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Effectiveness of BNT162b2 BA.4/5 Bivalent mRNA Vaccine Against Symptomatic COVID-19 Among Immunocompetent Individuals Testing at a Large US Retail Pharmacy

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Background. Data on the effectiveness of BA.4/5 bivalent vaccine stratified by age and prior infection are lacking.

Methods. This test-negative study used data from individuals ≥5 years of age testing for SARS-CoV-2 with symptoms (15 September 2022 to 31 January 2023) at a large national retail pharmacy chain. The exposure was receipt of 2–4 wild-type doses and a BNT162b2 BA.4/5 bivalent vaccine (>2 months since last wild-type dose). The outcome was a positive SARS-CoV-2 test. Absolute (vs unvaccinated) and relative (vs 2–4 wild-type doses) vaccine effectiveness (VE) were calculated as (1 − adjusted odds ratio from logistic regression) × 100. VE was stratified by age and self-reported prior infection.

Results. Overall, 307 885 SARS-CoV-2 tests were included (7916 aged 5–11, 16 329 aged 12–17, and 283 640 aged ≥18 years). SARS-CoV-2 positivity was 39%; 21% were unvaccinated, 70% received 2–4 wild-type doses with no bivalent vaccine, and 9% received a BNT162b2 BA.4/5 bivalent dose. At a median of 1–2 months after BNT162b2 BA.4/5 bivalent vaccination, depending on age group, absolute VE was 22%–60% and was significantly higher among those reporting prior infection (range, 55%–79%) than not (range, no protection to 50%). Relative VE was 31%–64%.

Conclusions. BNT162b2 BA.4/5 bivalent showed early additional protection against Omicron-related symptomatic COVID-19, with hybrid immunity offering greater protection.

Keywords. bivalent; BA.4/5; Omicron; VE; effectiveness; BNT162b2; SARS-CoV-2; COVID-19; United States; test negative.

Omicron and its sublineages have comprised the majority of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genomes sequenced by the Centers for Disease Control and Prevention (CDC) since December 2021 [1]. Omicron has key mutations that enhance immune escape and have resulted in reduced effectiveness of original Wuhan-Hu-1–encoding mRNA coronavirus disease 2019 (COVID-19) vaccines (hereafter referred to as "original wild-type" vaccines) [2–8]. Updated COVID-19 vaccines were developed to target both wild-type and Omicron BA.4/5 strains. The US Food and Drug Administration authorized a single dose of mRNA BA.4/5 bivalent vaccines as a booster for those who completed the primary vaccination series ≥2 months ago for individuals aged ≥12 years on 31 August 2022 and children aged 5–11 years on 11 October 2022. To date, real-world studies have suggested that a BA.4/5 bivalent vaccine improves protection against BA.4/5-related severe outcomes, including COVID-19–related hospitalization and death among adolescents [9] and adults [6, 9–14]. Only a few studies have reported effectiveness of a bivalent vaccine against Omicron-related symptomatic COVID-19 [13, 15–18], and these studies have not stratified effectiveness estimates by history of prior SARS-CoV-2 infection. Given >90% of US individuals have likely been infected with SARS-CoV-2 at least once [19], these data are needed to understand performance of Omicron-adapted vaccines. Furthermore, bivalent vaccine effectiveness estimates among 5–11 year olds are scarce [9]. To address these gaps, we estimated effectiveness of a Pfizer-BioNTech BNT162b2 BA.4/5 bivalent vaccine against Omicron-related symptomatic COVID-19 among those aged ≥5 years testing for SARS-CoV-2 at a large US pharmacy chain by age group and history of prior infection.

METHODS

We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The Advarra institutional review board approved the study

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(Pro00058582) and granted a waiver for informed consent under US Department of Health and Human Services regulation 45 CFR 46.104(d)(4) for research using deidentified data and a complete waiver of Health Insurance Portability and Accountability Act authorization.

Study Design and Participants

This test-negative case-control study was conducted at Walgreens, a US retail pharmacy chain where >35 million SARS-CoV-2 tests have been administered at >7100 locations. This analysis included (1) children aged 5–11 years who tested for SARS-CoV-2 at a Walgreens pharmacy between 26 October 2022 and 31 January 2023, and (2) individuals aged ≥12 years who were tested between 15 September 2022 and 31 January 2023. The beginning of each study period corresponds to 14 days after the authorization of BA.4/5 bivalent vaccines for each age group (ie, the earliest each age group could be considered vaccinated with a bivalent vaccine). Patients (or parents or guardians for children aged <18 years) completed an online appointment scheduler to select a Walgreens location and SARS-CoV-2 test type (real-time polymerase chain reaction [RT-PCR], rapid nucleic acid amplification test [NAAT], or rapid antigen) [20]. Records with only a rapid antigen test were not included. Availability of RT-PCR and rapid NAAT tests varied by location.

At the time of scheduling, demographic characteristics, symptoms, clinical history including comorbidities, prior SARS-CoV-2 infection, and COVID-19 vaccination history (including number received, dates for each [month and year], and manufacturer) were collected via a self-reported questionnaire (available in English or Spanish). Patients experiencing severe symptoms were directed to contact emergency services. Race and ethnicity were self-reported using categories defined by CDC [21]; the categories American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander were combined into one group (Native) due to limited sample size. At the appointment, individuals self-collected swab specimens of the anterior nares under supervision of trained Walgreens staff. All specimens were placed into a collection tube. RT-PCR specimens were transferred to an accredited laboratory and rapid NAAT specimens were processed onsite using the Abbott ID Now test (sensitivity and specificity of each test are reported in Supplementary Table 4).

Records were excluded if the individual (1) received any non-mRNA vaccine, (2) received an Omicron-adapted vaccine other than the BNT162b2 BA.4/5 bivalent, (3) received >1 dose of BNT162b2 bivalent, (4) received only 1 original wild-type dose or their last original wild-type dose ≤2 months ago (ie, not eligible for a bivalent vaccine), (5) received a BNT162b2 bivalent dose ≤2 months after their last original wild-type dose (ie, not according to current guidelines), (6) received a BNT162b2 bivalent dose <14 days ago (ie, individuals were not considered vaccinated until ≥14 days), (7) declined to report vaccination status or self-reported fewer vaccines in the current questionnaire than in a prior questionnaire (completed between 1 January 2022 and 31 January 2023), (8) were immunocompromised or received >4 original wild-type doses, (9) had invalid SARS-CoV-2 test results, (10) self-reported a prior SARS-CoV-2 infection ≤3 months ago, or (11) did not report symptoms on the testing survey. Finally, to ensure that cases and controls included in the analysis had similar healthcare seeking behaviors, we also excluded those reporting testing related to future travel or employment screening and those who tested multiple times during the study window.

