a bivalent COVID-19 vaccine dose against symptomatic COVID-19 was 49.4% (95% CI, 22.2%-70.7%). Among participants with symptomatic COVID-19, the median number of observation days after vaccination was 276 (IQR, 142-350 days) for those who received any monovalent COVID-19 vaccine doses and 50 (IQR, 27-74 days) for those who received a bivalent COVID-19 vaccine dose.

Compared with participants who did not receive the COVID-19 vaccine or received monovalent only doses 180 days or more ago, the adjusted vaccine effectiveness of a bivalent COVID-19 vaccine dose against SARS-CoV-2 infection was 51.3% (95% CI, 23.6%-71.9%) 7 to 60 days after vaccination and was 62.4% (95% CI, 38.5%-81.1%) 61 to 150 days after vaccination. The median number of observation days after vaccination was 350 (IQR, 303-392 days) for monovalent COVID-19 vaccine doses administered 180 days or more ago, 34 (IQR, 20-47 days) for a bivalent COVID-19 vaccine dose administered 7 to 60 days ago, and 81 (IQR, 70-95 days) for a bivalent COVID-19 vaccine dose administered 61 to 150 days ago.

Among participants who had prior SARS-CoV-2 infection before the start of the study, the adjusted effectiveness of bivalent COVID-19 vaccine against SARS-CoV-2 infection was 63.6% (95% CI, 33.0%-84.0%) (Table 3). Among participants with no prior SARS-CoV-2 infection, COVID-19 vaccine effectiveness was 47.2% (95% CI, 26.7%-67.8%) (Table 3). Among participants with prior SARS-CoV-2 infection, the median number of observation days after COVID-19 vaccination was 288 (IQR, 156-357 days) for monovalent doses and 47 (IQR, 25-71 days) for a bivalent dose. Among participants without prior SARS-CoV-2 infection, the median number of observation days after COVID-19 vaccination was 241 (IQR, 127-334 days) for monovalent doses and 54 (IQR, 29-78 days) for a bivalent dose.

In a sensitivity analysis restricting the reference group to persons who had received at least 1 dose of monovalent COVID-19 vaccine (ie, excluding unvaccinated individuals), the adjusted vaccine effectiveness of bivalent COVID-19 vaccine against SARS-CoV-2 infection was 56.3% (95% CI, 40.5%-70.1%) and was 51.1% (95% CI, 26.9%-72.1%) against symptomatic COVID-19 (Table 2). In a subsequent sensitivity analysis restricted to participants from the Arizona study site, the adjusted bivalent COVID-19 vaccine effectiveness was 51.5% (95% CI, 20.3%-77.2%) (eTable 4 in Supplement 1).

Discussion

In this analysis of data from 3 prospective cohort studies in the US, children and adolescents aged 5 to 17 years who received an mRNA bivalent COVID-19 vaccine dose were less likely to be infected with SARS-CoV-2 than those who were unvaccinated or who received only monovalent COVID-19 vaccine doses. The vaccine effectiveness of a bivalent COVID-19 vaccine dose against SARS-CoV-2 infection was not significantly different when stratified by age group (5-11 years vs 12-17 years).

There was no observed waning 61 to 150 days after receipt of a bivalent COVID-19 vaccine dose, although there may not have been sufficient follow-up time to assess waning. Nevertheless, these results suggest that, during a period when the Omicron BA.4/5 sublineages were the predominant circulating variants, bivalent COVID-19 vaccines provided protection against SARS-CoV-2 infection and symptomatic COVID-19 among children and adolescents.

We conducted several sensitivity analyses to address potential confounding, including using an alternative reference category and restricting the analysis only to participants from

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Table 2. Bivalent COVID-19 Vaccine Effectiveness Against Laboratory-Confirmed SARS-CoV-2 Infection and Symptomatic COVID-19 Among Children and Adolescents Aged 5 to 17 Years

