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CBER Surveillance Program Biologics Effectiveness and Safety (BEST) Initiative

Assessment of Effectiveness of a Primary Series of Monovalent COVID-19 Vaccination in Adults in the United States

Report

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List of Tables and Figures

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	US Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPT	Current Procedural Terminology
CVX	Vaccine Administered Code
DOB	date of birth
ED	emergency department
EUA	emergency use authorization
FDA	Food and Drug Administration
FIPS	Federal Information Processing System
HCPCS	Healthcare Common Procedure Coding System
HIV	human immunodeficiency virus
HR	hazard ratio
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 System
IPC	inverse probability of censoring
sIPT	stabilized inverse probability of treatment
sIPTW	stabilized inverse probability of treatment weighted
LTC	long-term care
NA	not applicable
NDC	National Drug Code
Q1, Q3	first and third quartiles
QBA	quantitative bias analysis
RCT	randomized controlled trial
RD	risk difference
RR	risk ratio
RVE	relative vaccine effectiveness
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
US	United States
VE	vaccine effectiveness

Executive Summary

Background

Several vaccines were authorized for emergency use and/or licensure by the United States (US) Food and Drug Administration (FDA) for the prevention of coronavirus disease 2019 (COVID-19) in adults between December 2020 and September 2023. This study focused on the first 3 authorized monovalent vaccine brands in the US—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).

Objectives

To estimate the effectiveness of receiving a complete primary series of BNT162b2, mRNA-1273, or JNJ-7836735 COVID-19 vaccine, compared with being unvaccinated, in US adults aged 18-64 years to prevent medically diagnosed COVID-19 and hospital/emergency department (ED)-diagnosed COVID-19.

Methods

Using data from 2 US health insurance claims databases (Optum preadjudicated commercial claims and CVS Health adjudicated commercial claims) supplemented with COVID-19 vaccination records from 16 Immunization Information Systems (IISs), cohorts of vaccinated and matched unvaccinated individuals aged 18-64 years were identified for each of the 3 vaccine brands. The study period started on 11 December 2020; the end of the study period was 15 January 2022 for Optum and 31 March 2022 for CVS Health. Vaccinated individuals were identified at their first record of a COVID-19 vaccination during the study period (Time 0), and unvaccinated individuals were matched by calendar date, US county of residence, age, sex, immunocompromised status, pregnancy status, history of COVID-19 diagnosis, influenza vaccination in the previous year, and presence of at least 1 of the conditions identified by the US Centers for Disease Control and Prevention as increasing individuals' risk of severe COVID-19. Patients were followed from Time 0 until the outcome occurred or the individual was censored at the first occurrence of one of the following: last day of the study period; disenrollment from health plan; relocation outside of catchment area of the combined claims-IIS data (for CVS Health); or, for the vaccinated, deviation from receiving the primary series (receipt of Dose 2 too early, failure to receive Dose 2 on time, receiving a booster/additional dose beyond the 1- or 2-dose primary series) or, for the unvaccinated, receipt of any COVID-19 vaccine. We estimated overall and time-specific vaccine effectiveness (VE) and 95% confidence intervals (CIs) against any medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 to describe potential waning effectiveness over time. VE was also estimated in different eras of predominant SARS-CoV-2 viral variants (pre-Delta, Delta, or Omicron) and in subgroups of immunocompromised status or previous COVID-19 diagnosis. Secondary objectives compared VE across vaccine brands and evaluated the effectiveness of receiving only a single dose of a 2-dose vaccine series. Data source–specific estimates were combined with meta-analysis methods. Negative control analyses and quantitative bias analyses evaluated the potential impact of residual confounding and misclassification.

Results

In Optum, 612,125 eligible individuals were identified who received a branded first COVID-19 vaccine dose during the study period. After matching, the analytic cohorts consisted of 341,097 matched pairs for BNT162b2, 201,604 for mRNA-1273, and 49,285 for JNJ-7836735. In CVS Health, 1,979,109 eligible individuals were identified who received a first COVID-19 vaccine dose during the study period. After matching, the analytic cohorts consisted of 1,151,775 matched pairs for BNT162b2, 651,545 for mRNA-1273, and 149,813 for JNJ-7836735. Receiving a complete primary series of any COVID-19 vaccine brand was associated with lower rates of medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 compared with being unvaccinated. Summary VE estimates from meta-analysis against hospital/ED-diagnosed COVID-19 were: BNT162b2, 77% (95% CI, 76%-78%); mRNA-1273, 84% (95% CI, 83%-85%), JNJ-7836735 66% (95% CI, 63%-68%). The observed VE estimates were generally higher for hospital/ED-diagnosed COVID-19 than for any medically diagnosed COVID-19: against any medically diagnosed COVID-19, summary VE estimates were: BNT162b2, 50% (95% CI, 50%-51%); mRNA-1273, 59% (95% CI, 58%-60%), JNJ-7836735 38% (95% CI, 36%-40%). VE estimates were highest in adults receiving the mRNA-1273 vaccine across all analyses in both data sources. VE was sustained for approximately 6 months for medically diagnosed and up to 9 months for hospital/ED-diagnosed COVID-19.

Conclusions

Compared with being unvaccinated, vaccination with a complete primary series of BNT162b2, mRNA-1273, or JNJ-7836735 was associated with reduced COVID-19 incidence in the US adult population. Findings indicate that the vaccines were effective for real-world use, although the observed VE estimates differed by vaccine brand and variant era. VE was generally sustained for several months following vaccination. Due to the rapidly changing dynamics of the COVID-19 pandemic, additional research using real-world data are needed, as recommendations for additional doses, authorizations of new vaccines, and circulating viral variants have changed over time.

1 Background

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affected all countries throughout the world including the United States (US). Several vaccines for the prevention of COVID-19 were rapidly made available in the US through either emergency use authorization and/or licensure by the US Food and Drug Administration (FDA), with varying authorization/approval dates for different age groups. Initially, COVID-19 vaccines were intended to be distributed as primary series consisting of 1 or 2 doses, depending on the brand. This study focused on the first 3 authorized monovalent vaccine brands in the US (i.e., those that were available in the US during the available study data)—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). Before authorization, these vaccines were found in large clinical trials to demonstrate efficacy in preventing various COVID-19 outcomes, including symptomatic infection,[1-3] moderate-to-severe COVID-19,[4] severe COVID-19 illness,[1-4] and death due to COVID-19.[4]

The original monovalent COVID-19 vaccines were widely administered throughout the US in real-world settings that differed from the original randomized controlled trials (RCTs). Different predominant SARS-CoV-2 viral variants were circulating at different periods, and the vaccines were administered in varying recommended dosing strategies (based on age, demographic characteristics, medical history, employment, and vaccine brand). The first COVID-19 vaccine brands were initially authorized for use in individuals aged 16 or 18 years or older (depending on the vaccine brand), but early vaccine rollout targeted those at high risk of severe COVID-19 illness or transmission (i.e., healthcare professionals, residents of long-term care facilities, older adults, and those with comorbidities). However, vaccine roll-out included tiered expansion to younger and lower-risk populations, and subsequent vaccine authorizations for other brands or booster doses; in addition, changing viral variants with different transmission patterns over time resulted in additional questions regarding the real-world vaccine effectiveness (VE) of COVID-19 vaccines, especially VE in populations of special interest, in different periods of circulating variants, and over time.

Some early real-world evidence suggested the potential for waning effectiveness over time since COVID-19 vaccination,[3,5-9] whereas other studies demonstrated only minimal or no meaningful decreases in VE over time against more severe COVID-19 disease or COVID-19-related hospitalization.[7,8,10-13] Additionally, the B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants that became predominant in the US during the study period contributed to large increases in COVID-19 cases among the unvaccinated and vaccinated in the US, which further complicated the evaluation of waning effectiveness over time since vaccination. To evaluate the real-world effectiveness of these vaccines in the US population, it is important to use methods accounting for time since vaccination, variants, calendar time, and confounding between exposure groups while avoiding the selection bias common to many studies comparing different lengths of exposure.[14] This surveillance activity evaluated the real-world effectiveness of receiving a primary series of the original, monovalent COVID-19 vaccines, by brand, in adults aged 18 years or older in the US.

2 Objectives

2.1 Primary Objectives

The following primary objectives were evaluated in this study during a study period from the time of the vaccines' original introduction through early 2022:

- To assess the overall effectiveness of receiving a complete primary series of COVID-19 vaccination in adults aged 18 to 64 years, by vaccine brand, compared with being unvaccinated, in preventing medically diagnosed COVID-19 and hospital/emergency department (ED)-diagnosed COVID-19. The following vaccine exposure patterns were compared:
    - Complete BNT162b2 primary series versus being unvaccinated
    - Complete mRNA-1273 primary series versus being unvaccinated
    - Complete JNJ-7836735 primary series versus being unvaccinated
- To describe/characterize the effectiveness over time, effectiveness across eras of different circulating variants, and potential waning effectiveness of receiving a complete primary series of COVID-19 vaccination in adults aged 18 to 64 years, by vaccine brand, compared with being unvaccinated, in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19. The following vaccine exposure patterns were compared:
    - Complete BNT162b2 primary series versus being unvaccinated
    - Complete mRNA-1273 primary series versus being unvaccinated
    - Complete JNJ-7836735 primary series versus being unvaccinated

2.2 Secondary Objectives

The following secondary objectives were evaluated:

- To assess the overall effectiveness of receiving a complete primary series of COVID-19 vaccination in adults aged 18 to 64 years, by vaccine brand, compared with being unvaccinated, in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in the following subgroups of special interest:
    - Immunocompromised individuals
    - Individuals with a diagnosis of COVID-19 in any setting before vaccination
- To assess the comparative effectiveness of the complete primary series of each brand of COVID-19 vaccine in adults aged 18 to 64 years in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19. The following vaccine exposure patterns were compared:
    - Complete mRNA-1273 primary series versus complete BNT162b2 primary series
    - Complete JNJ-7836735 primary series versus complete BNT162b2 primary series
    - Complete JNJ-7836735 primary series versus complete mRNA-1273 primary series

- To assess the effectiveness of receiving a single dose of a 2-dose primary series of COVID-19 vaccination in adults aged 18 to 64 years, by vaccine brand, compared with being unvaccinated, in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19. The following vaccine exposure patterns were compared:
    - A single dose of BNT162b2 versus being unvaccinated
    - A single dose of mRNA-1273 versus being unvaccinated

Note: Additional secondary objectives described in the study protocol[15]—evaluation of booster/additional doses and evaluation of pediatric subgroups—are reported separately.[16,17]

3 Methods

3.1 Data Sources

The study was conducted using 2 US insurance billing claims databases supplemented with vaccination records from immunization information system (IIS)–sourced COVID-19 vaccination data.[18] This study was restricted to individuals aged 18 to 64 years with commercial insurance and who were living in the catchment areas of the combined claims and IIS data.

3.1.1 Immunization Information Systems (IIS)

State, local, and/or territorial jurisdictions maintain registries of administered vaccines—IISs—as part of their public health functions.[18,19] Potential vaccination providers were required to report COVID-19 vaccinations (usually through established IIS infrastructure) as a condition of receiving federally purchased vaccines.[20] During the COVID-19 pandemic, many COVID-19 vaccines were administered outside traditional healthcare settings (e.g., mass vaccination clinics) and may not have resulted in submitted vaccine administration claims to payers for reimbursement. Reliance on insurance claims data alone for ascertainment of individuals' vaccination status may result in misclassification of vaccine status. Thus, IIS COVID-19 vaccine information was used to supplement commercial claims to improve COVID-19 vaccine capture. Each IIS is organized and maintained by the jurisdiction, and therefore data structure, completeness, and data access vary across IISs. Many IISs are organized at the level of the US state, but some IISs are organized at jurisdictions smaller than a state (e.g., region, city); thus, some unique states may contribute multiple IISs to this study.

IIS information was evaluated for completeness and usability (evaluation process and results are reported elsewhere[18]). Data from each IIS were 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. The proportion of individuals younger than 65 years in each state reported as having at least 1 COVID-19 vaccine dose and the proportion of individuals who are fully vaccinated using both IIS data and claims data were compared with state health department estimates, US Centers for Disease Control and Prevention (CDC) estimates, and capture-recapture adjusted estimates (i.e., where the proportion of vaccinated 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 both[21]). Using the state-specific sensitivity estimate derived from comparing claims-IIS estimates of completed vaccine series to the presumed gold standard of state health department estimates for completed vaccine series, a hypothetical quantitative bias analysis (QBA) was performed to determine which states should be included based on data completeness. We concluded that an acceptable level of bias for inclusion of an IIS in the study was being able to estimate VE within 10 percentage points of a hypothetical, prespecified VE estimate (i.e., an assumed 70% VE estimate and COVID-19 incidence among truly unvaccinated of 6%), after accounting for the state-specific sensitivity estimate. Additional considerations included the overall sample size of the state or jurisdiction, 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. After preliminary analyses, data from a total of 16 IISs from 14 unique US states were used (10 IISs from 10 states in Optum; 11 IISs from 9 states in CVS Health). The IISs and study periods selected for inclusion are presented in Table 1. Study periods could end on different calendar dates because of differences in the available data at the time the study was conducted.

Table 1. IIS Jurisdictions and Study Periods Utilized

IIS Jurisdiction	Optum Study Period	CVS Health Study Period
1	NA	11 December 2020 – 31 March 2022
2	11 December 2020 – 15 January 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	11 December 2020 – 15 January 2022	11 December 2020 – 31 March 2022
8	11 December 2020 – 15 January 2022	11 December 2020 – 31 March 2022
9	11 December 2020 – 15 January 2022	11 December 2020 – 31 March 2022
10	11 December 2020 – 15 January 2022	11 December 2020 – 31 March 2022
11	11 December 2020 – 15 January 2022	NA
12	11 December 2020 – 15 January 2022	11 December 2020 – 31 March 2022
13	11 December 2020 – 15 January 2022	NA
14	11 December 2020 – 15 January 2022	NA
15	11 December 2020 – 15 January 2022	NA
16	NA	11 December 2020 – 31 March 2022

IIS = immunization information system; NA = not applicable.

Note: Individual state and jurisdiction names anonymized per contractual requirements to protect privacy of the linked populations.

3.1.2 Optum Preadjudicated Commercial Health Insurance Claims

The Optum data include information on enrollment, prescription drug, and preadjudicated hospital and physician health insurance claims for enrollees with commercial coverage. Hospital and physician claims undergo initial processing on a daily basis from a large number of US health providers that accept patients with included health insurance plans. Optum established an ongoing schedule that made weekly updates incorporating newly processed claims into the preadjudicated claims database. This data

source was used to reduce the lag time between accessing healthcare services and recording them in the database. The preadjudicated claims have an approximately 2-month delay for 90% completeness for inpatient hospital claims. Because hospital/ED-diagnosed COVID-19 was one 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.

IISs were requested to link their COVID-19 vaccination data to individuals in the claims database to enhance COVID-19 vaccination capture (Section 3.1.1); these data were routinely refreshed.

3.1.3 CVS Health Commercial Health Insurance Claims

CVS Health transforms Aetna enrollment data, dispensed prescription drug claims, and adjudicated hospital, physician, and healthcare professional health insurance claims into the Observational Medical Outcomes Partnership (OMOP) common data model. The Aetna adjudicated hospital and physician health claims database includes enrollment and claims data for commercially-insured and Medicare Advantage enrollees of the Aetna health plan. The adjudicated claims are 80% complete for inpatient claims by 3 months and outpatient claims by 2 months of the date of service. 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 provider delay in claim submission to Aetna (i.e., claim lag time). To enhance vaccine administration capture, FDA requested that CVS Health collaborate with all IIS jurisdictions to obtain Aetna enrollee vaccine records regardless of Aetna health insurance claim status. The IIS data collaboration sharing process involved CVS Health providing a secure person-identifiable data file on Aetna health plan enrollees to collaborating IISs, and IISs returning vaccination records for the enrollees within the IIS.

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). 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 linkage to IISs; the end of the study period was 15 January 2022 for Optum and 31 March 2022 for CVS Health.

COVID-19 authorizations differed by brand throughout the study period, as shown in Table 2.

Table 2. Initial Authorization Dates for COVID-19 Vaccine Brands in the US During the Study Period

COVID-19 vaccine brand	Authorization date for adults aged ≥ 18 years
BNT162b2	11 December 2020
mRNA-1273	18 December 2020
JNJ-7836735	27 February 2021

COVID-19 = coronavirus disease 2019; FDA = Food and Drug Administration; US = United States.
Source: US FDA.[22-24]

3.3 Study Populations

This study population consisted of commercially insured adults aged 18 to 64 years who received a first dose of a COVID-19 primary series, and those who had not received any COVID-19 vaccine on a matched calendar date to the vaccinated individuals. Vaccine brand–specific cohorts were identified and evaluated separately for each brand-specific comparison.

3.3.1 Cohort Entry

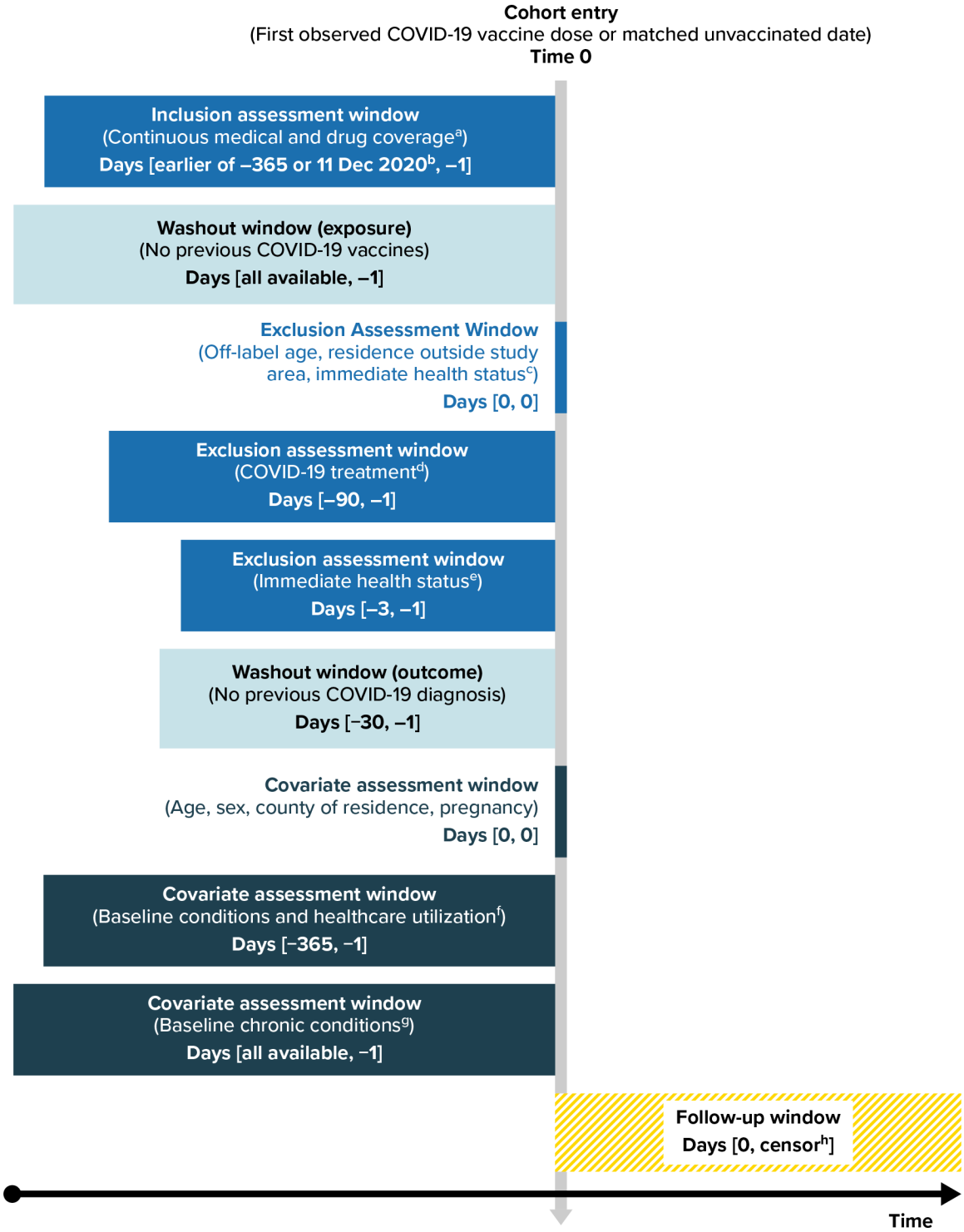
For each comparison, the evaluation of eligibility criteria, covariate assessment, and the beginning of follow-up in both the vaccinated and comparator groups were all aligned on the same date (Time 0), thus avoiding selection bias and immortal-time bias.[25-28] Vaccinated individuals were identified at the first recorded receipt of COVID-19 vaccine during the study period; the date of the first brand-specific vaccine dose (Section 3.4.1.1) became Time 0 for the vaccinated group (Figure 1). Unvaccinated individuals who met the study eligibility criteria were 1:1 exact-matched, with replacement, to the vaccinated individuals on the following characteristics:

- Calendar date
- Age, in approximately 5-year increments (18-24 years, 25-29 years, 30-34 years, etc.)
- Sex
- County and state of residence
- Immunocompromised status
- Pregnancy status for women
- History of COVID-19 diagnosis
- Presence of ≥ 1 of the conditions identified by CDC[29] as increasing individuals' risk of severe COVID-19 (Section 3.4.3), indicating potential prioritization for primary vaccine series receipt
- Receipt of influenza vaccine in previous year

The calendar date of Time 0 for the vaccinated individual became the Time 0 for the matched unvaccinated comparator individual (Figure 1).

Unvaccinated individuals were matched with replacement; unvaccinated individuals who were successfully matched and selected on a previous calendar date continued to be considered for the unvaccinated group on all days on which they met the eligibility criteria. Thus, an unvaccinated individual may have been selected multiple times on the same date and/or on different dates. Unvaccinated individuals who were successfully matched on a previous calendar date who were subsequently vaccinated were eligible for the vaccinated exposure group on the date of their first vaccination, and a new Time 0 was assigned for the vaccination group (i.e., individuals may be included in both matched exposure groups, although at different points of calendar time).

Figure 1. Schematic for Assessing Eligibility, Covariates, and COVID-19 Outcomes Among Vaccinated Individuals and Matched Unvaccinated Comparators



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

Note: Use of "all available" data indicates that the entire duration of an individual's available continuous enrollment information before Time 0, back to the beginning of data availability (Optum, 1 December 2017; CVS Health, 1 January 2018), was used; the duration of available data was at least 365 days but may vary for each individual.

[a] Gaps in medical and pharmacy coverage < 32 days permitted.

[b] Date of first COVID-19 vaccine authorization in the US.

[c] Off-label age was defined as receipt of the vaccine when it was not authorized for the age group of the recipient. Immediate health status on Time 0 refers to hospitalization or long-term care residence at Time 0.

[d] COVID-19 monoclonal antibodies or convalescent plasma.

[e] 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.

[f] Number of hospitalizations, number of 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/life support service, weakness, pregnancy completion before Time 0.

[g] Autoimmune disorders, cancer, chronic kidney disease or renal disease, chronic liver disease, chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, pulmonary embolism), dementia or other neurological conditions, diabetes mellitus type 1 or 2, Down syndrome, heart conditions (e.g., heart failure, coronary artery disease, arrhythmias), 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 (binary indicator of any test performed or none), COVID-19 diagnoses.

[h] End of study period, end of continuous health plan enrollment, relocation out of study area, deviation from the categorized vaccine exposure status.

3.3.2 Eligibility Criteria

The following eligibility criteria were evaluated relative to Time 0—the date of Dose 1 for the vaccinated group or the matched calendar date for the unvaccinated comparator group:

- Have continuous enrollment in the participating insurance plan for at least 365 days before Time 0 that also begins on or earlier than 11 December 2020 (the first date of COVID-19 vaccine authorization in the US), to characterize individual characteristics and ensure observation of all possible COVID-19 doses to accurately evaluate COVID-19 vaccination status. Some individuals may be required to have more than 365 days of coverage, but all must have at least 365 days. Considerations for defining continuous enrollment included the following:
    - Enrollment in plans with both medical and pharmacy coverage was required.
    - Gaps in coverage of fewer than 32 days were permitted for continuous enrollment.

To align the health statuses of vaccinated and unvaccinated groups, control for confounding, and ensure equivalence in data availability between groups, vaccinated and unvaccinated individuals were excluded for any of the following exclusion criteria:

- Being aged < 18 years or > 64 years on the calendar date of Time 0 (Table 2).
- Residing in a geographic region outside the catchment area of one of the IIS-claims data jurisdictions within the participating health plan.
- Having claims for monoclonal antibody treatment or convalescent plasma treatment for COVID-19 within the 90 days before Time 0; clinical guidelines did not recommend COVID-19 vaccination for individuals immediately after receiving COVID-19 treatments.[30]
- Having a diagnosis of COVID-19 assessed in any setting in the 30 days before Time 0. Individuals with previous diagnoses of COVID-19 are eligible for vaccination, but COVID-19 vaccination is not recommended for individuals with active COVID-19 or those in quarantine periods.[30] Thus, only a short washout window was required to differentiate new-onset cases during follow-up from continuing care for cases occurring before Time 0.
- Being hospitalized on the date of Time 0, as unvaccinated individuals with active illness were unlikely to be considered candidates for vaccination.

- Residing in a long-term care (LTC) facility on the date of Time 0, as factors affecting COVID-19 exposure and COVID-19 vaccination within LTC centers were highly variable and highly correlated within given LTC facilities.
- Having any of the following healthcare interactions occurring in the 3 days before Time 0, as these may be indicators of conditions that may affect an individual's likelihood to be vaccinated or may represent early manifestations of COVID-19 illness:
    - Diagnoses that may temporarily delay vaccination (fever, nausea/vomiting, rash)
    - Hospitalization
    - ED visit

3.3.3 Follow-Up

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

- Occurrence of 1 of the study COVID-19 outcomes, which were evaluated separately (Section 3.4.2); an individual who experiences both outcomes may have different follow-up times for each outcome.
- Censoring for any of the following:
    - Last date of the study period/end of data availability (Table 1)
    - Last date of individual continuous eligible health plan enrollment
    - Date of recorded change of residence to a location outside the study area (i.e., the catchment area of one of the IIS) (CVS Health only)
    - Deviation from the categorized exposure pattern (Section 3.4.1.2, Table 3)

3.4 Variables and Definitions

3.4.1 COVID-19 Vaccine Exposure

3.4.1.1 COVID-19 Vaccine Dose Identification

Vaccine doses were identified in medical and pharmacy claims and IIS COVID-19 vaccination records. In the 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.[31,32] COVID-19 vaccine doses were also identified in collaborating IIS databases using Vaccine Administered (CVX) codes. Vaccine brand was determined by using brand-specific 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 due to the possibility for a single vaccination event to result in multiple claims and/or records. An

unbranded COVID-19 vaccine record or a record for a COVID-19 vaccine of the same brand on or within 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 vaccine record for a different brand occurred within 3 days after a previous record, the first-occurring record was considered as an 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). The dose number was inferred from the order of observed doses within an individual's record; therefore, continuous enrollment before the index date for the entire period since the introduction of COVID-19 vaccines was required.

The first brand-specific dose identified during the study period was considered for the corresponding brand-specific cohort, and the date of the dose became Time 0.

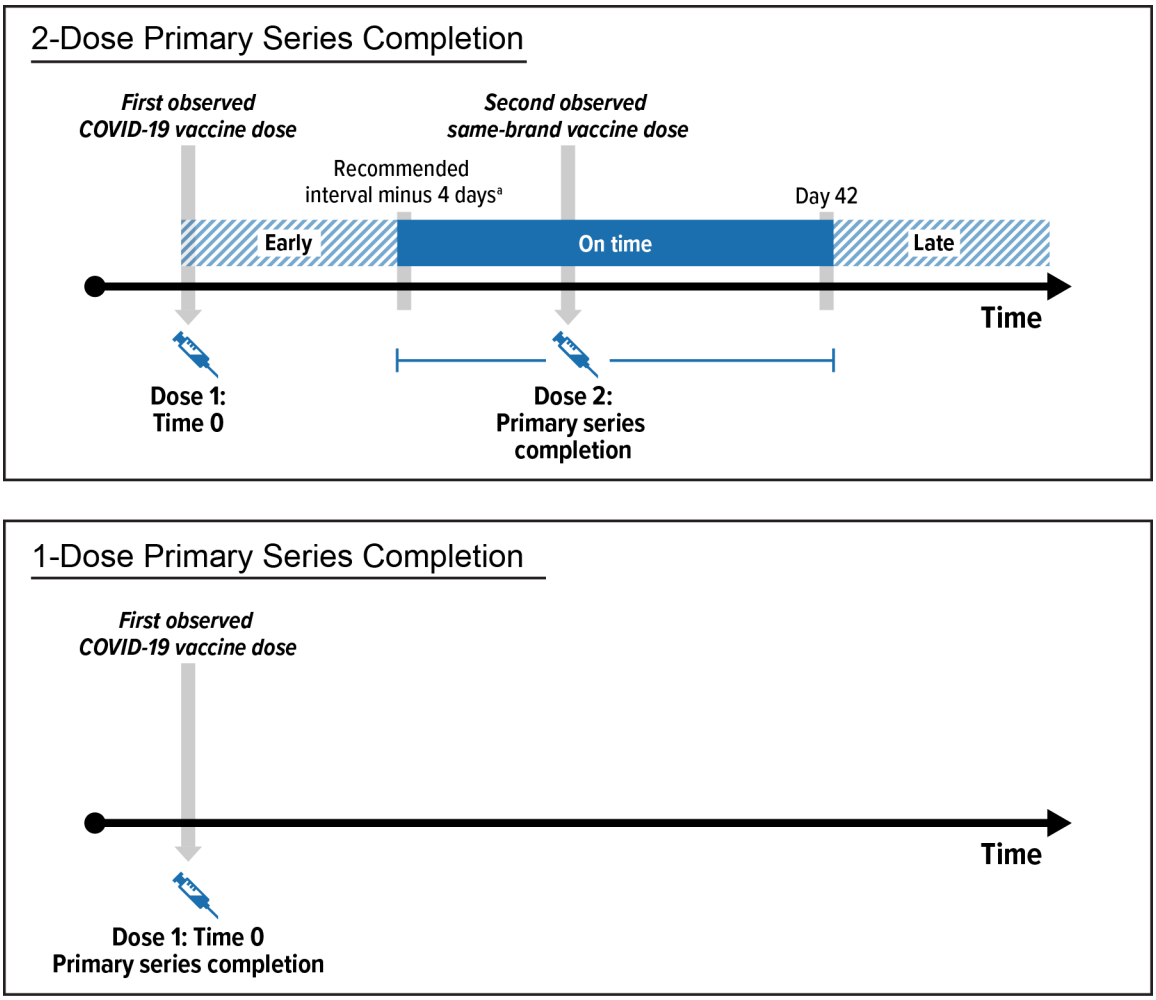
3.4.1.2 COVID-19 Vaccine Exposure Pattern Definition

All subsequent COVID-19 vaccines received by an individual after Time 0 during follow-up were identified. Many potential patterns of COVID-19 vaccination receipt were possible, both consistent and inconsistent with authorizations or licensure for the various available vaccines at the time. The following patterns of vaccination receipt ("vaccine exposure patterns") were defined based on receipt, brand, and timing of subsequent doses after Time 0:

- Receiving a complete primary series (Table 3)
- Being unvaccinated (Table 3, Table 4)
- Receiving a single dose of a multidose primary series (Table 4)

Each of the comparisons evaluated by this study required defining the exposure pattern of interest for both exposure groups.[33] Receiving a complete primary series required individuals to receive the authorized number of doses with appropriate spacing between doses without receiving extra doses, unclassifiable doses, or doses of a different brand (Figure 2). Although the 2-dose BNT162b2 series and mRNA-1273 vaccine series were recommended with spacing of 21 and 28 days, respectively, this study allowed a 42-day (inclusive) maximum time period to complete the primary series while still being considered adherent to allow for variation in real-world patterns of dose receipt, consistent with US CDC recommendations for COVID-19 vaccine administration deviations.[34] CDC recommendations also stated that receiving a second dose sooner than 4 days before the recommended interval constituted an invalid dose[34]; thus, individuals receiving a COVID-19 vaccine sooner than 4 days before the recommended interval were considered nonadherent to receiving the primary series. Individuals were followed from the date of Time 0 (Dose 1) and were censored when their vaccine receipt became inconsistent with receiving a complete primary series (for brands with a 2-dose primary series), either by failing to receive a second dose on time, receiving a second dose too early, receiving a vaccine of a different brand, or receiving another dose beyond the primary series (for either 1-dose or 2-dose primary series). In the unvaccinated comparison group, individuals were censored if they received any COVID-19 vaccine. Complete details of these vaccine exposure patterns for the analyses of a complete primary series, by vaccine brand, are given in Table 3.

Figure 2. Patterns of Primary Series Completion



COVID-19 = coronavirus disease 2019.
[a] Day 17 for BNT162b2, day 24 for mRNA-1273.

