

Assessment of Effectiveness of Booster/Additional Doses of COVID-19 Vaccines in the United States Report

**Center for Biologics Evaluation and Research
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List of Acronyms and Abbreviations

Acronym or abbreviation	Definition
ASD	absolute standardized difference
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CVX	vaccine administered codes
ED	emergency department
FDA	Food and Drug Administration
HR	hazard ratio
ICATT	Increasing Community Access to Testing
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, procedure coding system
IIS	immunization information systems
IPT	inverse probability of treatment
LTC	long-term care
min, max	minimum and maximum
NA	not applicable
NE	not estimable
NDC	National Drug Code
OMOP	Observational Medical Outcomes Partnership
Q1, Q3	first and third quartiles
RR	relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
US	United States
VE	vaccine effectiveness

Executive Summary

Background

The original monovalent booster doses or additional doses of coronavirus disease 2019 (COVID-19) vaccine were authorized in the United States for those who had already received a primary series of a COVID-19 vaccine. We evaluated the real-world effectiveness of receiving an original monovalent booster/additional dose of COVID-19 vaccine compared with receiving a primary vaccine series without a booster/additional dose in the United States (US).

Objectives

To assess the effectiveness of receiving a COVID-19 booster/additional dose compared with not receiving a booster/additional dose among individuals aged 12 to 64 years who previously received a complete primary series of a COVID-19 vaccine. Effectiveness in preventing medically diagnosed COVID-19 and hospital/emergency department (ED)-diagnosed COVID-19 was evaluated by brand.

Methods

Brand-specific cohorts of individuals receiving a COVID-19 booster/additional dose (“boosted” individuals) after receipt of a complete primary vaccine series were identified in 2 US administrative health insurance claims databases (Optum, CVS Health) supplemented with data from Immunization Information Systems (IIS) between August 2021 and March 2022. The vaccine brands included were BNT162b2 (Pfizer-BioNTech’s messenger ribonucleic acid [mRNA] COVID-19 vaccine, Comirnaty®), mRNA-1273 (Moderna’s mRNA COVID-19 vaccine, Spikevax®), and JNJ-7836735 (Janssen Pharmaceutical Company’s adenovirus COVID-19 vaccine). Individuals with a complete primary series but who had not yet received a booster/additional dose (“unboosted” individuals) were 1-to-1 matched to boosted individuals on calendar date of vaccine receipt, geography, age group, sex, brand and timing of the primary series, and other clinical factors. COVID-19 diagnoses were identified in any medical setting, or specifically in hospitals/Eds. Propensity score-weighted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox proportional hazards models; vaccine effectiveness (VE) was estimated as 1 minus the HR by vaccine brand overall and within subgroups of variant-specific eras, immunocompromised status, and homologous/heterologous booster status.

Results

Across both data sources, we identified 752,165 matched pairs for the BNT162b2 analysis, 410,501 for the mRNA-1273 analysis, and 11,398 for the JNJ-7836735 analysis. For any medically diagnosed COVID-19, meta-analyzed estimates of VE, comparing individuals who received a booster/additional dose compared with matched unboosted individuals, for BNT162b2, mRNA-1273, or JNJ-7836735, respectively, were: 54% (95% CI, 53%-56%); 58% (95% CI, 56%-59%); 34% (95% CI, 23%-44%). For hospital/ED-diagnosed COVID-19, all meta-analyzed VE estimates were high, ranging from 70% to 76%; BNT162b2 VE = 73% (95% CI, 70%-76%); mRNA-1273 VE = 76% (95% CI, 72%-79%); JNJ-7836735 VE = 70% (95% CI, 49%-82%). VE was generally lower during the Omicron era than the Delta era and for

immunocompromised individuals. Few differences were observed by homologous or heterologous booster status.

Conclusions

The original monovalent booster/additional doses were moderately effective in preventing COVID-19 diagnoses—particularly hospital/ED-diagnosed outcomes—among the populations for which they were indicated during the study period. Further studies and surveillance activities are needed in individuals receiving updated boosters and in time periods with new predominant viral variants.

1 Background

Coronavirus disease 2019 (COVID-19), caused by the novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in a global pandemic, affecting the United States (US) and countries throughout the world. Several vaccines for the prevention of COVID-19 were made available in the US through emergency use authorization or licensure by the US Food and Drug Administration (FDA). Over time, vaccine authorizations expanded to include different age groups and monovalent or bivalent forms that were approved for use as either primary vaccination series or as booster/additional doses. This study focused on the first 3 monovalent authorized vaccines in the US (i.e., those that were available as booster/additional doses in the US during the study period)—BNT162b2 (Pfizer-BioNTech’s messenger ribonucleic acid [mRNA] COVID-19 vaccine, Comirnaty®), mRNA-1273 (Moderna’s mRNA COVID-19 vaccine, Spikevax), and JNJ-7836735 (Janssen Pharmaceutical Company’s adenovirus COVID-19 vaccine). These vaccines were evaluated in large clinical trials before FDA authorization, and they have been demonstrated to increase antibody titers^{1,2} and be effective in preventing laboratory-confirmed COVID-19 infection.^{3,4}

The original monovalent COVID-19 vaccines were administered as booster/additional doses widely throughout the US in real-world settings. Since the vaccines’ original authorization for immunocompromised individuals, the indications for booster doses subsequently expanded to older adults, adults, and adolescents and children. Questions remain regarding the booster/additional doses’ real-world effectiveness in the general population, in populations of special interest, and in preventing different circulating variants. As the focus of COVID-19 response moves toward administering booster vaccinations, an understanding of booster vaccine effectiveness is crucial for public health programming. Approved vaccines may also have reduced effectiveness against circulating variants that became predominant in the US during the study period, including the B.1.617.2 (Delta) variant and B.1.1.529 (Omicron) variants.

Updated booster/additional dose vaccination strategies continue to be introduced for certain age groups and newer viral variants. To evaluate the real-world effectiveness of the original monovalent booster/additional COVID-19 vaccines in the US population, it is important to use methods that account for the time since vaccination, circulating variants of the virus, seasonality (i.e., calendar time), and differences between exposure groups while avoiding selection bias frequently caused by comparing different lengths of exposure.⁵

As part of its continued monitoring and surveillance of authorized vaccines, FDA and collaborating health data and scientific partners within the Biologics Effectiveness and Safety (BEST) Initiative evaluated the real-world effectiveness of the first receipt of an original monovalent COVID-19 booster/additional vaccine doses in the US. The objective of this study was to estimate the effectiveness of receiving an original monovalent booster/additional dose of a COVID-19 vaccine compared with not receiving a booster/additional dose in individuals who had previously received a complete primary vaccine series (either 1- or 2-dose, depending on the primary series brand). This report presents the results of the booster/additional dose analyses described in the publicly posted protocol “Assessment of

Effectiveness of COVID-19 Vaccination in the United States.”⁶ Other analyses described in the protocol (i.e., analyses of primary series vaccinations in pediatric and adult populations) are reported separately.

2 Objectives

The following primary objective was evaluated in this study:

- To assess the effectiveness of receiving a booster/additional dose compared with not receiving an additional dose or booster dose in individuals aged 12 to 64 years (those authorized to receive a booster/additional dose during the study period), by vaccine brand, in preventing medically diagnosed COVID-19 and hospital/emergency department (ED)-diagnosed COVID-19, among individuals with a complete primary series of COVID-19 vaccine. The following vaccination exposure patterns were compared among individuals receiving a complete primary series of any vaccine brand (i.e., timely receipt of 2 doses of the same brand of a 2-dose series or 1 JNJ-7836735 dose):
 - BNT162b2 booster/additional dose versus not receiving any booster/additional dose
 - mRNA-1273 booster/additional dose versus not receiving any booster/additional dose
 - JNJ-7836735 booster/additional dose versus not receiving any booster/additional dose

The following secondary objectives were evaluated in this study:

- To assess the effectiveness of receiving a booster/additional dose compared with not receiving an additional dose or booster dose in subgroups of immunocompromised status and calendar time eras corresponding to different predominant circulating viral variants.
- To assess the effectiveness of receiving a booster/additional dose when received after a primary series of the same brand (homologous) or of a different brand (heterologous) as the booster/additional dose.

3 Methods

3.1 Data Sources

The study was conducted using 2 US health insurance claims data sources—Optum preadjudicated health insurance billing claims and CVS Health (Aetna) adjudicated health claims—supplemented with immunization information system (IIS)-sourced COVID-19 vaccination data ([Table 1](#)).⁷ This study was restricted to individuals aged 12 to 64 years with commercial health insurance and individuals living in the catchment areas of both the insurance plans and the included IIS jurisdictions.

Table 1. IIS Jurisdictions and Study Periods Utilized

Jurisdiction	Study period, Optum	Study period, CVS Health
1	NA	11 December 2020–31 March 2022
2	11 December 2020–28 February 2022	NA
3	NA	11 December 2020–31 March 2022
4	NA	11 December 2020–31 March 2022
5	NA	11 December 2020–31 March 2022
6	NA	11 December 2020–31 March 2022
7	NA	11 December 2020–31 March 2022
8	11 December 2020–28 February 2022	11 December 2020–31 March 2022
9	11 December 2020–28 February 2022	11 December 2020–31 March 2022
10	11 December 2020–28 February 2022	11 December 2020–31 March 2022
11	11 December 2020–28 February 2022	NA
12	11 December 2020–28 February 2022	11 December 2020–31 March 2022
13	11 December 2020–28 February 2022	NA
14	11 December 2020–28 February 2022	NA
15	11 December 2020–28 February 2022	NA
16	NA	11 December 2020–31 March 2022

IIS = Immunization Information System; NA = not applicable.

Note: Optum used data from 9 IIS jurisdictions, and CVS Health used data from 11 IIS jurisdictions. Sixteen unique IIS jurisdictions were used in the study.

3.1.1 Immunization Information Systems

During the COVID-19 pandemic, many COVID-19 vaccines were administered outside traditional healthcare settings (e.g., mass vaccination clinics, public health departments), which may not have resulted in submitted health claims to payers for reimbursement. As a result, relying solely on health insurance claims data for determining individuals' vaccination status may result in missing vaccination information. Thus, COVID-19 vaccine information from IIS data was used to supplement commercial health insurance claims to improve COVID-19 vaccine capture.⁸ States, cities, or other jurisdictions maintain IIS registries of administered vaccines as part of their public health functions.^{7,9} Each IIS is organized and maintained by the jurisdiction, and thus the data structure, completeness, and data access may vary across IIS organizations. IIS are maintained by public health entities. Given the diffused nature of public health systems in the United States, the organization and governance of IIS structures may vary based on how public health is managed, which can vary geographically (e.g., state, metropolitan area, territory). Thus, some states may contribute multiple IIS organizations.

3.1.2 Optum Preadjudicated Commercial Health Insurance Claims and IIS Vaccine Records

The Optum data include enrollment, prescription drug, and preadjudicated hospital and physician health insurance claims for privately insured enrollees. Hospital and physician claims undergo initial processing on a daily basis from a large number of providers across the US that accept patients enrolled in included

health insurance plans. Optum established an ongoing weekly schedule to update and incorporate newly processed claims data into the preadjudicated claims database. This data source was used to reduce the delay between accessing healthcare services and their recording in the database. The preadjudicated claims have an approximately 2-month delay for reaching 90% completeness for inpatient hospital claims. Because hospital-diagnosed COVID-19 was 1 of the primary study outcomes, inpatient data completeness was prioritized, and the end of the study period was defined as 2 months before the end of the available data.

IIS organizations were requested to link their COVID-19 vaccination data to individuals in the claims database; these data are routinely refreshed. IIS information was evaluated for completeness and usability (process and results reported elsewhere⁷). The proportion of individuals aged younger than 65 years in each state reported as having at least 1 COVID-19 vaccine dose and the proportion of individuals who received a booster/additional dose using both IIS data and claims data were compared with state health department estimates, Centers for Disease Control and Prevention (CDC) estimates, and capture-recapture adjusted estimates (where the proportion of boosted individuals not captured with either IIS or claims data is estimated as a function of the proportion of those captured with either method alone or both¹⁰). To evaluate the data completeness of each IIS, an exploratory quantitative bias analysis was performed using the estimated vaccination misclassification (sensitivity) for each state to estimate the change in a hypothetical vaccine effectiveness (VE) estimate of 70% (assuming a COVID-19 incidence of 6% among unboosted individuals). We assumed that an acceptable level of bias for inclusion of an IIS in the study was within 10 percentage points compared with state health department estimates for completed vaccine series. Additional considerations for state inclusion in the analysis included the overall sample size of the state or territory, completeness of IIS data transfer, age ranges included in IIS data, the usability of IIS data (e.g., the ability to identify unique doses on specific calendar dates), and the magnitude of bias as measured by the effect of their inclusion on overall VE estimates. Data from 9 IIS organizations from 9 unique US states were used.

3.1.3 CVS Health Commercial Claims and IIS Vaccine Records

CVS Health transforms Aetna enrollment, dispensed prescription drug claims, and adjudicated hospital and physician health insurance claims into the BEST Observational Medical Outcomes Partnership (OMOP) common data model. The Aetna adjudicated hospital and physician health claims database includes claims for Aetna commercially insured and Aetna Medicare Advantage enrollees. The adjudicated claims are 80% complete for inpatient claims at 3 months and outpatient claims at 2 months. Therefore, the end of the study period for CVS Health was defined as 3 months before the end of the available data to account for delay in claim submission to Aetna (i.e., claim lag).

To enhance identification of vaccine administration, FDA requested that CVS Health collaborate with all IIS jurisdictions to obtain Aetna enrollee vaccine records that may not have been funded through Aetna health insurance. As of September 2023, CVS Health has active collaborations with 30 IIS organizations. In this analysis, COVID-19 vaccination records from 11 IIS collaborations from 9 unique US states met data completeness criteria and were included. The IIS data collaboration sharing process involves CVS

Health providing a secure person-identifiable data file on Aetna health plan enrollees to collaborating IIS organizations, and IIS organizations returning vaccination records for the enrollees within the IIS.

To assess usability of IIS information on beneficiaries in the CVS Health data, each IIS was evaluated to ensure that population characteristics appeared consistent across data sources and conformed to expectations. Additionally, vaccine uptake over time was evaluated to ensure that it appeared consistent with authorization dates and eligibility expansions. IIS data from jurisdictions meeting these initial checks were further evaluated to determine the potential impact on vaccination status misclassification. We assessed the amount of bias presented in these IIS jurisdictions using vaccine coverage estimates provided by state health departments age-adjusted based on CVS Health's population distribution; if state health department estimates were not available, CDC estimates of the state coverage were used. Using a bias estimate threshold of less than or equal to 10 percentage points (assuming 70% VE), the final selected group of 11 IIS jurisdictions were recommended to be included.

3.2 Study Period

The study period began on 11 December 2020 (the date of the first COVID-19 vaccine emergency use authorization in the US). Although booster/additional doses were not available in December 2020—they were first authorized in August 2021 ([Table 2](#))—data from 11 December 2020 were used to define primary series completion before the receipt of a booster/additional dose. Available data from before 11 December 2020—as far back as 1 December 2017 for Optum and 1 January 2018 for CVS Health—were used to define individual characteristics and eligibility criteria before Time 0.

The study period used the most recent complete data available at the time of the data extraction, accounting for potential lag times in the accumulation of hospitalization data and IIS data, as shown in [Table 1](#). The cutoff date for Optum was 28 February 2022; the cutoff date for CVS Health was 31 March 2022.

COVID-19 vaccine authorizations for booster/additional doses have changed during the study period ([Table 2](#)). Brand-specific analyses of a booster/additional dose were likewise restricted to time periods and age groups when the vaccine brand was authorized for use as a booster/additional dose.

Table 2. Dates of COVID-19 Vaccine Initial Authorization and Booster/Additional Dose Authorization by Brand in the United States During the Booster/Additional Dose Study Period, 11 December 2020–31 March 2022

COVID-19 vaccine	Doses in primary series	Date of US authorization as booster/additional dose	Authorized population for booster/additional dose
BNT162b2	2	12 August 2021	Immunocompromised individuals
		22 September 2021	Aged ≥ 65 years or at high risk of severe COVID-19
		19 November 2021	Aged ≥ 18 years
		3 January 2022	Aged ≥ 12 years
mRNA-1273	2	12 August 2021	Immunocompromised individuals

COVID-19 vaccine	Doses in primary series	Date of US authorization as booster/additional dose	Authorized population for booster/additional dose
		20 October 2021	Aged ≥ 65 years or at high risk of severe COVID-19
		19 November 2021	Aged ≥ 18 years
JNJ-7836735	1	20 October 2021	Aged ≥ 18 years

COVID-19 = coronavirus disease 2019; FDA = Food and Drug Administration; US = United States.

Source: US FDA.¹¹⁻¹³

Because the vaccines were available in different time periods and for different age groups, the results of vaccine brand-specific analyses should not be directly compared.

3.3 Study Populations

3.3.1 Cohort Entry

Among those who had completed a primary vaccine series the effectiveness of receiving a booster/additional dose of a COVID-19 vaccine was compared with having not received a booster/additional dose. The brand-specific booster/additional dose cohorts consisted of individuals aged 12 to 64 years (depending on the brand-specific age authorizations) who received a booster/additional dose after receiving a complete primary series, and matched individuals with a complete primary series without a booster/additional dose. During the study period, BNT162b2 was authorized as a booster/additional dose for individuals aged 12 years or greater, so the study population for the BNT162b2 cohort was aged 12 to 64 years, while mRNA-1273 and JNJ-7836735 were authorized as booster/additional doses for individuals aged 18 years or greater, so their study populations were aged 18 to 64 years. Receiving a complete primary series was defined as receiving any of the following, without any additional doses:

- 1 dose of JNJ-7836735
- 2 doses of BNT162b2, with the second dose occurring on or after 17 days and within 42 days (inclusive) of the first dose
- 2 doses of mRNA-1273 with the second dose occurring on or after 24 days and within 42 days (inclusive) of the first dose

The study period for the booster/additional dose analyses of each brand began on the date of authorization for a booster/additional dose for each brand ([Table 2](#)). Booster/additional dose recipients were identified at the first receipt of a booster/additional dose of a COVID-19 vaccine after completion of the primary series. The brand of the booster/additional dose was not required to match the brand of the primary series. The date of the booster/additional dose became Time 0 for this analysis. Individuals who received a primary series but who had not received a booster/additional dose at Time 0 were

eligible to be matched to those who received a booster/additional dose on the calendar date of Time 0 using a daily 1-to-1 exact matching process, with replacement, with the following matching factors:

- Calendar date of booster/additional dose receipt
- Age group, in years, in 5-year increments within age ranges corresponding to the tiered authorizations (18-64 years [16-64 for BNT162b2], 12-15 years [for BNT162b2])
- Sex
- County and state of residence
- Immunocompromised status
- Influenza vaccination in the previous year
- Presence of at least 1 of the conditions identified by CDC¹⁴ as increasing individuals' risk of severe COVID-19 ([Section 3.4.3](#)), indicating potential prioritization for booster/additional dose receipt
- Brand of the complete primary series
- Time since primary series completion (14-day increments)

The matched calendar date became Time 0 for the individuals without receipt of a booster/additional dose. For both groups, the eligibility criteria, covariates, and follow-up were assessed relative to Time 0 ([Figure 1](#)).

Figure 1. Schematic for Assessing Eligibility, Covariates, and COVID-19 Outcomes Among Individuals Receiving a Booster/Additional Dose and Matched Individuals Without a Booster/Additional Dose



COVID-19 = coronavirus disease 2019; ED = emergency department; LTC = long-term care.

- ^a Matching characteristics include calendar date of booster/additional dose receipt, age group, sex, US county and state of residence, immunocompromised status, receipt of influenza vaccination in the previous year, having a condition increasing risk of severe COVID-19, brand of primary series, and time since primary series.
- ^b Gaps in medical and pharmacy coverage < 32 days permitted. For individuals aged 12-15 years, continuous enrollment in the health insurance plan must have begun on or earlier than 10 May 2021—the first date of COVID 19 vaccine authorization in the US for individuals aged 12-15 years.
- ^c Primary series is 1 dose of JNJ-7836735 or 2 doses of BNT162b2 or mRNA-1273 with the second dose occurring on or after 17 or 24 days, respectively, and within 42 days (inclusive) of the first dose, without any additional doses.
- ^d Hospitalization or LTC residence on Time 0.
- ^e COVID-19 monoclonal antibodies or convalescent plasma.
- ^f Diagnoses of general acute symptoms (fever, nausea/vomiting, rash) and healthcare utilization (hospitalization, ED visit) serving as an indicator of health status at the time of vaccination.
- ^g Hospitalizations, ED visits, skilled nursing facility stay, influenza vaccination, pneumococcal vaccination, encounter for cancer screening, eye examination, colonoscopy, bone mineral density test, well-check/well-child preventive healthcare visit, arthritis, lipid abnormality, ambulance use of life support services, weakness, pregnancy completion.
- ^h Autoimmune disorders, cancer, chronic kidney disease or renal disease, chronic liver disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus (type 1 or 2), Down syndrome, heart conditions, hypertension, immunocompromised state, mental health conditions, obesity or severe obesity, sickle cell disease or thalassemia, stroke or cerebrovascular disease, tuberculosis, COVID-19 laboratory test performed, COVID-19 diagnoses occurring outside a hospital or ED setting, hospital/ED-diagnosed COVID-19, brand of the primary series, time since primary series completion.
- ⁱ End of study period, end of continuous health plan enrollment, death, or deviation from the categorized vaccine exposure status (receiving any COVID-19 vaccine dose after Time 0).

3.3.1.1 Eligibility Criteria

The following eligibility criteria were evaluated relative to Time 0—the date of receipt of the booster/additional dose in the boosted group or the matched date for the comparator group:

- Had continuous enrollment in the health insurance plan for at least 365 days before Time 0 and that also began on or earlier than the first date of COVID-19 vaccine authorization in the US for each age group (i.e., 11 Dec 2020 for individuals aged ≥ 16 years, 10 May 2021 for individuals aged 12-15 years).
 - Enrollment in both medical and pharmacy coverage was required.
 - Gaps in coverage of less than 32 days were permitted for continuous enrollment.

To align the health statuses of the booster/additional dose and comparator groups and control for confounding, individuals were excluded for any of the following criteria:

- Having an age outside the brand-specific age range authorized for a booster/additional dose on the calendar date of Time 0 ([Table 2](#))
- Residing in a geographic region outside the catchment area of the IIS jurisdictions and claims data
- Having claims for monoclonal antibody treatment or convalescent plasma treatment for COVID-19 within the 90 days before Time 0
- Having a diagnosis of COVID-19 assessed in any setting in the 30 days before Time 0
- Being hospitalized on the date of Time 0
- Residing in a long-term care facility on the date of Time 0
- Having any of the following healthcare interactions occurring in the 3 days before Time 0:
 - Diagnoses that may temporarily delay vaccination (e.g., fever, nausea/vomiting, rash)
 - Hospitalization

- ED visit
- Completion of the primary series < 28 days before Time 0

3.3.1.2 Follow-up

Follow-up began on the date of Time 0 and ended on the first occurrence of the following:

- Occurrence of the study COVID-19 outcome (the 2 outcomes were evaluated separately)
- Censoring for any of the following:
 - Last date of the study period
 - Last date of individual continuous eligible health plan enrollment, or date of death
 - Date of recorded change of residence to a location outside the study area
 - Deviation from the categorized exposure pattern ([Table 3](#))

3.4 Variables and Definitions

3.4.1 COVID-19 Vaccine Exposure

3.4.1.1 COVID-19 Vaccine Dose Identification

Brand-specific vaccine doses were identified in claims and IIS databases. In the health claims data, vaccines were identified in any care setting using procedure codes (*Current Procedural Terminology* [CPT®] or Healthcare Common Procedure Coding System [HCPCS]) for vaccine administration or National Drug Codes (NDC) for vaccine products.^{15,16} Vaccine doses were also identified in IIS databases using Vaccine Administered (CVX) codes. *International Classification of Diseases, 10th Revision, Procedure Coding System* (ICD-10-PCS) codes for COVID-19 vaccination do not specify the brand, and CVX codes for “brand-unspecified” COVID-19 vaccines also exist. Brand-unspecified codes without other accompanying claims or IIS records indicating the vaccine brand were not used to define patient exposure status but were used for exclusion criteria to indicate history of vaccination or as censoring criteria.

Deduplication of individuals’ vaccination records in both the IIS data and claims sources was performed because a single vaccination event may result in multiple claims or records. An unbranded COVID-19 vaccine record or a record for a COVID-19 vaccine of the same brand on or within the 3 days after a previous record was considered a duplicate and was ignored. If there were records for different COVID-19 brands on the same day, or if a different-brand vaccine record occurred within 3 days after a previous record, the first-occurring record was considered as a mixed or unclassifiable dose, and the later dose was ignored.

Some, but not all, vaccine record types indicate the dose number (e.g., dose 1, dose 2, additional dose, booster). Thus, the dose number was inferred from the order of observed doses within an individual’s record; therefore, continuous enrollment was required for the entire period since the introduction of COVID-19 vaccines (or since the introduction of COVID-19 vaccines in specific age groups or populations). Because of the inability to categorize the brand and vaccine exposure patterns of those with brand-unspecified vaccine codes, if brand-unspecified codes and any other brand-specified vaccination records occurred on the same day, the brand-unspecified codes were ignored.

3.4.1.2 COVID-19 Vaccine Exposure Pattern Definition

All subsequent COVID-19 vaccines received by an individual after Time 0 during follow-up were identified and used to evaluate continuing adherence to the 2 vaccine exposure patterns being evaluated in the study (Table 3). Individuals were identified at the receipt of a booster/additional dose, and individuals were censored at the receipt of any additional dose thereafter (Table 3).

Table 3. Details of Follow-up for the Secondary Analysis of Booster/Additional Doses

Vaccine exposure pattern	Included individuals	Time 0 (beginning of follow-up)	Deviation from exposure pattern after Time 0 resulting in censoring
BNT162b2 booster/additional dose after a complete primary series	All eligible individuals with a complete primary series receiving a booster/additional dose of BNT162b2	Date of booster/additional dose of BNT162b2	Receipt of an additional dose of any COVID-19 vaccine after booster/additional dose
mRNA-1273 booster/additional dose after a complete primary series	All eligible individuals with a complete primary series receiving a booster/additional dose of mRNA-1273	Date of booster/additional dose of mRNA-1273	Receipt of an additional dose of any COVID-19 vaccine after booster/additional dose
JNJ-7836735 booster/additional dose after a complete primary series	All eligible individuals with a complete primary series receiving a booster/additional dose of JNJ-7836735	Date of booster/additional dose of JNJ-7836735	Receipt of an additional dose of any COVID-19 vaccine after booster/additional dose
No booster/additional dose after a complete primary series	Matched eligible individuals with a complete primary series without receiving a booster/additional dose	Matched calendar date	Receipt of any COVID-19 vaccine booster/additional dose

COVID-19 = coronavirus disease 2019.

3.4.2 COVID-19 Outcome Assessment

COVID-19 outcomes were identified in claims data using ICD-10-CM diagnosis codes for COVID-19 (ICD-10-CM code U07.1). Medical claims with diagnosis codes for COVID-19 outcomes were identified from inpatient, ED, outpatient, or physician billing claims in any billing position.

To evaluate the vaccines' effectiveness against both milder and more severe COVID-19 cases, the study separately considered 2 sets of nested, non-mutually exclusive COVID-19 outcomes, as follows:

- Medically diagnosed COVID-19, identified as the first identified claim during follow-up from a hospital, ED, outpatient, or physician encounter with a COVID-19 diagnosis in any coding position. The date of the claim is the outcome date.
- Hospital/ED-diagnosed COVID-19, identified as the first identified claim during follow-up from a hospital or ED record with a COVID-19 diagnosis code in any coding position. The date of the hospital or ED claim is the outcome date.

Validation studies of the ICD-10-CM diagnosis code for COVID-19 have demonstrated reasonably good validity (positive predictive values generally > 80%, specificity > 98%), with higher validity for hospitalized COVID-19 than for non-hospitalized settings.^{[17-21](#)}

3.4.3 Covariates

Covariates were identified in health insurance enrollment and claims data to describe the identified individuals in each exposure group, evaluate the comparability of the exposure groups, serve as matching characteristics, and control for confounding in propensity score models. Demographic information was collected to identify authorized, recommended, or prioritized groups for vaccination, which has varied across geography and over time.

The following individual characteristics were evaluated on the date of Time 0:

- Age, in years
- Sex
- County and state of residence (further categorized as US geographic region for descriptive results)
- Pregnancy status at Time 0

Healthcare utilization data and data on the use of preventive healthcare services were collected to account for healthcare-seeking behavior, which may be associated with adherence to preventive recommendations (such as vaccination) and other behaviors resulting in better health outcomes.^{[22-24](#)} The following individual characteristics were defined as binary indicators (unless otherwise noted), using the 365 days before and not including Time 0 (unless otherwise noted) to evaluate health status, access to healthcare, healthcare-seeking behavior, and indicators of frailty:^{[25,26](#)}

- Hospitalizations (0, 1, ≥ 2)
- ED visits (0, 1, ≥ 2)
- Skilled nursing facility stay
- Influenza vaccination
- Pneumococcal vaccination
- Encounter for cancer screening
- Eye examination
- Colonoscopy
- Bone mineral density test
- Well-check/well-child preventive healthcare visit
- Arthritis^{[25](#)}
- Lipid abnormality^{[25](#)}
- Ambulance use or life support services^{[25](#)}
- Weakness^{[25](#)}
- Pregnancy completion before Time 0 (to differentiate from active pregnancy at Time 0)

Comorbidities known to increase an individual's risk of severe COVID-19 were identified to account for differences between exposure groups. The following conditions have been identified as potentially putting individuals at higher risk of severe COVID-19¹⁴ and may serve as indicators of eligibility or prioritization for vaccination or receipt of booster/additional doses. An overall binary indicator of history of any of these conditions was defined using all available baseline data to identify individuals who might have qualified for priority groups for vaccination or booster/additional dose eligibility:

- Autoimmune disorders
- Cancer^{27,28}
- Chronic kidney disease or renal disease^{27,28}
- Chronic liver disease^{27,28}
- Chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, pulmonary embolism)²⁸
- Dementia^{25,27,28} or other neurological conditions
- Diabetes mellitus, type 1 or 2
- Down syndrome
- Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)^{27,28}
- Hypertension²⁸
- Immunocompromised state, defined as either of the following: (1) at least 2 diagnostic codes for HIV, hematological malignancy, immune deficiencies, solid malignancy, or rheumatological/inflammatory condition; or (2) at least 1 claim containing evidence an organ transplant in the 6 months prior to but not including Time 0
- Mental health conditions^{25,28}
- Obese or severely obese²⁹
- Sickle cell disease or thalassemia
- Stroke or cerebrovascular disease²⁷
- Tuberculosis

To understand the history of COVID-19 exposure, diagnosis, and testing behavior, the following individual characteristics were identified using all available baseline data before and not including Time 0:

- COVID-19 laboratory test performed (binary indicator of any test performed or none)
- COVID-19 diagnoses occurring outside a hospital or ED setting
- Hospital/ED-diagnosed COVID-19

Additional covariates included the following:

- Brand of the complete primary series
- Time since primary series completion

3.5 Statistical Analysis

This analysis evaluated the effectiveness of receiving a booster/additional dose of COVID-19 vaccine compared with not receiving a booster/additional dose in individuals aged 12 to 64 years for BNT162b2 and in individuals aged 18 to 64 years for mRNA-1273 and JNJ-7836735. Each vaccine brand was evaluated separately, and analyses were not designed to compare brands to each other, given differences in authorized age groups and calendar time of authorizations. All analyses of each brand-specific cohort were performed separately in each data source and meta-analyzed to create summary estimates.

3.5.1 Descriptive Analyses

The number of individuals meeting all eligibility criteria to be included in each brand-specific study cohort was reported by exposure group in addition to the number and proportion of individuals excluded for each exclusion criterion.

The characteristics of the included individuals receiving a booster/additional dose and the matched comparators were described, by brand. Continuous variables were described using summary statistics (i.e., means, standard deviations [SDs], medians, and first and third quartiles [Q1, Q3]). Distributions of categorical variables were described with frequency counts and proportions. The balance of covariates between exposure groups was evaluated with absolute standardized differences (ASDs).³⁰

3.5.2 Propensity Score Approach

Within each cohort, differences in the distribution of baseline characteristics were addressed via inverse probability of treatment (IPT) weighting propensity score methods. The predicted probability of vaccine exposure (i.e., the propensity score) was estimated via a logistic regression model with the matching factors³¹ and the remaining identified baseline characteristics as independent variables. The distributions of the propensity scores by vaccine exposure group were plotted to visualize the degree of overlap between the vaccine exposure groups. To reduce the effect of extreme weights, the propensity score was used to compute stabilized IPT weights³² that were applied to the analytic cohorts.

3.5.3 Main Outcome Analyses

3.5.3.1 Overall

All outcome analyses were performed separately for the 2 COVID-19 outcomes: medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19.

Within each of the brand-specific cohorts, all individuals were followed from Time 0 until censoring ([Section 3.3.1.2](#)) or until the occurrence of the COVID-19 outcome of interest. The cumulative incidence of each COVID-19 outcome was estimated in each IPT-weighted vaccine exposure group as 1 minus the Kaplan-Meier estimator.³³ Cumulative incidence curves were plotted for the whole study period by vaccine exposure group.

As an overall summary of the relative incidence of COVID-19 outcomes in the boosted and unboosted groups across the entire study period, a hazard ratio (HR) and 95% confidence intervals (CIs) for each

outcome were estimated using an IPT-weighted Cox proportional hazards model with robust sandwich variance estimators. The overall VE was estimated as 1 minus the HR.

3.5.4 Subgroup Analyses

3.5.4.1 *Effectiveness by Immunocompromised Status*

For BNT-162b2 and mRNA-1273, there were authorizations and recommendations for receiving an additional dose for immunocompromised individuals; for all vaccine brands, there were also different authorizations and recommendations for receiving booster doses for the general population ([Table 2](#)).³⁴ Thus, subgroup analyses were performed among immunocompromised and immunocompetent individuals.

3.5.4.2 *Effectiveness by Variant-specific Eras*

To evaluate potential changes in VE over time because of circulating variants, the cumulative incidence and VE estimation analyses were performed separately within variant-specific eras, as follows:

- Delta era: individuals with Time 0 between 01 June 2021 (the start of the Delta era, but before booster authorization) and 24 December 2021, with follow-up censored on 24 December 2021
- Omicron era: individuals with Time 0 on or after 25 December 2021, with follow-up censored at the end of data availability

Because of the timing of booster/additional dose authorizations relative to variant eras, analyses were not performed for the pre-Delta variant era. Each era-specific analysis was restricted to individuals with a Time 0 (date of receipt of a booster/ additional dose or matched date) within the era, and follow-up was censored on the last calendar day of the era (or 1 of the other prespecified censoring criteria [[Section 3.3.1.2](#)], if they occurred first); era-specific HRs were estimated.

3.5.4.3 *Heterologous or Homologous Booster/Additional Dose Status*

Subgroup analyses by heterologous or homologous booster/additional dose status were performed. Homologous subgroups were defined as the brand of booster/additional dose matching the brand of the primary series. The heterologous subgroups were defined 2 separate ways: (1) any other primary series brand; and (2) individual brand primary series. The “any other primary series brand” analyses were defined as the brand of the primary series being any brand other than the brand of the booster/additional dose (e.g., all individuals with a BNT162b2 booster/additional dose after an mRNA-1273 or JNJ-7836735 primary series). The “individual brand primary series” analyses were defined as a specific combination of individual booster/additional dose and the primary series brand (e.g., all individuals with a BNT162b2 booster/additional dose after an mRNA-1273 primary series).

The interpretation of the 2 homologous/heterologous analyses are slightly different. The “any other primary series” brand analysis was meant to facilitate comparisons between individuals who receive a brand-specific additional dose/booster, regardless of what primary series was completed. The individual brand primary series analysis was intended to facilitate comparisons between individuals who received the same primary series, but different additional dose/booster brands, reflecting the clinical decision-making process at the time of additional dose/booster receipt.

3.5.5 Additional Analyses

3.5.5.1 Negative Outcome Control

As a negative control outcome to evaluate residual confounding due to unmeasured differences between individuals who did and did not receive an additional dose/booster, the cumulative incidence during the first 10 days after Time 0 was visually inspected and HRs estimated at day 10 were evaluated. A biologic effect of vaccination immediately after vaccination (i.e., by day 10) would not be expected because of a lack of a full immune response, and previous research has demonstrated reasonable overlap of cumulative incidence curves for the 7 to 10 days following receipt of a third dose of BNT162b2 vaccine.³⁵

3.5.5.2 Quantitative Bias Analysis for Exposure Misclassification

Although vaccinations were identified in both health insurance claims data and IIS vaccine records,⁷ the risk of exposure misclassification remains because patients may have obtained the COVID-19 vaccine without generating a record in the available data sources. Quantitative bias analyses^{36,37} were performed to estimate the impact of truly boosted individuals being misclassified as unboosted because of missing vaccine records. No gold standard for vaccine status is available, so estimates of statewide receipt of COVID-19 vaccine among individuals aged younger than 65 years from CDC, state departments of health, and capture-recapture methods^{10,38,39} were obtained at dates that most closely matched the last date of service in the IIS data (in Optum, the receipt of a booster/additional dose was evaluated; in CVS Health, the receipt of at least 1 dose of COVID-19 vaccine was evaluated). These estimates were compared with observed state-level estimates in the claims-IIS data sources⁷ to estimate maximum and minimum potential positive sensitivities of vaccine exposure.

Using the estimated vaccine exposure sensitivities, a simple quantitative bias analysis evaluating the impact of nondifferential exposure misclassification was performed. The primary analyses estimated HRs, but for the purposes of the quantitative bias analyses, relative risks (RRs) and 95% CIs were estimated in the weighted cohorts using a fixed 61-day follow-up time for both outcomes.

Specificity of the study's vaccine assessment was assumed to be 100% (i.e., all observed claims or IIS records were assumed to be true vaccination events, and no truly unboosted individual was misclassified as being boosted). Using the minimum and maximum estimated sensitivity estimates from CDC, state departments of health, or capture-recapture methods, 2 "corrected" RR estimates—a minimum and maximum corrected estimate—were generated for each outcome by reassigning exposure status from unboosted to boosted based on the sensitivity estimate. A correction factor was then estimated as follows:

$$\text{bias correction factor} = 1 - \frac{\text{corrected RR}}{\text{uncorrected RR}}$$

The bias correction factors were then applied to the observed HR estimates from the primary analyses.

3.5.6 Meta-analysis of Data Source–specific Results

All analyses were performed separately within each data source using a common protocol, and database-specific results were reported for all analyses. Meta-analyses across data sources were performed of the overall VE estimates, immunocompromised and immunocompetent subgroups, and homologous/heterologous boosting strategies as a summary of the results across both data sources. Given that a common study protocol was applied in the 2 similar, national commercial claims database that cover populations with similar demographics, data source–specific VE estimates from the 2 databases were combined with fixed-effects meta-analysis methods.⁴⁰ Statistical evidence of heterogeneity between data sources was evaluated by obtained log-transformed HR estimates and their standard errors. *P*-values less than 0.05 were considered evidence of statistical heterogeneity between study estimates. Meta-analyses were conducted using the package meta (version 5.2.0) of R Statistical Software (version 4.1.2; R Core Team 2021).

4 Results

We identified 1,413,329 eligible individuals receiving a booster/additional dose during the study period (62% BNT162b2, 37% mRNA-1273, 1% JNJ-7836735). The attrition of individuals into the matched, brand-specific booster/additional dose cohorts is shown in [Figure B-1-Optum](#) and [Figure B-1-CVS](#). Because the study populations, time periods of authorization, and vaccine products differ, the results are presented separately by vaccine brand in the following sections.

4.1 Descriptive Results

During the study period in Optum, we identified 150,433 eligible individuals receiving a booster/additional dose of BNT162b2, 97,027 receiving an booster/additional dose of mRNA-1273, and 3,000 receiving a booster/additional dose of JNJ-7836735 ([Figure B-1-Optum](#)). After matching, the final booster/additional dose analytic cohorts consisted of 118,326 in each group in for BNT162b2, 68,117 in each group for mRNA-1273, and 1,615 in each group for JNJ-7836735.