Exposure

COVID-19 vaccine history was determined using patient-reported data from the online questionnaire. To determine timing of vaccination, we ascertained whether the last dose was received in the past 14 days, or if received ≥14 days ago, the month and year of receipt. The exposure of interest was receipt of 2–4 original wild-type doses plus a BNT162b2 BA.4/5 bivalent vaccine ≥14 days before testing for SARS-CoV-2, with the most recent original wild-type dose received >2 months before the bivalent dose. For estimates of absolute vaccine effectiveness (VE), the unvaccinated were the reference group. Those who received 2–4 original wild-type doses >2 months ago but not a bivalent vaccine were the reference for relative VE estimates.

Outcomes

VE was evaluated by comparing the odds of vaccination among individuals testing positive for SARS-CoV-2 (cases) versus negative (controls) via RT-PCR or rapid NAAT.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics stratified by SARS-CoV-2 test result and vaccination status. Differences between groups according to case status and bivalent vaccination status were evaluated using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

Estimated VE was calculated as 1 minus the odds ratio from multivariable adjusted generalize estimating equations logistic regression models (clustered on US Census region of pharmacy), multiplied by 100. All VE estimates were stratified by age (5–11, 12–17, 18–49, 50–64, and ≥65 years). We tested for statistical interaction between bivalent vaccination status and self-reported prior infection >3 months ago (yes/no) in both the absolute and relative VE models. For relative VE we additionally tested for statistical interaction between bivalent vaccine status and time since last original wild-type dose (2–6 or ≥7 months). The following variables were considered for inclusion in adjusted models but excluded if they did not retain statistical significance ($P < .05$) after adjusting for other covariates or change the odds ratio estimate by ≥10% [22]: [1] demographic characteristics [ie, age [continuous], gender [male, female, or

other], and race and ethnicity), self-reported number of chronic medical conditions (0, 1, 2, or ≥3), recent close contact with someone with COVID-19 (yes/no), and test type (RT-PCR or rapid NAAT); (2) calendar week using a categorical term in 2-week increments; and (3) pharmacy-level characteristics (ie, rural, suburban, or urban Walgreens trade area designation, US Census region [Midwest, Northeast, South, or West], federal information processing system tract-level area deprivation index [ADI; continuous] [23], SARS-CoV-2 testing volume [number of tests conducted relative to the estimated catchment population of the pharmacy, continuous], and store-specific percent positivity [continuous] and COVID-19 incidence [county level] per 100 000 persons [24] [continuous], both measured in the week before the participant's SARS-CoV-2 test).

We additionally conducted 3 sensitivity analyses to assess the impact of removing those with symptomatic COVID-19 who tested multiple times during the study window and reported testing related to future travel or employment screening on age-stratified absolute and relative VE estimates. All analyses were performed using SAS, version 7.1 (SAS Institute, Inc).

RESULTS

After excluding 740 342 SARS-CoV-2 tests, our analysis included 307 885 test results (with corresponding questionnaire data; Figure 1) including 7916 (3%) 5–11 year olds, 16 329 (5%) 12–17 year olds, and 283 640 (92%) adults aged ≥18 years. Overall, 39% of SARS-CoV-2 tests were positive. A greater proportion of those testing were women (60%), but positivity was slightly higher for men (41%) than women (37%). Adults aged 50–64 years had the highest positivity (46%) and 5–11 year olds had the lowest (20%). The highest positivity by race/ethnicity was observed among those identifying as Asian/non-Hispanic (42%) and the lowest among those identifying as non-Hispanic Black/African Americans (36%). Over one-third reported ≥1 chronic condition, with hypertension (18%) and overweight/obesity (15%) most frequently reported. Those reporting ≥1 condition were more likely to test positive ($P < .0001$), and the likelihood of testing positive increased with the number of conditions reported (Table 1). The most frequently reported symptom was new or worsening cough (71%), followed by congestion or runny nose (61%), sore throat (60%), headache (58%), and fatigue (52%). Positivity was higher among those who reported chills (49%), low-grade fever (49%), muscle pain (46%), new or worsening cough (43%), and new loss of taste or smell (43%) (Table 1).

Overall, 21% were unvaccinated, 70% received 2–4 original wild-type doses and no bivalent vaccine, and 9% received 2–4 original wild-type doses plus a BA.4/5 bivalent vaccine (Table 2). Median time since receipt of a bivalent vaccine was 1 month for 5–11 year olds and 2 months for those aged ≥12 years (Supplementary Table 1). Of those with 2–4 original wild-type doses (11% of whom also received a bivalent vaccine), 88% received their last original wild-type dose ≥7 months ago.

A greater proportion of those aged ≥65 years (20%) or who had received ≥3 original wild-type doses (18%) had received a bivalent vaccine. Bivalent vaccine uptake increased with the number of comorbidities reported. Those testing at pharmacies in more disadvantaged areas (higher ADI scores) were less likely to have received a bivalent vaccine (mean ADI, 51 for those with a bivalent vaccine, 57 for only 2–4 original wild-type doses, and 66 for unvaccinated). Those least likely to have received a bivalent vaccine were 5–17 year olds (5%), those identifying as non-Hispanic Black/African American (5%), Hispanic (5%), or non-Hispanic Native (5%), and pregnant women (6%). Those testing at pharmacies in rural areas (7%) or the South (7%) were also less likely to have received a bivalent vaccine (Table 2).

Overall, 43% reported prior infection. Those reporting prior infection were less likely to test positive (27%) than those without prior infection (48%; $P < .0001$). Unvaccinated individuals were most likely to report prior infection (54% vs 41% of those with only 2–4 original wild-type doses and 32% of those with a bivalent vaccine; $P < .0001$; Table 2).

Absolute VE

Depending on age group, adjusted absolute VE (vs the unvaccinated) point estimates against symptomatic COVID-19 ranged from 22% to 60% overall (Table 3). For each age group, there was a statistically significant interaction between BA.4/5 bivalent vaccination status and prior infection. Across all age groups, absolute VE point estimates were significantly higher for those reporting prior SARS-CoV-2 infection (range, 55%–79%) than among those not reporting prior infection (range, 22%–50%) (Table 3). Absolute VE was highest among 5–11 year olds and tended to decrease as age increased (Table 3). Supplementary Table 2 presents unadjusted absolute VE estimates and strata-specific sample sizes.

