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Estimated Effectiveness of Coadministration of the BNT162b2 BA.4/5 COVID-19 Vaccine With Influenza Vaccine

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Abstract

IMPORTANCE No data comparing the estimated effectiveness of coadministering COVID-19 vaccines with seasonal influenza vaccine (SIV) in the community setting exist.

OBJECTIVE To examine the comparative effectiveness associated with coadministering the BNT162b2 BA.4/5 bivalent mRNA COVID-19 vaccine (BNT162b2-biv [Pfizer BioNTech]) and SIV vs giving each vaccine alone.

DESIGN, SETTING, AND PARTICIPANTS A retrospective comparative effectiveness study evaluated US adults aged 18 years or older enrolled in commercial health insurance or Medicare Advantage plans and vaccinated with BNT162b2-biv only, SIV only, or both on the same day between August 31, 2022, and January 30, 2023. Individuals with monovalent or another brand of mRNA bivalent COVID-19 vaccine were excluded.

EXPOSURE Same-day coadministration of BNT162b2-biv and SIV; receipt of BNT162b2-biv only (for COVID-19–related outcomes) or SIV only (for influenza-related outcomes) were the comparator groups. For adults aged 65 years or older, only enhanced SIVs were included.

MAIN OUTCOMES AND MEASURES COVID-19–related and influenza-related hospitalization, emergency department (ED) or urgent care (UC) encounters, and outpatient visits.

RESULTS Overall, 3 442 996 individuals (57.0% female; mean [SD] age, 65 [16.7] years) were included. A total of 627 735 individuals had BNT162b2-biv and SIV vaccine coadministered, 369 423 had BNT162b2-biv alone, and 2 445 838 had SIV alone. Among those aged 65 years or older (n = 2 210 493; mean [SD] age, 75 [6.7] years; 57.9% female), the coadministration group had a similar incidence of COVID-19–related hospitalization (adjusted hazard ratio [AHR], 1.04; 95% CI, 0.87-1.24) and slightly higher incidence of emergency department or urgent care encounters (AHR, 1.12; 95% CI, 1.02-1.23) and outpatient visits (AHR, 1.06; 95% CI, 1.01-1.11) compared with the BNT162b2-biv–only group. Among individuals aged 18 to 64 years (n = 1 232 503; mean [SD] age, 47 [13.1] years; 55.4% female), the incidence of COVID-19–related outcomes was slightly higher among those who received both vaccines vs BNT162b2-biv alone (AHR point estimate range, 1.14-1.57); however, fewer events overall in this age group resulted in wider CIs. Overall, compared with those who received SIV alone, the coadministration group had a slightly lower incidence of most influenza-related end points (AHR point estimates 0.83-0.93 for those aged ≥65 years vs 0.76-1.08 for those aged 18-64 years). Negative control outcomes suggested residual bias and calibration of COVID-19–related and influenza-related outcomes with negative controls moved all estimates closer to the null, with most CIs crossing 1.00.

(continued)

Key Points

Question Are the BNT162b2 BA.4/5 bivalent mRNA COVID-19 vaccine (BNT162b2-biv [Pfizer BioNTech]) and seasonal influenza vaccine (SIV) associated with comparable effectiveness when the vaccines are coadministered vs when given separately?

Findings This comparative effectiveness study included a cohort of 3 442 996 commercially insured US adults aged 18 years or older. After calibrating with negative control outcomes, coadministration of BNT162b2-biv and SIV were associated with similar effectiveness against COVID-19–related and influenza-related outcomes in the community setting compared with giving each vaccine alone.

Meaning The data from this study suggest the outcomes observed following coadministration of SIV with COVID-19 boosters may be similar to those seen with separate administration; including this information during autumn or winter vaccination campaigns may improve uptake for both of these underused and potentially life-saving public health interventions.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this study, coadministration of BNT162b2-biv and SIV was associated with generally similar effectiveness in the community setting against COVID-19–related and SIV-related outcomes compared with giving each vaccine alone and may help improve uptake of both vaccines.

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Introduction

Although SARS-CoV-2 continues to circulate year-round, in the Northern Hemisphere it has generally followed a seasonal pattern similar to other viral respiratory infections, such as influenza, where activity peaks during winter.[1] Based on this trend and accumulating evidence showing that the effectiveness of COVID-19 vaccines wanes over time and as new variants emerge[2,3] and better-matched Omicron-adapted vaccines improve protection,[4-11] the US Food and Drug Administration recently approved a monovalent COVID-19 vaccine targeting Omicron XBB sublineages to be used as a booster before the 2023-2024 winter respiratory infection season.[12] While some high-risk individuals may receive boosters more frequently,[13] it is anticipated that COVID-19 vaccines will likely be administered annually alongside seasonal influenza vaccines (SIVs) each autumn or winter for the foreseeable future.[13]

During the 2020-2021 and 2021-2022 influenza seasons, the US Centers for Disease Control and Prevention (CDC) recommended COVID-19 and influenza vaccines be administered 14 or more days apart, given that no data describing the safety, immunogenicity, or efficacy of coadministering these vaccines were available at the time.[14] Subsequently, data from clinical trials[15-18] and community settings[19-21] emerged showing the 2 vaccines could be safely coadministered. Based on these emerging safety data and evidence that coadministration improves uptake,[22-26] the CDC revised COVID-19 vaccine recommendations to allow coadministration with SIVs for the 2022-2023 season.[27]

In addition to safety data, several clinical studies have shown comparable immune responses when COVID-19 vaccines are coadministered with SIV compared with administering the vaccines separately.[15-17] To our knowledge, however, there are no data evaluating the effectiveness of coadministering these 2 vaccines in the community setting. Thus, we compared the effectiveness associated with coadministering the BNT162b2 BA.4/5 bivalent mRNA COVID-19 vaccine (BNT162b2-biv [Pfizer-BioNTech]) with SIV vs the effectiveness associated with giving the 2 vaccines separately among US adults aged 18 years or older enrolled in large nationwide health plans.