In CVS Health, we identified 727,811 eligible individuals receiving a booster/additional dose of BNT162b2, 420,449 receiving a booster/additional dose of mRNA-1273, and 14,609 receiving a booster/additional dose of JNJ-7836735 ([Figure B-1-CVS](#)). After matching, the final booster/additional dose analytic cohorts consisted 633,839 in each group for BNT162b2, 342,384 in each group for mRNA-1273, and 9,783 in each group for JNJ-7836735.

Selected characteristics of the brand-specific cohorts of individuals receiving a booster/additional dose and matched comparators are shown in [Table 4](#) (BNT162b2), [Table 5](#) (mRNA-1273), and [Table 6](#) (JNJ-7836735). Complete patient characteristics are shown in [Table B-1-Optum](#), [Table B-2-Optum](#), [Table B-3-Optum](#), [Table B-1-CVS](#), [Table B-2-CVS](#), and [Table B-3-CVS](#). The characteristics of individuals receiving a booster/additional dose who were excluded because of a failure to match are shown in [Table B-4-Optum](#) and [Table B-4-CVS](#).

Within each vaccine-specific cohort, the distribution of the propensity scores by exposure group suggested good exchangeability of the exposure groups ([Figure B-2-Optum](#), [Figure B-2-CVS](#)).

Table 4. Selected Characteristics of Individuals Aged 12–64 Years Receiving a BNT162b2 Booster/Additional Dose of COVID-19 Vaccine and Matched Individuals With a Complete Primary Series Without a Booster/Additional Dose

Characteristic	Optum, BNT162b2 boosted individuals N = 118,326	Optum, matched unboosted comparators N = 118,326	Optum, ASD	CVS Health, BNT162b2 boosted individuals N = 633,839	CVS Health, matched unboosted comparators N = 633,839	CVS Health, ASD
Age, years						
Median (Q1, Q3)	43 (31, 54)	43 (31, 54)		41 (28, 53)	41 (28, 53)	
Mean (SD)	41.45 (14.75)	41.44 (14.72)	0.00	40.22 (15.25)	40.21 (15.21)	0.00
Sex, N (%)						
Female	61,089 (51.63)	61,089 (51.63)	0.00	342,679 (54.06)	342,679 (54.06)	0.00
Male	57,237 (48.37)	57,237 (48.37)	0.00	291,160 (45.94)	291,160 (45.94)	0.00
Days since primary completion						
Median (Q1, Q3)	226 (209, 246)	226 (208, 246)		231 (212, 258)	231 (211, 257)	
Mean (SD)	228.10 (31.69)	227.75 (31.88)	0.01	236.31 (37.44)	236.09 (37.61)	0.01
Primary series brand, N (%)						
JNJ-7836735	5,026 (4.25)	5,026 (4.25)	0.00	20,496 (3.23)	20,496 (3.23)	0.00
mRNA-1273	6,336 (5.35)	6,336 (5.35)	0.00	29,869 (4.71)	29,869 (4.71)	0.00
BNT162b2	106,964 (90.40)	106,964 (90.40)	0.00	583,474 (92.05)	583,474 (92.05)	0.00
Region, N (%)						
Northeast	14,961 (12.64)	14,961 (12.64)	0.00	93,202 (14.70)	93,202 (14.70)	0.00
South	4,815 (4.07)	4,815 (4.07)	0.00	123,007 (19.41)	123,007 (19.41)	0.00
Midwest	68,497 (57.89)	68,497 (57.89)	0.00	116,633 (18.40)	116,633 (18.40)	0.00
West	30,053 (25.40)	30,053 (25.40)	0.00	300,997 (47.49)	300,997 (47.49)	0.00
Pregnant, N (%)	603 (0.99)	681 (1.11)	0.01	3,667 (0.58)	4,009 (0.63)	0.01
Immunocompromised state, N (%)	3,725 (3.15)	3,725 (3.15)	0.00	18,592 (2.93)	18,592 (2.93)	0.00
Influenza vaccination received, N (%)	45,631 (38.56)	45,631 (38.56)	0.00	206,451 (32.57)	206,451 (32.57)	0.00

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Table 5. Selected Characteristics of Individuals Aged 18–64 Years Receiving an mRNA-1273 Booster/Additional Dose of COVID-19 Vaccine and Matched Individuals With a Complete Primary Series Without a Booster/Additional Dose

Characteristic	Optum, mRNA-1273 boosted individuals N = 68,117	Optum, matched unboosted comparators N = 68,117	Optum, ASD	CVS Health, mRNA-1273 boosted individuals N = 342,384	CVS Health, matched unboosted comparators N = 342,384	CVS Health, ASD
Age, years						
Median (Q1, Q3)	45 (35, 56)	45 (35, 56)		46 (34, 56)	46 (34, 56)	
Mean (SD)	44.71 (12.46)	44.68 (12.44)	0.00	44.31 (13.11)	44.3 (13.1)	0.00
Sex, N (%)						
Female	34,613 (50.81)	34,613 (50.81)	0.00	177,495 (51.84)	177,495 (51.84)	0.00
Male	33,504 (49.19)	33,504 (49.19)	0.00	164,889 (48.16)	164,889 (48.16)	0.00
Days since primary completion						
Median (Q1, Q3)	229 (211, 250)	229 (211, 250)		233 (213, 258)	232 (213, 258)	
Mean (SD)	232.31 (31.36)	231.99 (31.60)	0.01	237.84 (35.54)	237.66 (35.74)	0.01
Primary series brand, N (%)						
JNJ-7836735	5,457 (8.01)	5,457 (8.01)	0.00	24,503 (7.16)	24,503 (7.16)	0.00
mRNA-1273	51,656 (75.83)	51,656 (75.83)	0.00	257,913 (75.33)	257,913 (75.33)	0.00
BNT162b2	11,004 (16.15)	11,004 (16.15)	0.00	59,968 (17.51)	59,968 (17.51)	0.00
Region, N (%)						
Northeast	8,357 (12.27)	8,357 (12.27)	0.00	58,817 (17.18)	58,817 (17.18)	0.00
South	1,959 (2.88)	1,959 (2.88)	0.00	43,146 (12.60)	43,146 (12.60)	0.00
Midwest	39,636 (58.19)	39,636 (58.19)	0.00	59,997 (17.52)	59,997 (17.52)	0.00
West	18,165 (26.67)	18,165 (26.67)	0.00	180,424 (52.70)	180,424 (52.70)	0.00
Pregnant, N (%)	393 (1.14)	426 (1.23)	0.01	1,749 (0.51)	2,036 (0.59)	0.01
Immunocompromised state, N (%)	1,932 (2.84)	1,932 (2.84)	0.00	10,432 (3.05)	10,432 (3.05)	0.00
Influenza vaccination received, N (%)	26,325 (38.65)	26,325 (38.65)	0.00	116,297 (33.97)	116,297 (33.97)	0.00

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Table 6. Selected Characteristics of Individuals Aged 18–64 Years Receiving a JNJ-7836735 Booster/Additional Dose of COVID-19 Vaccine and Matched Individuals With a Complete Primary Series Without a Booster/Additional Dose

Characteristic	Optum, JNJ-7836735 boosted individuals N = 1,615	Optum, matched unboosted comparators N = 1,615	Optum, ASD	CVS Health, JNJ-7836735 boosted individuals N = 9,783	CVS Health, matched unboosted comparators N = 9,783	CVS Health, ASD
Age, years						
Median (Q1, Q3)	50 (39, 58)	50 (39, 58)		51 (40, 58)	51 (40, 58)	0.00
Mean (SD)	47.85 (11.83)	47.71 (11.79)	0.01	47.65 (12.37)	47.65 (12.39)	0.00
Sex, N (%)						
Female	699 (43.28)	699 (43.28)	0.00	4,346 (44.42)	4,346 (44.42)	0.00
Male	916 (56.72)	916 (56.72)	0.00	5,437 (55.58)	5,437 (55.58)	0.00
Days since primary completion						
Median (Q1, Q3)	232 (214, 252)	232 (213, 252)		233 (213, 253)	233 (213, 253)	0.00
Mean (SD)	232.31 (33.90)	232.14 (33.94)	0.00	232.75 (36.83)	232.67 (36.83)	0.00
Primary series brand, N (%)						
JNJ-7836735	1,496 (92.63)	1,496 (92.63)	0.00	8,995 (91.95)	8,995 (91.95)	0.00
mRNA-1273	47 (2.91)	47 (2.91)	0.00	282 (2.88)	282 (2.88)	0.00
BNT162b2	72 (4.46)	72 (4.46)	0.00	506 (5.17)	506 (5.17)	0.00
Region, N (%)						
Northeast	191 (11.83)	191 (11.83)	0.00	2,173 (22.21)	2,173 (22.21)	0.00
South	32 (1.98)	32 (1.98)	0.00	1,340 (13.70)	1,340 (13.70)	0.00
Midwest	950 (58.82)	950 (58.82)	0.00	1,298 (13.27)	1,298 (13.27)	0.00
West	442 (27.37)	442 (27.37)	0.00	4,972 (50.82)	4,972 (50.82)	0.00
Pregnant, N (%)	0 (0.00)	< 11	0.11	19 (0.19)	26 (0.27)	0.01
Immunocompromised state, N (%)	37 (2.29)	37 (2.29)	0.00	222 (2.27)	222 (2.27)	0.00
Influenza vaccination received, N (%)	445 (27.55)	445 (27.55)	0.00	2,280 (23.31)	2,280 (23.31)	0.00

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

4.2 Outcome Results

For BNT162b2 and mRNA-1273, across vaccine brand and outcome, there was a maximum follow-up of 201 days in Optum and 232 days in CVS Health; for JNJ-7836735, the maximum follow-up was shorter (131 days, Optum; 186 days, CVS Health) given the later authorization date. In Optum, the median follow-up for all boosted groups was approximately 75 to 85 days (depending on the vaccine and outcome); in CVS Health, median follow-up among the boosted ranged from 107 to 119 days. Median follow-up was shorter for the unboosted comparator groups (Table 7) because they could be censored for receiving a booster/additional dose and had more COVID-19 events.

Table 7. Distribution of Follow-up Time by COVID-19 Outcome, Booster/Additional Dose Status, and Data Source

COVID-19 outcome	Booster/ additional dose exposure group	N	Sum of days of person- time	Mean days of person- time (SD)	Median days of person- time (Q1, Q3)	Min, max days of person- time
Optum						
Medically diagnosed	BNT162b2	118,326	8,807,161	74 (37)	75 (47, 99)	1, 201
	None	118,326	5,261,360	44 (33)	38 (17, 65)	1, 201
	mRNA-1273	68,117	5,143,221	76 (34)	79 (52, 101)	1, 201
	None	68,117	2,996,789	44 (33)	37 (16, 68)	1, 201
	JNJ-7836735	1,615	128,604	80 (33)	84 (57, 108)	1, 131
	None	1,615	81,651	51 (35)	45 (21, 78)	1, 131
Hospital/ED-diagnosed	BNT162b2	118,326	8,916,106	75 (37)	75 (48, 100)	1, 201
	None	118,326	5,387,213	46 (34)	39 (18, 68)	1, 201
	mRNA-1273	68,117	5,201,099	76 (34)	80 (53, 101)	1, 201
	None	68,117	3,066,068	45 (33)	38 (17, 69)	1, 201
	JNJ-7836735	1,615	131,182	81 (33)	85 (60, 108)	1, 131
	None	1,615	83,704	52 (35)	47 (21, 79)	1, 131
CVS Health						
Medically diagnosed	BNT162b2	633,839	67,365,604	106 (43)	107 (79, 135)	1, 232
	None	633,839	35,902,792	57 (44)	47 (18, 87)	1, 232
	mRNA-1273	342,384	36,334,171	106 (36)	112 (86, 132)	1, 232
	None	342,384	19,323,986	56 (44)	45 (18, 92)	1, 232
	JNJ-7836735	9,783	1,078,067	110 (36)	118 (88, 139)	1, 186
	None	9,783	653,948	67 (47)	60 (23, 109)	1, 161
Hospital/ED-diagnosed	BNT162b2	633,839	68,162,932	108 (42)	108 (80, 136)	1, 232
	None	633,839	36,766,210	58 (44)	49 (19, 88)	1, 232
	mRNA-1273	342,384	36,715,628	107 (36)	112 (87, 133)	1, 232
	None	342,384	19,786,800	58 (44)	47 (18, 94)	1, 232
	JNJ-7836735	9,783	1,098,347	112 (35)	119 (93, 140)	1, 186
	None	9,783	671,553	69 (47)	64 (25, 112)	1, 161

COVID-19 = coronavirus disease 2019; ED = emergency department; min, max = minimum and maximum; Q1, Q3 = first and third quartiles; SD = standard deviation.

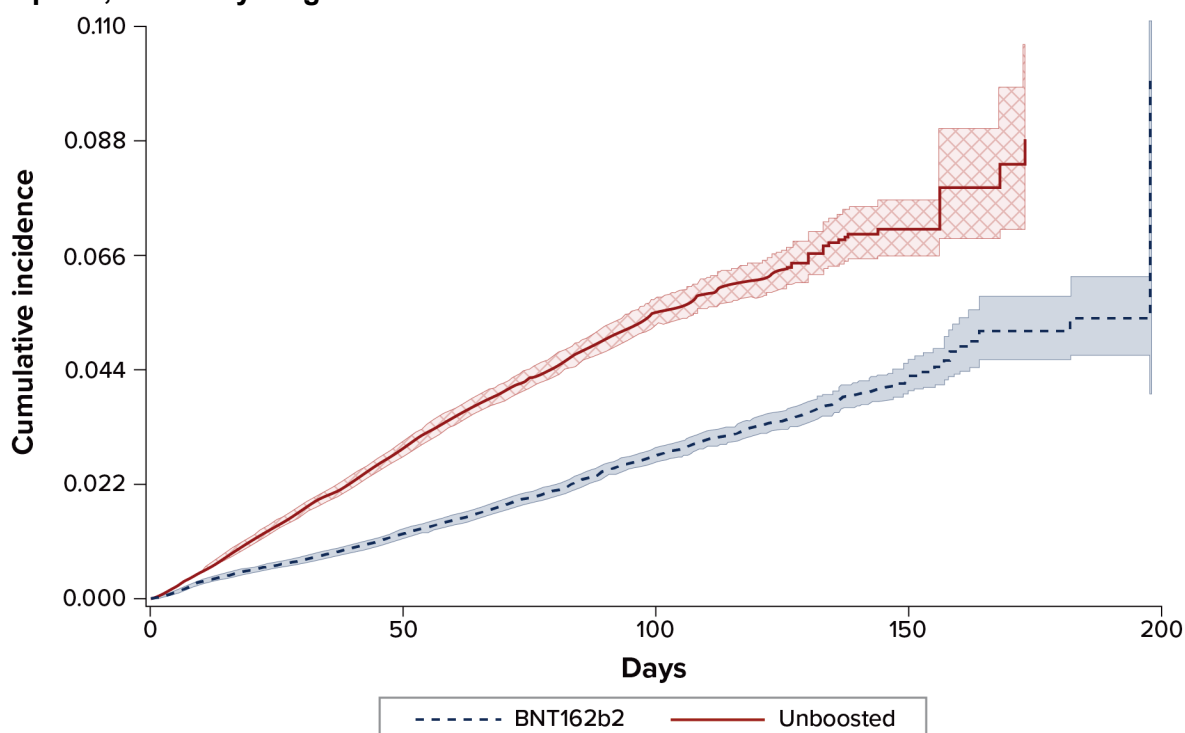
4.2.1 BNT162b2

4.2.1.1 Overall Results

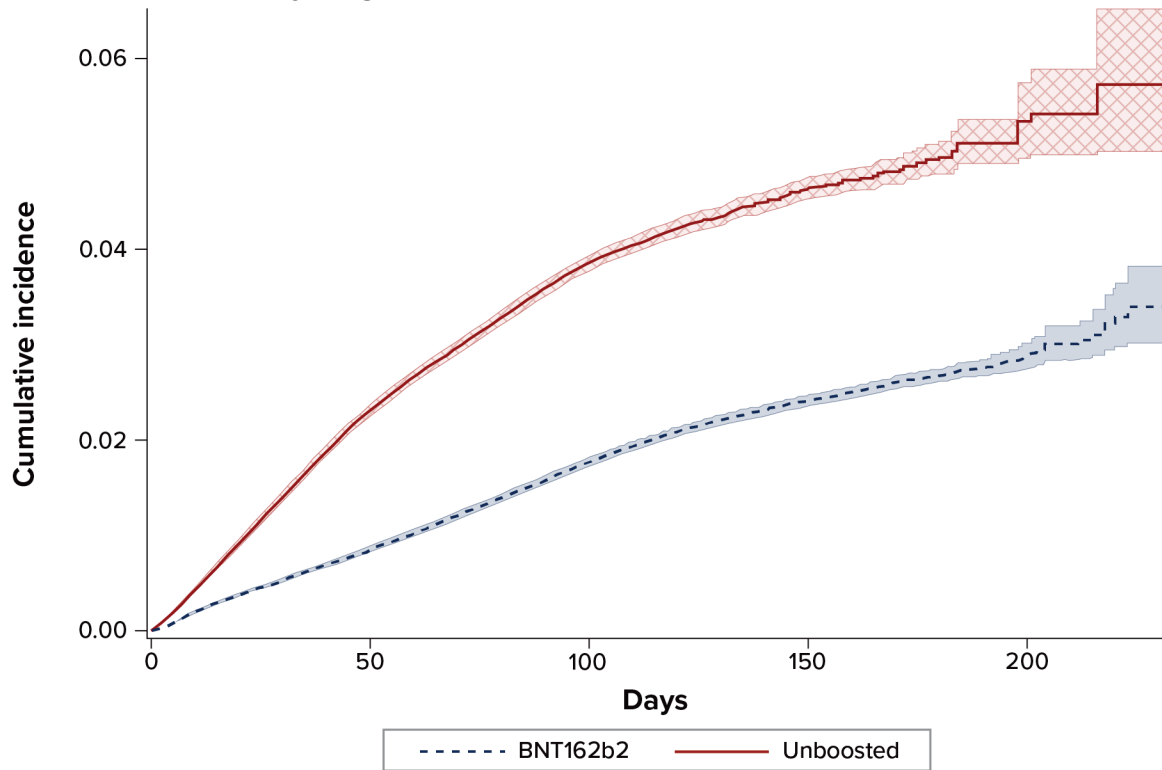
The cumulative incidence of COVID-19 outcomes over time by BNT162b2 booster/additional dose status is shown in [Figure 2](#). The risk of both COVID-19 outcomes was lower in the boosted group than the unboosted comparator group in both data sources across all of follow-up. The cumulative incidence of medically diagnosed COVID-19 was slightly higher in Optum compared with CVS Health for both exposure groups, but the cumulative incidence of hospitalized/ED-diagnosed COVID-19 was similar between the 2 data sources for both exposure groups.

Figure 2. Weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of BNT162b2 COVID-19 Vaccine and Matched, Unboosted Comparators

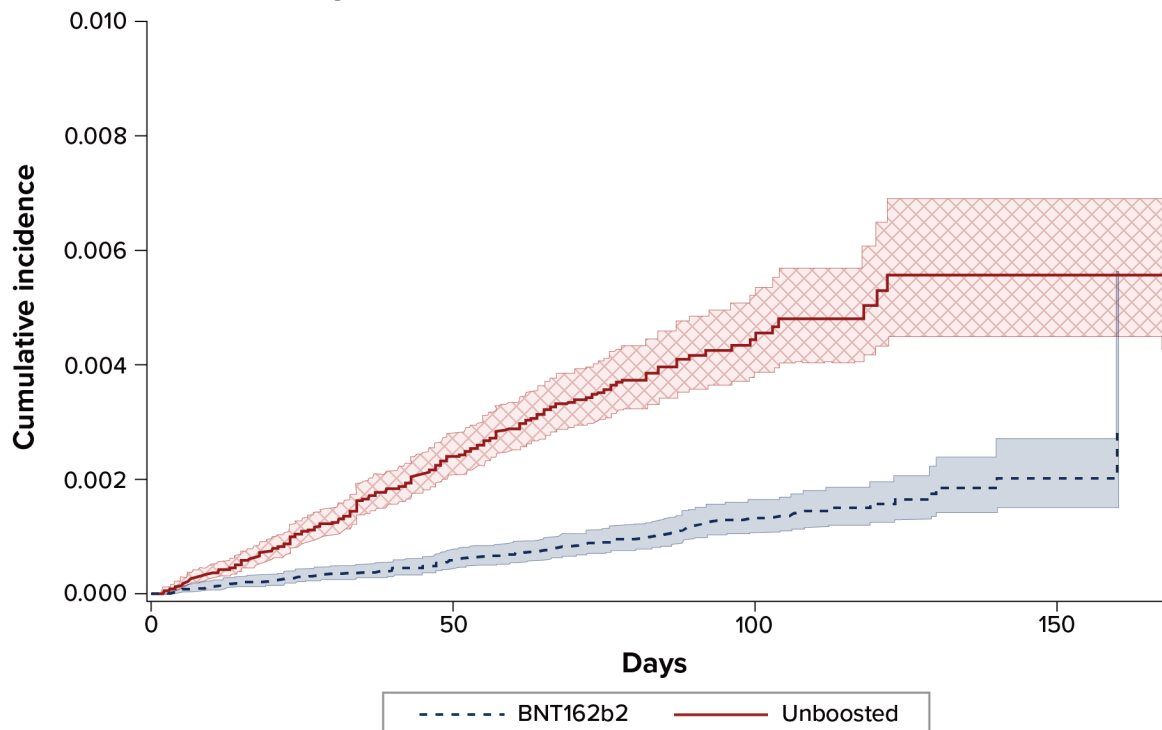
A. Optum, Medically diagnosed COVID-19



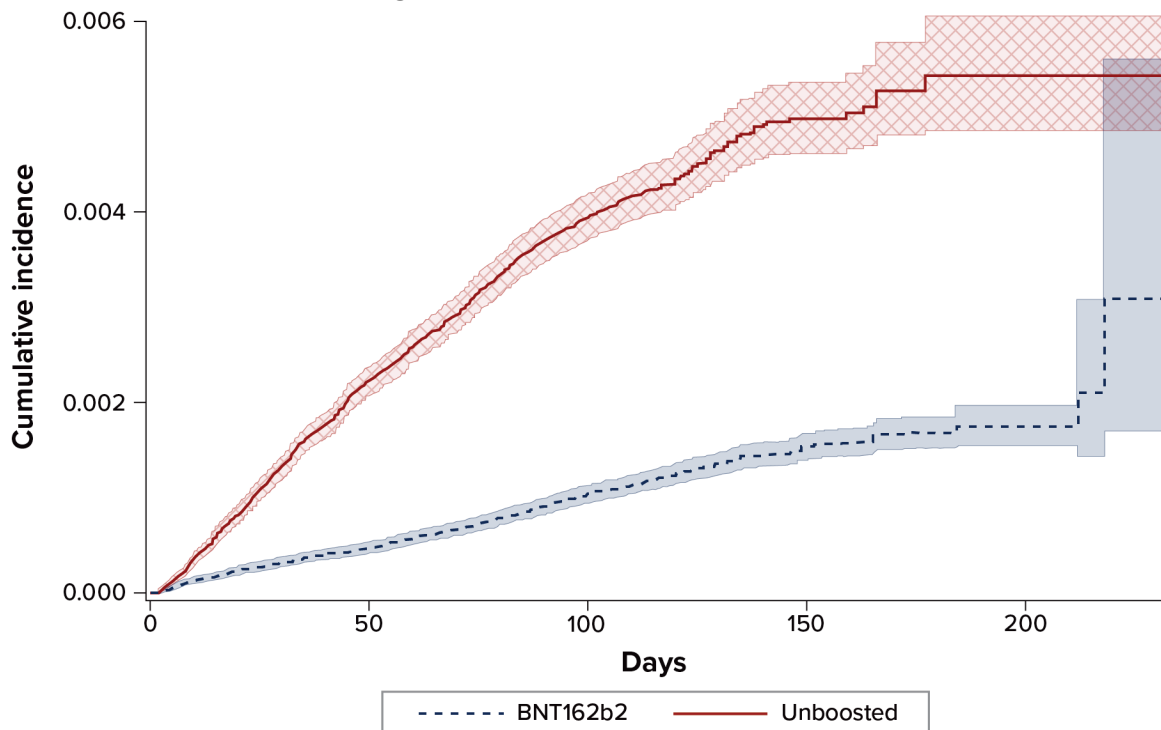
B. CVS Health, Medically diagnosed COVID-19



C. Optum, Hospital/ED-diagnosed COVID-19



D. CVS Health, Hospital/ED-diagnosed COVID-19



COVID-19 = coronavirus disease 2019; ED = emergency department.

The estimated effectiveness of receiving a BNT162b2 booster/additional dose against COVID-19 outcomes compared with not receiving a booster/additional dose is detailed in [Table B-5-Optum](#) and [Table B-5-CVS](#). A summary of VE estimates across data sources is shown in [Table 8](#). The meta-analyzed VE estimates for BNT162b2 were 54% (95% CI, 53%-56%) against any medically diagnosed COVID-19 and were higher against hospital/ED-diagnosed COVID-19: 73% (95% CI, 70%-76%). The VE estimates were similar across data sources.

Table 8. Estimated Effectiveness of Receiving a Booster/Additional Dose of BNT162b2 COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose, by Data Source and Meta-Analyzed

Outcome	Data source	Booster / additional dose exposure group	N	Events	VE (95% CI)
Medically diagnosed	Optum	BNT162b2	118,326	2,415	52% (49%-55%)
		None	118,326	3,001	—
	CVS Health	BNT162b2	633,839	11,760	55% (53%-56%)
		None	633,839	14,338	—
	Meta-analyzed	NA	NA	NA	54% (53%-56%) ^a
Hospital/ED-diagnosed	Optum	BNT162b2	118,326	113	73% (65%-78%)
		None	118,326	247	—
	CVS Health	BNT162b2	633,839	710	73% (70%-76%)
		None	633,839	1,452	—
	Meta-analyzed	NA	NA	NA	73% (70%-76%) ^b

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; NA = not applicable; VE = vaccine effectiveness.

^a *p*-value for heterogeneity = 0.09; *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source-specific VE estimates.

^b *p*-value for heterogeneity = 0.98; *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source-specific VE estimates.

— indicates reference group.

4.2.1.2 Quantitative Bias Analysis

The effect of exposure misclassification was estimated with assumed vaccine exposure sensitivities of 84% and 69% in Optum and 89% and 69% in CVS Health. Results of the quantitative bias analyses are detailed in [Table B-5-Optum](#) and [Table B-5-CVS](#). A summary of quantitative bias analysis results is shown in [Table 9](#). Any degree of missing vaccine records (i.e., vaccine exposure measurements < 100%) would result in the observed VE being an underestimate of the true VE, because truly boosted individuals would be included in the unboosted comparator, reducing the COVID-19 incidence in the comparator. Quantitative bias analyses suggest that the observed primary VE estimate for BNT162b2 may underestimate the true VE by 2 to 12 percentage points.

Table 9. Estimated Effectiveness of Receiving a Booster/Additional Dose of BNT162b2 COVID-19 Vaccine, Corrected for Potentially Missing Vaccine Records

COVID-19 outcome	Data source	Hypothesized sensitivity of vaccination exposure measurement	Corrected VE (95% CI)
Medically diagnosed	Optum	100% (uncorrected)	52% (49%-55%)
		84%	56% (53%-59%)
		69%	63% (61%-66%)
	CVS Health	100% (uncorrected)	55% (53%-56%)
Hospital/ED-diagnosed	Optum	89%	57% (56%-59%)
		69%	67% (66%-68%)
		100% (uncorrected)	73% (65%-78%)
	CVS Health	84%	77% (70%-81%)
		69%	82% (77%-86%)

COVID-19 outcome	Data source	Hypothesized sensitivity of vaccination exposure measurement	Corrected VE (95% CI)
	CVS Health	100% (uncorrected)	73% (70%-76%)
		89%	75% (73%-78%)
		69%	82% (81%-84%)

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

4.2.1.3 Negative Control Analysis

Cumulative incidence curves of COVID-19 outcomes in the first 10 days following and including Time 0 are detailed in [Figure B-4-Optum](#) and [Figure B-4-CVS](#). HRs and VE estimates considering only the first 10 days after and including Time 0 are shown in [Table B-9-Optum](#) and [Table B-9-CVS](#). A summary of the negative control analysis findings is shown in [Table 10](#). In both data sources, the incidence of both COVID-19 outcomes for all vaccines was very low during the negative control period (e.g., cumulative incidence of medically diagnosed COVID-19 of approximately 0.004 and of hospital/ED-diagnosed COVID-19 of approximately 0.0004 in the boosted group by day 9, i.e., the 10th day of follow-up), and the absolute differences in COVID-19 incidence between the booster/additional dose and unboosted comparator groups were small. However, the estimated VEs during the early negative control period indicated a non-null association of vaccination with COVID-19 outcomes ([Table 10](#)).

Table 10. Estimated Effectiveness of Receiving a Booster/Additional Dose of BNT162b2 COVID-19 Vaccine, 10 Days After and Including Time 0, Negative Control Outcome Analysis

COVID-19 outcome	Data source	Booster / additional dose events	Comparator events	VE (95% CI)
Medically diagnosed	Optum	400	584	35% (26%-43%)
	CVS Health	1,332	2,656	54% (51%-57%)
Hospital/ED-diagnosed	Optum	15	42	65% (37%-81%)
	CVS Health	88	220	64% (53%-72%)

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

4.2.1.4 Subgroup Analyses

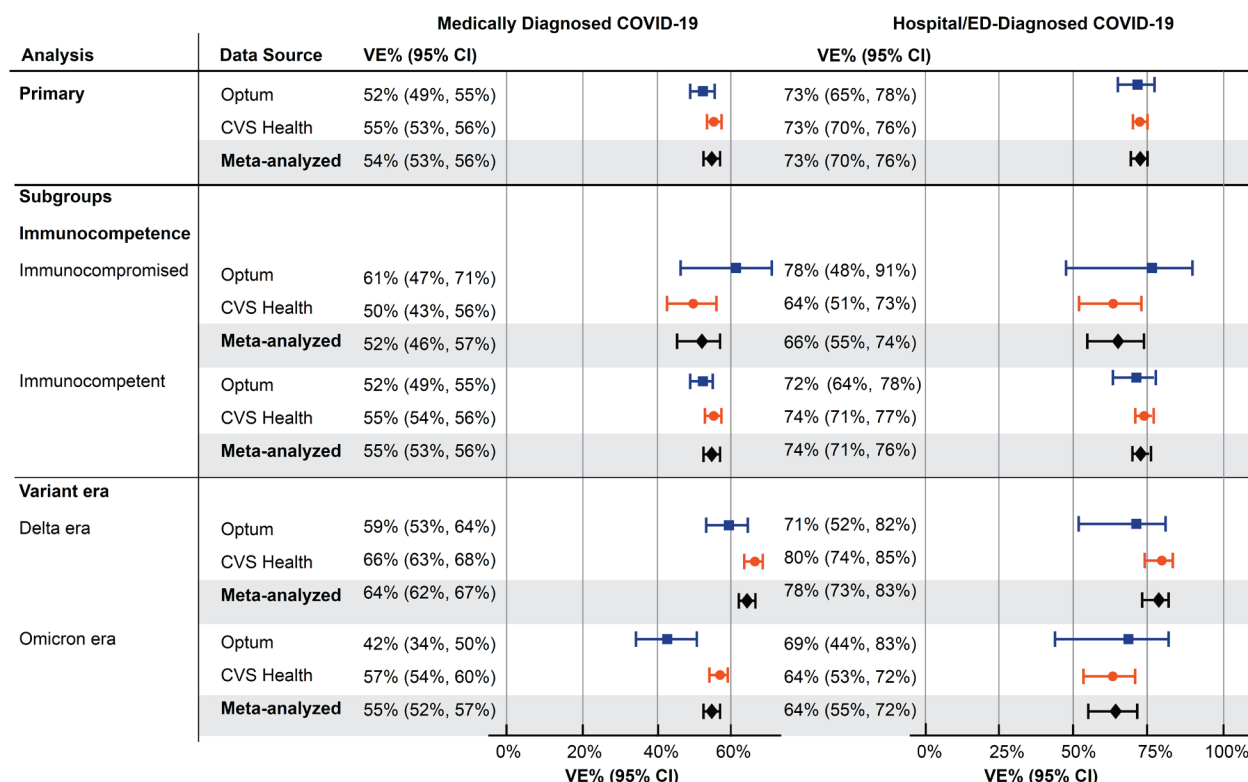
A summary of the VE estimates in subgroups of immunocompromised status and variant era is shown in [Figure 3](#). Details of the VE estimates in subgroups of individuals by immunocompromised status are shown in [Table B-6-Optum](#) and [Table B-6-CVS](#). The estimated effectiveness of a booster/additional dose against COVID-19 outcomes by variant era and brand is detailed in [Table B-7-Optum](#) and [Table B-7-CVS](#), and cumulative incidence of COVID-19 outcomes by brand and vaccine-specific era are shown in [Figure B-3-Optum](#) and [Figure B-3-CVS](#).

When evaluating BNT162b2 effectiveness by immunocompetence, there was little difference between meta-analyzed estimates for the immunocompromised (VE = 52%; 95% CI, 46%-57%) and immunocompetent (VE = 55%; 95% CI, 53%-56%) groups for medically diagnosed COVID-19, but the VE estimate against hospital/ED-diagnosed COVID-19 was lower in the immunocompromised subgroup (VE = 66%; 95% CI, 55%-74%) than the immunocompetent (VE = 74%; 95% CI, 71%-76%), although the immunocompromised estimate was imprecise. The immunocompromised subgroup, however, generally

had higher incidence of both COVID-19 outcomes than the immunocompetent group ([Table B-6-Optum](#), [Table B-6-CVS](#)).

When evaluating VE by variant era, VE estimates for both COVID-19 outcomes were lower in the Omicron era than the Delta era ([Figure 3](#)), although the incidence of both COVID-19 outcomes was higher in the Omicron era than the Delta era ([Table B-7-Optum](#), [Table B-7-CVS](#)).

Figure 3. Estimated Effectiveness of Receiving a Booster/Additional Dose of BNT162b2 COVID-19 Vaccine, by Immunocompetence Status and Variant Era

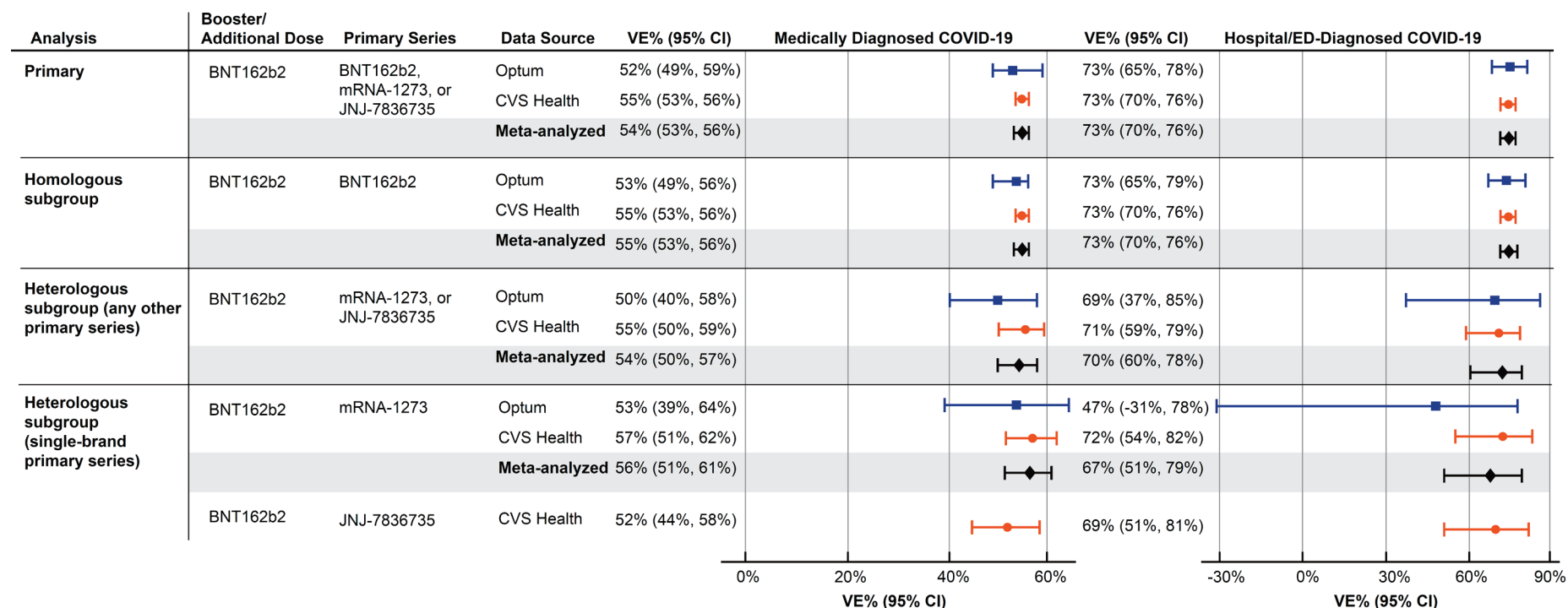


CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

Note: The Delta era was considered 1 June 2021 to 24 December 2021; the Omicron era was considered 25 December 2021 to the end of data availability.

A summary of the subgroup analyses by homologous or heterologous booster status is shown in [Figure 4](#). Details of these analyses by data source are given in [Table B-8-Optum](#) and [Table B-8-CVS](#). VE estimates for both medically diagnosed and hospital/ED-diagnosed COVID-19 were generally similar across homologous and heterologous boosting strategies, with meta-analyzed medically diagnosed COVID-19 VE estimates ranging from 54% to 56%, and hospital/ED-diagnosed COVID-19 VE estimates ranging from 67% to 73%.

Figure 4. Estimated Effectiveness of Receiving a Booster/Additional Dose of BNT162b2 COVID-19 Vaccine, by Homologous or Heterologous Booster Status



CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

Note: The heterologous (any other primary series) analyses defined exposure groups first by the brand of the booster/additional dose and then required that the primary series be of any other brand. The heterologous (single-brand primary series) analysis defined exposure groups first by the brand of the booster/additional dose and then divided into subgroups of individual brands of primary series.

