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Relative Effectiveness of Coronavirus Disease 2019 Vaccination and Booster Dose Combinations Among 18.9 Million Vaccinated Adults During the Early Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Period—United States, 1 January 2022 to 31 March 2022

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Abstract

Background.—Small sample sizes have limited prior studies' ability to capture severe COVID-19 outcomes, especially among Ad26.COV2.S vaccine recipients. This study of 18.9 million adults aged ≥18 years assessed relative vaccine effectiveness (rVE) in three recipient cohorts: (1) primary Ad26.COV2.S vaccine and Ad26.COV2.S booster (2 Ad26.COV2.S), (2) primary Ad26.COV2.S vaccine and mRNA booster (Ad26.COV2.S+mRNA), (3) two doses of primary mRNA vaccine and mRNA booster (3 mRNA).

Methods.—We analyzed two de-identified datasets linked using privacy-preserving record linkage (PPRL): insurance claims and retail pharmacy COVID-19 vaccination data. We assessed the presence of COVID-19 diagnosis during January 1-March 31, 2022 in: (1) any claim, (2) outpatient claim, (3) emergency department (ED) claim, (4) inpatient claim, and (5) inpatient

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

claim with intensive care unit (ICU) admission. rVE for each outcome comparing three recipient cohorts (reference: two Ad26.COV2.S doses) was estimated from adjusted Cox proportional hazards models.

Results.—Compared with two Ad26.COV2.S doses, Ad26.COV2.S+mRNA and three mRNA doses were more effective against all COVID-19 outcomes, including 57% (95% CI: 52–62) and 62% (95% CI: 58–65) rVE against an ED visit; 44% (95% CI: 34–52) and 54% (95% CI: 48–59) rVE against hospitalization; and 48% (95% CI: 22–66) and 66% (95% CI: 53–75) rVE against ICU admission, respectively.

Conclusions.—This study demonstrated that Ad26.COV2.S + mRNA doses were as good as three doses of mRNA, and better than two doses of Ad26.COV2.S. Vaccination continues to be an important preventive measure for reducing the public health impact of COVID-19.

Keywords

COVID-19; SARS-CoV-2 vaccine effectiveness; booster dose; J&J

Coronavirus disease 2019 (COVID-19) vaccines have been shown to protect against severe illness, hospitalization, and death due to infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including the Omicron variant [1, 2]. Prior studies have compared effectiveness of homologous vaccine schedules (ie, schedules using the same vaccine product) and heterologous vaccine schedules (ie, schedules using different vaccine products). For recipients of the Ad26.COV2.S (Johnson & Johnson) primary dose, heterologous boosting with BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) mRNA vaccines, has been shown to increase cellular and humoral immunity [3], resulting in increased efficacy compared to homologous boosting in health care workers [4], as well as vaccine effectiveness (VE) against infection in US veterans [5] and people tested at pharmacies [6]. However, small sample sizes have limited prior studies in their ability to capture severe COVID-19 outcomes, especially among recipients of the Ad26.COV2.S vaccine.

This study of nearly 19 million adults who completed a primary vaccination series and received a booster dose assessed relative vaccine effectiveness (rVE) of 3 complete COVID-19 vaccination schedules recommended during the early SARS-CoV-2 Omicron period (1 January 2022 to 31 March 2022), with the corresponding number of doses. Three cohorts of vaccine recipients were compared: (1) those with an Ad26.COV2.S vaccine and Ad26.COV2.S booster (2 Ad26.COV2.S), (2) those with an Ad26.COV2.S vaccine and an mRNA booster (Ad26.COV2.S + mRNA), or (3) those with 2 doses of an mRNA vaccine and an mRNA booster (3 MRNA). This evidence of vaccine schedule effectiveness can inform the public and public health efforts to prevent severe COVID-19 outcomes.