Table 3. Details of Follow-Up for the Complete Primary Vaccination Series Exposure Patterns

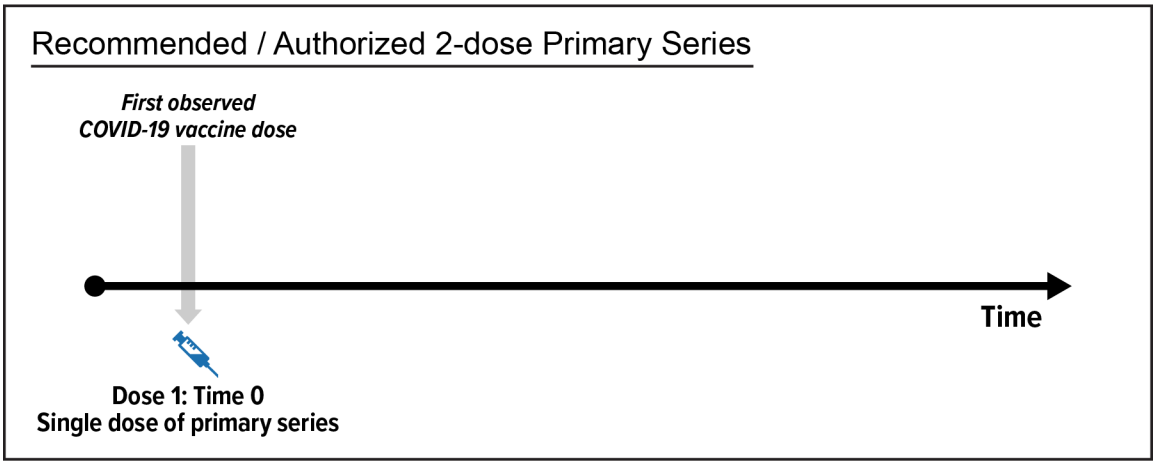
Vaccine exposure pattern	Included individuals	Time 0 (beginning of follow-up)	Deviation from vaccine exposure pattern after Time 0 resulting in censoring
BNT162b2 complete primary series	All eligible individuals receiving Dose 1 of BNT162b2	Date of Dose 1 of BNT162b2	• Receipt of Dose 2 of BNT162b2 < 17 days after Dose 1 • Failure to receive Dose 2 of BNT162b2 by day 42 after Dose 1 • Receipt of any other COVID-19 vaccine brand or unspecified/unclassifiable brand • Receipt of a third dose
mRNA-1273 complete primary series	All eligible individuals receiving Dose 1 of mRNA-1273	Date of Dose 1 of mRNA-1273	• Receipt of Dose 2 of mRNA-1273 < 24 days after Dose 1 • Failure to receive Dose 2 of mRNA-1273 by day 42 after Dose 1 • Receipt of any other COVID-19 vaccine brand or unspecified/unclassifiable brand • Receipt of a third dose

Vaccine exposure pattern	Included individuals	Time 0 (beginning of follow-up)	Deviation from vaccine exposure pattern after Time 0 resulting in censoring
JNJ-7836735 complete primary series	All eligible individuals receiving Dose 1 of JNJ-7836735	Date of Dose 1 of JNJ-7836735	• Receipt of any subsequent COVID-19 vaccine dose
Unvaccinated	Matched eligible unvaccinated comparator individuals	Matched calendar date	• Receipt of any COVID-19 vaccine dose

COVID-19 = coronavirus disease 2019.

As a secondary analysis, the exposure pattern of receiving a single dose of a multidose primary series was evaluated by identifying everyone who received the first dose of a COVID-19 brand with an authorized primary series consisting of 2 doses. Individuals who received a second dose were censored at the receipt of the second dose. This vaccine exposure pattern is displayed in Figure 3, and details are given in Table 4.

Figure 3. Patterns of Receiving a Single Dose of the BNT162b2 or mRNA-1273 Primary Series



COVID-19 = coronavirus disease 2019.

Table 4. Details of Follow-Up for the Secondary Analysis of a Single Dose of a 2-Dose Primary Series

Vaccine exposure pattern	Included individuals	Time 0 (beginning of follow-up)	Deviation from vaccine exposure pattern after Time 0 resulting in censoring
Single dose of a BNT162b2 primary series	All eligible individuals receiving Dose 1 of BNT162b2	Date of Dose 1 of BNT162b2	Receipt of any other COVID-19 vaccine dose
Single dose of an mRNA-1273 primary series	All eligible individuals receiving Dose 1 of mRNA-1273	Date of Dose 1 of mRNA-1273	Receipt of any other COVID-19 vaccine dose

Vaccine exposure pattern	Included individuals	Time 0 (beginning of follow-up)	Deviation from vaccine exposure pattern after Time 0 resulting in censoring
Unvaccinated	Matched eligible unvaccinated comparator individuals	Matched calendar date	Receipt of any COVID-19 vaccine

COVID-19 = coronavirus disease 2019.

3.4.2 COVID-19 Outcome Assessment

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

This study separately considered 2 sets of nested, non–mutually exclusive COVID-19 outcomes, as follows:

- Hospital/ED-diagnosed COVID-19, identified as the first recorded 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 became the outcome date.
- Medically diagnosed COVID-19, identified as the first recorded 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 became 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 nonhospitalized settings.[35-39] Our study only considered COVID-19 diagnoses recorded in medical claims rather than laboratory-confirmed COVID-19 or COVID-19 infection, because laboratory results or at-home test results were not available in the databases. COVID-19 testing and diagnosis practices changed over the course of the study period, with larger availability of at-home testing, healthcare capacity, and treatment options; therefore, identifying all COVID-19 infection or symptomatic infections was not possible. It is acknowledged that not all cases of COVID-19 result in medical interactions and recorded diagnoses. Although asymptomatic or mild cases would not be included by our outcome definitions, COVID-19-related hospitalizations were identified and may be the most relevant public health measure for contemporary surveillance and prevention efforts.[40,41]

3.4.3 Covariates

Covariates were identified in 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 and data on 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.[42-44] 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[45,46]:

- 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 preventive healthcare visit
- Arthritis[45]
- Lipid abnormality[45]
- Ambulance use or life support services[45]
- Weakness[45]
- Pregnancy completion before Time 0 (to differentiate from active pregnancy at Time 0)

Comorbidities increasing 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-19[29] and may have served as indicators of eligibility or prioritization for vaccination. An overall binary indicator of history of any of these conditions was defined using all available baseline data to identify individuals who may qualify for priority groups for vaccination during phased vaccination roll-out in many jurisdictions.

- Autoimmune disorders
- Cancer[47,48]
- Chronic kidney disease or renal disease[47,48]
- Chronic liver disease[47,48]

- Chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, pulmonary embolism)[48]
- Dementia[45,47,48] or other neurological conditions
- Diabetes mellitus, type 1 or 2
- Down syndrome
- Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)[47,48]
- Hypertension[48]
- Immunocompromised state, defined as either of the following: (1) at least 2 diagnostic codes for human immunodeficiency virus (HIV), hematological malignancy, immune deficiencies, solid malignancy, or rheumatological/inflammatory condition; (2) at least 1 claim containing evidence an organ transplant in the 6 months prior to but not including Time 0.
- Mental health conditions[45,48]
- Obese or severely obese[49]
- Sickle cell disease or thalassemia
- Stroke or cerebrovascular disease[47]
- Tuberculosis

To describe history of COVID-19 exposure, diagnoses, 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)
- Hospital/ED-diagnosed COVID-19 (binary indicator of any COVID-19 diagnosis in a hospital or ED setting)
- COVID-19 diagnoses occurring outside a hospital or ED setting (binary indicator of any COVID-19 diagnosis outside a hospital or ED setting)

3.5 Statistical Analysis

3.5.1 Descriptive Analyses

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

The distribution of individual characteristics was described by vaccine exposure groups. Continuous variables were described with means, standard deviations (SDs), medians, and first and third quartiles (Q1, Q3). Distributions of categorical variables were described with counts and proportions. The balance of covariates between exposure groups was evaluated with absolute standardized differences.[50]

3.5.2 Propensity Score Approach

Within each cohort, differences in the distribution of baseline characteristics were addressed via stabilized inverse probability of treatment (sIPT) 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 factors[51] and the remaining identified baseline characteristics as independent

variables (i.e., all characteristics described in Section 3.4.3). The distributions of the propensity scores by vaccine exposure group were plotted to visualize the degree of overlap between the vaccine exposure groups. The propensity score was used to compute sIPT weights[52] that were applied to the analytic cohorts. To reduce the effect of extreme weights, propensity scores were truncated below the 1st and above the 99th percentile of the distribution of all propensity scores.

3.5.3 Primary Overall Vaccine Effectiveness

3.5.3.1 Overall Vaccine Effectiveness

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

Within each of the brand-specific cohorts, all individuals were followed from Time 0 until censoring (Section 3.3.3) or until the occurrence of the COVID-19 outcome of interest. The cumulative incidence of each COVID-19 outcome was estimated in each sIPT-weighted vaccine exposure group as 1 minus the Kaplan-Meier estimator.[53] 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 vaccinated and unvaccinated groups across the entire study period, a hazard ratio (HR) and 95% CIs for each outcome were estimated using an sIPT-weighted Cox proportional hazards model with robust sandwich variance estimators. The overall VE was estimated as 1 minus the HR.

3.5.3.2 Quantitative Bias Analysis

3.5.3.2.1 Exposure Misclassification

Although vaccinations were identified in both insurance claims data and IIS data,[18] vaccine information could still be missing. Quantitative bias analyses[54,55] were performed to estimate the impact of truly vaccinated individuals being misclassified as unvaccinated due to missing vaccine records. No gold standard for vaccine status is available, so estimates of statewide receipt of at least 1 COVID-19 vaccine dose among individuals aged younger than 65 years from the CDC, state departments of health, and capture-recapture methods[21,56,57] were obtained at dates that most closely matched the last date of service in the IIS data. These external vaccination estimates were compared with observed state-level estimates in the linked data sources[18] to estimate minimum and maximum potential positive sensitivities of vaccine exposure. VEs were estimated accounting for the minimum and maximum potential exposure sensitivities.

Using the estimated vaccine exposure sensitivities, a simple QBA evaluating the impact of exposure misclassification (i.e., truly vaccinated individuals being misclassified as unvaccinated because of missing vaccine records) was performed. The primary analyses estimated HRs, but for the purposes of the quantitative bias analyses, risk ratios (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 unvaccinated individuals were misclassified as being vaccinated). Using the minimum and maximum estimated sensitivity estimates

from the 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 unvaccinated to vaccinated based on the sensitivity estimate. A correction factor was then estimated as follows:

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

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

3.5.3.2.2 Outcome Misclassification

A probabilistic bias analysis evaluating the effect of differential outcome misclassification was conducted on summary-level data. We assumed that measures of sensitivity and specificity for the outcome measurements followed a trapezoidal distribution with the following parameters:

- The sensitivity of medically diagnosed COVID-19 had a minimum of 50%, a low mode of 75%, a high mode of 90%, and a maximum of 100%.
- The specificity of medically diagnosed COVID-19 had a minimum of 99.5%, a low mode of 99.7%, a high mode of 99.8%, and a maximum of 100%.
- The sensitivity of hospitalized/ED-diagnosed COVID-19 had a minimum of 50%, a low mode of 80%, a high mode of 95%, and a maximum of 100%.
- The specificity of hospitalized/ED-diagnosed COVID-19 had a minimum of 99.95%, a low mode of 99.97%, a high mode of 99.98%, and a maximum of 100%.

The resulting VE estimates were simulated 100,000 times using a publicly available R program for QBA to estimate the distribution of potential corrected values.[58]

3.5.3.3 Secondary Subgroup Analyses

Subgroup analyses of overall VE were performed by drawing subgroups of interest from the brand-specific matched analytic cohorts used for the primary analysis. All the subgroup-defining characteristics were included as matching factors; thus, the 1:1 matching of vaccinated and unvaccinated individuals was maintained in the subgroups. The propensity score and sIPT weights from the overall analysis were used for each subgroup, the HRs and 95% CIs were estimated within each subgroup using sIPT-weighted Cox proportional hazards models, and the subgroup HRs were plotted on forest plots and compared with the overall HR from the primary analysis.

Analyses were performed in the following subgroups:

- Immunocompromised individuals
- Individuals with previous diagnoses of COVID-19
- Individuals without previous diagnoses of COVID-19

3.5.3.4 Sensitivity Analyses

Sensitivity analyses were performed to evaluate the robustness of the overall VE results against variations in the study design. The overall HR and 95% CI estimates from the primary analyses and sensitivity analyses were plotted to observe consistency across analyses.

3.5.3.4.1 Inverse Probability of Censoring Weighted Analyses

To evaluate the potential impact of informative censoring not accounted for by baseline characteristics, the primary analysis was repeated using inverse probability of censoring (IPC) weighting. The IPC weight was computed from a propensity score model where the dependent variable was a binary indicator of whether an individual deviated from their baseline vaccination pattern within 28-day intervals. This propensity score model included time-fixed baseline variables (i.e., vaccine status, age category, region) and time-varying healthcare utilization measures (i.e., influenza vaccination, encounter for cancer screening, well-check preventive healthcare visits) as covariates to account for potential selection bias caused by differential censoring.[59] Interactions between baseline vaccine status and each of age category, region, time-varying influenza indicator, time-varying cancer screening indicator, and time-varying well-check preventive visit indicator were also included in the model. IPC weights were estimated and multiplied by the sIPT to calculate a combined weight, which was truncated below the 1st and above the 99th percentile of the distribution and then used to estimate overall HRs and 95% CIs correcting for potential selection bias from censoring throughout follow-up.

3.5.3.4.2 Delayed Censoring After Vaccination

To account for potential informative censoring, the censoring criteria were amended so that censoring occurred 7 days after receipt of a censoring vaccine dose (e.g., individuals in the unvaccinated group receiving any vaccine, or individuals in the vaccinated group receiving Dose 2 too early, Dose 2 of a different brand [or unspecified or unclassifiable brand], or a third dose) instead of censoring on the day of receipt of the vaccine dose, as there would not be an expected effect of the new dose during this time.

3.5.3.5 Negative Control Outcome Analysis

As a negative control outcome to evaluate residual bias, the cumulative incidence during the first 14 days after Time 0 (during which a biologic effect of vaccination would not be expected due to a lack of a full immune response) was visually inspected, and the time-specific HR, RR, and risk difference (RD) estimates at day 14 were evaluated.

3.5.4 Vaccine Effectiveness Over Time

3.5.4.1 Time Since Vaccination

To evaluate changing VE over time since vaccination, time-specific RRs of COVID-19 outcomes were calculated from the daily cumulative incidence estimates as the risk in the vaccinated exposure group on a specified day divided by the risk in the comparator group on the same day. The 95% CIs for the RRs were estimated with nonparametric bootstrapping[60,61] with 500 samples; the 95% CI was estimated as the 2.5th and 97.5th percentiles of the distribution of bootstrap estimates. RDs were similarly estimated as the daily vaccinated risk estimate minus the unvaccinated risk estimate. Time-specific VEs were estimated as 1 minus the RR.[62] Time period–specific RR, VE, and RD measures were estimated and

reported at days 14 (the end of the negative outcome control period, Section 3.5.3.5), 28 (for BNT162b2 and mRNA-1273), 42 (for BNT162b2 and mRNA-1273), 60, 90, and 183.

Additionally, time-specific VE estimates were estimated as 1 minus the RR for each day of follow-up, and daily VE estimates were plotted to evaluate changing VE over time since vaccination.

3.5.4.2 Variant-Specific Eras

To evaluate potential changes in VE over calendar time due to circulating variants, the cumulative incidence and time-specific VE estimation analyses (Section 3.5.4.1) were stratified and plotted by variant-specific era to observe changing incidence over time since vaccination in variant-specific eras:

- Pre-Delta era: Individuals with Time 0 on or before 31 May 2021, with follow-up censored on 31 May 2021
- Delta era: Individuals with Time 0 between 1 June 2021 and 24 December 2021 (inclusive), 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 in each data source

3.5.5 Secondary Comparative Effectiveness Analysis

This secondary objective evaluated the comparative effectiveness of receiving a complete primary series of different COVID-19 vaccine brands. The vaccinated individuals eligible for these comparisons were the same as those considered for the primary vaccinated versus unvaccinated comparisons before matching, with the same Time 0 and measured covariates. However, each unique comparison between vaccine brands required a separate analytic cohort. For each comparison, to increase comparability of exposure groups, the study period was restricted to time periods when both vaccine brands being used in that comparison were authorized. The details of specific comparisons are shown in Table 5.

Table 5. Details of Comparison-Specific Study Cohorts for the Secondary Comparative Effectiveness Analyses

Comparison	Exposure group	Comparator group	Study period
Complete mRNA-1273 primary series versus complete BNT162b2 primary series	mRNA-1273	BNT162b2	18 December 2020 – end of study
Complete JNJ-7836735 primary series versus complete BNT162b2 primary series	JNJ-7836735	BNT162b2	27 February 2021 – end of study
Complete JNJ-7836735 primary series versus complete mRNA-1273 primary series	JNJ-7836735	mRNA-1273	27 February 2021 – end of study

For all vaccinated individuals, Time 0 was the date of receipt of vaccine Dose 1 in each group. Follow-up for a complete primary series was the same as that in the primary analysis (Section 3.3.3).

Within each comparison, all vaccinated individuals in either exposure group with an eligible Time 0 during the comparison-specific study period were identified. To account for variation in local COVID-19

burden between the 2 exposure groups, vaccinated individuals in both exposure groups were exact-matched 1:1, without replacement, on the following characteristics:

- Calendar week of Time 0
- Age (years), in 5-year increments
- Sex
- County and state of residence

Fewer matching criteria were used in this head-to-head analysis than in the primary analysis of vaccinated versus unvaccinated groups, as all vaccinated individuals in both exposure groups already had a Time 0 assigned (the calendar date of Dose 1), all vaccinated individuals in both groups presumably met the time-specific local criteria for vaccination, and the extent of confounding between vaccinated groups was expected to be less than that between vaccinated and unvaccinated groups. All vaccinated individuals in both vaccine exposure groups who were successfully matched were included in the final matched comparative cohorts.

The distribution and balance of baseline characteristics were described, and differences between vaccine groups were accounted for with sIPT weighting. The propensity score and sIPT weights were re-estimated with each brand-to-brand comparison. Hazard ratios and 95% CIs with the corresponding relative VE (RVE) were estimated using Cox proportional hazards models.

3.5.6 Secondary Single-Dose Analysis (BNT162b2, mRNA-1273)

This secondary analysis evaluated the effectiveness of receiving only a single dose of a 2-dose primary series (BNT162b2 or mRNA-1273) compared with being unvaccinated (Figure 3).

The individuals included in this analysis were drawn from the same brand-specific matched analytic cohorts used for the primary analysis (complete vaccine series versus being unvaccinated). Time 0 for both the vaccinated (receipt of Dose 1) and unvaccinated (matched unvaccinated date) comparator groups were the same as the primary series analysis, and the same 1:1 matching of vaccinated (with an eligible Dose 1 of BNT162b2 or mRNA-1273) and unvaccinated individuals was maintained. However, because this analysis evaluated a different vaccine exposure pattern than the primary analysis (i.e., receiving a single dose of a 2-dose primary series rather than receiving a complete primary series), vaccinated individuals were censored at the receipt of any additional COVID-19 vaccine dose after Dose 1 (Table 4). The censoring of unvaccinated individuals due to deviation in exposure pattern was the same as the primary analysis (i.e., at receipt of any COVID-19 vaccine dose).

The same propensity scores and sIPT weights used in the primary analysis were used in this analysis. The sIPT-weighted cumulative incidence curves of COVID-19 outcomes were plotted by exposure group, and HRs and 95% CIs with the corresponding VE were estimated using sIPT-weighted Cox proportional hazards models.

3.5.7 Meta-analysis of Data Source–Specific Results

All analyses were performed separately by data source using the common protocol,[15] and data source–specific results were reported for all analyses. Meta-analyses across data sources were performed of the

overall VE estimates, variant era–specific VE estimates, subgroup analyses by immunocompromised status and previous COVID-19 diagnosis, and secondary comparative effectiveness and single-dose analyses as a summary of the results across both data sources. Given that a common study protocol was applied in 2 similar, national commercial claims data sources that cover similar demographic populations, the 2 data source–specific VE estimates were combined with fixed-effects meta-analysis methods.[63] Statistical evidence of heterogeneity between data sources was evaluated by obtaining log-transformed HR estimates and their standard errors, with *p* values less than 0.05 indicating evidence of statistical heterogeneity between study estimates. Even if the analyses suggested statistical heterogeneity between data sources, the summary VE estimates from the meta-analysis are presented with the statistical heterogeneity noted. 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

4.1 Primary Vaccinated vs. Unvaccinated Comparison

4.1.1 Descriptive Analyses

The attrition of individuals into the matched, brand-specific cohorts is shown in Figure C-1-Optum and Figure C-1-CVS. In Optum, we identified 612,125 eligible individuals receiving a first branded COVID-19 vaccine dose during the study period. After matching unvaccinated comparators to the vaccinated adults, the analytic cohorts consisted of 341,097 matched pairs for BNT162b2, 201,604 for mRNA-1273, and 49,285 for JNJ-7836735. In CVS Health, we identified 1,979,109 eligible individuals receiving a first COVID-19 vaccine dose during the study period. After matching, the analytic cohorts consisted of 1,151,775 matched pairs for BNT162b2, 651,545 for mRNA-1273, and 149,813 for JNJ-7836735.

Selected characteristics of individuals who received a COVID-19 vaccine dose and matched unvaccinated comparators for each brand-specific cohort are shown in Table 6. The characteristics of individuals who received a COVID-19 vaccine who were excluded due to a failure to match are shown in Table C-4-Optum and Table C-4-CVS.

Across both data sources, the mean age was approximately 42 to 43 years for each vaccine-specific cohort. The BNT162b2 and mRNA-1273 matched cohorts were slightly more female (51%-52%), but the JNJ-7836735 matched cohort was slightly more male (56%). For all cohorts, the largest proportion of individuals were identified in the Midwest for Optum, and the West for CVS Health. A very small proportion of each cohort was pregnant at the time of vaccination (< 0.6%), and approximately 4% of each cohort were immunocompromised. Age, sex, geography, pregnancy status, COVID-19 history, and immunocompromised status were all perfectly balanced between vaccinated and comparator groups, as these were exact matching characteristics. Additionally, all other measured characteristics (i.e., healthcare utilization, comorbidities, frailty markers) were all well balanced between treatment groups as indicated by standardized differences close to 0 in each cohort, even before propensity score weighting (Table C-1-Optum, Table C-1-CVS, Table C-2-Optum, Table C-2-CVS, Table C-3-Optum, and Table C-3-CVS).

Table 6. Selected Characteristics of Adults Aged 18-64 Years Vaccinated With COVID-19 Vaccine and Matched Unvaccinated Adults, by Vaccine Brand

A. BNT162b2

Characteristic	Optum, BNT162b2 vaccinated N = 341,097	Optum, unvaccinated matched to BNT162b2 N = 341,097	CVS Health, BNT162b2 vaccinated N = 1,151,775	CVS Health, unvaccinated matched to BNT162b2 N = 1,151,775
Age, years				
Median (Q1, Q3)	42 (32, 53)	42 (32, 53)	42 (31, 53)	42 (31, 53)
Mean (SD)	42.03 (12.95)	42.02 (12.95)	41.92 (13.22)	41.91 (13.23)
Sex, n (%)				
Female	175,029 (51.31%)	175,029 (51.31%)	615,551 (53.44%)	615,551 (53.44%)
Male	166,068 (48.69%)	166,068 (48.69%)	536,224 (46.56%)	536,224 (46.56%)
Region, n (%)				
Midwest	144,657 (42.41%)	144,657 (42.41%)	206,280 (17.91%)	206,280 (17.91%)
Northeast	40,009 (11.73%)	40,009 (11.73%)	204,777 (17.78%)	204,777 (17.78%)
South	86,610 (25.39%)	86,610 (25.39%)	251,233 (21.81%)	251,233 (21.81%)
West	69,821 (20.47%)	69,821 (20.47%)	489,485 (42.50%)	489,485 (42.50%)
Pregnant at Time 0, n (%)[a]	1,837 (0.54%)	1,837 (0.54%)	6,611 (0.57%)	6,611 (0.57%)
Immunocompromised state	15,135 (4.44%)	15,135 (4.44%)	49,753 (4.32%)	49,753 (4.32%)

COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.
[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.
Source: Table C-1-Optum and Table C-1-CVS.

B. mRNA-1273

Characteristic	Optum, mRNA-1273 vaccinated N = 201,604	Optum, unvaccinated matched to mRNA-1273 N = 201,604	CVS Health, mRNA-1273 vaccinated N = 651,545	CVS Health, unvaccinated matched to mRNA-1273 N = 651,545
Age, years				
Median (Q1, Q3)	44 (33, 54)	44 (33, 54)	44 (33, 55)	44 (32, 55)
Mean (SD)	43.23 (12.95)	43.19 (12.97)	43.37 (13.40)	43.33 (13.42)
Sex, n (%)				
Female	103,947 (51.56%)	103,947 (51.56%)	338,084 (51.89%)	338,084 (51.89%)
Male	97,657 (48.44%)	97,657 (48.44%)	313,461 (48.11%)	313,461 (48.11%)
Region, n (%)				
Midwest	85,564 (42.44%)	85,564 (42.44%)	114,493 (17.57%)	114,493 (17.57%)
Northeast	26,580 (13.18%)	26,580 (13.18%)	139,585 (21.42%)	139,585 (21.42%)
South	47,138 (23.38%)	47,138 (23.38%)	113,510 (17.42%)	113,510 (17.42%)
West	42,322 (20.99%)	42,322 (20.99%)	283,957 (43.58%)	283,957 (43.58%)

Characteristic	Optum, mRNA-1273 vaccinated N = 201,604	Optum, unvaccinated matched to mRNA-1273 N = 201,604	CVS Health, mRNA-1273 vaccinated N = 651,545	CVS Health, unvaccinated matched to mRNA-1273 N = 651,545
Pregnant at Time 0, n (%)[a]	759 (0.38%)	759 (0.38%)	2,557 (0.39%)	2,557 (0.39%)
Immunocompromised state	9,000 (4.46%)	9,000 (4.46%)	31,211 (4.79%)	31,211 (4.79%)

COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.
[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.
Source: Table C-2-Optum and Table C-2-CVS.

C. JNJ-7836735

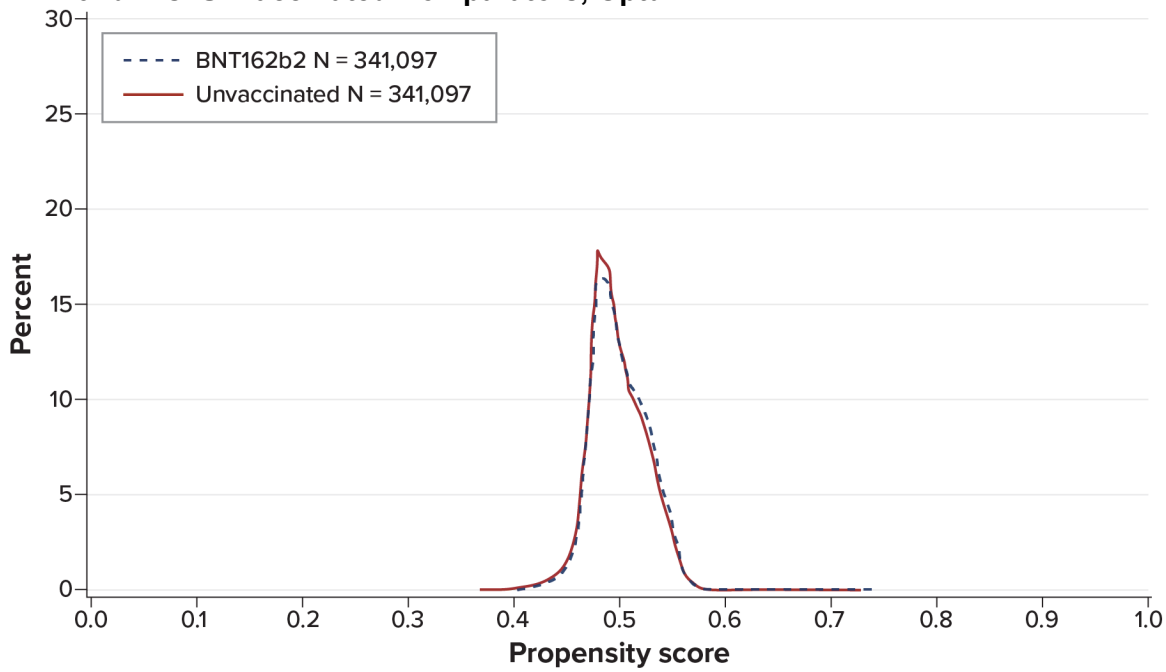
Characteristic	Optum, JNJ-7836735 vaccinated N = 49,285	Optum, unvaccinated matched to JNJ-7836735 N = 49,285	CVS Health, JNJ-7836735 vaccinated N = 149,813	CVS Health, unvaccinated matched to JNJ-7836735 N = 149,813
Age, years				
Median (Q1, Q3)	44 (33, 54)	44 (33, 54)	44 (32, 54)	44 (32, 54)
Mean (SD)	42.91 (12.88)	42.89 (12.87)	42.98 (13.31)	42.97 (13.32)
Sex, n (%)				
Female	21,443 (43.51%)	21,443 (43.51%)	67,116 (44.80%)	67,116 (44.80%)
Male	27,842 (56.49%)	27,842 (56.49%)	82,697 (55.20%)	82,697 (55.20%)
Region, n (%)				
Midwest	22,568 (45.79%)	22,568 (45.79%)	28,431 (18.98%)	28,431 (18.98%)
Northeast	5,838 (11.85%)	5,838 (11.85%)	29,728 (19.84%)	29,728 (19.84%)
South	10,032 (20.36%)	10,032 (20.36%)	26,237 (17.51%)	26,237 (17.51%)
West	10,847 (22.01%)	10,847 (22.01%)	65,417 (43.67%)	65,417 (43.67%)
Pregnant at Time 0, n (%)[a]	72 (0.15%)	72 (0.15%)	274 (0.18%)	274 (0.18%)
Immunocompromised state	1,865 (3.78%)	1,865 (3.78%)	5,561 (3.71%)	5,561 (3.71%)

COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.
[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.
Source: Table C-3-Optum and Table C-3-CVS.

In each vaccine-specific cohort, propensity scores were estimated, and the distributions of propensity scores by treatment groups were plotted (Figure 4). The substantial overlap of propensity score distributions for all cohorts indicated a high degree of exchangeability between vaccinated and unvaccinated groups for all measured covariates.

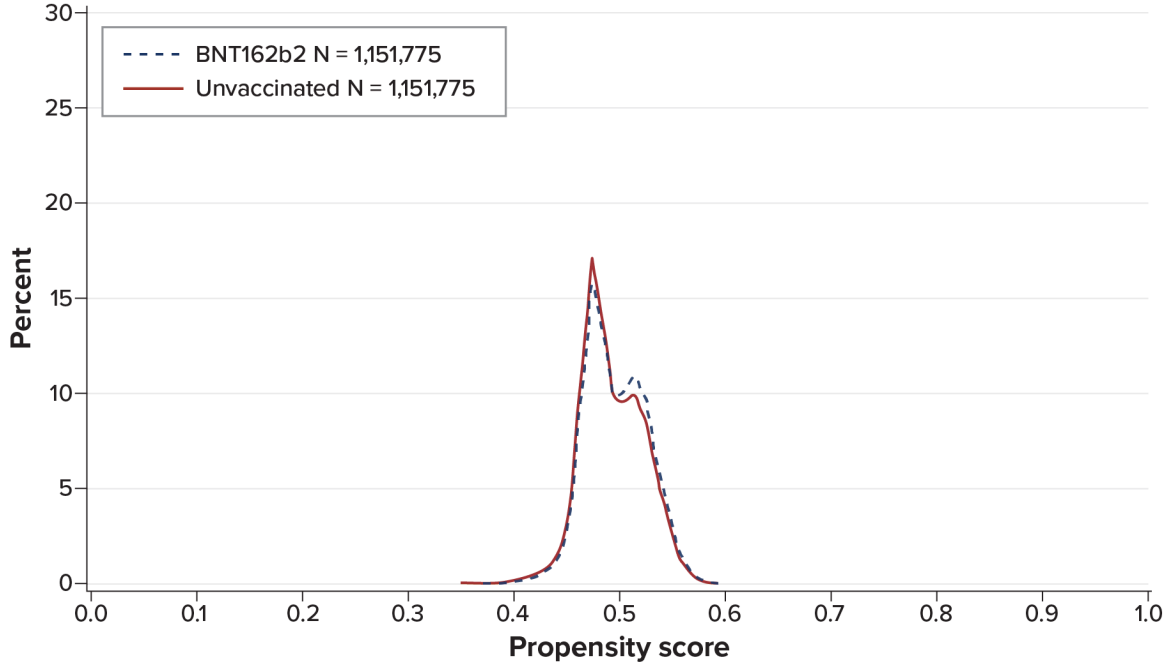
Figure 4. Propensity Score Distributions by COVID-19 Vaccine Exposure Group in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Adults

A. BNT162b2 vs. Unvaccinated Comparators, Optum



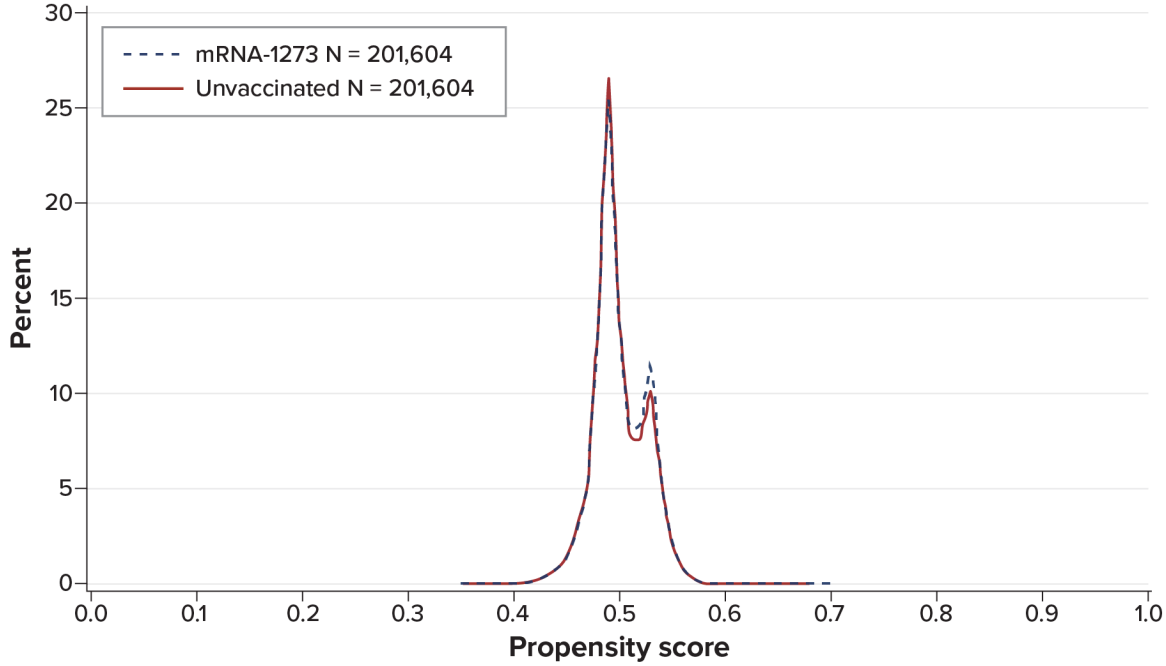
Note: Propensity score variables included the following: age at index date (linear); female sex indicator; state indicator (categorical with indicator variables); pregnant at Time 0; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); ED visits (categorical with indicator variables: 2+, 1, reference = 0); skilled nursing facility stay indicator; influenza vaccination indicator; pneumococcal vaccination indicator; encounter for cancer screening indicator; eye examination indicator; colonoscopy indicator; bone mineral density test indicator; well-check/well-child preventive healthcare visit indicator; arthritis indicator; lipid abnormality indicator; ambulance use or life support services indicator; weakness indicator; autoimmune disorders indicator; cancer indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; dementia or other neurological conditions indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; hypertension indicator; immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies) indicator; mental health conditions indicator; obese or severely obese indicator; sickle cell disease or thalassemia indicator; stroke or cerebrovascular disease indicator; tuberculosis indicator; at least 1 COVID-19 laboratory performed indicator; COVID-19 diagnosis in any setting indicator; Delta or Omicron variant era indicator; increased risk of COVID-19 indicator; interaction term of Delta/Omicron era indicator and COVID-19 laboratory test indicator.