Relative VE

Relative VE (vs receipt of 2–4 wild-type doses) decreased with increasing age (adjusted VE point estimates, 64% among 5–11 year olds, 53% among 12–17 year olds, 47% among 18–49 year olds, 38% among 50–64 year olds, and 31% among those aged ≥65 years; Table 4). No statistically significant interaction was observed by time since last original wild-type dose (Supplementary Table 5). Interaction between BA.4/5 bivalent vaccination status and prior infection was statistically significant only for 5–11 year olds (VE for those with and without prior infection was 76% and 59%, respectively; Table 4). Supplementary Table 3 presents unadjusted relative VE estimates and strata-specific sample sizes.

Sensitivity Analyses

Sensitivity analyses showed that excluding those who tested related to future travel or employment screening or who tested

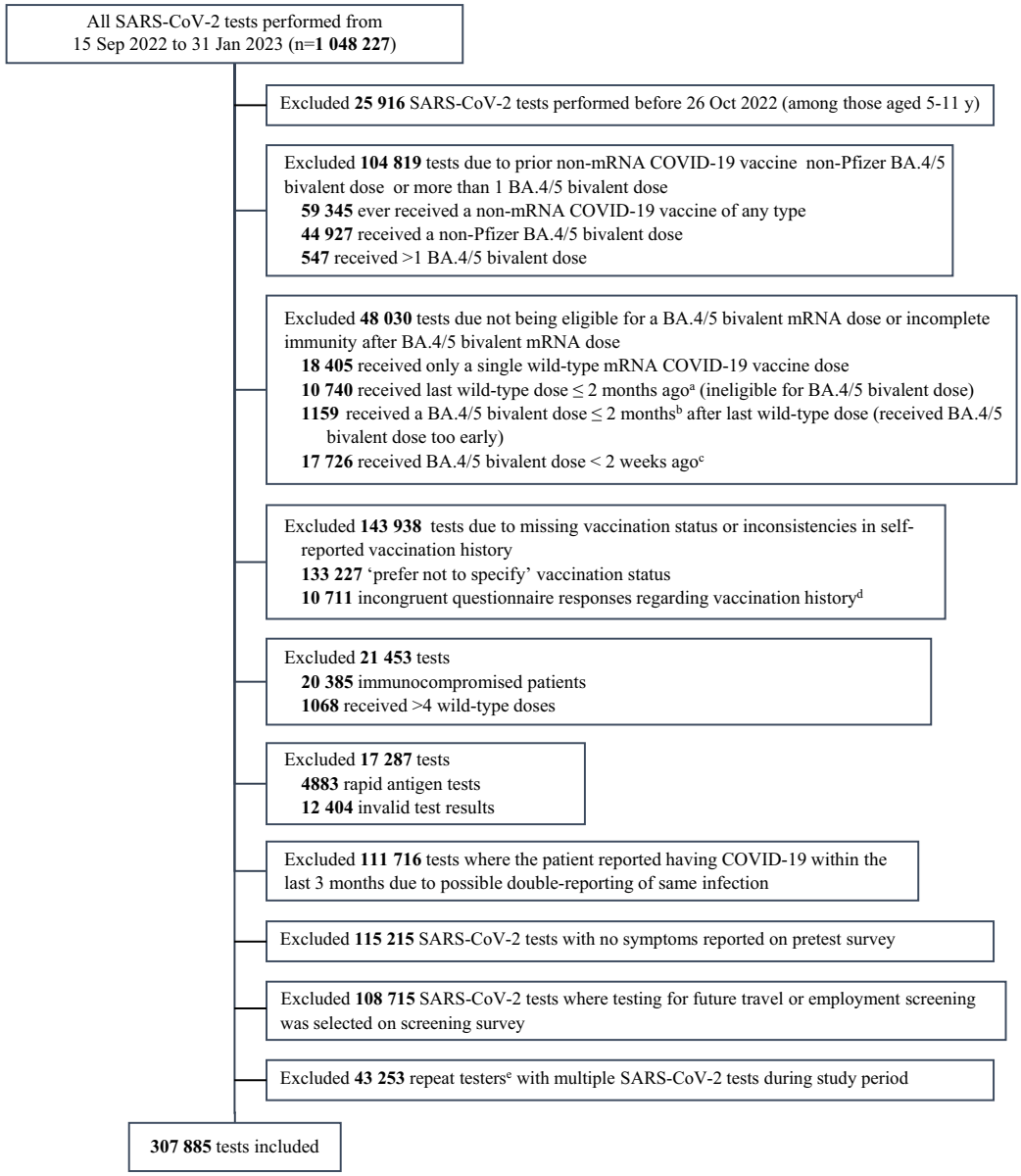

Figure 1. Selection criteria. [a]The number of months between the last original wild-type COVID-19 mRNA dose and the testing date was calculated as the whole number representing the difference between the month and year of the last original wild-type COVID-19 mRNA dose and the month and year of the SARS-CoV-2 test date. Due to not having days, removing those with a difference of 0–2 months may remove some patients who have a difference of 3 months between the last original wild-type COVID-19 mRNA dose and the SARS-CoV-2 test date (ie, last original wild-type COVID-19 mRNA dose on the first day of July and SARS-CoV-2 test on the last day of September). Using this decision rule ensured that individuals who received their BA.4/5 bivalent dose too early or those who had received 2–4 original wild-type doses but were not yet eligible to receive a BA.4/5 bivalent dose were removed from the analysis, but may have also excluded some individuals who received their dose 2 months ago. Furthermore, the dichotomization of time since last original wild-type dose (2–6 months ago vs ≥7 months ago) could result in some misclassification of individuals classified as having received their last original wild-type dose 6 or 7 months ago. For example, the 2–6 month category could include some individuals who were vaccinated closer to 7 months ago and those in the ≥7 month category could include some individuals who received their last original wild-type dose closer to 6 months ago. [b]The number of months between vaccine doses is calculated as the whole number representing the difference between the month and year of the last original wild-type COVID-19 mRNA dose and the month and year of the BA.4/5 bivalent dose. Due to not having days, removing those with a difference of 0–2 months may remove some patients who had a difference of 3 months between the last original wild-type COVID-19 mRNA dose and the BA.4/5 bivalent dose (ie, last original wild-type COVID-19 mRNA dose on the first day of July and BA.4/5 bivalent dose on the last day of September). [c]The number of months between the last BA.4/5 bivalent mRNA vaccine dose and the testing date is a whole number calculated as the difference between the month and year of the testing date and the month and year of the last BA.4/5 bivalent vaccine dose. For doses received in the same month or the month before completing the SARS-CoV-2 test scheduling questionnaire, an additional question was asked to specify whether the dose was received ≥2 weeks before testing, and only doses received ≥2 weeks before testing were included. Doses received ≥2 weeks before testing but in the same month of testing were coded as having their last bivalent dose 0 months ago. [d]Individuals testing multiple times at a Walgreens pharmacy between 1 January 2022 and 31 January 2023 were identified by merging testing questionnaire data based on the patient's first name, last name, phone number, address state, date of birth, and gender. We removed records where the patient reported having received fewer vaccine doses than they had in an earlier questionnaire (from 1 January 2022 to 31 January 2023). [e]Repeat testers were identified by merging questionnaire data based on the patient's first name, last name, phone number, address state, date of birth, and gender. We removed records where the patient reported having received fewer vaccines than they had in an earlier survey.