METHODS

Data Source

This study used 2 independent, de-identified patient-level data sets that were anonymously linked using privacy-preserving record linkage (PPRL) [7–9]. PPRL methods allow for

private patient records from disparate data sources to be linked without sharing or transmitting personally identifiable information (PII) [10–13]. Using PPRL, healthcare data owners can share data in a Health Insurance Portability and Accountability (HIPAA)-compliant manner that safeguards against risk of patient re-identification while also allowing for linking de-identified patient data across various healthcare data sources (eg, electronic health records, claims, immunization information systems). The 2 data sets used for this study were medical and pharmacy claims data licensed from HealthVerity, Inc, a healthcare data technology company specializing in PPRL [14], and COVID-19 vaccine administration data from the Federal Retail Pharmacy Program (FRPP) [15].

The Centers for Disease Control and Prevention (CDC) used real-world data from HealthVerity, Inc, from 1 January 2019 to 31 May 2022, that included medical and pharmacy claims for 217 M patients (as of May 2022) with a healthcare encounter related to COVID-19 (based on laboratory test, diagnosis codes, or medications) or COVID-19 vaccination. The FRPP receives COVID-19 vaccination administration data on all individuals who were vaccinated at 1 of the 21 retail pharmacies across the country participating in the program. As of May 2022, the FRPP data included 184 M COVID-19 vaccination doses administered to 103.8 M unique individuals. First, the identities of individuals in the HealthVerity real-world data and the FRPP were tokenized separately using HealthVerity PPRL technology. Even though the technology used to tokenize identities is the same, to preserve privacy, the tokens generated for an individual in each data set are unique and cannot directly be used to link individuals across data sets. In order to link individuals across these two datasets, HealthVerity generated a crosswalk file that provided CDC with a HIPAA-compliant method of linking tokens across the 2 data sets. The resulting linkage provided a longitudinal and more comprehensive picture of healthcare encounters before and after COVID-19 vaccination for individuals with both medical claims and vaccination data. This data linkage was compliant with HIPAA standards for patient protection, did not involve the use of PII for COVID-19 vaccine recipients in FRPP, and was approved by HealthVerity and participating retail pharmacies.

Inclusion Criteria

Sample selection is outlined in Supplementary Figure 1. Of 140 738 610 people with at least 1 record of COVID-19 vaccination in medical claims, pharmacy claims, or FRPP, the sequence and brands of the vaccines were analyzed to determine whether the individual completed the vaccination schedule according to federal guidelines [16–19]. Individuals were flagged for inclusion in the 2 Ad26.COV2.S group if they received the Ad26.COV2.S booster at least 60 days after the single dose Ad26.COV2.S primary series. Individuals were flagged for inclusion in the Ad26.COV2.S + mRNA group if they received either mRNA vaccine (BNT162b2 Pfizer–BioNTech or mRNA-1273 Moderna) at least 60 days after the single dose Ad26.COV2.S primary series. Individuals were flagged for inclusion in the 3 mRNA group if they received either mRNA booster (BNT162b2 Pfizer–BioNTech or mRNA-1273 Moderna) at least 120 days after completing an mRNA primary series. For individuals who received an BNT162b2 Pfizer–BioNTech vaccine as their first dose, they were considered to have completed the primary series within guidelines if they received a second dose of BNT162b2 Pfizer–BioNTech 17–42 days after the first. For individuals

who received an mRNA-1273 Moderna vaccine as their first dose, they were considered to have completed the primary series within guidelines if they received a second dose of mRNA-1273 Moderna 24–42 days after the first.

Exclusion Criteria

Of 25 660 789 people satisfying the inclusion criteria (Supplementary Figure 1), individuals were flagged for exclusion if they (1) were under the age of 18 at first vaccine administration date (n = 1 935 533), (2) had missing or unknown age (n = 7761), (3) had missing or unknown sex (n = 30 356), (4) received a booster before 23 September 2021 or after 15 March 2022 (n = 3 953 053), and (5) were classified as immunocompromised (n = 2 817 955). Immunocompromised individuals were excluded due to having a different vaccination schedule (compared to the general population) [20, 21], elevated likelihood of severe COVID-19 [22], and reduced protection from COVID-19 vaccination [23]. Patients with Ad26.COV2.S booster after 2 mRNA primary doses were also excluded from the main analysis, as this sequence was not typically recommended [24], and only 12 259 people (0.06% of the final sample) had this vaccination schedule; a supplemental analysis with this additional cohort was performed. After all exclusion and inclusion criteria were imposed, the final sample included 18 912 378 adults, which represents 73.7% of people satisfying the inclusion criteria and 13.4% of the initial sample of all people in the PPRL-linked data set who received at least 1 vaccine on or after 1 December 2020.