			Laboratory-confirmed SARS-CoV-2 infection				Symptomatic COVID-19			
	No.[a]	Observation time after vaccination, median (IQR), d[b]	No. of cases	Crude incidence rate/1000 person-days (95% CI)	COVID-19 vaccine effectiveness, % (95% CI)		No. of cases[d]	Crude incidence rate/1000 person-days (95% CI)	COVID-19 vaccine effectiveness, % (95% CI)	
					Unadjusted	Adjusted[c]			Unadjusted	Adjusted[c]
Primary analysis										
COVID-19 vaccine effectiveness										
Unvaccinated or received any monovalent vaccine[e]	2703	276 (142 to 350)	383	1.38 (1.25 to 1.53)	[Reference]	[Reference]	164	0.59 (0.51 to 0.69)	[Reference]	[Reference]
Bivalent vaccine[f]	795	50 (27 to 74)	43	0.84 (0.62 to 1.12)	48.1 (27.7 to 62.8)	54.0 (36.6 to 69.1)	20	0.39 (0.25 to 0.59)	40.6 (5.3 to 62.7)	49.4 (22.2 to 70.7)
Secondary analysis										
COVID-19 vaccine effectiveness[g]										
Unvaccinated or ≥180 d after received any monovalent vaccine[e]	1898	350 (303 to 392)	218	1.63 (1.42 to 1.86)	[Reference]	[Reference]	94	0.70 (0.57 to 0.86)	[Reference]	[Reference]
7-60 d after bivalent vaccination[f]	737	34 (20 to 47)	25	0.86 (0.57 to 1.25)	46.4 (12.8 to 67.0)	51.3 (23.6 to 71.9)	9	0.31 (0.15 to 0.57)	53.8 (−2.5 to 79.2)	57.0 (18.4 to 83.3)
61-150 d after bivalent vaccination[f]	637	81 (70 to 95)	18	0.91 (0.56 to 1.40)	47.1 (4.8 to 70.6)	62.4 (38.5 to 81.1)	11	0.55 (0.29 to 0.96)	21.9 (−62.7 to 62.5)	46.5 (−7.8 to 78.7)
Sensitivity analysis										
COVID-19 vaccine effectiveness										
Any monovalent vaccine[e]	2171	276 (142 to 350)	315	1.50 (1.34 to 1.67)	[Reference]	[Reference]	138	0.66 (0.55 to 0.77)	[Reference]	[Reference]
Bivalent vaccine[f]	795	50 (27 to 74)	43	0.84 (0.62 to 1.12)	52.2 (32.9 to 65.9)	56.3 (40.5 to 70.1)	20	0.39 (0.25 to 0.59)	52.7 (24.1 to 70.6)	51.1 (26.9 to 72.1)

[a] Participants could contribute to more than 1 vaccination category (vaccination status is a time-varying covariate).

[b] Those who were unvaccinated were excluded.

[c] Control for penalized coefficient estimates of age, sex, race, ethnicity, underlying health conditions, time since prior infection (calculated as the date of the prior infection to each week of follow-up time), geographic site, 7-day average of COVID-19 cases per 100 000 by site, and proportion of circulating variants by site from L2 regularization.

[d] Defined as those with a positive reverse transcriptase–polymerase chain reaction test result and at least 2 COVID-19 symptoms (defined in eTable 2 in Supplement 1) reported within 7 days of the specimen collection date.

[e] The monovalent vaccine contained components of only the SARS-CoV-2 ancestral strain.

[f] The bivalent vaccine contained components from the SARS-CoV-2 ancestral and Omicron BA.4/5 strains.

[g] Data limited to period from October 30, 2022, to January 31, 2023, to allow both categories to possess the same amount of calendar time at risk.

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Table 3. Bivalent COVID-19 Vaccine Effectiveness Against Laboratory-Confirmed SARS-CoV-2 Infection Among Children and Adolescents Aged 5 to 17 Years by Age Group and Prior Infection Status

			Laboratory-confirmed SARS-CoV-2 infection			
					COVID-19 vaccine effectiveness, % (95% CI)	
	No.[a]	Observation time after vaccination, median (IQR), d[b]	No. of cases	Crude incidence rate/1000 person-days (95% CI)	Unadjusted	Adjusted[c]
Aged 5-11 y[d]						
Unvaccinated or received any monovalent vaccine[e]	1628	221 (140 to 349)	209	1.55 (1.35 to 1.77)	[Reference]	[Reference]
Bivalent vaccine[f]	491	44 (24 to 66)	23	0.72 (0.47 to 1.06)	59.3 (34.2 to 74.8)	58.3 (34.0 to 76.5)
Aged 12-17 y						
Unvaccinated or received any monovalent vaccine[e]	975	313 (241 to 404)	137	1.38 (1.17 to 1.63)	[Reference]	[Reference]
Bivalent vaccine[f]	308	59 (32 to 87)	20	0.90 (0.57 to 1.37)	39.0 (−0.5 to 63.0)	47.5 (18.2 to 71.9)
Prior SARS-CoV-2 infection[g]						
Unvaccinated or received any monovalent vaccine[e]	1704	288 (156 to 357)	160	0.87 (0.74 to 1.01)	[Reference]	[Reference]
Bivalent vaccine[f]	445	47 (25 to 71)	11	0.39 (0.21 to 0.68)	65.7 (36.4 to 81.5)	63.6 (33.0 to 84.0)
No prior SARS-CoV-2 infection						
Unvaccinated or received any monovalent vaccine[e]	999	241 (127 to 334)	223	2.40 (2.10 to 2.73)	[Reference]	[Reference]
Bivalent vaccine[f]	350	54 (29 to 78)	32	1.38 (0.96 to 1.93)	47.2 (21.8 to 64.3)	47.2 (26.7 to 67.8)

[a] Participants could contribute to more than 1 vaccination category (vaccination status is a time-varying covariate).