Methods

This study used deidentified data and thus was exempted from institutional review board review by the Sterling Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies. This study used deidentified data and thus was exempted from institutional review board review by the Sterling Institutional Review Board and did not require informed consent.

Study Design and Participants

We conducted a retrospective comparative effectiveness study using insurance claims from the Optum deidentified Clinformatics Data Mart Database, which includes geographically diverse members of US commercial and Medicare Advantage health plans. The database contains patient-level information for all medical (inpatient and outpatient diagnoses or procedures) and pharmacy services. We included adults aged 18 years or older enrolled in a participating insurance plan as of

August 31, 2022 (date bivalent COVID-19 boosters were authorized[28]), who received BNT162b2-biv, SIV, or both between August 31, 2022, and January 30, 2023, and had 365 days of continuous enrollment before their study index date. The index date was defined as the earliest date of receipt of either vaccine. Individuals who (1) died, disenrolled, had a COVID-19 or influenza diagnosis, or received a second dose of either vaccine 14 days or less after their first dose; (2) had a COVID-19 diagnosis 90 days or less prior to the index date; (3) received SIV between August 1 and August 30, 2022; or (4) received any type of COVID-19 vaccine other than BNT162b2-biv on the index date were excluded (eFigure 1 in Supplement 1).

Exposure

Vaccination status was determined using *Current Procedural Terminology* (*CPT*), Healthcare Common Procedure Coding System (HCPCS), *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Procedure Coding System* (*ICD-10-PCS*), and National Drug Codes (NDC) from any care setting (eTable 1 in Supplement 1). The primary exposure was same-day coadministration of BNT162b2-biv and SIV. Receipt of BNT162b2-biv alone on the index date (for COVID-19–related outcomes) and, separately, SIV alone on the index date (for influenza-related outcomes) were the 2 comparator groups. For adults aged 65 years or older, only enhanced SIVs (ie, high-dose, adjuvanted, or recombinant) were included as they are preferentially recommended by the CDC[29] and account for most SIVs given in this age group.

Outcomes

We compared the rate of COVID-19–related and influenza-related outcomes across vaccine exposure groups. Two types of relative risks (RRs) corresponding to outcome type were estimated: the RR of COVID-19–related outcomes comparing the risk among those who received coadministered vaccines with those who received only BNT162b2-biv (hereinafter referred to as RR-COVID), and the RR of influenza-related outcomes comparing the risk of the coadministration group with those who received only SIV (hereinafter referred to as RR-flu). Three outcomes were assessed: hospitalization, emergency department (ED) or urgent care (UC) encounters, and outpatient visits. End points were identified using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification* (*ICD-10-CM*) diagnosis code U07.1 for COVID-19 and J09.X-J11.X for influenza. In primary analyses, *ICD-10-CM* codes were identified in any diagnosis position. In exploratory analyses, hospitalizations with disease-specific codes in the primary position were used to limit incidental admissions.

We evaluated 2 negative control outcomes (NCOs) to detect residual bias between vaccination groups: urinary tract infection and unintentional injury. These outcomes were prespecified a priori because they (1) were unlikely to be related to vaccination status, (2) likely exhibited similar patterns of bias caused by differences in health care–seeking behaviors, (3) have been used in other effectiveness studies, and (4) occurred frequently enough in both age groups.[30,31] Following peer review, 2 additional end points (ingrown toenail and atopic dermatitis) were also assessed as NCOs in post hoc analyses.

Follow-up started 15 days after vaccination[32,33] and continued until one of the following occurred: (1) outcome of interest, (2) disenrollment, (3) death, (4) receipt of a second COVID-19 or influenza vaccine, (5) receipt of a COVID-19 vaccine if in the SIV-only cohort, (6) receipt of an SIV if in the COVID-19 vaccine–only cohort, or (7) end of study follow-up (February 14, 2023). Experiencing one disease-specific outcome was not a censoring event for the other disease (ie, a COVID-19–related diagnosis was not a censoring event for an influenza-related outcome and vice versa).

Covariates

Covariates were predefined and measured in the 365 days before the index date, unless otherwise specified. Demographic information included age (at index date and continuous), sex (male, female, or unknown), geographic region of residence based on US census categories (Northeast, Midwest,

South, West, other, or unknown), and month of index date. Race and ethnicity data were not available in the data source. Clinical characteristics were identified using *ICD-10-CM* diagnosis or procedure, HCPCS, and *CPT-4* codes, and included (yes or no): pneumonia or respiratory failure, chronic lung disease, asthma, heart disease, diabetes, kidney disorders, immunocompromising conditions, CDC-defined high-risk conditions for severe COVID-19 (yes or no),[34] Charlson Comorbidity Index score[35] (0, 1, or ≥2), or a prior COVID-19 (yes or no) or influenza (yes or no) diagnosis. Other dichotomous (yes or no) health status measures included receiving skilled nursing care, a nursing home stay, or a wellness visit, or having decreased functional status. Earlier influenza vaccination was assessed in the prior season (yes or no) and during the previous year for COVID-19 (yes or no), pneumococcal (yes or no), and herpes zoster (yes or no) vaccines based on NDC and *CPT-4* vaccine codes. To assess health-seeking behavior, we also included number of outpatient visits (0, 1, 2, or ≥3) and inpatient admissions in the previous 180 days (0, 1, or ≥2), and number of documented SARS-CoV-2 tests (0, 1, or ≥2), influenza tests (yes or no), telehealth visits (0, 1, or ≥2), and lipid or glycated hemoglobin laboratory tests ordered (0, 1, or ≥2) in the previous year.