Outcomes

COVID-19 outcomes were identified by the presence of the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code of U07.1 in the closed (adjudicated) medical claims and open medical claims (pre-adjudicated claims data that come from the electronic data hubs, also referred to as clearing house centers). The study assessed the following non-mutually exclusive outcomes during the Omicron B.1.1.529 and BA.1-predominant or “early Omicron” period (1 January 2022 to 31 March 2022): (1) any claim with COVID-19, (2) an outpatient claim with COVID-19, (3) an emergency department (ED) claim with COVID-19, (4) an inpatient claim with COVID-19, and (5) an inpatient claim with COVID-19 and ICU admission.

Statistical Analysis

Incidence (occurrence per 100 000 person-years) of each outcome during follow-up period was calculated. Index date was defined as 7 days after booster date [1, 2]. Person-time at risk was calculated as the number of days from index date to outcome (if an outcome occurred), or from index date to the end of the study period of 31 March 2022 (if no outcome occurred).

The rVE was estimated using hazard ratios for each outcome for persons receiving Ad26.COV2.S + mRNA or 3 mRNA doses, compared with those receiving 2 Ad26.COV2.S doses (reference group), using Cox proportional hazards models [25], adjusted for sex, age group (18–49, 50–64, ≥65), prior SARS-CoV-2 infection indicated by the presence of a U07.1 diagnosis code on a medical claim or presence of a positive diagnostic lab test at any date prior to the booster, and presence of at least 1 underlying medical condition in

the 2 years before the booster date (Supplementary Table 1) [26, 27]. The same models were estimated separately for 3 age groups (18–49, 50–64, and ≥65 years). The rVE was calculated as (1-adjusted hazard ratio) × 100. As a sensitivity analysis, models were re-estimated without the prior SARS-CoV-2 infection, which could be under-documented in these data.

A supplemental analysis including a fourth cohort of 12 259 persons with Ad26.COV2.S booster after 2 mRNA primary doses was performed for the 2 mildest outcomes only (any claim with COVID-19 and an outpatient claim with COVID-19), due to small sample sizes for the more severe outcomes in that cohort.

Analyses were conducted using Databricks (version 9.1 LTS, Databricks, Inc), which included Spark (version 3.1.2, Apache Software Foundation) and Python (version 3.8, Python Software Foundation). The 5% level of significance was used for all analyses. This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy (see, eg, 45 C.F.R. part 46; 21 C.F.R. part 56; 42 U.S.C. §241(d), 5 U.S.C. §552a, 44 U.S.C. §3501 et seq).

RESULTS

The final analytic sample included 18 912 378 adults with documentation of a completed primary series and single booster dose. Of these, 10 684 829 individuals were identified in the HealthVerity data alone and 8 227 549 individuals were identified after linkage with the FRPP COVID-19 vaccination data. The final sample included 3 cohorts: (1) those with an Ad26.COV2.S vaccine and Ad26.COV2.S booster (2 Ad26.COV2.S; n = 320 103), (2) those with an Ad26.COV2.S vaccine and an mRNA booster (Ad26.COV2.S + mRNA; n = 1 116 973), or (3) those with 2 doses of an mRNA vaccine and an mRNA booster (3 mRNA; n = 17 475 302).