B. BNT162b2 vs. Unvaccinated Comparators, CVS Health



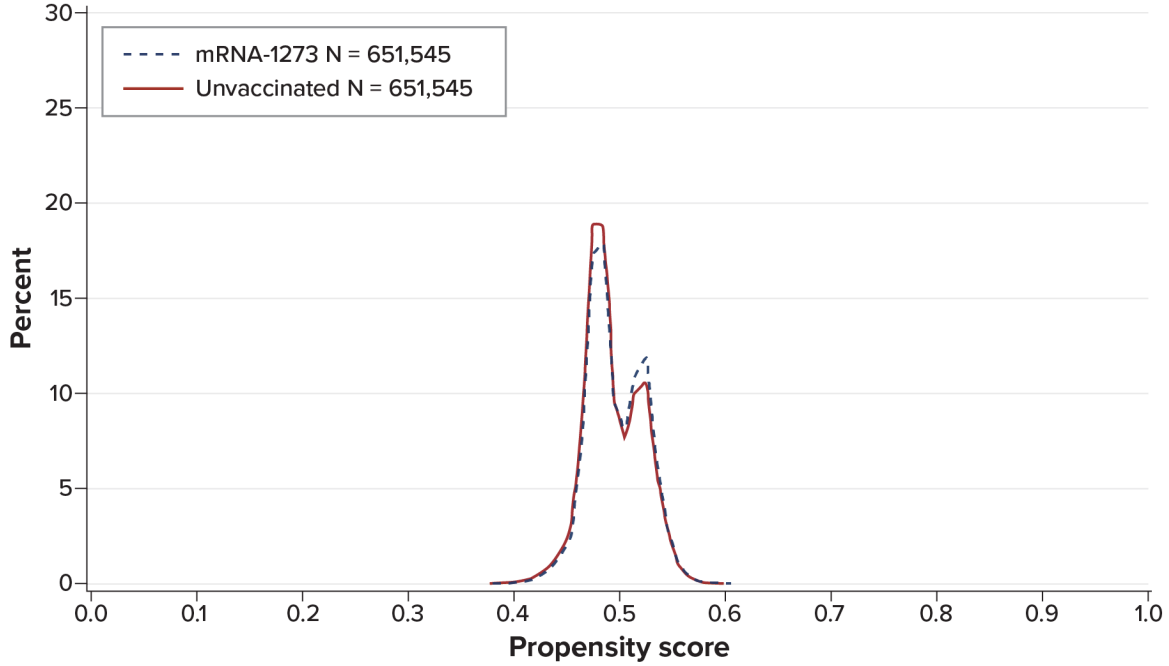
Note: Propensity score variables included the following: age (categorical with indicator variables: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years); ambulance use of life support services indicator; arthritis indicator; autoimmune disorders indicator; bone mineral density test indicator; cancer indicator; encounter for cancer screening indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; colonoscopy indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; county FIPS codes (categorical with indicator variables); pregnant at Time 0 indicator; COVID-19 diagnoses in any setting indicator; hospital/ED-diagnosed COVID-19 indicator; at least 1 COVID-19 laboratory performed indicator, COVID-19 diagnoses occurring outside of hospital or ED indicator; interaction term of COVID-19 vaccination after 31 May 2021 and 1 or more COVID-19 laboratory tests performed; COVID-19 vaccination index date in the Delta/Omicron era indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; ED visits (categorical with indicator variables: 2+, 1, reference = 0); eye examination indicator; influenza vaccination indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; overall binary indicator of the presence of any of these conditions will be defined to identify individuals who may qualify for priority groups for vaccination eligibility; hypertension indicator; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); lipid abnormality indicator; mental health conditions indicator; dementia or other neurological conditions indicator; obese or severely obese indicator; pneumococcal vaccination indicator; female indicator; male indicator; sickle cell disease or thalassemia indicator; skilled nursing facility stay indicator; IIS jurisdiction (categorical with indicator variables); stroke or cerebrovascular disease indicator; tuberculosis indicator; immunocompromised state indicator; pregnancy completion before Time 0 indicator; weakness indicator; well-check/well-child preventive healthcare visit indicator.

C. mRNA-1273 vs. Unvaccinated Comparators, Optum



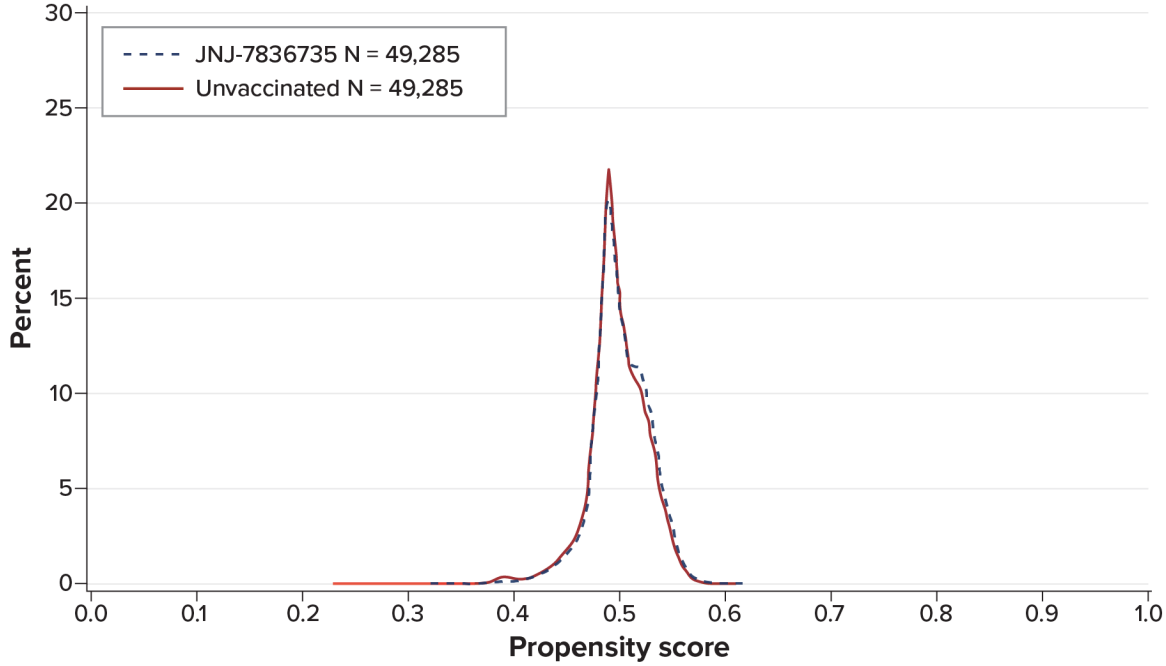
Note: Propensity score variables included the following: age at index date (linear); female sex indicator; state indicator (categorical with indicator variables); pregnant at Time 0; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); ED visits (categorical with indicator variables: 2+, 1, reference = 0); skilled nursing facility stay indicator; influenza vaccination indicator; pneumococcal vaccination indicator; encounter for cancer screening indicator; eye examination indicator; colonoscopy indicator; bone mineral density test indicator; well-check/well-child preventive healthcare visit indicator; arthritis indicator; lipid abnormality indicator; ambulance use or life support services indicator; weakness indicator; autoimmune disorders indicator; cancer indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; dementia or other neurological conditions indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; hypertension indicator; immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies) indicator; mental health conditions indicator; obese or severely obese indicator; sickle cell disease or thalassemia indicator; stroke or cerebrovascular disease indicator; tuberculosis indicator; at least 1 COVID-19 laboratory performed indicator; COVID-19 diagnosis in any setting indicator; Delta or Omicron variant era indicator; increased risk of COVID-19 indicator; interaction term of Delta/Omicron era indicator and COVID-19 laboratory test indicator.

D. mRNA-1273 vs. Unvaccinated Comparators, CVS Health



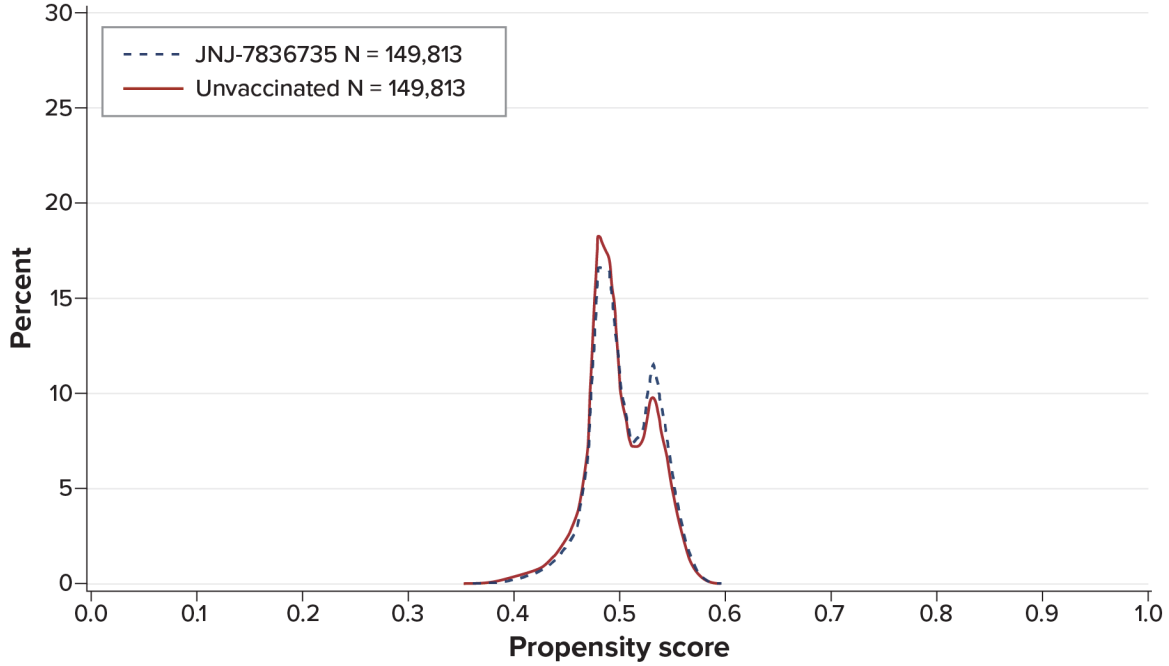
Note: Propensity score variables included the following: age (categorical with indicator variables: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years); ambulance use of life support services indicator; arthritis indicator; autoimmune disorders indicator; bone mineral density test indicator; cancer indicator; encounter for cancer screening indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; colonoscopy indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; county FIPS codes (categorical with indicator variables); pregnant at Time 0 indicator; COVID-19 diagnoses in any setting indicator; hospitalization or emergency department-diagnosed COVID-19 indicator; at least 1 COVID-19 laboratory performed indicator, COVID-19 diagnoses occurring outside of hospital or ED indicator; interaction term of COVID-19 vaccination after 31 May 2021 and 1 or more COVID-19 laboratory tests performed; COVID-19 vaccination index date in the Delta/Omicron era indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; ED visits (categorical with indicator variables: 2+, 1, reference = 0); eye examination indicator; influenza vaccination indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; overall binary indicator of the presence of any of these conditions will be defined to identify individuals who may qualify for priority groups for vaccination eligibility; hypertension indicator; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); lipid abnormality indicator; mental health conditions indicator; dementia or other neurological conditions indicator; obese or severely obese indicator; pneumococcal vaccination indicator; female indicator; male indicator; sickle cell disease or thalassemia indicator; skilled nursing facility stay indicator; IIS jurisdiction (categorical with indicator variables); stroke or cerebrovascular disease indicator; tuberculosis indicator; immunocompromised state indicator; pregnancy completion before Time 0 indicator; weakness indicator; well-check/well-child preventive healthcare visit indicator.

E. JNJ-7836735 vs. Unvaccinated Comparators, Optum



Note: Propensity score variables included the following: age at index date (linear); female sex indicator; state indicator (categorical with indicator variables); pregnant at Time 0; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); ED visits (categorical with indicator variables: 2+, 1, reference = 0); skilled nursing facility stay indicator; influenza vaccination indicator; pneumococcal vaccination indicator; encounter for cancer screening indicator; eye examination indicator; colonoscopy indicator; bone mineral density test indicator; well-check/well-child preventive healthcare visit indicator; arthritis indicator; lipid abnormality indicator; ambulance use or life support services indicator; weakness indicator; autoimmune disorders indicator; cancer indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; dementia or other neurological conditions indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; hypertension indicator; immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies) indicator; mental health conditions indicator; obese or severely obese indicator; sickle cell disease or thalassemia indicator; stroke or cerebrovascular disease indicator; tuberculosis indicator; at least 1 COVID-19 laboratory performed indicator; COVID-19 diagnosis in any setting indicator; Delta or Omicron variant era indicator; increased risk of COVID-19 indicator; interaction term of Delta/Omicron era indicator and COVID-19 laboratory test indicator.

F. JNJ-7836735 vs. Unvaccinated Comparators, CVS Health



Note: Propensity score variables included the following: age (categorical with indicator variables: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years); ambulance use of life support services indicator; arthritis indicator; autoimmune disorders indicator; bone mineral density test indicator; cancer indicator; encounter for cancer screening indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; colonoscopy indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; county FIPS codes (categorical with indicator variables); pregnant at Time 0 indicator; COVID-19 diagnoses in any setting indicator; hospitalization or emergency department-diagnosed COVID-19 indicator; at least 1 COVID-19 laboratory performed indicator, COVID-19 diagnoses occurring outside of hospital or ED indicator; interaction term of COVID-19 vaccination after 31 May 2021 and 1 or more COVID-19 laboratory tests performed; COVID-19 vaccination index date in the Delta/Omicron era indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; ED visits (categorical with indicator variables: 2+, 1, reference = 0); eye examination indicator; influenza vaccination indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; overall binary indicator of the presence of any of these conditions will be defined to identify individuals who may qualify for priority groups for vaccination eligibility; hypertension indicator; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); lipid abnormality indicator; mental health conditions indicator; dementia or other neurological conditions indicator; obese or severely obese indicator; pneumococcal vaccination indicator; female indicator; male indicator; sickle cell disease or thalassemia indicator; skilled nursing facility stay indicator; IIS jurisdiction (categorical with indicator variables); stroke or cerebrovascular disease indicator; tuberculosis indicator; immunocompromised state indicator; pregnancy completion before Time 0 indicator; weakness indicator; well-check/well-child preventive healthcare visit indicator.

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ED = emergency department; FIPS = Federal Information Processing System; IIS = immunization information system.

4.1.2 Outcome Analyses

Individuals were followed from the index date, and medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 events were identified during follow-up. The length of follow-up varied across vaccine brands and outcome analyses, but in Optum, the median length of follow-up ranged from 232 to 248 days for the vaccinated groups, and 85 to 114 days for the unvaccinated; in CVS Health, the median length of follow-up ranged from 244 to 258 days in the vaccinated groups, and from 102 to 129 days in the unvaccinated groups. In each vaccine comparison, there were longer follow-up times among the COVID-19 vaccinated group than among the unvaccinated comparison group (Table C-5-Optum, Table C-5-CVS). A large proportion of the unvaccinated group in each brand-specific cohort was censored relatively early after the index date as they received vaccination (Figure C-2-Optum; figure not

generated in CVS Health), with 25% of the unvaccinated group having follow-up of approximately 30 days or less (Table C-5-Optum, Table C-5-CVS). The majority of the vaccinated group ended follow-up much later (i.e., 200-300 days after index date) for receipt of boosters or end of the study period. However, for each exposure group in each comparison, there were millions of person-days of follow-up, and hundreds or thousands of COVID-19 outcome events (Table C-6-Optum, Table C-6-CVS).

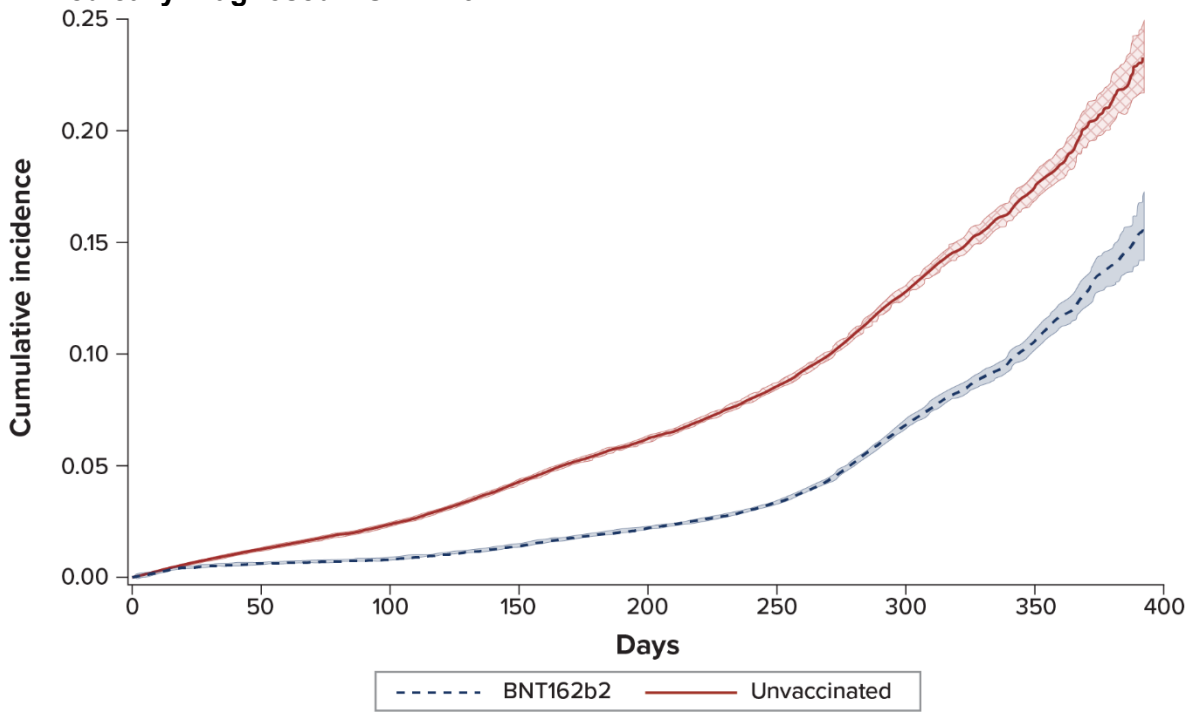
In each cohort, incidence of medically diagnosed COVID-19 was much higher than the incidence of hospital/ED-diagnosed COVID-19 (e.g., the Optum BNT162b2 vaccinated group had 11,399 medically diagnosed cases and 1,066 hospital/ED-diagnosed cases in nearly 70 million person-days of follow-up; in CVS Health, the BNT162b2 vaccinated group had 40,116 medically diagnosed cases and 4,496 hospital/ED-diagnosed cases in nearly 270 million person-days of follow-up).

The cumulative incidence of COVID-19 outcomes over time by vaccination status and vaccine brand is shown in Figure 5. Due to its introduction later in the study period, there is less available follow-up time for the JNJ-7836735 vaccine than the other available vaccine brands. For each COVID-19 vaccine comparison and outcomes, outcome rates were higher in the unvaccinated group. Generally, differences between the 2 groups were initially very small but then widened over time.

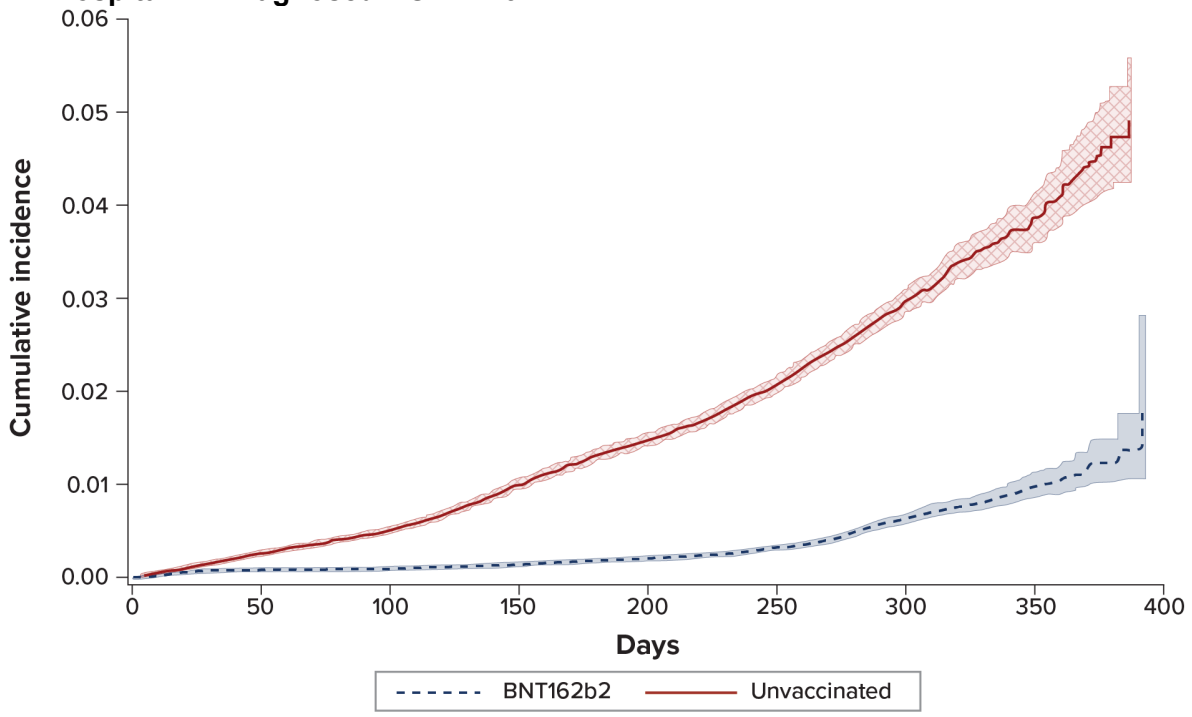
Figure 5. Inverse Probability of Treatment-Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Adults, by Vaccine Exposure Group