Table 1. Sample Characteristics for Those Testing for SARS-CoV-2 at Walgreens Pharmacies Between 15 September 2022 and 31 January 2023, Overall and by SARS-CoV-2 Testing Status (n = 307 855)

Characteristic	Total No. (%)	SARS-CoV-2 Positive No. (%)	SARS-CoV-2 Negative No. (%)	Positivity %	*P* Value[a]
Total	307 885 (8.76)	118 706 (21.06)	189 024 (70.18)	38.56	
Age, y					
5–11	7916 (2.57)	1611 (1.36)	6305 (3.33)	20.35	<.0001[b]
12–17	16 329 (5.30)	4132 (3.48)	12 197 (6.45)	25.30	<.0001[b]
≥18	283 640 (92.13)	112 963 (95.16)	170 677 (90.22)	39.83	<.0001[c]
18–49	190 921 (62.01)	70 456 (59.35)	120 465 (63.68)	36.90	Ref
50–64	57 448 (18.66)	26 593 (22.40)	30 855 (16.31)	46.29	<.0001[b]
≥65	35 271 (11.46)	15 914 (13.41)	19 357 (10.23)	45.12	<.0001[b]
Mean (SD)	40.26 (18.00)	43.10 (17.77)	38.48 (17.92)		<.0001
Gender					
Female	184 892 (60.05)	67 980 (57.27)	116 912 (61.80)	36.77	<.0001
Male	122 031 (39.64)	50 436 (42.49)	71 595 (37.85)	41.33	Ref
Other	962 (0.31)	290 (0.24)	672 (0.36)	30.15	<.0001
Race/ethnicity					
Hispanic/any race	63 091 (20.49)	24 553 (20.68)	38 538 (20.37)	38.92	.6793
Asian/non-Hispanic or Latino	22 535 (7.32)	9386 (7.91)	13 149 (6.95)	41.65	.0006
Black or African American/non-Hispanic or Latino	46 710 (15.17)	16 637 (14.02)	30 073 (15.90)	35.62	.0204
Native/non-Hispanic or Latino[d]	2932 (0.95)	1073 (0.90)	1859 (0.98)	36.60	.2609
White/non-Hispanic or Latino	152 388 (49.50)	59 229 (49.90)	93 159 (49.24)	38.87	Ref
Decline to answer	20 229 (6.57)	7828 (6.59)	12 401 (6.56)	38.70	.7967
Currently pregnant?					
No	224 984 (73.07)	85 340 (71.89)	139 644 (73.82)	37.93	Ref
Yes	4287 (1.39)	1543 (1.30)	2744 (1.45)	35.99	.0026
Does not apply	78 614 (25.53)	31 823 (26.81)	46 791 (24.73)	40.48	<.0001
Recent close contact with someone diagnosed with or presumed to have COVID-19					
No	176 854 (57.44)	63 607 (53.58)	113 247 (59.86)	35.97	Ref
Yes	131 031 (42.56)	55 099 (46.42)	75 932 (40.14)	42.05	<.0001
Chronic conditions reported					
At least 1	112 905 (36.67)	46 771 (39.40)	66 134 (34.96)	41.43	<.0001[e]
Chronic lung disease, eg, COPD, moderate to severe asthma, cystic fibrosis, or pulmonary embolism	14 365 (4.67)	4971 (4.19)	9394 (4.97)	34.60	<.0001
Cirrhosis of the liver	574 (0.19)	226 (0.19)	348 (0.18)	39.37	.7132
Current or former smoker	27 522 (8.94)	11 484 (9.67)	16 038 (8.48)	41.73	<.0001
Diabetes	23 095 (7.50)	9956 (8.39)	13 139 (6.95)	43.11	<.0001
Heart condition	15 410 (5.01)	6365 (5.36)	9045 (4.78)	41.30	<.0001
High blood pressure	56 970 (18.50)	25 061 (21.11)	31 909 (16.87)	43.99	<.0001
Overweight or obesity	47 410 (15.40)	18 992 (16.00)	28 418 (15.02)	40.06	<.0001
Kidney failure or end-stage renal disease	1409 (0.46)	605 (0.51)	804 (0.42)	42.94	<.0001
None	194 980 (63.33)	71 935 (60.60)	123 045 (65.04)	36.89	
Number of condition(s) reported					
0	194 980 (63.33)	71 935 (60.60)	123 045 (64.04)	36.89	Ref
1	64 287 (20.88)	26 399 (22.24)	37 888 (20.03)	41.06	<.0001
2	30 349 (9.86)	12 697 (10.70)	17 652 (9.33)	41.84	<.0001
≥ 3	18 269 (5.93)	7675 (6.47)	10 594 (5.60)	42.01	<.0001
Symptoms reported					
Low-grade fever, <102°F	107 854 (35.03)	52 651 (44.35)	55 203 (29.18)	48.82	<.0001
Chills	109 231 (35.48)	53 936 (45.44)	55 295 (29.23)	49.38	<.0001
Fatigue	159 834 (51.91)	65 711 (55.36)	94 123 (49.75)	41.11	<.0001
Headache	178 744 (58.06)	73 383 (61.82)	105 361 (55.69)	41.05	<.0001
Muscle pain	113 489 (36.86)	52 037 (43.84)	61 452 (32.48)	45.85	<.0001
Congestion/runny nose	188 160 (61.11)	78 515 (66.14)	109 645 (57.96)	41.73	<.0001
New loss of taste or smell	29 915 (9.72)	12 816 (10.80)	17 099 (9.04)	42.84	<.0001
Sore throat	185 864 (60.37)	76 239 (64.23)	109 625 (57.95)	41.02	<.0001