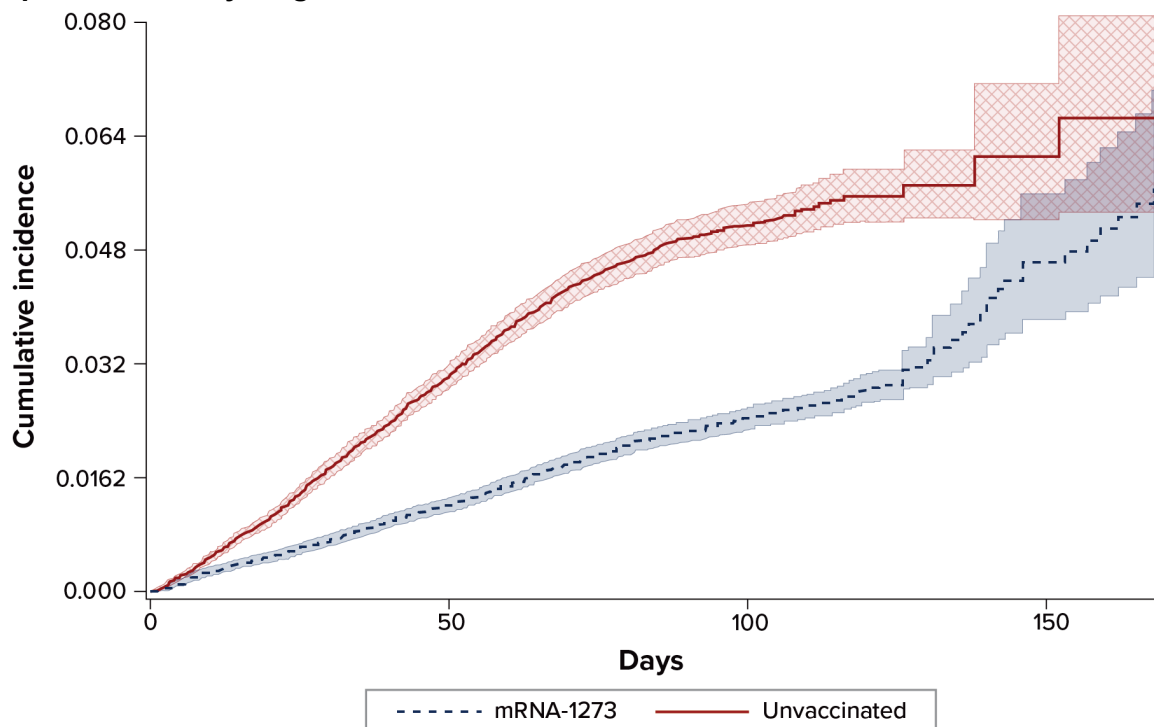
4.2.2 mRNA-1273

4.2.2.1 Overall Results

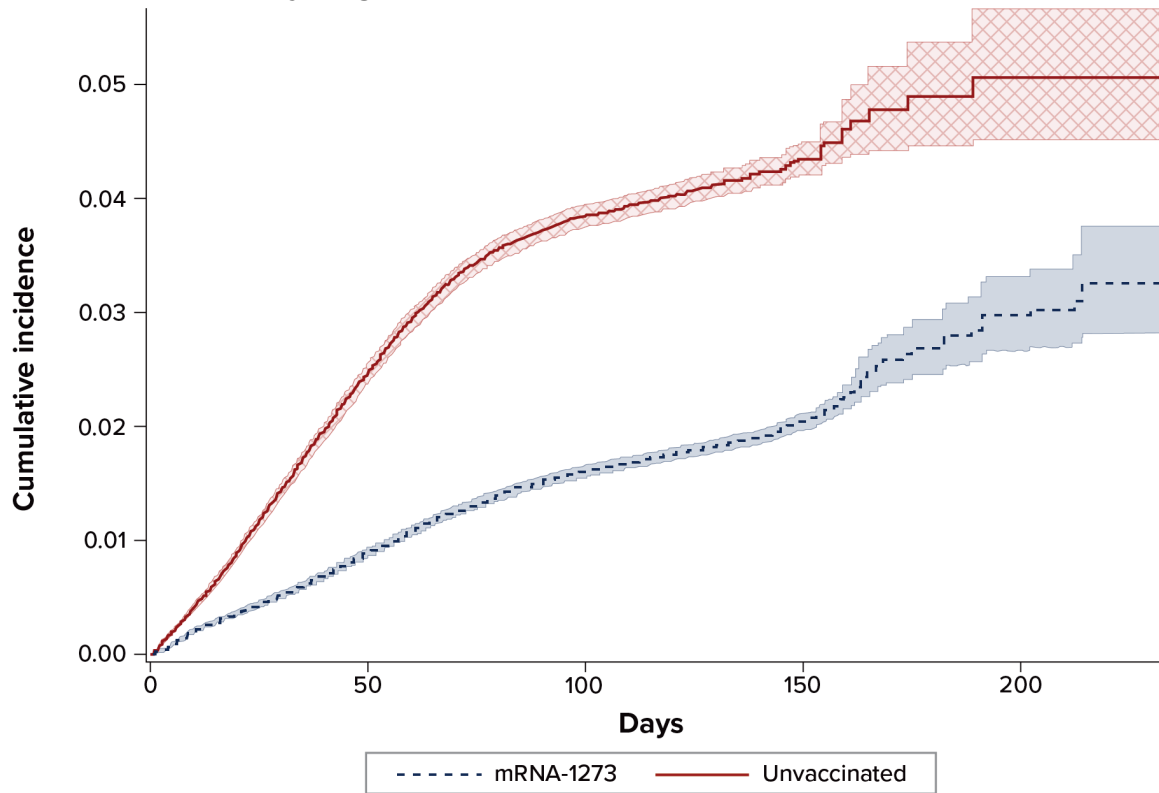
The cumulative incidence of COVID-19 outcomes over time by mRNA-1273 booster/additional dose status is shown in [Figure 5](#). The risk of both COVID-19 outcomes was generally higher in the unboosted comparator group throughout follow-up. The differences in the cumulative incidence curves were most pronounced in the initial 100 days of follow-up, after which the curves generally became more parallel. Additionally, the CIs around the curves became much wider after approximately 120-130 days of follow-up in Optum and approximately 150 days in CVS Health as the number of individuals remaining in follow-up at these time points was very small.

Figure 5. Weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of mRNA-1273 COVID-19 Vaccine and Matched, Unboosted Comparators

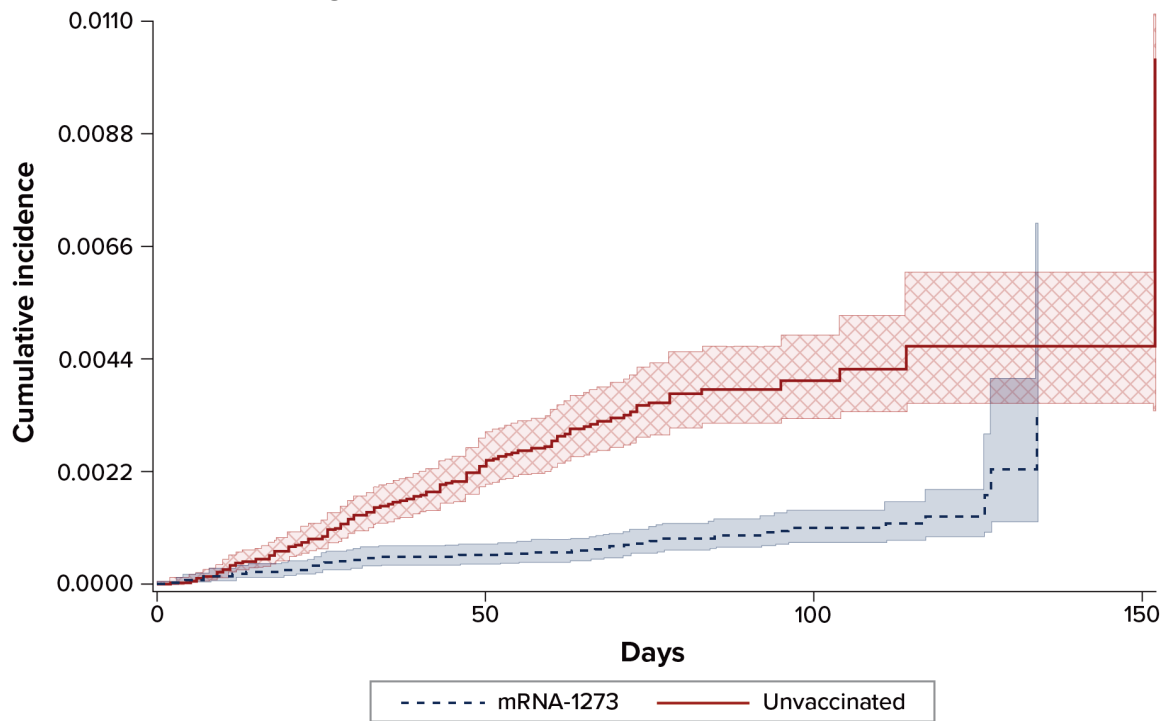
A. Optum, Medically diagnosed COVID-19



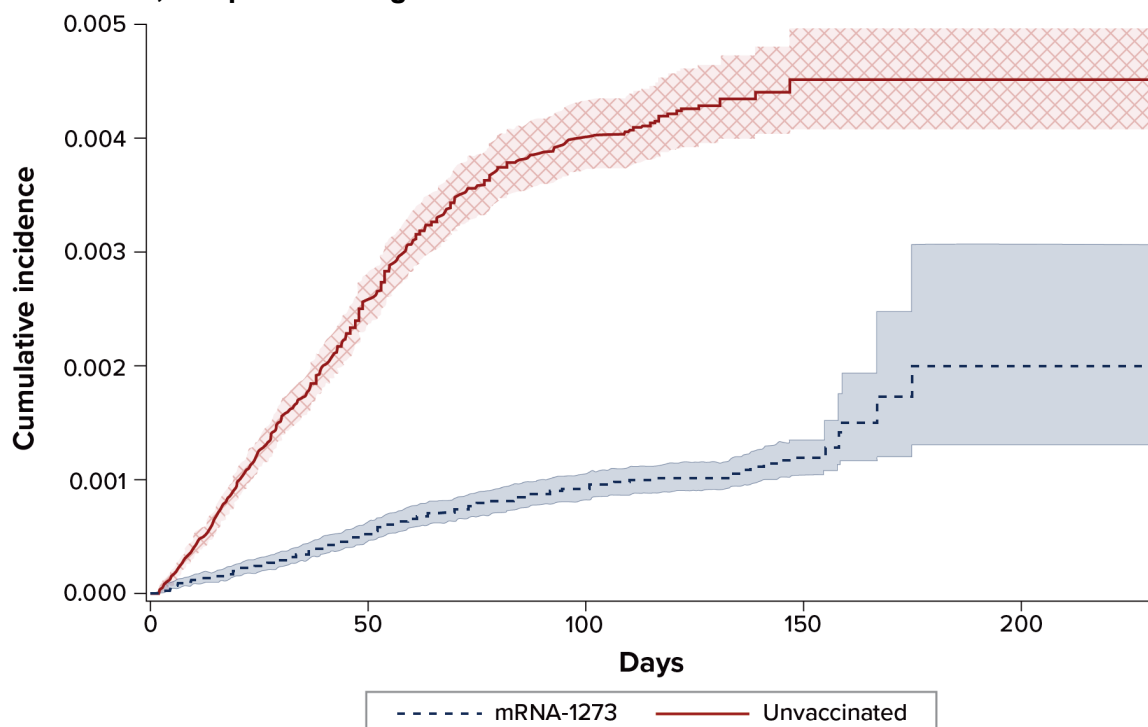
B. CVS Health, Medically diagnosed COVID-19



C. Optum, Hospital/ED-diagnosed COVID-19



D. CVS Health, Hospital/ED-diagnosed COVID-19



COVID-19 = coronavirus disease 2019; ED = emergency department.

The estimated effectiveness of receiving an mRNA-1273 booster/additional dose against COVID-19 outcomes compared with not receiving a booster/additional dose is detailed in [Table B-5-Optum](#) and [Table B-5-CVS](#). A summary of VE estimates across data sources is shown in [Table 11](#). The meta-analyzed VE estimates for mRNA-1273 were 58% (95% CI, 56%-59%) against any medically diagnosed COVID-19 and were higher against hospital/ED-diagnosed COVID-19: 76% (95% CI, 72%-79%). The VE estimates were similar across data sources.

Table 11. Estimated Effectiveness of Receiving a Booster/Additional Dose of mRNA-1273 COVID-19 Vaccine Compared with Not Receiving a Booster/Additional Dose, by Data Source

Outcome	Data source	Booster / additional dose exposure group	N	Events	VE (95% CI)
Medically diagnosed	Optum	mRNA-1273	68,117	1,297	55% (52%-59%)
		None	68,117	1,710	—
	CVS Health	mRNA-1273	342,384	5,722	59% (57%-60%)
		None	342,384	7,763	—
	Meta-analyzed	NA	NA	NA	58% (56%-59%) ^a
Hospital/ED-diagnosed	Optum	mRNA-1273	68,117	59	73% (63%-81%)
		None	68,117	133	—
	CVS Health	mRNA-1273	342,384	323	76% (73%-79%)
		None	342,384	823	—
	Meta-analyzed	NA	NA	NA	76% (72%-79%) ^b

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; NA = not applicable; VE = vaccine effectiveness.

^a *p*-value for heterogeneity = 0.07. *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source-specific VE estimates.

^b *p*-value for heterogeneity = 0.48. *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source-specific VE estimates.

— indicates reference group.

4.2.2.2 Quantitative Bias Analysis

The effect of exposure misclassification was estimated with assumed vaccine exposure sensitivities of 84% and 69% in Optum, and 89% and 69% in CVS Health. Results of the quantitative bias analyses are detailed in [Table B-5-Optum](#) and [Table B-5-CVS](#). A summary of quantitative bias analysis results is shown in [Table 12](#). These results suggest that the observed VE estimates may underestimate the true VE by 2 to 11 percentage points, depending on the data source and outcome.

Table 12. Estimated Effectiveness of Receiving a Booster/Additional Dose of mRNA-1273 COVID-19 Vaccine, Corrected for Potentially Missing Vaccine Records

COVID-19 outcome	Data source	Hypothesized sensitivity of vaccination exposure measurement	Corrected VE (95% CI)
Medically diagnosed	Optum	100% (uncorrected)	55% (52%-59%)
		84%	59% (56%-63%)
		69%	66% (64%-69%)
	CVS Health	100% (uncorrected)	59% (57%-60%)
		89%	61% (59%-62%)
		69%	70% (68%-71%)
Hospital/ED-diagnosed	Optum	100% (uncorrected)	73% (63%-81%)
		84%	77% (68%-84%)
		69%	82% (76%-88%)
	CVS Health	100% (uncorrected)	76% (73%-79%)
		89%	78% (75%-81%)
		69%	85% (82%-87%)

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

4.2.2.3 Negative Control Analysis

Cumulative incidence curves of COVID-19 outcomes in the first 10 days following and including Time 0 are detailed in [Figure B-4-Optum](#) and [Figure B-4-CVS](#). HRs and VE estimates considering only the first 10 days after and including Time 0 are shown in [Table B-8-Optum](#) and [Table B-8-CVS](#). A summary of the negative control analysis findings for mRNA-1273 is shown in [Table 13](#). In both data sources, the incidence of both COVID-19 outcomes for all vaccines was very low during the negative control period (e.g., cumulative incidence of medically diagnosed COVID-19 of approximately 0.004 and of hospital/ED-diagnosed COVID-19 of approximately 0.0004 in the unboosted group by day 9, i.e., the tenth day of follow-up), and the absolute differences in COVID-19 incidence between the booster/additional dose and unboosted comparator groups were small. However, the VE estimates during the early negative control period suggest a non-null association of vaccination with COVID-19 outcomes.

Table 13. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 mRNA-1273 Vaccine, 10 Days After and Including Time 0, Negative Control Outcome Analysis

COVID-19 outcome	Data source	Booster / additional dose events	Comparator events	VE (95% CI)
Medically diagnosed	Optum	195	312	42% (30%-51%)
	CVS Health	721	1,335	51% (46%-56%)
Hospital/ED-diagnosed	Optum	< 11	18	48% (-15% to 76%)
	CVS Health	42	133	72% (60%-81%)

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

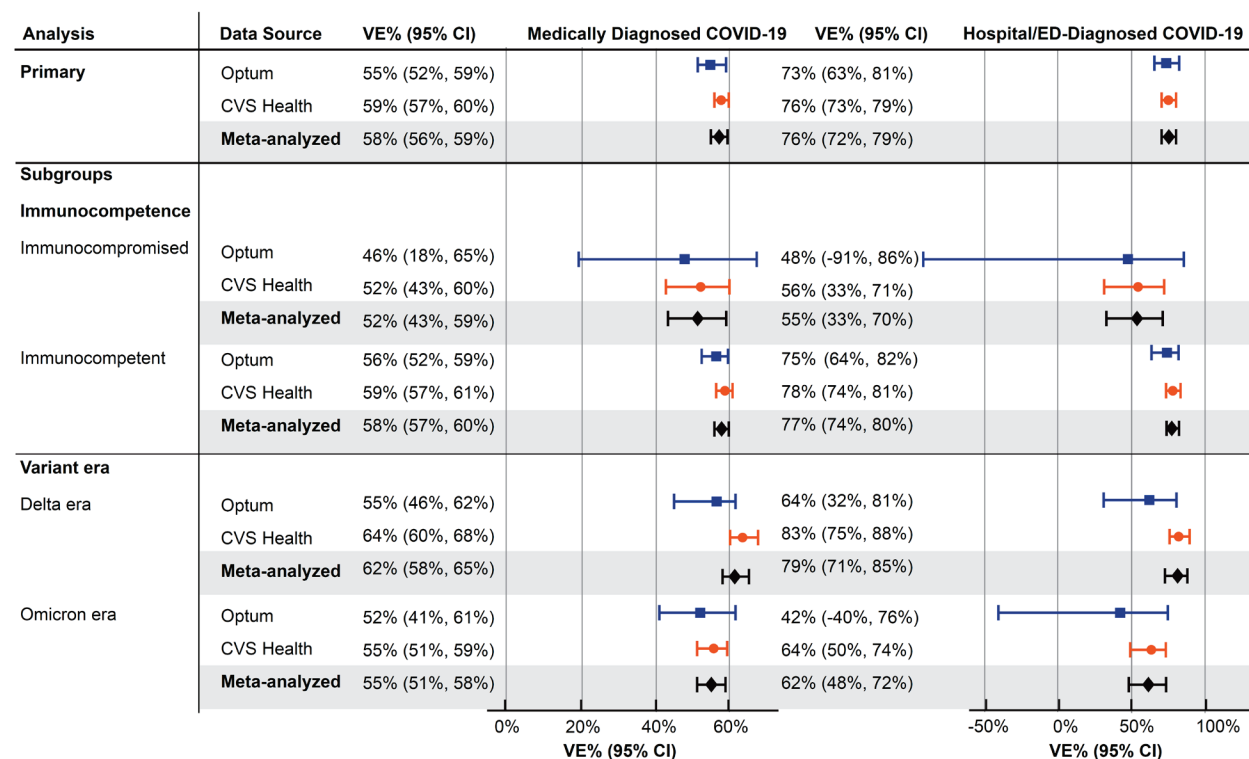
4.2.2.4 Subgroup Analyses

A summary of the VE estimates in subgroups of immunocompromised status and variant era is shown in [Figure 6](#). Details of the VE estimates in subgroups of individuals by immunocompromised status are shown in [Table B-6-Optum](#) and [Table B-6-CVS](#). The estimated effectiveness of a booster/additional dose against COVID-19 outcomes by variant era and brand is detailed in [Table B-7-Optum](#) and [Table B-7-CVS](#), and cumulative incidence of COVID-19 outcomes by brand and vaccine-specific era is shown in [Figure B-3-Optum](#) and [Figure B-3-CVS](#).

When evaluating mRNA-1273 effectiveness by immunocompetence status, COVID-19 outcomes were generally more common among the immunocompromised subgroup ([Table B-6-Optum](#), [Table B-6-CVS](#)). For medically diagnosed COVID-19, there was little difference between the meta-analyzed VE estimates for the immunocompromised group (VE = 52%; 95% CI, 43%-59%) and the immunocompetent group (VE = 58%; 95% CI, 57%-60%). However, for hospital/ED-diagnosed COVID-19, the meta-analyzed VE estimate was lower in the immunocompromised group (VE = 55%; 95% CI, 33%-70%) than the immunocompetent group (VE = 77%; 95% CI, 74%-80%).

When evaluating results by variant era, both COVID-19 outcomes were more common in the Omicron era than the Delta era ([Table B-7-Optum](#), [Table B-7-CVS](#)), but the VE estimates for both COVID-19 outcomes were lower in the Omicron era than the Delta era ([Figure 6](#)).

Figure 6. Estimated Effectiveness of Receiving a Booster/Additional Dose of mRNA-1273 COVID-19 Vaccine, by Immunocompetence Status and Variant Era

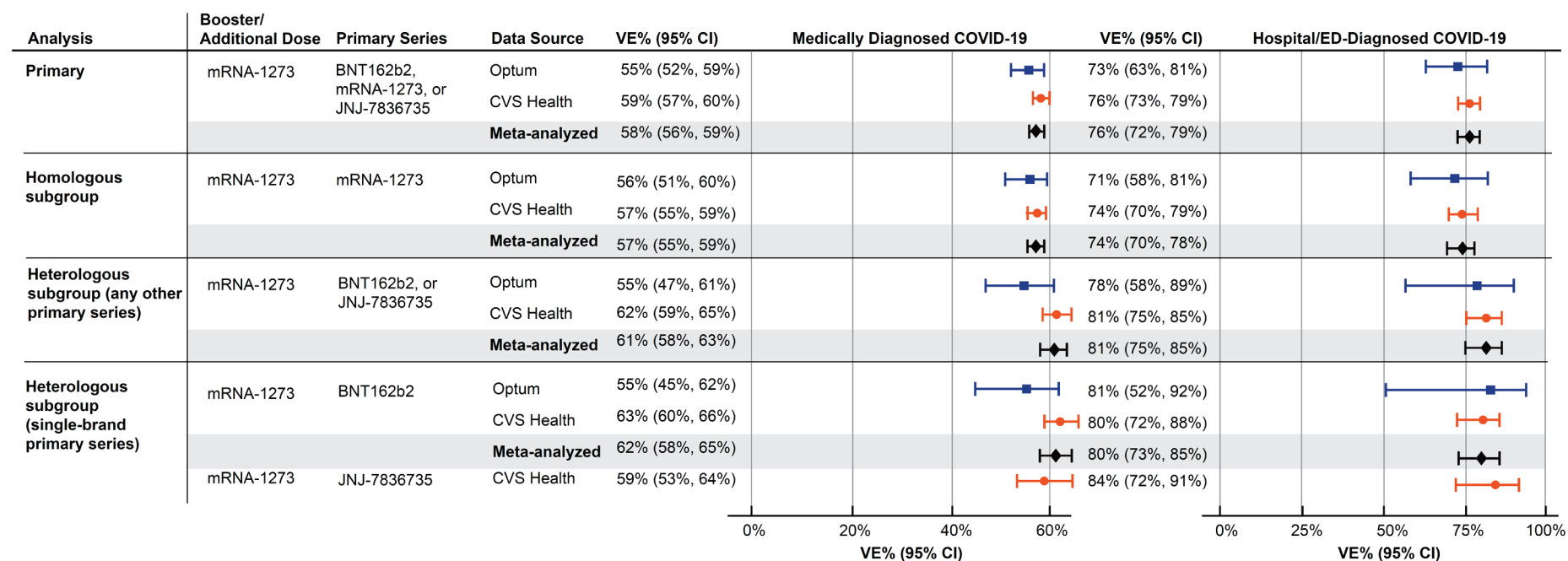


CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

Note: The Delta era was considered 1 June 2021 to 24 December 2021; the Omicron era was considered 25 December 2021 to the end of data availability.

A summary of the subgroup analyses by homologous or heterologous booster status is shown in [Figure 7](#). Details of these analyses by data source are given in [Table B-8-Optum](#) and [Table B-8-CVS](#). The VE estimates for both medically diagnosed and hospital/ED-diagnosed COVID-19 were generally slightly higher for heterologous boosting strategies than homologous boosting. For medically diagnosed COVID-19, the meta-analyzed homologous VE was 57% (95% CI, 55%-59%), and VE estimates for heterologous boosting strategies ranging from 55% to 63%, depending on the strategy. For hospital/ED-diagnosed COVID-19, VE estimates followed the same pattern, with heterologous VE estimates (VEs ranging from 78% to 84%) higher than homologous (meta-analyzed VE = 74%; 95% CI, 70%-78%).

Figure 7. Estimated Effectiveness of Receiving a Booster/Additional Dose of mRNA-1273 COVID-19 Vaccine, by Homologous or Heterologous Booster Status



CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

Note: The heterologous (any other primary series) analyses defined exposure groups first by the brand of the booster/additional dose and then required that the primary series be of any other brand. The heterologous (single-brand primary series) analysis defined exposure groups first by the brand of the booster/additional dose and then divided into subgroups of individual brands of primary series.

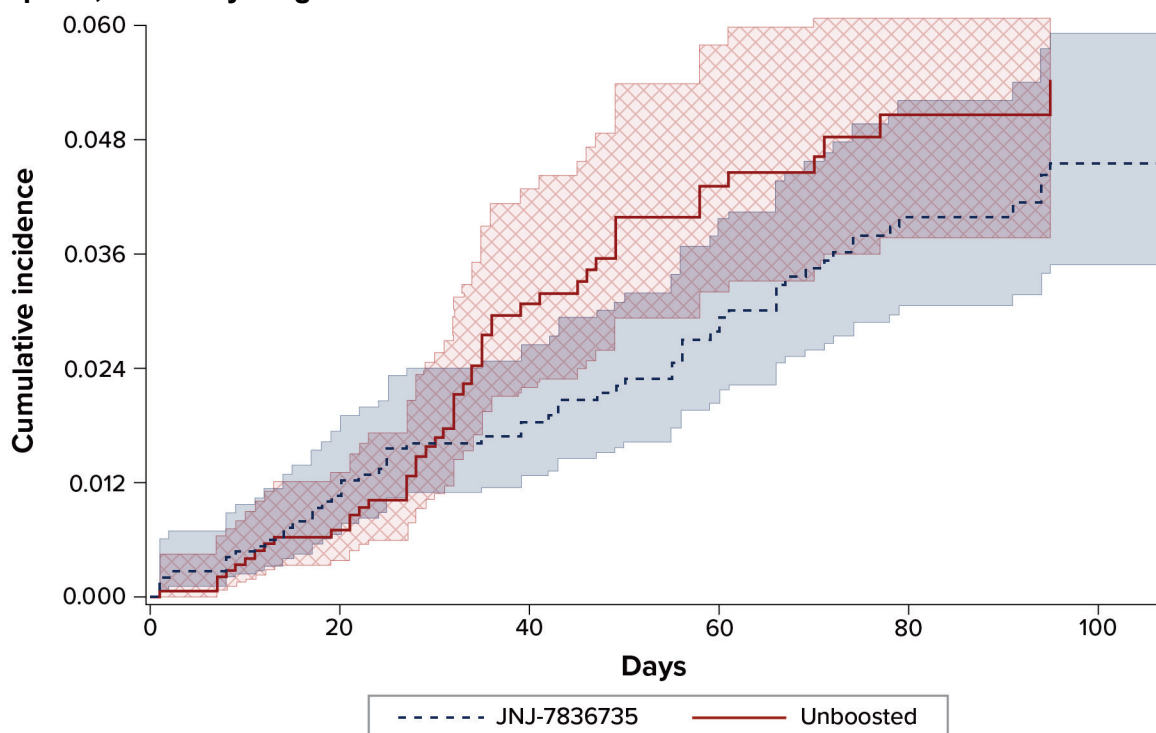
4.2.3 JNJ-7836735

4.2.3.1 Overall Results

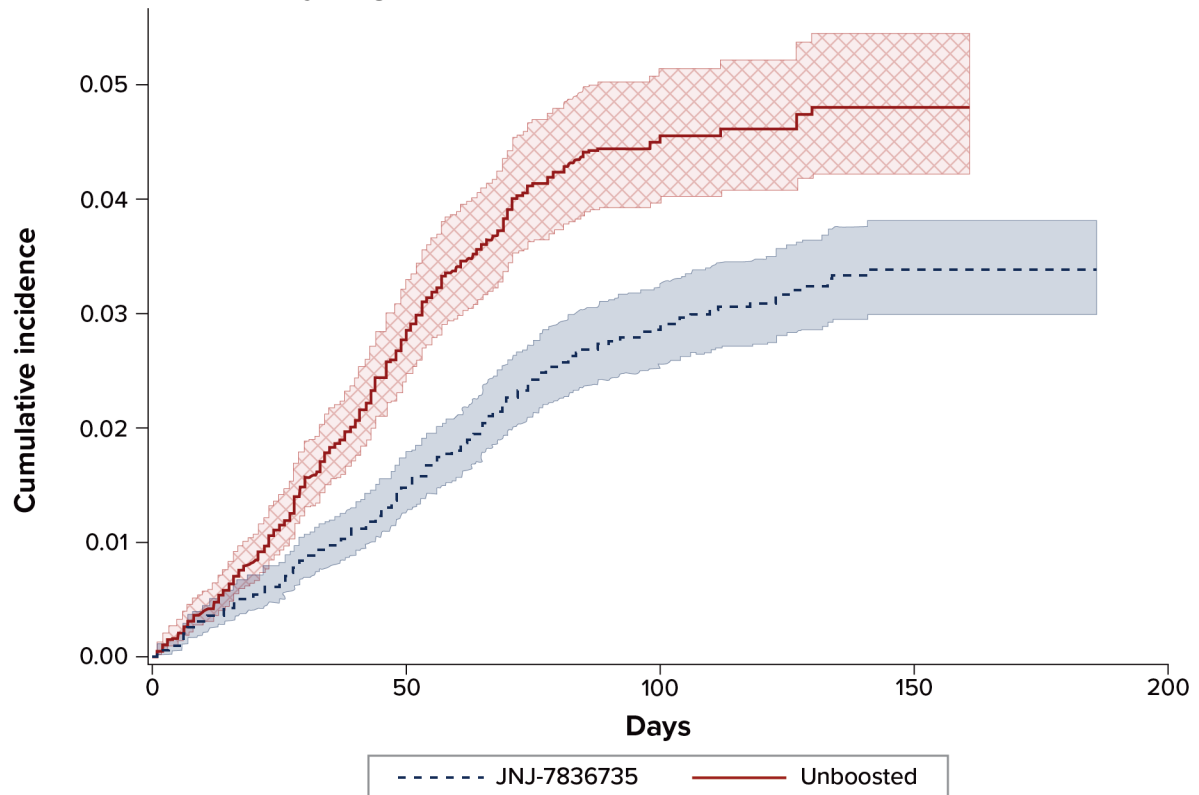
Relative to the BNT162b2 and mRNA-1273 groups, the sample sizes for JNJ-7836735 cohorts were small. The cumulative incidence of COVID-19 outcomes over time by JNJ-7836735 booster/additional dose status is shown in [Figure 8](#). For medically diagnosed COVID-19 in Optum, there was little difference between the booster and comparator groups for approximately the first month of follow-up, with higher risk of medically diagnosed COVID-19 in the comparator group afterward, although with wide and overlapping confidence intervals throughout. In CVS Health, the risk in the exposure groups was similar for approximately the first 20 days, with increased risks observed in the comparator group consistently throughout the rest of follow-up. For hospital/ED-diagnosed COVID-19, little difference throughout follow-up was observed in Optum, but small sample sizes and case counts resulted in wide CIs. In CVS Health, higher risk of COVID-19 was observed throughout follow-up after an initial period of overlap.

Figure 8. Inverse Probability of Treatment-weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of JNJ-7836735 COVID-19 Vaccine and Matched, Unboosted Comparators

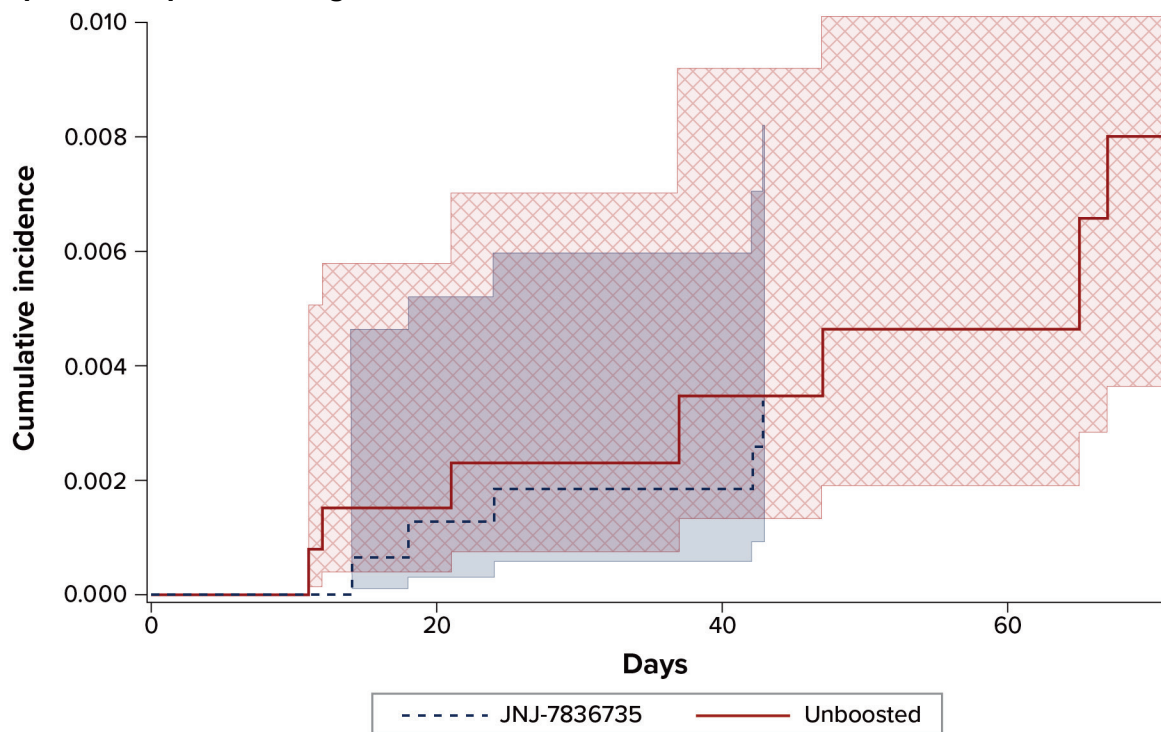
A. Optum, Medically diagnosed COVID-19



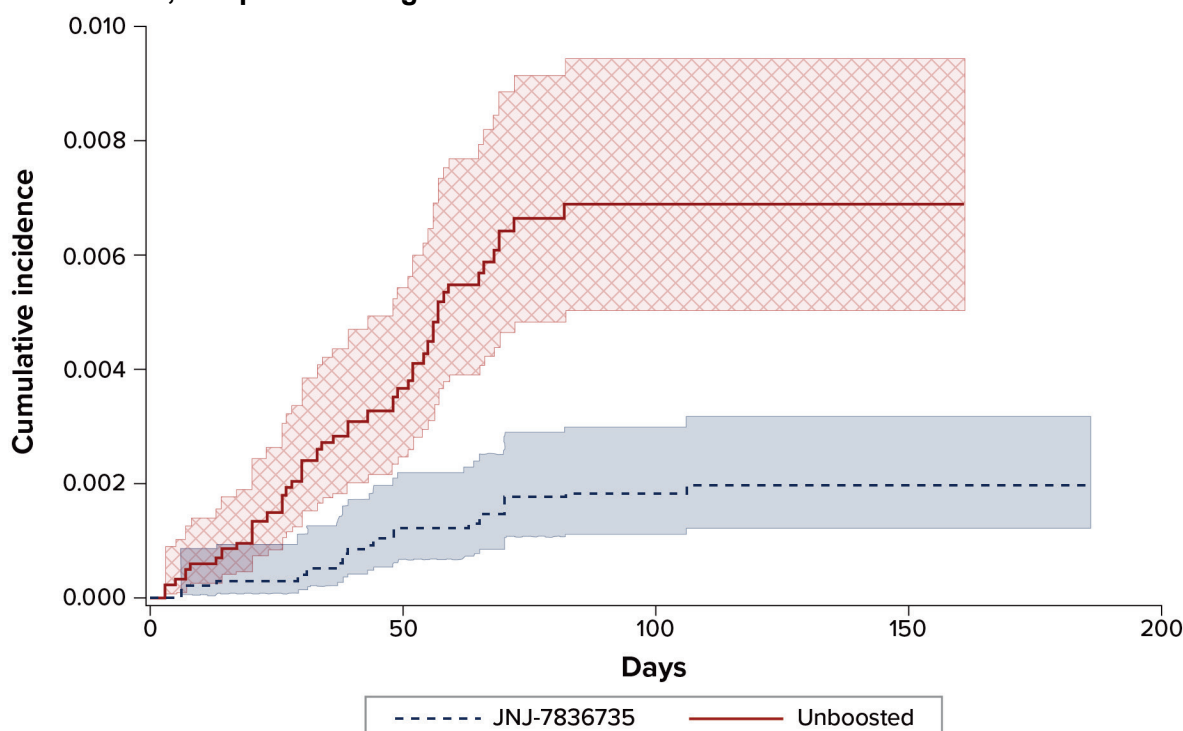
B. CVS Health, Medically diagnosed COVID-19



C. Optum, Hospital/ED-diagnosed COVID-19



D. CVS Health, Hospital/ED-diagnosed COVID-19



COVID-19 = coronavirus disease 2019; ED = emergency department.

The estimated effectiveness of receiving a JNJ-7836735 booster/additional dose against COVID-19 outcomes compared with not receiving a booster/additional dose is detailed, by vaccine brand, in [Table B-5-Optum](#) and [Table B-5-CVS](#). A summary of VE estimates across data sources is shown in [Table 14](#). The data source–specific VE estimates were generally consistent for both outcomes, although smaller case counts (particularly for hospital/ED-diagnosed COVID-19) resulted in wide CIs. The meta-analyzed VE against medically diagnosed COVID-19 was 34% (95% CI, 23%-44%) and against hospital/ED-diagnosed COVID-19 was 70% (95% CI, 49%-82%).

Table 14. Estimated Effectiveness of Receiving a Booster/Additional Dose of JNJ-7836735 COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose, by Data Source

Outcome	Data source	Booster / additional dose exposure group	N	Events	VE (95% CI)
Medically diagnosed	Optum	JNJ-7836735	1,615	58	22% (-17% to 47%)
		None	1,615	49	—
	CVS Health	JNJ-7836735	9,783	298	36% (24%-46%)
		None	9,783	285	—
	Meta-analyzed	NA	NA	NA	34% (23%-44%) ^a
Hospital/ED-diagnosed	Optum	JNJ-7836735	1,615	< 11	58% (-35% to 87%)
		None	1,615	< 11	—
	CVS Health	JNJ-7836735	9,783	19	72% (50%-85%)
		None	9,783	41	—

Outcome	Data source	Booster / additional dose exposure group	N	Events	VE (95% CI)
	Meta-analyzed	NA	NA	NA	70% (49%-82%) ^b

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; NA = not applicable; VE = vaccine effectiveness.

^a *p*-value for heterogeneity = 0.36. *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source-specific VE estimates.

^b *p*-value for heterogeneity = 0.53. *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source-specific VE estimates.

— indicates reference group.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

4.2.3.2 Quantitative Bias Analysis

The effect of exposure misclassification was estimated with assumed vaccine exposure sensitivities of 84% and 69% in Optum and 89% and 69% in CVS Health. Results of the quantitative bias analyses are detailed in [Table B-5-Optum](#) and [Table B-5-CVS](#). A summary of quantitative bias analyses results is shown in [Table 15](#). In Optum, the relatively smaller sample size and case counts resulted in the VE estimates being relatively insensitive to exposure misclassification; VE estimates corrected for a range of vaccination sensitivities up to 69% (i.e., potentially up to 31% of truly boosted individuals being identified as unboosted) suggested that the observed VE may underestimate the true VE by up to 3 percentage points. In CVS Health, corrected estimates up to 11 percentage points higher than the original estimates were observed.