Statistical Analysis

Descriptive statistics were calculated for baseline characteristics by vaccination group. Two separate logistic regression models (ie, comparing individuals with coadministered vaccines with those with BNT162b2-biv only and SIV only) were fit to create propensity scores and calculate stabilized inverse probability of treatment weights (IPTWs). Covariate balance before and after weighting was assessed using standardized mean differences. Due to small sample size and positivity problems with constructing weights, individuals whose geographic region was unknown or other were removed from RR-flu analyses. All variables listed in the previous paragraph were included in propensity scores. Variables with residual imbalance were included in final models for further adjustment. To measure RR-COVID and RR-flu, adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs for each outcome. Death was rare (<1% for all groups); thus, competing risk models were not used. Additionally, we used NCOs to calibrate the main results to account for unmeasured residual confounding.[36] We conducted a sensitivity analysis by censoring for COVID-19 treatment (nirmatrelvir with ritonavir combination) or influenza treatment (oseltamivir phosphate, zanamivir, peramivir, or baloxavir marboxil) during follow-up. Analyses were stratified by age group (18-64 and ≥65 years). Formal testing for statistical significance was not conducted. All analyses were performed using SAS, version 9.4 (SAS Institute Inc) and R, version 4.1.2 (R Foundation for Statistical Computing).

Results

There were 16 966 484 individuals enrolled in the database as of August 31, 2022; of these, 3 442 996 (20.3%) met the criteria for analysis (57.0% female, 43.0% male; mean [SD] age, 65 [16.7] years). Overall, 627 735 individuals (18.2%) received BNT162b2-biv coadministered with SIV, 369 423 (10.7%) received BNT162b2-biv only, and 2 445 838 (71.0%) received SIV only (**Figure 1**).

Among individuals aged 65 years or older (n = 2 210 493; 57.9% female; 42.1% male; mean [SD] age, 75 [6.7] years), 382 835 (17.3%; mean [SD] age, 75 [6.5] years; 54.4% female) received both vaccines, 225 680 (10.2%; age, 75 [6.7] years; 58.6% female) had BNT162b2-biv only, and 1 601 978 (72.5%; age, 76 [6.7] years; 58.7% female) had SIV only. There were slightly more women than men in all exposure groups and approximately one-third of individuals in this age group had a Charlson Comorbidity Index score greater than or equal to 2 (**Table 1**; eTable 2 in Supplement 1). The BNT162b2-biv (either with SIV or alone) was most often administered in the retail pharmacy setting (>80%); however, for those who received SIV only, administration was more evenly split between office (39%) and pharmacy (54%) settings. Fluzone high-dose quadrivalent was the most commonly administered SIV among those aged 65 years or older (eTable 3 in Supplement 1). Compared with those who received coadministered vaccines, individuals who received SIV only more often had

comorbidities, prior health care use, and a lower proportion who received COVID-19 vaccination in the previous year. After applying IPTWs, all covariates were well balanced (eTable 2 and eTable 4 in Supplement 1). Median days of follow-up were 109 (IQR, 89-125) for the coadministration group, 51 (IQR, 17-99) for the BNT162b2-biv–only group, and 90 (IQR, 49-112) for the SIV-only group.

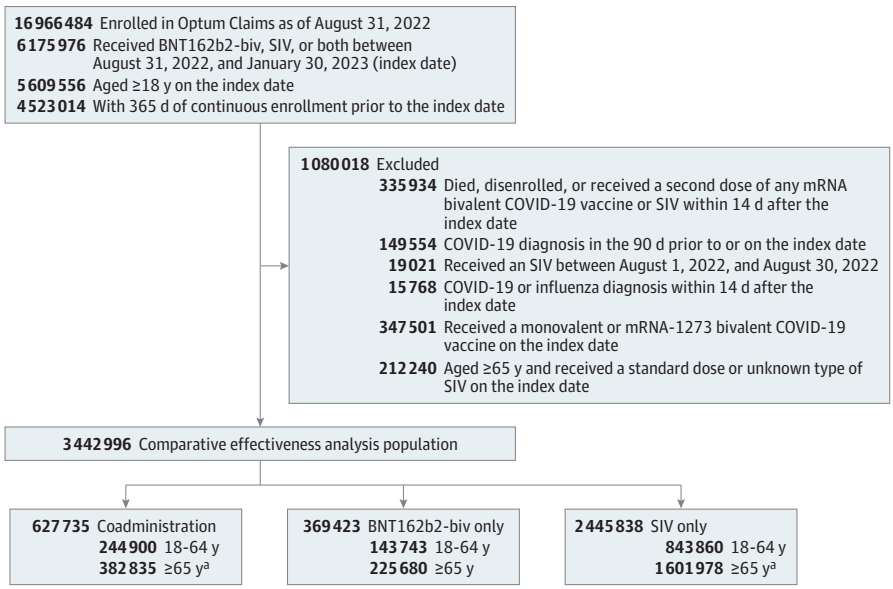
Among individuals aged 18 to 64 years (n = 1 232 503), patterns were similar to those observed in individuals aged 65 years or older (**Table 2**; eTable 5 in Supplement 1). Egg- and cell-based standard-dose vaccines were the most common types of SIV administered in this age group (eTable 3 in Supplement 1). After applying IPTWs, all covariates were balanced except for region and month of index date, which were included in doubly robust RR-flu models (eTable 5 in Supplement 1). Median days of follow-up were 96 (IQR, 69-117) for the coadministration group, 68 (IQR, 29-104) for the BNT162b2-biv–only group, and 84 (IQR, 51-109) for the SIV-only group.

RR-COVID

Weighted cumulative incidence of all COVID-19–specific end points by 150 days was 2% or less (eTable 6 and eTable 8 in Supplement 1). Among those aged 65 years or older, the coadministration group had a similar incidence of COVID-19–related hospitalization (adjusted HR [AHR], 1.04; 95% CI, 0.87-1.24) and slightly higher incidence of ED or UC encounters (AHR, 1.12; 95% CI, 1.02-1.23) and outpatient visits (AHR, 1.06; 95% CI, 1.01-1.11) (**Figure 2**A; eTable 6 in Supplement 1). Negative control outcomes suggested minimal residual bias for urinary tract infection, but some residual bias for unintentional injury that could have slightly inflated the risk of COVID-19–related outcomes for the coadministration group (eFigure 2 in Supplement 1). Using unintentional injury to calibrate estimates resulted in COVID-19–related end points moving closer to the null (AHRs, 0.92-1.00) (Figure 2A). Similar patterns were also observed after calibrating for the 2 post hoc NCOs (eTable 10 and eTable 11 in Supplement 1).

