ORIGINAL ARTICLE

Association of 2024–2025 Covid-19 Vaccine with Covid-19 Outcomes in U.S. Veterans

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ABSTRACT

BACKGROUND

Amid the declining clinical severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and diminishing public uptake of annual coronavirus disease 2019 (Covid-19) vaccines, contemporary evidence on vaccine effectiveness against clinically relevant outcomes is needed.

METHODS

We conducted an observational study that used the electronic health records of the Department of Veterans Affairs to evaluate the effectiveness of the 2024–2025 Covid-19 vaccine among veterans who received the Covid-19 and influenza vaccines on the same day (164,132 participants) and in an active-comparator group of veterans who received the influenza vaccine only (131,839 participants), between September 3 and December 31, 2024. Participants were followed for 180 days or until the occurrence of an outcome, whichever came first. We used inverse-probability–weighted models to estimate vaccine effectiveness (calculated as 1 minus the risk ratio) against Covid-19–associated emergency department visits, hospitalizations, and deaths at 6 months.

RESULTS

At 6 months of follow-up, the estimated vaccine effectiveness was 29.3% (95% confidence interval [CI], 19.1 to 39.2) against Covid-19–associated emergency department visits (risk difference per 10,000 persons, 18.3; 95% CI, 10.8 to 27.6), 39.2% (95% CI, 21.6 to 54.5) against Covid-19–associated hospitalizations (risk difference per 10,000 persons, 7.5; 95% CI, 3.4 to 13.0), and 64.0% (95% CI, 23.0 to 85.8) against Covid-19–associated deaths (risk difference per 10,000 persons, 2.2; 95% CI, 0.5 to 6.9). Vaccine effectiveness against a composite of these outcomes was 28.3% (95% CI, 18.2 to 38.2), with a risk difference per 10,000 persons of 18.2 (95% CI, 10.7 to 27.5). The Covid-19 vaccine was associated with decreased risks of these outcomes across prespecified subgroups defined according to age (<65 years, 65 to 75 years, and >75 years), the presence or absence of major coexisting conditions, and immunocompetence status.

CONCLUSIONS

In this national cohort of U.S. veterans, the receipt of the 2024–2025 Covid-19 vaccine was associated with decreased risks of severe clinical outcomes. (Funded by the Department of Veterans Affairs.)

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In 2020, the rapid development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represented one of the most remarkable scientific feats in recent history. Randomized trials, mostly in previously uninfected populations, showed approximately 95% efficacy against symptomatic SARS-CoV-2 infection and near-complete protection from severe disease.[1,2]

However, much has changed since then. SARS-CoV-2 has undergone substantial mutations, and immunity from repeated infections and vaccinations has attenuated the clinical severity of SARS-CoV-2 infections.[3]

These shifts have fueled broad public uncertainty about the continued value of annual coronavirus disease 2019 (Covid-19) vaccines. In the United States, adult uptake in the 2024–2025 season stalled at approximately 21% by late December 2024, the lowest since Covid-19 vaccines became available and half the influenza-vaccine uptake (42%) in the same period.[4] Policymakers are asking a key question: do updated Covid-19 vaccines still confer meaningful protection in the current epidemiologic context?

This question underscores the urgent need for contemporary evidence evaluating the effectiveness of the 2024–2025 Covid-19 vaccines across clinically meaningful outcomes. Contemporary evidence of vaccine effectiveness is crucial to inform Covid-19 vaccine policy deliberations for the 2025–2026 season.

In this study, we used the electronic health care databases of the Department of Veterans Affairs (VA) to evaluate the effectiveness of receipt of the Covid-19 and influenza vaccines as compared with receipt of the influenza vaccine only. We followed cohort members for 6 months to evaluate the risks of three outcomes, including Covid-19–associated emergency department visit, Covid-19–associated hospitalization, and Covid-19–associated death.

Methods

Specification of the Target Trial

We conducted an observational study that used the VA electronic health care databases to emulate a target trial — that is, to present data for a defined cohort in a way that is similar to an actual trial. We attempted to emulate a randomized pragmatic target trial to evaluate the effectiveness of receiving the 2024–2025 Covid-19 vaccine concurrently with a seasonal influenza vaccine (on the same day) as compared with receiving the seasonal influenza vaccine alone, in reducing the risk of several Covid-19–associated outcomes. By comparing persons who received both the Covid-19 and influenza vaccines on the same day with those who received only the influenza vaccine, this approach ensures that all the participants had at least one documented vaccination. This approach attempts to isolate the effect of the Covid-19 vaccine while reducing the risk of "healthy vaccinee" bias commonly encountered in observational studies comparing vaccinated with unvaccinated persons.[5,6]

This study used data from the VA Covid-19 Shared Data Resource. The design features of the study are shown in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study setting and data sources are detailed in the Methods section in the Supplementary Appendix. The study was approved by the institutional review board of the VA St. Louis Health Care System, which also granted a waiver of informed consent. The contributions of the authors are described in the Supplementary Appendix.

Cohort

The study cohort was selected from among VA patients seeking care in the interval between September 3, 2024, and December 31, 2024. The catchment period began approximately 2 weeks after the Food and Drug Administration approved the 2024–2025 Covid-19 vaccine on August 22, 2024, and 2 months after the approval of the 2024–2025 seasonal influenza vaccine on July 10, 2024. By September 3 (the beginning of the observation period), both vaccines were broadly available across the VA system, which allowed every eligible veteran a genuine opportunity to receive both vaccines or the influenza vaccine alone and thus enhanced the comparability between the two groups. Data through June 29, 2025, were included, which allowed at least 180 days of follow-up for all the participants.