Table 1. Continued

Characteristic	Total No. (%)	SARS-CoV-2 Positive No. (%)	SARS-CoV-2 Negative No. (%)	Positivity %	*P* Value[a]
New or worsening cough	218 845 (71.08)	95 164 (80.17)	123 681 (65.38)	43.48	<.0001
Shortness of breath/difficulty breathing, not severe	61 023 (19.82)	22 797 (19.20)	38 226 (20.21)	37.36	<.0001
Diarrhea	38 683 (12.56)	13 807 (11.63)	24 876 (13.15)	35.69	<.0001
Vomiting	18 988 (6.17)	6322 (5.33)	12 666 (6.70)	33.29	<.0001
SARS-CoV-2 test type					
PCR	99 490 (32.31)	40 430 (34.06)	59 060 (31.22)	40.64	Ref
Rapid NAAT	208 395 (67.69)	78 276 (65.94)	130 119 (68.78)	37.56	.0008
Original wild-type vaccination history					
Unvaccinated	64 846 (21.06)	21 417 (18.04)	43 429 (22.96)	33.03	Ref
2 doses only	110 560 (35.91)	42 321 (35.65)	68 239 (36.07)	38.28	<.0001[f,g]
≥ 3 doses	132 479 (43.03)	54 968 (46.31)	77 511 (40.97)	41.49	<.0001[f]
3 doses only	109 141 (35.45)	44 992 (37.90)	64 149 (33.91)	41.22	<.0001[g]
4 doses only	23 338 (7.58)	9976 (8.40)	13 362 (7.06)	42.75	<.0001[g]
Months since last original wild-type dose[h]					
2–6	29 224 (12.02)	11 048 (11.36)	18 176 (12.47)	37.80	<.0001
≥ 7	213 815 (87.98)	86 241 (88.64)	127 574 (87.53)	40.33	Ref
BA.4/5 bivalent vaccination status					
Did not receive bivalent vaccine	280 924 (91.24)	109 798 (92.50)	171 126 (90.46)	39.08	<.0001[i]
≥ 2 original wild-type doses but no bivalent vaccine	216 078 (70.18)	88 381 (74.45)	127 697 (67.50)	40.90	<.0001[j]
Unvaccinated	64 846 (21.06)	21 417 (18.04)	43 429 (22.96)	33.03	.8149[j]
Prior SARS-CoV-2 infection					<.0001
No	174 591 (56.71)	83 362 (70.23)	91 229 (48.22)	47.75	Ref
Yes, > 3 mo ago[k]	133 294 (43.29)	35 344 (29.77)	97 950 (51.78)	26.52	<.0001
Average weekly incidence rate (per 100 000) in participating counties over study period, mean (SD)	109.77 (60.55)	114.00 (60.75)	107.10 (60.28)	NA	<.0001
Average store-specific percent positivity (No. of tests in a store, divided by the store trade area's population size) in participating stores over study period, mean (SD)	38.56 (29.43)	61.02 (25.05)	24.46 (22.37)	NA	<.0001
US census region					<.0001
Midwest	80 982 (26.30)	31 397 (26.45)	49 585 (26.21)	38.77	
Northeast	36 187 (11.75)	15 098 (12.72)	21 089 (11.15)	41.72	
South	130 215 (42.29)	47 870 (40.33)	82 345 (43.53)	36.76	
West	60 501 (19.65)	24 341 (20.51)	36 160 (19.11)	40.23	
Rural/urban area of pharmacy trade region					
Rural	76 298 (24.78)	29 675 (25.00)	46 623 (24.64)	38.89	.9519
Suburban	206 825 (67.18)	79 208 (66.73)	127 617 (67.46)	38.30	.5471
Urban	24 762 (8.04)	9823 (8.28)	14 939 (7.90)	39.67	Ref
Area deprivation index of pharmacy, mean (SD)	58.51 (28.49)	58.24 (28.37)	58.67 (28.56)	NA	.9851
Average store-specific testing volume per 100 persons in pharmacy trade area over study period, mean (SD)	0.26 (0.16)	0.27 (0.16)	0.26 (0.16)	NA	<.0001

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NA, Not Applicable; ICC, intraclass correlation coefficient.

[a]Statistical significance was assessed using bivariate generalized estimating equations logistic regression models that clustered on US Census region of pharmacy to account for Intraclass Correlation Coefficient (ICC) by Walgreens pharmacy region.

[b]Comparing categories: 5–11, 12–17, 18–49, 50–64, and ≥65 years.

[c]Comparing categories: ≥ 18 vs <18 years.

[d]Includes American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander.

[e]Comparing categories: any chronic conditions vs no chronic conditions.

[f]Comparing categories: unvaccinated, 2 doses only, ≥3 doses.

[g]Comparing unvaccinated, 2 doses, 3 doses, and 4 doses.

[h]Because only month and year are available for vaccine doses, 2–6 months may include some patients who were vaccinated 7 months ago; 7–11 months may include some patients who were vaccinated 6 or 12 months ago.

[i]Comparing categories: did vs did not receive bivalent vaccine.

[j]Compared with receipt of the bivalent vaccine.

[k]History of prior COVID-19 infection included the following response options: No; Yes, within the last week; Yes, 1 week to 3 months ago; and Yes, >3 months ago. Those indicating a prior COVID-19 infection within the last week or 1 week to 3 months ago were excluded from the analysis. This variable represents self-reported prior COVID-19 infection >3 months ago (yes vs no).

Table 2. Sample Characteristics for Those Testing for SARS-CoV-2 at Walgreens Pharmacies Between 15 September 2022 and 31 January 2023, Overall and by Vaccination Status (n = 307 885)