A. BNT162b2 vs. Unvaccinated Comparators, Optum

i. Medically Diagnosed COVID-19

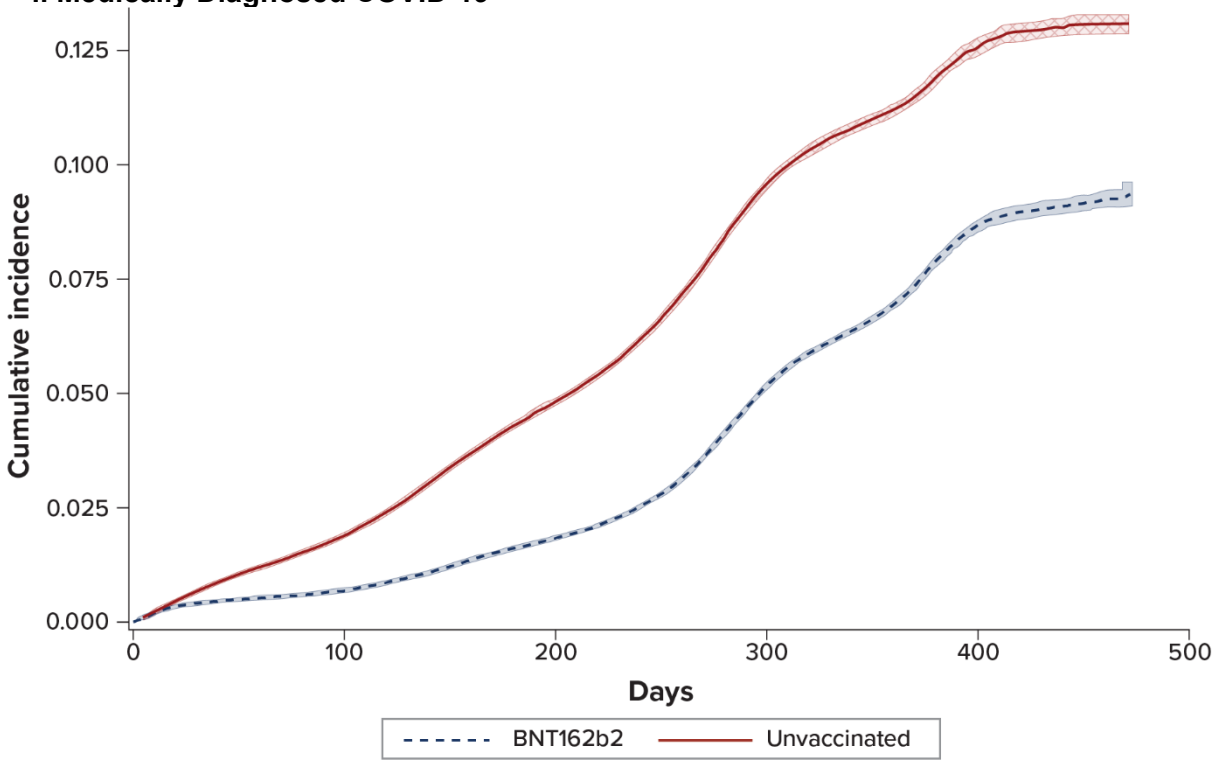


ii. Hospital/ED-Diagnosed COVID-19

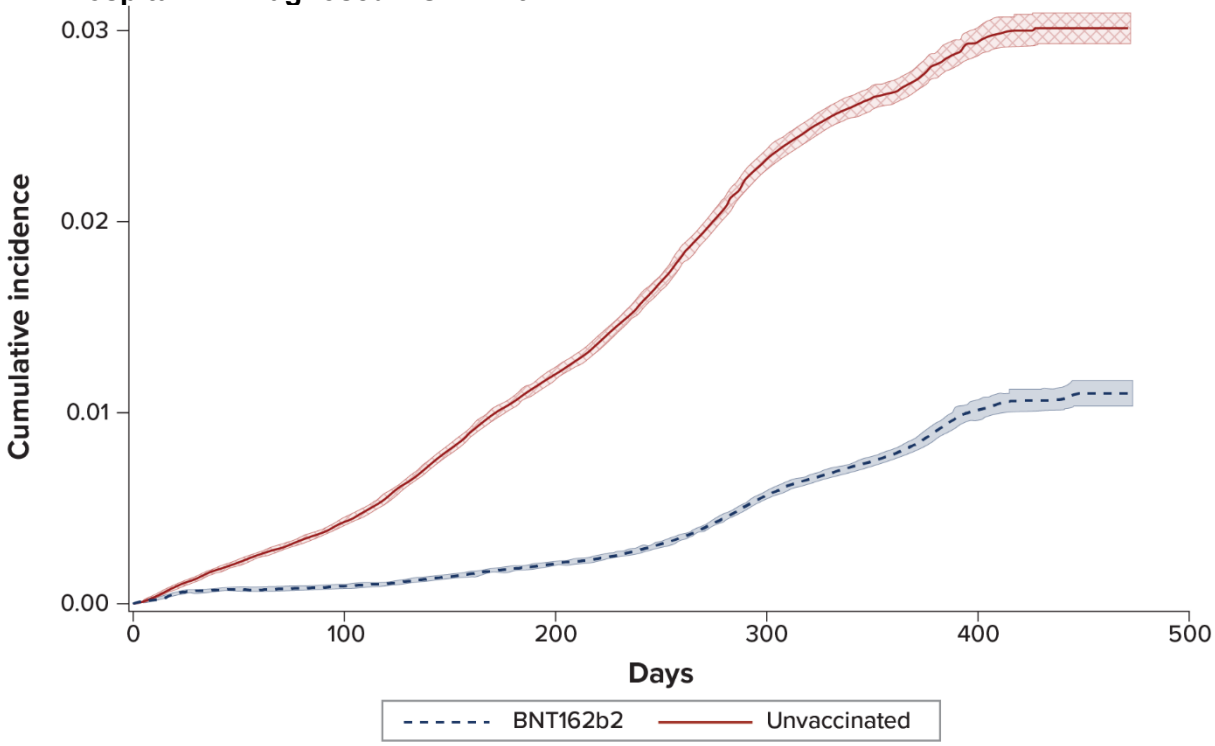


B. BNT162b2 vs. Unvaccinated Comparators, CVS Health

i. Medically Diagnosed COVID-19

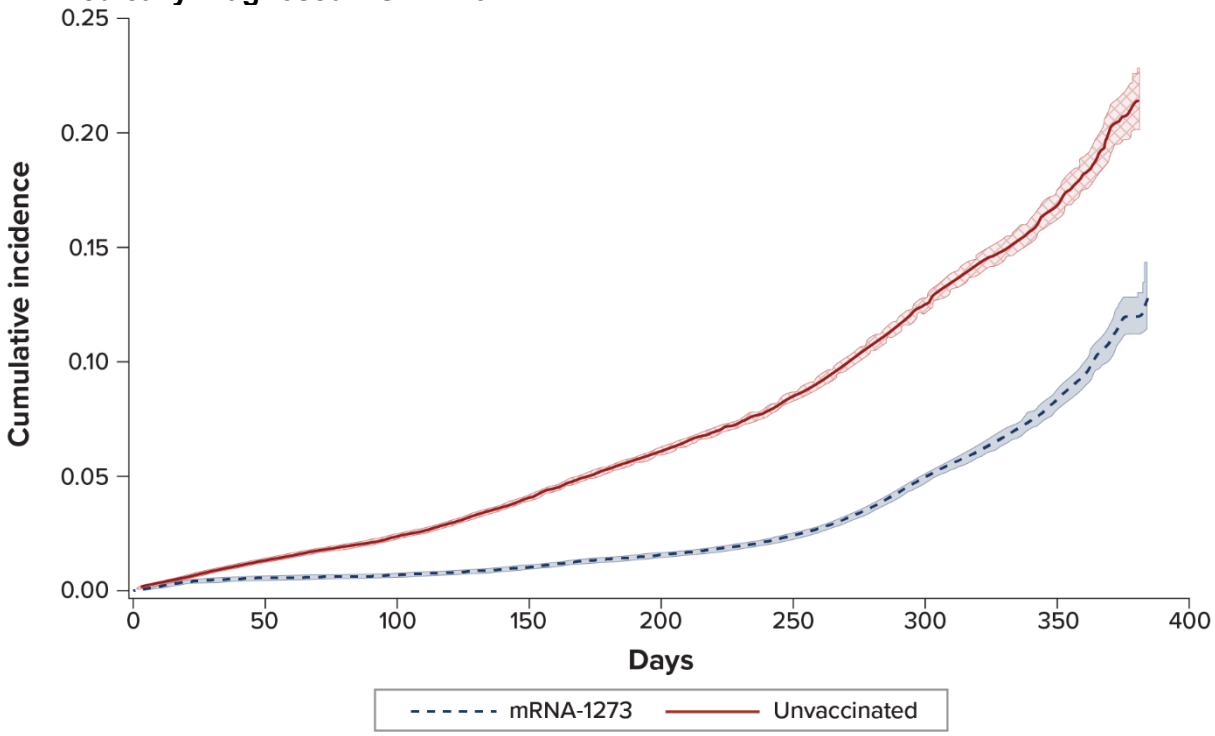


ii. Hospital/ED-Diagnosed COVID-19

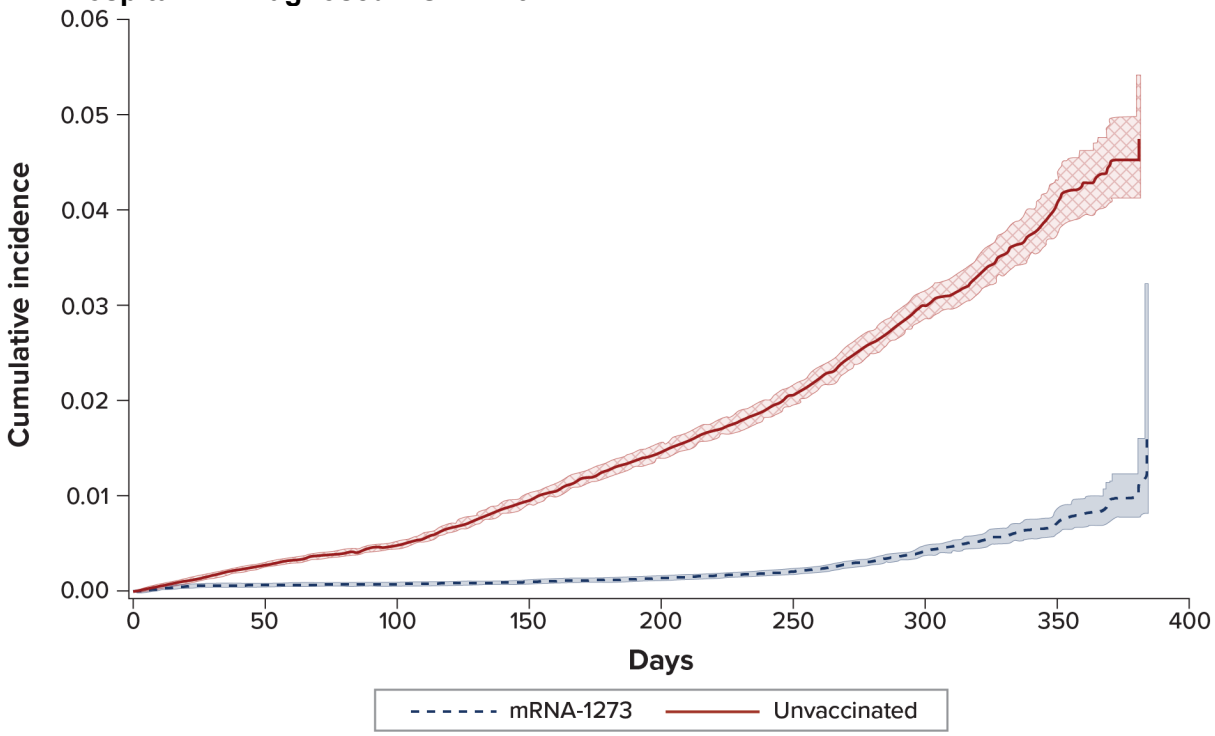


C. mRNA-1273 vs. Unvaccinated Comparators, Optum

i. Medically Diagnosed COVID-19

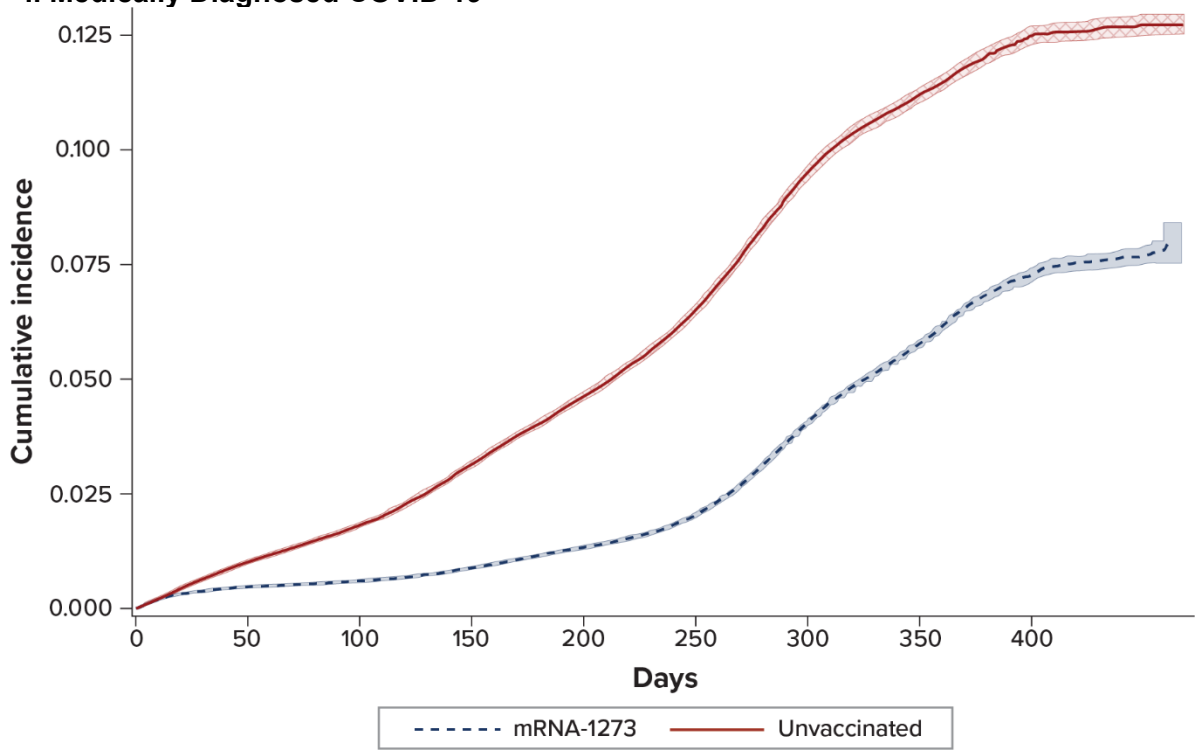


ii. Hospital/ED-Diagnosed COVID-19

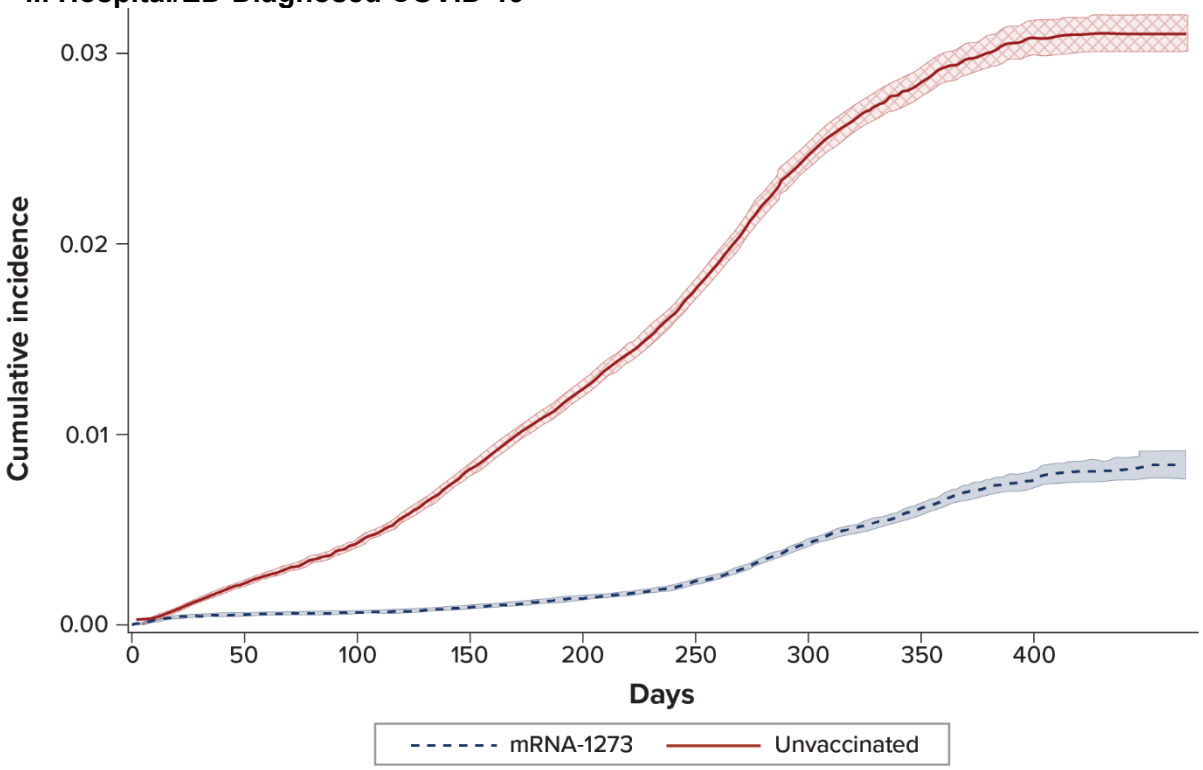


D. mRNA-1273 vs. Unvaccinated Comparators, CVS Health

i. Medically Diagnosed COVID-19

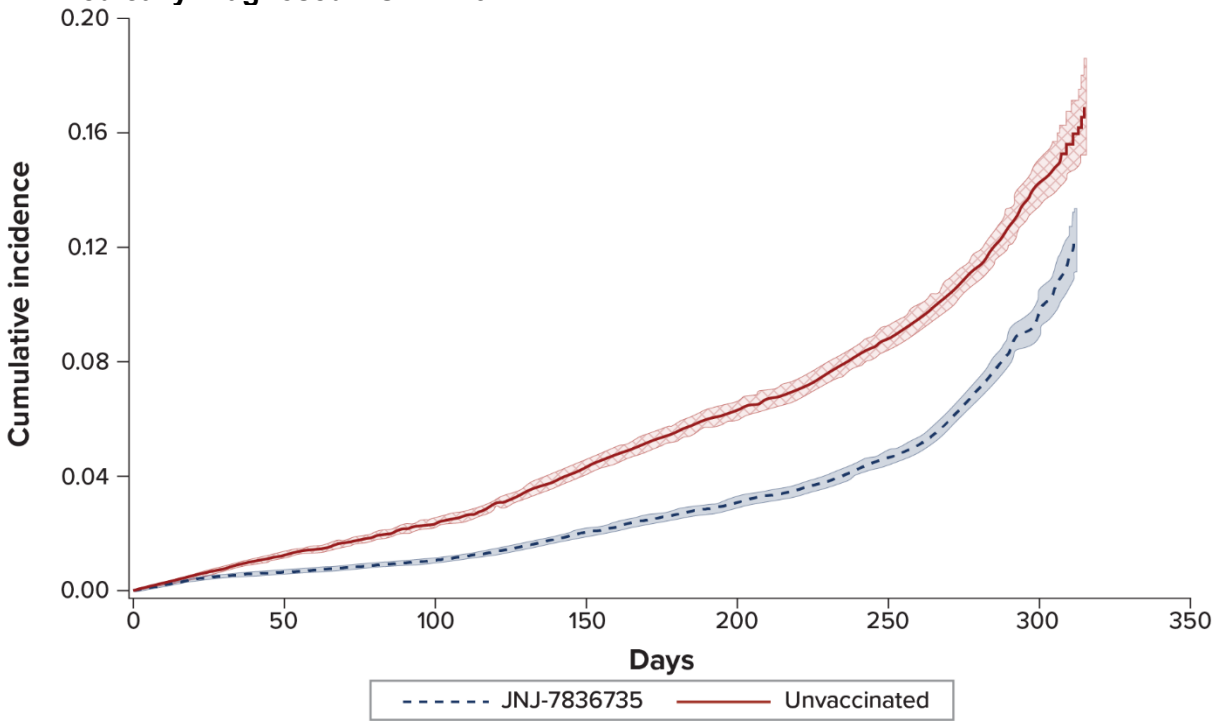


ii. Hospital/ED-Diagnosed COVID-19

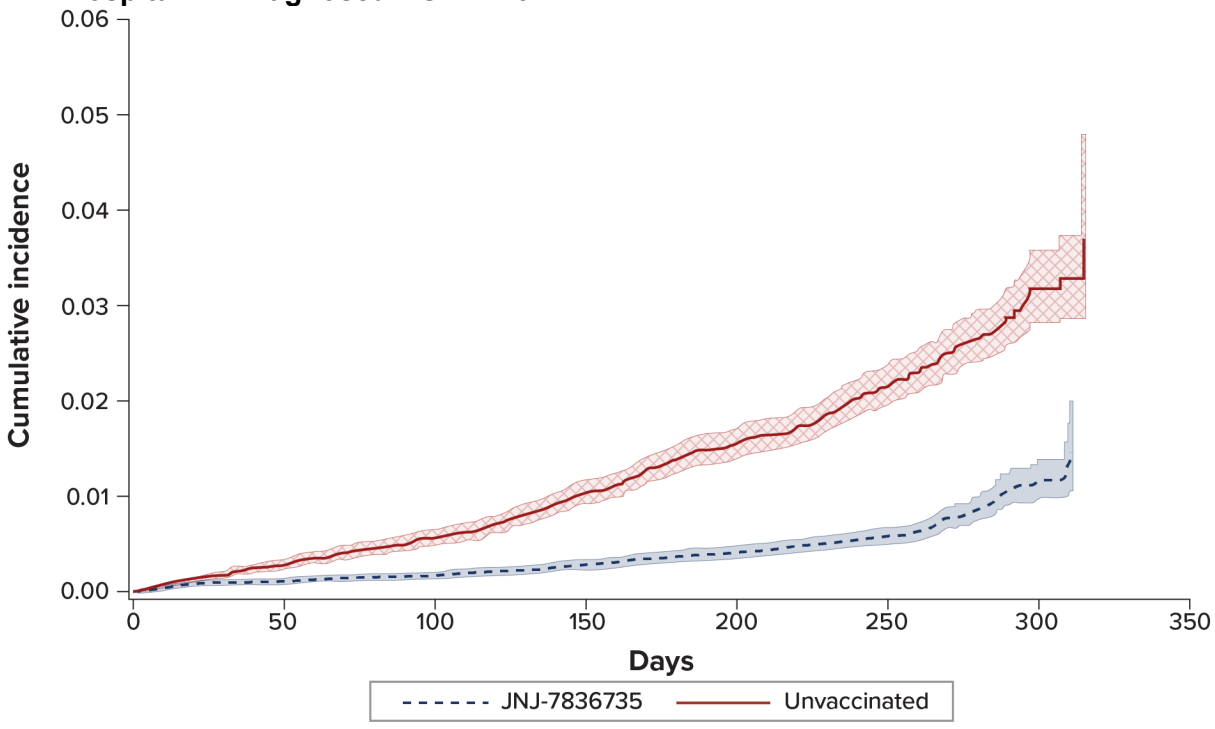


E. JNJ-7836735 vs. Unvaccinated Comparators, Optum

i. Medically Diagnosed COVID-19

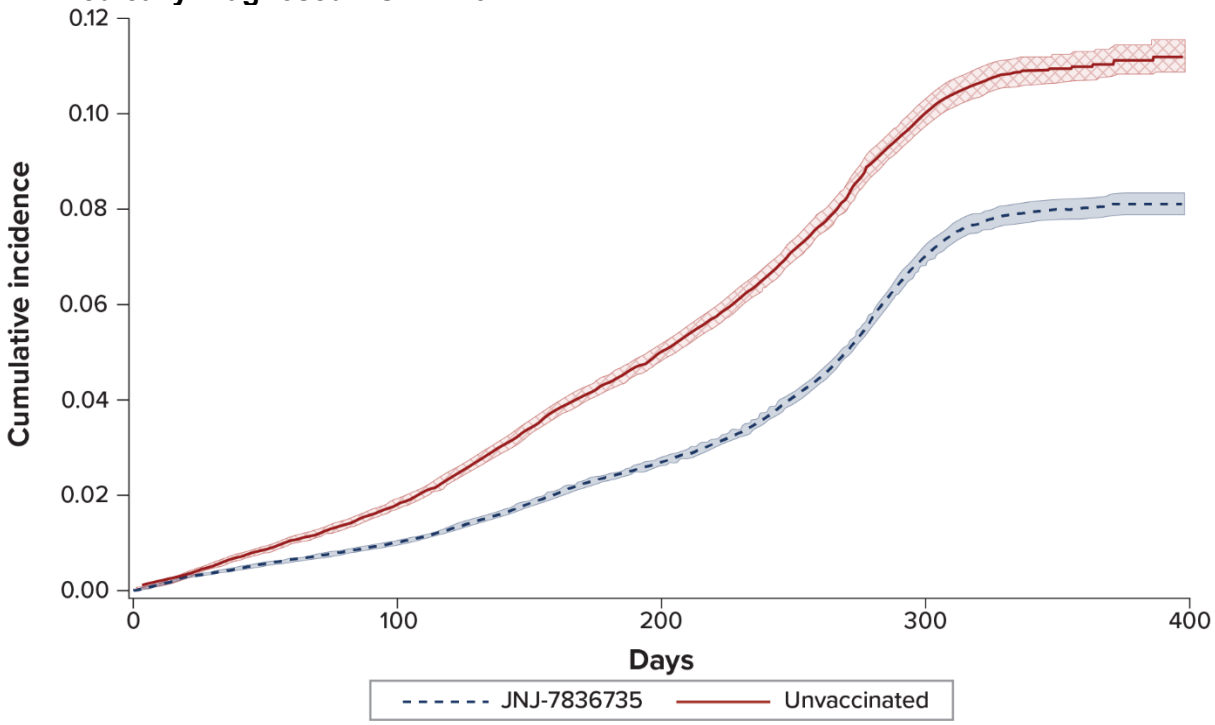


ii. Hospital/ED-Diagnosed COVID-19

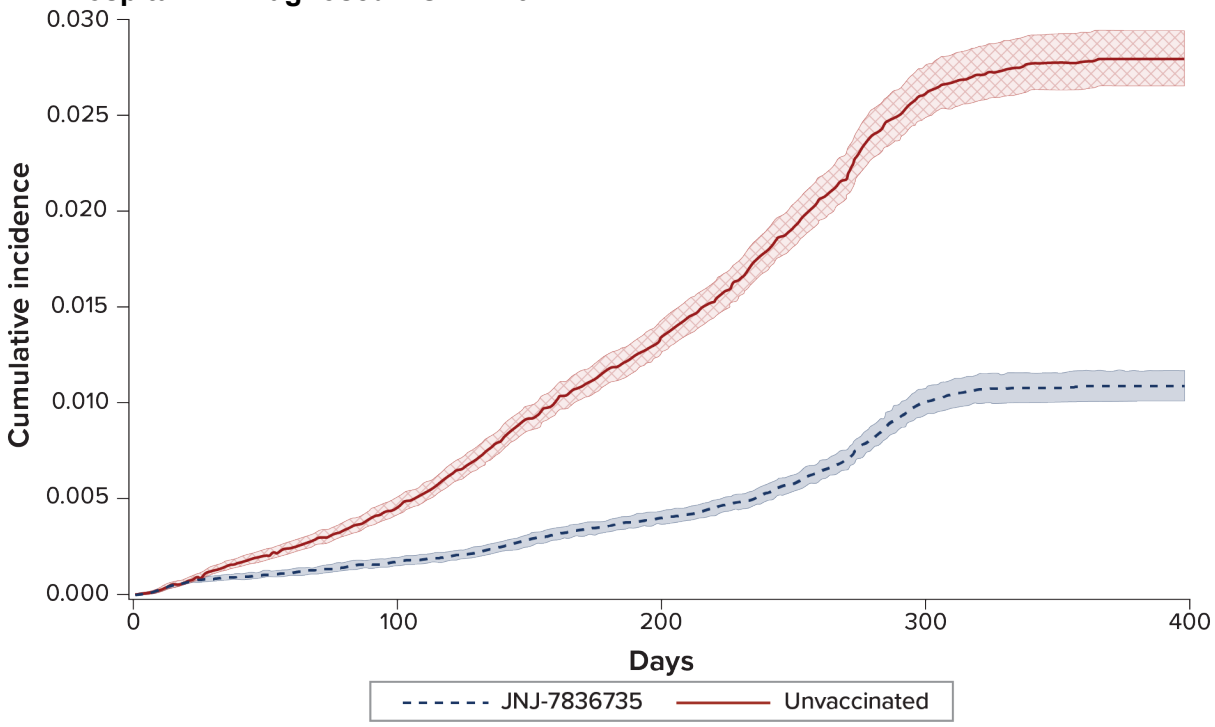


F. JNJ-7836735 vs. Unvaccinated Comparators, CVS Health

i. Medically Diagnosed COVID-19



ii. Hospital/ED-Diagnosed COVID-19

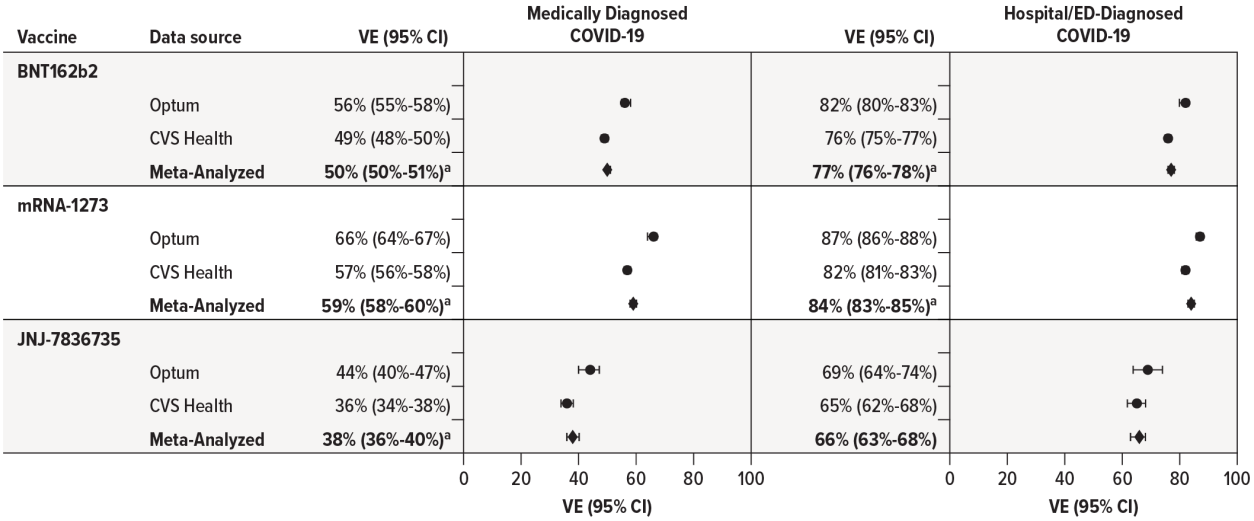


COVID-19 = coronavirus disease 2019; ED = emergency department.

4.1.2.1 Overall Vaccine Effectiveness

The sIPT-weighted HRs comparing COVID-19 risk across all available follow-up times were estimated for each vaccine, and overall VE estimates were calculated from the HRs. An overview of the data source–specific and summary estimates of the effectiveness of the COVID-19 vaccines are shown, by vaccine brand, in Figure 6, Table C-6-Optum, and Table C-6-CVS. Summary VE estimates from meta-analysis against medically diagnosed COVID-19 for receiving the complete primary series compared with being unvaccinated ranged from 38% to 59% (BNT162b2, 50% [95% CI, 50%-51%]; mRNA-1273, 59% [95% CI, 58%-60%]; JNJ-7836735, 38% [95% CI, 36%-40%]). Summary VE estimates against hospital/ED-diagnosed COVID-19 were higher, ranging from 66% to 84% (BNT162b2, 77% [95% CI, 76%-78%]; mRNA-1273, 84% [95% CI, 83%-85%]; JNJ-7836735, 66% [95% CI, 63%-68%]). For all outcomes and vaccine brands, Optum VE estimates were slightly higher than those in CVS Health. Statistical heterogeneity was observed in most summary estimates of overall VE due to the precision of the study estimates; however, given that the estimated magnitudes were clinically similar, summary VEs were reported for all estimates as summaries across both data sources.

Figure 6. Estimated Vaccine Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated Among Adults Aged 18-64 Years



CI = confidence interval; ED = emergency department; VE = vaccine effectiveness.
[a] *p* value for heterogeneity < 0.05.
Source: Table C-6-Optum, Table C-6-CVS.

4.1.2.1.1 Exposure Misclassification Quantitative Bias Analyses

Comparisons of the observed vaccination rates in the linked claims-IIS data to the reported vaccination rates from the CDC and state health departments and capture-recapture estimates[18] suggested that underreporting of receiving at least 1 COVID-19 vaccine dose may range from 17% to 29% in Optum (i.e., sensitivity of COVID-19 vaccine ascertainment of 83% to 71%) and 11% to 31% in CVS Health (i.e., sensitivities of 89% to 69%); thus, some of the observed unvaccinated individuals in our study may have truly been vaccinated. VE estimates corrected for potential ranges of misclassification were calculated (Table 7). In all cases, the corrected VE estimates were higher than the original estimates. Misclassification of truly vaccinated individuals as unvaccinated could lead to vaccinated person-time (with presumably lower outcome rates) being counted as unvaccinated time; thus, correcting for this misclassification would induce higher outcome rates in the comparator than observed. The results of QBA for potentially missing vaccine records suggest that the observed overall VE estimates may underestimate the true VE by 2% to 14%, depending on the analysis parameters and data source.

Table 7. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine, by Brand, Corrected for Potentially Missing Vaccine Records

COVID-19 Outcome	Vaccine exposure comparison vs. being unvaccinated	Primary analysis (uncorrected) VE (95% CI)	Corrected (high sensitivity estimate) VE (95% CI)	Corrected (low sensitivity estimate) VE (95% CI)
Optum		**sensitivity = 100%**	**sensitivity = 83%**	**sensitivity = 71%**
Medically diagnosed	BNT162b2	56% (55%-58%)	61% (60%-63%)	67% (66%-68%)
	mRNA-1273	66% (64%-67%)	70% (68%-71%)	75% (74%-76%)
	JNJ-7836735	44% (40%-47%)	49% (45%-52%)	56% (53%-58%)
Hospital/ED-diagnosed	BNT162b2	82% (80%-83%)	85% (83%-85%)	88% (86%-88%)
	mRNA-1273	87% (86%-88%)	89% (88%-90%)	91% (91%-92%)
	JNJ-7836735	69% (64%-74%)	73% (69%-77%)	78% (74%-81%)
CVS Health		**sensitivity = 100%**	**sensitivity = 89%**	**sensitivity = 69%**
Medically diagnosed	BNT162b2	49% (48%-50%)	52% (52%-53%)	63% (62%-64%)
	mRNA-1273	57% (56%-58%)	60% (59%-61%)	69% (69%-70%)
	JNJ-7836735	36% (34%-38%)	38% (36%-40%)	46% (44%-48%)
Hospital/ED-diagnosed	BNT162b2	76% (75%-77%)	78% (77%-79%)	84% (83%-85%)
	mRNA-1273	82% (81%-83%)	84% (83%-85%)	89% (88%-89%)
	JNJ-7836735	65% (62%-68%)	67% (64%-70%)	74% (72%-76%)

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

Note: Sensitivities represent the hypothesized proportion of truly vaccinated individuals with vaccine records identified in the data sources. Specificity was assumed to be 100% for all bias analyses shown.

Source: Table C-6-Optum, Table C-6-CVS

4.1.2.1.2 Outcome Misclassification Quantitative Bias Analyses

The potential effect of differential outcome misclassification was evaluated with a probabilistic QBA (Table 8). Compared with the primary analysis VE estimates, the VE estimates corrected for potential differential outcome misclassification were 4 to 16 percentage points higher.

Table 8. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Overall and Quantitative Bias Analysis Evaluating Potential Impact of Differential Outcome Misclassification

Data source	COVID-19 outcome	Vaccine exposure comparison vs. being unvaccinated	Primary analysis (uncorrected) VE (95% CI)	Outcome misclassification probabilistic QBA VE (95% CI)
Optum	Medically diagnosed	BNT162b2	56% (55%-58%)	67% (67%-69%)
		mRNA-1273	66% (64%-67%)	77% (76%-78%)
		JNJ-7836735	44% (40%-47%)	55% (51%-57%)
	Hospital/ED-diagnosed	BNT162b2	82% (80%-83%)	86% (85%-87%)
		mRNA-1273	87% (86%-88%)	91% (90%-92%)
		JNJ-7836735	69% (64%-74%)	73% (69%-77%)
CVS Health	Medically diagnosed	BNT162b2	49% (48%-50%)	65% (65%-66%)
		mRNA-1273	57% (56%-58%)	72% (72%-73%)
		JNJ-7836735	36% (34%-38%)	46% (44%-47%)
	Hospital/ED-diagnosed	BNT162b2	76% (75%-77%)	82% (81%-82%)
		mRNA-1273	82% (81%-83%)	89% (88%-90%)
		JNJ-7836735	65% (62%-68%)	69% (67%-72%)

CI = confidence interval; ED = emergency department; QBA = quantitative bias analysis; VE = vaccine effectiveness.

4.1.2.1.3 Negative Control Outcome Analyses

Cumulative incidence curves of COVID-19 outcomes in adults in the first 14 days following and including Time 0 are shown in Figure C-3-Optum and Figure C-3-CVS. HR estimates for the first 14 days following and including Time 0 are shown in Table C-7-Optum and Table C-7-CVS; RR and RD estimates considering the first 14 days after and including Time 0 are shown in Table C-12-Optum, Table C-13-Optum, Table C-14-Optum, Table C-12-CVS, Table C-13-CVS, and Table C-14-CVS.

The cumulative incidence curves for the negative control period demonstrate very low incidence rates during the first 14 days after index date in both exposure groups. However, some separation of the cumulative incidence curves during this period was noted (Figure C-3-Optum, Figure C-3-CVS). Although the absolute differences in risk were small between the vaccine exposure groups during this time—as indicated by day 14 RD estimates for both outcomes ranging from −0.0011 to 0.0001 (Table C-12-Optum, Table C-13-Optum, Table C-14-Optum, Table C-12-CVS, Table C-13-CVS, and Table C-14-CVS)—the HR estimates indicated a difference in COVID-19 incidence between the groups, with VE estimates ranging from −15% to 46% (Table C-7-Optum, Table C-7-CVS), indicating potential residual confounding or early outcome misclassification between exposure groups for some comparisons.

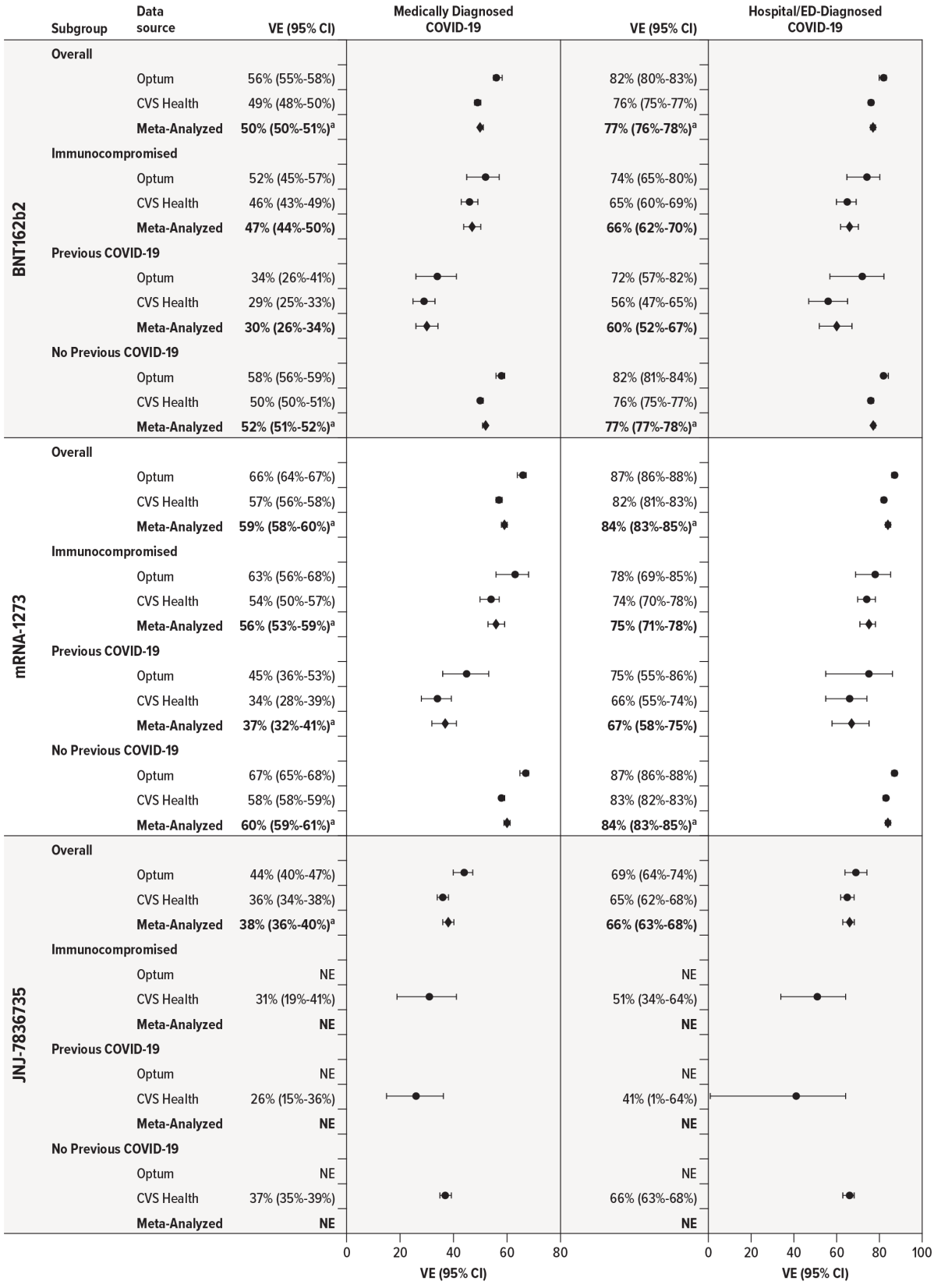
Although the differences were very small, the cumulative incidence of medically diagnosed COVID-19 on Time 0 (indicated as day 1, or the first day of follow-up, in the cumulative incidence plots) was lower or equivalent in the BNT162b2 groups than the unvaccinated groups, but was higher in the mRNA-1273 and JNJ-7836735 groups than the unvaccinated groups (Figure C-3-Optum, Figure C-3-CVS). Ad hoc analyses of vaccinated individuals in each brand with and without COVID-19 diagnoses on Time 0 (Table C-8-Optum, Table C-8-CVS) demonstrated that vaccinated individuals with a COVID-19 diagnosis on the day of vaccination were more likely to be vaccinated in physician/provider offices and generally less likely to be vaccinated in pharmacy or mass vaccination settings than those without a concurrent COVID-19 diagnosis. Additionally, those with a concurrent COVID-19 diagnosis were more likely to have previous COVID-19 laboratory tests and diagnoses. Overall, BNT162b2 was more likely to be administered outside of traditional healthcare settings (e.g., mass vaccination settings identified through IIS records only), thus potentially explaining why concurrent COVID-19 diagnoses were less likely with BNT162b2 than other COVID-19 vaccine brands.