Persons receiving 2 Ad26.COV2.S doses were generally older (median age: 57) than persons receiving Ad26.COV2.S + mRNA or 3 mRNA doses (median age of 48 and 52 years, respectively) (Table 1). The South US Census region had the largest percentage of adults in all 3 cohorts (38.6%, 32.6% and 34.9%, respectively). Over 80.0% participants had no prior underlying medical conditions known to be associated with severe COVID-19 [26], and over 92.0% had no record of previous SARS-CoV-2 infection in HealthVerity database.

Unadjusted incidence of all outcomes was the highest in the cohort with 2 Ad26.COV2.S doses (Table 2), ranging from 45 per 100 000 person-years (those admitted to the ICU) to 5869 per 100 000 person-years (those with any claim with COVID-19). Cohorts receiving Ad26.COV2.S + mRNA or 3 mRNA doses were similar in their unadjusted incidence of all outcomes, ranging from 15 per 100 000 person-years (incidence of an ICU admission with COVID-19) to ~3700 per 100 000 person-years (incidence of any claim with COVID-19).

Compared with the cohort that received two Ad26.COV2.S doses, cohorts with an mRNA booster had significantly higher vaccine effectiveness against all outcomes (Figure 1). Persons with Ad26.COV2.S + mRNA doses (compared with those receiving 2 Ad26.COV2.S doses) had 37% (95% confidence interval [CI]: 35–39) rVE against any

COVID-19 claim, 41% (95% CI: 39–44) rVE against an outpatient claim with COVID-19, 57% (95% CI: 52–62) rVE against an ED claim with COVID-19, 44% (95% CI: 34–52) rVE against hospitalization, and 48% (95% CI: 22–66) rVE against ICU admission. Persons receiving 3 mRNA doses (compared with those receiving 2 Ad26.COV2.S doses) had 34% (95% CI: 32–36) rVE against of having any claim with COVID-19, 40% (95% CI: 38–42) rVE against an outpatient claim with COVID-19, 62% (95% CI: 58–65) rVE against an ED claim with COVID-19, 54% (95% CI: 48–59) rVE against hospitalization, and 66% (95% CI: 53–75) rVE against ICU admission. The rVE estimates for Ad26.COV2.S + mRNA and 3 mRNA were not significantly different from each other.

Age-stratified results exhibited similar patterns of vaccine effectiveness across all COVID-19 outcomes. Among adults aged 18–49 years, Ad26.COV2.S + mRNA doses and 3 mRNA doses had higher rVE against the three mildest outcomes (any claim with COVID-19, any outpatient claim with COVID-19, and an ED claim with COVID-19), compared with two Ad26.COV2.S doses. Relative VE against the two most severe outcomes (inpatient claim and ICU claim) were not estimated in this age group due to low number of persons with 2 mRNA doses and severe outcomes. Among adults aged 50–64 and ≥65 years, 3 mRNA doses and Ad26.COV2.S + mRNA also had significantly higher rVE against most outcomes compared to two Ad26.COV2.S doses. For example, rVE of 3 mRNA vaccines against ICU admission was 65% (95% CI: 38–80) among those aged 50–64 years and 69% (95% CI: 55–79) among those aged 65 years and older (compared to two Ad26.COV2.S doses). The rVE of Ad26.COV2.S + mRNA vaccines against ICU admission was 57% (95% CI: 9–80) among those aged 50–64 years and not significantly different among those aged ≥65 years (40%; 95% CI: −2–64), as compared to 2 Ad26.COV2.S doses.

A sensitivity analysis without controlling for prior SARS-CoV-2 infection found estimates to be similar to the main analysis (Supplementary Table 2).