Table 15. Estimated Effectiveness of Receiving a Booster/Additional Dose of JNJ-7836735 COVID-19 Vaccine, Corrected for Potentially Missing Vaccine Records

COVID-19 outcome	Data source	Hypothesized sensitivity of vaccination exposure measurement	Corrected VE (95% CI)
Medically diagnosed	Optum	100% (uncorrected)	22% (-17% to 47%)
		84%	23% (-16% to 48%)
		69%	25% (-12% to 49%)
	CVS Health	100% (uncorrected)	36% (24%-46%)
		89%	38% (27%-48%)
		69%	47% (37%-56%)
Hospital/ED-diagnosed	Optum	100% (uncorrected)	58% (-35% to 87%)
		84%	58% (-34% to 87%)
		69%	59% (-30% to 87%)
	CVS Health	100% (uncorrected)	72% (50%-85%)
		89%	75% (54%-86%)
		69%	82% (68%-90%)

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

4.2.3.3 Negative Control Analysis

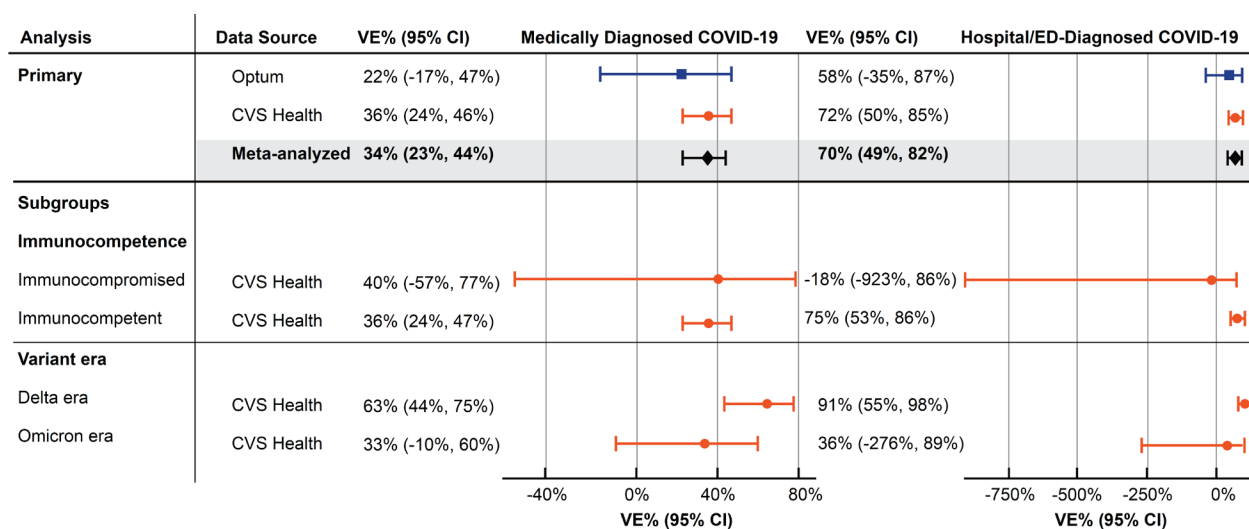
Cumulative incidence curves of COVID-19 outcomes in the first 10 days following and including Time 0 are detailed in [Figure B-4-CVS](#); cumulative incidence curves in Optum were not generated because of

small case counts, but the cumulative incidence during the negative control periods can be seen in [Figure 8](#). HRs and VE estimates considering the first 10 days after and including Time 0 were also not estimated in either data source because of small case counts. However, the cumulative incidence curves for JNJ-7836735 demonstrate little difference between the boosted and comparator groups during the 10-day negative control period for both outcomes.

4.2.3.4 Subgroup Analyses

A summary of the VE estimates in subgroups of immunocompromised status and variant era in CVS Health are shown in [Figure 9](#). Subgroup analyses of JNJ-7836735 were not performed in Optum because of low sample sizes and case counts. Details of the VE estimates in subgroups of individuals by immunocompromised status are shown in [Table B-6-CVS](#). The estimated effectiveness of a booster/additional dose against COVID-19 outcomes by variant era and brand is detailed in [Table B-7-CVS](#), and cumulative incidence of COVID-19 outcomes by brand and vaccine-specific era is shown in [Figure B-3-CVS](#). In CVS Health, VE estimates in the immunocompromised group were imprecise because of small sample sizes. Estimates for the Omicron era were also generally imprecise due to small sample sizes, but the VE estimates in the Omicron era were generally lower than those in the Delta era.

Figure 9. Estimated Effectiveness of Receiving a Booster/Additional Dose of JNJ-7836735 COVID-19 Vaccine, by Immunocompetence Status and Variant Era

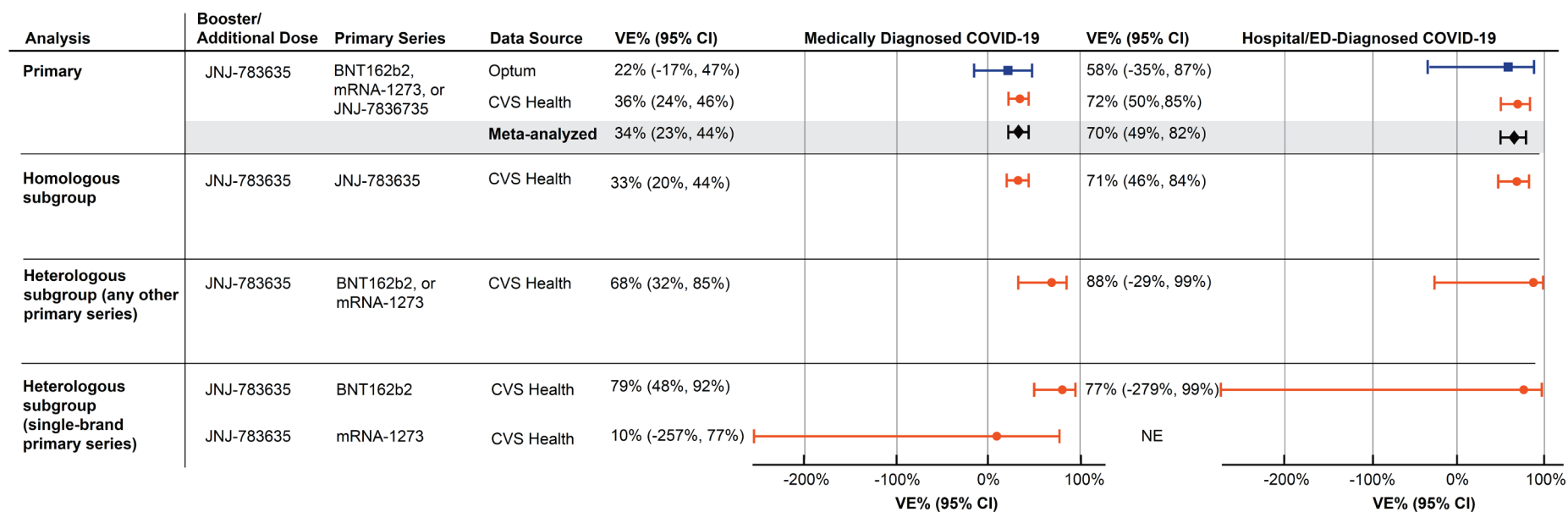


CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

Note: The Delta era was considered 1 June 2021 to 24 December 2021; the Omicron era was considered 25 December 2021 to the end of data availability.

A summary of the subgroup analyses by homologous or heterologous booster status for CVS Health is shown in [Figure 10](#) (analyses were not performed in Optum because of small sample sizes). Details of these analyses are given in [Table B-8-CVS](#). The majority of JNJ-7836735 boosters observed were homologous boosters, administered after an initial JNJ-7836735 primary series ([Table B-8-CVS](#)). The estimates for heterologous boosting patterns were imprecise because of small sample sizes. Although the VE against medically diagnosed COVID-19 estimates for receiving JNJ-7836735 as a heterologous booster after receiving any other brand of primary series generally displayed higher VEs than receiving JNJ-7836735 as a homologous booster, estimates for hospital/ED-diagnosed COVID-19 were generally too imprecise for meaningful comparisons.

Figure 10. Estimated Effectiveness of Receiving a Booster/Additional Dose of JNJ-7836735 COVID-19 Vaccine, by Homologous or Heterologous Booster Status



CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; NE = not estimable; VE = vaccine effectiveness.

Note: The heterologous (any other primary series) analyses defined exposure groups first by the brand of the booster/additional dose and then required that the primary series be of any other brand. The heterologous (single-brand primary series) analysis defined exposure groups first by the brand of the booster/additional dose and then divided into subgroups of individual brands of primary series.

5 Discussion

This large, real-world evaluation of the effectiveness of receipt of a booster/additional dose of the original monovalent COVID-19 vaccine observed lower rates of COVID-19 diagnoses in individuals who received a booster/additional dose after a complete primary series than those who received only a complete primary series but no booster/additional dose, although there was variation by vaccine brand and variant era. For all brands, receipt of a booster or additional dose demonstrated stronger protective associations against hospital/ED-diagnosed COVID-19 than for any medically diagnosed COVID-19. This effectiveness appears generally sustained for 3-4 months after vaccination (approximately the median duration of follow-up). The effectiveness of boosters may last longer, but the number of patients with follow-up past 4 months was limited. The boosters of different brands were authorized during differing time periods and for different age ranges, so brand-specific results cannot be directly compared. However, all 3 brands demonstrated relatively high effectiveness against hospital/ED-diagnosed COVID-19 (meta-analyzed VE $\geq 70\%$). BNT162b2—the brand with the largest age authorization during the study period—and mRNA-1273 both demonstrated effectiveness against any medically diagnosed COVID-19, with meta-analyzed VE estimates of approximately 54% to 58%. JNJ-7836735's observed meta-analyzed VE against medically diagnosed COVID-19 was lower (34%), but it was authorized later in the study period with a greater proportion of follow-up time in the Omicron era (Omicron subgroup analyses were found to have lower VE estimates compared to the Delta era).

The effectiveness of the original monovalent booster or additional doses in different variant eras have been evaluated in the US in many settings, data sources, methodologic approaches, and study designs, generally demonstrating the effectiveness of receiving a booster/additional dose of any COVID-19 vaccine. Analysis of VISION Networks data from ED and urgent care clinics across 10 states indicated that during the Delta era, VE of any mRNA vaccine against COVID-19 associated ED and urgent care visits among patients who had received 3 vaccine doses compared with being unvaccinated was 94%, and was 86% in patients who received 2 doses in the prior 14-179 days compared with being unvaccinated.⁴¹ The same study found that in the Omicron era, there was a similar pattern but overall lower VE; VE against COVID-19-associated ED and urgent care visits was 82% among adults who had received 3 doses, and 52% among those who had received 2 doses in the previous 14-179 days.⁴¹ Another study also using VISION Networks data reported similar results and found that although protection against ED and urgent care visits increased after a third dose, during the Omicron era, VE of a third dose declined to 66% by 4 months after vaccination, whereas in the Delta era, VE of a third dose remained at 89% at 4 months after vaccination.⁴² In a test-negative case-control study in Japan, VE against symptomatic infection of 3 doses (mostly of BNT162b2 or mRNA-1273, but a small proportion had mixed doses or other vaccines) was 74% during the Omicron era.⁴³

Booster dose VE has also been evaluated by age group in previous studies. A US-based retrospective cohort study indicated that the effectiveness of 3 doses of BNT162b2 against SARS-CoV-2 infection was 89% (95% CI, 87%-91%) compared with being unvaccinated in adults aged 18 to 64 years, and 77% compared with having received only 2 doses.⁴⁴ In the same study, VE of 3 doses ranged from 84% to 89% across all age groups compared with being unvaccinated, and ranged from 70% to 78% compared with

receiving only 2 doses.⁴⁴ Among adolescents aged 16-17 years, reasonably high effectiveness was found for a third dose of BNT162b2 in a US-based test-negative case-control study. Among adolescents ages 16-17 years, VE against ED and urgent care encounters after a third dose was 86% compared with being unvaccinated.⁴⁵ However, in an analysis of clinical data from electronic health records in Hong Kong, VE of a third dose of BNT162b2 was only 59% against COVID-19-related hospitalizations and 60% against severe COVID-19, respectively, compared with being unvaccinated in children and adolescents ages 3-17 years.⁴⁶

Given the complex environment in which vaccine boosters are administered, the methodologies for assessing VE have varied. Test-negative case-control studies were often used to examine VE. Some studies relied on community-based data, such as the Increasing Community Access to Testing (ICATT) CDC program, which provides free COVID-19 testing in US communities, leveraging contracts with pharmacies and community-based testing vendors. At the time of testing, sites participating in the ICATT CDC program collect information on COVID-19 symptoms, prior COVID-19 infections, and vaccination status.⁴⁷ Total number of doses received, vaccine manufacturer, and year of vaccination are also collected from patients or their guardians if the patient is a minor.⁴⁷ Other studies used hospital-based data, such as the VISION Network studies, and extracted vaccination status from electronic health records of patients with COVID-19 symptoms and diagnosed infection.⁴⁵ Although commonly used for VE research, test-negative studies have been criticized for not fully addressing selection bias and confounding by healthcare-seeking behavior.⁴⁸ Large cohort studies, especially nationwide studies, were generally based outside the US, where national or centralized healthcare systems may make these types of studies more feasible.^{46,49} One large retrospective cohort study based in the US was identified, which included nearly 19 million adults and used linked data from 2 independent, de-identified patient-level data sets.⁵⁰ The study's outcomes of interest were "(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."⁵⁰ The study evaluated booster strategies using patients from 3 cohorts: those with an JNJ-7836735 vaccine and JNJ-7836735 booster, those with a JNJ-7836735 vaccine and an mRNA booster, and those with 2 doses of an mRNA vaccine and an mRNA booster. The cohorts of patients who received mRNA boosters were compared with those that received 2 Ad26.COVS.2 vaccine doses (primary and booster) to determine relative VE and found that a booster dose of mRNA vaccine after 2 doses of JNJ-7836735, or receiving 3 mRNA doses, was more effective than 2 JNJ-7836735 doses alone.⁵⁰

The present study used national health insurance claims databases supplemented with IIS records and robust methodology to avoid time-related biases⁵ while evaluating the VE of boosters or additional doses for different brands in subgroups of interest, viral variant eras, and homologous and heterologous booster doses. This study includes a large sample of individuals receiving booster/additional doses and receiving care in a variety of settings. Pandemic conditions varied widely in the US over time and across geography, and thus we granularly matched boosted individuals and unboosted comparator individuals on calendar day and county to account for these differences. Additionally, the study eligibility and matching criteria were designed to only identify unboosted comparators who were eligible for vaccination on each calendar day, avoiding selection bias.⁵

This study evaluated booster doses (a dose received after the completion of the primary series) and additional doses (an additional dose received as part of an extended primary series among immunocompromised individuals)¹¹⁻¹³ together. Operationalization of vaccine rollout, prioritization, and definitions of immunocompromised status may have differed across geography and over time, making it difficult to differentiate those receiving a booster dose and immunocompromised individuals receiving an additional dose. Subgroup analyses in immunocompromised and immunocompetent individuals demonstrated that the immunocompromised group generally had a higher incidence of COVID-19 outcomes, and the estimated effectiveness of the vaccines against hospital/ED-diagnosed COVID-19 was slightly lower than the immunocompetent group; however, the VEs for any medically diagnosed COVID-19 were generally comparable across immunocompetence groups. The smaller sample sizes in the immunocompromised group resulted in generally wider confidence intervals for the immunocompromised VE estimates.

The current cohort study of booster/additional doses evaluated COVID-19 outcomes in a population of individuals who had received a complete primary series. Rather than comparing boosted individuals to completely unvaccinated individuals, this comparison among individuals with complete primary series reflects the real-world decision previously vaccinated individuals face about whether to receive a booster dose. We aligned the evaluation of eligibility criteria and the start of follow-up at Time 0 in the boosted and unboosted groups; starting follow-up on Time 0 without considering future vaccination behaviors avoiding immortal person-time bias.⁵

This real-world study is subject to limitations common to observational research using existing data sources. Not all cases of COVID-19 result in medical interactions and recorded diagnoses. Our study only considered COVID-19 diagnoses recorded in medical claims rather than laboratory-confirmed COVID-19, because laboratory results or at-home test results were not available in the databases. We used combined claims and IIS records to identify vaccination status, improving vaccination capture compared to either data source alone. However, some vaccines may still be missed, resulting in misclassification of vaccine exposure. This was evaluated with quantitative bias analysis, which suggested that the observed VE estimates may slightly underestimate true VE.

Individuals were only observed while enrolled in the respective data sources. Gaps in continuous enrollment of up to 31 days were permitted to maximize follow-up time, but recent evidence suggests that this may introduce the potential for some missed claims during follow-up.⁵¹ The data sources evaluated slightly different study periods due to differences in data availability (i.e., the cutoff date for Optum was 28 February 2022; the cutoff date for CVS Health was 31 March 2022). The differences in the duration of follow-up and the characteristics of the time periods included (e.g., differences in COVID-19 incidence and circulating variants) may explain some of the observed differences between data sources, particularly during the Omicron era at the end of the study period.

Despite both matching on important demographic and clinical characteristics and applying propensity score weighting, residual confounding may remain. The negative control analysis suggested a potential difference between the exposure groups during a time when vaccines are assumed to have no biologic effect for 10-14 days after vaccination while the body mounts an immune response to a novel antigen.

Although the absolute differences between groups during this period is small, differences in COVID-19 testing, care-seeking, and diagnosis recording may differ in boosted individuals on or immediately after vaccination compared with individuals not receiving a vaccine, as noted in other studies.⁵² However, longer term differences in healthcare-seeking behavior and confounding cannot be ruled out.

This study assessed the first booster/additional dose following primary series completion, and it only evaluated the originally authorized monovalent booster/additional doses containing the same protein target as the primary series. However, subsequent authorizations have been made for additional vaccine brands and platforms, additional rounds of boosters in select populations, expanded pediatric age groups, and updated boosters against more recent viral variants. Thus, these results may not be applicable to the entire population, future periods of the COVID-19 pandemic, or bivalent booster formulations.

6 Conclusions

The original monovalent booster/additional doses were effective in real-world use in preventing medically diagnosed and hospital/ED-diagnosed COVID-19 among the populations for which they were indicated during the study period. Among those who had received primary series of COVID-19 vaccination, receipt of any booster/additional dose conveyed some level of additional protection for at least a few months. In the setting of a rapidly evolving pandemic, vaccination authorizations and recommendations have also changed rapidly; updated vaccines targeting new variants have been approved or authorized, and vaccination schedules for updated vaccines have been modified to no longer consider a primary series and separate boosters. Additional studies and surveillance activities are needed in individuals receiving updated boosters and in time periods with new predominant viral variants to evaluate the effectiveness of evolving vaccination strategies.

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Appendix A. Deviations, Modifications, or Clarifications From Study Protocol

Protocol section(s)	Change	Rationale
4.2.2.2, 4.4.1	Individuals with claims for 2 different vaccine brands on Time 0, or with a different vaccine brand within 3 days of Time 0, were excluded.	The vaccine brand of individuals with records of 2 different brands could not be accurately classified.
5.1.2.1	An additional matching criterion was added: influenza vaccination in the 365 days before Time 0.	To further reduce differences in healthcare-seeking behaviors between vaccine exposure groups.
5.1.2.3	Propensity scores were truncated below the 1st percentile and above the 99th percentile of the distribution of all propensity scores.	To reduce the influence of extreme weights.
5.1.2.4	The end of the Delta variant era was defined as 24 December 2021.	To correct an error in the protocol draft and align the end of the Delta era with the beginning of the Omicron era.
5.1.2.6	Subgroup analyses were not performed for pregnant individuals.	Feasibility analyses indicated sample sizes were too small for meaningful analysis.
5.1.2.9	Heterologous booster status was defined 2 ways: (1) any other primary series; and (2) specific-brand primary series. These required defining different study cohorts based on the brands of the primary series rather than the brands of the booster doses.	These 2 approaches addressed different clinically relevant study questions.

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CVS Health

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Supplementary Tables

Table B-1-Optum. Characteristics of Individuals Aged 12–64 Years Receiving a BNT162b2 COVID-19 Vaccine Booster/Additional Dose and Matched, Unboosted Comparators, Optum

Characteristic	Individuals receiving a booster/additional dose of BNT162b2 COVID-19 vaccine N = 118,326	Matched individuals not receiving a booster/ additional dose N = 118,326	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	43 (31, 54)	43 (31, 54)	
Mean (SD)	41.45 (14.75)	41.44 (14.72)	0.00
Sex, N (%)			
Male	57,237 (48.37)	57,237 (48.37)	0.00
Female	61,089 (51.63)	61,089 (51.63)	0.00
Days since primary completion			
Median (Q1, Q3)	226 (209, 246)	226 (208, 246)	
Mean (SD)	228.10 (31.69)	227.75 (31.88)	0.01
Primary series brand, N (%)			
JNJ-7836735	5,026 (4.25)	5,026 (4.25)	0.00
mRNA-1273	6,336 (5.35)	6,336 (5.35)	0.00
BNT162b2	106,964 (90.40)	106,964 (90.40)	0.00
Region, N (%)			
Northeast	14,961 (12.64)	14,961 (12.64)	0.00
South	4,815 (4.07)	4,815 (4.07)	0.00
Midwest	68,497 (57.89)	68,497 (57.89)	0.00
West	30,053 (25.40)	30,053 (25.40)	0.00
Pregnant at Time 0, N (%)	603 (0.99)	681 (1.11)	0.01
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	78,142 (66.04)	78,529 (66.37)	0.01
1	21,589 (18.25)	21,585 (18.24)	0.00
2+	18,595 (15.72)	18,212 (15.39)	0.01
Emergency department visits			
0	107,606 (90.94)	106,631 (90.12)	0.03
1	9,020 (7.62)	9,751 (8.24)	0.02
2+	1,700 (1.44)	1,944 (1.64)	0.02
Skilled nursing facility stay	299 (0.25)	318 (0.27)	0.00
Influenza vaccination	45,631 (38.56)	45,631 (38.56)	0.00

Characteristic	Individuals receiving a booster/additional dose of BNT162b2 COVID-19 vaccine N = 118,326	Matched individuals not receiving a booster/ additional dose N = 118,326	ASD
Pneumococcal vaccination	1,474 (1.25)	1,308 (1.11)	0.01
Encounter for cancer screening	36,989 (31.26)	35,783 (30.24)	0.02
Eye examination	10,758 (9.09)	9,857 (8.33)	0.03
Colonoscopy	6,187 (5.23)	5,887 (4.98)	0.01
Bone mineral density test	1,735 (1.47)	1,604 (1.36)	0.01
Well-check/well-child preventive healthcare visit	60,497 (51.13)	59,055 (49.91)	0.02
Arthritis	17,187 (14.53)	17,340 (14.65)	0.00
Lipid abnormality	22,363 (18.90)	22,198 (18.76)	0.00
Ambulance use or life support services	1,627 (1.38)	1,763 (1.49)	0.01
Weakness	2,564 (2.17)	2,488 (2.10)	0.00
Pregnancy completion before Time 0	1,583 (2.59)	1,508 (2.47)	0.01
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	5,637 (4.76)	5,338 (4.51)	0.01
Cancer	7,554 (6.38)	7,357 (6.22)	0.01
Chronic kidney disease or renal disease	2,269 (1.92)	2,255 (1.91)	0.00
Chronic liver disease	5,498 (4.65)	5,411 (4.57)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	14,298 (12.08)	13,771 (11.64)	0.01
Dementia or other neurological conditions	8,675 (7.33)	8,472 (7.16)	0.01
Diabetes mellitus, type 1 or 2	9,320 (7.88)	9,129 (7.72)	0.01
Down syndrome	48 (0.04)	33 (0.03)	0.01
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	16,916 (14.30)	16,895 (14.28)	0.00
Hypertension	25,073 (21.19)	25,290 (21.37)	0.00
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	3,725 (3.15)	3,725 (3.15)	0.00
Mental health conditions	38,183 (32.27%)	37,749 (31.90%)	0.01
Obese or severely obese	24,829 (20.98)	25,557 (21.60)	0.02
Sickle cell disease or thalassemia	282 (0.24)	285 (0.24)	0.00
Stroke or cerebrovascular disease	1,930 (1.63)	1,952 (1.65)	0.00
Tuberculosis	68 (0.06)	77 (0.07)	0.00

Characteristic	Individuals receiving a booster/additional dose of BNT162b2 COVID-19 vaccine N = 118,326	Matched individuals not receiving a booster/ additional dose N = 118,326	ASD
≥ 1 COVID-19 laboratory test performed	56,192 (47.49)	56,271 (47.56)	0.00
COVID-19 diagnoses occurring outside a hospital or emergency department setting	6,765 (5.72)	7,608 (6.43)	0.03
Hospitalization or emergency department–diagnosed COVID-19	899 (0.76)	998 (0.84)	0.01

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Table B-1-CVS. Characteristics of Individuals Aged 12–64 Years Receiving a BNT162b2 COVID-19 Vaccine Booster/Additional Dose and Matched, Unboosted Comparators, CVS Health

Characteristic	Individuals receiving a booster/additional dose of BNT162b2 COVID-19 vaccine N = 633,839	Matched individuals not receiving a booster/additional dose N = 633,839	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	41 (28, 53)	41 (28, 53)	0.00
Mean (SD)	40.22 (15.25)	40.21 (15.21)	0.00
Sex, N (%)			
Male	291,160 (45.94)	291,160 (45.94)	0.00
Female	342,679 (54.06)	342,679 (54.06)	0.00
Days since primary completion			
Median (Q1, Q3)	231 (212, 258)	231 (211, 257)	0.00
Mean (SD)	236.31 (37.44)	236.09 (37.61)	0.01
Primary series brand, N (%)			
JNJ-7836735	20,496 (3.23)	20,496 (3.23)	0.00
mRNA-1273	29,869 (4.71)	29,869 (4.71)	0.00
BNT162b2	583,474 (92.05)	583,474 (92.05)	0.00
Region, N (%)			
Northeast	93,202 (14.70)	93,202 (14.70)	0.00
South	123,007 (19.41)	123,007 (19.41)	0.00
Midwest	116,633 (18.40)	116,633 (18.40)	0.00
West	300,997 (47.49)	300,997 (47.49)	0.00
Pregnant at Time 0, N (%)	3,667 (0.58)	4,009 (0.63)	0.01
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	443,572 (69.98)	491,807 (77.59)	0.17
1	100,255 (15.82)	85,212 (13.44)	0.07
2+	90,012 (14.20)	56,820 (8.96)	0.16
Emergency department visits			
0	579,614 (91.44)	592,731 (93.51)	0.08
1	45,317 (7.15)	35,554 (5.61)	0.06
2+	8,908 (1.41)	5,554 (0.88)	0.05
Skilled nursing facility stay	352 (0.06)	300 (0.05)	0.00
Influenza vaccination	206,451 (32.57)	206,451 (32.57)	0.00
Pneumococcal vaccination	6,995 (1.10)	4,259 (0.67)	0.05
Encounter for cancer screening	189,088 (29.83)	132,812 (20.95)	0.21

Characteristic	Individuals receiving a booster/additional dose of BNT162b2 COVID-19 vaccine N = 633,839	Matched individuals not receiving a booster/additional dose N = 633,839	ASD
Eye examination	72,089 (11.37)	46,217 (7.29)	0.14
Colonoscopy	31,799 (5.02)	19,835 (3.13)	0.10
Bone mineral density test	11,001 (1.74)	6,598 (1.04)	0.06
Well-check/well-child preventive healthcare visit	315,634 (49.80)	218,001 (34.39)	0.32
Arthritis	95,248 (15.03)	72,449 (11.43)	0.11
Lipid abnormality	124,567 (19.65)	97,636 (15.40)	0.11
Ambulance use or life support services	8,401 (1.33)	6,156 (0.97)	0.03
Weakness	12,544 (1.98)	8,646 (1.36)	0.05
Pregnancy completion before Time 0	9,310 (1.47)	5,354 (0.84)	0.06
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	30,123 (4.75)	28,983 (4.57)	0.01
Cancer	39,806 (6.28)	39,190 (6.18)	0.00
Chronic kidney disease or renal disease	13,694 (2.16)	13,657 (2.15)	0.00
Chronic liver disease	32,361 (5.11)	33,076 (5.22)	0.01
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	76,489 (12.07)	77,146 (12.17)	0.00
Dementia or other neurological conditions	48,030 (7.58)	48,879 (7.71)	0.01
Diabetes mellitus, type 1 or 2	48,729 (7.69)	46,566 (7.35)	0.01
Down syndrome	304 (0.05)	277 (0.04)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	92,360 (14.57)	94,711 (14.94)	0.01
Hypertension	129,629 (20.45)	129,594 (20.45)	0.00
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	18,592 (2.93)	18,592 (2.93)	0.00
Mental health conditions	190,966 (30.13)	190,578 (30.07)	0.00
Obese or severely obese	128,939 (20.34)	132,631 (20.93)	0.01
Sickle cell disease or thalassemia	2,528 (0.40)	2,247 (0.35)	0.01
Stroke or cerebrovascular disease	11,343 (1.79)	11,775 (1.86)	0.01
Tuberculosis	668 (0.11)	707 (0.11)	0.00
≥ 1 COVID-19 laboratory test performed	363,436 (57.34)	368,756 (58.18)	0.02

Characteristic	Individuals receiving a booster/additional dose of BNT162b2 COVID-19 vaccine N = 633,839	Matched individuals not receiving a booster/additional dose N = 633,839	ASD
COVID-19 diagnoses occurring outside a hospital or emergency department setting	32,113 (5.07)	9,816 (1.55)	0.20
Hospitalization or emergency department–diagnosed COVID-19	4,195 (0.66)	4,305 (0.68)	0.00

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: The analysis of JNJ-786735 includes individuals aged 12–64 years.

Table B-2-Optum. Characteristics of Individuals Aged 18–64 Receiving an mRNA-1273 COVID-19 Vaccine Booster/Additional Dose and Matched, Unboosted Comparators, Optum

Characteristic	Individuals receiving a booster/additional dose of mRNA-1273 COVID-19 vaccine N = 68,117	Matched individuals not receiving a booster/ additional dose N = 68,117	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	45 (35, 56)	45 (35, 56)	
Mean (SD)	44.71 (12.46)	44.68 (12.44)	0.00
Sex, N (%)			
Male	33,504 (49.19)	33,504 (49.19)	0.00
Female	34,613 (50.81)	34,613 (50.81)	0.00
Days since primary completion			
Median (Q1, Q3)	229 (211, 250)	229 (211, 250)	
Mean (SD)	232.31 (31.36)	231.99 (31.60)	0.01
Primary series brand, N (%)			
JNJ-7836735	5,457 (8.01)	5,457 (8.01)	0.00
mRNA-1273	51,656 (75.83)	51,656 (75.83)	0.00
BNT162b2	11,004 (16.15)	11,004 (16.15)	0.00
Region, N (%)			
Northeast	8,357 (12.27)	8,357 (12.27)	0.00
South	1,959 (2.88)	1,959 (2.88)	0.00
Midwest	39,636 (58.19)	39,636 (58.19)	0.00
West	18,165 (26.67)	18,165 (26.67)	0.00
Pregnant at Time 0, N (%)	393 (1.14)	426 (1.23)	0.01
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	43,843 (64.36)	44,305 (65.04)	0.01
1	12,857 (18.87)	12,589 (18.48)	0.01
2+	11,417 (16.76)	11,223 (16.48)	0.01
Emergency department visits			
0	62,104 (91.17)	61,292 (89.98)	0.04
1	5,053 (7.42)	5,648 (8.29)	0.03
2+	960 (1.41)	1,177 (1.73)	0.03
Skilled nursing facility stay	86 (0.13)	106 (0.16)	0.01
Influenza vaccination	26,325 (38.65)	26,325 (38.65)	0.00
Pneumococcal vaccination	945 (1.39)	870 (1.28)	0.01
Encounter for cancer screening	23,832 (34.99)	23,022 (33.80)	0.03

Characteristic	Individuals receiving a booster/additional dose of mRNA-1273 COVID-19 vaccine N = 68,117	Matched individuals not receiving a booster/ additional dose N = 68,117	ASD
Eye examination	5,317 (7.81)	4,763 (6.99)	0.03
Colonoscopy	4,176 (6.13)	3,715 (5.45)	0.03
Bone mineral density test	1,183 (1.74)	994 (1.46)	0.02
Well-check/well-child preventive healthcare visit	33,498 (49.18)	32,554 (47.79)	0.03
Arthritis	10,500 (15.41)	10,224 (15.01)	0.01
Lipid abnormality	14,660 (21.52)	14,730 (21.62)	0.00
Ambulance use or life support services	900 (1.32)	1,031 (1.51)	0.02
Weakness	1,434 (2.11)	1,410 (2.07)	0.00
Pregnancy completion before Time 0	910 (2.63)	879 (2.54)	0.01
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	3,398 (4.99)	3,106 (4.56)	0.02
Cancer	4,903 (7.20)	4,543 (6.67)	0.02
Chronic kidney disease or renal disease	1,426 (2.09)	1,510 (2.22)	0.01
Chronic liver disease	3,384 (4.97)	3,439 (5.05)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	8,190 (12.02)	8,073 (11.85)	0.01
Dementia or other neurological conditions	5,192 (7.62)	5,126 (7.53)	0.00
Diabetes mellitus, type 1 or 2	5,714 (8.39)	6,273 (9.21)	0.03
Down syndrome	15 (0.02)	12 (0.02)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	10,333 (15.17)	10,575 (15.52)	0.01
Hypertension	16,015 (23.51)	16,812 (24.68)	0.03
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	1,932 (2.84)	1,932 (2.84)	0.00
Mental health conditions	22,766 (33.42)	21,806 (32.01)	0.03
Obese or severely obese	15,163 (22.26)	16,325 (23.97)	0.04
Sickle cell disease or thalassemia	144 (0.21)	148 (0.22)	0.00
Stroke or cerebrovascular disease	1,217 (1.79)	1,348 (1.98)	0.01
Tuberculosis	54 (0.08)	70 (0.10)	0.01
≥ 1 COVID-19 laboratory test performed	32,244 (47.34)	31,739 (46.59)	0.01

Characteristic	Individuals receiving a booster/additional dose of mRNA-1273 COVID-19 vaccine N = 68,117	Matched individuals not receiving a booster/ additional dose N = 68,117	ASD
COVID-19 diagnoses occurring outside a hospital or emergency department setting	3,845 (5.64)	4,464 (6.55)	0.04
Hospitalization or emergency department–diagnosed COVID-19	479 (0.70)	619 (0.91)	0.02

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Table B-2-CVS. Characteristics of Individuals Aged 18–64 Receiving an mRNA-1273 COVID-19 Vaccine Booster/Additional Dose and Matched, Unboosted Comparators, CVS Health

Characteristic	Individuals receiving a booster/additional dose of mRNA-1273 COVID-19 vaccine N = 342,384	Matched individuals not receiving a booster/ additional dose N = 342,384	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	46 (34, 56)	46 (34, 56)	0.00
Mean (SD)	44.31 (13.11)	44.3 (13.1)	0.00
Sex, N (%)			
Male	164,889 (48.16)	164,889 (48.16)	0.00
Female	177,495 (51.84)	177,495 (51.84)	0.00
Days since primary completion			
Median (Q1, Q3)	233 (213, 258)	232 (213, 258)	0.00
Mean (SD)	237.84 (35.54)	237.66 (35.74)	0.01
Primary series brand, N (%)			
JNJ-7836735	24,503 (7.16)	24,503 (7.16)	0.00
mRNA-1273	257,913 (75.33)	257,913 (75.33)	0.00
BNT162b2	59,968 (17.51)	59,968 (17.51)	0.00
Region, N (%)			
Northeast	58,817 (17.18)	58,817 (17.18)	0.00
South	43,146 (12.60)	43,146 (12.60)	0.00
Midwest	59,997 (17.52)	59,997 (17.52)	0.00
West	180,424 (52.70)	180,424 (52.70)	0.00
Pregnant at Time 0, N (%)	1,749 (0.51)	2,036 (0.59)	0.01
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	240,125 (70.13)	264,602 (77.28)	0.16
1	54,795 (16.00)	46,803 (13.67)	0.07
2+	47,464 (13.86)	30,979 (9.05)	0.15
Emergency department visits			
0	313,426 (91.54)	319,278 (93.25)	0.06
1	24,154 (7.05)	19,712 (5.76)	0.05
2+	4,804 (1.40)	3,394 (0.99)	0.04
Skilled nursing facility stay	223 (0.07)	207 (0.06)	0.00
Influenza vaccination	116,297 (33.97)	116,297 (33.97)	0.00
Pneumococcal vaccination	4,300 (1.26)	2,815 (0.82)	0.04
Encounter for cancer screening	114,993 (33.59)	81,301 (23.75)	0.22

Characteristic	Individuals receiving a booster/additional dose of mRNA-1273 COVID-19 vaccine N = 342,384	Matched individuals not receiving a booster/ additional dose N = 342,384	ASD
Eye examination	30,968 (9.04)	19,988 (5.84)	0.12
Colonoscopy	19,955 (5.83)	12,508 (3.65)	0.10
Bone mineral density test	6,902 (2.02)	4,137 (1.21)	0.06
Well-check/well-child preventive healthcare visit	156,504 (45.71)	107,801 (31.49)	0.30
Arthritis	55,049 (16.08)	42,189 (12.32)	0.11
Lipid abnormality	81,428 (23.78)	65,376 (19.09)	0.11
Ambulance use or life support services	4,851 (1.42)	3,810 (1.11)	0.03
Weakness	6,802 (1.99)	4,595 (1.34)	0.05
Pregnancy completion before Time 0	4,453 (1.30)	2,462 (0.72)	0.06
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	17,811 (5.20)	17,430 (5.09)	0.01
Cancer	25,132 (7.34)	24,341 (7.11)	0.01
Chronic kidney disease or renal disease	9,110 (2.66)	9,340 (2.73)	0.00
Chronic liver disease	20,365 (5.95)	21,399 (6.25)	0.01
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	42,656 (12.46)	43,388 (12.67)	0.01
Dementia or other neurological conditions	27,802 (8.12)	28,462 (8.31)	0.01
Diabetes mellitus, type 1 or 2	30,841 (9.01)	31,730 (9.27)	0.01
Down syndrome	156 (0.05)	130 (0.04)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	55,913 (16.33)	57,605 (16.82)	0.01
Hypertension	83,254 (24.32)	85,496 (24.97)	0.02
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	10,432 (3.05)	10,432 (3.05)	0.00
Mental health conditions	108,934 (31.82)	106,744 (31.18)	0.01
Obese or severely obese	77,750 (22.71)	81,662 (23.85)	0.03
Sickle cell disease or thalassemia	1,171 (0.34)	1,205 (0.35)	0.00
Stroke or cerebrovascular disease	7,707 (2.25)	8,162 (2.38)	0.01
Tuberculosis	374 (0.11)	384 (0.11)	0.00
≥ 1 COVID-19 laboratory test performed	192,721 (56.29)	194,790 (56.89)	0.01

Characteristic	Individuals receiving a booster/additional dose of mRNA-1273 COVID-19 vaccine N = 342,384	Matched individuals not receiving a booster/ additional dose N = 342,384	ASD
COVID-19 diagnoses occurring outside a hospital or emergency department setting	16,381 (4.78)	4,287 (1.25)	0.21
Hospitalization or emergency department–diagnosed COVID-19	2,188 (0.64)	2,546 (0.74)	0.01

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: The analysis of mRNA-1273 includes individuals aged 18–64 years.