VA patients who were eligible for inclusion in the study cohort (355,599 persons) were 18 years of age or older; had at least one primary care physician encounter within the VA system in the 18 months before the date of vaccination; had a clinical encounter for vaccination within the VA

system between September 3, 2024, and December 31, 2024; and had received at least one dose of the 2023–2024 season Covid-19 vaccine within the VA system. The last of these criteria was intended to enhance comparability between the two groups.

We excluded 59,628 persons: 45,271 who did not receive the 2024–2025 seasonal influenza vaccine (to enforce an active-comparator design and reduce the risk of healthy-vaccinee bias), 11,280 who received a Covid-19 vaccine within 90 days before the date of enrollment, and 3077 who had a laboratory-confirmed positive test for SARS-CoV-2 or seasonal influenza within 90 days before the date of enrollment. After these exclusions, 295,971 VA patients were eligible for inclusion in the study (Fig. 1).

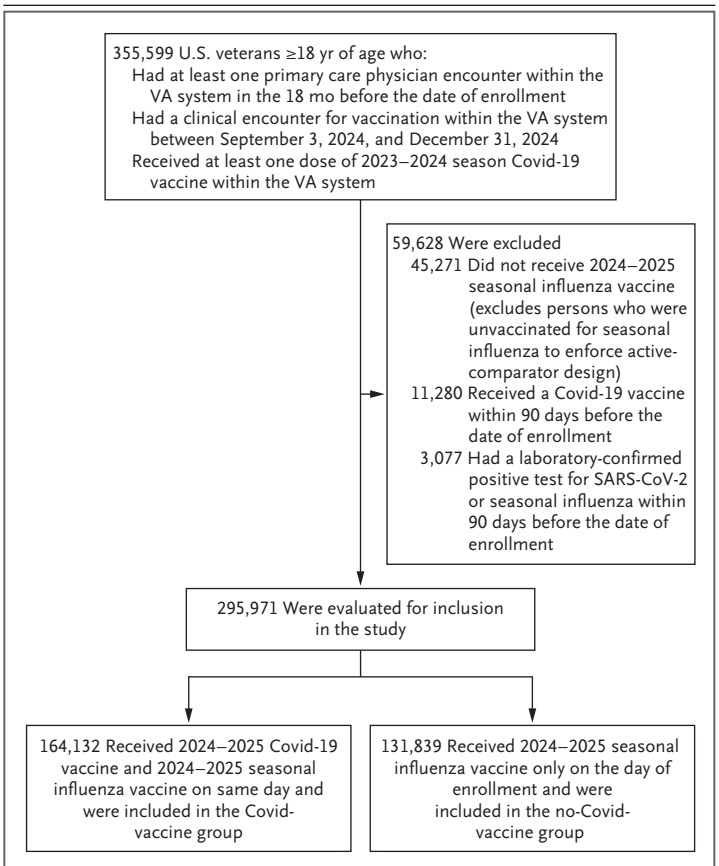

Figure 1. Selection of Study Participants.

This observational study compared same-day coadministration of the 2024–2025 coronavirus disease 2019 (Covid-19) vaccine and the 2024–2025 seasonal influenza vaccine (Covid-vaccine group) with administration of the 2024–2025 seasonal influenza vaccine alone (no-Covid-vaccine group). SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2, and VA Veterans Affairs.

EXPOSURE

Persons who received same-day coadministration of the 2024–2025 Covid-19 vaccine and the 2024–2025 influenza vaccine within the VA health care system were classified into the Covid-vaccine group, with the vaccination date denoted as time zero (T0) (164,132 participants). Persons who received the 2024–2025 influenza vaccine alone within the VA health care system were classified into the no-Covid-vaccine group, with the influenza vaccination date as T0 (131,839 participants). In the Covid-vaccine group, 105,040 (64.0%) received the 2024–2025 formula of mRNA-1273 vaccine (Moderna), 57,941 (35.3%) received the 2024–2025 formula of the BNT162b2 messenger RNA (mRNA) vaccine (Pfizer–BioNTech), and 1151 (0.7%) received other Covid-19 vaccines. The 2024–2025 mRNA-1273 vaccine and BNT162b2 mRNA vaccine target the KP.2 omicron subvariant. Among all the participants in the study cohort, 219,411 (74.1%) received high-dose trivalent formulation of the 2024–2025 seasonal influenza vaccine: 122,547 (74.7%) in the Covid-vaccine group and 96,864 (73.5%) in the no-Covid-vaccine group.

OUTCOMES

The study had three primary outcomes that have been validated for use in VA electronic health records: Covid-19–associated emergency department visit, Covid-19–associated hospitalization, and Covid-19–associated death.[7-14] Covid-19–associated emergency department visit was defined as an emergency department or urgent care visit 24 hours before or after a positive laboratory-confirmed SARS-CoV-2 test. Covid-19–associated hospitalization was defined as an inpatient admission occurring within 2 days before to 7 days after a positive laboratory-confirmed SARS-CoV-2 test and an inpatient diagnosis code for respiratory infection. Covid-19–associated death was defined as death which occurred within 30 days after a positive laboratory-confirmed SARS-CoV-2 test. In addition, a composite outcome was constructed as the first occurrence of any of the above three outcomes. The study cohort was observed from T0, and data were censored at the earliest of 180 days, death, the first outcome event, or receipt of a Covid-19 vaccine after T0; the last criterion applied only to participants who received the

2024–2025 influenza vaccine alone at T0 (the influenza-only cohort).