A supplemental analysis including a fourth cohort of 12 259 persons with 2 mRNA doses and Ad26.COV2.S booster was performed for the 2 mildest outcomes only (any claim with COVID-19, an outpatient claim with COVID-19), due to low number of persons with 2 mRNA + Ad26.COV2.S and severe outcomes. This cohort had a median age of 50 and a higher crude prevalence of prior SARS-CoV-2 infection (9.0%) and underlying medical conditions (22.9%), compared to other cohorts (Supplementary Table 3). Crude incidence of 3 milder outcomes was higher in this cohort, compared to other cohorts, ranging from 365 for an inpatient claim with COVID-19 to 7392 for any claim with COVID-19 (per 100 000 person-years). Compared with reference (two Ad26.COV2.S doses), rVE among those with 2mRNA + Ad26.COV2.S was 16% (95% CI: 5–26) against any claim with COVID-19 and 23% (95% CI: 10–34) against an outpatient claim with COVID-19 (Supplementary Table 4). Compared with the other 2 cohorts (3mRNA and Ad26.COV2.S + mRNA), 2mRNA + Ad26.COV2.S exhibited a significantly lower effectiveness of both outcomes (based on non-overlapping CIs).

DISCUSSION

This large study of nearly 19 million vaccinated individuals demonstrated that Ad26.COV2.S + mRNA doses were as good as 3 doses of mRNA, and overall better than 2 doses of Ad26.COV2.S. Among patients aged 65 years and older, Ad26.COV2.S + mRNA doses were better than 2 doses of Ad26.COV2.S for most outcomes, and not significantly different from 2 doses of Ad26COV2.S for the most severe outcome (ICU admission). This study's strength is its ability to capture rare events, such as severe COVID-19 outcomes, by leveraging large open and closed claims data linked to vaccination data. A previous study of ED or urgent care encounters and hospitalizations 7–120 days after the most recent dose found that 2 doses of Ad26.COV2.S were less effective in preventing ED or urgent care encounters and hospitalizations than Ad26.COV2.S + mRNA doses and those with 3 mRNA doses [28]. That study used absolute VE, that is, comparing the number of cases in a vaccinated group of people to an unvaccinated group of people. Additionally, our study found better effectiveness of schedules with 3 mRNA doses or Ad26.COV2.S + mRNA doses for less severe outcomes (such as any diagnosis of COVID-19 or outpatient encounter with COVID-19) and more severe outcomes (such as ICU admission with COVID-19). In the same prior study, the absolute VE was lowest for those with 2 Ad26.COV2.S doses, increased (but with overlapping confidence intervals) for those with 1 Ad26.COV2.S dose and 1 mRNA dose, and was highest for those with 3 mRNA doses. Our analyses of relative VE found the same pattern of VE estimates, although we did not find a statistically significant difference between the groups with 3 mRNA versus Ad26.COV2.S followed by an mRNA vaccination.

Another prior study assessed absolute VE against symptomatic infection during the period of Omicron predominance in a sample of adults with 512 928 laboratory-based nucleic acid amplification tests at pharmacies evaluated using a test negative design [6]. In this study, VE at 2–4 months since last dose was lower among participants with 2 Ad26.COV2.S doses and participants with Ad26.COV2.S + mRNA doses compared with participants with three mRNA doses. Our analysis of any claim with COVID-19 as an outcome also found that Ad26.COV2.S + mRNA, and 3 mRNA doses had higher effectiveness during the period of early Omicron predominance than 2 Ad26.COV2.S doses, although the effect was similar for those with 1 Ad26.COV2.S dose and 1 mRNA dose and participants with 3 mRNA doses.

A supplemental analysis of a small fourth cohort who received 2 doses of mRNA followed by 1 dose of Ad26.COV2.S found that this schedule was relatively more effective against two assessed outcomes (any claim with COVID-19 and an outpatient claim with COVID-19) than 2 doses of Ad26.COV2.S. At the same time, its rVE was lower than that of 3 mRNA doses or Ad26.COV2.S + mRNA. This suggests a potential beneficial effect of a third dose (booster), although that effect is lower when the booster is Ad26.COV2.S, compared to mRNA.