Among individuals aged 18 to 64 years (n = 1 232 503; mean [SD] age, 47 [13.1] years; 55.4% female), the incidence of COVID-19–related outcomes was slightly higher among those with coadministered vaccines compared with BNT162b2-biv vaccine only (eTable 8 in Supplement 1). However, fewer events in this age group resulted in wider CIs, especially for hospitalization (AHR, 1.55; 95% CI, 0.88-2.73); (Figure 2B). After calibration with NCOs, these end points moved closer to the null and most CIs crossed 1.00.

Figure 1. Study Participant Flowchart



The first box of the flow represents the first 4 inclusion criteria requirements that individuals had to fulfill to be included in the study. The numbers next to each row represent the number of individuals who met that specific inclusion criteria requirement. The second box of the flow summarizes the exclusion criteria for the study. The first row represents an aggregate of the total individuals excluded, while each indented row below depicts the number of individuals that were excluded for each specific exclusion criteria. BNT162b2 indicates BNT162b2 BA.4/5 bivalent mRNA COVID-19 vaccine (Pfizer-BioNTech); SIV, seasonal influenza vaccine.

[a] Only includes adults ages 65 years and older who received an enhanced influenza vaccine.

Table 1. Baseline Characteristics for Individuals Aged 65 Years or Older

Variable	No. (%)		SMD		No. (%)		SMD	
	Coadministration	BNT162b2-biv only	Unweighted	Weighted	Coadministration	SIV only	Unweighted	Weighted
Total	382 835 (100)	225 680 (100)	NA	NA	382 626 (100)	1 600 981 (100)	NA	NA
Age, mean (SD), y	75 (6.5)	75 (6.6)	−0.0054	−0.0006	75 (6.5)	76 (6.7)	−0.1075	0.0028
Sex								
Female	208 166 (54.4)	132 345 (58.6)	0.1010	<0.0001	208 044 (54.4)	939 216 (58.7)	0.1010	<0.0001
Male	174 651 (45.6)	93 327 (41.4)			174 564 (45.6)	661 737 (41.3)		
Region								
Northeast	49 833 (13.0)	39 076 (17.3)	0.2575	<0.0001	49 833 (13.0)	236 566 (14.8)	0.3160	0.0669
Midwest	110 501 (28.9)	52 332 (23.2)			110 501 (28.9)	362 916 (22.7)		
South	107 817 (28.2)	77 345 (34.3)			107 817 (28.2)	655 784 (41.0)		
West	114 475 (29.9)	56 771 (25.2)			114 475 (29.9)	345 715 (21.6)		
Other or unknown	209 (0.1)	156 (0.1)			NA	NA		
Month of index date								
August or September	125 667 (32.8)	94 525 (41.9)	0.4476	<0.0001	125 607 (32.8)	439 115 (27.4)	0.2557	0.1023
October	178 131 (46.5)	70 228 (31.1)			178 056 (46.5)	741 486 (46.3)		
November	55 791 (14.6)	32 305 (14.3)			55 758 (14.6)	296 078 (18.5)		
December	19 589 (5.1)	19 328 (8.6)			19 551 (5.1)	106 744 (6.7)		
January	3657 (1.0)	9294 (4.1)			3654 (1.0)	17 558 (1.1)		
Vaccine administration location								
Pharmacy	314 797 (82.2)	190 382 (84.4)	0.1008	<0.0001	314 634 (82.2)	859 052 (53.7)	0.6498	0.0434
Office	48 720 (12.7)	22 263 (9.9)			48 692 (12.7)	621 664 (38.8)		
Other[a]	19 318 (5.0)	13 035 (5.8)			19 300 (5.0)	120 265 (7.5)		
Prior comorbidities or poor health status								
Pneumonia or respiratory failure	17 571 (4.6)	9728 (4.3)	0.0135	−0.0017	17 559 (4.6)	92 133 (5.8)	−0.0527	−0.0061
Asthma	26 172 (6.8)	15 115 (6.7)	0.0055	0.0004	26 160 (6.8)	115 028 (7.2)	−0.0136	−0.0034
Heart disease	115 783 (30.2)	66 263 (29.4)	0.0193	0.0004	115 719 (30.2)	545 125 (34.1)	−0.0816	−0.0172
Kidney disease	77 939 (20.4)	42 714 (18.9)	0.0360	−0.0006	77 901 (20.4)	366 247 (22.9)	−0.0612	−0.0091
Diabetes	104 262 (27.2)	57 788 (25.6)	0.0369	0.0005	104 198 (27.2)	498 563 (31.1)	−0.0861	−0.0100
Chronic lung disease	51 604 (13.5)	26 710 (11.8)	0.0495	−0.0018	51 580 (13.5)	248 224 (15.5)	−0.0575	−0.0117
Charlson Comorbidity Index score								
0	183 790 (48.0)	114 200 (50.6)	0.0600	<0.0001	183 693 (48.0)	701 149 (43.8)	0.0810	<0.0001
1	68 326 (17.9)	37 320 (16.5)			68 297 (17.9)	298 467 (18.6)		
≥2	130 719 (34.1)	74 160 (32.9)			130 636 (34.1)	601 365 (37.6)		
Decreased functional status	35 378 (9.2)	22 175 (9.8)	−0.0199	−0.0022	35 357 (9.2)	172 377 (10.8)	−0.0509	−0.0030
Prior COVID-19 diagnosis	23 745 (6.2)	15 402 (6.8)	−0.0252	−0.0004	23 731 (6.2)	123 659 (7.7)	−0.0598	−0.0072
Immunocompromised status	37 180 (9.7)	20 208 (9.0)	0.0260	−0.0011	37 163 (9.7)	163 716 (10.2)	−0.0171	−0.0041
High risk for severe COVID-19	342 265 (89.4)	196 075 (86.9)	0.0780	−0.0001	342 079 (89.4)	1 468 659 (91.7)	−0.0799	−0.0183
Vaccinations or healthy user wellness visits								
Prior influenza vaccine	167 069 (43.6)	84 340 (37.4)	0.1280	0.0011	166 989 (43.6)	660 434 (41.3)	0.0484	−0.0335
Prior COVID-19 vaccine in the last year	230 124 (60.1)	129 224 (57.3)	0.0579	−0.0040[b]	230 006 (60.1)	659 039 (41.2)	0.3860	0.0225
Prior shingles vaccine	33 813 (8.8)	17 827 (7.9)	0.0337	−0.0017	33 795 (8.8)	122 361 (7.6)	0.0433	0.0006
Wellness visit	237 861 (62.1)	136 938 (60.7)	0.0299	0.0011	237 745 (62.1)	967 244 (60.4)	0.0353	−0.0119
Health care use								
No. of outpatient visits								
0	25 120 (6.6)	17 409 (7.7)	0.0382	<0.0001	25 100 (6.6)	78 858 (4.9)	0.0967	0.0441
1	26 436 (6.9)	14 806 (6.6)			26 414 (6.9)	97 653 (6.1)		
2	32 442 (8.5)	17 954 (8.0)			32 421 (8.5)	121 604 (7.6)		
≥3	298 837 (78.1)	175 511 (77.8)			298 691 (78.1)	1 302 866 (81.4)		