COVARIATES

This study captured two sets of covariates: baseline covariates and time-varying covariates. Baseline covariates were selected to balance the characteristics between the Covid-vaccine group and the no-Covid-vaccine group and were identified on the basis of previous knowledge of their associations with both Covid-19 vaccine uptake and Covid-19–associated outcomes.[15-27] Baseline covariates were collected from 1 year before T0 through T0, unless otherwise specified, and were organized into seven categories: demographic and socioeconomic characteristics, health behavior, spatiotemporal factors, laboratory and vital-sign measures, clinical risk and frailty scores, coexisting conditions, and health care use variables. Details of the baseline covariates are provided in the Methods section in the Supplementary Appendix. Temporal distribution of T0 after weighting is shown in Figure S1.

To address informative censoring in the influenza-only group (i.e., when a participant in this group received a Covid-19 vaccine after T0), we constructed inverse-probability-of-censoring weights using baseline and time-varying covariates. Time-varying covariates were chosen on the basis of previous knowledge of their association with vaccine uptake[28] and were collected from T0 until the end of each 15-day time interval: days 1 to 15 after T0, days 1 to 30 after T0, and so on up to days 1 to 180 after T0, for a total of 12 time-varying intervals during 180 days of follow-up. Details of time-varying covariates are provided in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

The baseline characteristics of the Covid-vaccine group and the no-Covid-vaccine group are reported as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Between-group differences in baseline characteristics were assessed with the use of absolute standardized differences, with values of less than 0.1 indicating good covariate balance.[7]

Inverse-probability weighting was used to balance baseline differences between the Covid-vaccine group and the no-Covid-vaccine group and to allow estimation of the average treatment effect among participants who received the Covid-19 vaccine. A logistic-regression model was constructed to estimate each cohort member's probability of receiving the Covid-19 vaccine given all baseline covariates. Inverse-probability weights were calculated as 1 for participants in the Covid-vaccine group and as the odds of vaccination — estimated probability divided by 1 minus estimated probability — for those in the no-Covid-vaccine group.

During the 6-month follow-up period, data from 63,579 (48.2%) of the 131,839 participants in the influenza-vaccine-only comparator group (i.e., those who had received no Covid-19 vaccine at T0) were censored on subsequent receipt of a Covid-19 vaccine after T0 (Fig. S2), with inverse-probability-of-censoring weights applied to account for potential informative censoring. Inverse-probability-of-censoring weights were calculated at each 15-day interval (12 intervals in total) during the 6-month follow-up period. Among patients still at risk in the no-Covid-vaccine group at each interval, logistic regression was used to estimate the probability of not being censored, conditional on baseline and time-varying covariates. The inverse-probability-of-censoring weight for each participant was computed as the cumulative product of the inverse probabilities of the data remaining uncensored and was stabilized by the overall observed probability of the data not being censored.

Risks per 10,000 persons at 6 months were estimated with the use of weighted generalized estimating equations (GEE) with a logit link and binomial distribution for discrete-time survival analyses. We estimated cause-specific hazard in which death was considered to be a competing risk in nonfatal outcomes (emergency department visit and hospitalization), and non–Covid-19–associated death was considered to be a competing risk event in analyses of Covid-19–associated death. The model included Covid-19 vaccination status, time period modeled with the use of restricted cubic spline terms, and the interaction between Covid-19 vaccination status and each spline term for time as covariates. The risk ratio was calculated as the ratio of estimated cumulative risks at 6 months, and the risk difference at 6 months was calculated as the risk in the no-Covid-vaccine group minus the risk in the Covid-vaccine group. Vaccine effectiveness was defined as 1 minus the risk ratio and reported as a per-

centage. The 95% confidence intervals for vaccine effectiveness and absolute risk reduction were estimated with the use of parametric bootstrapping with 1000 simulations on the basis of the covariance matrix generated from the GEE-based model. We estimated cumulative incidence functions with the same weighted GEE-based approach, applying the previously described inverse-probability-of-censoring weights, with temporal resolution enhanced from 15-day intervals to 1-day intervals by using the same inverse-probability-of-censoring weights value for each 1-day interval within the corresponding 15-day interval. Detailed methods for the time-interval, subgroup, sensitivity, and negative control outcome analyses and E values for unmeasured confounding are provided in the Methods section in the Supplementary Appendix. The widths of the confidence intervals reported in this article were not adjusted for multiplicity and should not be interpreted as hypothesis tests.

Vaccine effectiveness and absolute risk reduction are reported with associated 95% confidence intervals. Analyses were conducted with the use of SAS Enterprise Guide, version 8.3 (SAS Institute), and data visualizations were created with the use of R software, version 4.3.0 (R Foundation for Statistical Computing).

RESULTS

COHORT CHARACTERISTICS

A total of 164,132 persons were included in the Covid-vaccine group, and 131,839 were included in the no-Covid-vaccine group. The demographic and clinical characteristics of the two groups before and after weighting are presented in Table 1. We estimated the standardized mean differences for all baseline covariates and for each of the 12 sets of time-varying covariates — the latter incorporated into inverse-probability-of censoring weights calculated at 12 discrete time intervals — across the weighted groups. All standardized mean differences were below the conventional threshold of 0.1 after weighting, which suggests that adequate covariate balance was achieved (Figs. S3 and S4).