This study demonstrates the utility of PPRL in combining disparate de-identified healthcare datasets for advancing clinical and public health research. Specifically, the resulting linked dataset significantly increased the analytic sample size and precision of results,

especially for rare outcomes, to improve understanding of COVID-19 VE. PPRL provides a mechanism for linking public health and clinical data records at the individual level without disclosing personally identifiable information. Evaluations have shown that linkages resulting from PPRL are comparable to those resulting from other matching techniques, as long as the underlying data are complete and accurate; however, PPRL is not without risk, and care must be taken to minimize processing and linkage errors and unintended patient re-identification [7–9]. Potential risks have been assessed by several government organizations, with the determination that data can be shared securely without compromising sensitive information when the proper guardrails are in place [29, 30]. The value of PPRL has been demonstrated in several important public health and clinical contexts [31, 32] and can be leveraged by federal, state, and non-governmental data providers to strengthen the capacity for novel research and insights.

This study has limitations. First, misclassification of vaccination status is possible if the data sources missed doses or misclassified the vaccine type. Second, this study did not consider all possible outcomes: mild non-hospital outcomes (ie, self-testing at home or asymptomatic infections), outcomes without the ICD-10-CM code of U07.1, or severe outcomes (ie, death) were not captured within the claims data. Third, these estimates may not be generalizable to the general vaccinated population, although they represent a large sample of vaccinated individuals. Fourth, absolute vaccine effectiveness was not assessed because the unvaccinated status in HealthVerity data may be misclassified. Relative VE alone may not be able to estimate the full impact of a vaccine on a population and recommendations are to provide both absolute and relative VE [33]. Fifth, patients who received 2 Ad26.COV2.S were older and had more underlying medical conditions than those who received mRNA booster. This difference could bias the results toward reduced effectiveness for those with 2 Ad26.COV2.S doses; however, these characteristics were adjusted for in the models. Sixth, the information on vaccine administration setting was missing and not examined in the analysis, although the settings with congregate nature (eg, long-term care facilities) could increase the number of people at risk for severe COVID-19. Seventh, PPRL techniques have potential for false-positive linkages between the vaccination and clinical data sources; this random error could bias results. Eighth, this dataset did not allow us to identify people with COVID-19-like illness symptoms; therefore, whether a patient was tested due to COVID-19-like illness or as a part of routine screening is unknown. Finally, this study did not account for a receipt of a second booster or additional doses, which may have affected the probability of severe COVID-19 illness.

This study demonstrates the utility and value proposition of PPRL for public health research, and the results suggest that Ad26.COV2.S + mRNA and 3 mRNA dose schedules provide a greater protection against a variety of outcomes as compared to 2 Ad26.COV2.S doses. These findings may be helpful when developing COVID-19 vaccine recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Outcome (reference: 2 Ad26.COV2.S)	Ad26.COV2.S + mRNA	3 mRNA
All ages		
Any claim with COVID-19	37 (35–39)	34 (32–36)
An outpatient claim with COVID-19	41 (39–44)	40 (38–42)
An ED claim with COVID-19	57 (52–62)	62 (58–65)
An inpatient claim with COVID-19	44 (34–52)	54 (48–59)
An inpatient claim and ICU admission with COVID-19	48 (22–66)	66 (53–75)
Aged 18–49 years		
Any claim with COVID-19	37 (34–40)	35 (32–38)
An outpatient claim with COVID-19	39 (35–42)	37 (34–40)
An ED claim with COVID-19	61 (53–67)	64 (59–69)
An inpatient claim with COVID-19	—[b]	—[b]
An inpatient claim and ICU admission with COVID-19	—[b]	—[b]
Aged 50–64 years		
Any claim with COVID-19	39 (36–42)	35 (33–38)
An outpatient claim with COVID-19	41 (37–44)	38 (35–41)
An ED claim with COVID-19	54 (44–61)	58 (52–64)
An inpatient claim with COVID-19	42 (24–57)	50 (37–60)
An inpatient claim and ICU admission with COVID-19	57 (9–80)	65 (38–80)
Aged ≥65 years		
Any claim with COVID-19	35 (29–40)	32 (28–36)
An outpatient claim with COVID-19	46 (40–51)	46 (42–50)
An ED claim with COVID-19	56 (45–65)	64 (58–69)
An inpatient claim with COVID-19	44 (29–56)	61 (54–67)
An inpatient claim and ICU admission with COVID-19	40 (-2–64)	69 (55–79)