4.1.2.1.4 Subgroup Analyses

The adult HR estimates by vaccine brand and by subgroup (i.e., immunocompromised status, history of COVID-19 before Time 0) are shown in Figure 7 (full details in Table C-9-Optum, Table C-9-CVS, Table C-10-Optum, Table C-10-CVS, Table C-11-Optum, and Table C-11-CVS). Subgroup analyses were not performed for JNJ-7836735 in Optum due to small samples sizes.

For both BNT162b2 and mRNA-1273 and for both COVID-19 outcomes, the precision of the HR estimates for the subgroups was much lower than that of the primary analysis due to the much smaller sample sizes. However, for both vaccine brands, there were notable differences across subgroups. For the immunocompromised group and the hospital/ED-diagnosed COVID-19 outcome, the summary VE estimate was highest for patients receiving mRNA-1273 (75%; 95% CI, 71%-78%), which was 9 percentage points higher than BNT162b2 (66%; 95% CI, 62%-70%). However, COVID-19 outcomes were more common in those who were immunocompromised than in the general sample (Table C-9-Optum, Table C-9-CVS). Among patients with documented prior COVID-19, summary VE estimates were smaller, with mRNA-1273 again having the highest VE (67%; 95% CI, 58%-75%), followed by BNT162b2 (60%; 95% CI, 52%-67%). Finally, among those with no previous history of COVID-19, summary VE estimates were again highest in mRNA-1273 (84%; 95% CI, 83%-85%), which was 7 percentage points higher than BNT162b2 (77%; 95% CI, 77%-78%). For medically diagnosed COVID-19, the same pattern was observed, but VE estimates were smaller for all subgroups, with the highest VE observed among patients with no history of COVID-19 diagnosis who received mRNA-1273 compared with unvaccinated persons with no history of COVID-19 diagnosis.

Figure 7. Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccines, Compared With Being Unvaccinated, Inverse Probability of Treatment-Weighted Vaccine Exposure Groups, Overall and Within Subgroups in Adults Aged 18-64 Years

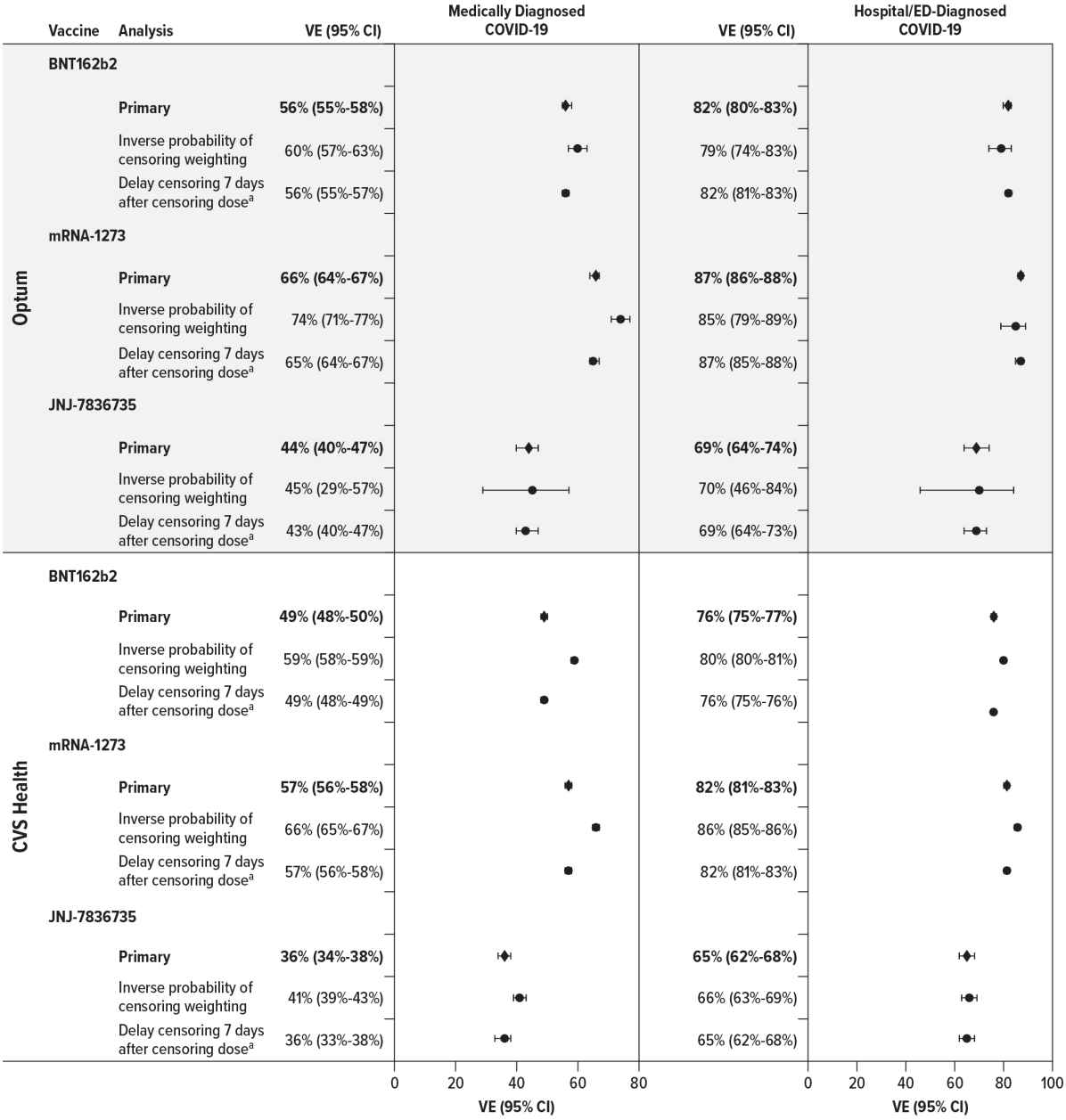


CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; NE = not estimable; VE = vaccine effectiveness.
[a] *p* value for heterogeneity < 0.05.
Source: Table C-9-Optum, Table C-9-CVS, Table C-10-Optum, Table C-10-CVS, Table C-11-Optum, and Table C-11-CVS.

4.1.2.1.5 Sensitivity Analyses

The results of the sensitivity analyses compared with those for the overall analysis for each vaccine are shown in Figure 8. Sensitivity analyses were generally consistent with the primary analyses, but the IPC-weighted analyses resulted in higher VE estimates for the medically diagnosed COVID-19 outcome.

Figure 8. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccines, Compared With Being Unvaccinated, in Adults Aged 18-64 Years, Primary Analyses and Sensitivity Analyses



CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.
[a] Censoring doses consisted of individuals in the unvaccinated group receiving any vaccine, or individuals in the vaccinated group receiving Dose 2 too early, Dose 2 of a different brand, or receiving a third dose.

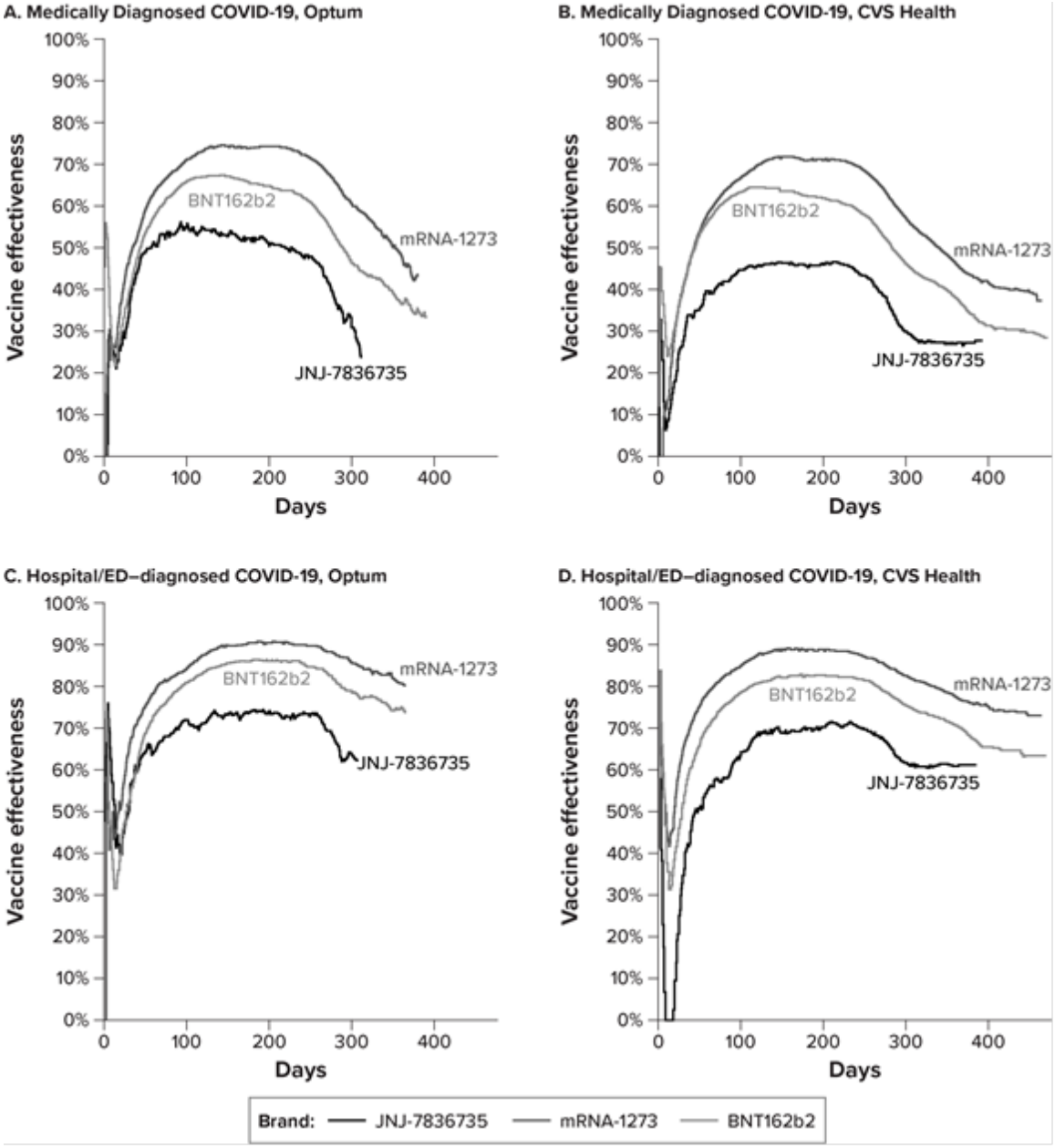
4.1.2.2 Vaccine Effectiveness Over Time

4.1.2.2.1 Vaccine Effectiveness by Time Since Vaccination

To evaluate potential changing VE over time for the primary vaccinated versus unvaccinated comparison, the cumulative incidence of COVID-19 outcomes over time by vaccination status and vaccine brand was plotted (Figure 5). For all vaccine brands, outcomes, and data sources, the incidence of COVID-19 outcomes was higher in the unvaccinated group throughout follow-up. Because of its introduction later in the study period, there was less available follow-up time for the JNJ-7836735 vaccine than the other available vaccine brands (Table C-5-Optum, Table C-5-CVS).

Daily RRs, RDs, and VE measurements throughout follow-up were estimated, and the VEs were plotted over time (Figure 9). Complete details of RRs and RDs at prespecified points during follow-up are shown in Table C-12-Optum, Table C-13-Optum, Table C-14-Optum, Table C-12-CVS, Table C-13-CVS, and Table C-14-CVS. Daily VE estimates fluctuated widely during the first few days after Time 0 (as the early time periods have the smallest number of events, and estimates were highly subject to small changes in the daily numbers of cases), and negative control outcome analyses of the first 14 days revealed some small differences between vaccinated and unvaccinated groups, mainly in the first few days immediately after vaccination (Section 4.1.2.1.3). Following the initial few days after vaccination, all vaccines followed similar patterns: for medically diagnosed COVID-19, VE estimates increased over time until approximately 90 days and were sustained through at least day 183, and there is evidence of waning afterward by day 270. For hospital/ED-diagnosed COVID-19, the pattern was very similar, but the VE estimates were higher throughout and a smaller degree of waning was observed by day 270 (Figure 9, Table C-12-Optum, Table C-13-Optum, Table C-14-Optum, Table C-12-CVS, Table C-13-CVS, Table C-14-CVS). Despite evidence of waning of the VE estimate, absolute RD estimates showed increasing reductions in numbers of cases through at least day 270 after vaccination (Table C-12-Optum, Table C-13-Optum, Table C-14-Optum, Table C-12-CVS, Table C-13-CVS, Table C-14-CVS).

Figure 9. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccines, Compared With Being Unvaccinated, by Vaccine Brand Among Adults Aged 18-64 Years

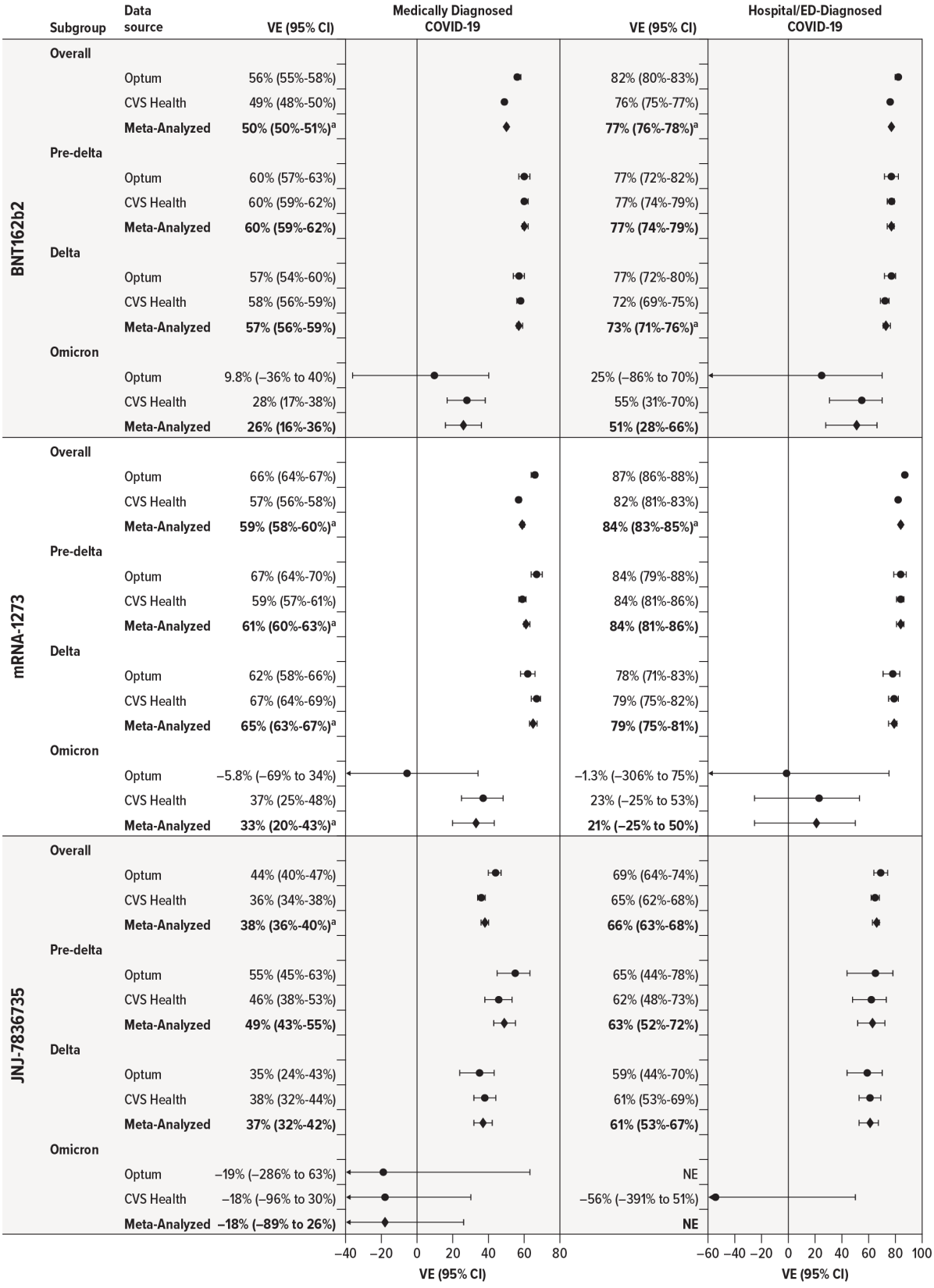


COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.

4.1.2.2.2 Vaccine Effectiveness by Variant-Specific Era

A summary of VE estimates by vaccine brand and variant-specific era by data source and from meta-analyses across data source are shown in Figure 10 (complete details shown in Table C-13-Optum and Table C-13-CVS). Cumulative incidence of COVID-19 outcomes over time since vaccination within SARS-CoV-2 variant eras are shown in Figure C-4-Optum and Figure C-4-CVS.

Figure 10. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, by SARS-CoV-2 Variant Era



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

[a] *p* value for heterogeneity < 0.05.
Source: Table C-15-Optum, Table C-15-CVS.

Due to the timing of the SARS-CoV-2 variant eras and the varying dates of introduction of the primary series of each vaccine, the largest amount of accumulated person-time for all vaccine brands occurred during the pre-Delta period (because fewer individuals received their primary series during the Delta or Omicron eras). The Delta era was the longest era in the study period, and due to end of the study period, much less follow-up time was available for the Omicron era (e.g., fewer than 20 days of follow-up in Optum occurred during the Omicron era). VE against both COVID-19 outcomes generally declined between the pre-Delta and Omicron eras. For hospital/ED-diagnosed COVID-19, modest changes in VE were observed between the pre-Delta and Delta eras; the summary VE of JNJ-7836735 declined by 2 percentage points, followed by BNT162b2 with a 4–percentage point decline and mRNA-1273 with a decline of 5 percentage points. Much larger decreases in VE were observed between the Delta and Omicron eras; the summary VE of mRNA-1273 declined by 58 percentage points, followed by BNT162b2 with a 22–percentage point decline (meta-analysis of JNJ-7836735 was not possible due to small sample sizes). Due to the limited follow-up and small sample sizes in the Omicron era, estimates may not be indicative of the true VE for that era. For medically diagnosed COVID-19, a similar pattern was observed, and VE estimates for all vaccine brands against medically diagnosed COVID-19 in the Omicron era were reduced.

4.2 Secondary Comparative Effectiveness Analysis

4.2.1 Descriptive Analyses

The vaccinated groups from the brand-specific analytic cohorts used in the primary analyses were used to create pairs of matched vaccinated groups. Pairs of vaccine-specific vaccinated groups were matched with one another within calendar time periods and age groups where both vaccine brands were authorized, resulting in Optum in 142,771 matched pairs for mRNA-1273 versus BNT162b2, 40,012 matched pairs for JNJ-7836735 versus BNT162b2, and 33,274 matched pairs for JNJ-7836735 versus mRNA-1273. In CVS Health, there were 515,403 matched pairs for mRNA-1273 versus BNT162b2, 131,597 matched pairs for JNJ-7836735 versus BNT162b2, and 117,170 matched pairs for JNJ-7836735 versus mRNA-1273. Complete characteristics of each brand-specific comparison are shown in Table C-16-Optum, Table C-16-CVS, Table C-17-Optum, Table C-17-CVS, Table C-18-Optum, and Table C-18-CVS. For each of the pairwise comparisons in both data sources, individual characteristics were very well-balanced between vaccination groups. Plots of the propensity score distributions by vaccine brand received indicate very good overlap for all comparisons (Figure C-1-Optum, Figure C-5-CVS).

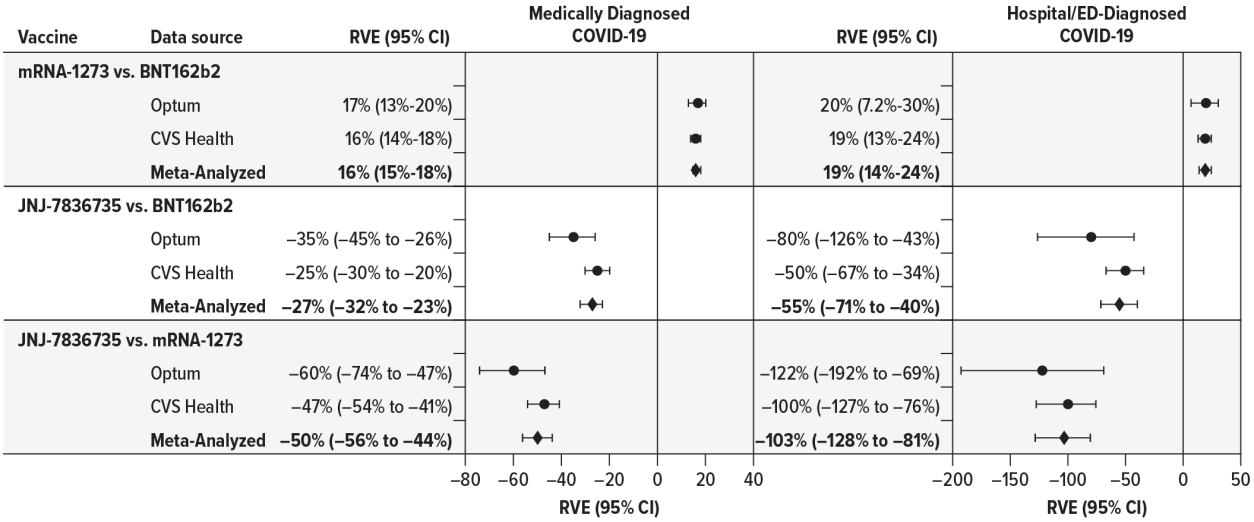
4.2.2 Outcome Analyses

4.2.2.1 Overall Comparative Effectiveness Analyses

The cumulative incidence of COVID-19 outcomes over time by vaccine brand within each brand-specific pair is shown in Figure C-6-Optum and Figure C-6-CVS. The cumulative incidence curves for each comparison in both data sources generally showed similar patterns, with minimal differences observed over the first 50 to 100 days, and then separation of the curves afterward.

Estimates of the RVE for each pairwise comparison are shown in Figure 11 (full details are shown in Table C-19-Optum and Table C-19-CVS); note that because RVE are comparisons of one brand to another, a negative RVE estimate indicates that the reference brand was more effective than exposure brand, not that the vaccines were ineffective. When estimating the overall RVE for each vaccine brand during time periods when both brands were available, the summary VE estimates for mRNA-1273 demonstrated 16% (95% CI, 15%-18%) to 19% (95% CI, 14%-24%) higher effectiveness than BNT162b2 for medically diagnosed and hospital/ED-diagnosed COVID 19, respectively. The RVE of the 1-dose JNJ-7836735 series was lower than both of the 2-dose mRNA vaccine brands for both outcomes.

Figure 11. Estimated Relative Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Receiving a Complete Primary Series of a Different COVID-19 Vaccine in Adults Aged 18-64 Years



CI = confidence interval; ED = emergency department; RVE = relative vaccine effectiveness.
[a] *p* value for heterogeneity < 0.05.
Source: Table C-19-Optum, Table C-19-CVS.

4.2.2.2 Negative Control Analyses

Cumulative incidence curves of COVID-19 outcomes in adults in the matched comparisons during the first 14 days following and including Time 0 are shown in Figure C-7-Optum and Figure C-7-CVS. RVE estimates considering the first 14 days after and including the Time 0 are shown in Table C-20-Optum and Table C-20-CVS. There were some small differences between vaccine brands, mainly in the first few days immediately after vaccination for medically diagnosed COVID-19. In both data sources, mRNA-1273 and JNJ-7836735 had more medically diagnosed COVID-19 cases on Time 0 than BNT162b2 (Table C-8-Optum, Table C-8-CVS), resulting in early separation of the cumulative incidence curves that generally converged by the end of the negative control periods (similar to the results seen for the primary overall vaccinated versus unvaccinated comparisons). No meaningful differences in hospital/ED-diagnosed COVID-19 during the negative control periods were observed between brands.

4.3 Secondary Single-Dose Analysis

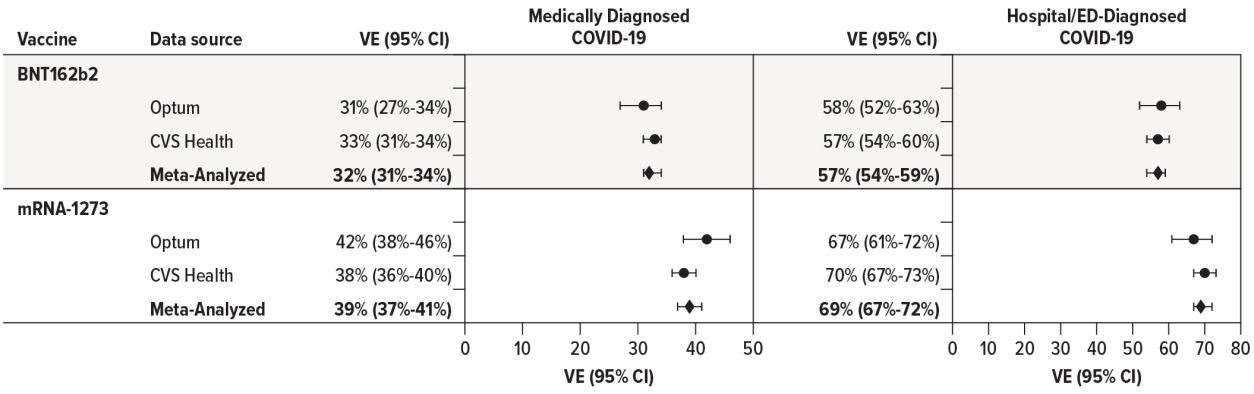
4.3.1 Descriptive Analyses

The individuals included in the analyses of receiving only a single dose of a 2-dose series were all those receiving a first dose of the COVID-19 vaccines of interest and the matched unvaccinated individuals—the same as those included in the matched overall vaccinated versus unvaccinated analyses. Only the censoring rules differ between the analysis of the complete primary series and the analysis of receiving only a single dose of a 2-dose series. Therefore, the characteristics of the individuals for these analyses are the same as those for the primary analyses (Table C-1-Optum and Table C-1-CVS for BNT162b2; Table C-2-Optum and Table C-2-CVS for mRNA-1273).

4.3.2 Outcome Analyses

The cumulative incidence of COVID-19 outcomes over time by vaccination status and vaccine brand is shown in Figure C-8-Optum and Figure C-8-CVS. There was separation in the cumulative incidence curves in the vaccinated and unvaccinated groups, but the difference between curves was much smaller for the medically diagnosed outcome than for the hospital/ED-diagnosed outcome. Estimates of the effectiveness of receiving only a single dose of a multidose primary series are shown, by vaccine brand, in Figure 12 (complete details are shown in Table C-21-Optum and Table C-21-CVS). While still demonstrating some overall effectiveness, the VE estimates for a single dose were much lower compared with the estimates for receiving the complete primary series (Section 4.1.2.1). For medically diagnosed COVID-19, the difference between the VE estimates for a single dose and the 2-dose series was as much as 25 percentage points (BNT162b2, Optum); for the hospital/ED-diagnosed, the difference was as much as 24 percentage points (BNT162b2, Optum).

Figure 12. Estimated Effectiveness of Receiving a Single Dose of a 2-Dose Primary Series of COVID-19 Vaccine, Compared with Being Unvaccinated, Among Adults Aged 18-64 Years



COVD-19 = coronavirus disease 2019; CI = confidence interval; ED = emergency department; VE = vaccine effectiveness.
Source: Table C-21-Optum and Table C-21-CVS.

5 Discussion and Conclusions

5.1 Overview of Results

This large, real-world evaluation of the effectiveness of receiving a complete primary series of COVID-19 vaccination in adults aged 18 to 64 showed reasonably strong VE against medically diagnosed COVID-19

and hospital/ED-diagnosed COVID-19 associated with receiving a complete primary series of any COVID-19 vaccine brand compared with being unvaccinated. The vaccines' effectiveness was generally sustained for at least 9 months against hospital/ED-diagnosed COVID-19 and for approximately 6 months against any medically diagnosed COVID-19. The observed VE estimates were generally higher for hospital/ED-diagnosed COVID-19 than for any medically diagnosed COVID-19 and were highest in adults receiving the mRNA-1273 vaccine across all analyses in both data sources. Summary estimates of VE from meta-analysis for medically diagnosed COVID-19 among patients who received the complete primary series compared to being unvaccinated ranged from 38% for JNJ-7836735 to 59% for mRNA-1273. For hospital/ED-diagnosed COVID-19, summary VE estimates ranged from 66% for JNJ-7836735 to 84% for mRNA-1273. Results from both data sources suggested lower VE in adults receiving the JNJ-7836735 vaccine.

When evaluating VE by SARS-CoV-2 variant era, VE was lower in the Omicron era than in the Delta or pre-Delta eras for all vaccine brands and both outcomes, although sample sizes were too small for the hospital/ED-diagnosed COVID-19 results to be meaningful. Although waning of the VE for the primary series and lower VE in later variant eras was observed, subsequent public health recommendations for booster dosing have also been demonstrated to be effective,[16] and updated vaccines targeting newer viral variants have subsequently been authorized or approved.[22,23]

Effectiveness of the 3 vaccine brands was compared in subgroups, including (a) immunocompromised persons, (b) those with a previous diagnosis of COVID-19, and (c) those with no previous history of a COVID-19 diagnosis. The VE estimates of COVID-19 outcomes were slightly attenuated for the immunocompromised. Although the VE estimate (a relative measure of effect) was reduced in the immunocompromised individuals, the higher incidence of COVID-19 diagnoses means that more modest relative reductions in COVID-19 could translate to meaningful decreases in the overall burden of COVID-19. Additionally, VE estimates were lower among those with a previous diagnosis of COVID-19 compared to those with no previous history of a COVID-19 diagnosis. If natural infection conferred absolute immunity against subsequent medically diagnosed and hospital/ED-diagnosed COVID-19, we would expect there to be no additional benefits from vaccination. However, we observed that vaccination provided additional protection against both medically diagnosed and hospital/ED-diagnosed COVID-19 compared to having only a prior COVID-19 diagnosis, indicating vaccination continued to have benefits, particularly for severe outcomes, among those who had a previous COVID-19 diagnosis.

The effectiveness of the 3 vaccine brands was estimated comparing the VE of each brand to the other brands. In alignment with other results, the RVE of mRNA-1273 was highest, with an RVE of 16% (95% CI, 15%-18%) over BNT162b2 for medically diagnosed COVID-19, and 19% (95% CI, 14%-24%) for hospital/ED-diagnosed COVID-19. The RVE of the 1-dose JNJ-7836735 series was lower than both of the 2-dose mRNA vaccine brands for both outcomes.

To evaluate for the presence of unmeasured confounding, in which treated patients differ from untreated patients on unobserved factors, a negative control analysis was performed. During the 14-day period after receipt of the vaccination, cumulative incidence curves for mRNA-1273 and BNT162b2 did display a small protective signal for receipt of vaccination compared to being unvaccinated, suggesting

that residual confounding or misclassification may be present. Previous studies have also suggested that differences in laboratory testing immediately after vaccination may account for observed differences between vaccinated and unvaccinated groups in the negative control period.[17,64]

5.2 Contextualizing Literature

The efficacy and effectiveness of the 3 COVID-19 vaccine brands available in the US has been the subject of a large volume of research over the past several years. Clinical trial data has indicated that the COVID-19 vaccines are safe, with the incidence of adverse events remaining very low.[65] In clinical trials, 2 doses of the BNT162b2 vaccine showed 91.3% efficacy against symptomatic COVID-19 and 96.7% efficacy against severe disease.[65] But real-world estimates of the vaccines' effectiveness have varied significantly depending on geography, severity of disease, and the variant in circulation at the time of data collection.[65] One review that examined multiple RCTs found that the BNT162b2 and mRNA-1273 vaccines reduced the incidence of symptomatic COVID-19; BNT162b2 had 97.8% efficacy (95% CI, 44.3%-99.9%), and mRNA-1273 had 93.2% efficacy (95% CI, 91.1%-94.8%).[66] However, this review only had data for 2 RCTs per vaccine brand, with a total patient sample of less than 45,000 for each vaccine brand,[66] substantially lower than the patient sample in this study. During the time that the Delta variant was circulating, a systematic review published in March 2023 reported that the overall effectiveness of BNT162b2, mRNA-1273, and JNJ-7836735 against hospitalization was 82%-95% with a mean of 89%.[67] Additionally, it reported that mRNA-1273 showed higher levels of effectiveness than the other 2 vaccine brands during this time, including the highest effectiveness against hospitalization and emergency room visits (VE = 92%).[67] Overall, most studies focused on the BNT162b2 and mRNA-1273 vaccines, though this review found that of the 3 vaccine brands, JNJ-7836735 had the lowest effectiveness against the Delta variant, with a VE of 65% against hospitalization.[67]

A retrospective observational study conducted in France between June 2021 and February 2022 using a test-negative design among adults over 50 years of age found that the adjusted VE against symptomatic infection with the Delta variant peaked at 86% (95% CI, 75%-92%), whereas protection against the Omicron variant peaked at 70% (95% CI, 58%-79%) a month after the second dose of any mRNA vaccine.[68] The same study found that VE against symptomatic infection with the Delta variant waned slightly over time to 67% (95% CI, 63%-71%) by 91-120 days after the second dose, with effectiveness against symptomatic infection with the Omicron variant being even lower at day 91-120, at 28% (95% CI, 22%-36%); however, VE against hospitalization for COVID-19 remained high with minimal evidence of waning in both eras.[68] In Japan, another test-negative design study conducted during both the Delta- and Omicron-dominant periods found that the VE of the BNT162b2 and mRNA-1273 vaccines during the Delta-dominant period was 88% (95% CI, 82%-93%) 3 months after Dose 2, and 56% (95% CI, 37%-70%) 3 months after Dose 2 for the Omicron period.[69] Our study's use of a cohort design rather than a test-negative design allowed for more granular evaluation of changing VE over time; while our study showed similarly decreased VE estimates against Omicron as compared with Delta, our results suggested a longer duration of effectiveness before meaningful waning of VE, particularly for severe outcomes.