VACCINE EFFECTIVENESS

At 6 months of follow-up, the Covid-19 vaccine, as compared with no Covid-19 vaccine, was associated with lower risks of Covid-19–associated emergency department visits (vaccine effectiveness, 29.3% [95% confidence interval {CI}, 19.1 to 39.2]; risk difference per 10,000 persons, 18.32 [95% CI, 10.84 to 27.57]), Covid-19–associated hospitalizations (vaccine effectiveness, 39.2% [95% CI, 21.6 to 54.5]; risk difference per 10,000 persons, 7.47 [95% CI, 3.44 to 13.04]), and Covid-19–associated deaths (vaccine effectiveness, 64.0% [95% CI, 23.0 to 85.8]; risk difference per 10,000 persons, 2.20 [95% CI, 0.49 to 6.91]). Vaccine effectiveness against a composite of these three outcomes was 28.3% (95% CI, 18.2 to 38.2), and the risk difference per 10,000 persons was 18.23 (95% CI, 10.69 to 27.52) (Table 2). The cumulative risks of the four outcomes are shown in Figure 2. Covid-19 vaccine use was associated with an estimated vaccine effectiveness against the composite outcome of 37.1% (95% CI, 19.5 to 49.9) at 1 to 60 days, 32.5% (95% CI, 14.3 to 45.6) at 61 to 120 days, and 21.4% (95% CI, 0.3 to 37.0) at 121 to 180 days (Fig. S5 and Table S2).

SUBGROUP ANALYSES

We evaluated Covid-19 vaccine effectiveness in subgroups defined according to age and several coexisting conditions against the composite outcome of Covid-19–associated emergency department visit, hospitalization, or death. Covid-19 vaccination, as compared with no such vaccination, appeared to be associated with a lower incidence of these outcomes across age groups (<65 years, 65 to 75 years, and >75 years) and among persons with and without cardiovascular disease, cerebrovascular disease, chronic kidney disease, or chronic lung disease and among both immunocompetent and immunocompromised persons (Fig. 3 and Table S3).

SENSITIVITY ANALYSES AND NEGATIVE CONTROL OUTCOME ANALYSES

We assessed the robustness of our results in multiple sensitivity analyses, including using alternative propensity-score methods (overlap weighting, doubly robust estimation, and algorithmic covariate augmentation), varying the thresholds for propensity-score truncation and trimming, modifying the follow-up period (applying a 14-day grace period, performing a landmark analysis at 14 days, and not censoring for subsequent Covid-19 vaccination in the influenza-vaccine-only group), relaxing the inclusion criterion with respect to the 2023–2024 Covid-19 vaccine, treating death

Table 1. Demographic and Health Characteristics of the Participants Who Received 2024–2025 Covid-19 Vaccine and Those Who Did Not.*

Characteristic	Before Weighting			After Weighting		
	Covid-19 Vaccine (N=164,132)	No Covid-19 Vaccine (N=131,839)	SMD	Covid-19 Vaccine (N=164,132)	No Covid-19 Vaccine (N=131,839)	SMD
Age — yr	71.45±10.66	71.94±10.76	0.046	71.45±10.66	71.47±10.89	0.002
Sex — no. (%)						
Male	151,291 (92.18)	120,841 (91.66)	0.019	151,291 (92.18)	121,375 (92.06)	0.004
Female	12,841 (7.82)	10,998 (8.34)	0.019	12,841 (7.82)	10,464 (7.94)	0.004
Race — no. (%)†						
White	116,159 (70.77)	91,703 (69.56)	0.027	116,159 (70.77)	92,866 (70.44)	0.007
Black	41,733 (25.43)	34,230 (25.96)	0.012	41,733 (25.43)	33,925 (25.73)	0.007
Other	6,240 (3.80)	5,906 (4.48)	0.034	6,240 (3.80)	5,048 (3.83)	0.001
Smoking status — no. (%)						
Never smoked	61,375 (37.39)	52,404 (39.75)	0.048	61,375 (37.39)	49,850 (37.81)	0.009
Former smoker	72,337 (44.07)	57,020 (43.25)	0.017	72,337 (44.07)	57,902 (43.92)	0.003
Current smoker	30,420 (18.53)	22,415 (17.00)	0.040	30,420 (18.53)	24,087 (18.27)	0.007
Area deprivation index score‡	51.98±19.88	55.74±19.46	0.191	51.98±19.88	52.26±19.8	0.014
Care assessment need score§	0.19±0.16	0.21±0.18	0.120	0.19±0.16	0.19±0.16	0.011
VA frailty index score¶	0.15±0.10	0.17±0.11	0.161	0.15±0.10	0.15±0.10	0.014
Formulation of 2024–2025 seasonal influenza vaccine — no. (%)						
High-dose formulation for adults ≥65 yr of age	122,547 (74.66)	96,864 (73.47)	0.027	122,547 (74.66)	96,339 (73.07)	0.036
Standard-dose formulation	41,585 (25.34)	34,975 (26.53)	0.027	41,585 (25.34)	35,500 (26.93)	0.036
Covid-19 vaccine original series — no. (%)	161,224 (98.23)	128,911 (97.78)	0.032	161,224 (98.23)	129,492 (98.22)	0.001
Covid-19 vaccine 2021–2022 formula — no. (%)	152,160 (92.71)	119,111 (90.35)	0.085	152,160 (92.71)	121,891 (92.45)	0.010
Covid-19 vaccine 2022–2023 formula — no. (%)	125,812 (76.65)	90,113 (68.35)	0.187	125,812 (76.65)	100,132 (75.95)	0.017
Covid-19 vaccine 2023–2024 formula — no. (%)‖	164,132 (100)	131,839 (100)	0	164,132 (100)	131,839 (100)	0
Coexisting conditions — no. (%)						
Cardiovascular disease	38,645 (23.55)	34,343 (26.05)	0.058	38,645 (23.55)	31,338 (23.77)	0.005
Cerebrovascular disease	15,527 (9.46)	14,110 (10.70)	0.041	15,527 (9.46)	12,553 (9.52)	0.002
Chronic lung disease	31,465 (19.17)	27,346 (20.74)	0.039	31,465 (19.17)	25,390 (19.26)	0.002
Diabetes	45,846 (27.93)	38,912 (29.51)	0.035	45,846 (27.93)	36,856 (27.96)	0.001
Gastrointestinal disease	14,259 (8.69)	12,488 (9.47)	0.027	14,259 (8.69)	11,606 (8.80)	0.004
Hyperlipidemia	36,592 (22.29)	29,732 (22.55)	0.006	36,592 (22.29)	29,430 (22.32)	0.001
Immunocompromised status	20,678 (12.60)	19,308 (14.65)	0.060	20,678 (12.60)	16,753 (12.71)	0.003
Peripheral artery disease	4,037 (2.46)	3,762 (2.85)	0.024	4,037 (2.46)	3,287 (2.49)	0.002
Laboratory or vital-sign measures						
Body-mass index**	30.08±6.07	29.87±6.06	0.034	30.08±6.07	30.04±6.09	0.006
eGFR — ml/min/1.73 m^2	73.31±19.86	72.44±20.67	0.043	73.31±19.86	73.23±20.15	0.004
Glycated hemoglobin — %	6.18±1.09	6.22±1.12	0.044	6.18±1.09	6.17±1.08	0.002