Characteristic	Received BA.4/5 Bivalent Vaccine (n = 26 961) No. (%)	Unvaccinated[a] (n = 64 846) No. (%)	*P* Value[c,d]	2–4 Original Wild-Type Doses but no Bivalent Vaccine[b] (n = 216 078) No. (%)	*P* Value[d,e]
Age, y					
5–11	370 (1.37)	4702 (7.25)	<.0001[f]	2844 (1.32)	<.0001[f]
12–17	762 (2.83)	6107 (9.42)	<.0001[f]	9460 (4.38)	<.0001[f]
≥ 18	25 829 (95.80)	54 037 (83.33)	<.0001[f,g]	203 774 (94.31)	<.0001[g]
18–49	12 404 (46.01)	44 070 (67.96)	Ref	134 447 (62.22)	Ref
50–64	6270 (23.26)	7359 (11.35)	<.0001[f]	43 819 (20.28)	<.0001[f]
≥65	7155 (26.54)	2608 (4.02)	<.0001[f]	25 508 (11.80)	<.0001[f]
Mean (SD)	49.47 (19.06)	32.60 (15.98)	<.0001	41.41 (17.62)	<.0001
Gender					
Female	16 627 (61.67)	36 734 (56.65)	<.0001	131 531 (60.87)	.1579
Male	10 202 (37.84)	28 019 (43.21)	Ref	83 810 (38.79)	Ref
Other	132 (0.49)	93 (0.14)	<.0001	737 (0.34)	<.0001
Race/ethnicity					
Hispanic/any race	3001 (11.13)	14 436 (22.26)	<.0001	45 654 (21.13)	<.0001
Asian/non-Hispanic or Latino	2551 (9.46)	1396 (2.15)	<.0001	18 588 (8.60)	<.0001
Black or African American/non-Hispanic or Latino	2177 (8.07)	13 890 (21.42)	<.0001	30 643 (14.18)	<.0001
Native/non-Hispanic or Latino[h]	148 (0.55)	792 (1.22)	<.0001	1992 (0.92)	<.0001
White/non-Hispanic or Latino	17 818 (66.09)	29 176 (44.99)	Ref	105 394 (48.78)	Ref
Decline to answer	1266 (4.70)	5156 (7.95)	<.0001	13 807 (6.39)	<.0001
Currently pregnant?					
No	19 710 (73.11)	46 635 (71.92)	Ref	158 639 (73.42)	Ref
Yes	238 (0.88)	1148 (1.77)	<.0001	2901 (1.34)	<.0001
Does not apply	7013 (26.01)	17 063 (26.31)	.3877	54 538 (25.24)	.1805
Recent close contact with someone diagnosed with or presumed to have COVID-19					<.0001
No	15 220 (56.45)	37 617 (58.01)	Ref	124 017 (57.39)	Ref
Yes	11 741 (43.55)	27 229 (41.99)	<.0001	92 061 (42.61)	<.0001
Chronic conditions reported					
At least 1	13 066 (48.46)	17 444 (26.90)	<.0001	82 395 (38.13)	<.0001[i]
Chronic lung disease, eg, COPD, moderate to severe asthma, cystic fibrosis, or pulmonary embolism	1769 (6.56)	2459 (3.79)	<.0001	10 137 (4.69)	<.0001
Cirrhosis of the liver	71 (0.26)	114 (0.18)	.0012	389 (0.18)	.0007
Current or former smoker	2705 (10.03)	5888 (9.08)	.3628	18 929 (8.76)	.0404
Diabetes	2774 (10.29)	2885 (4.45)	<.0001	17 436 (8.07)	<.0001
Heart condition	2166 (8.03)	2164 (3.34)	<.0001	11 080 (5.13)	<.0001
High blood pressure	7243 (26.86)	7297 (11.25)	<.0001	42 430 (19.64)	<.0001
Overweight or obesity	5891 (21.85)	6220 (9.59)	<.0001	35 299 (16.34)	<.0001
Kidney failure or end-stage renal disease	167 (0.62)	204 (0.31)	<.0001	1038 (0.48)	.0061
None	13 895 (51.54)	47 402 (73.10)	Ref	133 683 (61.87)	Ref
Number of condition(s) reported					
0	13 895 (51.54)	47 402 (73.10)	Ref	133 683 (61.87)	Ref
1	6878 (25.51)	10 919 (16.84)	<.0001	46 490 (21.52)	<.0001
2	3670 (13.61)	4209 (6.49)	<.0001	22 470 (10.40)	<.0001
≥ 3	2518 (9.34)	2316 (3.57)	<.0001	13 435 (6.22)	<.0001
Symptoms reported					
Low-grade fever, <102°F	6223 (23.08)	27 402 (42.26)	<.0001	74 229 (34.35)	<.0001
Chills	7064 (26.20)	25 440 (39.23)	<.0001	76 727 (35.51)	<.0001
Fatigue	12 905 (47.87)	33 163 (51.14)	.0091	113 766 (52.65)	<.0001
Headache	12 834 (47.60)	40 895 (63.06)	<.0001	125 015 (57.86)	<.0001
Muscle pain	6962 (25.82)	27 261 (42.04)	<.0001	79 266 (36.68)	<.0001
Congestion/runny nose	17 207 (63.82)	37 134 (57.26)	<.0001	133 819 (61.93)	.0011
New loss of taste or smell	1560 (5.79)	8238 (12.70)	<.0001	20 117 (9.31)	<.0001
Sore throat	16 127 (59.82)	36 465 (56.23)	<.0001	133 272 (61.68)	<.0001

Table 2. Continued

Characteristic	Received BA.4/5 Bivalent Vaccine (n = 26 961) No. (%)	Unvaccinated[a] (n = 64 846) No. (%)	*P* Value[c,d]	2–4 Original Wild-Type Doses but no Bivalent Vaccine[b] (n = 216 078) No. (%)	*P* Value[d,e]
New or worsening cough	17 558 (65.12)	47 005 (72.49)	<.0001	154 282 (71.40)	<.0001
Shortness of breath/difficulty breathing, not severe	3612 (13.40)	15 873 (24.48)	<.0001	41 538 (19.22)	<.0001
Diarrhea	2363 (8.76)	10 475 (16.15)	<.0001	25 845 (11.96)	<.0001
Vomiting	802 (2.97)	6532 (10.07)	<.0001	11 654 (5.39)	<.0001
SARS-CoV-2 test type					
PCR	11 728 (43.50)	15 583 (24.03)	Ref	72 179 (33.40)	Ref
Rapid NAAT	15 233 (56.50)	49 263 (75.97)	<.0001	143 899 (66.60)	<.0001
Wild-type vaccination history					
Unvaccinated	NA	64 846 (100.00)	NA	NA	NA
2 doses only	3501 (12.99)	NA	NA	107 059 (49.55)	Ref
≥ 3 doses	23 460 (87.01)	NA	NA	109 019 (50.45)	<.0001[j]
3 doses only	16 229 (60.19)	NA	NA	92 912 (43.00)	<.0001[k]
4 doses only	7231 (26.82)	NA	NA	16 107 (7.45)	<.0001[k]
Months since last wild-type dose[l]					
2–6	3199 (11.87)	NA	NA	26 025 (12.04)	.2513
≥7	23 762 (88.13)	NA	NA	190 053 (87.96)	Ref
SARS-CoV-2 test status					
Negative	18 053 (66.96)	43 429 (66.97)	Ref	127 697 (59.10)	Ref
Positive	8908 (33.04)	21 417 (33.03)	.7554	88 381 (40.90)	<.0001
Prior SARS-CoV-2 infection					
No	18 279 (67.80)	29 821 (45.99)	Ref	126 491 (58.54)	Ref
Yes, > 3 mo ago[m]	8682 (32.20)	35 025 (54.01)	<.0001	89 587 (41.46)	<.0001
Average weekly incidence rate (per 100 000) in participating counties over study period, mean (SD)	110.40 (57.95)	108.30 (62.56)	.9698	110.10 (60.25)	.8095
Average store-specific percent positivity (No. of positive tests in a store, divided by the number of total tests) in participating stores over study period, mean (SD)	36.74 (29.06)	36.12 (29.42)	.9780	39.51 (29.43)	.0023
US census region					
Midwest	7882 (29.23)	18 074 (27.87)	<.0001	55 026 (25.47)	<.0001
Northeast	3779 (14.02)	5388 (8.31)	<.0001	27 020 (12.50)	<.0001
South	9224 (34.21)	30 576 (47.15)	Ref	90 415 (41.84)	Ref
West	6076 (22.54)	10 808 (16.67)	<.0001	43 617 (20.19)	<.0001
Rural/urban area of pharmacy trade region					
Rural	5593 (20.74)	20 650 (31.84)	.0113	50 055 (23.17)	.4568
Suburban	18 981 (70.40)	40 398 (62.30)	.4372	147 446 (68.24)	.6422
Urban	2387 (8.85)	3798 (5.86)	Ref	18 577 (8.60)	Ref
Area deprivation index of pharmacy, mean (SD)	50.52 (28.91)	65.91 (26.57)	<.0001	57.28 (28.54)	<.0001
Average store-specific testing volume per 100 persons in pharmacy trade area over study period, mean (SD)	0.13 (0.15)	0.27 (0.15)	<.0001	0.27 (0.15)	<.0001