(continued)

Table 1. Baseline Characteristics for Individuals Aged 65 Years or Older (continued)

Variable	No. (%)		SMD		No. (%)		SMD	
	Coadministration	BNT162b2-biv only	Unweighted	Weighted	Coadministration	SIV only	Unweighted	Weighted
No. of COVID-19 tests								
0	262 775 (68.6)	152 858 (67.7)	0.0598	<0.0001	262 640 (68.6)	1 084 555 (67.7)	0.0262	<0.0001
1	69 207 (18.1)	39 272 (17.4)			69 161 (18.1)	297 251 (18.6)		
≥2	50 853 (13.3)	33 550 (14.9)			50 825 (13.3)	219 175 (13.7)		
No. of telehealth visits								
0	293 743 (76.7)	171 214 (75.9)	0.0329	<0.0001	293 596 (76.7)	1 231 041 (76.9)	<0.0001	<0.0001
1	48 557 (12.7)	28 999 (12.9)			48 525 (12.7)	205 204 (12.8)		
≥2	40 535 (10.6)	25 467 (11.3)			40 505 (10.6)	164 736 (10.3)		
No. of lipid or HbA_{1c} tests								
0	91 499 (23.9)	59 012 (26.2)	0.0510	<0.0001	91 447 (23.9)	338 247 (21.1)	0.1258	0.0416
1	157 976 (41.3)	87 937 (39.0)			157 891 (41.3)	605 478 (37.8)		
≥2	133 360 (34.8)	78 731 (34.9)			133 288 (34.8)	657 256 (41.1)		

Abbreviations: BNT162b2-biv, BNT162b2 BA.4/5 bivalent mRNA COVID-19 vaccine; HbA_{1c}, glycated hemoglobin; NA, not applicable; SIV, seasonal influenza vaccine; SMD, standardized mean difference.

[a] Other vaccination locations include hospital, emergency department, urgent care, assisted living, retail health clinic, skilled nursing facility, hospice, federally qualified health center, treatment facility (substance use, psychiatric, or end stage kidney disease), mass immunization center, state/local public health clinic, or school.

[b] COVID-19 vaccine in the prior year was included as a 3-level variable (≤60 days before index, >60 days before index, no evidence in prior year) for the coadministration vs BNT162b2-biv–only propensity score model.

RR-Flu

Weighted cumulative incidence of all influenza-related end points by 150 days was less than 1% (eTable 7 and eTable 9 in Supplement 1). Among individuals aged 65 years or older, the coadministration group had a lower incidence of all influenza-related outcomes (AHR, 0.83; 95% CI, 0.72-0.95 for hospitalization; AHR, 0.93; 95% CI, 0.86-1.01 for ED or UC encounters; AHR, 0.86; 95% CI, 0.81-0.91 for outpatient visits) (**Figure 3**A; eTable 7 in Supplement 1). There was residual bias detected with both NCOs, with the coadministration group having lower risk compared with the SIV-only group (eFigure 2 in Supplement 1). When NCOs were used to calibrate RR-flu estimates, all influenza-related outcomes moved closer to the null (Figure 3A). Similar to older adults, for those aged 18 to 64 years, the coadministration group had a comparable or lower incidence of all influenza-related outcomes (eg, AHR, 0.92; 95% CI, 0.69-1.23 for hospitalization) (Figure 3B; eTable 9 in Supplement 1). After calibration with NCOs, RR-flu estimates moved closer to the null (Figure 3B) and most CIs crossed 1.00. Similar patterns were also observed after calibrating for the 2 post hoc NCOs (eTables 12 and 13 in Supplement 1).

Sensitivity Analyses

Results were similar for all outcomes and both age groups when patients were censored on receipt of COVID-19 or influenza treatment (eFigures 3 and 4 in Supplement 1). Additionally, results were similar for the analysis requiring a primary position diagnosis code for hospitalization, although CIs were wide (eTables 6-9 in Supplement 1).