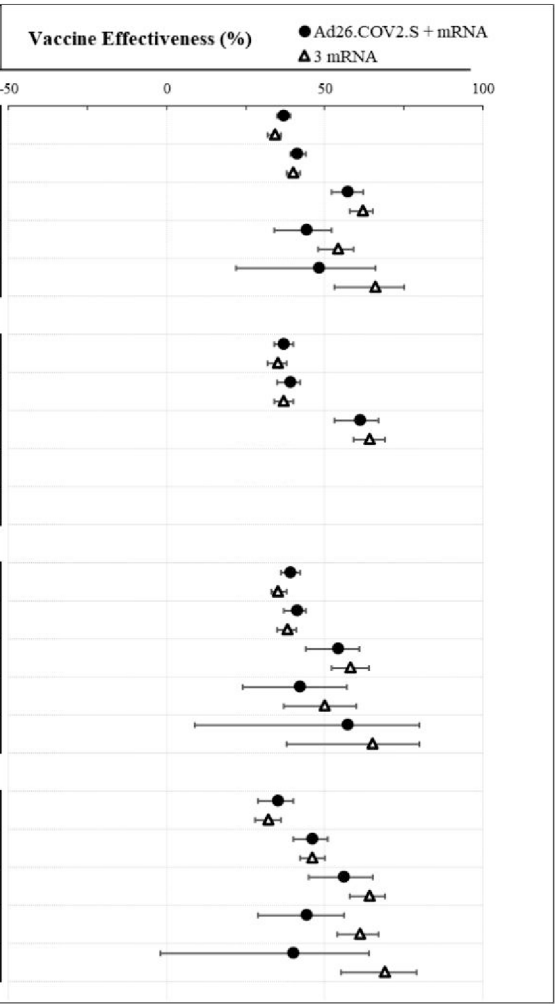

Figure 1.

Relative vaccine effectiveness[a] against COVID-19 outcomes, total and by age group[b] (reference: 2 Ad26.COV2.S)—linked data from HealthVerity claims and Federal Retail Pharmacy Program for COVID-19 vaccination, United States, 1 January 2022–31 March 2022. Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. [a]The sample included 3 cohorts of individuals: (1) those with Ad26.COV2.S vaccine and Ad26.COV2.S booster (2 Ad26.COV2.S; reference); (2) those with an Ad26.COV2.S vaccine and an mRNA booster (Ad26.COV2.S + mRNA), and (3) those with two doses of an mRNA vaccine and an mRNA booster (3 mRNA). Vaccine effectiveness was measured as (1-adjusted hazard ratio)*100. Each adjusted hazard ratio was obtained from a single Cox proportional hazards model, with the specific COVID-19 severity outcome as the dependent variable and the following covariates: cohort with Ad26.COV2.S + mRNA or cohort with 3 mRNA (reference: cohort with 2 Ad26.COV2.S), age (as a continuous variable), sex, prior SARS-CoV-2 infection, and having at least 1 underlying condition during the 2 years prior to booster. The models were estimated in the full sample, as well as stratified by age group.

[b]Age-stratified analyses were only performed when n ≥ 10 in a specific outcome in each cohort.

Table 1.

Cohort Characteristics—Linked Data From HealthVerity Claims and Federal Retail Pharmacy Program for COVID-19 Vaccination, United States, 1 January 2022 to 31 March 2022