Recent studies provide further information on the longevity of COVID-19 VE, though differences in the studies' geography and vaccine availability may impact VE estimates. When investigating waning of VE

over longer time frames (i.e., beyond 3 months), several studies found that though there was waning of VE over time, vaccines still provided at least some protection against severe COVID-19 outcomes over the longer time frame. A case-control study among individuals aged 18 and older in Hong Kong found that there was a reduction in risk of COVID-19-associated hospitalization for at least 240 days after the second dose of BNT162b2 compared with unvaccinated individuals. The study found that VE against COVID-19-associated hospitalization after the second dose of BNT162b2 decreased from 81.1% (0-13 days) to 46.6% (211-240 days). For COVID-19-related mortality, the VE estimates remained much more consistent across the assessment period, starting at 94.6% (0-13 days) and decreasing slightly to 87.3% (181-210 days) and 73.8% (211-240 days).[70]

Some studies have investigated waning through the assessment of antibody levels, such as an analysis of antibody levels in a sample of adults in Canada who received 2 doses of either BNT162b2 or mRNA-1273.[71] This study found that the half-lives of total antibody, anti-spike immunoglobulin G, and anti-receptor binding domain IgG concentrations were 94 days, 68 days, and 61 days, respectively.[71] A prospective cohort study in South Korea found that the Omicron variant had a significant impact on humoral immunity induced by the standard 2-dose regimen, with neutralization ability falling below the detection threshold at 16-24 weeks after vaccination with either BNT162b2 or ChAdOx1 nCoV (adenovirus vector-based COVID-19 vaccine), the 2 vaccines available to that population.[72]

One US-based study of COVID-19 surveillance data reported waning of VE over time, though it was minimal for older (and therefore more vulnerable) age groups, and not for the most severe outcomes of COVID-19 infection. This study indicated that 19 weeks after BNT162b vaccination, all age groups showed a decrease in the percent reduction in the relative hazard rates of any COVID-19 infection compared with the unvaccinated, but that between week 2 and 19 after vaccination, the percent reductions in hazard rates for vaccinated people compared with unvaccinated people fell from 77.2% to 65.5%, 82.9% to 73.3%, 86.0% to 80.7%, and 89.6% to 81.0% for ages 18-29 years, 30-49 years, 50-64 years, and 65 years or older, respectively.[73] A review of international real-world studies of COVID-19 VE against laboratory-confirmed COVID-19 infection suggested similar waning across age groups.[74]

5.3 Strengths and Limitations

This study used insurance billing data and IIS records to include a large sample of adults being vaccinated and receiving care in a variety of settings from jurisdictions around the US. Our primary exposure considered the receipt of a complete primary series, though we started follow-up on the recorded date of the first dose (censoring if the individual failed to received Dose 2 on time); starting follow-up on Time 0 without considering future vaccination behaviors avoided immortal person-time bias.[75]

Initial vaccination rollout focused on older adults, high-risk individuals, and those in LTC facilities; exact prioritization procedures and rollout priority groups varied by jurisdiction and changed over time. To ensure comparability between vaccinated and unvaccinated groups, we ensured that unvaccinated individuals would only be included during periods when they were eligible for vaccination. Because eligibility criteria varied so rapidly over time and by geography, defining time period and geography-specific eligibility criteria for the entire study population was impractical, so we matched unvaccinated

individuals to vaccinated on multiple indicators of eligibility status, including calendar date, immunocompromised status, pregnancy, comorbidities, and age; this matching approximated the rolling eligibility criteria by identifying unvaccinated individuals who were similar to vaccinated individuals on each calendar day in each US county of residence.

This real-world study is subject to many limitations related to the use of existing data sources including that key study elements may be misclassified or missing, the observed VEs may be subject to confounding by unmeasured characteristics, and these results may not be generalizable to other populations. The analysis combined claims and IIS records to identify vaccination status, substantially increasing vaccination capture compared to either data source alone. However, the sensitivity of insurance claims supplemented with IIS data is not likely to be 100%, and we expect that some vaccinated persons may have been classified as unvaccinated due to missing records, recording errors, or other technical challenges that resulted in incomplete recording of vaccination information. Given this potential for less than 100% sensitivity of exposure classification, VE may be underestimated, as patients who were vaccinated may have been included in the unvaccinated group. These patients, along with their presumably lower risk of COVID-19, would contribute lower-risk person-time to the unvaccinated pool, and thus decrease estimates of VE. To address this potential misclassification, a QBA was performed to determine how observed estimates of VE would change based on hypothesized rates of underreporting of vaccination. However, the extent of vaccination completeness and exposure misclassification was estimated using CDC and state-level estimates from the entire population aged less than 65 years, which may not always perfectly align with the study population. For medically diagnosed COVID-19, VE estimates for all vaccine brands increased by a maximum of 9%-14% under the assumption of 71% sensitivity of vaccination exposure measurement. For the hospital/ED-diagnosed COVID-19 outcome, potential misclassification of truly vaccinated persons as unvaccinated had a smaller absolute percentage effect on VE, ranging from 4%-9% under the assumption of 71% sensitivity in Optum and 69% in the CVS Health data. The results of these bias analyses should be interpreted as suggestions for general estimates on the direction and magnitude of bias, but they are not perfectly corrected estimates.

Despite matching on demographic and clinical characteristics and 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 not expected to have a biological effect, using the 10-14 days after vaccination during which the body mounts an antibody response to a novel antigen. However, post hoc negative control analyses demonstrated differential COVID-19 testing and diagnoses by vaccination group in the 3-4 days after Time 0, which has been noted in other studies[64,76] and is reasonable given recently vaccinated individuals may not seek COVID-19 testing, attributing symptoms to vaccine side effects.[64] This difference in testing and diagnosis behavior appeared to resolve after day 5 through the rest of the negative control period. Additionally, unexpected differences in the negative control period were noted in the comparative effectiveness analyses where both groups were vaccinated; many of these differences were the result of COVID-19 diagnoses recorded on the vaccination date, and the differences between groups generally resolved or lessened by the end of the 14-day period. Post hoc analyses revealed that BNT162b2 was more likely than other vaccine brands to

be administered in nonhealthcare provider settings without the structure for recording and reporting a diagnosis (e.g., pharmacies, mass vaccination centers), whereas mRNA-1273 and JNJ-7836735 were more likely than BNT162b2 to be administered in healthcare settings where diagnoses could be recorded. Previous validation studies have shown that recorded COVID-19 diagnoses have been used to indicate history of COVID-19, to justify COVID-19 laboratory testing, or for vaccine-related reasons.[35] The differences in vaccination settings and the associated probability of same-day COVID-19 diagnoses (either true or false positives) may result in temporary differences in observed RVE during the negative control period. However, longer-term differences in healthcare-seeking behavior or residual unmeasured confounding cannot be ruled out.

COVID-19 testing capacity and capability have changed rapidly throughout the course of the pandemic, and COVID-19 laboratory testing results are not widely available in the databases utilized for this study, so COVID-19 diagnoses were used as outcomes rather than confirmed COVID-19 infections. COVID-19 severity is not accurately represented in diagnosis coding, so we evaluated COVID-19 diagnoses overall in any medically diagnosed setting, and separately in hospital/ED settings as a proxy for severity. However, as the pandemic has progressed, COVID-19-related hospitalizations may be the most relevant public health measure for surveillance and prevention efforts. Although, as the dynamics of the pandemic have changed over time (e.g., healthcare practice, treatment options, transmissibility, severity), hospitalizations with COVID-19 diagnoses may not always be reflective of true severe COVID-19.[41] We matched vaccination groups on calendar time and evaluated outcomes over calendar time to account for the potentially changing meaning of a COVID-19 diagnosis over time.

Since the original emergency use authorizations of the vaccines, vaccine formulations have been updated in response to changing circulating viral variants, indications for vaccination (e.g., age groups) have expanded, and the recommended dosing schedules have been revised (i.e., additional doses for immunocompromised individuals, multiple booster doses in different populations, heterologous vaccine series or boosters, updated bivalent boosters, additional updated vaccines in 2023-2024). Results for the evaluation of the effectiveness of a primary series of BNT162b2 in children and adolescents and the evaluation of the effectiveness of original monovalent additional/booster doses are reported elsewhere.[16,17] Continuing public health surveillance for recommended updated COVID-19 vaccines is necessary.

Our study utilized 2 US data sources, representing commercially insured adults from jurisdictions across the US with participating IISs, receiving vaccination and healthcare in a variety of treatment settings and geographic locations. The overall results and many of the age and variant subgroup results were consistent across data sources. For the purposes of summarization and clarity of the following analyses in the 2 data sources, summary VE estimates are presented. It is important to note that statistical heterogeneity was observed in many of these results, based on the I^2 statistic, which in some settings would prompt reconsideration of the appropriateness of meta-analysis. As our analytical approaches in each data source were identical and the populations similar, we did not find evidence of clinical heterogeneity and thus considered meta-analysis to be a reasonable approach to summarizing, smoothing, and inference.[77,78]

5.4 Conclusion

Vaccination with a complete primary series of BNT162b2, mRNA-1273, or JNJ-7836735, compared with being unvaccinated, was associated with reduced COVID-19 incidence in the US adult population, although the observed VE estimates differed by vaccine brand and over time. The observed VE against medically diagnosed COVID-19 was sustained for at least 6 months, and effectiveness against hospital/ED-diagnosed COVID-19 was sustained for 9 months. While some waning effectiveness of the relative VE measure was observed, large numbers of COVID-19 diagnoses were prevented during the study period, as evidenced by the sustained RD estimates. Observed VE estimates differed by vaccine brand and variant era. In the rapidly changing dynamics of the COVID-19 pandemic, additional real-world research is needed as authorizations and recommendations for updated vaccines and new variants have changed over time.

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

Protocol section(s)	Change	Rationale
4.1	The 42-day period after Dose 1 to receiving Dose 2 while still being considered adherent to the primary series was retained.	Feasibility evaluations demonstrated that most individuals received Dose 2 within the 42-day period.
4.2.1.3, 5.1.1.3	The Phase 1 feasibility analyses evaluating incidence of COVID-19 outcomes only in vaccinated individuals were not performed.	These analyses were determined to be uninformative for feasibility purposes, and these analyses would be performed in both vaccinated individuals and unvaccinated comparators in the Phase 2 comparative analyses.
4.2.2.2	Exclusion criterion for COVID-19 diagnosis assessed in any setting in the 30 days before Time 0 was retained.	Feasibility evaluations demonstrated that very few vaccinated individuals had recorded diagnoses of COVID-19 in the 30 days before vaccination.
4.2.2.2	Any healthcare interaction in the 3 days before the index date was not used as an exclusion criterion, nor was it added as a covariate in propensity score models.	It was concluded that application of this nonspecific exclusion criterion would exclude too many vaccinated individuals.
4.2.2.2	Exclusion criteria for having the following healthcare interactions in the 3 days before Time 0 were retained: • Fever • Nausea/vomiting • Rash • Hospitalization • ED visit	Feasibility evaluations demonstrated that very few vaccinated individuals had these characteristics in the 3 days before Time 0, thus making them appropriate for exclusion criteria to ensure equivalent health status between vaccinated and unvaccinated individuals.
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.
5.1.1.2	The characteristics of individuals receiving and not receiving a complete primary series were not described.	The vast majority of individuals received a complete primary series, and these results were determined to be uninformative for feasibility purposes.
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 Dec 2021.	To correct an error in the protocol draft and align the end of the Delta era with the beginning of the Omicron era.

Protocol section(s)	Change	Rationale
5.1.2.5	Clarification that a “censoring dose” consists of individuals in the unvaccinated group receiving any vaccine, or individuals in the vaccinated group receiving Dose 2 too early, Dose 2 of a different brand, or receiving a third dose.	To clarify all potential censoring doses, including those not explicitly mentioned in the protocol.
5.1.2.6	Subgroup analyses were not performed for pregnant women.	Feasibility analyses indicated sample sizes were too small for meaningful analysis.
5.1.2.10	The comparative exploratory analyses were not performed.	The counts of individuals with mixed primary series and delayed primary series were described in Phase 1, but counts were too low for meaningful comparative analyses.

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

Appendix B. Preliminary Descriptive and Feasibility Analyses

Feasibility Tables and Figures

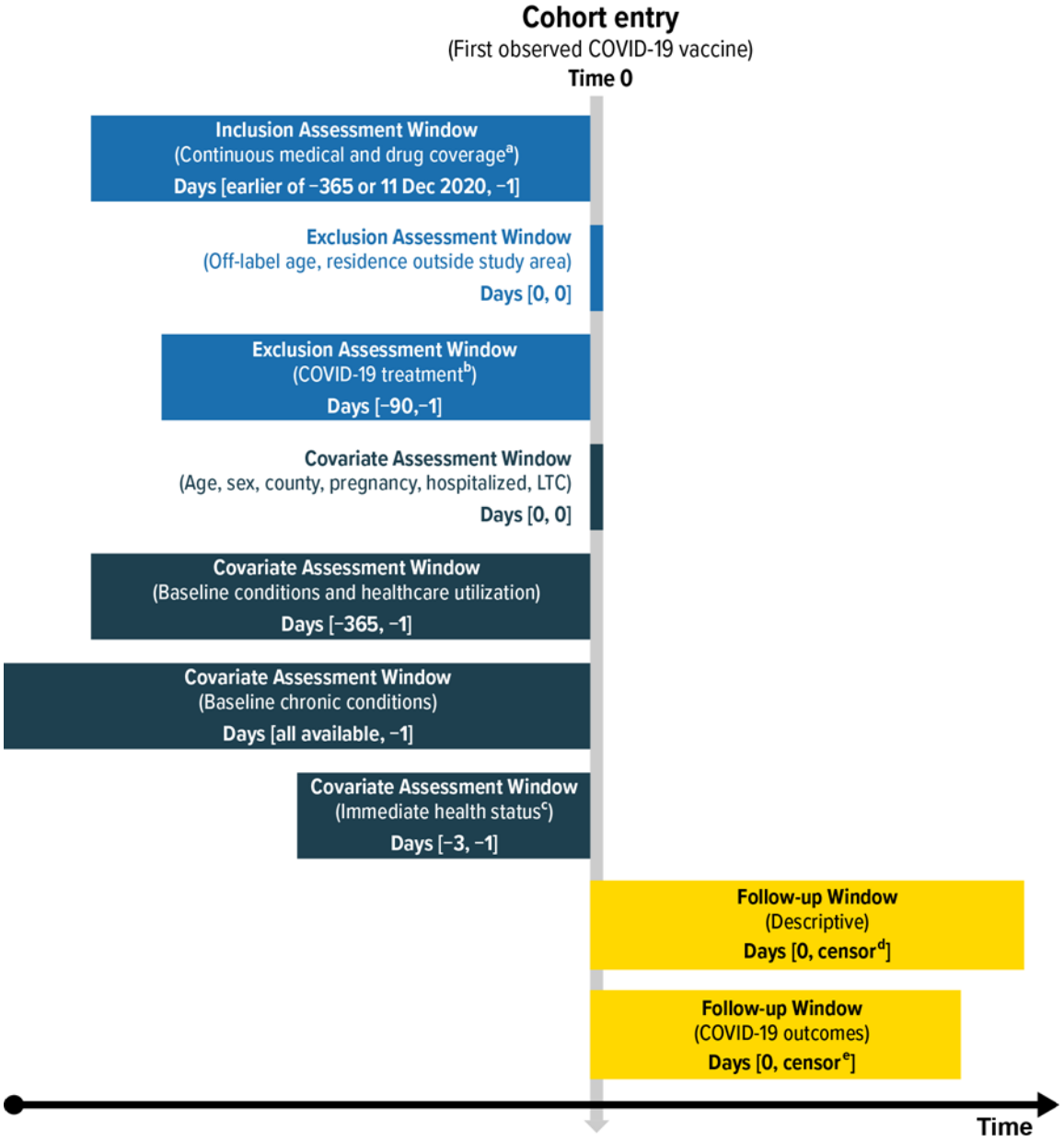
Analytical Approach

Population

Phase 1 feasibility analyses were performed in Optum to inform certain assumptions and decisions before conducting the full, comparative analyses. Vaccinated individuals were identified at their first COVID-19 vaccine dose recorded during the study period (11 December 2020 – 11 December 2021). These feasibility analyses were performed in Optum preadjudicated claims linked with COVID-19 vaccine records from 12 IIS jurisdictions. Note: Because of the timing of the analyses and ongoing feasibility assessments, the full list of IIS jurisdictions used for the Phase 1 feasibility analyses differed from the list used for the full comparative analyses.

The date of the first vaccine dose became Time 0 upon which the assessment periods for eligibility criteria, covariates, and follow-up were defined (Figure B-1).

Figure B-1. Schematic for Assessing Eligibility, Covariates, and COVID-19 Outcomes of Vaccinated Individuals for the Descriptive and Feasibility Evaluation



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

Note: Use of "all available" data indicates that the entire duration of an individual's available continuous enrollment information before Time 0, back to the beginning of data availability (Optum, 1 December 2017; CVS Health, 1 January 2018), was used; the duration of available data was at least 365 days but may vary for each individual.

[a] Gaps in medical and pharmacy coverage of < 32 days were permitted.

[b] COVID-19 monoclonal antibodies or convalescent plasma.

[c] Diagnoses of general acute symptoms (fever, nausea/vomiting, rash) and healthcare utilization (hospitalization, ED visit, any healthcare interaction) serving as an indicator of health status at the time of vaccination.

[d] End of study period, end of continuous health plan enrollment, relocation out of study area.

[e] End of study period, end of continuous health plan enrollment, relocation out of study area, deviation from receipt of the complete primary series.

Eligibility

Eligibility criteria were evaluated relative to Time 0, the calendar date on which Dose 1 was received. Inclusion and exclusion criteria were applied in the order shown in Figure B-1, from top to bottom. Vaccinated individuals were required to have continuous enrollment in the participating insurance plan for at least 365 days before Time 0 and beginning on or earlier than the first date of COVID-19 vaccine authorization in the US for each age group (i.e., 11 December 2020 for individuals aged ≥ 16 years, 10 May 2021 for individuals aged 12-15 years, 29 October 2021 for individuals aged 5-11 years). Enrollment in both medical and pharmacy coverage was required, and gaps in coverage of fewer than 32 days were permitted for continuous enrollment.

Vaccinated individuals were excluded if any of the following exclusion criteria were met:

- Were aged outside the brand-authorized age range on the calendar date of Time 0 (Table 2)
- Resided in a geographic region outside the catchment area of the linked IIS-claims data
- Had claims for monoclonal antibody treatment or convalescent plasma treatment for COVID-19 within the 90 days before Time 0, as these individuals are not recommended for COVID-19 vaccination[30]

Follow-Up

For descriptive analyses of individual characteristics, additional vaccine dose receipt, and series completion, follow-up began at Time 0 and consisted of all available data after vaccination to observe and describe all subsequent doses. Follow-up for each individual was censored at the first occurrence of any of the following on or after Time 0:

- Last date of the study period
- Last date of individual continuous eligible health plan enrollment
- Date of recorded change of residence to a location outside the study area

All vaccinated individuals meeting the eligibility criteria at their first observed eligible COVID-19 dose receipt were included. No unvaccinated individuals were included in these preliminary analyses.

Statistical Analysis

The attrition of the final brand-specific vaccinated cohorts and the numbers of vaccinated individuals excluded by application of each eligibility criterion were reported.

Characteristics of all included vaccinated individuals at Time 0 regardless of their ultimate series completion were described, overall and by vaccine brand. Binary or ordinal variables were described with counts and proportions. Continuous variables were expressed as medians and first and third quartiles (Q1, Q3) as well as means with SDs. Descriptive characteristics also included prespecified demographic and subgroup-defining characteristics (e.g., pregnancy status at Time 0, immunocompromised status) and a data-driven approach identifying the 100 most commonly occurring diagnosis, procedure, or medication codes occurring in the 365 days before Time 0.

The feasibility of including additional exclusion criteria in Phase 2 was evaluated. The proportion of vaccine recipients with COVID-19 diagnoses in the 14 and 30 days before Time 0 were described, along with the time distribution from the most recent COVID-19 diagnosis before Time 0. The prevalence of indicators of immediate health status (e.g., hospitalization, LTC residence, fever, nausea/vomiting, rash, hospitalization, ED visit, any healthcare interaction) on or immediately before Time 0 was also described.

The receipt and timing of additional COVID-19 vaccinations after Dose 1 were described. Time between doses in days, consistency of vaccine brand across doses, and adherence to recommended dosing schedules were described.

Patterns of primary series completion (the vaccination exposure pattern evaluated in the primary analyses), receipt of other vaccine exposure patterns, and receipt of booster/additional doses were described. The distribution of days between Dose 1 and Dose 2 were described by the brand of Dose 1. Individuals who had not received Dose 2 and were censored for other reasons unrelated to their vaccine series completions (e.g., end of the study period, health plan disenrollment) before the end of the 42-day window were categorized as having received the complete series, as their behavior at the time of censoring was consistent with receiving a complete primary series. Individuals receiving only a single dose of a 2-dose primary series were identified as those not receiving Dose 2 by day 42 (inclusive).

Other nonstandard permutations of the primary series—including off-label, not recommended, or nonauthorized patterns—were evaluated, including the following:

- Mixed vaccine primary series (2 doses of different vaccine brands).
- Substantially delayed primary series completion (received Dose 2 > 42 days after receiving Dose 1).
- Slightly delayed primary series completion (received Dose 2 ≥ 7 days after the recommended interval but ≤ 42 days [6 weeks] after receiving Dose 1). This vaccine exposure pattern is a subset of the primary analysis of a complete primary series; all individuals with a slightly delayed primary series completion also met the criteria for primary series completion.

Feasibility Results

Descriptive Results

Overall, the preliminary feasibility analysis identified 846,770 individuals receiving the first dose of a COVID-19 vaccine (Table B-1). The majority (62%) received BNT162b2, followed by mRNA-1273 (31%), with the smallest proportion receiving JNJ-7836735 (7%). The vaccinated individuals had a mean age of 39 years (SD 16 years), and 52% were female. A very small percentage of the identified vaccinated individuals had evidence of being pregnant (<1%), and 4% had evidence of being immunocompromised.

Individuals receiving BNT162b2 were slightly younger than those receiving mRNA-1273 or JNJ-7836735 (median 37 years vs. 44 years). Individuals receiving JNJ-7836735 were more likely to be male than female (44% female, 56% male), whereas individuals receiving BNT162b2 or mRNA-1273 were more

likely to be female (52% female, 48% male for both groups). Geographic distributions were generally similar across the 3 brands (Table B-1).

A very small proportion of the vaccinated individuals had a recorded COVID-19 diagnosis in the 14 days (0.2%) or 30 days (0.6%) before vaccination. The median time since a recorded COVID-19 diagnosis was 131 days (Table B-2).

Very few individuals had markers of acute illness at the time of vaccination. Of the vaccinated individuals, only 0.4% were hospitalized and 0.02% were LTC residents at the time of vaccination. Less than 0.1% of vaccinated individuals had recorded diagnoses of each of the following: fever, nausea/vomiting, rash, or an ED visit in the 3 days before vaccination. Of the vaccinated individuals, 0.6% had a hospital admission in the 3 days before vaccination. Approximately 8% had any healthcare interaction in the 3 days before vaccination (Table B-2).

The majority of observed vaccination records did not have a specific dose number associated with the record (71.9% of observed Dose 1, 72.7% of observed Dose 2, 87.1% of observed booster/additional dose records were unspecified) (Table B-3), so the observed ordering of doses in the data was used to define dose number rather than dose numbering information from the record.

Primary Series Completion

Of individuals receiving a first dose of BNT162b2 or mRNA-1273 (i.e., vaccines with 2-dose primary series), the majority (approximately 80%) completed the primary series by receiving a second dose within the specified on-time window. The timing of the received second dose was generally very precise to the recommended intervals: BNT162b2, median (Q1, Q3) 21 days (21, 22); mRNA-1273, 28 days (28, 29). Approximately 8% of BNT162b2 recipients and 4% of mRNA-1273 recipients had a slightly delayed Dose 2 (i.e., 7 days or greater after than recommended interval but still within the on-time window). Most patients received a complete primary series of the same brand, but 6% of individuals who received Dose 1 of BNT162b2 and 9% who received Dose 1 of mRNA-1273 received a Dose 2 of a brand different than their Dose 1 (i.e., a mixed series).

Receipt of a booster/additional dose was observed in approximately 25% of vaccinated individuals. The median (Q1, Q3) time between the last dose of the primary series and the additional/booster dose was 206 days (83, 229).

Conclusions

Based on the results of the Phase 1 feasibility analyses, the following decisions were made for the Phase 2 comparative analyses:

- The 30-day washout period for COVID-19 diagnoses before Time 0 was maintained.
- The following exclusion criteria based on immediate health status on or immediately before Time 0 were maintained:
    - Hospitalized on Time 0
    - LTC resident on Time 0

- Hospitalization or ED visit in the days −3 to −1 before Time 0
- Diagnosis of fever, nausea/vomiting, or rash in the days −3 to −1 before Time 0

- Exclusions based on any healthcare interaction in the 3 days before Time 0 were concluded to potentially exclude too many vaccinated individuals.
- The 42-day maximum length of time after Dose 1 during which individuals must receive Dose 2 to be categorized as having received a complete vaccine series was maintained, as most individuals received their second dose within 42 days.
- Some primary, secondary, and exploratory analyses may not be feasible given anticipated small numbers, as follows:

  - The observed sample sizes for JNJ-7836735 were much smaller than for the other vaccine brands. The precision of all estimates of JNJ-7836735 may limited, and subgroup or stratified analyses may not be feasible.
  - Some subgroup analyses may not be feasible in each analysis, particularly for pregnancy and immunocompromised status (depending on the specific comparison).
  - Exploratory analyses of mixed primary series and delayed primary series will not be performed.

Table B-1. Exploratory Characteristics of Individuals Receiving at Least 1 Dose of COVID-19 Vaccine: Overall and by Vaccine Brand

Characteristic	Overall N = 846,770	BNT162b2 N = 522,447 (62%)	mRNA-1273 N = 264,605 (31%)	JNJ-7836735 N = 59,718 (7%)
Age, years				
Median (Q1, Q3)	40.00 (27.00, 53.00)	37.00 (22.00, 51.00)	44.00 (33.00, 55.00)	44.00 (32.00, 54.00)
Mean (SD)	39.17 (15.69)	36.68 (16.60)	43.20 (13.15)	43.06 (13.16)
Sex, n (%)				
Female	436,721 (51.57%)	272,453 (52.15%)	137,957 (52.14%)	26,311 (44.06%)
Male	410,049 (48.43%)	249,994 (47.85%)	126,648 (47.86%)	33,407 (55.94%)
Region, n (%)				
Midwest	302,088 (35.68%)	186,674 (35.73%)	91,802 (34.69%)	23,612 (39.54%)
Northeast	85,448 (10.09%)	53,529 (10.25%)	26,658 (10.07%)	5,261 (8.81%)
South	225,992 (26.69%)	136,820 (26.19%)	73,399 (27.74%)	15,773 (26.41%)
West	233,242 (27.54%)	145,424 (27.84%)	72,746 (27.49%)	15,072 (25.24%)
Characteristics assessed during the 365-day baseline period, n (%)				
Pregnancy[a]	3,580 (0.42%)	2,399 (0.46%)	1,090 (0.41%)	91 (0.15%)
Characteristics assessed during all available baseline time, n (%)				
Immunocompromised status[b]	37,560 (4.44%)	21,602 (4.13%)	13,351 (5.05%)	2,607 (4.37%)

COVID-19 = coronavirus disease 2019; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; N = sample frequency; Q1, Q3 = first and third quartiles; SD = standard deviation.

[a] Pregnancy defined as an ICD-10-CM diagnosis code beginning with "Z3A" and no pregnancy outcome code during the 365-day baseline period. Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

[b] Immunocompromised status defined as at least 2 diagnostic codes or ≥ 1 transplant code from the FDA BEST Immunocompromised Population List in the 6 months before Time 0.

Table B-2. Descriptive Exploration of Characteristics of Vaccinated Individuals Relative to the Date of Receipt of the First Vaccine Dose, Which May Inform the Design of the Comparative Vaccine Effectiveness Study

Characteristic	Overall N = 846,770	BNT162b2 N = 522,447	mRNA-1273 N = 264,605	JNJ-7836735 N = 59,718
COVID-19 diagnosis in any setting at any point before Dose 1, n (%)	55,145 (6.51%)	33,379 (6.39%)	17,410 (6.58%)	4,356 (7.29%)
14 days before Dose 1	1,925 (0.23%)	1,212 (0.23%)	589 (0.22%)	124 (0.21%)
30 days before Dose 1	4,710 (0.56%)	2,839 (0.54%)	1,577 (0.60%)	294 (0.49%)
Days since most recent COVID-19 diagnosis[a]				
Median (Q1, Q3)	131.00 (77.00, 212.00)	135.00 (78.00, 218.00)	125.00 (73.00, 201.00)	139.00 (86.00, 211.00)
Minimum, maximum	1.00, 365.00	1.00, 365.00	1.00, 365.00	1.00, 365.00
Mean (SD)	147.38 (90.98)	149.75 (92.01)	141.69 (89.45)	152.01 (87.97)
Indicators of immediate health status at Time 0, n (%)				
Hospitalized	3,101 (0.37%)	1,932 (0.37%)	943 (0.36%)	226 (0.38%)
LTC resident	139 (0.02%)	37 (0.01%)	76 (0.03%)	26 (0.04%)
Indicators of immediate health status in the 3 days before Time 0, n (%)				
Fever	133 (0.02%)	78 (0.01%)	45 (0.02%)	10 (0.02%)
Nausea/vomiting	383 (0.05%)	220 (0.04%)	142 (0.05%)	21 (0.04%)
Rash	213 (0.03%)	141 (0.03%)	57 (0.02%)	15 (0.03%)
Hospital admission	4,804 (0.57%)	2,856 (0.55%)	1,615 (0.61%)	333 (0.56%)
ED visit	703 (0.08%)	411 (0.08%)	239 (0.09%)	53 (0.09%)
Any healthcare interaction	65,369 (7.72%)	39,841 (7.63%)	21,170 (8.00%)	4,358 (7.30%)

COVID-19 = coronavirus disease 2019; ED = emergency department; LTC = long-term care; N = sample frequency; Q1, Q3 = first and third quartiles; SD = standard deviation.

[a] Only among those with a COVID-19 diagnosis in any setting at any point before Dose 1.

Table B-3. Characteristics of Vaccine Dose Receipt and Vaccine Exposure Patterns Among Individuals Receiving at Least 1 Dose of COVID-19 Vaccine, Overall and by Vaccine Brand

Characteristic	Overall	BNT162b2	mRNA-1273	JNJ-7836735
Individuals with receipt of an eligible first observed COVID-19 vaccine dose [a]	846,770	522,447	264,605	59,718
Total doses	1,733,896	1,092,179	564,714	77,003
Vaccine dose number according to vaccine record; n (%)				
Labeled as Dose 1	225,609 (26.64%)	147,543 (28.24%)	66,541 (25.15%)	11,525 (19.30%)
Labeled as Dose 2	7,621 (0.90%)	5,354 (1.02%)	2,267 (0.86%)	NA
Labeled as Dose 3	1,518 (0.18%)	1,060 (0.20%)	458 (0.17%)	NA
Labeled as booster/additional dose	3,005 (0.35%)	1,680 (0.32%)	1,289 (0.49%)	36 (0.06%)
Dose number not specified	609,017 (71.92%)	366,810 (70.21%)	194,050 (73.34%)	48,157 (80.64%)
Individuals with an observed second dose [b], n (%)	675,705 (79.80%)	447,472 (85.65%)	228,233 (86.25%)	NA
Labeled as Dose 1	6,175 (0.91%)	4,088 (0.91%)	2,087 (0.91%)	NA
Labeled as Dose 2	177,307 (26.24%)	121,723 (27.20%)	55,584 (24.35%)	NA
Labeled as Dose 3	419 (0.06%)	239 (0.05%)	180 (0.08%)	NA
Labeled as booster/additional dose	757 (0.11%)	430 (0.10%)	327 (0.14%)	NA
Dose number not specified	491,047 (72.67%)	320,992 (71.73%)	170,055 (74.51%)	NA
Days between first and second doses, median (Q1, Q3)	NA	21 (21, 22)	28 (28, 29)	NA
Vaccine brand of Dose 2 matches Dose 1, n (%) yes	NA	441,949 (98.77%)	223,562 (97.95%)	NA
Status of primary series completion; n (%)				
Complete primary series [c]	692,830 (81.82%)	422,473 (80.86%)	210,639 (79.61%)	59,718 (100.0%)
Slightly delayed primary series completion [d]	NA	35,632 (8.43%)	9,285 (4.41%)	NA
Nonstandard primary series [e]	NA	99,974 (19.14%)	53,966 (20.39%)	NA
Single dose of primary series (Dose 2 not received before the end of the recommended window)	NA	84,094 (84.12%)	42,600 (78.94%)	NA
Substantially delayed primary series completion [f]	NA	9,119 (10.84%)	6,228 (14.62%)	NA
Dose 2 received too early	NA	10,357 (10.36%)	6,695 (12.41%)	NA
Mixed series (Dose 2 different brand than Dose 1)	NA	5,523 (5.52%)	4,671 (8.66%)	NA

Characteristic	Overall	BNT162b2	mRNA-1273	JNJ-7836735
Individuals with receipt of an observed booster/additional dose; n (%)	211,421 (24.97%)	122,260 (23.40%)	71,876 (27.16%)	17,285 (28.94%)
Labeled as Dose 1	1,757 (0.83%)	973 (0.80%)	433 (0.60%)	351 (2.03%)
Labeled as Dose 2	4,915 (2.32%)	3,355 (2.74%)	1,447 (2.01%)	113 (0.65%)
Labeled as Dose 3	6,427 (3.04%)	4,162 (3.40%)	2,072 (2.88%)	193 (1.12%)
Labeled as booster/additional dose	14,130 (6.68%)	7,882 (6.45%)	5,143 (7.16%)	1,105 (6.39%)
Labeled as unspecified	184,192 (87.12%)	105,888 (86.61%)	62,781 (87.35%)	15,523 (89.81%)
Booster/additional dose after complete primary series[g]	188,435 (89.13%)	108,392 (88.66%)	62,758 (87.31%)	17,285 (100.0%)
Booster/additional dose was the same brand as the complete primary series	146,335 (77.66%)	90,307 (83.32%)	52,263 (83.28%)	3,765 (21.78%)
Booster/additional dose received after receiving the nonstandard primary series	22,986 (10.87%)	13,868 (11.34%)	9,118 (12.69%)	NA
Booster/additional dose received after receiving a mixed primary series	7,367 (32.05%)	4,141 (29.86%)	3,226 (35.38%)	NA
Booster/additional dose received after Dose 2 was received too early	14,282 (62.13%)	8,915 (64.28%)	5,367 (58.86%)	NA
Booster/additional dose received after a substantially delayed Dose 2	1,337 (5.82%)	812 (5.86%)	525 (5.76%)	NA
Days between last dose of the primary series and a booster/additional dose; median (Q1, Q3)	206 (83, 229)	204 (77, 227)	207 (84, 231)	215 (145, 235)

COVID-19 = coronavirus disease 2019; IIS = immunization information system; NA = not applicable; Q1, Q3 = first and third quartiles.