Discussion

In this retrospective comparative effectiveness study conducted in the community setting, our results suggest that coadministration of BNT162b2-biv with SIV was associated with similar effectiveness compared with giving either vaccine alone for both age groups. Results that were unadjusted for NCOs showed that patients with coadministration had a slightly higher incidence of some COVID-19–related outcomes (incidence 4%-12% higher; AHRs, 1.04-1.12 for those aged ≥65 years; and incidence 14%-55% higher; AHRs, 1.14-1.57 for those aged 18-64 years) compared with those who received only BNT162b2-biv, but a slightly lower incidence of certain influenza-related

Table 2. Baseline Characteristics for Individuals Aged 18 to 64 Years

Variable	No. (%)		SMD		No. (%)		SMD	
	Coadministration	BNT162b2-biv only	Unweighted	Weighted	Coadministration	SIV only	Unweighted	Weighted
Total	244 900 (100)	143 743 (100)	NA	NA	244 820 (100)	843 412 (100)	NA	NA
Age, mean (SD)	46 (12.9)	47 (12.6)	−0.0632	0.0029	46 (12.9)	47 (13.2)	−0.0822	0.0125
Sex								
Female	127 108 (51.9)	78 029 (54.3)	0.0401	<0.0001	127 066 (51.9)	477 067 (56.6)	0.1005	0.0201
Male	117 692 (48.1)	65 655 (45.7)			117 654 (48.1)	366 067 (43.4)		
Region								
Northeast	32 070 (13.1)	21 634 (15.1)	0.1635	<0.0001	32 070 (13.1)	101 471 (12.0)	0.2648	0.1132
Midwest	78 942 (32.2)	42 035 (29.2)			78 942 (32.2)	238 278 (28.3)		
South	74 425 (30.4)	44 485 (31.0)			74 425 (30.4)	352 666 (41.8)		
West	59 383 (24.3)	35 524 (24.7)			59 383 (24.3)	150 997 (17.9)		
Other or unknown	80 (0.0)	65 (0.1)			NA	NA		
Month of index date								
August or September	57 509 (23.5)	45 941 (32.0)	0.2968	<0.0001	57 499 (23.5)	168 495 (20.0)	0.0987	0.1348
October	96 557 (39.4)	42 268 (29.4)			96 522 (39.4)	342 659 (40.6)		
November	56 252 (23.0)	27 026 (18.8)			56 230 (23.0)	211 944 (25.1)		
December	27 553 (11.3)	18 896 (13.2)			27 543 (11.3)	94 399 (11.2)		
January	7029 (2.9)	9612 (6.7)			7026 (2.9)	25 915 (3.1)		
Vaccine administration location								
Pharmacy	201 271 (82.2)	118 195 (82.2)	<0.0001	<0.0001	201 205 (82.2)	383 332 (45.5)	0.8504	0.0491
Office	35 156 (14.4)	20 277 (14.1)			35 145 (14.4)	415 506 (49.3)		
Other[a]	8473 (3.5)	5271 (3.7)			8470 (3.5)	44 574 (5.3)		
Prior comorbidities or poor health status								
Pneumonia or respiratory failure	3490 (1.4)	1833 (1.3)	0.0130	−0.0031	3489 (1.4)	20 831 (2.5)	−0.0757	0.0004
Asthma	16 690 (6.8)	8939 (6.2)	0.0242	−0.0034	16 686 (6.8)	65 930 (7.8)	−0.0385	−0.0001
Heart disease	15 616 (6.4)	8839 (6.2)	0.0094	−0.0020	15 607 (6.4)	80 296 (9.5)	−0.1165	−0.0044
Kidney disease	10 205 (4.2)	5750 (4.0)	0.0084	−0.0022	10 201 (4.2)	52 961 (6.3)	−0.0951	−0.0004
Diabetes	25 616 (10.5)	14 042 (9.8)	0.0229	−0.0021	25 605 (10.5)	128 999 (15.3)	−0.1448	0.0001
Chronic lung disease	9030 (3.7)	4299 (3.0)	0.0388	−0.0031	9027 (3.7)	50 959 (6.0)	−0.1096	−0.0006
Charlson Comorbidity Index score								
0	194 627 (79.5)	115 976 (80.7)	0.0501	<0.0001	194 563 (79.5)	620 888 (73.6)	0.1190	<0.0001
1	24 378 (10.0)	13 165 (9.2)			24 372 (10.0)	101 026 (12.0)		
≥2	25 895 (10.6)	14 602 (10.2)			25 885 (10.6)	121 498 (14.4)		
Decreased functional status	4791 (2.0)	2541 (1.8)	0.0139	−0.0041	4789 (2.0)	26 791 (3.2)	−0.0772	0.0035
Prior COVID-19 diagnosis	23 214 (9.5)	13 033 (9.1)	0.0142	−0.0013	23 207 (9.5)	89 963 (10.7)	−0.0395	−0.0075
Immunocompromised status	14 882 (6.1)	8338 (5.8)	0.0117	−0.0041	14 879 (6.1)	61 585 (7.3)	−0.049	−0.0011
High risk for severe COVID-19	145 102 (59.3)	80 536 (56.0)	0.0652	−0.0041	145 059 (59.3)	556 369 (66.0)	−0.1391	−0.016
Vaccinations or healthy user wellness visits								
Prior influenza vaccine	100 681 (41.1)	37 516 (26.1)	0.3219	0.0066	100 662 (41.1)	290 406 (34.4)	0.1382	−0.0340
Prior COVID-19 vaccine in the last year	168 618 (68.9)	92 622 (64.4)	0.0938	0.0047[b]	168 578 (68.9)	436 440 (51.8)	0.3552	0.0268
Prior shingles vaccine	18 717 (7.6)	10 574 (7.4)	0.0109	−0.0024	18 710 (7.6)	59 127 (7.0)	0.0243	0.0140
Wellness visit	128 627 (52.5)	76 777 (53.4)	−0.0178	−0.0015	128 591 (52.5)	452 509 (53.7)	−0.0226	−0.0158
Health care use								
No. of outpatient visits								
0	44 230 (18.1)	27 484 (19.1)	0.0268	<0.0001	44 207 (18.1)	120 717 (14.3)	0.1228	0.0301
1	34 180 (14.0)	19 957 (13.9)			34 173 (14.0)	109 693 (13.0)		
2	29 223 (11.9)	17 206 (12.0)			29 215 (11.9)	98 415 (11.7)		
≥3	137 267 (56.1)	79 096 (55.0)			137 225 (56.1)	514 587 (61.0)		

(continued)

Table 2. Baseline Characteristics for Individuals Aged 18 to 64 Years (continued)