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; Ref, reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness; NA, Not Applicable; ICC, intraclass correlation coefficient.

[a]Unexposed group for absolute VE.

[b]Unexposed group for relative VE.

[c]*P* value for received BA.4/5 bivalent vaccine vs unvaccinated.

[d]*P* value for received BA.4/5 bivalent vaccine vs received 2–4 original wild-type doses but no bivalent vaccine.

[e]Statistical significance was assessed using bivariate generalized estimating equations logistic regression models that clustered on US Census region of pharmacy to account for intraclass correlation coefficient (ICC) by Walgreens pharmacy region.

[f]Comparing categories: 5–11, 12–17, 18–49, 50–64, and ≥65 years.

[g]Comparing categories: ≥ 18 vs <18 years.

[h]Includes American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander.

[i]Comparing categories: any chronic conditions vs no chronic conditions.

[j]Comparing categories: unvaccinated, 2 doses only, ≥3 doses.

[k]Comparing unvaccinated, 2 doses, 3 doses, and 4 doses.

[l]Because only month and year are available for vaccine doses, 2–6 months may include some patients who were vaccinated 7 months ago; 7–11 months may include some patients who were vaccinated 6 or 12 months ago.

[m]History of prior COVID-19 infection included the following response options: No; Yes, within the last week; Yes, 1 week to 3 months ago; and Yes, >3 months ago. Those indicating a prior COVID-19 infection within the last week or 1 week to 3 months ago were excluded from the analysis. This variable represents self-reported prior COVID-19 infection >3 months ago (yes vs no).

Table 3. Adjusted Absolute VE and Corresponding 95% CIs Against Symptomatic COVID-19, Stratified by Age Group and by Age Group and History of Prior SARS-CoV-2 Infection

Age, y	Overall VE (95% CI)	No Prior Infection VE (95% CI)	Prior Infection, >3 mo Ago VE (95% CI)
5–11	60.17 (32.42–99.48)	49.77 (9.77–72.04)[a]	79.43 (64.48–88.09)[a]
12–17	38.98 (17.49–98.80)	27.60 (−2.61 to 48.92)	61.77 (48.59–71.57)
18–49	41.99 (35.67–95.09)	29.71 (22.04–36.61)	57.72 (53.73–61.36)
50–64	36.15 (15.96–95.22)	23.94 (10.74–35.20)	55.03 (49.58–59.88)
≥65	22.48 (16.75–39.75)	21.51 (10.47–31.20)	56.09 (48.89–62.29)

Absolute VE compares those who received 2–4 original wild-type doses plus a BNT162b2 BA.4/5 bivalent vaccine ≥14 days before testing for SARS-CoV-2 and the unvaccinated. All models used generalized estimating equations (clustered on US Census region of pharmacy) and adjusted for age (continuous), gender, race/ethnicity, prior SARS-CoV-2 infection, calendar week of SARS-CoV-2 test (categorical; 2-week intervals), recent contact with someone with confirmed or presumed to have COVID-19, US Census region of pharmacy, and store-specific percent positivity in the week prior to the SARS-CoV-2 testing date.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

[a]Two individuals with gender Other removed from the absolute model due to zero cell errors when stratified by prior infection and inability to compute estimates.

Table 4. Adjusted Relative VE and Corresponding 95% CIs for Symptomatic COVID-19, Stratified by Age Group and by Age Group and History of Prior SARS-CoV-2 Infection

Age, y	Overall VE (95% CI)	No Prior Infection VE (95% CI)	Prior Infection >3 mo Ago VE (95% CI)
5–11[a]	63.64 (45.42–75.79)	58.89 (33.87–74.45)[b]	75.74 (64.98–83.20)[b]
12–17	52.82 (40.58–62.53)	50.35 (36.14–61.40)	59.64 (40.84–72.46)
18–49	47.08 (43.52–50.41)	46.94 (42.18–51.35)	47.31 (45.59–49.90)
50–64	37.91 (34.77–40.90)	37.54 (33.56–41.28)	39.06 (38.90–42.07)
≥65	31.44 (27.74–34.95)	30.81 (27.10–34.32)	34.64 (17.81–48.01)

Relative vaccine effectiveness compares those who received 2–4 original wild-type doses plus a BNT162b2 BA.4/5 bivalent vaccine ≥14 days before testing for SARS-CoV-2 and those who received 2–4 original wild-type mRNA doses >2 months ago but not a BA.4/5 bivalent vaccine.

Models clustered on US Census region of pharmacy and adjusted for age (continuous), gender, race/ethnicity, recent contact with someone with confirmed or presumed to have COVID-19, prior SARS-CoV-2 infection, time since last wild-type dose, calendar week of SARS-CoV-2 test (categorical; 2-week intervals), US Census region of pharmacy, area deprivation index for pharmacy location (continuous), store-specific percent positivity in the week prior to the SARS-CoV-2 testing date, and local county-level case incidence per 100 000 persons during the week prior to the SARS-CoV-2 testing date.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

[a]Two individuals with gender Other removed from the stratified estimates due to zero cell counts and failure of model to run as a result.

[b]On the multiplicative scale, effect modification by prior infection was statistically significant for the 5–11-year-old age group.

more than once during the study period did not meaningfully impact results (Supplementary Tables 6–8). Those excluded due to testing related to future travel or employment screening were less likely to have received the BA.4/5 bivalent vaccine and more likely to test positive (P value < .0001). Individuals excluded because they tested more than once during the study period were more likely to have received the BA.4/5 bivalent vaccine and less likely to test positive (P value < .0001).