Table 1. (Continued.)

Characteristic	Before Weighting			After Weighting		
	Covid-19 Vaccine (N=164,132)	No Covid-19 Vaccine (N=131,839)	SMD	Covid-19 Vaccine (N=164,132)	No Covid-19 Vaccine (N=131,839)	SMD
Hemoglobin — g/dl	13.17±3.60	13.32±3.06	0.044	13.17±3.60	13.17±3.57	0
HDL cholesterol — mg/dl	47.67±14.64	47.34±14.52	0.023	47.67±14.64	47.65±14.75	0.001
LDL cholesterol — mg/dl	84.95±34.46	84.36±34.2	0.017	84.95±34.46	85.12±34.24	0.005
Laboratory tests††						
No. of inpatient eGFR measurements in the 12 mo before T0	0.49±1.88	0.71±2.33	0.105	0.49±1.88	0.51±1.91	0.008
No. of outpatient eGFR measurements in the 12 mo before T0	2.29±1.83	2.53±1.95	0.125	2.29±1.83	2.31±1.84	0.010
No. of SARS-CoV-2 positive tests in the 12 mo before T0	0.02±0.14	0.03±0.16	0.039	0.02±0.14	0.02±0.14	0.002
No. of SARS-CoV-2 tests in the 12 mo before T0	0.27±1.14	0.46±2.24	0.107	0.27±1.14	0.28±1.15	0.014
SARS-CoV-2 test positivity rate at participant's medical center in the 3 mo before T0 — %	13.53±6.57	14.93±7.15	0.203	13.53±6.57	13.54±6.55	0.002

* Plus–minus values are means ±SD. All the participants received the 2024–2025 influenza vaccine. To convert values for high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. Covid-19 denotes coronavirus disease 2019, eGFR estimated glomerular filtration rate, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and SMD standardized mean difference.
† Race was determined from patient-reported data.
‡ The area deprivation index is a geographic measure of socioeconomic disadvantage. Scores range from 1 to 100, with higher scores indicating greater deprivation.
§ The care assessment need score reflects the predicted risk of death within 90 days. Scores range from 0 to 1, with higher scores indicating greater risk.
¶ The Veterans Affairs (VA) frailty index is a composite measure based on 31 conditions. Scores range from 0 to 1, with higher scores indicating greater frailty.
‖ Receipt of the Covid-19 vaccine 2023–2024 was the cohort entry criterion, and the corresponding percentages were 100% across groups.
** Body-mass index is the weight in kilograms divided by the square of the height in meters.
†† In the Covid-vaccine group, time zero (T0) was defined as the date of same-day coadministration of the 2024–2025 Covid-19 vaccine and the 2024–2025 influenza vaccine within the VA health care system. In the no-Covid-vaccine group, T0 was defined as the date of administration of the 2024–2025 influenza vaccine alone within the VA health care system.

as a competing risk with time-varying inverse-probability-of-censoring weights, and performing multiple imputation. The results appeared to be consistent (in direction and magnitude) with those of the primary analysis (Table S4).

Testing of several negative control outcomes, including emergency department visits for renal colic, emergency department visits for ankle sprain, and clinical encounters for tinnitus, yielded null results that were consistent with a priori expectations (Table S5). We also tested several influenza-associated negative control outcomes. Results showed null associations with influenza-associated emergency department visits, influenza-associated hospitalizations, receipt of influenza testing, and influenza test positivity.

Sensitivity to unmeasured confounding was assessed with the use of E values (higher values indicate more robust treatment–outcome associations). For the point estimates, E values were 2.18 for emergency department visit, 2.67 for hospitalization, 5.00 for death, and 2.13 for the composite outcome (Table S6). For the boundaries of the 95% confidence intervals closest to the null, E values were 1.78, 1.87, 1.92, and 1.74, respectively. These findings suggest that — independent of the 184 prespecified covariates that we already accounted for — an unmeasured confounder would need to be associated with both vaccination and the outcome by risk ratios of at least 1.7 to 2.0 (or stronger with one and weaker with the other) to move the boundary of the confidence interval to include the null.