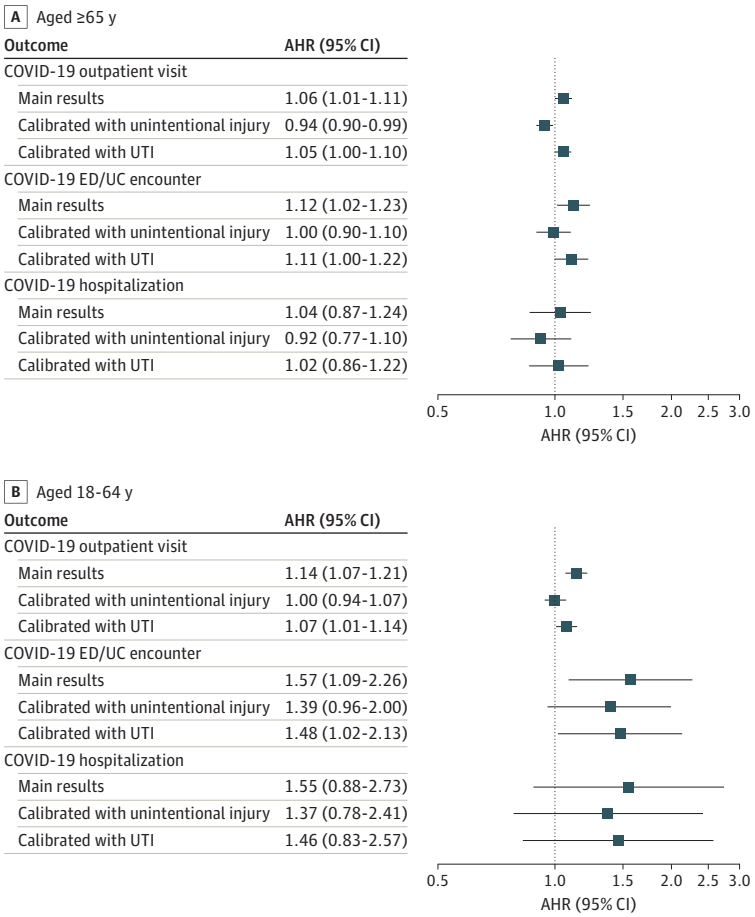
Variable	No. (%)		SMD		No. (%)		SMD	
	Coadministration	BNT162b2-biv only	Unweighted	Weighted	Coadministration	SIV only	Unweighted	Weighted
No. of COVID tests								
0	136 800 (55.9)	80 511 (56.0)			136 754 (55.9)	484 056 (57.4)		
1	52 738 (21.5)	29 367 (20.4)	0.0604	<0.0001	52 722 (21.5)	184 898 (21.9)	0.0253	<0.0001
≥2	55 362 (22.6)	33 865 (23.6)			55 344 (22.6)	174 458 (20.7)		
No. of telehealth visits								
0	166 509 (68.0)	101 796 (70.8)			166 451 (68.0)	597 104 (70.8)		
1	33 620 (13.7)	19 162 (13.3)	0.0663	<0.0001	33 612 (13.7)	114 980 (13.6)	0.0822	<0.0001
≥2	44 771 (18.3)	22 785 (15.9)			44 757 (18.3)	131 328 (15.6)		
No. of lipid or HbA_{1c} tests								
0	120 430 (49.2)	70 594 (49.1)			120 390 (49.2)	369 633 (43.8)		
1	88 144 (36.0)	52 038 (36.2)	<0.0001	<0.0001	88 117 (36.0)	297 257 (35.2)	0.1607	0.0271
≥2	36 326 (14.8)	21 111 (14.7)			36 313 (14.8)	176 522 (20.9)		

Abbreviations: BNT162b2-biv, BNT162b2 BA.4/5 bivalent mRNA COVID-19 vaccine; HbA_{1c}, glycated hemoglobin; NA, not applicable; SIV, seasonal influenza vaccine; SMD, standardized mean difference.

[a] Other vaccination locations include hospital, emergency department, urgent care, assisted living, retail health clinic, skilled nursing facility, hospice, federally qualified health center, treatment facility (substance use, psychiatric, or end stage kidney disease), mass immunization center, state/local public health clinic, or school.

[b] COVID-19 vaccine in the prior year was included as a 3-level variable (≤60 days before index, >60 days before index, no evidence in prior year) for the coadministration vs BNT162b2-biv–only propensity score model.

Figure 2. Adjusted Hazard Ratios (AHRs) for COVID-19–Specific Outcomes



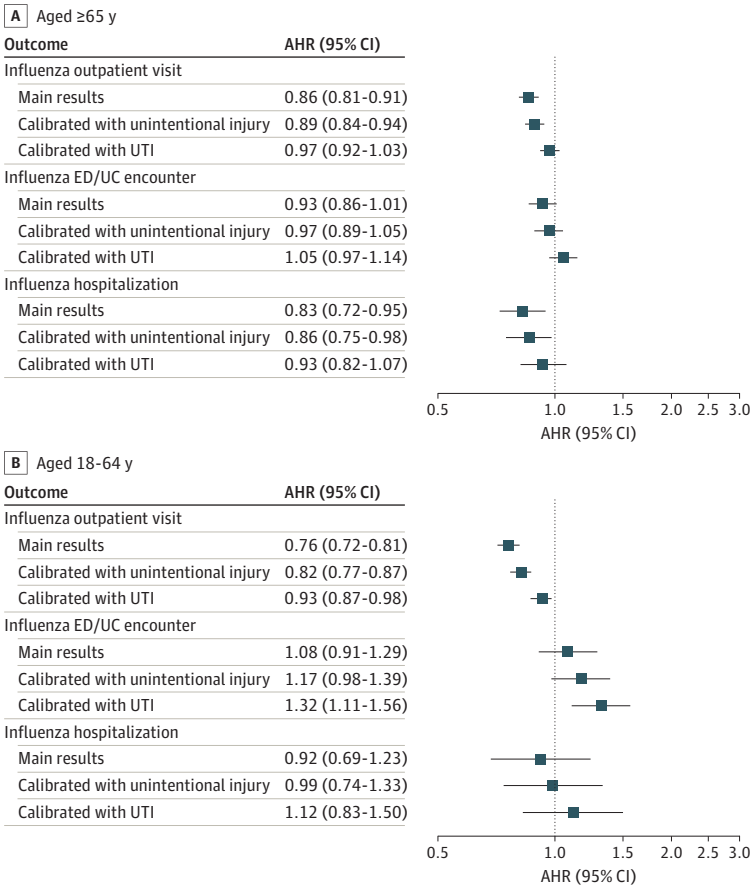
ED/UC indicates emergency department or urgent care; UTI, urinary tract infection.