[a] First observed vaccine dose meeting eligibility requirements, not necessarily labeled as a first dose by the claims/IIS record.

[b] Dose 2 of the primary series is the same brand as Dose 1; individuals receiving Dose 1 of JNJ-7836735 were not considered, as they are considered to have completed the primary series, and receipt of any subsequent dose after Dose 1 would be considered a booster/additional dose.

[c] Complete primary series defined as either Dose 1 of JNJ-7836735 or Dose 1 and Dose 2 of the same brand of either BNT162b2 or mRNA-1273.

[d] Slightly delayed primary series defined as receiving Dose 2 ≥ 7 days after the recommended interval but ≤ 42 days after receiving Dose 1.

[e] Nonstandard primary series defined as mixed series, Dose 2 received too early, or substantially delayed primary series completion.

[f] Substantially delayed primary series defined as receiving Dose 2 > 42 days after receiving Dose 1; these individuals are a subset of those labeled single dose of a primary series (Dose 2 not received before the end of the recommended window).

[g] Booster/additional dose does not need to be the same brand as that of the first and second doses.

Appendix C. Adult Analyses Supplementary Tables and Figures

This appendix includes results tables and figures from each data source. The tables and figures are numbered equivalently across data source (e.g., Table B-1-Optum and Table B-1-CVS contain the results of the same data source–specific analyses). If an analysis was performed in only 1 data source, the table/figure number and title are still presented for both data sources to retain the equivalent ordering, with a note when the analysis was not performed.

In this appendix, data results from both data sources are presented together, grouped by number (e.g., Table B-1-Optum is followed by Table B-1-CVS, then Table B-2-Optum is followed by Table B-2-CVS). For ease of navigation, the following table of tables and table of figures are grouped by data source.

Overall Adult Effectiveness Analyses

Table C-1-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With BNT162b2 COVID-19 Vaccine and Matched Unvaccinated Adults

Characteristic	Individuals vaccinated with BNT162b2 N = 341,097	Matched unvaccinated individuals N = 341,097	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	42 (32, 53)	42 (32, 53)	
Mean (SD)	42.03 (12.95)	42.02 (12.95)	0.00
Sex, n (%)			
Male	166,068 (48.69%)	166,068 (48.69%)	0.00
Female	175,029 (51.31%)	175,029 (51.31%)	0.00
Region, n (%)			
Northeast	40,009 (11.73%)	40,009 (11.73%)	0.00
South	86,610 (25.39%)	86,610 (25.39%)	0.00
Midwest	144,657 (42.41%)	144,657 (42.41%)	0.00
West	69,821 (20.47%)	69,821 (20.47%)	0.00
Pregnant at Time 0, n (%)[a]	1,837 (0.54%)	1,837 (0.54%)	0.00
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	231,487 (67.87%)	231,943 (68.00%)	0.00
1	60,877 (17.85%)	60,921 (17.86%)	0.00
2+	48,733 (14.29%)	48,233 (14.14%)	0.00
ED visits			
0	307,322 (90.10%)	303,855 (89.08%)	0.03
1	27,521 (8.07%)	29,610 (8.68%)	0.02
2+	6,254 (1.83%)	7,632 (2.24%)	0.03
Skilled nursing facility stay	536 (0.16%)	254 (0.07%)	0.02
Influenza vaccination	132,439 (38.83%)	132,439 (38.83%)	0.00
Pneumococcal vaccination	4,732 (1.39%)	4,316 (1.27%)	0.01
Encounter for cancer screening	96,432 (28.27%)	91,430 (26.80%)	0.03
Eye examination	21,650 (6.35%)	20,043 (5.88%)	0.02
Colonoscopy	14,213 (4.17%)	13,179 (3.86%)	0.02
Bone mineral density test	4,011 (1.18%)	3,684 (1.08%)	0.01
Well-check/well-child preventive healthcare visit	146,908 (43.07%)	139,588 (40.92%)	0.04
Arthritis	44,721 (13.11%)	45,255 (13.27%)	0.00
Lipid abnormality	60,872 (17.85%)	58,489 (17.15%)	0.02
Ambulance use or life support services	5,239 (1.54%)	6,070 (1.78%)	0.02
Weakness	6,580 (1.93%)	6,492 (1.90%)	0.00

Characteristic	Individuals vaccinated with BNT162b2 N = 341,097	Matched unvaccinated individuals N = 341,097	ASD
Pregnancy completion before Time 0[a]	7,183 (2.11%)	7,389 (2.17%)	0.01
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	15,710 (4.61%)	15,224 (4.46%)	0.01
Cancer	20,072 (5.88%)	19,337 (5.67%)	0.01
Chronic kidney disease or renal disease	6,231 (1.83%)	6,313 (1.85%)	0.00
Chronic liver disease	14,482 (4.25%)	14,576 (4.27%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	36,710 (10.76%)	36,427 (10.68%)	0.00
Dementia or other neurological conditions	23,297 (6.83%)	23,987 (7.03%)	0.01
Diabetes mellitus, type 1 or 2	25,169 (7.38%)	24,030 (7.04%)	0.01
Down syndrome	83 (0.02%)	61 (0.02%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	45,648 (13.38%)	46,051 (13.50%)	0.00
Hypertension	72,219 (21.17%)	71,842 (21.06%)	0.00
Immunocompromised state	15,135 (4.44%)	15,135 (4.44%)	0.00
Mental health conditions	96,696 (28.35%)	95,899 (28.11%)	0.01
Obese or severely obese	71,294 (20.90%)	70,829 (20.77%)	0.00
Sickle cell disease or thalassemia	816 (0.24%)	904 (0.27%)	0.01
Stroke or cerebrovascular disease	5,025 (1.47%)	5,159 (1.51%)	0.00
Tuberculosis	210 (0.06%)	223 (0.07%)	0.00
≥ 1 COVID-19 laboratory test performed	127,334 (37.33%)	115,959 (34.00%)	0.07
COVID-19 diagnoses occurring outside a hospital or ED setting	18,045 (5.29%)	17,947 (5.26%)	0.00
Hospital/ED-diagnosed COVID-19	2,810 (0.82%)	2,777 (0.81%)	0.00

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-1-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With BNT162b2 COVID-19 Vaccine and Matched Unvaccinated Adults

Characteristic	Individuals vaccinated with BNT162b2 N = 1,151,775	Matched unvaccinated individuals N = 1,151,775	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	42 (31, 53)	42 (31, 53)	0.00
Mean (SD)	41.92 (13.22)	41.91 (13.23)	0.00
Sex, n (%)			
Male	536,224 (46.56%)	536,224 (46.56%)	0.00
Female	615,551 (53.44%)	615,551 (53.44%)	0.00
Region, n (%)			
Northeast	204,777 (17.78%)	204,777 (17.78%)	0.00
South	251,233 (21.81%)	251,233 (21.81%)	0.00
Midwest	206,280 (17.91%)	206,280 (17.91%)	0.00
West	489,485 (42.50%)	489,485 (42.50%)	0.00
Pregnant at Time 0, n (%)[a]	6,611 (0.57%)	6,611 (0.57%)	0.00
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	812,173 (70.51%)	814,894 (70.75%)	0.01
1	180,041 (15.63%)	179,387 (15.57%)	0.00
2+	159,561 (13.85%)	157,494 (13.67%)	0.01
ED visits			
0	1,041,322 (90.41%)	1,027,640 (89.22%)	0.04
1	88,687 (7.70%)	96,968 (8.42%)	0.03
2+	21,766 (1.89%)	27,167 (2.36%)	0.03
Skilled nursing facility stay	837 (0.07%)	870 (0.08%)	0.00
Influenza vaccination	388,801 (33.76%)	388,801 (33.76%)	0.00
Pneumococcal vaccination	15,854 (1.38%)	14,639 (1.27%)	0.01
Encounter for cancer screening	309,502 (26.87%)	290,259 (25.20%)	0.04
Eye examination	89,086 (7.73%)	80,665 (7.00%)	0.03
Colonoscopy	46,035 (4.00%)	42,535 (3.69%)	0.02
Bone mineral density test	16,067 (1.39%)	14,520 (1.26%)	0.01
Well-check/well-child preventive healthcare visit	455,406 (39.54%)	428,537 (37.21%)	0.05
Arthritis	156,828 (13.62%)	159,792 (13.87%)	0.01
Lipid abnormality	215,402 (18.70%)	207,851 (18.05%)	0.02
Ambulance use or life support services	17,857 (1.55%)	21,695 (1.88%)	0.03
Weakness	21,292 (1.85%)	21,612 (1.88%)	0.00
Pregnancy completion before Time 0[a]	25,139 (2.18%)	25,011 (2.17%)	0.00

Characteristic	Individuals vaccinated with BNT162b2 N = 1,151,775	Matched unvaccinated individuals N = 1,151,775	ASD
Characteristics Assessed Using all Available Data, n (%)			
Autoimmune disorders	56,025 (4.86%)	54,760 (4.75%)	0.01
Cancer	70,717 (6.14%)	66,968 (5.81%)	0.01
Chronic kidney disease or renal disease	25,567 (2.22%)	26,629 (2.31%)	0.01
Chronic liver disease	56,281 (4.89%)	56,607 (4.91%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	131,033 (11.38%)	132,083 (11.47%)	0.00
Dementia or other neurological conditions	85,608 (7.43%)	87,745 (7.62%)	0.01
Diabetes mellitus, type 1 or 2	88,515 (7.69%)	86,908 (7.55%)	0.01
Down syndrome	427 (0.04%)	364 (0.03%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	163,592 (14.20%)	166,283 (14.44%)	0.01
Hypertension	243,221 (21.12%)	243,503 (21.14%)	0.00
Immunocompromised state	49,753 (4.32%)	49,753 (4.32%)	0.00
Mental health conditions	323,819 (28.11%)	326,266 (28.33%)	0.00
Obese or severely obese	241,844 (21.00%)	244,264 (21.21%)	0.01
Sickle cell disease or thalassemia	4,042 (0.35%)	3,904 (0.34%)	0.00
Stroke or cerebrovascular disease	20,848 (1.81%)	22,258 (1.93%)	0.01
Tuberculosis	1,145 (0.10%)	1,098 (0.10%)	0.00
≥ 1 COVID-19 laboratory test performed	527,313 (45.78%)	484,001 (42.02%)	0.08
COVID-19 diagnoses occurring outside of a hospital or ED	52,778 (4.58%)	52,350 (4.55%)	0.00
Hospital/ED-diagnosed COVID-19	8,983 (0.78%)	9,161 (0.80%)	0.00

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-2-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With an mRNA-1273 COVID-19 Vaccine and Matched Unvaccinated Adults

Characteristic	Individuals vaccinated with mRNA-1273 N = 201,604	Matched unvaccinated individuals N = 201,604	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (33, 54)	44 (33, 54)	
Mean (SD)	43.23 (12.95)	43.19 (12.97)	0.00
Sex, n (%)			
Male	97,657 (48.44%)	97,657 (48.44%)	0.00
Female	103,947 (51.56%)	103,947 (51.56%)	0.00
Region, n (%)			
Northeast	26,580 (13.18%)	26,580 (13.18%)	0.00
South	47,138 (23.38%)	47,138 (23.38%)	0.00
Midwest	85,564 (42.44%)	85,564 (42.44%)	0.00
West	42,322 (20.99%)	42,322 (20.99%)	0.00
Pregnant at Time 0, n (%)[a]	759 (0.38%)	759 (0.38%)	0.00
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	134,597 (66.76%)	134,239 (66.59%)	0.00
1	36,616 (18.16%)	36,784 (18.25%)	0.00
2+	30,391 (15.07%)	30,581 (15.17%)	0.00
ED visits			
0	181,625 (90.09%)	179,425 (89.00%)	0.04
1	16,280 (8.08%)	17,696 (8.78%)	0.03
2+	3,699 (1.83%)	4,483 (2.22%)	0.03
Skilled nursing facility stay	210 (0.10%)	123 (0.06%)	0.02
Influenza vaccination	84,003 (41.67%)	84,003 (41.67%)	0.00
Pneumococcal vaccination	3,293 (1.63%)	2,916 (1.45%)	0.02
Encounter for cancer screening	59,499 (29.51%)	57,384 (28.46%)	0.02
Eye examination	13,344 (6.62%)	12,829 (6.36%)	0.01
Colonoscopy	8,905 (4.42%)	8,366 (4.15%)	0.01
Bone mineral density test	2,526 (1.25%)	2,522 (1.25%)	0.00
Well-check/well-child preventive healthcare visit	85,408 (42.36%)	83,689 (41.51%)	0.02
Arthritis	27,688 (13.73%)	27,843 (13.81%)	0.00
Lipid abnormality	40,255 (19.97%)	38,246 (18.97%)	0.03
Ambulance use or life support services	3,211 (1.59%)	3,669 (1.82%)	0.02
Weakness	3,741 (1.86%)	3,908 (1.94%)	0.01
Pregnancy completion before Time 0[a]	3,593 (1.78%)	4,090 (2.03%)	0.03

Characteristic	Individuals vaccinated with mRNA-1273 N = 201,604	Matched unvaccinated individuals N = 201,604	ASD
Characteristics Assessed Using all Available Data, n (%)			
Autoimmune disorders	9,343 (4.63%)	9,329 (4.63%)	0.00
Cancer	12,495 (6.20%)	12,215 (6.06%)	0.01
Chronic kidney disease or renal disease	4,027 (2.00%)	3,925 (1.95%)	0.00
Chronic liver disease	9,056 (4.49%)	9,026 (4.48%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	23,005 (11.41%)	22,562 (11.19%)	0.01
Dementia or other neurological conditions	14,078 (6.98%)	14,325 (7.11%)	0.00
Diabetes mellitus, type 1 or 2	17,003 (8.43%)	16,045 (7.96%)	0.02
Down syndrome	50 (0.02%)	41 (0.02%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	28,052 (13.91%)	28,853 (14.31%)	0.01
Hypertension	47,534 (23.58%)	46,870 (23.25%)	0.01
Immunocompromised state	9,000 (4.46%)	9,000 (4.46%)	0.00
Mental health conditions	59,501 (29.51%)	58,206 (28.87%)	0.01
Obese or severely obese	44,965 (22.30%)	44,041 (21.85%)	0.01
Sickle cell disease or thalassemia	433 (0.21%)	450 (0.22%)	0.00
Stroke or cerebrovascular disease	3,236 (1.61%)	3,501 (1.74%)	0.01
Tuberculosis	142 (0.07%)	109 (0.05%)	0.01
≥ 1 COVID-19 laboratory test performed	72,155 (35.79%)	65,871 (32.67%)	0.07
COVID-19 diagnoses occurring outside of a hospital or ED	9,428 (4.68%)	9,380 (4.65%)	0.00
Hospital/ED-diagnosed COVID-19	1,476 (0.73%)	1,445 (0.72%)	0.00

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-2-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With an mRNA-1273 COVID-19 Vaccine and Matched Unvaccinated Adults

Characteristic	Individuals vaccinated with mRNA-1273 N = 651,545	Matched unvaccinated individuals N = 651,545	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (33, 55)	44 (32, 55)	0.00
Mean (SD)	43.37 (13.4)	43.33 (13.42)	0.00
Sex, n (%)			
Male	313,461 (48.11%)	313,461 (48.11%)	0.00
Female	338,084 (51.89%)	338,084 (51.89%)	0.00
Region, n (%)			
Northeast	139,585 (21.42%)	139,585 (21.42%)	0.00
South	113,510 (17.42%)	113,510 (17.42%)	0.00
Midwest	114,493 (17.57%)	114,493 (17.57%)	0.00
West	283,957 (43.58%)	283,957 (43.58%)	0.00
Pregnant at Time 0, n (%)[a]	2,557 (0.39%)	2,557 (0.39%)	0.00
Characteristics in the 365 Days Before Time 0, n (%)			
Hospitalizations			
0	456,478 (70.06%)	453,734 (69.64%)	0.01
1	103,083 (15.82%)	103,735 (15.92%)	0.00
2+	91,984 (14.12%)	94,076 (14.44%)	0.01
ED visits			
0	587,420 (90.16%)	580,072 (89.03%)	0.04
1	51,337 (7.88%)	55,763 (8.56%)	0.02
2+	12,788 (1.96%)	15,710 (2.41%)	0.03
Skilled nursing facility stay	567 (0.09%)	550 (0.08%)	0.00
Influenza vaccination	239,416 (36.75%)	239,416 (36.75%)	0.00
Pneumococcal vaccination	10,819 (1.66%)	9,675 (1.48%)	0.01
Encounter for cancer screening	182,176 (27.96%)	174,072 (26.72%)	0.03
Eye examination	52,718 (8.09%)	48,741 (7.48%)	0.02
Colonoscopy	28,306 (4.34%)	26,338 (4.04%)	0.02
Bone mineral density test	10,114 (1.55%)	9,424 (1.45%)	0.01
Well-check/well-child preventive healthcare visit	251,488 (38.60%)	241,716 (37.10%)	0.03
Arthritis	95,284 (14.62%)	95,699 (14.69%)	0.00
Lipid abnormality	140,791 (21.61%)	134,374 (20.62%)	0.02
Ambulance use or life support services	11,600 (1.78%)	12,988 (1.99%)	0.02
Weakness	12,206 (1.87%)	12,208 (1.87%)	0.00
Pregnancy completion before Time 0[a]	11,057 (1.70%)	12,237 (1.88%)	0.01

Characteristic	Individuals vaccinated with mRNA-1273 N = 651,545	Matched unvaccinated individuals N = 651,545	ASD
Characteristics Assessed Using all Available Data, n (%)			
Autoimmune disorders	34,439 (5.29%)	33,671 (5.17%)	0.01
Cancer	43,865 (6.73%)	42,441 (6.51%)	0.01
Chronic kidney disease or renal disease	17,312 (2.66%)	17,201 (2.64%)	0.00
Chronic liver disease	35,180 (5.40%)	35,288 (5.42%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	81,057 (12.44%)	80,729 (12.39%)	0.00
Dementia or other neurological conditions	51,559 (7.91%)	52,066 (7.99%)	0.00
Diabetes mellitus, type 1 or 2	59,510 (9.13%)	56,297 (8.64%)	0.02
Down syndrome	313 (0.05%)	212 (0.03%)	0.01
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	100,214 (15.38%)	101,431 (15.57%)	0.01
Hypertension	158,070 (24.26%)	156,296 (23.99%)	0.01
Immunocompromised state	31,211 (4.79%)	31,211 (4.79%)	0.00
Mental health conditions	193,580 (29.71%)	191,353 (29.37%)	0.01
Obese or severely obese	151,991 (23.33%)	149,445 (22.94%)	0.01
Sickle cell disease or thalassemia	2,011 (0.31%)	2,055 (0.32%)	0.00
Stroke or cerebrovascular disease	14,143 (2.17%)	14,716 (2.26%)	0.01
Tuberculosis	575 (0.09%)	614 (0.09%)	0.00
≥ 1 COVID-19 laboratory test performed	290,717 (44.62%)	266,802 (40.95%)	0.07
COVID-19 diagnoses occurring outside of a hospital or ED	27,212 (4.18%)	27,004 (4.14%)	0.00
Hospital/ED-diagnosed COVID-19	4,739 (0.73%)	4,899 (0.75%)	0.00

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-3-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With JNJ-7836735 COVID-19 Vaccine and Matched Unvaccinated Adults

Characteristic	Individuals vaccinated with JNJ-7836735 N = 49,285	Matched unvaccinated individuals N = 49,285	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (33, 54)	44 (33, 54)	
Mean (SD)	42.91 (12.88)	42.89 (12.87)	0.00
Sex, n (%)			
Male	27,842 (56.49%)	27,842 (56.49%)	0.00
Female	21,443 (43.51%)	21,443 (43.51%)	0.00
Region, n (%)			
Northeast	5,838 (11.85%)	5,838 (11.85%)	0.00
South	10,032 (20.36%)	10,032 (20.36%)	0.00
Midwest	22,568 (45.79%)	22,568 (45.79%)	0.00
West	10,847 (22.01%)	10,847 (22.01%)	0.00
Pregnant at Time 0, n (%)[a]	72 (0.15%)	72 (0.15%)	0.00
Characteristics in the 365 Days Before Time 0, n (%)			
Hospitalizations			
0	34,682 (70.37%)	34,074 (69.14%)	0.03
1	8,388 (17.02%)	8,557 (17.36%)	0.01
2+	6,215 (12.61%)	6,654 (13.50%)	0.03
ED visits			
0	44,621 (90.54%)	43,909 (89.09%)	0.05
1	3,803 (7.72%)	4,308 (8.74%)	0.04
2+	861 (1.75%)	1,068 (2.17%)	0.03
Skilled nursing facility stay	31 (0.06%)	36 (0.07%)	0.00
Influenza vaccination	16,343 (33.16%)	16,343 (33.16%)	0.00
Pneumococcal vaccination	568 (1.15%)	538 (1.09%)	0.01
Encounter for cancer screening	13,424 (27.24%)	12,875 (26.12%)	0.03
Eye examination	2,976 (6.04%)	2,837 (5.76%)	0.01
Colonoscopy	2,006 (4.07%)	1,981 (4.02%)	0.00
Bone mineral density test	529 (1.07%)	493 (1.00%)	0.01
Well-check/well-child preventive healthcare visit	19,704 (39.98%)	18,851 (38.25%)	0.04
Arthritis	6,600 (13.39%)	6,455 (13.10%)	0.01
Lipid abnormality	8,711 (17.67%)	8,650 (17.55%)	0.00
Ambulance use or life support services	791 (1.60%)	890 (1.81%)	0.02
Weakness	941 (1.91%)	924 (1.87%)	0.00
Pregnancy completion before Time 0[a]	568 (1.15%)	856 (1.74%)	0.08

Characteristic	Individuals vaccinated with JNJ-7836735 N = 49,285	Matched unvaccinated individuals N = 49,285	ASD
Characteristics Assessed Using all Available Data, n (%)			
Autoimmune disorders	2,186 (4.44%)	1,994 (4.05%)	0.02
Cancer	2,822 (5.73%)	2,622 (5.32%)	0.02
Chronic kidney disease or renal disease	861 (1.75%)	929 (1.88%)	0.01
Chronic liver disease	1,943 (3.94%)	2,068 (4.20%)	0.01
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	5,011 (10.17%)	5,031 (10.21%)	0.00
Dementia or other neurological conditions	3,168 (6.43%)	3,115 (6.32%)	0.00
Diabetes mellitus, type 1 or 2	3,400 (6.90%)	3,489 (7.08%)	0.01
Down syndrome	< 11	< 11	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	6,147 (12.47%)	6,519 (13.23%)	0.02
Hypertension	10,468 (21.24%)	10,757 (21.83%)	0.01
Immunocompromised state	1,865 (3.78%)	1,865 (3.78%)	0.00
Mental health conditions	13,612 (27.62%)	13,198 (26.78%)	0.02
Obese or severely obese	9,764 (19.81%)	9,928 (20.14%)	0.01
Sickle cell disease or thalassemia	63 (0.13%)	122 (0.25%)	0.03
Stroke or cerebrovascular disease	714 (1.45%)	822 (1.67%)	0.02
Tuberculosis	23 (0.05%)	24 (0.05%)	0.00
≥ 1 COVID-19 laboratory test performed	17,668 (35.85%)	16,423 (33.32%)	0.05
COVID-19 diagnoses occurring outside of a hospital or ED	2,761 (5.60%)	2,749 (5.58%)	0.00
Hospital/ED-diagnosed COVID-19	393 (0.80%)	440 (0.89%)	0.01

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

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-3-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With JNJ-7836735 COVID-19 Vaccine and Matched Unvaccinated Adults

Characteristic	Individuals vaccinated with JNJ-7836735 N = 149,813	Matched unvaccinated individuals N = 149,813	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (32, 54)	44 (32, 54)	0.00
Mean (SD)	42.98 (13.31)	42.97 (13.32)	0.00
Sex, n (%)			
Male	82,697 (55.20%)	82,697 (55.20%)	0.00
Female	67,116 (44.80%)	67,116 (44.80%)	0.00
Region, n (%)			
Northeast	29,728 (19.84%)	29,728 (19.84%)	0.00
South	26,237 (17.51%)	26,237 (17.51%)	0.00
Midwest	28,431 (18.98%)	28,431 (18.98%)	0.00
West	65,417 (43.67%)	65,417 (43.67%)	0.00
Pregnant at Time 0, n (%)[a]	274 (0.18%)	274 (0.18%)	0.00
Characteristics in the 365 Days Before Time 0, n (%)			
Hospitalizations			
0	110,435 (73.72%)	108,225 (72.24%)	0.03
1	21,706 (14.49%)	22,499 (15.02%)	0.01
2+	17,672 (11.80%)	19,089 (12.74%)	0.03
ED visits			
0	136,145 (90.88%)	134,052 (89.48%)	0.05
1	11,123 (7.42%)	12,310 (8.22%)	0.03
2+	2,545 (1.70%)	3,451 (2.30%)	0.04
Skilled nursing facility stay	110 (0.07%)	103 (0.07%)	0.00
Influenza vaccination	44,501 (29.70%)	44,501 (29.70%)	0.00
Pneumococcal vaccination	1,675 (1.12%)	1,661 (1.11%)	0.00
Encounter for cancer screening	37,861 (25.27%)	36,403 (24.30%)	0.02
Eye examination	10,930 (7.30%)	10,443 (6.97%)	0.01
Colonoscopy	6,043 (4.03%)	5,801 (3.87%)	0.01
Bone mineral density test	1,839 (1.23%)	1,778 (1.19%)	0.00
Well-check/well-child preventive healthcare visit	54,304 (36.25%)	51,984 (34.70%)	0.03
Arthritis	21,142 (14.11%)	20,700 (13.82%)	0.01
Lipid abnormality	28,124 (18.77%)	28,063 (18.73%)	0.00
Ambulance use or life support services	2,439 (1.63%)	2,882 (1.92%)	0.02
Weakness	2,689 (1.79%)	2,676 (1.79%)	0.00
Pregnancy completion before Time 0[a]	1,703 (1.14%)	2,198 (1.47%)	0.03

Characteristic	Individuals vaccinated with JNJ-7836735 N = 149,813	Matched unvaccinated individuals N = 149,813	ASD
Characteristics Assessed Using all Available Data, n (%)			
Autoimmune disorders	6,805 (4.54%)	6,812 (4.55%)	0.00
Cancer	8,817 (5.89%)	8,438 (5.63%)	0.01
Chronic kidney disease or renal disease	3,300 (2.20%)	3,559 (2.38%)	0.01
Chronic liver disease	6,946 (4.64%)	7,437 (4.96%)	0.02
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	16,433 (10.97%)	16,778 (11.20%)	0.01
Dementia or other neurological conditions	10,781 (7.20%)	10,868 (7.25%)	0.00
Diabetes mellitus, type 1 or 2	10,737 (7.17%)	11,694 (7.81%)	0.02
Down syndrome	51 (0.03%)	29 (0.02%)	0.01
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	20,073 (13.40%)	21,716 (14.50%)	0.03
Hypertension	31,615 (21.10%)	33,133 (22.12%)	0.02
Immunocompromised state	5,561 (3.71%)	5,561 (3.71%)	0.00
Mental health conditions	42,143 (28.13%)	41,064 (27.41%)	0.02
Obese or severely obese	30,537 (20.38%)	31,435 (20.98%)	0.01
Sickle cell disease or thalassemia	359 (0.24%)	415 (0.28%)	0.01
Stroke or cerebrovascular disease	2,563 (1.71%)	3,018 (2.01%)	0.02
Tuberculosis	98 (0.07%)	131 (0.09%)	0.01
≥ 1 COVID-19 laboratory test performed	67,266 (44.90%)	61,505 (41.05%)	0.08
COVID-19 diagnoses occurring outside of a hospital or ED	7,207 (4.81%)	7,095 (4.74%)	0.00
Hospital/ED-diagnosed COVID-19	1,076 (0.72%)	1,271 (0.85%)	0.01

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-4-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With a COVID-19 Vaccine Who Were Excluded From the Analytic Cohort Due to Failing to Match, by Vaccine Brand

Characteristic	Unmatched Vaccinated with BNT162b2 N = 9,373	Unmatched Vaccinated with mRNA-1273 N = 8,961	Unmatched Vaccinated with JNJ-7836735 N = 1,805
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (33, 55)	47 (36, 57)	48 (36, 56)
Mean (SD)	43.39 (13.06)	45.69 (12.72)	45.74 (12.64)
Sex, n (%)			
Male	4,121 (43.97%)	3,937 (43.93%)	981 (54.35%)
Female	5,252 (56.03%)	5,024 (56.07%)	824 (45.65%)
Region, n (%)			
Northeast	1,497 (15.97%)	1,123 (12.53%)	221 (12.24%)
South	2,907 (31.01%)	3,415 (38.11%)	418 (23.16%)
Midwest	3,817 (40.72%)	3,392 (37.85%)	894 (49.53%)
West	1,152 (12.29%)	1,031 (11.51%)	272 (15.07%)
Pregnant at Time 0, n (%)[a]	481 (5.13%)	265 (2.96%)	26 (1.44%)
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	4,587 (48.94%)	4,435 (49.49%)	924 (51.19%)
1	2,033 (21.69%)	1,961 (21.88%)	391 (21.66%)
2+	2,753 (29.37%)	2,565 (28.62%)	490 (27.15%)
ED visits			
0	7,623 (81.33%)	7,381 (82.37%)	1,497 (82.94%)
1	1,257 (13.41%)	1,155 (12.89%)	227 (12.58%)
2+	493 (5.26%)	425 (4.74%)	81 (4.49%)
Skilled nursing facility stay	12 (0.13%)	< 11	< 11
Influenza vaccination	5,781 (61.68%)	5,564 (62.09%)	989 (54.79%)
Pneumococcal vaccination	248 (2.65%)	222 (2.48%)	28 (1.55%)
Encounter for cancer screening	3,175 (33.87%)	3,185 (35.54%)	589 (32.63%)
Eye examination	782 (8.34%)	772 (8.62%)	134 (7.42%)
Colonoscopy	583 (6.22%)	548 (6.12%)	112 (6.20%)
Bone mineral density test	191 (2.04%)	206 (2.30%)	33 (1.83%)
Well-check/well-child preventive healthcare visit	4,196 (44.77%)	3,846 (42.92%)	691 (38.28%)
Arthritis	1,749 (18.66%)	1,685 (18.80%)	348 (19.28%)
Lipid abnormality	2,110 (22.51%)	2,238 (24.97%)	417 (23.10%)
Ambulance use or life support services	282 (3.01%)	306 (3.41%)	50 (2.77%)
Weakness	285 (3.04%)	252 (2.81%)	57 (3.16%)

Characteristic	Unmatched Vaccinated with BNT162b2 N = 9,373	Unmatched Vaccinated with mRNA-1273 N = 8,961	Unmatched Vaccinated with JNJ-7836735 N = 1,805
Pregnancy completion before Time 0[a]	335 (3.57%)	201 (2.24%)	32 (1.77%)
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	1,088 (11.61%)	905 (10.10%)	194 (10.75%)
Cancer	1,008 (10.75%)	880 (9.82%)	186 (10.30%)
Chronic kidney disease or renal disease	382 (4.08%)	339 (3.78%)	63 (3.49%)
Chronic liver disease	695 (7.41%)	629 (7.02%)	129 (7.15%)
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	1,272 (13.57%)	1,249 (13.94%)	238 (13.19%)
Dementia or other neurological conditions	807 (8.61%)	788 (8.79%)	143 (7.92%)
Diabetes mellitus, type 1 or 2	909 (9.70%)	1,032 (11.52%)	166 (9.20%)
Down syndrome	< 11	< 11	0 (0.00%)
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	1,683 (17.96%)	1,627 (18.16%)	314 (17.40%)
Hypertension	2,379 (25.38%)	2,787 (31.10%)	530 (29.36%)
Immunocompromised state	2,422 (25.84%)	2,075 (23.16%)	422 (23.38%)
Mental health conditions	2,960 (31.58%)	2,796 (31.20%)	520 (28.81%)
Obese or severely obese	2,568 (27.40%)	2,553 (28.49%)	440 (24.38%)
Sickle cell disease or thalassemia	24 (0.26%)	17 (0.19%)	< 11
Stroke or cerebrovascular disease	206 (2.20%)	206 (2.30%)	25 (1.39%)
Tuberculosis	< 11	< 11	< 11
≥ 1 COVID-19 laboratory test performed	5,302 (56.57%)	4,690 (52.34%)	966 (53.52%)
COVID-19 diagnoses occurring outside a hospital or ED setting	3,354 (35.78%)	2,708 (30.22%)	624 (34.57%)
Hospital/ED-diagnosed COVID-19	587 (6.26%)	464 (5.18%)	92 (5.10%)