[b] Those who were unvaccinated were excluded.

[c] Control for penalized coefficient estimates of age, sex, race, ethnicity, underlying health conditions, time since prior infection (calculated as the date of the prior infection to each week of follow-up time), geographic site, 7-day average of COVID-19 cases per 100 000 by site, and proportion of circulating variants by site from L2 regularization.

[d] Surveillance started on October 16, 2022.

[e] The monovalent vaccine contained components of only the SARS-CoV-2 ancestral strain.

[f] The bivalent vaccine contained components from the SARS-CoV-2 ancestral and Omicron BA.4/5 strains.

[g] Defined as laboratory confirmation of infection by reverse transcriptase–polymerase chain reaction from a study-collected specimen prior to the study period, positive antinucleocapsid SARS-CoV-2 antibody, or self-report of infection prior to enrollment or study period start (whichever occurred later).

the Arizona study site because they constituted half of all study participants. We found the bivalent COVID-19 vaccine effectiveness estimates from these analyses to be consistent with the overall estimate. We also examined COVID-19 vaccine effectiveness by prior SARS-CoV-2 infection status to determine whether hybrid immunity from both vaccination and prior infection provided greater protection than COVID-19 vaccination alone.[39,40] Even though the bivalent COVID-19 vaccine effectiveness estimate among those with reported SARS-CoV-2 infection or with evidence of prior SARS-CoV-2 infection was higher than among those without prior SARS-CoV-2 infection, the difference was not statistically significant.

These findings are consistent with the limited other data available on protection provided by the bivalent vaccine for children and adolescents. In a study by Lin et al[21] among children aged 5 to 11 years, effectiveness of the bivalent COVID-19 vaccine 2 months after receipt was 47.3% (95% CI, −17.9% to 76.4%). The estimate for vaccine effectiveness 1 month after receipt of a bivalent COVID-19 vaccine dose (76.7% [95% CI, 45.7 to 90.0]) by Lin et al[21] was higher than the estimate (51.3% [95% CI, 23.6% to 71.9%]) in the current study for those who received a bivalent COVID-19 vaccine dose within 7 to 60 days. However, the 95% CIs overlap, and the difference in vaccine effectiveness may be due to different sites and study periods.

In addition, the current multistate study followed up participants through January 31, 2023, whereas Lin et al[21] followed up North Carolina residents until January 6, 2023. National surveillance data[37] show increased circulation of variants other than BA.4/5 during those 4 weeks, and it is possible that the bivalent COVID-19 vaccine may not be as protective against those variants (eg, XBB), thus decreasing the vaccine effectiveness estimate for the entire study period.

This study had many strengths, including almost 3000 participants enrolled from 6 diverse sites across multiple states in the US. Participants collected weekly swabs regardless of symptoms, which greatly reduces the risk of missing an asymptomatic SARS-CoV-2 infection, and adherence to weekly swabbing was high (median, 94%). Weekly and quarterly surveys, as well as data from the state immunization information systems and electronic medical records, ensured detailed and complete information on potential confounding variables and vaccination status. Although there was no observed waning 61 to 150 days after receipt of the bivalent COVID-19 vaccine dose, the 95% CIs were wide because of small sample size and this analysis could not examine vaccine waning beyond 150 days. The continuation of the participant cohorts will present future opportunities for examination of longer-term waning patterns to support future vaccine decision-making.

Limitations

There are several important limitations of this study. First, RT-PCR testing methods and the list of COVID-19 symptoms surveyed varied by cohort; therefore, some differences in the definition of SARS-CoV-2 infection or symptomatic COVID-19 may be present.

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Second, weekly or symptomatic RT-PCR testing prior to the analytic study start date for estimation of prior SARS-CoV-2 infection history was only available among a subset of participants. To address this concern, we incorporated serological data to identify additional prior SARS-CoV-2 infections. The sensitivity and specificity of the serological assays varied by cohort site and, due to antinucleocapsid SARS-CoV-2 antibody waning, the assays may not have detected some prior infections.

Third, social desirability or recall bias may have affected self- or parent-report of prior SARS-CoV-2 infection when RT-PCR and serological test results were unavailable, and self- or parent-reported vaccination status when data were unavailable from the state immunization information systems and electronic medical records.

Fourth, our analysis did not account for the social vulnerability index and immunocompromised status, which may be associated with vaccine uptake and risk of SARS-CoV-2 infection.

Fifth, limited sample sizes resulted in imprecise subgroup estimates and precluded us from examining vaccine effectiveness against symptomatic COVID-19 and vaccine waning by age group.

Conclusions

The bivalent COVID-19 vaccine protected children and adolescents against SARS-CoV-2 infection and symptomatic COVID-19. These data demonstrate the benefit of COVID-19 vaccine in children and adolescents. All eligible children and adolescents should remain up to date with recommended COVID-19 vaccinations.

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