Table B-3-Optum. Characteristics of Individuals Aged 18–64 Years Receiving a JNJ-7836735 COVID-19 Vaccine Booster/Additional Dose and Matched Unboosted Comparators, Optum

Characteristic	Individuals receiving a booster/additional dose of JNJ-7836735 COVID-19 vaccine N = 1,615	Matched individuals not receiving a booster/additional dose N = 1,615	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	50 (39, 58)	50 (39, 58)	
Mean (SD)	47.85 (11.83)	47.71 (11.79)	0.01
Sex, N (%)			
Male	916 (56.72)	916 (56.72)	0.00
Female	699 (43.28)	699 (43.28)	0.00
Days since primary completion			
Median (Q1, Q3)	232 (214, 252)	232 (213, 252)	
Mean (SD)	232.31 (33.90)	232.14 (33.94)	0.00
Primary series brand, N (%)			
JNJ-7836735	1,496 (92.63)	1,496 (92.63)	0.00
mRNA-1273	47 (2.91)	47 (2.91)	0.00
BNT162b2	72 (4.46)	72 (4.46)	0.00
Region, N (%)			
Northeast	191 (11.83)	191 (11.83)	0.00
South	32 (1.98)	32 (1.98)	0.00
Midwest	950 (58.82)	950 (58.82)	0.00
West	442 (27.37)	442 (27.37)	0.00
Pregnant at Time 0, N (%)	0 (0.00)	< 11	0.11
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	1,064 (65.88)	1,049 (64.95)	0.02
1	303 (18.76)	282 (17.46)	0.03
2+	248 (15.36)	284 (17.59)	0.06
Emergency department visits			
0	1,465 (90.71)	1,425 (88.24)	0.08
1	117 (7.24)	154 (9.54)	0.08
2+	33 (2.04)	36 (2.23)	0.01
Skilled nursing facility stay	< 11	< 11	0.00
Influenza vaccination	445 (27.55)	445 (27.55)	0.00
Pneumococcal vaccination	15 (0.93)	17 (1.05)	0.01
Encounter for cancer screening	576 (35.67)	544 (33.68)	0.04

Characteristic	Individuals receiving a booster/additional dose of JNJ-7836735 COVID-19 vaccine N = 1,615	Matched individuals not receiving a booster/additional dose N = 1,615	ASD
Eye examination	115 (7.12)	128 (7.93)	0.03
Colonoscopy	110 (6.81)	98 (6.07)	0.03
Bone mineral density test	30 (1.86)	26 (1.61)	0.02
Well-check/well-child preventive healthcare visit	747 (46.25)	725 (44.89)	0.03
Arthritis	274 (16.97)	236 (14.61)	0.06
Lipid abnormality	406 (25.14)	380 (23.53)	0.04
Ambulance use or life support services	34 (2.11)	24 (1.49)	0.05
Weakness	32 (1.98)	33 (2.04)	0.00
Pregnancy completion before Time 0	< 11	< 11	0.01
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	82 (5.08)	54 (3.34)	0.09
Cancer	126 (7.80)	117 (7.24)	0.02
Chronic kidney disease or renal disease	37 (2.29)	32 (1.98)	0.02
Chronic liver disease	94 (5.82)	80 (4.95)	0.04
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	194 (12.01)	196 (12.14)	0.00
Dementia or other neurological conditions	111 (6.87)	107 (6.63)	0.01
Diabetes mellitus, type 1 or 2	182 (11.27)	147 (9.10)	0.07
Down syndrome	0 (0.00)	0 (0.00)	
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	259 (16.04)	285 (17.65)	0.04
Hypertension	497 (30.77)	480 (29.72)	0.02
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	37 (2.29)	37 (2.29)	0.00
Mental health conditions	471 (29.16)	509 (31.52)	0.05
Obese or severely obese	445 (27.55)	411 (25.45)	0.05
Sickle cell disease or thalassemia	< 11	< 11	0.04
Stroke or cerebrovascular disease	34 (2.11)	40 (2.48)	0.02
Tuberculosis	< 11	< 11	0.00
≥ 1 COVID-19 laboratory test performed	714 (44.21)	707 (43.78)	0.01
COVID-19 diagnoses occurring outside a hospital or emergency department setting	106 (6.56)	111 (6.87)	0.01

Characteristic	Individuals receiving a booster/additional dose of JNJ-7836735 COVID-19 vaccine N = 1,615	Matched individuals not receiving a booster/additional dose N = 1,615	ASD
Hospitalization or emergency department–diagnosed COVID-19	18 (1.11)	13 (0.80)	0.03

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019;

Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: The analysis of JNJ-786735 includes individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-3-CVS. Characteristics of Individuals Aged 18–64 Years Receiving a JNJ-7836735 COVID-19 Vaccine Booster/Additional Dose and Matched, Unboosted Comparators, CVS Health

Characteristic	Individuals receiving a booster/additional dose of JNJ-7836735 COVID-19 vaccine N = 9,783	Matched individuals not receiving a booster/additional dose N = 9,783	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	51 (40, 58)	51 (40, 58)	0.00
Mean (SD)	47.65 (12.37)	47.65 (12.39)	0.00
Sex, N (%)			
Male	5,437 (55.58)	5,437 (55.58)	0.00
Female	4,346 (44.42)	4,346 (44.42)	0.00
Days since primary completion			
Median (Q1, Q3)	233 (213, 253)	233 (213, 253)	0.00
Mean (SD)	232.75 (36.83)	232.67 (36.83)	0.00
Primary series brand, N (%)			
JNJ-7836735	8,995 (91.95)	8,995 (91.95)	0.00
mRNA-1273	282 (2.88)	282 (2.88)	0.00
BNT162b2	506 (5.17)	506 (5.17)	0.00
Region, N (%)			
Northeast	2,173 (22.21)	2,173 (22.21)	0.00
South	1,340 (13.70)	1,340 (13.70)	0.00
Midwest	1,298 (13.27)	1,298 (13.27)	0.00
West	4,972 (50.82)	4,972 (50.82)	0.00
Pregnant at Time 0, N (%)	19 (0.19)	26 (0.27)	0.01
Characteristics assessed in the 365 days before Time 0			
Hospitalizations			
0	7,029 (71.85)	7,810 (79.83)	0.19
1	1,491 (15.24)	1,221 (12.48)	0.08
2+	1,263 (12.91)	752 (7.69)	0.17
Emergency department visits			
0	8,916 (91.14)	9,134 (93.37)	0.08
1	720 (7.36)	571 (5.84)	0.06
2+	147 (1.50)	78 (0.80)	0.07
Skilled nursing facility stay	< 11	< 11	0.01
Influenza vaccination	2,280 (23.31)	2,280 (23.31)	0.00
Pneumococcal vaccination	128 (1.31)	69 (0.71)	0.06
Encounter for cancer screening	3,305 (33.78)	2,293 (23.44)	0.23

Characteristic	Individuals receiving a booster/additional dose of JNJ-7836735 COVID-19 vaccine N = 9,783	Matched individuals not receiving a booster/additional dose N = 9,783	ASD
Eye examination	851 (8.70)	546 (5.58)	0.12
Colonoscopy	618 (6.32)	380 (3.88)	0.11
Bone mineral density test	179 (1.83)	116 (1.19)	0.05
Well-check/well-child preventive healthcare visit	4,176 (42.69)	2,791 (28.53)	0.30
Arthritis	1,629 (16.65)	1,318 (13.47)	0.09
Lipid abnormality	2,626 (26.84)	2,099 (21.46)	0.13
Ambulance use or life support services	136 (1.39)	101 (1.03)	0.03
Weakness	196 (2.00)	137 (1.40)	0.05
Pregnancy completion before Time 0	47 (0.48)	40 (0.41)	0.01
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	483 (4.94)	480 (4.91)	0.00
Cancer	764 (7.81)	747 (7.64)	0.01
Chronic kidney disease or renal disease	332 (3.39)	303 (3.10)	0.02
Chronic liver disease	610 (6.24)	668 (6.83)	0.02
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	1,253 (12.81)	1,198 (12.25)	0.02
Dementia or other neurological conditions	819 (8.37)	829 (8.47)	0.00
Diabetes mellitus, type 1 or 2	1,072 (10.96)	1,022 (10.45)	0.02
Down syndrome	< 11	0 (0.00)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	1,661 (16.98)	1,668 (17.05)	0.00
Hypertension	2,951 (30.16)	2,821 (28.84)	0.03
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	222 (2.27)	222 (2.27)	0.00
Mental health conditions	2,821 (28.84)	2,883 (29.47)	0.01
Obese or severely obese	2,471 (25.26)	2,424 (24.78)	0.01
Sickle cell disease or thalassemia	37 (0.38)	20 (0.20)	0.03
Stroke or cerebrovascular disease	266 (2.72)	267 (2.73)	0.00
Tuberculosis	< 11	< 11	0.02
≥ 1 COVID-19 laboratory test performed	5,134 (52.48)	5,401 (55.21)	0.05
COVID-19 diagnoses occurring outside a hospital or emergency department setting	532 (5.44)	205 (2.10)	0.18

Characteristic	Individuals receiving a booster/additional dose of JNJ-7836735 COVID-19 vaccine N = 9,783	Matched individuals not receiving a booster/additional dose N = 9,783	ASD
Hospitalization or emergency department–diagnosed COVID-19	92 (0.94)	85 (0.87)	0.01

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019;

Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: The analysis of JNJ-786735 includes individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-4-Optum. Characteristics of Individuals Receiving a Booster/Additional COVID-19 Vaccine Dose Who Were Excluded From the Analytic Cohort for Failing to Match, by Vaccine Brand, Optum

Characteristic	Individuals with BNT162b2 booster/additional dose N = 32,197	Individuals with mRNA-1273 booster/additional dose N = 28,910	Individuals with JNJ-7836735 booster/additional dose N = 1,385
Age, years			
Median (Q1, Q3)	45 (32, 55)	47 (36, 57)	51 (41, 58)
Mean (SD)	42.81 (14.50)	45.70 (12.72)	48.55 (11.95)
Sex, N (%)			
Male	14,516 (45.21)	13,326 (46.09)	755 (54.51)
Female	17,591 (54.79)	15,584 (53.91)	630 (45.49)
Days since primary completion			
Median (Q1, Q3)	240 (214, 267)	242 (218, 270)	230 (204, 254)
Mean (SD)	240.76 (44.04)	244.26 (41.23)	223.45 (49.46)
Primary series brand, N (%)			
JNJ-7836735	2,717 (8.46)	3,113 (10.77)	1,347 (97.26)
mRNA-1273	2,587 (8.06)	23,415 (80.99)	22 (1.59)
BNT162b2	26,803 (83.48)	2,382 (8.24)	16 (1.16)
Region, N (%)			
Northeast	7,635 (23.78)	6,727 (23.27)	316 (22.82)
South	2,473 (7.70)	2,528 (8.74)	111 (8.01)
Midwest	15,580 (48.53)	14,083 (48.71)	657 (47.44)
West	6,419 (19.99)	5,572 (19.27)	301 (21.73)
Pregnant at Time 0, N (%)	247 (1.40)	159 (1.02)	< 11
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	19,016 (59.23)	17,025 (58.89)	786 (56.75)
1	6,406 (19.95)	5,809 (20.09)	290 (20.94)
2+	6,685 (20.82)	6,076 (21.02)	309 (22.31)
Emergency department visits			

Characteristic	Individuals with BNT162b2 booster/additional dose N = 32,197	Individuals with mRNA-1273 booster/additional dose N = 28,910	Individuals with JNJ-7836735 booster/additional dose N = 1,385
0	28,437 (88.57)	25,766 (89.12)	1,214 (87.65)
1	2,985 (9.30)	2,564 (8.87)	136 (9.82)
2+	685 (2.13)	580 (2.01)	35 (2.53)
Skilled nursing facility stay	139 (0.43)	34 (0.12)	< 11
Influenza vaccination	15,620 (48.65)	14,205 (49.14)	537 (38.77)
Pneumococcal vaccination	537 (1.67)	496 (1.72)	27 (1.95)
Encounter for cancer screening	11,013 (34.30)	10,838 (37.49)	523 (37.76)
Eye examination	3,139 (9.78)	2,556 (8.84)	126 (9.10)
Colonoscopy	2,051 (6.39)	2,057 (7.12)	108 (7.80)
Bone mineral density test	579 (1.80)	588 (2.03)	37 (2.67)
Well-check/well-child preventive healthcare visit	15,907 (49.54)	13,883 (48.02)	640 (46.21)
Arthritis	5,435 (16.93)	4,904 (16.96)	252 (18.19)
Lipid abnormality	6,777 (21.11)	6,807 (23.55)	389 (28.09)
Ambulance use or life support services	576 (1.79)	531 (1.84)	22 (1.59)
Weakness	769 (2.40)	604 (2.09)	35 (2.53)
Pregnancy completion before Time 0	545 (3.10)	366 (2.35)	< 11
Characteristics assessed using all available data before Time 0, N (%)			
Autoimmune disorders	2,644 (8.23)	2,208 (7.64)	110 (7.94)
Cancer	2,950 (9.19)	2,592 (8.97)	138 (9.96)
Chronic kidney disease or renal disease	870 (2.71)	745 (2.58)	45 (3.25)
Chronic liver disease	1,871 (5.83)	1,727 (5.97)	89 (6.43)
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	4,061 (12.65)	3,724 (12.88)	179 (12.92)
Dementia or other neurological conditions	2,548 (7.94)	2,337 (8.08)	130 (9.39)
Diabetes mellitus, type 1 or 2	2,689 (8.38)	2,612 (9.03)	150 (10.83)
Down syndrome	22 (0.07)	14 (0.05)	0 (0.00)

Characteristic	Individuals with BNT162b2 booster/additional dose N = 32,197	Individuals with mRNA-1273 booster/additional dose N = 28,910	Individuals with JNJ-7836735 booster/additional dose N = 1,385
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	5,080 (15.82)	4,699 (16.25)	272 (19.64)
Hypertension	7,284 (22.69)	7,453 (25.78)	459 (33.14)
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	4,661 (14.52)	3,645 (12.61)	139 (10.04)
Mental health conditions	10,383 (32.34)	9,294 (32.15)	413 (29.82)
Obese or severely obese	7,581 (23.61)	7,418 (25.66)	392 (28.30)
Sickle cell disease or thalassemia	76 (0.24)	47 (0.16)	< 11
Stroke or cerebrovascular disease	611 (1.90)	556 (1.92)	45 (3.25)
Tuberculosis	35 (0.11)	30 (0.10)	< 11
≥ 1 COVID-19 laboratory test performed	15,413 (48.01)	13,657 (47.24)	584 (42.17)
COVID-19 diagnoses occurring outside a hospital or emergency department setting	2,278 (7.10)	1,854 (6.41)	109 (7.87)
Hospitalization or emergency department–diagnosed COVID-19	338 (1.05)	276 (0.95)	30 (2.17)

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-4-CVS. Characteristics of Individuals Receiving a Booster/Additional COVID-19 Vaccine Dose Who Were Excluded From the Analytic Cohort for Failing to Match, by Vaccine Brand, CVS Health

Characteristic	Individuals with BNT162b2 booster/additional dose N = 93,972	Individuals with mRNA-1273 booster/additional dose N = 78,065	Individuals with JNJ-7836735 booster/additional dose N = 4,826
Age, years			
Median (Q1, Q3)	45 (32, 56)	48 (36, 58)	51 (40, 59)
Mean (SD)	42.8 (14.69)	45.92 (13.09)	48.08 (12.73)
Sex, N (%)			
Male	41,862 (44.55)	35,842 (45.91)	2,525 (52.32)
Female	52,070 (55.41)	42,196 (54.05)	2,298 (47.62)
Days since primary completion			
Median (Q1, Q3)	242 (211, 273)	245 (217, 277)	227 (189, 253)
Mean (SD)	243.49 (51.82)	247.08 (47.72)	215.46 (64.87)
Primary series brand, N (%)			
JNJ-7836735	7,483 (7.96)	8,580 (10.99)	4,395 (91.07)
mRNA-1273	6,663 (7.09)	62,754 (80.39)	161 (3.34)
BNT162b2	79,826 (84.95)	6,731 (8.62)	270 (5.59)
Region, N (%)			
Northeast	15,154 (16.13)	13,494 (17.29)	931 (19.29)
South	23,894 (25.43)	16,104 (20.63)	1,149 (23.81)
Midwest	27,522 (29.29)	24,387 (31.24)	1,208 (25.03)
West	27,402 (29.16)	24,080 (30.85)	1,538 (31.87)
Pregnant at Time 0, N (%)	681 (0.72)	512 (0.66)	< 11
Characteristics assessed in the 365 days before Time 0, N (%)			
Hospitalizations			
0	54,433 (57.92)	45,118 (57.80)	2,925 (60.61)
1	17,188 (18.29)	14,277 (18.29)	849 (17.59)
2+	22,351 (23.78)	18,670 (23.92)	1,052 (21.80)
Emergency department visits			

Characteristic	Individuals with BNT162b2 booster/additional dose N = 93,972	Individuals with mRNA-1273 booster/additional dose N = 78,065	Individuals with JNJ-7836735 booster/additional dose N = 4,826
0	82,571 (87.87)	68,515 (87.77)	4,277 (88.62)
1	8,877 (9.45)	7,376 (9.45)	417 (8.64)
2+	2,524 (2.69)	2,174 (2.78)	132 (2.74)
Skilled nursing facility stay	178 (0.19)	132 (0.17)	9 (0.19)
Influenza vaccination	50,029 (53.24)	39,973 (51.20)	1,877 (38.89)
Pneumococcal vaccination	2,023 (2.15)	1,759 (2.25)	99 (2.05)
Encounter for cancer screening	32,784 (34.89)	29,412 (37.68)	1,805 (37.40)
Eye examination	11,533 (12.27)	8,973 (11.49)	513 (10.63)
Colonoscopy	6,408 (6.82)	5,703 (7.31)	327 (6.78)
Bone mineral density test	2,330 (2.48)	2,046 (2.62)	108 (2.24)
Well-check/well-child preventive healthcare visit	46,495 (49.48)	36,621 (46.91)	2,152 (44.59)
Arthritis	17,869 (19.02)	15,553 (19.92)	1,016 (21.05)
Lipid abnormality	22,548 (23.99)	21,314 (27.30)	1,485 (30.77)
Ambulance use or life support services	2,096 (2.23)	1,922 (2.46)	134 (2.78)
Weakness	2,691 (2.86)	2,239 (2.87)	155 (3.21)
Pregnancy completion before Time 0	1,703 (1.81)	1,084 (1.39)	28 (0.58)
Characteristics assessed using all available data before Time 0, N (%)			
Autoimmune disorders	9,432 (10.04)	7,487 (9.59)	406 (8.41)
Cancer	9,384 (9.99)	8,343 (10.69)	454 (9.41)
Chronic kidney disease or renal disease	3,962 (4.22)	3,572 (4.58)	215 (4.46)
Chronic liver disease	6,801 (7.24)	5,969 (7.65)	384 (7.96)
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	13,417 (14.28)	11,542 (14.79)	752 (15.58)
Dementia or other neurological conditions	9,000 (9.58)	7,787 (9.98)	494 (10.24)
Diabetes mellitus, type 1 or 2	9,284 (9.88)	8,798 (11.27)	608 (12.60)
Down syndrome	89 (0.09)	86 (0.11)	< 11

Characteristic	Individuals with BNT162b2 booster/additional dose N = 93,972	Individuals with mRNA-1273 booster/additional dose N = 78,065	Individuals with JNJ-7836735 booster/additional dose N = 4,826
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	17,250 (18.36)	14,984 (19.19)	966 (20.02)
Hypertension	23,667 (25.19)	22,228 (28.47)	1,549 (32.10)
Immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies)	16,279 (17.32)	12,707 (16.28)	580 (12.02)
Mental health conditions	31,476 (33.50)	26,416 (33.84)	1,531 (31.72)
Obese or severely obese	23,637 (25.15)	21,074 (27.00)	1,462 (30.29)
Sickle cell disease or thalassemia	306 (0.33)	242 (0.31)	17 (0.35)
Stroke or cerebrovascular disease	2,439 (2.60)	2,375 (3.04)	152 (3.15)
Tuberculosis	156 (0.17)	119 (0.15)	< 11
≥ 1 COVID-19 laboratory test performed	54,328 (57.81)	44,056 (56.44)	2,516 (52.13)
COVID-19 diagnoses occurring outside a hospital or emergency department setting	6,226 (6.63)	4,669 (5.98)	286 (5.93)
Hospitalization or emergency department–diagnosed COVID-19	996 (1.06)	774 (0.99)	54 (1.12)

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Note: Privacy rules requiring masking cell sizes fewer than 11 individuals.

Table B-5-Optum. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose Among Individuals Who Have Previously Received a Complete Primary Series, Overall and Sensitivity Analyses Accounting for Potentially Missing Vaccine Records, Optum

COVID-19 outcome	Vaccine booster / additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)	Sensitivity analysis assuming 84% exposure misclassification VE (95% CI)	Sensitivity analysis assuming 69% exposure misclassification VE (95% CI)
Medically diagnosed	BNT162b2	118,326	2,415	8,807,161	0.48 (0.45-0.51)	52% (49%-55%)	56% (53%-59%)	63% (61%-66%)
	None	118,326	3,001	5,261,360	—	—	—	—
	mRNA-1273	68,117	1,297	5,143,221	0.45 (0.41-0.48)	55% (52%-59%)	59% (56%-63%)	66% (64%-69%)
	None	68,117	1,710	2,996,789	—	—	—	—
	JNJ-7836735	1,615	58	128,604	0.78 (0.53-1.17)	22% (-17% to 47%)	23% (-16% to 48%)	25% (-12% to 49%)
	None	1,615	49	81,651	—	—	—	—
Hospital/ED-diagnosed	BNT162b2	118,326	113	8,916,106	0.27 (0.22-0.35)	73% (65%-78%)	77% (70%-81%)	82% (77%-86%)
	None	118,326	247	5,387,213	—	—	—	—
	mRNA-1273	68,117	59	5,201,099	0.27 (0.19-0.37)	73% (63%-81%)	77% (68%-84%)	82% (76%-88%)
	None	68,117	133	3,066,068	—	—	—	—
	JNJ-7836735	1,615	< 11	131,182	0.42 (0.13-1.35)	58% (-35% to 87%)	58% (-34% to 87%)	59% (-30% to 87%)
	None	1,615	< 11	83,704	—	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of cell sizes fewer than 11 individuals.

Table B-5-CVS. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose Among Individuals Who Have Previously Received a Complete Primary Series, Overall and Sensitivity Analyses Accounting for Potentially Missing Vaccine Records, CVS Health

COVID-19 outcome	Vaccine booster / additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)	Sensitivity analysis assuming 89% exposure misclassification VE (95% CI)	Sensitivity analysis assuming 69% exposure misclassification VE (95% CI)
Medically diagnosed	BNT162b2	633,839	11,760	67,365,604	0.45 (0.44-0.47)	55% (53%-56%)	57% (56%-59%)	67% (66%-68%)
	None	633,839	14,338	35,902,792	—	—	—	—
	mRNA-1273	342,384	5,722	36,334,171	0.41 (0.40-0.43)	59% (57%-60%)	61% (59%-62%)	70% (68%-71%)
	None	342,384	7,763	19,323,986	—	—	—	—
	JNJ-7836735	9,783	298	1,078,067	0.64 (0.54-0.76)	36% (24%-46%)	38% (27%-48%)	47% (37%-56%)
	None	9,783	285	653,948	—	—	—	—
Hospital/ED-diagnosed	BNT162b2	633,839	710	68,162,932	0.27 (0.24-0.30)	73% (70%-76%)	75% (73%-78%)	82% (81%-84%)
	None	633,839	1,452	36,766,210	—	—	—	—
	mRNA-1273	342,384	323	36,715,628	0.24 (0.21-0.27)	76% (73%-79%)	78% (75%-81%)	85% (82%-87%)
	None	342,384	823	19,786,800	—	—	—	—
	JNJ-7836735	9,783	19	1,098,347	0.28 (0.15-0.50)	72% (50%-85%)	75% (54%-86%)	82% (68%-90%)
	None	9,783	41	671,553	—	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Table B-6-Optum. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine, by Immunocompromised Status, Optum

Subgroup	COVID-19 outcome	Booster/additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Immunocompromised	Medically diagnosed	BNT162b2	3,725	101	363,450	0.39 (0.29-0.53)	61% (47%-71%)
		None	3,725	131	196,333	—	—
		mRNA-1273	1,932	61	182,469	0.54 (0.35-0.82)	46% (18%-65%)
		None	1,932	54	97,367	—	—
	Hospital/ED-diagnosed	BNT162b2	3,725	< 11	368,189	0.22 (0.09-0.52)	78% (48%-91%)
		None	3,725	18	202,106	—	—
		mRNA-1273	1,932	< 11	185,269	0.52 (0.14-1.91)	48% (-91% to 86%)
		None	1,932	< 11	99,630	—	—
Immunocompetent	Medically diagnosed	BNT162b2	114,601	2,314	8,443,711	0.48 (0.45-0.51)	52% (49%-55%)
		None	114,601	2,870	5,065,027	—	—
		mRNA-1273	66,185	1,236	4,960,752	0.44 (0.41-0.48)	56% (52%-59%)
		None	66,185	1,656	2,899,422	—	—
	Hospital/ED-diagnosed	BNT162b2	114,601	105	8,547,917	0.28 (0.22-0.36)	72% (64%-78%)
		None	114,601	229	5,185,107	—	—
		mRNA-1273	66,185	52	5,015,830	0.25 (0.18-0.36)	75% (64%-82%)
		None	66,185	127	2,966,438	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analysis of mRNA-1273 includes individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes fewer than 11 individuals.

Table B-6-CVS. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine, by Immunocompromised Status, CVS Health

Subgroup	COVID-19 outcome	Booster/additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Immunocompromised	Medically diagnosed	BNT162b2	18,592	688	2,353,434	0.50 (0.44-0.57)	50% (43%-56%)
		None	18,592	643	1,133,288	—	—
		mRNA-1273	10,432	334	1,245,563	0.48 (0.40-0.57)	52% (43%-60%)
		None	10,432	343	606,156	—	—
		JNJ-7836735	222	< 11	25,470	0.60 (0.23-1.57)	40% (-57% to 77%)
		None	222	< 11	14,328	—	—
	Hospital/ED-diagnosed	BNT162b2	18,592	99	2,397,791	0.36 (0.27-0.49)	64% (51%-73%)
		None	18,592	129	1,170,346	—	—
		mRNA-1273	10,432	46	1,267,064	0.44 (0.29-0.67)	56% (33%-71%)
		None	10,432	54	626,175	—	—
		JNJ-7836735	222	< 11	25,976	1.18 (0.14-10.23)	-18% (-923% to 86%)
		None	222	< 11	14,795	—	—
Immunocompetent	Medically diagnosed	BNT162b2	615,247	11,072	65,012,170	0.45 (0.44-0.46)	55% (54%-56%)
		None	615,247	13,695	34,769,504	—	—
		mRNA-1273	331,952	5,388	35,088,608	0.41 (0.39-0.43)	59% (57%-61%)
		None	331,952	7,420	18,717,830	—	—
		JNJ-7836735	9,561	289	1,052,597	0.64 (0.53-0.76)	36% (24%-47%)
		None	9,561	277	639,620	—	—
	Hospital/ED-diagnosed	BNT162b2	615,247	611	65,765,141	0.26 (0.23-0.29)	74% (71%-77%)
		None	615,247	1,323	35,595,864	—	—
		mRNA-1273	331,952	277	35,448,564	0.22 (0.19-0.26)	78% (74%-81%)
		None	331,952	769	19,160,625	—	—
		JNJ-7836735	9,561	17	1,072,371	0.25 (0.14-0.47)	75% (53%-86%)
		None	9,561	40	656,758	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-7-Optum. Estimated Effectiveness of Receiving a COVID-19 Booster/Additional Dose, by Variant-specific Era, Optum

Variant era	COVID-19 outcome	Booster/additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Delta	Medically diagnosed	BNT162b2	84,690	452	2,820,646	0.41 (0.36-0.47)	59% (53%-64%)
		None	84,690	805	2,133,612	—	—
		mRNA-1273	53,575	260	1,602,038	0.45 (0.38-0.54)	55% (46%-62%)
		None	53,575	422	1,206,185	—	—
	Hospital/ED-diagnosed	BNT162b2	84,690	24	2,826,838	0.29 (0.18-0.48)	71% (52%-82%)
		None	84,690	57	2,144,976	—	—
		mRNA-1273	53,575	17	1,605,500	0.36 (0.19-0.68)	64% (32%-81%)
		None	53,575	35	1,211,270	—	—
Omicron	Medically diagnosed	BNT162b2	33,636	379	1,414,884	0.58 (0.50-0.66)	42% (34%-50%)
		None	33,636	584	1,151,232	—	—
		mRNA-1273	14,542	147	642,360	0.48 (0.39-0.59)	52% (41%-61%)
		None	14,542	267	531,647	—	—
	Hospital/ED-diagnosed	BNT162b2	33,636	15	1,429,104	0.31 (0.17-0.56)	69% (44%-83%)
		None	33,636	45	1,171,042	—	—
		mRNA-1273	14,542	< 11	647,670	0.58 (0.24-1.40)	42% (-40% to 76%)
		None	14,542	12	541,166	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analysis of mRNA-1273 includes individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-7-CVS. Estimated Effectiveness of Receiving a COVID-19 Booster/Additional Dose, by Variant-specific Era, CVS Health

Variant era	COVID-19 outcome	Booster/additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Delta	Medically diagnosed	BNT162b2	419,532	1,563	15,499,273	0.34 (0.32-0.37)	66% (63%-68%)
		None	419,532	2,902	10,945,112	—	—
		mRNA-1273	250,665	727	7,502,444	0.36 (0.32-0.40)	64% (60%-68%)
		None	250,665	1,351	5,588,962	—	—
		JNJ-7836735	7,674	42	251,764	0.37 (0.25-0.56)	63% (44%-75%)
		None	7,674	77	198,450	—	—
	Hospital/ED-diagnosed	BNT162b2	419,532	98	15,520,422	0.20 (0.15-0.26)	80% (74%-85%)
		None	419,532	310	10,987,676	—	—
		mRNA-1273	250,665	36	7,512,304	0.17 (0.12-0.25)	83% (75%-88%)
		None	250,665	157	5,605,491	—	—
		JNJ-7836735	7,674	< 11	252,343	0.09 (0.02-0.45)	91% (55%-98%)
		None	7,674	14	199,204	—	—
Omicron	Medically diagnosed	BNT162b2	214,307	1,736	14,698,293	0.43 (0.40-0.46)	57% (54%-60%)
		None	214,307	3,339	11,089,811	—	—
		mRNA-1273	91,719	903	6,597,858	0.45 (0.41-0.49)	55% (51%-59%)
		None	91,719	1,668	5,105,313	—	—
		JNJ-7836735	2,109	29	147,763	0.67 (0.40-1.10)	33% (-10% to 60%)
		None	2,109	38	125,888	—	—
	Hospital/ED-diagnosed	BNT162b2	214,307	110	14,798,731	0.36 (0.28-0.47)	64% (53%-72%)
		None	214,307	255	11,266,005	—	—
		mRNA-1273	91,719	60	6,651,335	0.36 (0.26-0.50)	64% (50%-74%)
		None	91,719	145	5,195,674	—	—
		JNJ-7836735	2,109	< 11	149,583	0.64 (0.11-3.76)	36% (-276% to 89%)
		None	2,109	< 11	127,897	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-8-Optum. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose Among Individuals Who Have Received a Complete Primary Series, by Homologous or Heterologous Primary Series Status, Optum

COVID-19 outcome	Booster/additional dose exposure group	Primary series	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Homologous booster^a							
Medically diagnosed	BNT162b2	BNT162b2	106,964	2,182	7,963,968	0.47 (0.44-0.51)	53% (49%-56%)
	None	BNT162b2	106,964	2,704	4,731,389	—	—
	mRNA-1273	mRNA-1273	51,656	984	3,934,742	0.44 (0.40-0.49)	56% (51%-60%)
	None	mRNA-1273	51,656	1,280	2,266,346	—	—
Hospital/ED-diagnosed	BNT162b2	BNT162b2	106,964	100	8,062,247	0.27 (0.21-0.35)	73% (65%-79%)
	None	BNT162b2	106,964	220	4,844,752	—	—
	mRNA-1273	mRNA-1273	51,656	45	3,978,840	0.29 (0.19-0.42)	71% (58%-81%)
	None	mRNA-1273	51,656	93	2,318,115	—	—
Heterologous booster^b							
Medically diagnosed	BNT162b2	mRNA-1273 or JNJ-7836735	11,362	233	843,193	0.50 (0.42-0.60)	50% (40%-58%)
	None	mRNA-1273 or JNJ-7836735	11,362	297	529,971	—	—
	mRNA-1273	BNT162b2 or JNJ-7836735	16,461	313	1,208,479	0.45 (0.39-0.53)	55% (47%-61%)
	None	BNT162b2 or JNJ-7836735	16,461	430	730,443	—	—
Hospital/ED-diagnosed	BNT162b2	mRNA-1273 or JNJ-7836735	11,362	13	853,859	0.31 (0.15-0.63)	69% (37%-85%)
	None	mRNA-1273 or JNJ-7836735	11,362	27	542,461	—	—
	mRNA-1273	BNT162b2 or JNJ-7836735	16,461	14	1,222,259	0.22 (0.11-0.42)	78% (58%-89%)
	non-mRNA-1273	BNT162b2 or JNJ-7836735	16,461	40	747,953	—	—
Heterologous booster^c							
Medically diagnosed	BNT162b2	mRNA-1273	6,336	107	444,654	0.47 (0.36-0.61)	53% (39%-64%)
	None	mRNA-1273	6,336	140	269,940	—	—
	mRNA-1273	BNT162b2	11,004	199	766,967	0.45 (0.38-0.55)	55% (45%-62%)
	None	BNT162b2	11,004	274	457,615	—	—
Hospital/ED-diagnosed	BNT162b2	mRNA-1273	6,336	< 11	449,278	0.53 (0.22-1.31)	47% (-31% to 78%)
	None	mRNA-1273	6,336	< 11	275,563	—	—

COVID-19 outcome	Booster/additional dose exposure group	Primary series	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
	mRNA-1273	BNT162b2	11,004	< 11	775,891	0.19 (0.08-0.48)	81% (52%-92%)
	None	BNT162b2	11,004	20	468,519	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

^a Homologous booster/additional doses are of the same brand as the primary series received by the individual.

^b The heterologous booster/additional doses (any other primary series brand) analysis defined exposure groups first by the brand of the booster/additional dose and then required that the primary series be of any other brand.

^c The heterologous booster/additional doses (single-brand primary series) analysis defined exposure groups first by the brand of the booster/additional dose and then divided into subgroups of individual brands of primary series.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analysis of mRNA-1273 includes individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-8-CVS. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose Among Individuals Who Have Received a Complete Primary Series, by Homologous or Heterologous Primary Series Status, CVS Health

COVID-19 outcome	Booster/additional dose exposure group	Primary series	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Homologous booster^a							
Medically diagnosed	BNT162b2	BNT162b2	583,474	10,835	62,132,093	0.45 (0.44-0.47)	55% (53%-56%)
	None	BNT162b2	583,474	13,117	32,932,878	—	—
	mRNA-1273	mRNA-1273	257,913	4,393	27,416,278	0.43 (0.41-0.45)	57% (55%-59%)
	None	mRNA-1273	257,913	5,740	14,468,540	—	—
	JNJ-7836735	JNJ-7836735	8,995	286	993,948	0.67 (0.56-0.80)	33% (20%-44%)
	None	JNJ-7836735	8,995	265	609,433	—	—
Hospital/ED-diagnosed	BNT162b2	BNT162b2	583,474	652	62,867,496	0.27 (0.24-0.30)	73% (70%-76%)
	None	BNT162b2	583,474	1,329	33,723,241	—	—
	mRNA-1273	mRNA-1273	257,913	249	27,710,788	0.26 (0.21-0.30)	74% (70%-79%)
	None	mRNA-1273	257,913	590	14,810,757	—	—
	JNJ-7836735	JNJ-7836735	8,995	18	1,013,407	0.29 (0.16-0.54)	71% (46%-84%)
	None	JNJ-7836735	8,995	37	625,846	—	—
Heterologous booster^b							
Medically diagnosed	BNT162b2	mRNA-1273 or JNJ-7836735	50,365	925	5,233,511	0.45 (0.41-0.50)	55% (50%-59%)
	None	mRNA-1273 or JNJ-7836735	50,365	1,221	2,969,914	—	—
	mRNA-1273	BNT162b2 or JNJ-7836735	84,471	1,329	8,917,893	0.38 (0.35-0.41)	62% (59%-65%)
	None	BNT162b2 or JNJ-7836735	84,471	2,023	4,855,446	—	—
	JNJ-7836735	BNT162b2 or mRNA-1273	788	12	84,119	0.32 (0.15-0.68)	68% (32%-85%)
	None	BNT162b2 or mRNA-1273	788	20	44,515	—	—
Hospital/ED-diagnosed	BNT162b2	mRNA 1273 or JNJ-7836735	50,365	58	5,295,436	0.29 (0.21-0.41)	71% (59%-79%)
	None	mRNA 1273 or JNJ-7836735	50,365	123	3,042,969	—	—
	mRNA-1273	BNT162b2 or JNJ-7836735	84,471	74	9,004,840	0.19 (0.15-0.25)	81% (75%-85%)
	None	BNT162b2 or JNJ-7836735	84,471	233	4,976,043	—	—
	JNJ-7836735	BNT162b2 or mRNA-1273	788	< 11	84,940	0.12 (0.01-1.29)	88% (-29% to 99%)
	None	BNT162b2 or mRNA-1273	788	< 11	45,707	—	—

COVID-19 outcome	Booster/additional dose exposure group	Primary series	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Heterologous booster^c							
Medically diagnosed	BNT162b2	mRNA-1273	29,869	514	3,045,525	0.43 (0.38-0.49)	57% (51%-62%)
	None	mRNA-1273	29,869	694	1,670,124	—	—
	BNT162b2	JNJ-7836735	20,496	411	2,187,986	0.48 (0.42-0.56)	52% (44%-58%)
	None	JNJ-7836735	20,496	527	1,299,790	—	—
	mRNA-1273	BNT162b2	59,968	901	6,189,658	0.37 (0.34-0.40)	63% (60%-66%)
	None	BNT162b2	59,968	1,396	3,286,651	—	—
	mRNA-1273	JNJ-7836735	24,503	428	2,728,235	0.41 (0.36-0.47)	59% (53%-64%)
	None	JNJ-7836735	24,503	627	1,568,795	—	—
	JNJ-7836735	BNT162b2	506	< 11	53,993	0.21 (0.08-0.52)	79% (48%-92%)
	None	BNT162b2	506	16	29,132	—	—
	JNJ-7836735	mRNA-1273	282	< 11	30,126	0.90 (0.23-3.57)	10% (-257% to 77%)
	None	mRNA-1273	282	< 11	15,383	—	—
Hospital/ED-diagnosed	BNT162b2	mRNA-1273	29,869	28	3,079,930	0.28 (0.18-0.46)	72% (54%-82%)
	None	mRNA-1273	29,869	62	1,711,440	—	—
	BNT162b2	JNJ-7836735	20,496	30	2,215,506	0.31 (0.19-0.49)	69% (51%-81%)
	None	JNJ-7836735	20,496	61	1,331,529	—	—
	mRNA-1273	BNT162b2	59,968	57	6,247,428	0.20 (0.15-0.28)	80% (72%-85%)
	None	BNT162b2	59,968	167	3,367,860	—	—
	mRNA-1273	JNJ-7836735	24,503	17	2,757,412	0.16 (0.09-0.28)	84% (72%-91%)
	None	JNJ-7836735	24,503	66	1,608,183	—	—
	JNJ-7836735	BNT162b2	506	< 11	54,428	0.23 (0.01-3.79)	77% (-279% to 99%)
	None	BNT162b2	506	< 11	30,239	—	—
	JNJ-7836735	mRNA-1273	282	0	30,512	0.00 (0.00-0.00)	100% (100%-100%)
	None	mRNA-1273	282	< 11	15,468	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

^a Homologous booster/additional doses are of the same brand as the primary series received by the individual.

^b The heterologous booster/additional doses (any other primary series brand) analysis defined exposure groups first by the brand of the booster/additional dose and then required that the primary series be of any other brand.

^c The heterologous booster/additional doses (single-brand primary series) analysis defined exposure groups first by the brand of the booster/additional dose and then divided into subgroups of individual brands of primary series.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analyses of mRNA-1273 and JNJ-7836735 include individuals aged 18–64 years.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Table B-9-Optum. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine, 10 Days After and Including Time 0, Negative Control Outcome Analysis, Optum

COVID-19 outcome	Booster/additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	118,326	400	1,165,612	0.65 (0.57-0.74)	35% (26%-43%)
	None	118,326	584	1,107,741	—	—
	mRNA-1273	68,117	195	671,236	0.58 (0.49-0.70)	42% (30%-51%)
	None	68,117	312	635,304	—	—
Hospital/ED-diagnosed	BNT162b2	118,326	15	1,167,241	0.35 (0.19-0.63)	65% (37%-81%)
	None	118,326	42	1,110,208	—	—
	mRNA-1273	68,117	< 11	672,041	0.52 (0.24-1.15)	48% (-15% to 76%)
	None	68,117	18	636,622	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analysis of mRNA-1273 includes individuals aged 18–64 years.

Note: Privacy rules requiring masking cell sizes of fewer than 11 individuals.