Table 2. Estimated Vaccine Effectiveness, Risks at 6 Months in the Covid-Vaccine Group as Compared with the No-Covid-Vaccine Group, and Risk Differences at 6 Months in the 2024–2025 Season.*

Outcome	Vaccine Effectiveness (95% CI)†	Risk in Covid-Vaccine Group (95% CI)	Risk in No-Covid-Vaccine Group (95% CI)	Risk Difference (95% CI) ‡
	percent	*per 10,000 persons*		*per 10,000 persons*
Covid-19–associated emergency department visit	29.3 (19.1–39.2)	44.15 (40.98–47.56)	62.39 (55.62–70.75)	18.32 (10.84–27.57)
Covid-19–associated hospitalization	39.2 (21.6–54.5)	11.55 (10.01–13.33)	19.06 (15.14–24.39)	7.47 (3.44–13.04)
Covid-19–associated death	64.0 (23.0–85.8)	1.25 (0.78–2.05)	3.49 (1.98–8.07)	2.20 (0.49–6.91)
Covid-19–associated composite outcome	28.3 (18.2–38.2)	46.04 (42.80–49.53)	64.20 (57.36–72.64)	18.23 (10.69–27.52)

* Models were adjusted for both baseline characteristics through baseline inverse-probability weights and inverse-probability-of-censoring weights (with the use of both baseline characteristics and time-updated characteristics), with adjustment for censoring due to Covid-19 vaccination during the follow-up in the no-Covid-vaccine group. Confidence intervals were not adjusted for multiplicity and should not be interpreted as hypothesis tests.

† Vaccine effectiveness was defined as 1 minus the risk ratio (the risk in the Covid-vaccine group divided by the risk in the no-Covid-vaccine group).

‡ Risk difference was measured as the risk in the no-Covid-vaccine group minus the risk in the Covid-vaccine group.

DISCUSSION

In this large cohort of U.S. veterans, receipt of the 2024–2025 Covid-19 vaccine was associated with decreased risks of Covid-19–associated emergency department visits, hospitalizations, and deaths during 6 months of follow-up. The Covid-19 vaccine was associated with an estimated vaccine effectiveness ranging from 29% against emergency department visits to 39% against hospitalization and 64% against death, findings that closely mirror the immunologic gradient observed in trials and mechanistic studies.[29-32] The absolute risk reductions associated with vaccination were small (18.3 emergency department visits, 7.5 hospitalizations, and 2.2 deaths per 10,000 vaccinated persons) and may reflect the decreased baseline severity of contemporary SARS-CoV-2 infection.[3]

Public discussion increasingly questions the need for additional Covid-19 vaccination on the grounds that contemporary SARS-CoV-2 variants cause milder illness because of lower intrinsic pathogenicity and higher population immunity from previous infection and vaccination.[33-35] In the current epidemiologic landscape and among veterans who had already received the 2023–2024 formulation, receipt of the updated 2024–2025 Covid-19 vaccine was associated with additional protection against emergency department visits, hospitalizations, and deaths. Covid-19 vaccination appeared to be associated with effectiveness across prespecified age subgroups (<65 years, 65 to 75 years, and >75 years) and in persons with or without major chronic conditions, including immunocompetent and immunocompromised adults, findings that support applicability across these clinically relevant strata. The results should be interpreted in the context of a person's risk of severe Covid-19 and the potential benefit of vaccination against the small but recognized risk of vaccine-related adverse events, including myocarditis.[36]

Vaccine effectiveness against the composite outcome appeared to wane modestly over a period of 6 months. Understanding the mechanisms and implications of waning (including possible contributions to summer surges) and evaluating strategies to enhance durability of protection are warranted.[37]

Our study expands the limited evidence base for the 2024–2025 Covid-19 vaccine effectiveness. An interim analysis involving multiple U.S. states showed a vaccine effectiveness of 33% against Covid-19–associated emergency department or urgent care visits among adults 18 years of age or older and approximately 45% against Covid-19–associated hospitalizations among immunocompetent adults 65 years of age or older.[38] In a different analysis of VA data, which evalu-