DISCUSSION

In this test-negative case-control study among immunocompetent individuals aged ≥5 years testing for SARS-CoV-2 at Walgreens retail pharmacies, the Pfizer-BioNTech BNT162b2 BA.4/5 bivalent vaccine improved protection against symptomatic COVID-19 during a period when BA.4/5 and XBB-related Omicron sublineages were circulating. Consistent with other reports highlighting the benefit of hybrid immunity in both clinical studies of neutralization activity [25–27] and real-world studies [7, 28–31], effectiveness was highest among those with prior infection, with absolute VE point estimates ranging from 55% to 79% against symptomatic COVID-19 across all age groups. Relative VE estimates, which estimated improvement in protection provided by a BNT162b2 bivalent vaccine among individuals who previously received 2–4 original wild-type doses, showed a statistically significant additional benefit of receiving a bivalent vaccine regardless of age, history of prior infection, or time since receipt of the most recent original wild-type dose. Point estimates of relative VE ranged from 59% to 76% for 5–11 year olds (depending on history of prior infection), and from 31% to 53% among those aged ≥12 years. Median time since receiving a bivalent vaccine was only 1–2 months, thus our results should be interpreted as early evidence of increased protection following a bivalent vaccine. Longer-term studies of durability are needed.

Our findings have important public health implications, particularly for informing the debate about whether mRNA COVID-19 vaccines are currently only useful for preventing severe COVID-19. Recent estimates suggest that >90% of US residents have been previously infected with SARS-CoV-2 [19]. Thus, our findings showing early effectiveness of a BNT162b2 BA.4/5 bivalent vaccine against symptomatic COVID-19, especially among those who self-reported prior infection, suggest

that there are wider public health benefits of COVID-19 vaccination beyond preventing severe illness alone. Even if durability against these milder end points is relatively short, a well-timed booster campaign that utilizes a well-matched vaccine (eg, like the 2023/2024 vaccination campaign) will likely (1) reduce SARS-CoV-2 infections, which may in turn lessen transmission; and (2) help prevent human and economic burden stemming from symptomatic illness in a broader population beyond just those at highest risk of severe disease.

It was unclear why VE was higher among 5–11 year olds compared to other age groups, especially compared to the elderly. Higher VEs among this age group may reflect more recent receipt of a bivalent vaccine (median time since a bivalent vaccine was 1 month) due to more recent approval for this age group, compared to those aged ≥12 years where median time since a bivalent vaccine was 2 months. It is also possible that lower VE among older age groups reflects increased susceptibility, reduced immune responses, or both—particularly for individuals aged ≥50 years [32, 33]. Finally, other studies have shown that VE against infection may be higher when the doses are administered with more months between them, which may also explain the lower VE observed in older age groups who have received additional doses with shorter intervals between doses [34, 35].

There is limited data describing the effectiveness of BA.4/5 bivalent vaccines against symptomatic SARS-CoV-2 infection, especially during periods of XBB circulation. Only one publication described effectiveness of a bivalent vaccine in 5–11 years olds [36]. Our relative VE estimates in this age group were consistent with this report [36], but were conducted in a broader nationwide population. Importantly, we also provided absolute VE estimates for comparability and stratified VE by history of prior infection. For individuals aged ≥12 years, only 2 published studies have reported effectiveness against infection or mild illness [13, 16]. One study conducted among North Carolina residents aged ≥12 years reported relative VE against any infection ranging from 4% to 29% [13], and point estimates that were lower than ours for this age group (31% to 53%). However, our study was conducted in a broader population and in the retail pharmacy setting, which may partially explain differences in study findings. The second published study was conducted by CDC and reported absolute and relative VE against symptomatic COVID-19 in adults aged ≥18 years [16]. Our VE estimates in this age group were consistent with this CDC report [16] but are unique in that we stratified by self-reported prior SARS-CoV-2 infection.

Despite evidence of their effectiveness, only 19% of US adults and 4% of 5–17 year olds had received a BA.4/5 bivalent vaccine by 31 January 2023 [37]. Slow uptake is likely due to a combination of factors including low awareness and confusion about eligibility for the bivalent vaccine; pandemic and vaccine fatigue; a lower perceived risk of severe outcomes associated with Omicron and high levels of preexisting immunity from prior infection, vaccination, or both; and persistent misinformation regarding the safety or performance of COVID-19 vaccines [38, 39]. Continued efforts are needed to improve uptake of current and future COVID-19 vaccines (eg, XBB-adapted vaccines for the 2023–2024 viral respiratory season) through targeted and tailored campaigns focused on simplified communication to help clarify risks and vaccine eligibility [39, 40].

Like all observational studies, our results may be biased by unmeasured confounding. Additionally, because prior infection, symptoms, comorbidities, and vaccination history were self-reported, all were subject to misclassification and recall bias. For example, individuals may not know if they were previously infected (e.g., asymptomatic, paucisymptomatic, or not tested). Although we stratified by self-reported prior infection, we were unable to account for time since infection or the variant causing prior infection, both of which may impact VE estimates [17, 18]. Moreover, if unvaccinated individuals were more likely to have unreported prior infections, especially during the first Omicron wave, a phenomenon known as "differential depletion of susceptibles" [41–43] could occur and bias absolute VE estimates against subsequent Omicron sublineages downward. To help mitigate this, we also presented relative VE estimates, which confirmed a benefit of bivalent vaccines. Another limitation was that although we had information about whether the bivalent vaccine was given ≥14 days before completing the SARS-CoV-2 test questionnaire, for COVID-19 vaccine doses given >14 days prior, only month and year of administration were recorded. This could lead to imprecision in defining time since last original wild-type or bivalent dose and time between the last original wild-type and bivalent dose. As most bivalent doses were administered in the past 3 months, this was unlikely to largely influence our results. Additionally, given slow uptake of bivalent vaccines [17], our estimates reflect VE among early adopters, who may differ from those who receive bivalent vaccines later with respect to underlying risk factors, health care-seeking behaviors, or other characteristics. Further, individuals testing at pharmacies may differ from those testing at other locations like clinics or at home. However, pharmacy-based testing captures a broad and diverse population of mild COVID-19 cases. Finally, median time since receiving a bivalent vaccine was only 1–2 months in our study. Thus, long-term durability remains unknown.

CONCLUSION

Our findings suggest that the BNT162b2 BA.4/5 bivalent vaccine provided early additional protection against Omicron-related symptomatic COVID-19 among immunocompetent individuals aged ≥5 years when BA.4/5 and XBB-related sublineages were circulating. In general, effectiveness was highest among those self-reporting prior SARS-CoV-2 infection. Longer-term studies of vaccine durability are needed.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/).

Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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