Table B-9-CVS. Estimated Effectiveness of Receiving a Booster/Additional Dose of COVID-19 Vaccine Compared With Not Receiving a Booster/Additional Dose Among Individuals Who Have Previously Received a Complete Primary Series, 10 Days After and Including Time 0, Negative Control Outcome Analysis

COVID-19 outcome	Booster/additional dose exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	633,839	1,332	6,295,203	0.46 (0.43-0.49)	54% (51%-57%)
	None	633,839	2,656	5,948,978	—	—
	mRNA-1273	342,384	721	3,403,134	0.49 (0.44-0.54)	51% (46%-56%)
	None	342,384	1,335	3,212,054	—	—
Hospital/ED-diagnosed	BNT162b2	633,839	88	6,300,227	0.36 (0.28-0.47)	64% (53%-72%)
	None	633,839	220	5,960,018	—	—
	mRNA-1273	342,384	42	3,405,907	0.28 (0.19-0.40)	72% (60%-81%)
	None	342,384	133	3,217,373	—	—

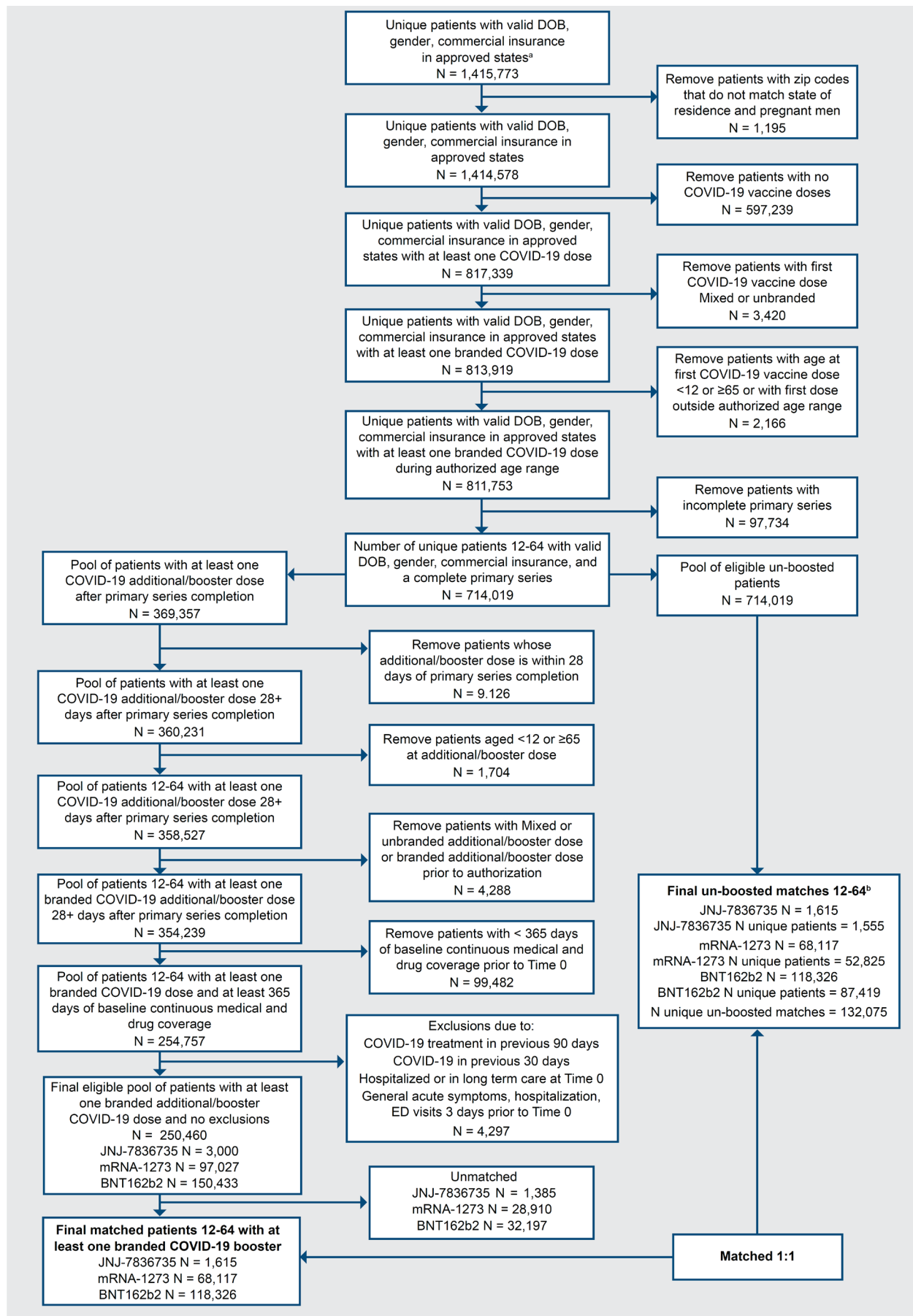
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

Note: — indicates the reference group.

Note: The analysis of BNT162b2 includes individuals aged 12–64 years; the analysis of mRNA-1273 includes individuals aged 18–64 years.

Supplementary Figures

Figure B-1-Optum. Attrition of Individuals Aged 12–64 Years in the Booster/Additional Dose Primary Analytic Cohort: Optum Preadjudicated Claims Supplemented With IIS Data, 11 December 2020–28 February 2022

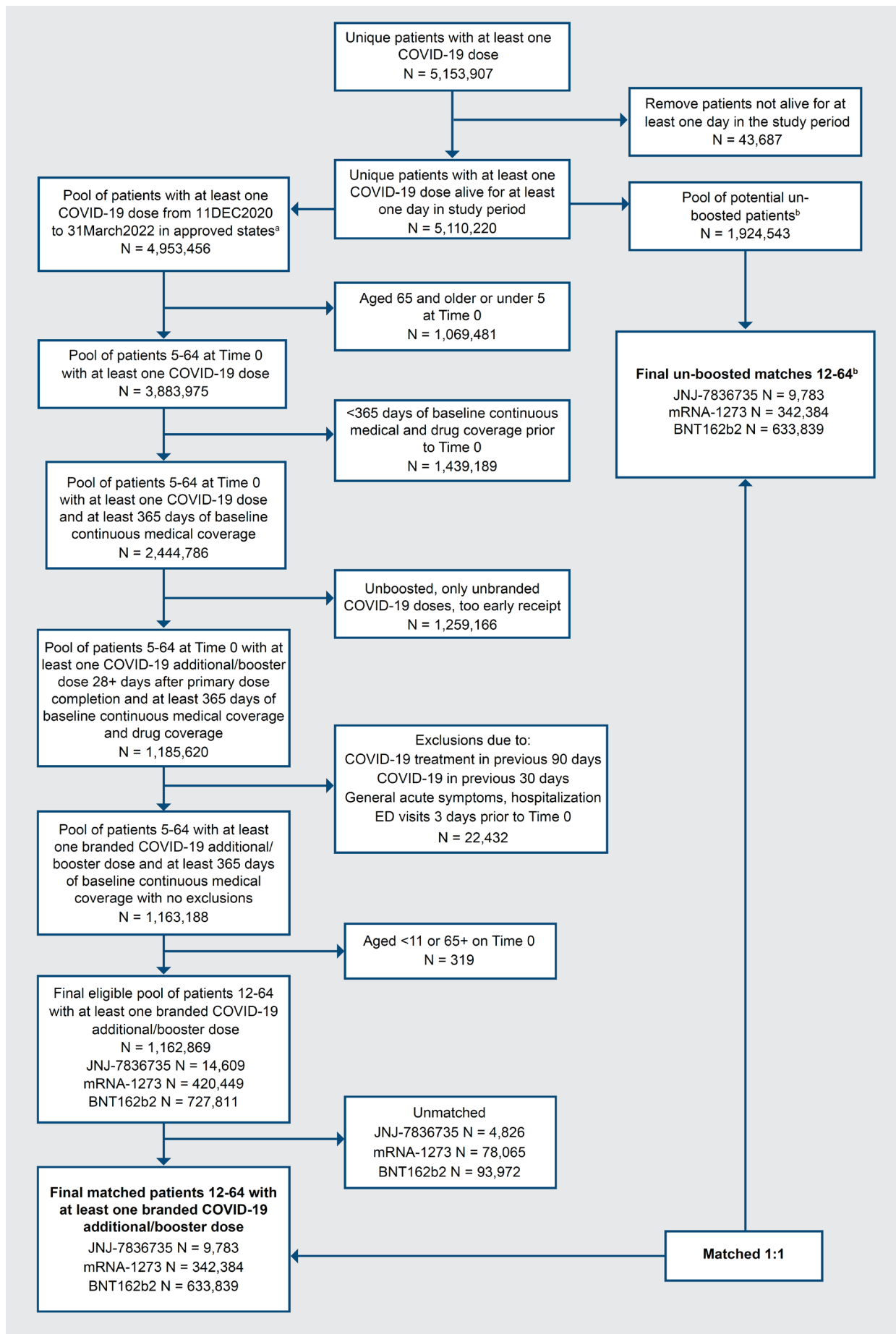


COVID-19 = coronavirus disease 2019; DOB = date of birth; ED = emergency department; IIS = immunization information system.

^a 9 IIS jurisdictions from 9 unique US states.

^b Individuals in the unboosted comparator group may also appear in the boosted group or serve as matches to multiple individuals in the boosted group.

**Figure B-1-CVS. Attrition Flowchart of Individuals Aged 12–64 Years in the
Booster/Additional Dose Primary Analytic Cohort: CVS Health Claims
Supplemented With IIS Data, 11 December 2020–28 February 2022**



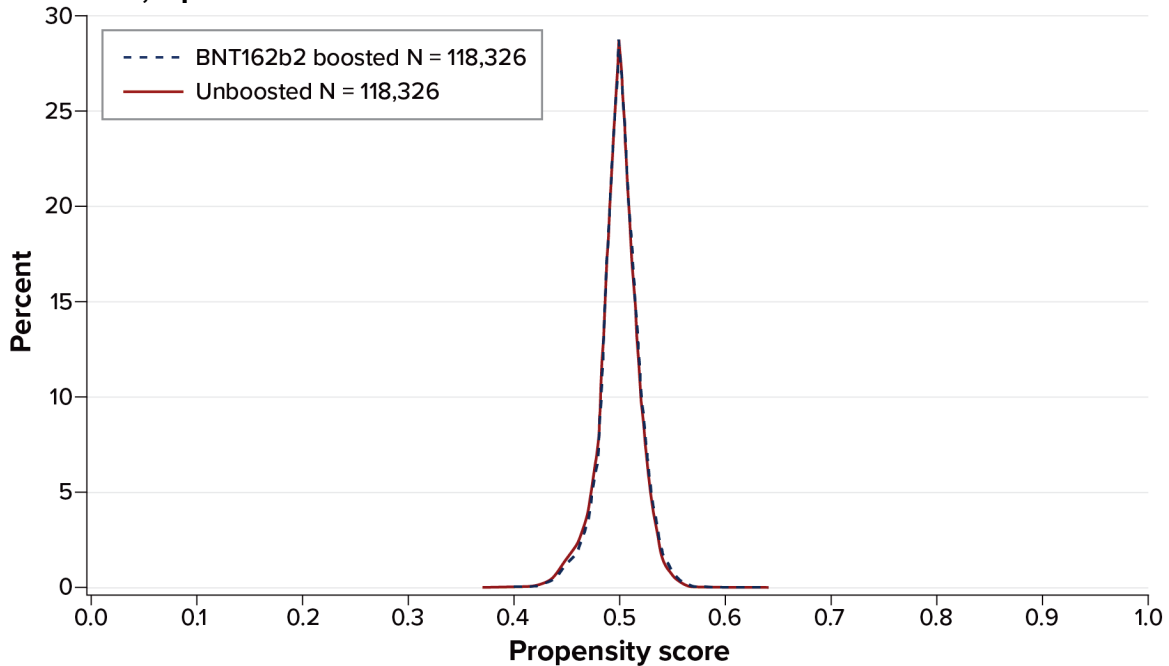
COVID-19 = coronavirus disease 2019; ED = emergency department; IIS = immunization information system.

^a 11 IIS jurisdictions from 9 US states.

^b Individuals in the unboosted comparator group may also appear in the boosted group or serve as matches to multiple individuals in the boosted group.

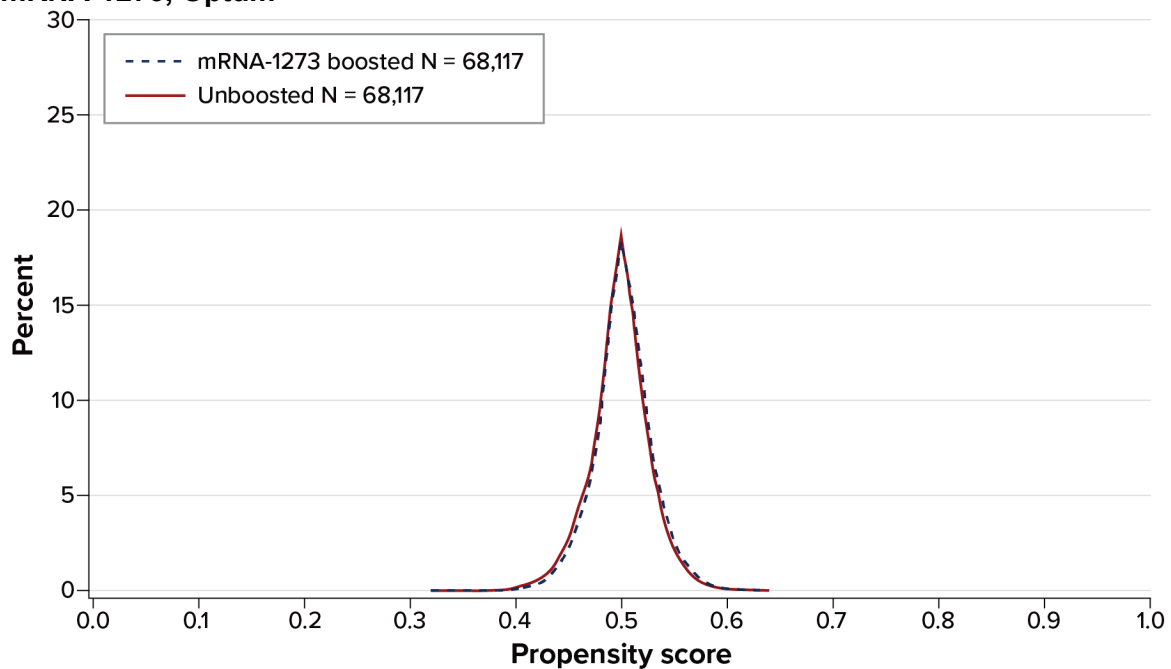
Figure B-2-Optum. Distribution of Propensity Scores in Vaccine-specific Cohorts After Matching

A. BNT162b2, Optum



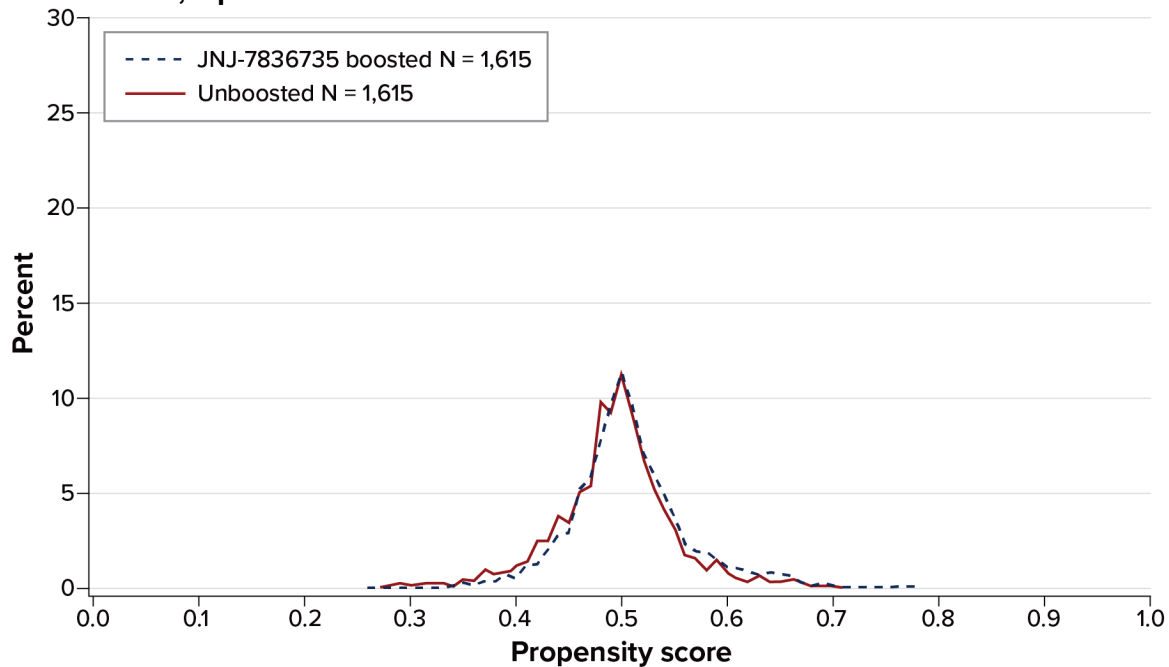
Propensity score variables included the following (binary unless otherwise noted): age (linear), female sex, brand of primary series (categorical: reference = BNT162b2), state (categorical), pregnant at Time 0, hospitalizations (categorical: ≥ 2 , 1, reference = 0); ED visits (categorical: ≥ 2 , 1, reference = 0); skilled nursing facility stay, influenza vaccination, pneumococcal vaccination, encounter for cancer screening, eye examination, colonoscopy, bone mineral density test, well-check/well-child preventive healthcare visit, arthritis, lipid abnormality, ambulance use or life support services, weakness, autoimmune disorders, cancer, chronic kidney disease or renal disease, chronic liver disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus (type 1 or 2), Down syndrome, heart conditions, hypertension, immunocompromised state, mental health conditions, obese or severely obese, sickle cell disease or thalassemia, stroke or cerebrovascular disease, tuberculosis, COVID-19 laboratory test performed, COVID-19 diagnoses occurring outside of a hospital or ED, hospitalization or ED-diagnosed COVID-19, Omicron variant era, condition increasing risk of severe COVID-19, Omicron variant era*COVID-19 diagnoses occurring outside of a hospital or ED (interaction term).

B. mRNA-1273, Optum



Propensity score variables included the following (binary unless otherwise noted): age (linear), female sex, brand of primary series (categorical: reference = mRNA-1273), state (categorical), pregnant at Time 0, hospitalizations (categorical: ≥ 2 , 1, reference = 0); ED visits (categorical: ≥ 2 , 1, reference = 0); skilled nursing facility stay, influenza vaccination, pneumococcal vaccination, encounter for cancer screening, eye examination, colonoscopy, bone mineral density test, well-check/well-child preventive healthcare visit, arthritis, lipid abnormality, ambulance use or life support services, weakness, autoimmune disorders, cancer, chronic kidney disease or renal disease, chronic liver disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus (type 1 or 2), Down syndrome, heart conditions, hypertension, immunocompromised state, mental health conditions, obese or severely obese, sickle cell disease or thalassemia, stroke or cerebrovascular disease, tuberculosis, COVID-19 laboratory test performed, COVID-19 diagnoses occurring outside of a hospital or ED, hospitalization or ED-diagnosed COVID-19, Omicron variant era, condition increasing risk of severe COVID-19, Omicron variant era*obese or severely obese (interaction term).

C. JNJ-7836735, Optum

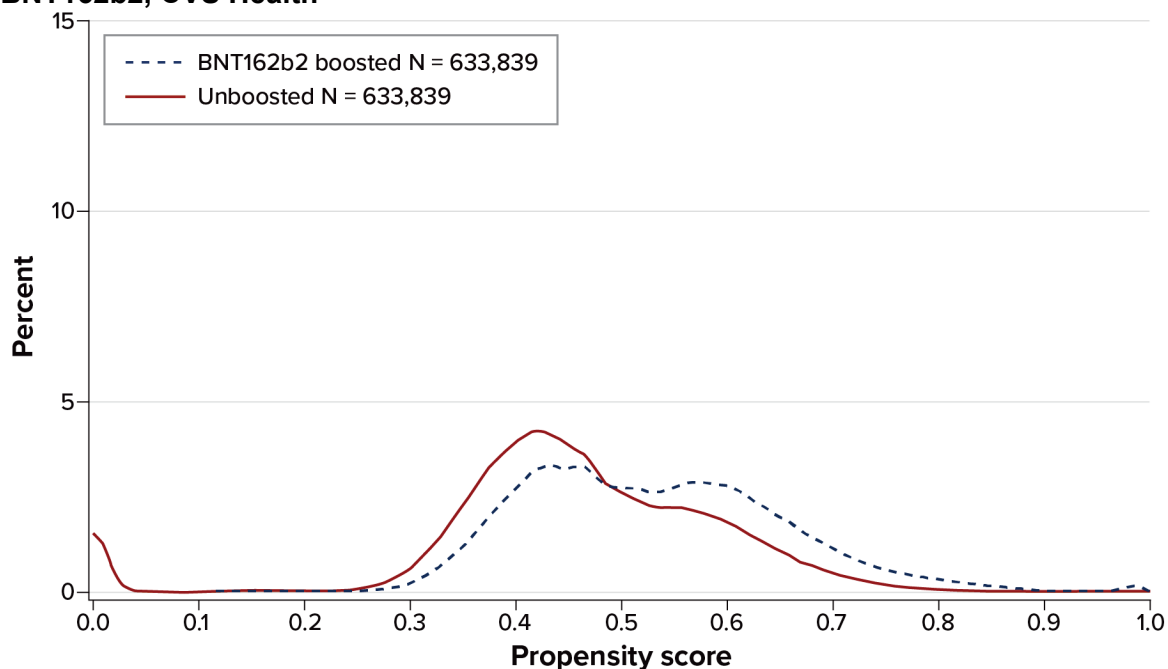


Propensity score variables included the following (binary unless otherwise noted): age (linear), female sex, brand of primary series (categorical: reference = JNJ-7836735), state (categorical), pregnant at Time 0, hospitalizations (categorical: ≥ 2 , 1, reference = 0); ED visits (categorical: ≥ 2 , 1, reference = 0); skilled nursing facility stay, influenza vaccination, pneumococcal vaccination, encounter for cancer screening, eye examination, colonoscopy, bone mineral density test, well-check/well-child preventive healthcare visit, arthritis, lipid abnormality, ambulance use or life support services, weakness, autoimmune disorders, cancer, chronic kidney disease or renal disease, chronic liver disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus (type 1 or 2), Down syndrome, heart conditions, hypertension, immunocompromised state, mental health conditions, obese or severely obese, sickle cell disease or thalassemia, stroke or cerebrovascular disease, tuberculosis, COVID-19 laboratory test performed, COVID-19 diagnoses occurring outside of a hospital or ED, hospitalization or ED-diagnosed COVID-19, Omicron variant era, condition increasing risk of severe COVID-19, Omicron variant era*autoimmune disorders (interaction term).

COVID-19 = coronavirus disease 2019; ED = emergency department.

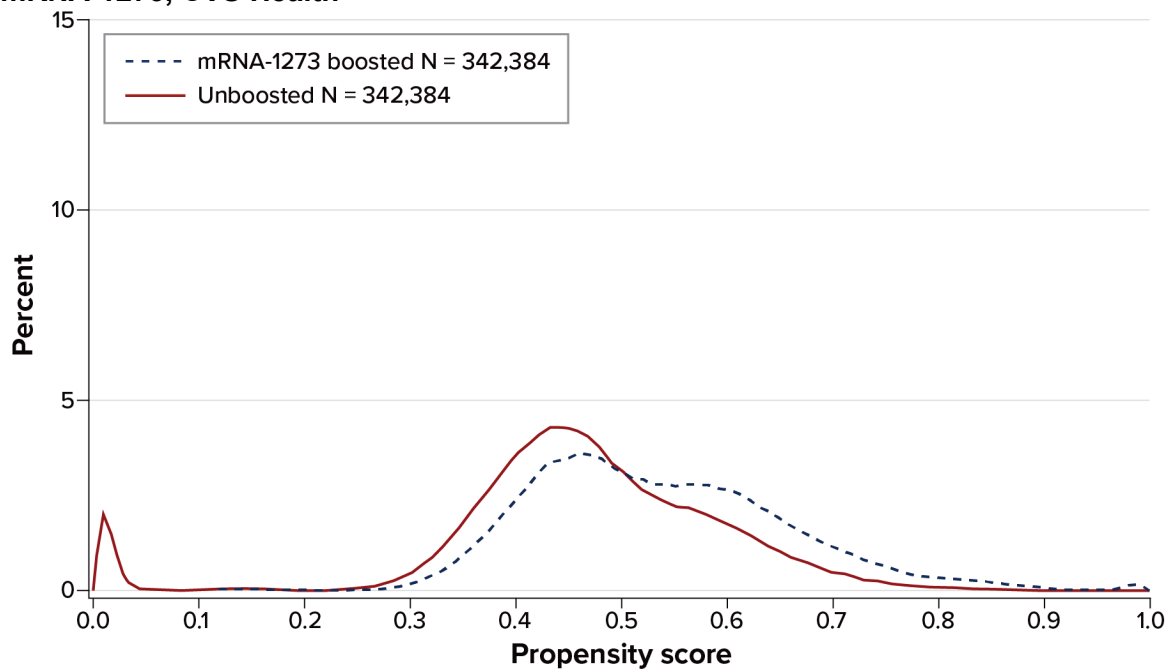
Figure B-2-CVS. Distribution of Propensity Scores in Vaccine-specific Cohorts After Matching

A. BNT162b2, CVS Health



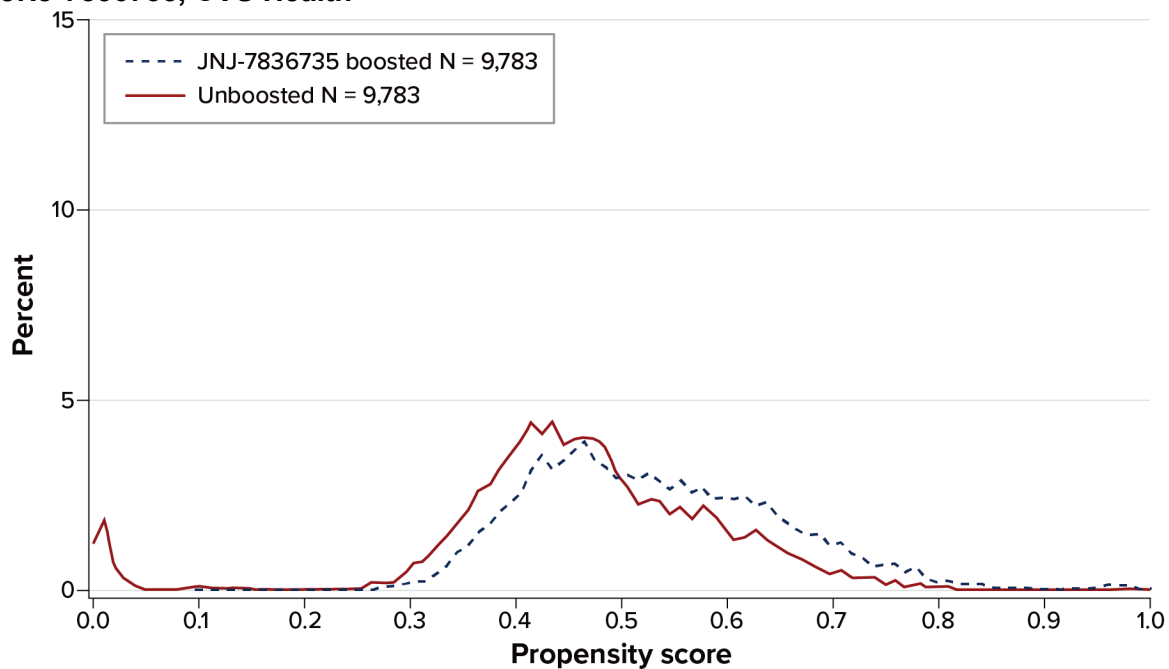
Propensity score variables included the following (binary unless otherwise noted): age (categorical: 12-15, 16-17, 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, reference = 60-64), ambulance use of life support services, arthritis, autoimmune disorders, bone mineral density test, cancer, encounter for cancer screening, chronic kidney disease or renal disease, chronic liver disease, colonoscopy, chronic lung diseases, US state (categorical), pregnant at Time 0, COVID-19 diagnoses in any setting, hospitalization or ED-diagnosed COVID-19, COVID-19 laboratory performed, COVID-19 diagnoses occurring outside of hospital or ED, diabetes mellitus (type 1 or 2), Down syndrome, ED visits (categorical: ≥ 2 , 1, reference = 0), eye examination, influenza vaccination, heart conditions, any condition increasing risk of severe COVID-19, hypertension, hospitalizations (categorical: ≥ 2 , 1, reference = 0), lipid abnormality, mental health condition, time since primary vaccination (categorical: 14-day increments), dementia or other neurological conditions, obese or severely obese, pneumococcal vaccination, sex (categorical: reference = female), sickle cell disease or thalassemia, skilled nursing facility stay, Immunization Information System jurisdiction (categorical), stroke or cerebrovascular disease, tuberculosis, immunocompromised state, pregnancy completion before Time 0, primary series brand (categorical: reference = BNT162b2), weakness, well-check/well-child preventive healthcare visit, COVID-19 vaccination after 31 May 2021*one or more COVID-19 laboratory tests performed (interaction term), well-check/well-child preventive healthcare visit* Omicron era (interaction term).

B. mRNA-1273, CVS Health



Propensity score variables included the following (binary unless otherwise noted): age (categorical: 12-15, 16-17, 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, reference = 60-64), ambulance use of life support services, arthritis, autoimmune disorders, bone mineral density test, cancer, encounter for cancer screening, chronic kidney disease or renal disease, chronic liver disease, colonoscopy, chronic lung diseases, US state (categorical), pregnant at Time 0, COVID-19 diagnoses in any setting, hospitalization or ED-diagnosed COVID-19, COVID-19 laboratory performed, COVID-19 diagnoses occurring outside of hospital or ED, diabetes mellitus (type 1 or 2), Down syndrome, ED visits (categorical: ≥ 2 , 1, reference = 0), eye examination, influenza vaccination, heart conditions, any condition increasing risk of severe COVID-19, hypertension, hospitalizations (categorical: ≥ 2 , 1, reference = 0), lipid abnormality, mental health condition, time since primary vaccination (categorical: 14-day increments), dementia or other neurological conditions, obese or severely obese, pneumococcal vaccination, sex (categorical: reference = female), sickle cell disease or thalassemia, skilled nursing facility stay, Immunization Information System jurisdiction (categorical), stroke or cerebrovascular disease, tuberculosis, immunocompromised state, pregnancy completion before Time 0, primary series brand (categorical: reference = mRNA-1273), weakness, well-check/well-child preventive healthcare visit, COVID-19 vaccination after 31 May 2021*one or more COVID-19 laboratory tests performed (interaction term), well-check/well-child preventive healthcare visit* Omicron era (interaction term).

C. JNJ-7836735, CVS Health

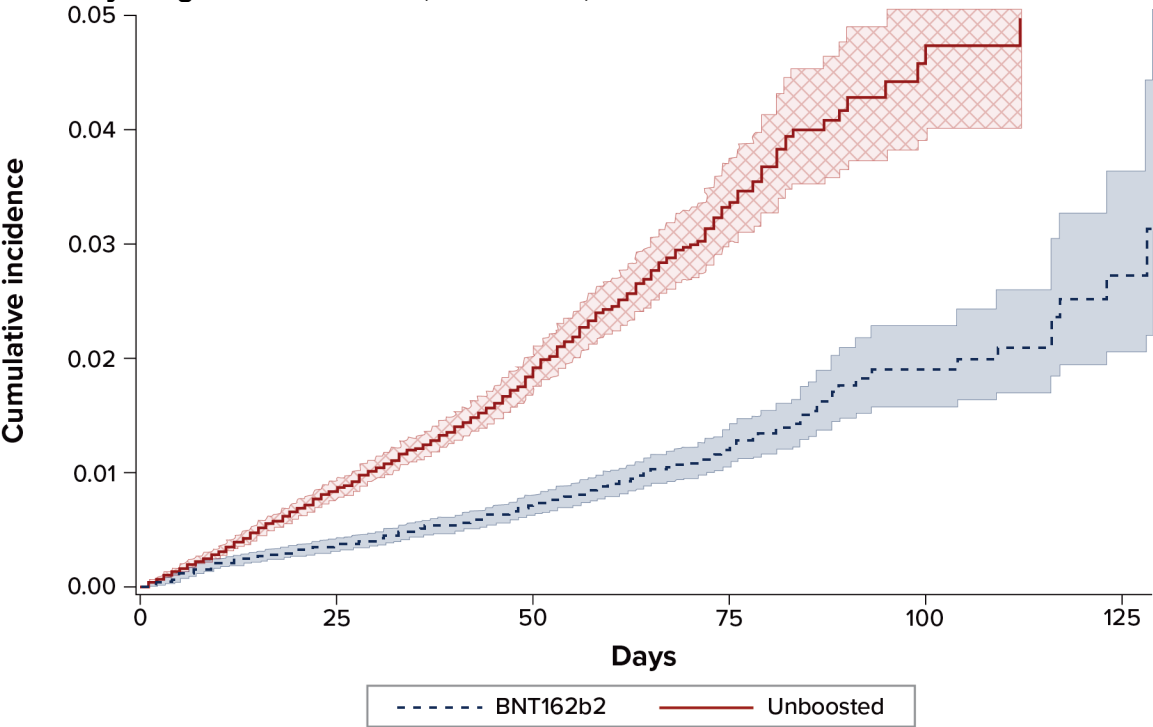


Propensity score variables included the following (binary unless otherwise noted): age (categorical: 12-15, 16-17, 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, reference = 60-64), ambulance use of life support services, arthritis, autoimmune disorders, bone mineral density test, cancer, encounter for cancer screening, chronic kidney disease or renal disease, chronic liver disease, colonoscopy, chronic lung diseases, US state (categorical), pregnant at Time 0, COVID-19 diagnoses in any setting, hospitalization or ED-diagnosed COVID-19, COVID-19 laboratory performed, COVID-19 diagnoses occurring outside of hospital or ED, diabetes mellitus (type 1 or 2), Down syndrome, ED visits (categorical: ≥ 2 , 1, reference = 0), eye examination, influenza vaccination, heart conditions, any condition increasing risk of severe COVID-19, hypertension, hospitalizations (categorical: ≥ 2 , 1, reference = 0), lipid abnormality, mental health condition, time since primary vaccination (categorical: 14-day increments), dementia or other neurological conditions, obese or severely obese, pneumococcal vaccination, sex (categorical: reference = male), sickle cell disease or thalassemia, skilled nursing facility stay, Immunization Information System jurisdiction (categorical), stroke or cerebrovascular disease, tuberculosis, immunocompromised state, pregnancy completion before Time 0, primary series brand (categorical: reference = JNJ-7836735), weakness, well-check/well-child preventive healthcare visit, COVID-19 vaccination after 31 May 2021*one or more COVID-19 laboratory tests performed (interaction term), well-check/well-child preventive healthcare visit* Omicron era (interaction term).