end points (incidence 7%-17% lower; AHRs, 0.83-0.93 for those aged ≥65 years and incidence 24% lower to 8% higher; AHRs, 0.76-1.08 for those aged 18-64 years) compared with those who received SIV alone. However, NCOs (urinary tract infection, unintentional injury) suggested that residual bias between vaccine exposure groups most likely explained these small differences in risk of COVID-19–related and influenza-related outcomes. Accordingly, calibration of COVID-19–related and influenza-related outcomes with NCOs[36] consistently moved all AHR estimates closer to the null and nearly all CIs crossed 1.00, suggesting no meaningful differences in effectiveness for the coadministration group.

We believe the findings from our study are novel and have important public health implications for future autumn or winter vaccination campaigns. While the CDC recommended coadministration of COVID-19 vaccine and SIV in the 2022-2023 season,[27] this was based primarily on safety data from clinical trial and community settings that suggested similar or only marginally higher rates of reactogenicity with coadministration.[15-17,19,20] However, to our knowledge, no data describing the impact of coadministration of COVID-19 vaccines and SIV were available before our study. Our findings, which describe coadministering these vaccines in a diverse population of more than 3 million US adults during the most recent 2022-2023 respiratory infection season, provide contemporary data from routine clinical practice, and may help reassure health care professionals that giving these vaccines together is not only safe, but likely to yield similar effectiveness against COVID-19– and influenza-related outcomes.

Our community setting vaccine effectiveness results are consistent with immunogenicity data from clinical trials,[15,16,18] which have shown that coadministration of COVID-19 and influenza vaccines does not lead to immune interference and, in some cases, may provide a stronger immune response

Figure 3. Adjusted Hazard Ratios (AHRs) for Influenza-Specific Outcomes



ED/UC indicates emergency department or urgent care; UTI, urinary tract infection.

to SIV. One study conducted in the UK, which evaluated humoral responses to SIV when coadministered with a second dose of wild-type BNT162b2 vaccine compared with placebo, showed SIV responses were similar or better when administered with COVID-19 vaccines.[15] A second study evaluated the immunogenicity of the NVX-CoV2373 COVID-19 vaccine when coadministered with SIV, and reported no change in SIV response, although there was a slight reduction in antibody response for NVX-CoV2372 vaccine.[16] A third trial compared coadministration of a third dose of mRNA-1273 vaccine with high-dose SIV and found similar levels of antibody response against all influenza strains and SARS-CoV-2. Similar findings were shown against all influenza strains when coadministration occurred after 3 BNT162b2 vaccine doses.[18] Given that there is no perfect immunologic correlate of protection for COVID-19 vaccines or for SIV, our community setting comparative effectiveness data provide important additional context to these prior immunologic studies.

Limitations

Our study has several limitations. First, COVID-19 and influenza vaccinations may have been underascertained, particularly for wild-type COVID-19 vaccine doses given early in the pandemic. However, we observed a similar proportion of adults who received any mRNA bivalent COVID-19 booster (22% through January 16, 2023) compared with the CDC national estimates in the same age group (20% through March 29, 2023)[37]; thus, BNT162b2-biv was likely ascertained with high validity. Admittedly, missing data for SIV may have occurred, especially for younger adults who received SIV through employer clinics—which likely would not be included in claims data. Therefore, it is possible that the BNT162b2-biv–only group may have included patients who received SIV. However, because we used an active comparator that did not rely on unvaccinated individuals as a reference group, misclassification of vaccination status was less likely to meaningfully impact our results. Second, our study population included employer-sponsored health plans and Medicare Advantage. Thus, results may not be generalizable to patients with different insurance (eg, Medicare fee-for-service, Medicaid) or the uninsured. Third, it is possible that unmeasured residual confounding remained. Although we used IPTWs to control for many sociodemographic and clinical characteristics, applied an active comparator design, and calibrated results with NCOs, there were notable differences between some exposure groups (eg, differences in health care–seeking behavior, such as location of vaccination) that could have led to additional confounding through mechanisms not shared by our NCOs. Fourth, we assessed overall effectiveness for all SIVs, rather than individual products. To ensure comparability, however, we restricted the analysis in adults aged 65 years or older to those who received enhanced SIV only. Among individuals aged 18 to 64 years, less than 10% received recombinant SIV, and this percentage was similar between the coadministration (10%) and SIV-only (8%) groups. Fifth, COVID-19 and influenza end points were identified using diagnosis codes rather than via laboratory confirmation; thus, some cases could be misclassified. Sixth, our results included only one influenza season when influenza A (H3N2) was predominant; however, the initial estimate of vaccine effectiveness against A strains was high (54%; 95% CI, 23%-73%).[38] Regarding COVID-19, BA.4/5-related sublineages predominated during our study; however, XBB-related strains were increasing by the end of the study period. It is possible that future coadministration effectiveness estimates may vary if either vaccine is not well matched against circulating strains. Thus, confirmatory studies during future seasons capturing additional COVID-19 and influenza strains are needed.

Conclusions

In this comparative effectiveness study, BNT162b2-biv coadministered with SIV were associated with generally similar effectiveness against both COVID-19– and influenza-related outcomes compared with giving the 2 vaccines separately. These results add to the growing body of research suggesting that coadministration of COVID-19 and influenza vaccines has a similar safety, immunogenicity, and

effectiveness profile in the community setting. These data support coadministration of SIV with COVID-19 boosters during future autumn or winter vaccination campaigns, which may improve uptake for both of these underutilized and potentially life-saving public health interventions.

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SUPPLEMENT 1.

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