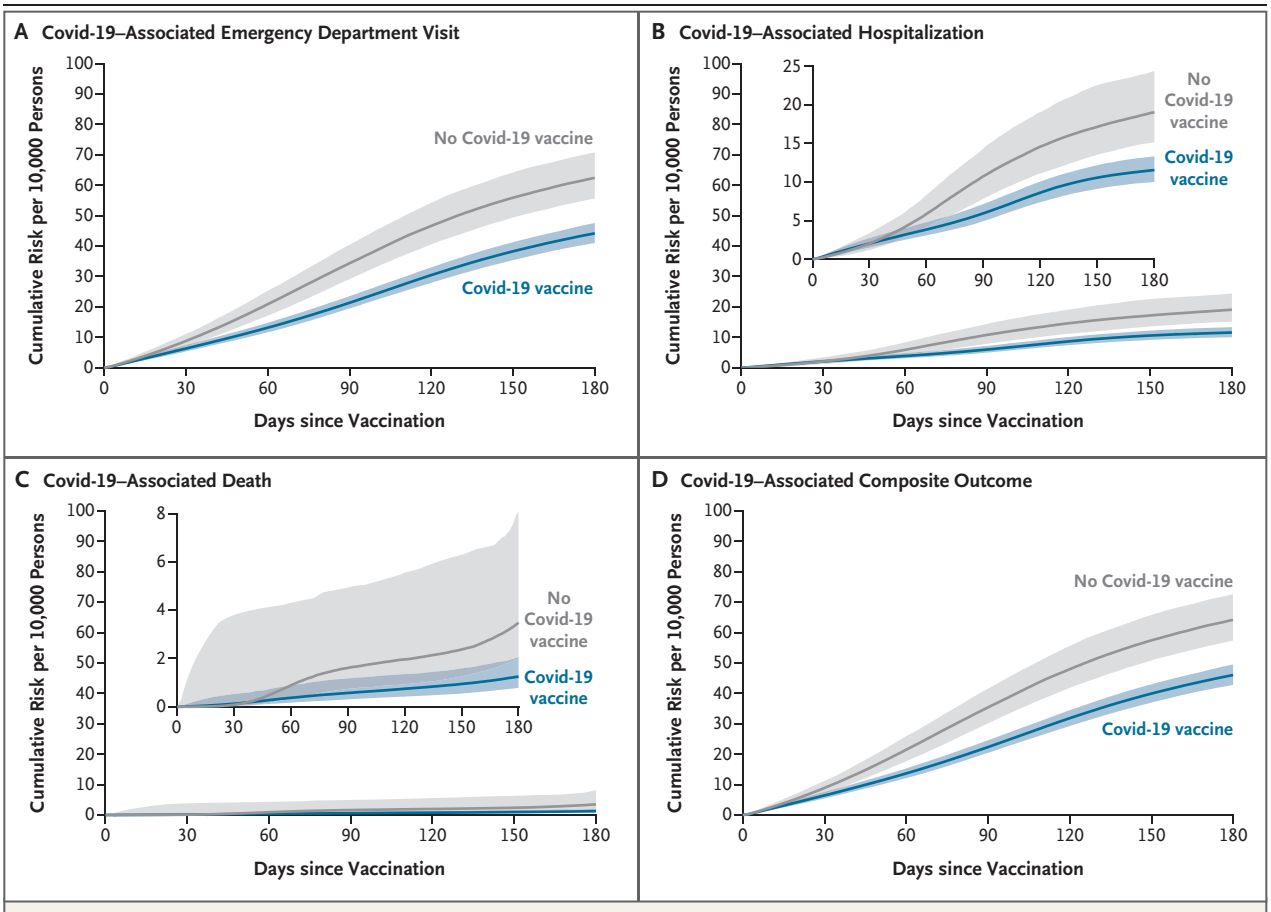

Figure 2. Cumulative Risks of Covid-19–Associated Outcomes over 180 Days in the 2024–2025 Vaccination Season.

The composite outcome was defined as the first occurrence of any of the other three outcomes. The insets show the same data on an expanded y axis. The 95% confidence intervals (shaded areas) were not adjusted for multiplicity and should not be interpreted as hypothesis tests.

ated only the 2024–2025 formulation of the BNT162b2 KP.2 vaccine with the use of a test-negative case–control design, the vaccine effectiveness at 3 months was 57% (95% CI, 46 to 65) against Covid-19–associated emergency department or urgent care visits and 68% (95% CI, 42 to 82) against Covid-19–associated hospitalizations.[39]

During 2024–2025, the Centers for Disease Control and Prevention recommended influenza and Covid-19 vaccination for everyone 6 months of age or older, with coadministration permissible at the same visit.[40] Although both vaccines were broadly available across the U.S. health care ecosystem, uptake diverged. By late December 2024, influenza vaccine uptake was approximately 42% and Covid-19 vaccine uptake was approximately 21%.[4] The lower uptake of the Covid-19 vaccine than of the influenza vaccine reflects the interaction of various drivers, including patient-level health and demographic characteristics, risk–benefit perceptions (e.g., perceived risk of Covid-19, concerns about vaccine-related adverse events, and aversion to mRNA vaccines),[25] geography, workplace policies (some employers require the influenza vaccine but not the Covid-19 vaccine), economic context, social and informational environment, and trust.[25,41,42]

This study has several limitations. Causality cannot be established with observational data. The demographic composition of our cohort (in which the majority of persons were older, White, and male) may limit the generalizability of the study findings; however, 8030 participants were younger than 45 years of age, 88,109 were of non-White race, and 23,839 were women. We used