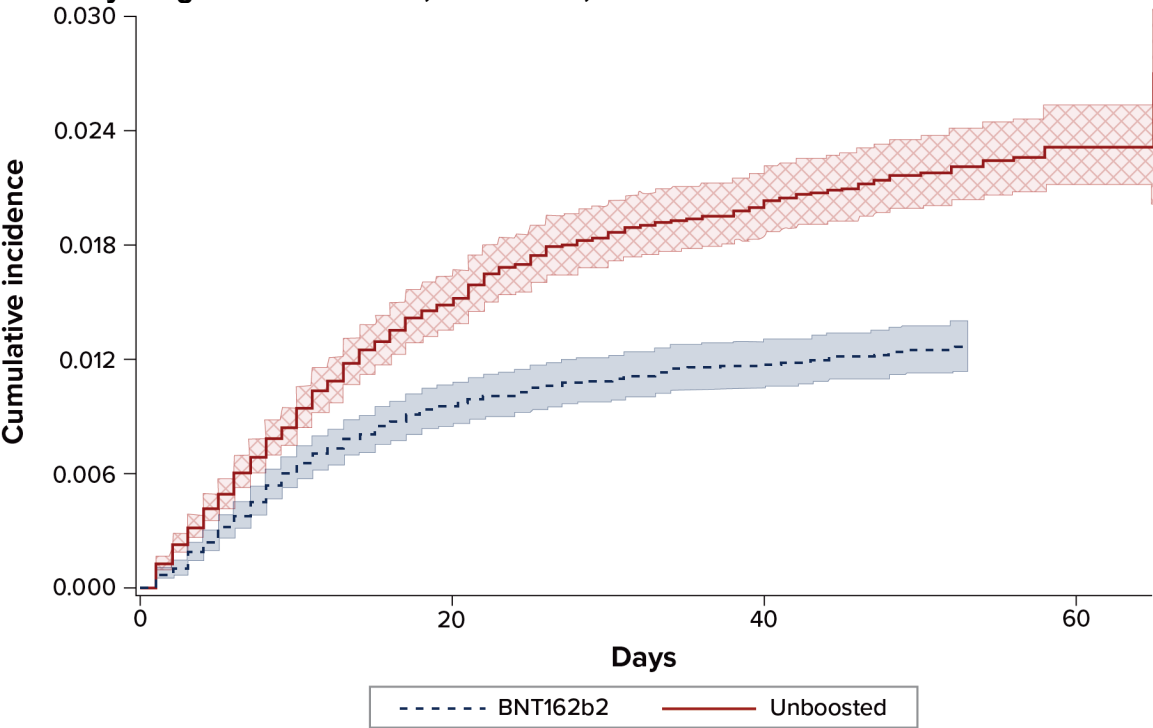
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure B-3-Optum. Inverse Probability of Treatment-weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of COVID-19 Vaccine and Matched, Unboosted Comparators, by Vaccine Brand and Variant-Specific Era, Optum

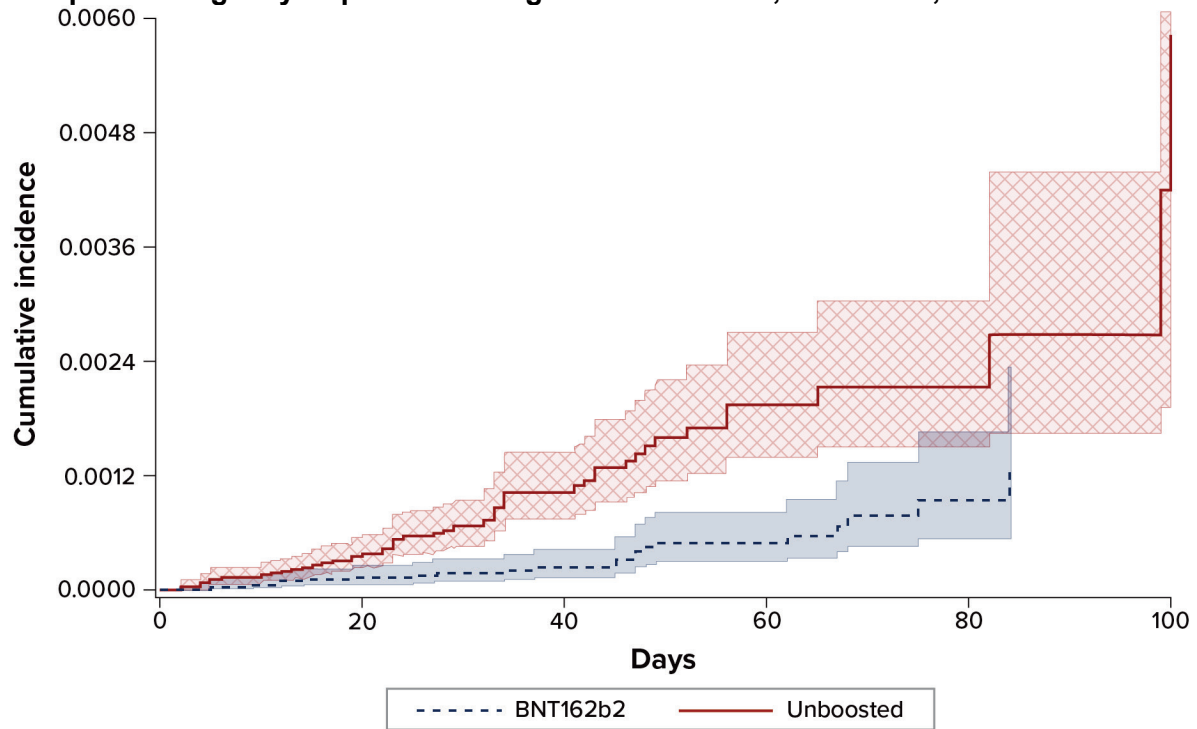
A. Medically Diagnosed COVID-19, BNT162b2, Delta Era



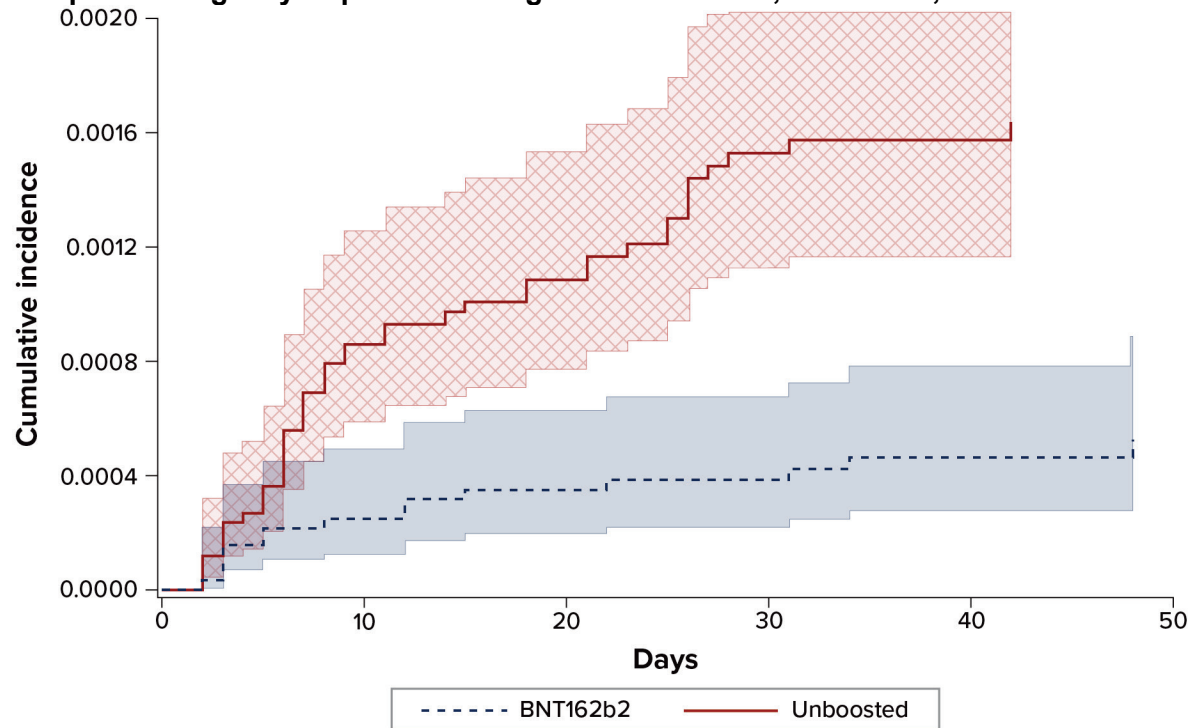
B. Medically Diagnosed COVID-19, BNT162b2, Omicron Era



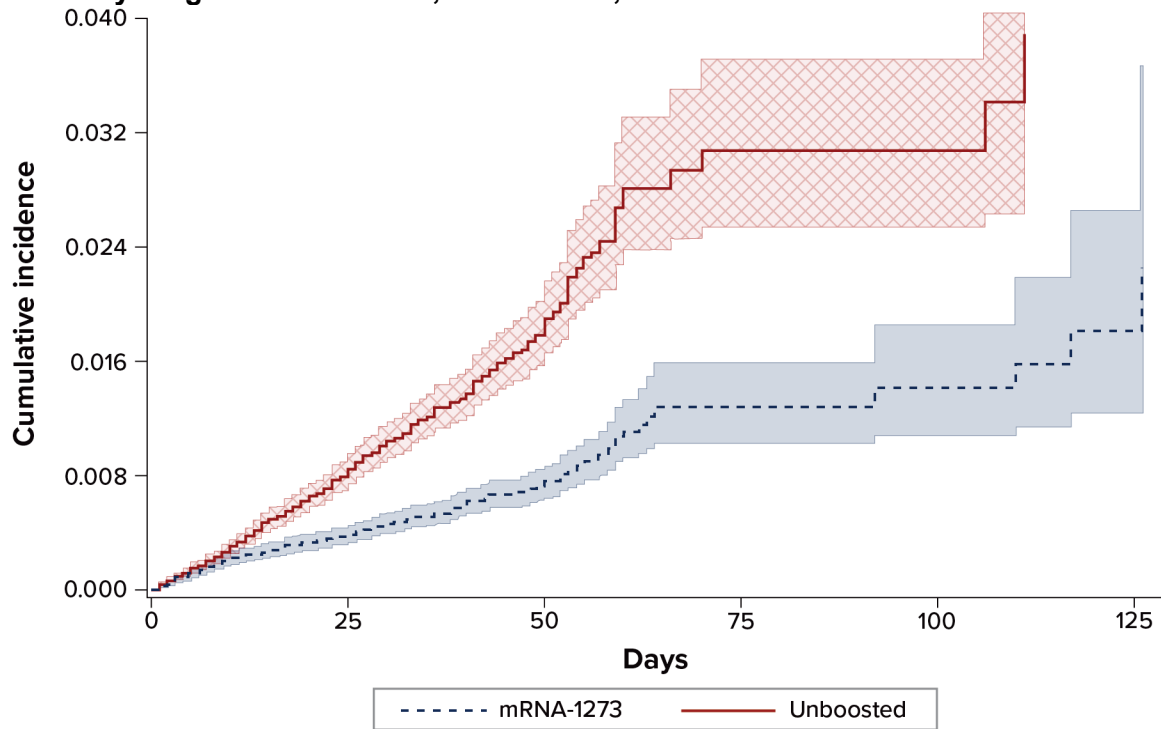
C. Hospital/Emergency Department–diagnosed COVID-19, BNT162b2, Delta Era



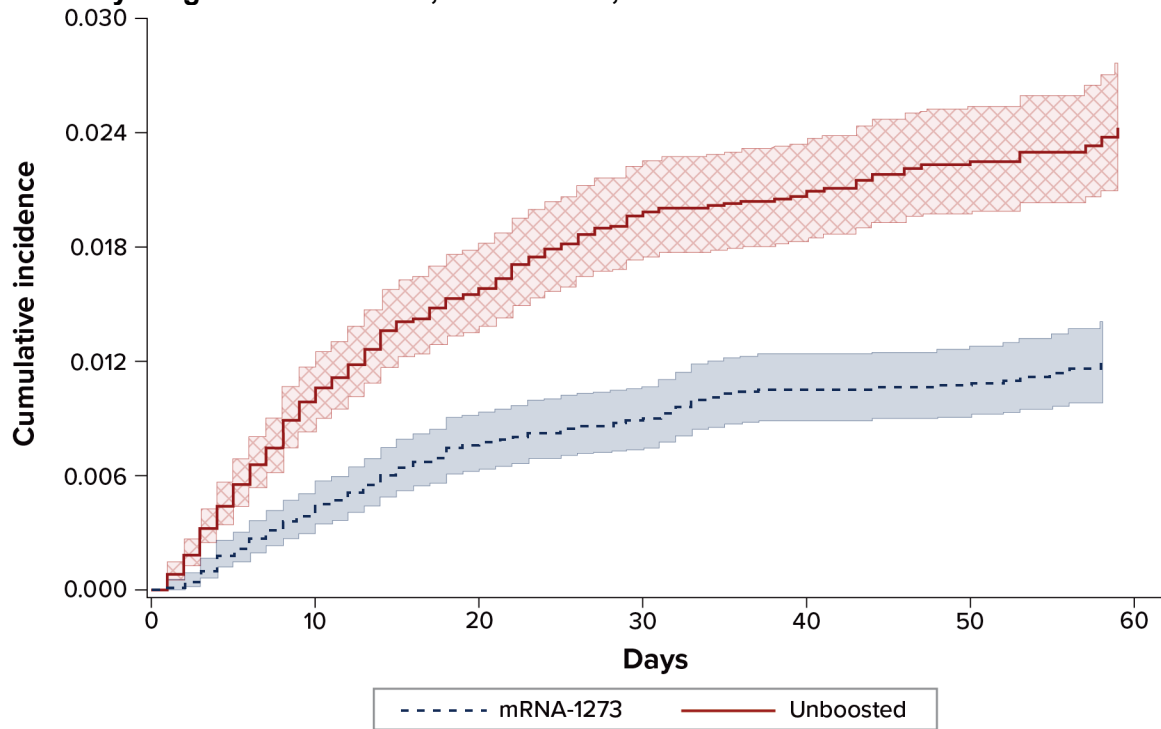
D. Hospital/Emergency Department–diagnosed COVID-19, BNT162b2, Omicron Era



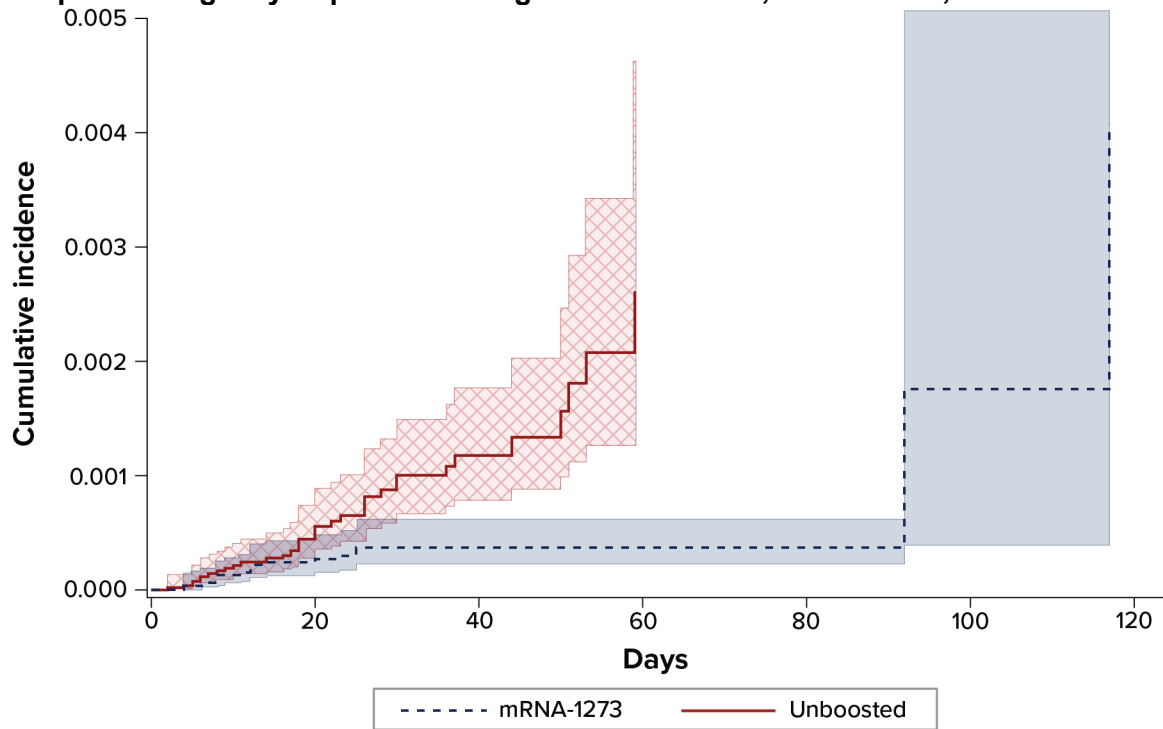
E. Medically Diagnosed COVID-19, mRNA-1273, Delta Era



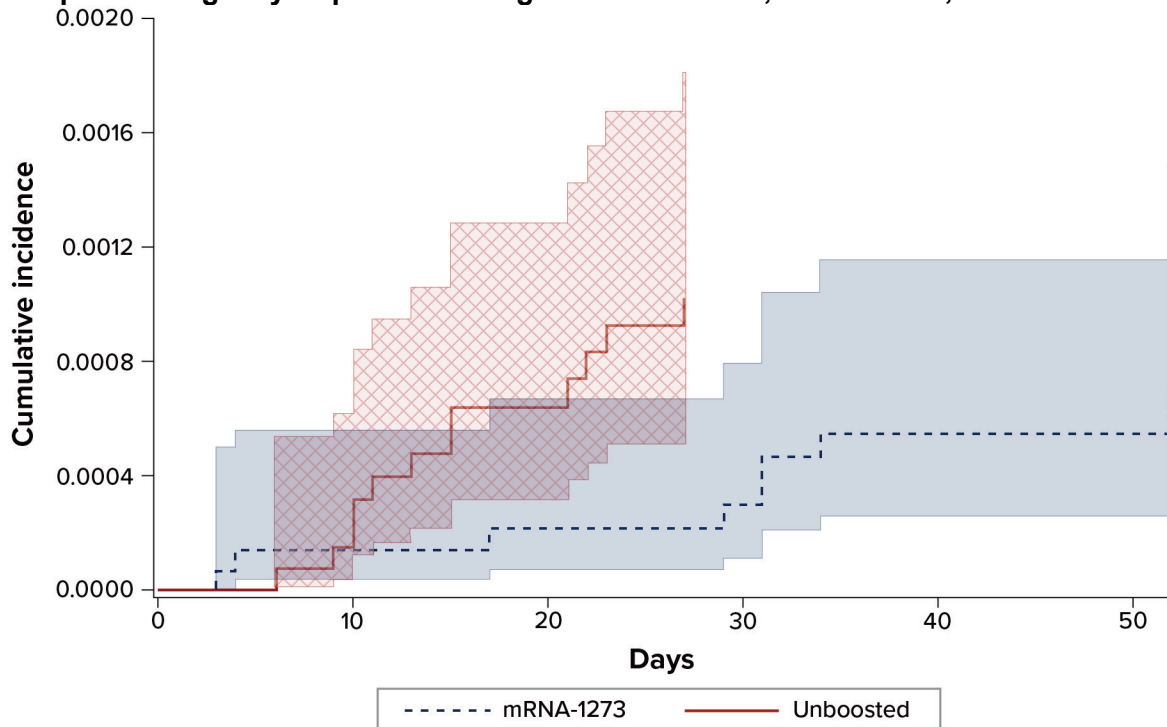
F. Medically Diagnosed COVID-19, mRNA-1273, Omicron Era



G. Hospital/Emergency Department–diagnosed COVID-19, mRNA-1273, Delta Era



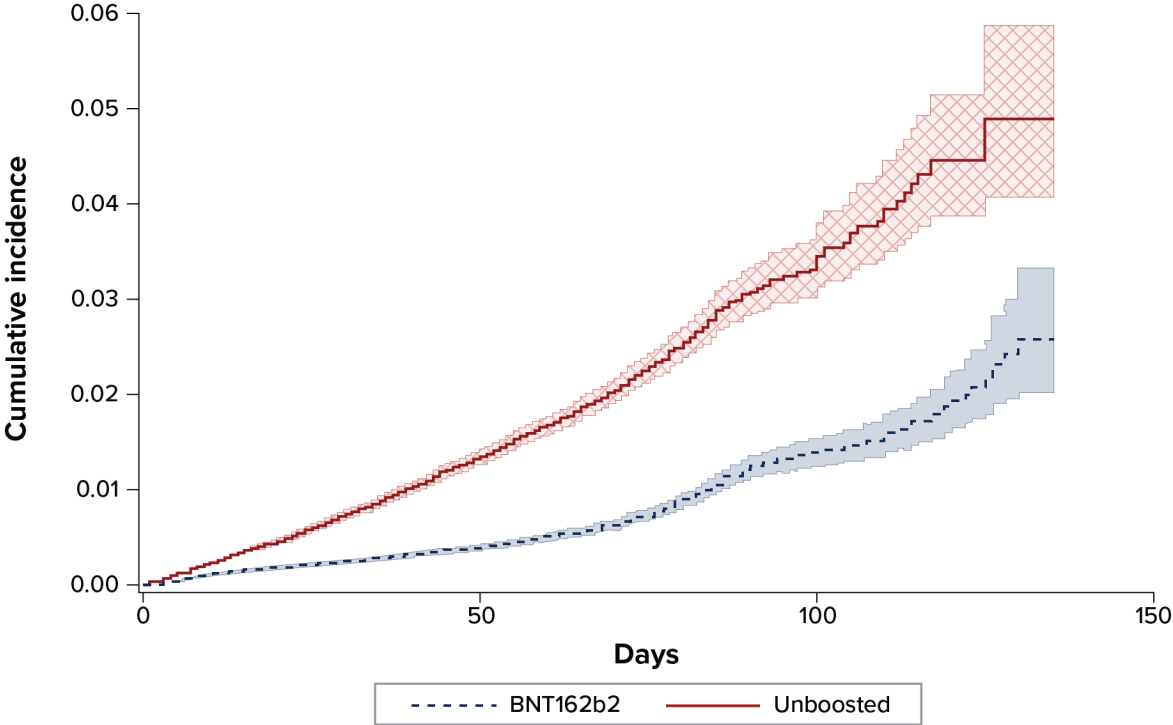
H. Hospital/Emergency Department–diagnosed COVID-19, mRNA-1273, Omicron Era



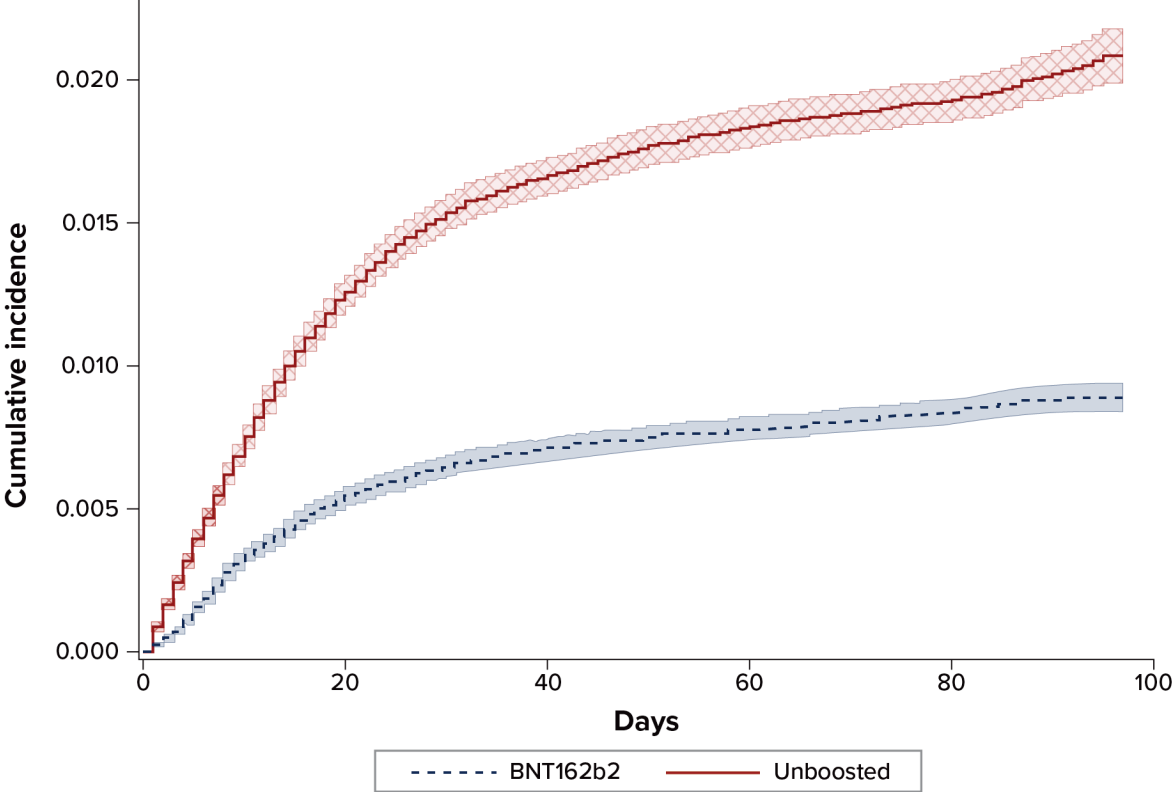
COVID-19 = coronavirus disease 2019.

Figure B-3-CVS. Inverse Probability of Treatment-weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of COVID-19 Vaccine and Matched, Unboosted Comparators, by Vaccine Brand and Variant-Specific Era, CVS Health

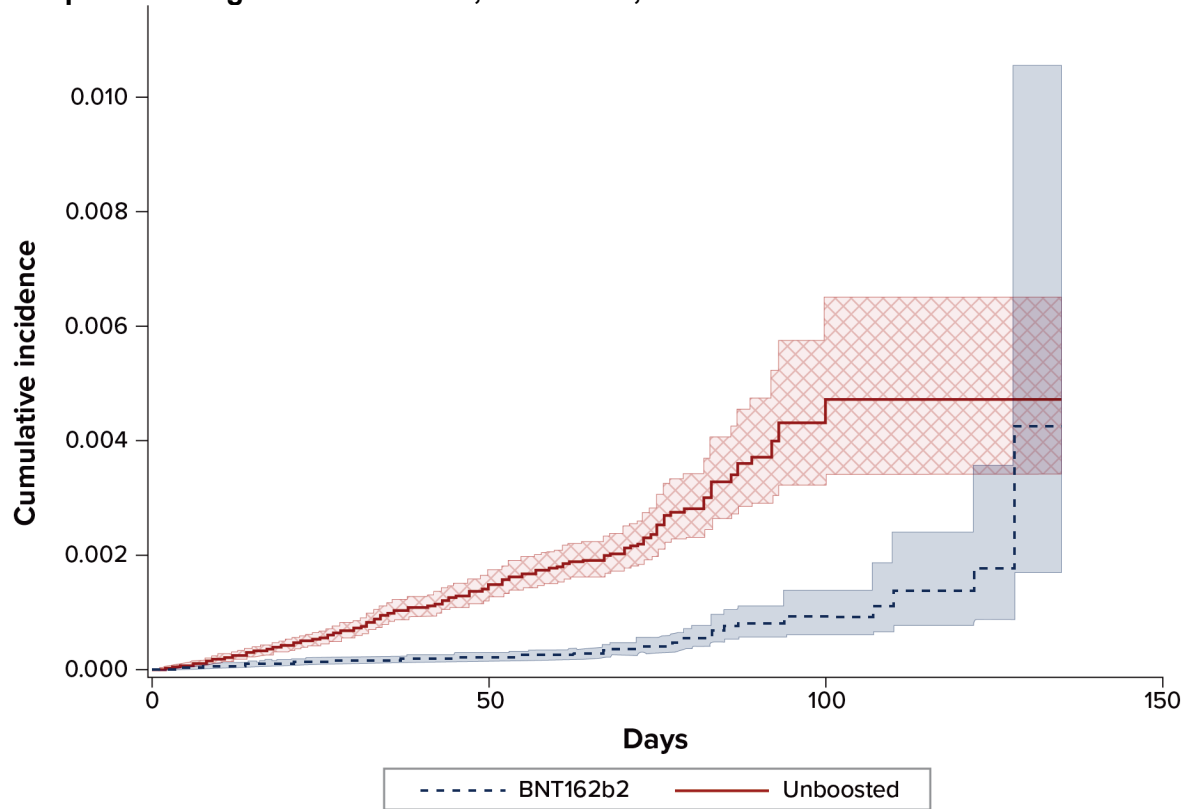
A. Medically Diagnosed COVID-19, BNT162b2, Delta Era



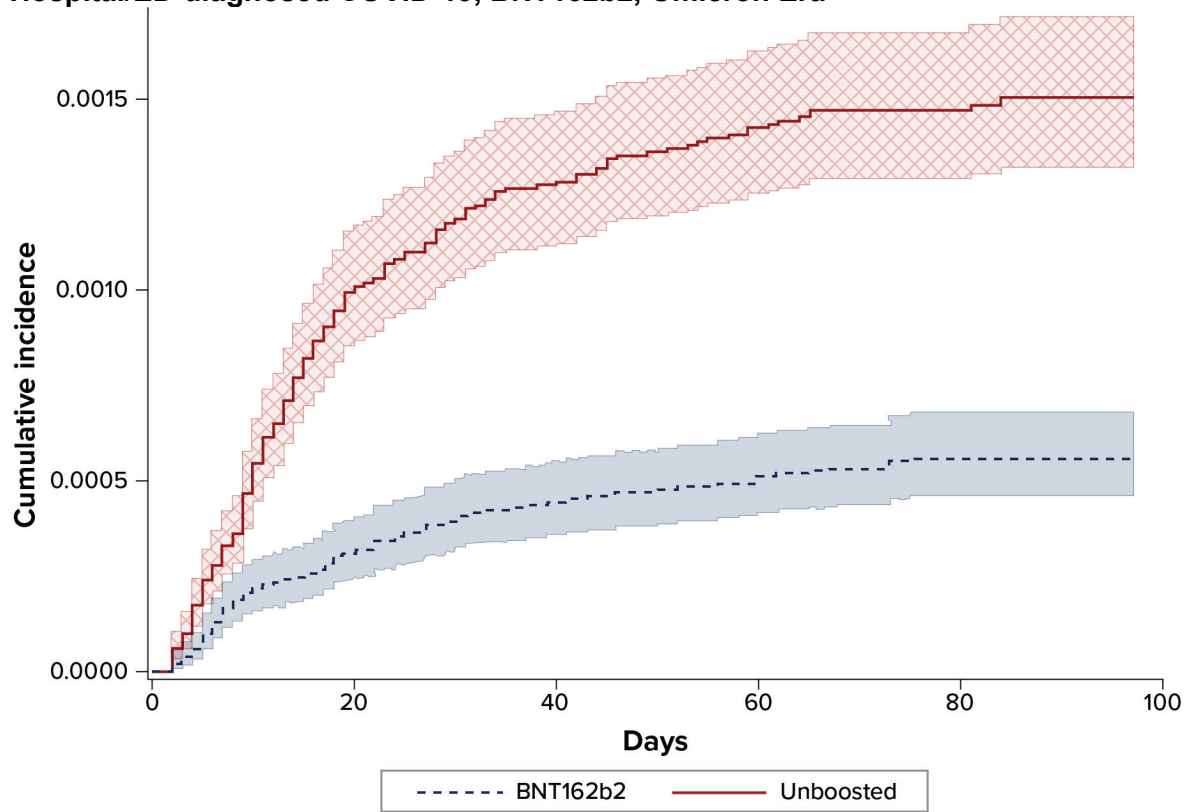
B. Medically Diagnosed COVID-19, BNT162b2, Omicron Era



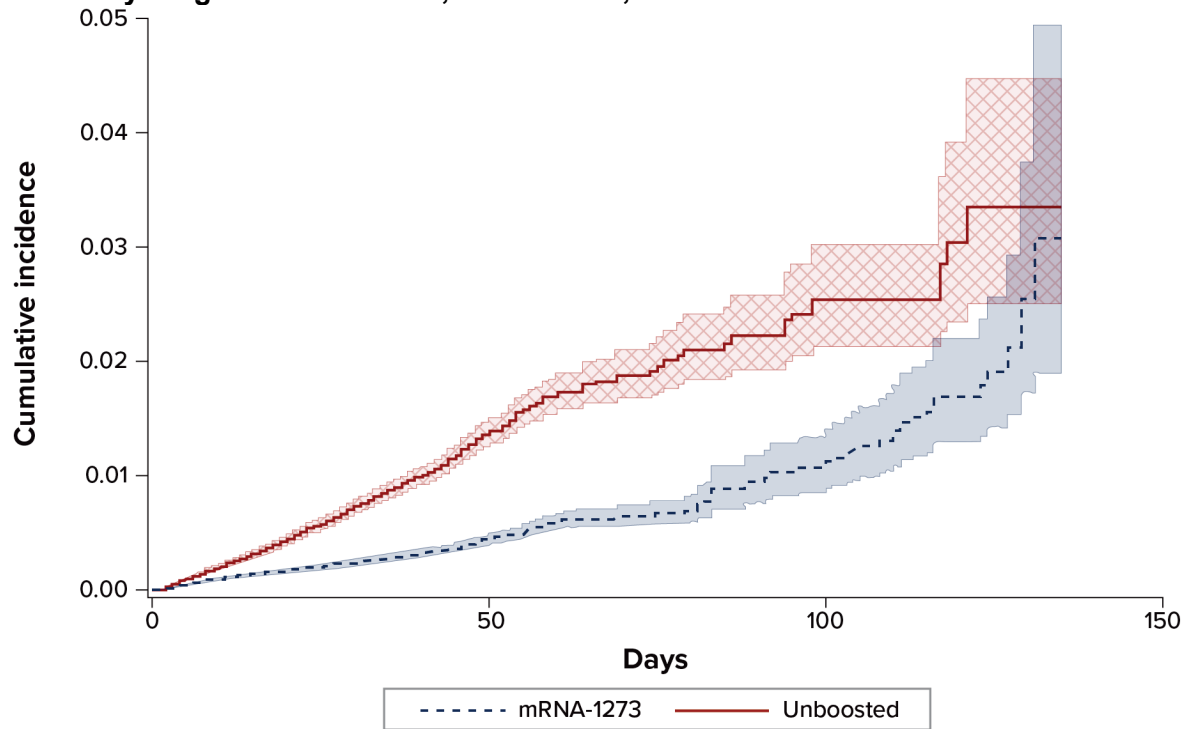
C. Hospital/ED-diagnosed COVID-19, BNT162b2, Delta Era



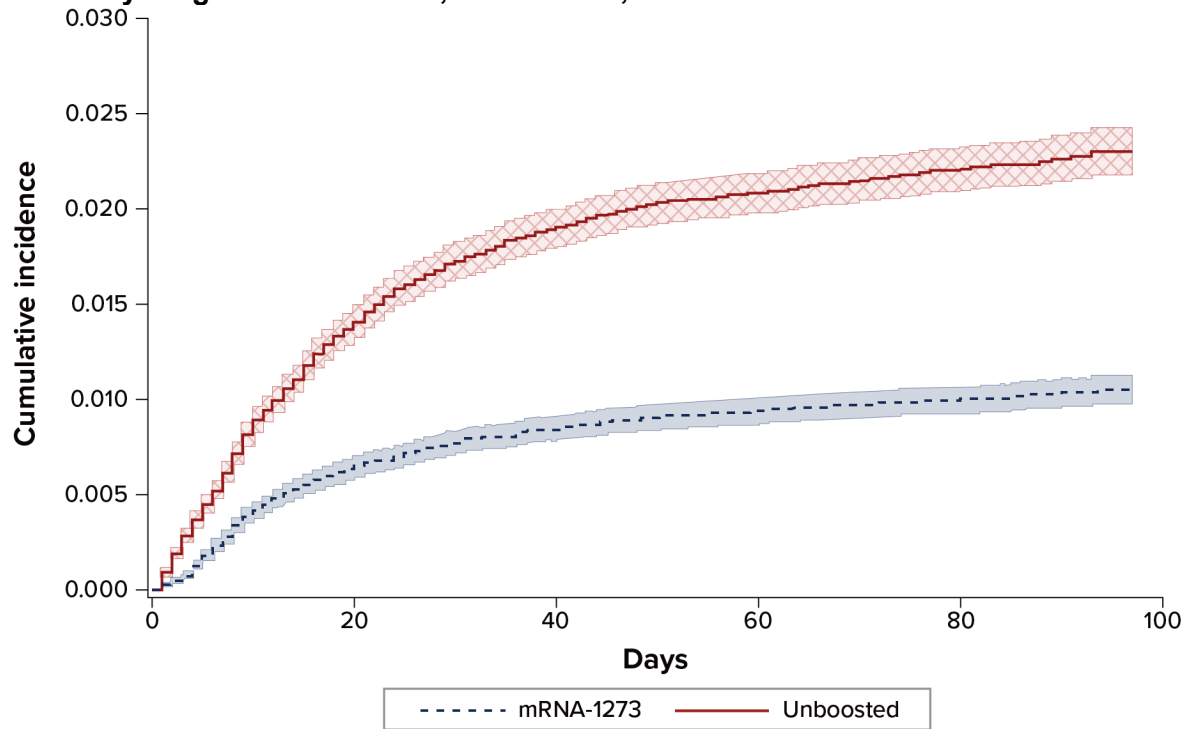
D. Hospital/ED-diagnosed COVID-19, BNT162b2, Omicron Era



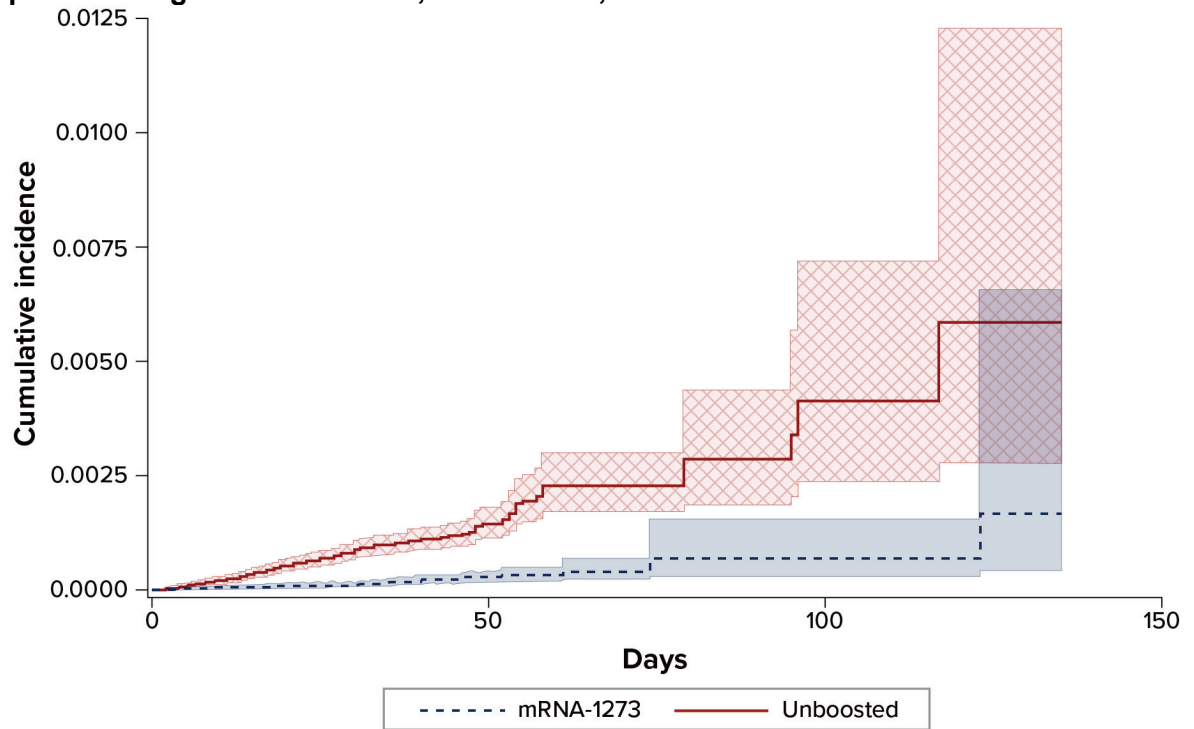
E. Medically Diagnosed COVID-19, mRNA-1273, Delta Era



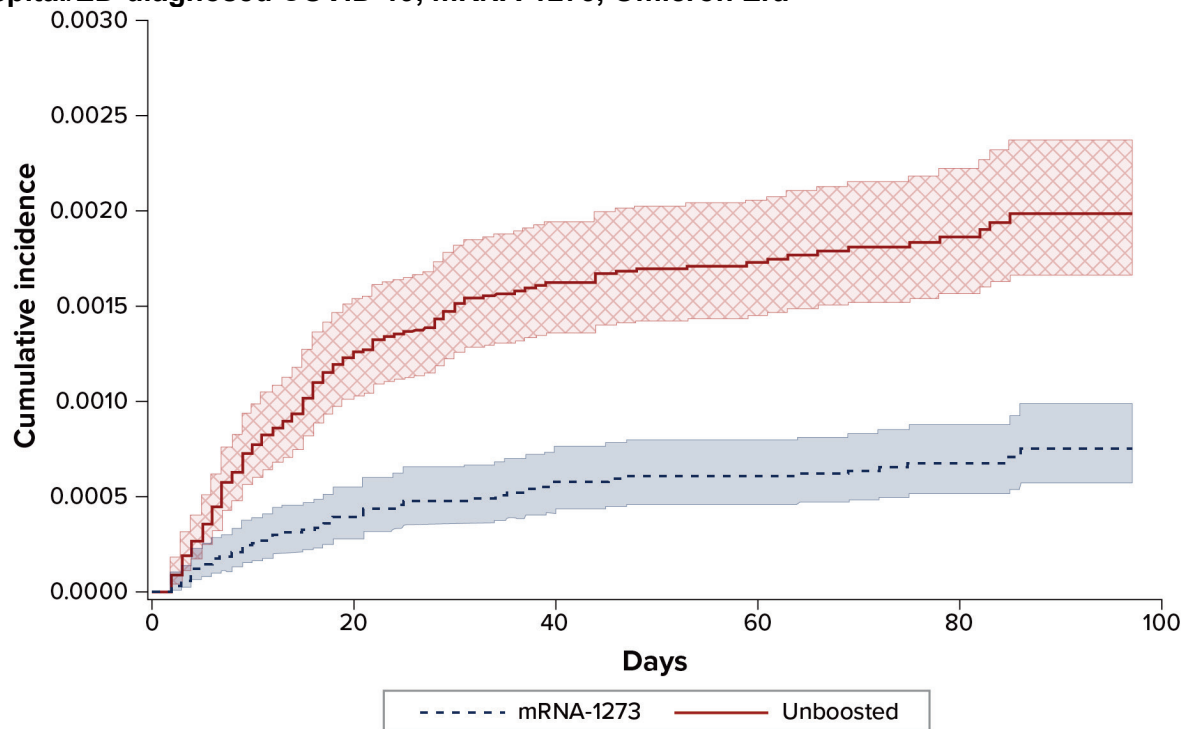
F. Medically Diagnosed COVID-19, mRNA-1273, Omicron Era



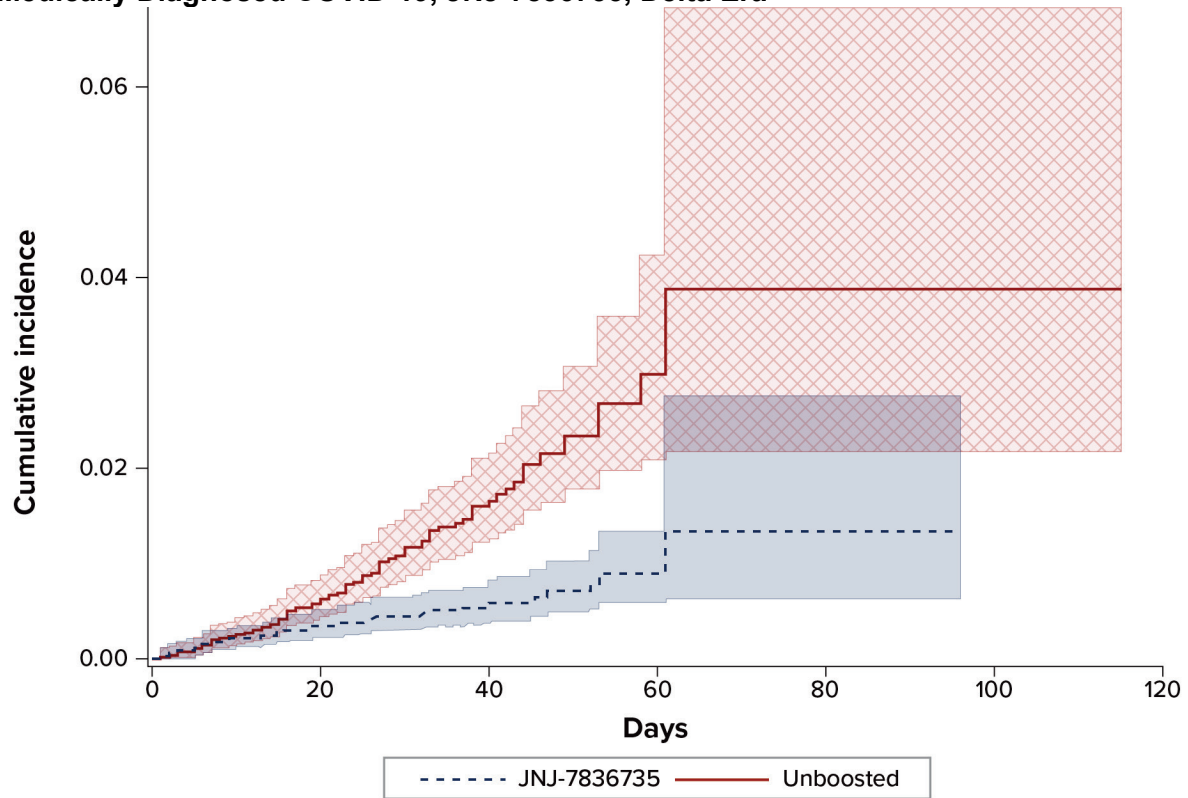
G. Hospital/ED-diagnosed COVID-19, mRNA-1273, Delta Era