Characteristics	N (column %)		
Total	18 912 378		
	2 Ad26.COV2.S[a]	Ad26.COV2.S + mRNA[a]	3 mRNA[a]
Subtotal	320 103 (100.0)	1 116 973 (100.0)	17 475 302 (100.0)
Age (y)			
Mean, median (IQR)	54.5, 57 (45, 65)	47.2, 48 (34, 60)	50.6, 52 (36, 64)
18–49	105 478 (33.0)	586 405 (52.5)	7 989 824 (45.7)
50–64	133 297 (41.6)	381 104 (34.1)	5 364 622 (30.7)
65 and older	81 328 (25.4)	149 464 (13.4)	4 120 856 (23.6)
Sex			
Male	163 853 (51.2)	562 875 (50.4)	7 779 700 (44.5)
Female	156 250 (48.8)	554 098 (49.6)	9 695 602 (55.5)
US Census region			
Northeast	65 259 (20.4)	231 916 (20.8)	3 323 919 (19.0)
Midwest	69 450 (21.7)	271 921 (24.3)	4 262 409 (24.4)
South	123 638 (38.6)	363 600 (32.6)	6 106 569 (34.9)
West	54 950 (17.2)	229 318 (20.5)	3 312 492 (19.0)
Unknown	6806 (2.1)	20 218 (1.8)	469 913 (2.7)
Any underlying medical conditions during 2 y prior to booster[b]			
Yes	64 114 (20.0)	178 977 (16.0)	3 197 807 (18.3)
No	255 989 (80.0)	937 996 (84.0)	14 277 495 (81.7)
Prior SARS-CoV-2 infection[c]			
Yes	21 573 (6.7)	85 945 (7.7)	1 139 304 (6.5)
No	298 530 (93.3)	1 031 028 (92.3)	16 335 998 (93.5)

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Column 2 represents those with an Ad26.COV2.S vaccine and Ad26.COV2.S booster (2 Ad26.COV2.S); column 2 represents those with an Ad26.COV2.S vaccine and an mRNA booster (Ad26.COV2.S + mRNA); column 4 represents those with two doses of an mRNA vaccine and an mRNA booster (3 mRNA).

[b] Presence of at least one of the following conditions: asthma, cancer, congenital malformations, cerebrovascular disease, chromosomal abnormalities, chronic kidney disease, chronic obstructive pulmonary disease, cystic fibrosis, diabetes, Down syndrome, epilepsy, fibrosis, heart disease, hypertension, liver disease, neurodevelopmental disorders, neurological disorders, other status, sickle cell disease, thalassemia.

[c] Presence of a positive diagnostic lab test or the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code of U07.1 in the medical claims at any date prior to booster. This may be an underestimate of true prevalence of prior SARS-CoV-2 infection.

Table 2.

Incidence of Severe COVID-19 Outcomes by Vaccination Type—Linked Data From HealthVerity Claims and Federal Retail Pharmacy Program for COVID-19 Vaccination, United States, 1 January 2022 to 31 March 2022

	N (%); Incidence per 100 000 person-y					
	2 Ad26.COV2.S[a]		Ad26.COV2.S + mRNA[a]		3 mRNA[a]	
Outcome	**N (%)**	**Incidence**	**N (%)**	**Incidence**	**N (%)**	**Incidence**
Any claim with COVID-19	5 479 (1.7%)	5869	11 436 (1.0%)	3626	186 886 (1.1%)	3752
An outpatient claim with COVID-19	3 980 (1.2%)	4251	8 100 (0.7%)	2563	123 718 (0.7%)	2478
An ED claim with COVID-19	571 (0.2%)	606	725 (0.1%)	228	10 996 (0.1%)	219
An inpatient claim with COVID-19	248 (0.1%)	263	339 (0.0%)	107	5 818 (0.0%)	116
An inpatient claim and ICU admission with COVID-19	42 (0.0%)	45	47 (0.0%)	15	5 818 (0.0%)	15

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; ICU, intensive care unit.

[a]Number, percent, and incidence per 100 000 person-years are presented for each outcome. Columns 2–3 represent those with an Ad26.COV2.S vaccine and Ad26.COV2.S booster (2 Ad26.COV2.S); columns 4–5 represent those with an Ad26.COV2.S vaccine and an mRNA booster (Ad26.COV2.S + mRNA); columns 6–7 represent those with two doses of an mRNA vaccine and an mRNA booster (3 mRNA).