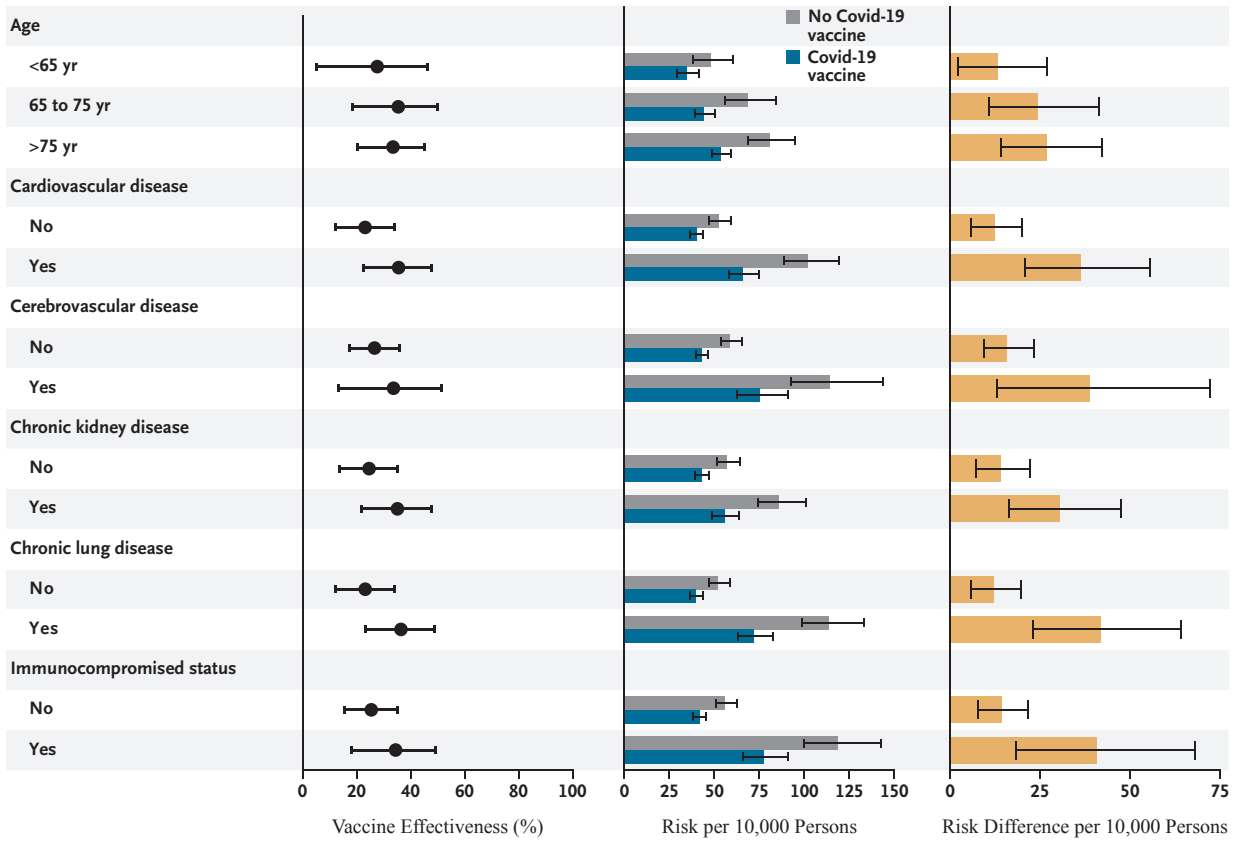

Figure 3. Subgroup Analyses.

Shown are subgroup analyses of 2024–2025 Covid-19 vaccine effectiveness, risk differences per 10,000 persons, and risks per 10,000 persons at 6 months for the composite outcome of Covid-19–associated emergency department visit, Covid-19–associated hospitalization, or Covid-19–associated death, with stratification according to age, cardiovascular disease, cerebrovascular disease, chronic kidney disease, chronic lung disease, and immunocompromised status. Vaccine effectiveness was defined as 1 minus the risk ratio (the risk in the Covid-vaccine group divided by the risk in the no-Covid-vaccine group). Risk difference was measured as the risk in the no-Covid-vaccine group minus the risk in the Covid-vaccine group. The 95% confidence intervals (error bars) were not adjusted for multiplicity and should not be interpreted as hypothesis tests.

VA electronic health care databases to conduct this study, and although we took care to adjust the analyses for a large set of covariates and we used validated definitions to define variables, we cannot rule out the possibility of residual confounding and misclassification bias. For example, we had no way to adjust for differences in behaviors that affect risk for Covid-19 exposure; veterans who opted to receive Covid-19 vaccination may also have been more careful to avoid exposure to Covid-19. Our analysis of the influence of potential unmeasured confounders shows E values for point estimates higher than 2 (indicating that an unmeasured confounder would need to be associated with both vaccination and the outcome by risk ratios of ≥2 each); E values for their 95% confidence intervals were greater than 1.7. Given the breadth of adjustment (184 covariates), such independent residual confounding appears to be unlikely; however, given the observational nature of this analysis, it cannot be fully ruled out. The 2024–2025 KP.2 vaccine was antigenically matched to predominant variants (including KP.3 and XEC) during the study, although antibody data showed modest immune escape by the later LP variant; we did not examine variant-specific effectiveness.[43] We assumed no interaction between Covid-19 and influenza vaccines. We did not evaluate adverse events.

This study has several strengths. We used an

active-comparator design evaluating the effectiveness of receipt of the Covid-19 and influenza vaccines or the influenza vaccine alone; this approach reduces healthy-vaccinee bias commonly encountered in observational studies evaluating vaccinated as compared with unvaccinated persons.[5,6] We specified a hypothetical pragmatic target trial that would address our research question and its corresponding estimand and used this hypothetical trial to inform the design of our observational study; this approach reduces the risk of biases such as immortal time bias, because the date of influenza vaccination anchored time zero (T0) for both study groups, thus aligning eligibility, exposure ascertainment, and follow-up.[44,45] We leveraged the breadth and depth of VA data to account for a comprehensive array of covariates from multiple data domains, including demographic characteristics, diagnoses, laboratory test results, medications, vital signs, health care use, and contextual characteristics. We used inverse-weighting methods at baseline to balance the groups and inverse-probability-of-censoring weights during follow-up to address bias from informative censoring. The results were robust to challenge in multiple sensitivity analyses and analyses of negative control outcomes.

In a large cohort of U.S. veterans, receipt of Covid-19 vaccination was associated with added protection against serious clinical sequelae up to 6 months after administration. The absolute differences in outcomes between participants who received Covid-19 vaccination and those who did not were small. The evidence may help inform ongoing discussions about the value of Covid-19 vaccines in the current epidemiologic landscape.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the U.S. government.

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