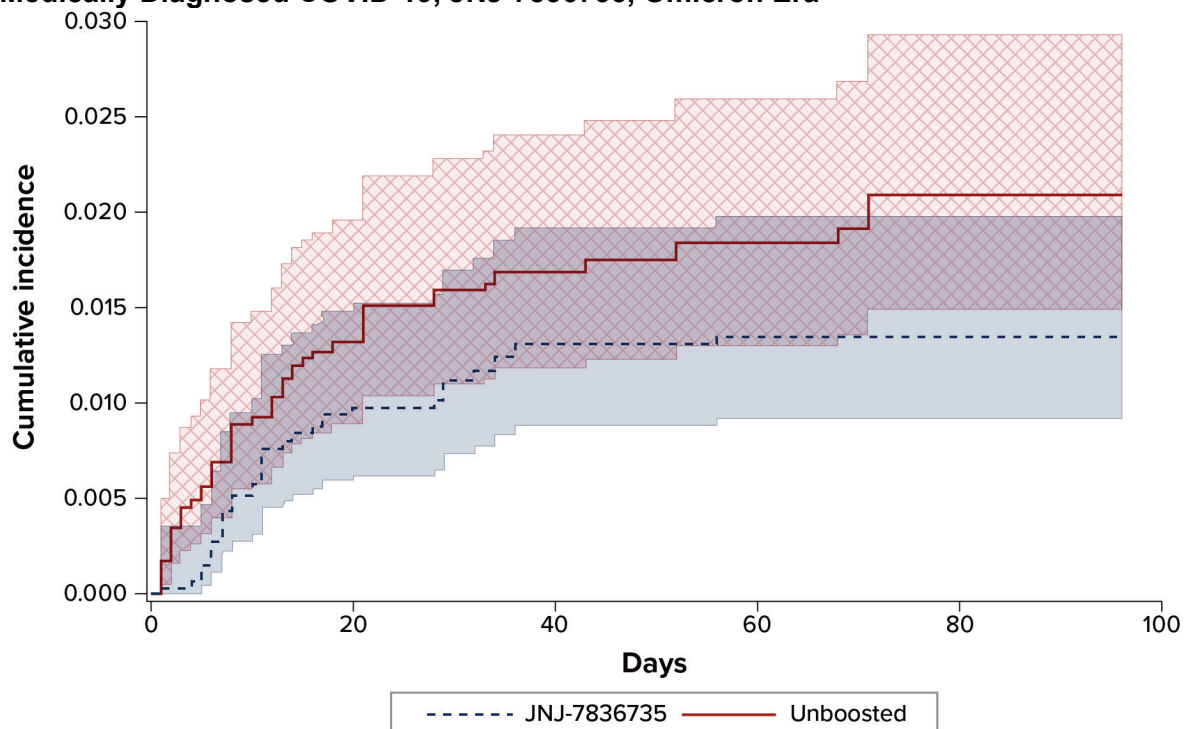
H. Hospital/ED-diagnosed COVID-19, mRNA-1273, Omicron Era



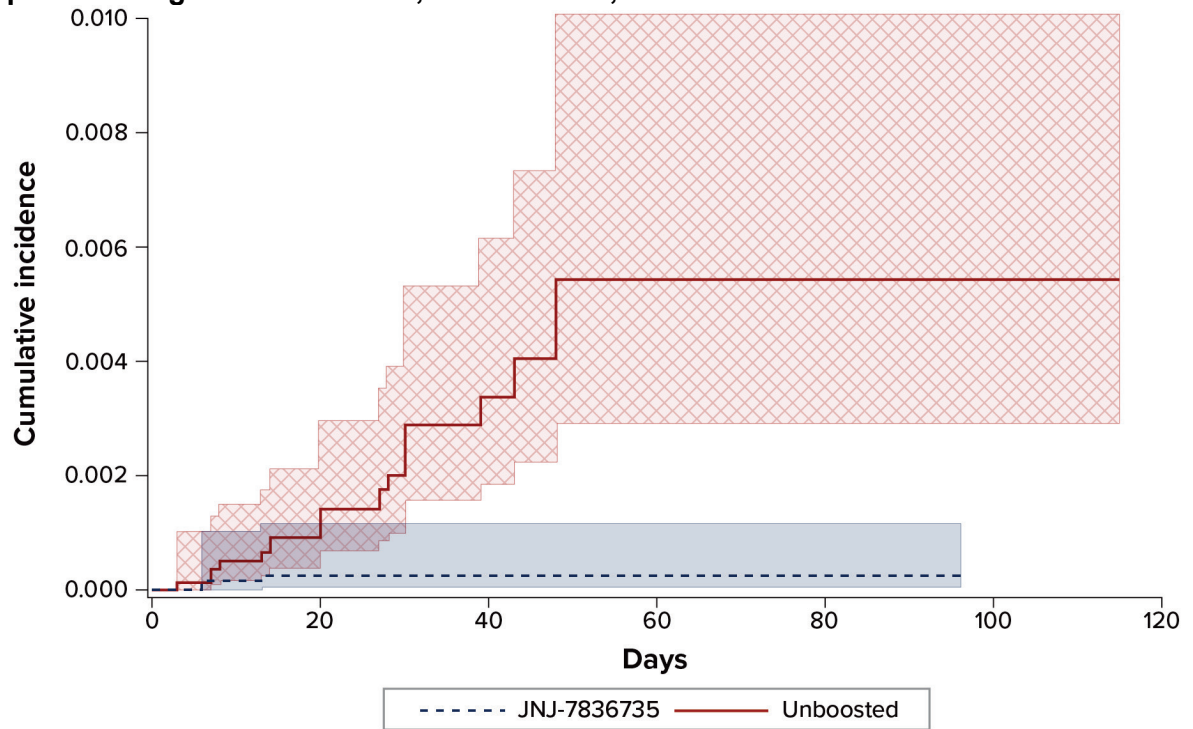
I. Medically Diagnosed COVID-19, JNJ-7836735, Delta Era



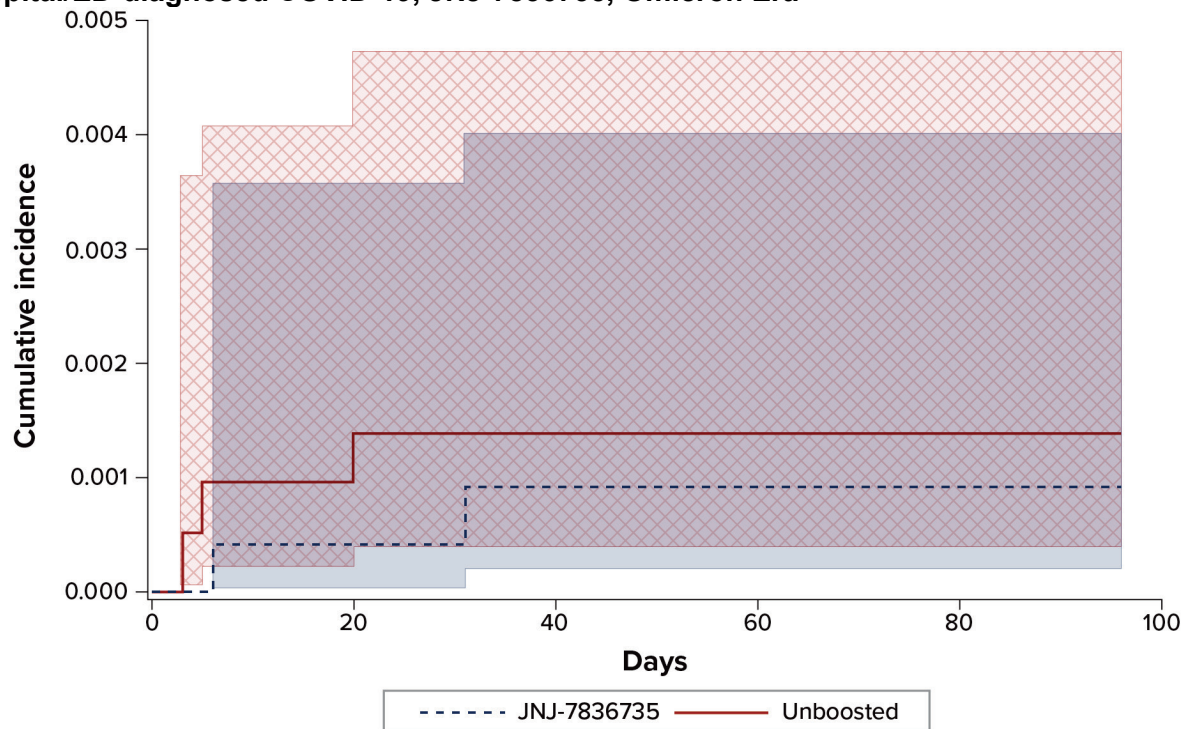
J. Medically Diagnosed COVID-19, JNJ-7836735, Omicron Era



K. Hospital/ED-diagnosed COVID-19, JNJ-7836735, Delta Era



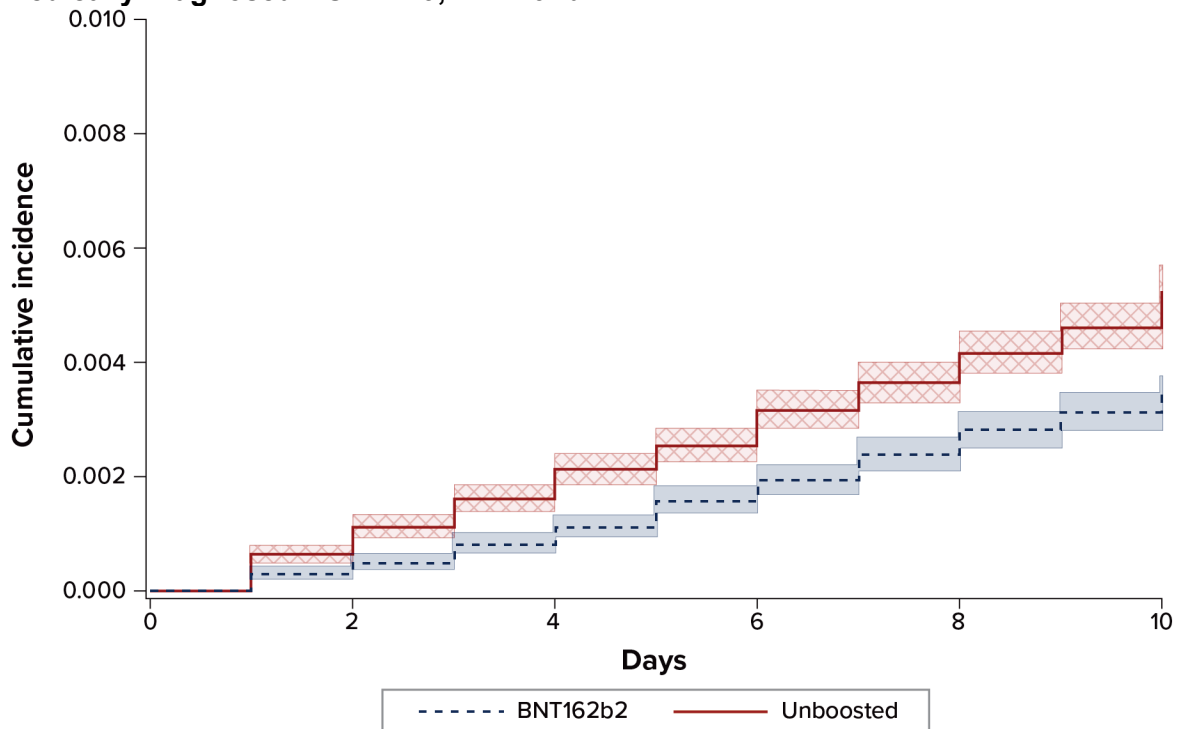
L. Hospital/ED-diagnosed COVID-19, JNJ-7836735, Omicron Era



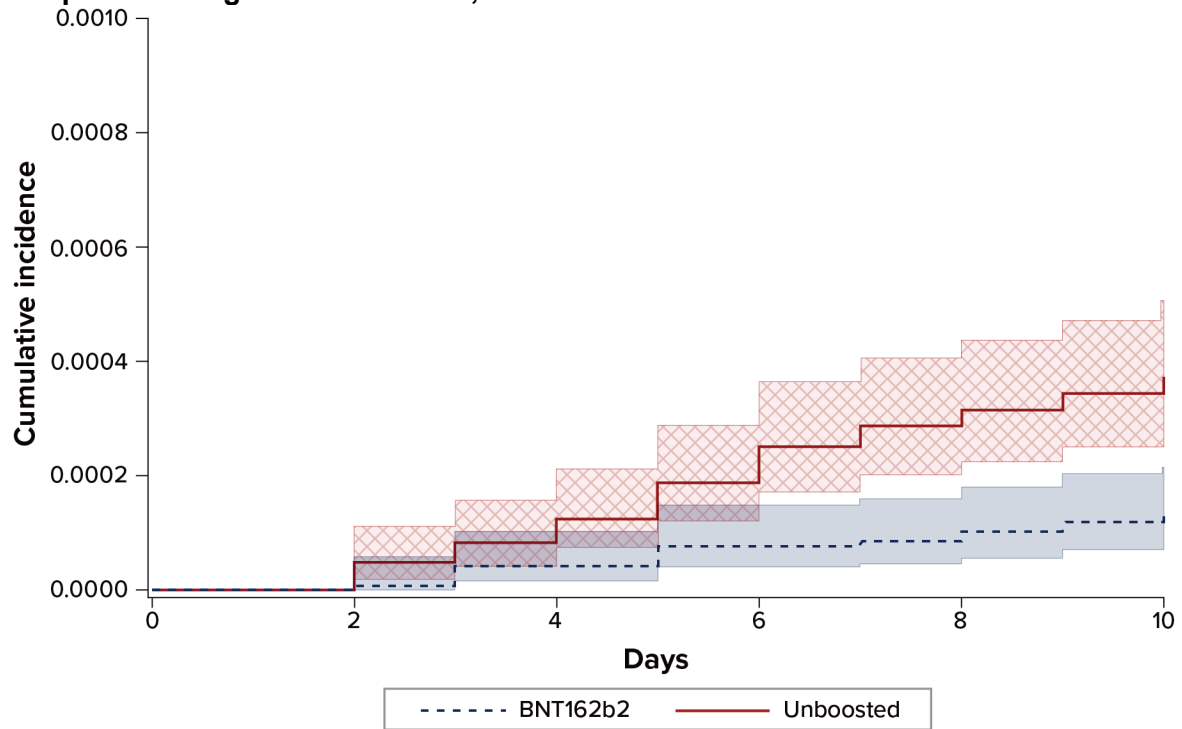
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure B-4-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of COVID-19 Vaccine and Matched, Unboosted Comparators, 10 Days After and Including Time 0, Negative Control Outcome Analysis, Optum

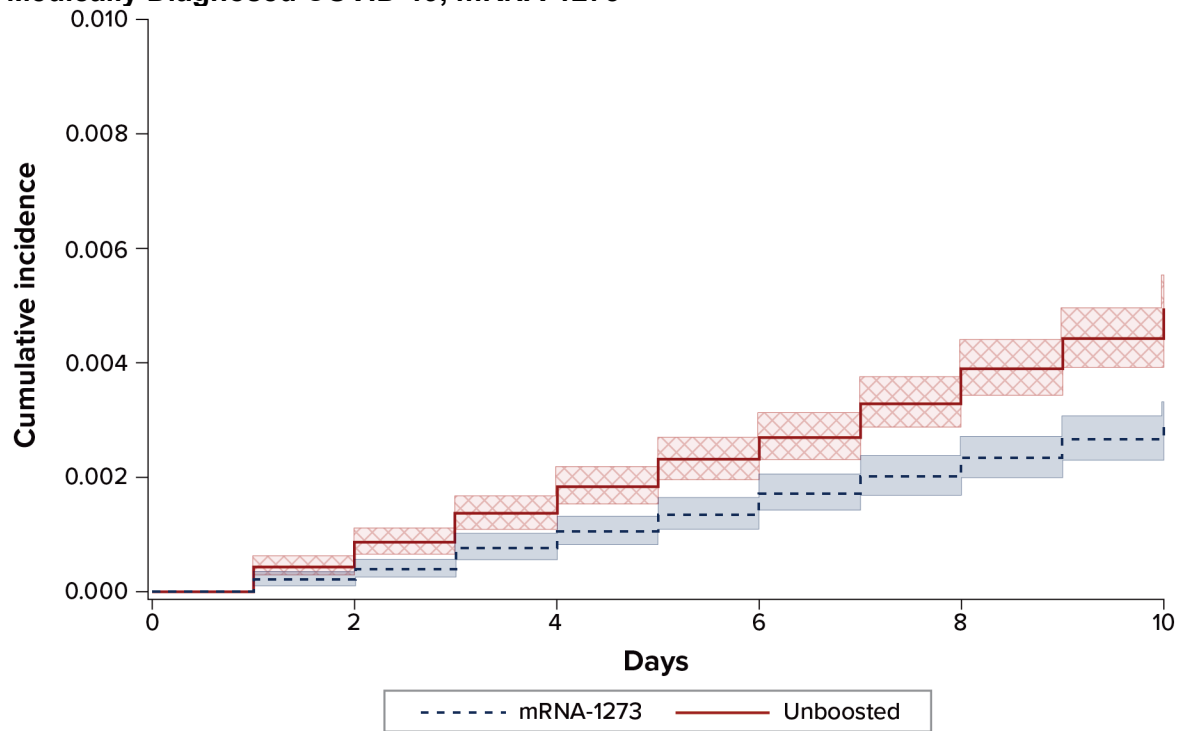
A. Medically Diagnosed COVID-19, BNT162b2



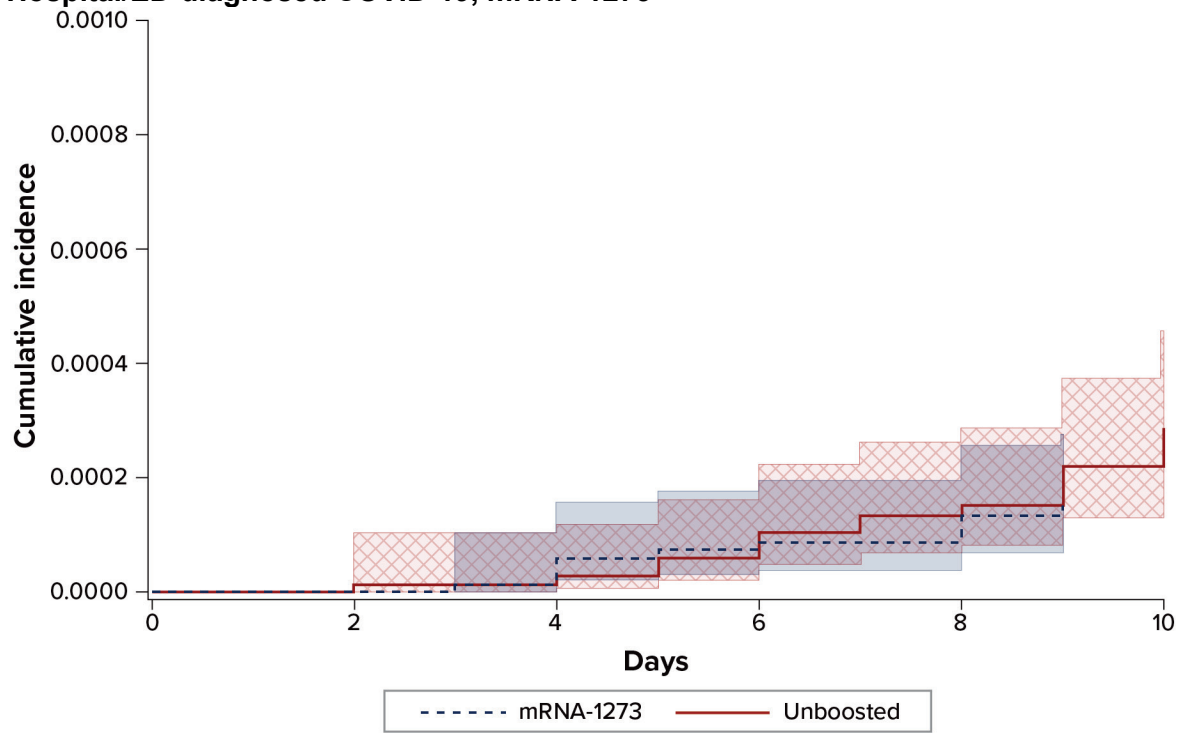
B. Hospital/ED-diagnosed COVID-19, BNT162b2



C. Medically Diagnosed COVID-19, mRNA-1273



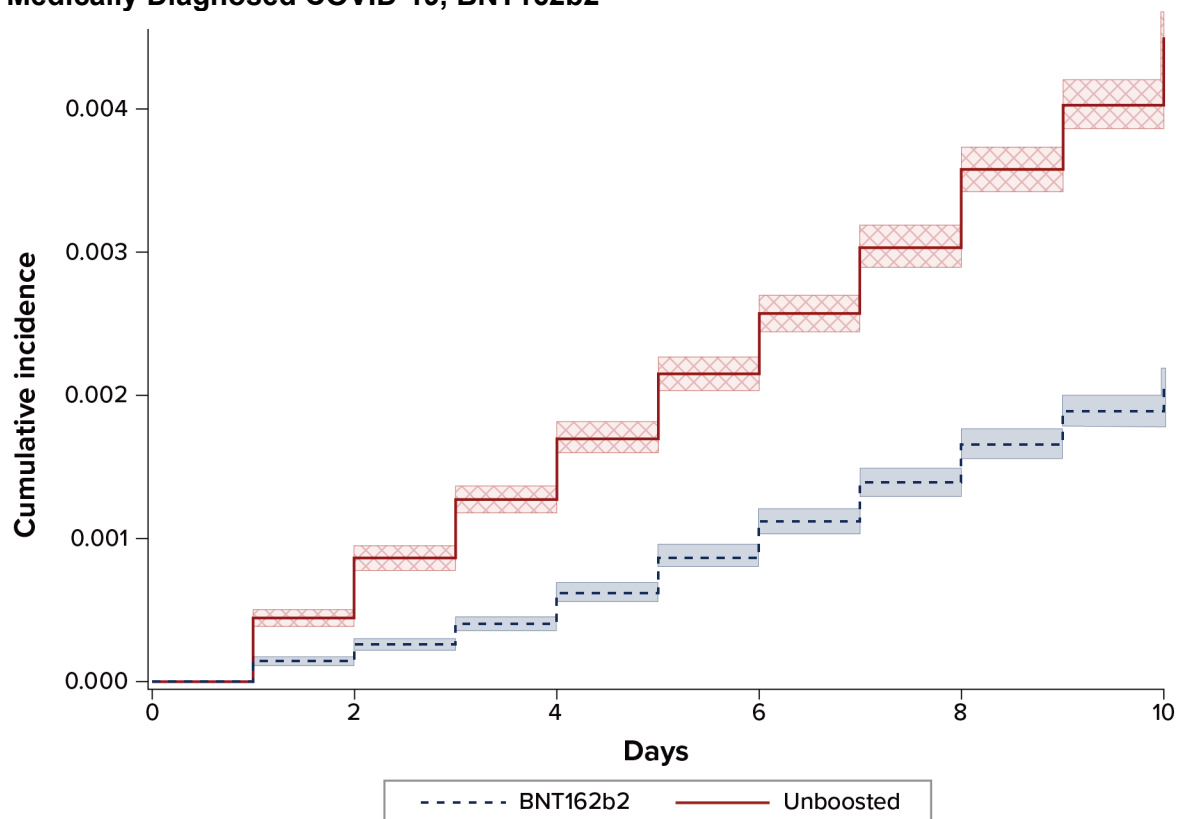
D. Hospital/ED-diagnosed COVID-19, mRNA-1273



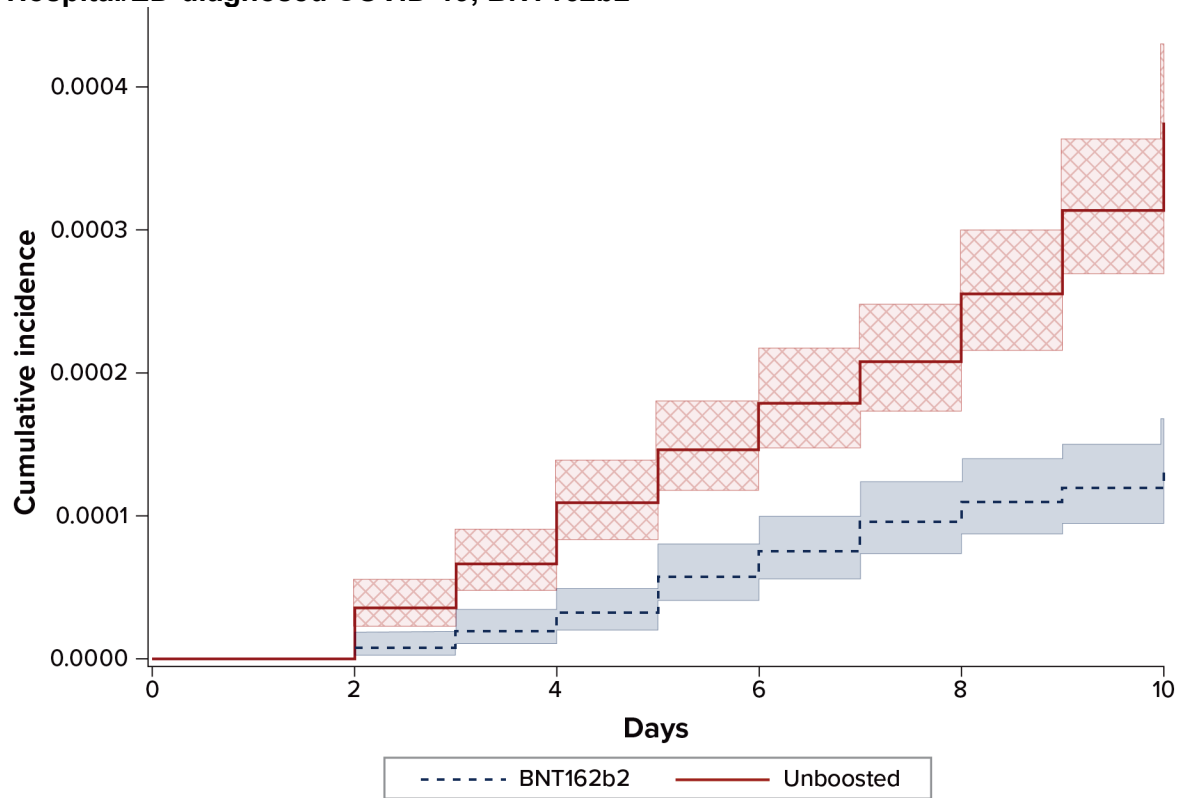
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure B-4-CVS. Inverse Probability of Treatment-weighted Cumulative Incidence of COVID-19 Outcomes in Individuals Receiving a Booster/Additional Dose of COVID-19 Vaccine and Matched, Unboosted Comparators, 10 Days After and Including Time 0, Negative Control Outcome Analysis

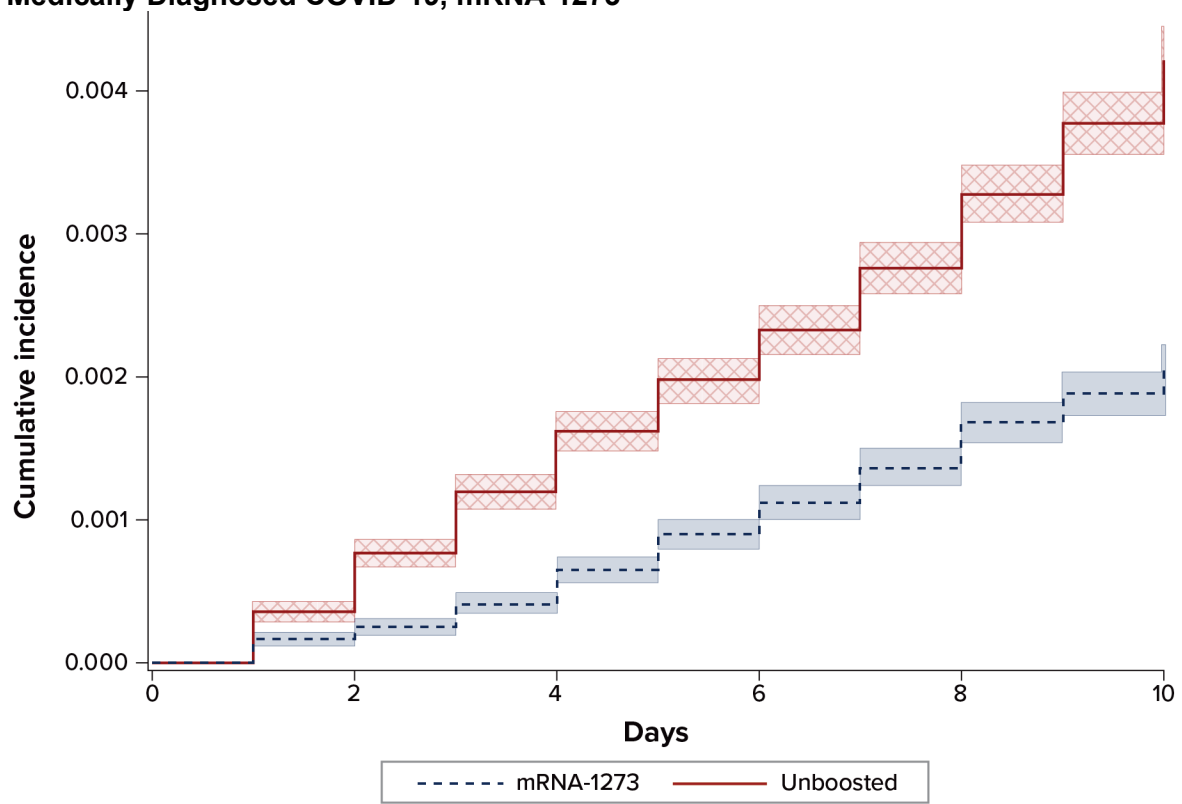
A. Medically Diagnosed COVID-19, BNT162b2



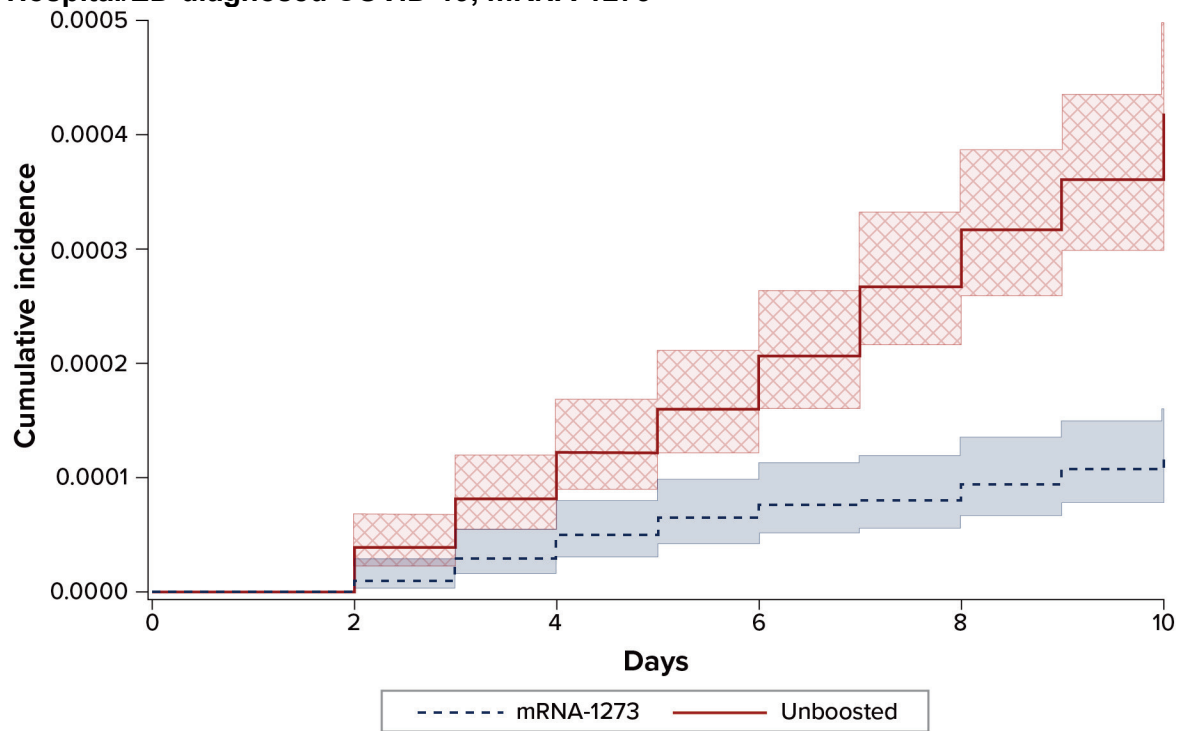
B. Hospital/ED-diagnosed COVID-19, BNT162b2



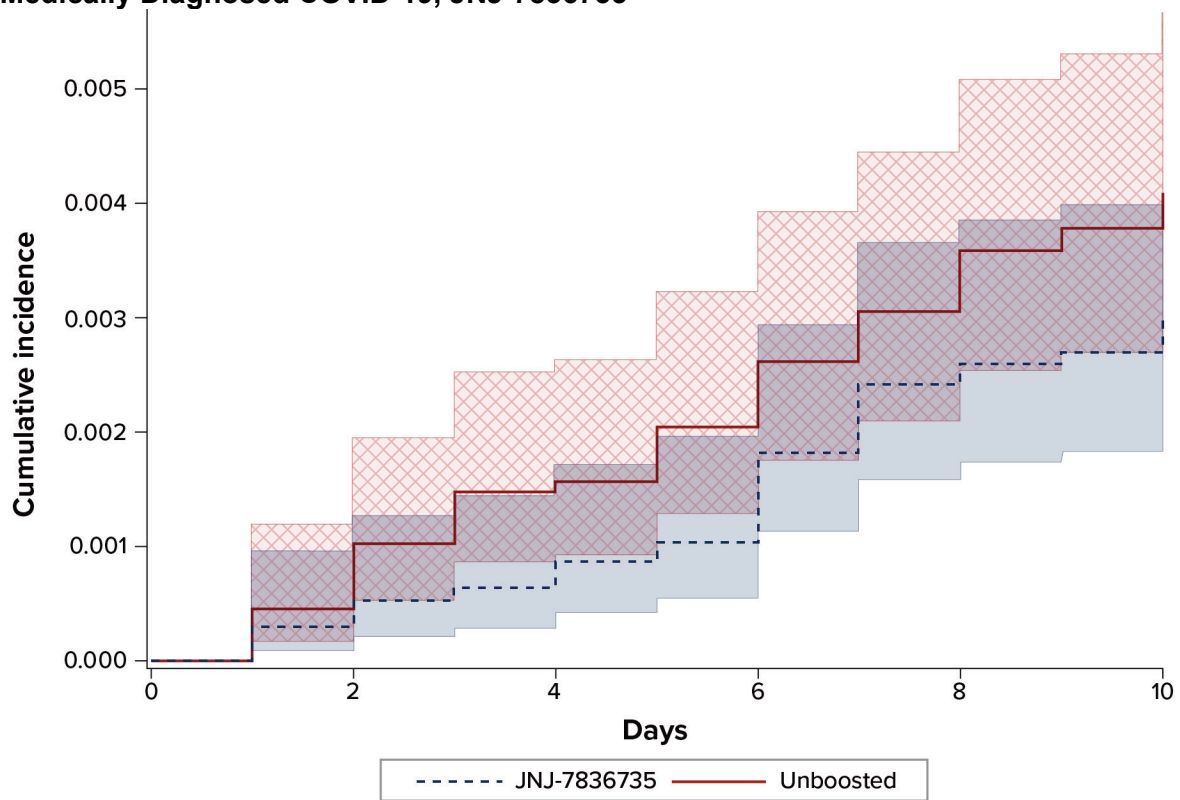
C. Medically Diagnosed COVID-19, mRNA-1273



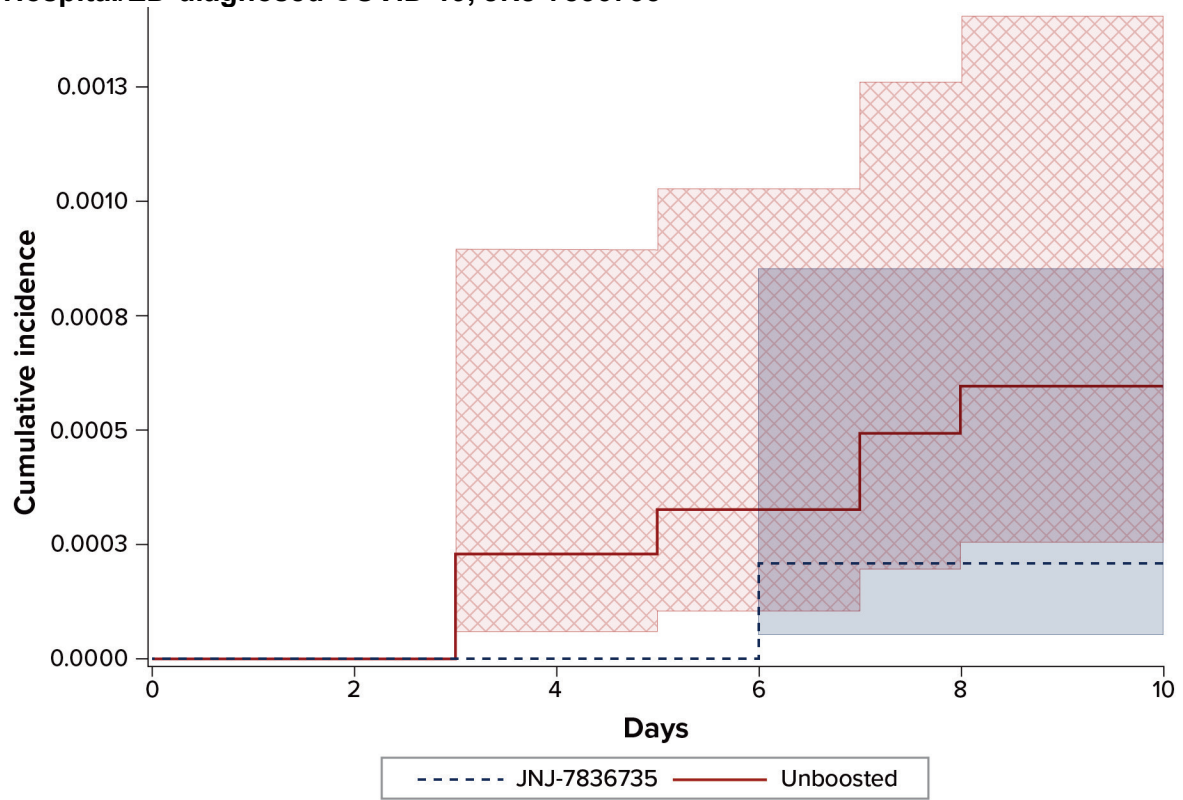
D. Hospital/ED-diagnosed COVID-19, mRNA-1273



E. Medically Diagnosed COVID-19, JNJ-7836735



F. Hospital/ED-diagnosed COVID-19, JNJ-7836735



COVID-19 = coronavirus disease 2019; ED = emergency department.