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

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

Table C-4-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With a COVID-19 Vaccine Who Were Excluded From the Analytic Cohort Due to Failing to Match, by Vaccine Brand

Characteristic	Unmatched Vaccinated with BNT162b2 N = 12,971	Unmatched Vaccinated with mRNA-1273 N = 10,441	Unmatched Vaccinated with JNJ-7836735 N = 2,564
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	43 (32, 54)	47 (35, 57)	47 (36, 56)
Mean (SD)	42.85 (12.95)	45.39 (12.82)	45.44 (12.55)
Sex, n (%)			
Male	5,506 (42.45%)	4,733 (45.33%)	1,354 (52.81%)
Female	7,411 (57.14%)	5,681 (54.41%)	1,206 (47.04%)
Region, n (%)			
Northeast	1,352 (10.42%)	920 (8.81%)	177 (6.90%)
South	4,202 (32.40%)	3,242 (31.05%)	646 (25.20%)
Midwest	5,136 (39.60%)	4,257 (40.77%)	1,281 (49.96%)
West	2,281 (17.59%)	2,022 (19.37%)	460 (17.94%)
Pregnant at Time 0, n (%)[a]	1,050 (8.09%)	482 (4.62%)	56 (2.18%)
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	5,999 (46.25%)	4,848 (46.43%)	1,264 (49.30%)
1	2,675 (20.62%)	2,113 (20.24%)	508 (19.81%)
2+	4,297 (33.13%)	3,480 (33.33%)	792 (30.89%)
ED visits			
0	10,209 (78.71%)	8,273 (79.24%)	2,064 (80.50%)
1	1,917 (14.78%)	1,514 (14.50%)	361 (14.08%)
2+	845 (6.51%)	654 (6.26%)	139 (5.42%)
Skilled nursing facility stay	38 (0.29%)	38 (0.36%)	*
Influenza vaccination	8,177 (63.04%)	6,721 (64.37%)	1,475 (57.53%)
Pneumococcal vaccination	335 (2.58%)	332 (3.18%)	75 (2.93%)
Encounter for cancer screening	4,371 (33.70%)	3,704 (35.48%)	844 (32.92%)
Eye examination	1,377 (10.62%)	1,159 (11.10%)	247 (9.63%)
Colonoscopy	843 (6.50%)	739 (7.08%)	173 (6.75%)
Bone mineral density test	293 (2.26%)	239 (2.29%)	43 (1.68%)
Well-check/well-child preventive healthcare visit	5,711 (44.03%)	4,422 (42.35%)	1,061 (41.38%)
Arthritis	2,637 (20.33%)	2,258 (21.63%)	511 (19.93%)
Lipid abnormality	3,052 (23.53%)	2,926 (28.02%)	623 (24.30%)
Ambulance use or life support services	554 (4.27%)	457 (4.38%)	99 (3.86%)

Characteristic	Unmatched Vaccinated with BNT162b2 N = 12,971	Unmatched Vaccinated with mRNA-1273 N = 10,441	Unmatched Vaccinated with JNJ-7836735 N = 2,564
Weakness	490 (3.78%)	359 (3.44%)	105 (4.10%)
Pregnancy completion before Time 0[a]	569 (4.39%)	310 (2.97%)	53 (2.07%)
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	1,742 (13.43%)	1,289 (12.35%)	290 (11.31%)
Cancer	1,438 (11.09%)	1,203 (11.52%)	250 (9.75%)
Chronic kidney disease or renal disease	711 (5.48%)	638 (6.11%)	145 (5.66%)
Chronic liver disease	1,058 (8.16%)	928 (8.89%)	199 (7.76%)
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	1,949 (15.03%)	1,750 (16.76%)	441 (17.20%)
Dementia or other neurological conditions	1,354 (10.44%)	1,157 (11.08%)	256 (9.98%)
Diabetes mellitus, type 1 or 2	1,351 (10.42%)	1,361 (13.04%)	283 (11.04%)
Down syndrome	11 (0.08%)	< 11	< 11
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	2,603 (20.07%)	2,314 (22.16%)	507 (19.77%)
Hypertension	3,360 (25.90%)	3,200 (30.65%)	746 (29.10%)
Immunocompromised state	3,568 (27.51%)	2,758 (26.42%)	588 (22.93%)
Mental health conditions	4,458 (34.37%)	3,709 (35.52%)	828 (32.29%)
Obese or severely obese	3,597 (27.73%)	3,169 (30.35%)	706 (27.54%)
Sickle cell disease or thalassemia	41 (0.32%)	32 (0.31%)	< 11
Stroke or cerebrovascular disease	368 (2.84%)	342 (3.28%)	57 (2.22%)
Tuberculosis	23 (0.18%)	14 (0.13%)	< 11
≥ 1 COVID-19 laboratory test performed	8,613 (66.40%)	6,442 (61.70%)	1,599 (62.36%)
COVID-19 diagnoses occurring outside a hospital or ED setting	4,948 (38.15%)	3,353 (32.11%)	931 (36.31%)
Hospital/ED-diagnosed COVID-19	968 (7.46%)	680 (6.51%)	172 (6.71%)

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

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

Table C-5-Optum. Distribution of Follow-Up Time by Vaccine Exposure Group and Outcome

COVID-19 outcome	Vaccine 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
Medically diagnosed	BNT162b2	341,097	68,335,369	200 (96)	236 (134, 271)	1, 400
	Unvaccinated	341,097	41,954,661	123 (105)	93 (26, 222)	1, 397
	mRNA-1273	201,604	42,145,941	209 (102)	247 (139, 281)	1, 391
	Unvaccinated	201,604	25,093,307	124 (109)	85 (27, 229)	1, 391
	JNJ-7836735	49,285	10,249,729	208 (80)	232 (165, 270)	1, 321
	Unvaccinated	49,285	6,337,889	129 (104)	110 (26, 233)	1, 321
Hospital/ED-diagnosed	BNT162b2	341,097	69,030,682	202 (96)	237 (137, 273)	1, 400
	Unvaccinated	341,097	42,860,899	126 (107)	96 (26, 228)	1, 397
	mRNA-1273	201,604	42,501,963	211 (101)	248 (143, 282)	1, 391
	Unvaccinated	201,604	25,680,890	127 (110)	88 (28, 238)	1, 391
	JNJ-7836735	49,285	10,387,121	211 (80)	234 (172, 273)	1, 321
	Unvaccinated	49,285	6,480,273	131 (105)	114 (27, 237)	1, 321

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

Table C-5-CVS. Distribution of Follow-Up Time by Vaccine Exposure Group and Outcome

COVID-19 outcome	Vaccine 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
Medically diagnosed	BNT162b2	1,151,775	268,538,241	233 (105)	249 (201, 297)	1, 473
	Unvaccinated	1,151,775	167,925,461	146 (127)	106 (31, 244)	1, 472
	mRNA-1273	651,545	153,442,531	236 (111)	256 (196, 309)	1, 467
	Unvaccinated	651,545	95,983,285	147 (130)	102 (32, 252)	1, 468
	JNJ-7836735	149,813	36,342,423	243 (86)	244 (205, 303)	1, 398
	Unvaccinated	149,813	22,691,059	151 (126)	123 (30, 262)	1, 398
Hospital/ED-diagnosed	BNT162b2	1,151,775	272,234,682	236 (105)	251 (206, 301)	1, 473
	Unvaccinated	1,151,775	172,260,575	150 (129)	109 (32, 251)	1, 472
	mRNA-1273	651,545	155,254,572	238 (112)	258 (205, 314)	1, 467
	Unvaccinated	651,545	98,442,974	151 (132)	105 (33, 260)	1, 468
	JNJ-7836735	149,813	37,004,803	247 (85)	247 (208, 311)	1, 398
	Unvaccinated	149,813	23,256,138	155 (127)	129 (31, 268)	1, 398

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

Table C-6-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Overall and Sensitivity Analyses Accounting for Potentially Missing Vaccine Records Resulting in Exposure Misclassification

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)	Sensitivity analysis assuming 83% sensitivity of exposure classification VE (95% CI)	Sensitivity analysis assuming 71% sensitivity of exposure classification VE (95% CI)
Medically diagnosed	BNT162b2	341,097	11,399	68,335,369	0.44 (0.42-0.45)	56% (55%-58%)	61% (60%-63%)	67% (66%-68%)
	Unvaccinated	341,097	15,007	41,954,661	—	—	—	—
	mRNA-1273	201,604	5,691	42,145,941	0.34 (0.33-0.36)	66% (64%-67%)	70% (68%-71%)	75% (74%-76%)
	Unvaccinated	201,604	9,122	25,093,307	—	—	—	—
	JNJ-7836735	49,285	2,215	10,249,729	0.56 (0.53-0.60)	44% (40%-47%)	49% (45%-52%)	56% (53%-58%)
	Unvaccinated	49,285	2,327	6,337,889	—	—	—	—
Hospital/ED-diagnosed	BNT162b2	341,097	1,066	69,030,682	0.18 (0.17-0.20)	82% (80%-83%)	85% (83%-85%)	88% (86%-88%)
	Unvaccinated	341,097	3,470	42,860,899	—	—	—	—
	mRNA-1273	201,604	494	42,501,963	0.13 (0.12-0.14)	87% (86%-88%)	89% (88%-90%)	91% (91%-92%)
	Unvaccinated	201,604	2,131	25,680,890	—	—	—	—
	JNJ-7836735	49,285	274	10,387,121	0.31 (0.26-0.36)	69% (64%-74%)	73% (69%-77%)	78% (74%-81%)
	Unvaccinated	49,285	548	6,480,273	—	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-6-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Overall and Sensitivity Analyses Accounting for Potentially Missing Vaccine Records Resulting in Exposure Misclassification

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)	Sensitivity analysis assuming 89% sensitivity of exposure classification VE (95% CI)	Sensitivity analysis assuming 69% sensitivity of exposure classification VE (95% CI)
Medically diagnosed	BNT162b2	1,151,775	40,116	268,538,241	0.51 (0.5-0.52)	49% (48%-50%)	52% (52%-53%)	63% (62%-64%)
	Unvaccinated	1,151,775	47,292	167,925,461	—	—	—	—
	mRNA-1273	651,545	19,347	153,442,531	0.43 (0.42-0.44)	57% (56%-58%)	60% (59%-61%)	69% (69%-70%)
	Unvaccinated	651,545	27,079	95,983,285	—	—	—	—
	JNJ-7836735	149,813	6,931	36,342,423	0.64 (0.62-0.66)	36% (34%-38%)	38% (36%-40%)	46% (44%-48%)
	Unvaccinated	149,813	6,507	22,691,059	—	—	—	—
Hospital/ED-diagnosed	BNT162b2	1,151,775	4,496	272,234,682	0.24 (0.23-0.25)	76% (75%-77%)	78% (77%-79%)	84% (83%-85%)
	Unvaccinated	1,151,775	11,464	172,260,575	—	—	—	—
	mRNA-1273	651,545	2,042	155,254,572	0.18 (0.17-0.19)	82% (81%-83%)	84% (83%-85%)	89% (88%-89%)
	Unvaccinated	651,545	6,884	98,442,974	—	—	—	—
	JNJ-7836735	149,813	957	37,004,803	0.35 (0.32-0.38)	65% (62%-68%)	67% (64%-70%)	74% (72%-76%)
	Unvaccinated	149,813	1,702	23,256,138	—	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-7-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Restricted to 14 Days After Dose 1 (Negative Outcome Control Analysis)

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (Days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	341,097	1,020	4,712,153	0.78 (0.72-0.85)	22% (15%-28%)
	Unvaccinated	341,097	1,213	4,430,528	—	—
	mRNA-1273	201,604	620	2,775,669	0.74 (0.66-0.82)	26% (18%-34%)
	Unvaccinated	201,604	788	2,633,992	—	—
	JNJ-7836735	49,285	147	681,618	0.77 (0.62-0.95)	23% (4.6%-38%)
	Unvaccinated	49,285	179	640,274	—	—
Hospital/ED-diagnosed	BNT162b2	341,097	162	4,717,225	0.68 (0.55-0.83)	32% (17%-45%)
	Unvaccinated	341,097	220	4,437,274	—	—
	mRNA-1273	201,604	77	2,779,305	0.54 (0.41-0.72)	46% (28%-59%)
	Unvaccinated	201,604	133	2,638,288	—	—
	JNJ-7836735	49,285	24	682,510	0.57 (0.34-0.95)	43% (4.8%-66%)
	Unvaccinated	49,285	39	641,231	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group

Table C-7-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Restricted to 14 Days After Dose 1 (Negative Outcome Control Analysis)

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (Days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	1,151,775	2,811	16,033,703	0.75 (0.71-0.79)	25% (21%-29%)
	Unvaccinated	1,151,775	3,467	15,110,575	—	—
	mRNA-1273	651,545	1,732	9,061,448	0.84 (0.79-0.90)	16% (10%-21%)
	Unvaccinated	651,545	1,927	8,584,260	—	—
	JNJ-7836735	149,813	319	2,086,796	0.90 (0.77-1.05)	10% (−5% to 23%)
	Unvaccinated	149,813	328	1,958,454	—	—
Hospital/ED-diagnosed	BNT162b2	1,151,775	443	16,048,496	0.65 (0.58-0.74)	35% (26%-42%)
	Unvaccinated	1,151,775	643	15,129,554	—	—
	mRNA-1273	651,545	207	9,073,347	0.58 (0.49-0.69)	42% (31%-51%)
	Unvaccinated	651,545	334	8,595,080	—	—
	JNJ-7836735	149,813	74	2,088,425	1.15 (0.82-1.63)	−15% (−63% to 18%)
	Unvaccinated	149,813	60	1,960,267	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group

Table C-8-Optum. Characteristics of Vaccinated Individuals With and Without Concurrent COVID-19 Diagnoses on Time 0

A. BNT162b2

Characteristic	COVID-19 diagnosis on Time 0 N = 52	No COVID-19 diagnosis on Time 0 N = 341,045	ASD
Setting of vaccination, n (%)			
Home health	0 (0.00%)	≥ 11 (0.00%)	0.01
Hospital	< 11	19,308 (5.66%)	0
Mass vaccination center	0 (0.00%)	19,631 (5.76%)	0.35
Missing	< 11	4,581 (1.34%)	0.16
Physician office	16 (30.77%)	29,610 (8.68%)	0.58
Other	< 11	4,504 (1.32%)	0.24
Pharmacy	22 (42.31%)	146,679 (43.01%)	0.01
Skilled nursing facility	0 (0.00%)	< 11	0
Immunization information system record only	< 11	116,719 (34.22%)	0.56
Region, n (%)			
Northeast	< 11	40,004 (11.73%)	0.07
South	11 (21.15%)	86,599 (25.39%)	0.1
Midwest	26 (50.00%)	144,631 (42.41%)	0.15
West	< 11	69,811 (20.47%)	0.03
COVID-19 history, n (%)			
≥ 1 COVID-19 laboratory test performed	30 (57.69%)	127,304 (37.33%)	0.42
COVID-19 diagnoses outside of a hospital/ED	12 (23.08%)	18,033 (5.29%)	0.53
Hospital/ED-diagnosed COVID-19	< 11	2,805 (0.82%)	0.4

B. mRNA-1273

Characteristic	COVID-19 diagnosis on Time 0 N = 94	No COVID-19 diagnosis on Time 0 N = 201,510	ASD
Setting of vaccination, n (%)			
Home health	0 (0.00%)	≥ 11	0.01
Hospital	< 11	3,920 (1.95%)	0.22
Mass vaccination center	< 11	7,231 (3.59%)	0.17
Missing	< 11	3,860 (1.92%)	0.18
Physician office	52 (55.32%)	21,654 (10.75%)	1.08
Other	< 11	4,984 (2.47%)	0.19
Pharmacy	15 (15.96%)	99,899 (49.58%)	0.77
Skilled nursing facility	0 (0.00%)	< 11	0.01

Characteristic	COVID-19 diagnosis on Time 0 N = 94	No COVID-19 diagnosis on Time 0 N = 201,510	ASD
Immunization information system record only	< 11	59,945 (29.75%)	0.52
Region, n (%)			
Northeast	36 (38.30%)	26,544 (13.17%)	0.6
South	28 (29.79%)	47,110 (23.38%)	0.15
Midwest	< 11	85,542 (42.45%)	0.41
West	< 11	42,314 (21.00%)	0.36
COVID-19 history, n (%)			
≥ 1 COVID-19 laboratory test performed	41 (43.62%)	72,114 (35.79%)	0.16
COVID-19 diagnoses outside of a hospital/ED	< 11	9,419 (4.67%)	0.19
Hospital/ED-diagnosed COVID-19	< 11	1,470 (0.73%)	0.31

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; NE = not estimable.

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

Table C-8-CVS. Characteristics of Vaccinated Individuals With and Without Concurrent COVID-19 Diagnoses on Time 0

A. BNT162b2

Characteristic	COVID-19 diagnosis on Time 0 N = 219	No COVID-19 diagnosis on Time 0 N = 1,151,556	ASD
Setting of vaccination, n (%)			
Home Health	< 11	220 (0.02%)	0.00
Hospital	15 (6.85%)	88,241 (7.66%)	0.03
Mass vaccination centers	< 11	77,868 (6.76%)	0.16
Missing	47 (21.46%)	604,946 (52.53%)	0.68
Multiple	< 11	≥ 11	0.00
Physician office	124 (56.62%)	86,071 (7.47%)	1.24
Other	< 11	43,819 (3.81%)	0.02
Pharmacy	17 (7.76%)	250,276 (21.73%)	0.40
Skilled Nursing Facility	< 11	< 11	0.00
Region, n (%)			
Northeast	26 (11.87%)	204,751 (17.78%)	0.17
South	53 (24.20%)	251,180 (21.81%)	0.06
Midwest	25 (11.42%)	206,255 (17.91%)	0.18
West	115 (52.51%)	489,370 (42.50%)	0.20
COVID-19 history, n (%)			
≥ 1 COVID-19 laboratory test performed	123 (56.16%)	527,190 (45.78%)	0.21
COVID-19 diagnoses outside of a hospital/ED	33 (15.07%)	52,745 (4.58%)	0.36
Hospital/ED-diagnosed COVID-19	11 (5.02%)	8,972 (0.78%)	0.25

B. mRNA-1273

Characteristic	COVID-19 diagnosis on Time 0 N = 441	No COVID-19 diagnosis on Time 0 N = 651,104	ASD
Setting of vaccination, n (%)			
Home Health	< 11	205 (0.03%)	0.00
Hospital	13 (2.95%)	25,209 (3.87%)	0.05
Mass Vaccination Centers	< 11	26,850 (4.12%)	0.11
Missing	27 (6.12%)	327,034 (50.23%)	1.12
Multiple	< 11	215 (0.03%)	0.00
Physician Office	375 (85.03%)	75,477 (11.59%)	2.17
Other	< 11	32,265 (4.96%)	0.16
Pharmacy	< 11	163,836 (25.16%)	0.74
Skilled Nursing Facility	< 11	13 (0.00%)	0.00

Characteristic	COVID-19 diagnosis on Time 0 N = 441	No COVID-19 diagnosis on Time 0 N = 651,104	ASD
Region, n (%)			
Northeast	288 (65.31%)	139,297 (21.39%)	0.99
South	42 (9.52%)	113,468 (17.43%)	0.23
Midwest	18 (4.08%)	114,475 (17.58%)	0.45
West	93 (21.09%)	283,864 (43.60%)	0.50
COVID-19 history, n (%)			
≥ 1 COVID-19 laboratory test performed	226 (51.25%)	290,491 (44.62%)	0.13
COVID-19 diagnoses outside of a hospital/ED	42 (9.52%)	27,170 (4.17%)	0.21
Hospital/ED-diagnosed COVID-19	11 (2.49%)	4,728 (0.73%)	0.14

C. JNJ-7836735

Characteristic	COVID-19 diagnosis on Time 0 N = 32	No COVID-19 diagnosis on Time 0 N = 149,781	ASD
Setting of vaccination, n (%)			
Home Health	< 11	53 (0.04%)	0.00
Hospital	< 11	3,632 (2.42%)	0.04
Mass Vaccination Centers	< 11	3,756 (2.51%)	0.18
Missing	< 11	89,019 (59.43%)	0.74
Multiple	< 11	≥ 11	0.00
Physician Office	19 (59.38%)	9,763 (6.52%)	1.36
Other	< 11	7,314 (4.88%)	0.09
Pharmacy	< 11	36,205 (24.17%)	0.64
Skilled Nursing Facility	< 11	< 11	0.00
Region, n (%)			
Northeast	< 11	29,724 (19.84%)	0.20
South	< 11	26,232 (17.51%)	0.05
Midwest	14 (43.75%)	28,417 (18.97%)	0.55
West	< 11	65,408 (43.67%)	0.33
COVID-19 history, n (%)			
≥ 1 COVID-19 laboratory test performed	18 (56.25%)	67,248 (44.90%)	0.23
COVID-19 diagnoses outside of a hospital/ED	< 11	7,198 (4.81%)	0.66
Hospital/ED-diagnosed COVID-19	< 11	1,071 (0.72%)	0.57

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; NE = not estimable.

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

Table C-9-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated Among Immunocompromised Adults Aged 18-64 Years

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	15,135	630	3,057,755	0.48 (0.43-0.55)	52% (45%-57%)
	Unvaccinated	15,135	704	1,714,950	—	—
	mRNA-1273	9,000	312	1,888,790	0.37 (0.32-0.44)	63% (56%-68%)
	Unvaccinated	9,000	438	1,035,384	—	—
Hospital/ED-diagnosed	BNT162b2	15,135	93	3,097,423	0.26 (0.20-0.35)	74% (65%-80%)
	Unvaccinated	15,135	200	1,759,229	—	—
	mRNA-1273	9,000	44	1,910,394	0.22 (0.15-0.31)	78% (69%-85%)
	Unvaccinated	9,000	110	1,063,995	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-9-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated Among Immunocompromised Adults Aged 18-64 Years

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	49,753	2,456	11,251,956	0.54 (0.51-0.57)	46% (43%-49%)
	Unvaccinated	49,753	2,755	6,765,412	—	—
	mRNA-1273	31,211	1,328	7,154,558	0.46 (0.43-0.50)	54% (50%-57%)
	Unvaccinated	31,211	1,658	4,202,370	—	—
	JNJ-7836735	5,561	368	1,340,144	0.69 (0.59-0.81)	31% (19%-41%)
	Unvaccinated	5,561	315	804,804	—	—
Hospital/ED-diagnosed	BNT162b2	49,753	509	11,468,402	0.35 (0.31-0.40)	65% (60%-69%)
	Unvaccinated	49,753	898	6,984,325	—	—
	mRNA-1273	31,211	253	7,271,647	0.26 (0.22-0.30)	74% (70%-78%)
	Unvaccinated	31,211	570	4,333,330	—	—
	JNJ-7836735	5,561	82	1,373,006	0.49 (0.36-0.66)	51% (34%-64%)
	Unvaccinated	5,561	101	828,993	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-10-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years With a Previous COVID-19 Diagnosis

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	18,962	759	3,389,905	0.66 (0.59-0.74)	34% (26%-41%)
	Unvaccinated	18,962	779	2,334,640	—	—
	mRNA-1273	9,914	341	1,857,921	0.55 (0.47-0.64)	45% (36%-53%)
	Unvaccinated	9,914	409	1,248,699	—	—
Hospital/ED-diagnosed	BNT162b2	18,962	39	3,454,998	0.28 (0.18-0.43)	72% (57%-82%)
	Unvaccinated	18,962	92	2,381,274	—	—
	mRNA-1273	9,914	16	1,886,452	0.25 (0.14-0.45)	75% (55%-86%)
	Unvaccinated	9,914	42	1,280,414	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-10-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years With a Previous COVID-19 Diagnosis

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	56,266	2,768	12,001,685	0.71 (0.67-0.75)	29% (25%-33%)
	Unvaccinated	56,266	2,745	8,365,317	—	—
	mRNA-1273	29,029	1,350	6,297,879	0.66 (0.61-0.72)	34% (28%-39%)
	Unvaccinated	29,029	1,436	4,371,147	—	—
	JNJ-7836735	7,660	406	1,743,282	0.74 (0.64-0.85)	26% (15%-36%)
	Unvaccinated	7,660	371	1,164,613	—	—
Hospital/ED-diagnosed	BNT162b2	56,266	186	12,324,343	0.44 (0.35-0.53)	56% (47%-65%)
	Unvaccinated	56,266	306	8,644,775	—	—
	mRNA-1273	29,029	87	6,472,352	0.34 (0.26-0.45)	66% (55%-74%)
	Unvaccinated	29,029	174	4,519,359	—	—
	JNJ-7836735	7,660	28	1,790,309	0.59 (0.36-0.99)	41% (1%-64%)
	Unvaccinated	7,660	34	1,198,980	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-11-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years Without a Previous COVID-19 Diagnosis

COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	322,135	10,640	64,945,464	0.42 (0.41-0.44)	58% (56%-59%)
	Unvaccinated	322,135	14,228	39,620,021	—	—
	mRNA-1273	191,690	5,350	40,288,020	0.33 (0.32-0.35)	67% (65%-68%)
	Unvaccinated	191,690	8,713	23,844,608	—	—
Hospital/ED-diagnosed	BNT162b2	322,135	1,027	65,575,684	0.18 (0.16-0.19)	82% (81%-84%)
	Unvaccinated	322,135	3,378	40,479,625	—	—
	mRNA-1273	191,690	478	40,615,511	0.13 (0.12-0.14)	87% (86%-88%)
	Unvaccinated	191,690	2,089	24,400,476	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

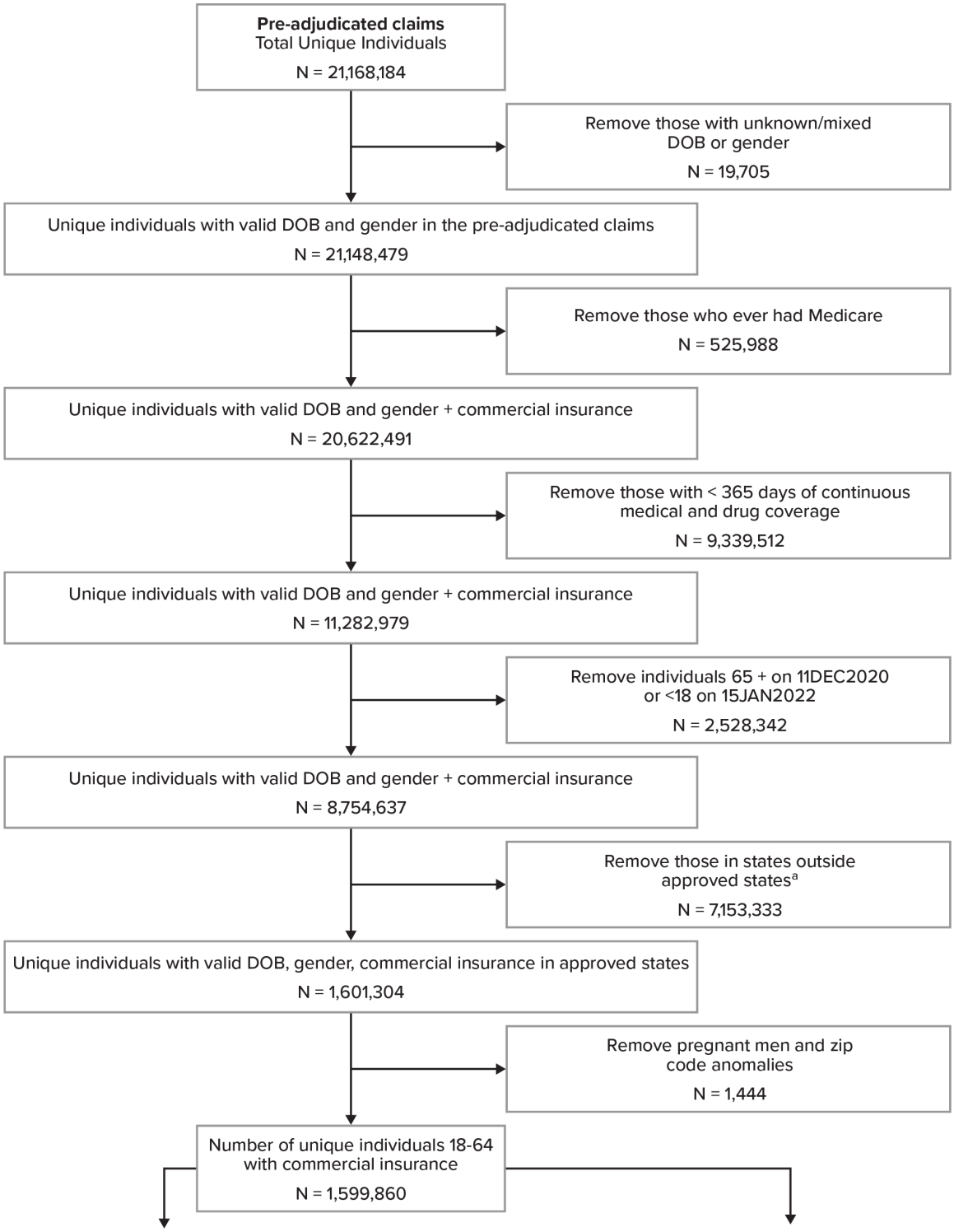
Table C-11-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years Without a Previous COVID-19 Diagnosis

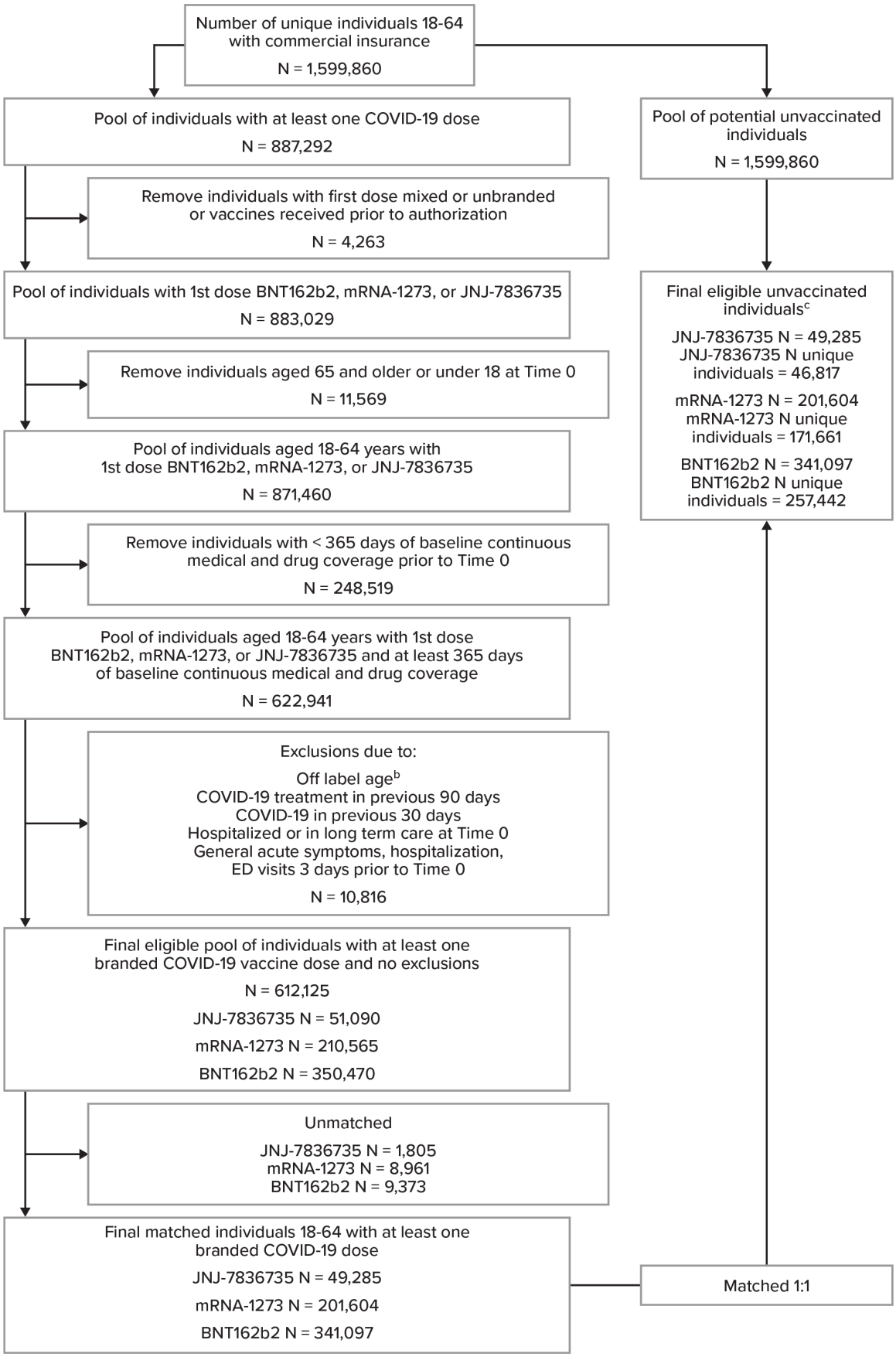
COVID-19 outcome	Vaccine exposure group	N	Number of events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	1,095,509	37,348	256,536,556	0.50 (0.49-0.50)	50% (50%-51%)
	Unvaccinated	1,095,509	44,547	159,560,144	—	—
	mRNA-1273	622,516	17,997	147,144,652	0.42 (0.41-0.42)	58% (58%-59%)
	Unvaccinated	622,516	25,643	91,612,138	—	—
	JNJ-7836735	142,153	6,525	34,599,141	0.63 (0.61-0.65)	37% (35%-39%)
	Unvaccinated	142,153	6,136	21,526,446	—	—
Hospital/ED-diagnosed	BNT162b2	1,095,509	4,310	259,910,339	0.24 (0.23-0.25)	76% (75%-77%)
	Unvaccinated	1,095,509	11,158	163,615,800	—	—
	mRNA-1273	622,516	1,955	148,782,220	0.17 (0.17-0.18)	83% (82%-83%)
	Unvaccinated	622,516	6,710	93,923,615	—	—
	JNJ-7836735	142,153	929	35,214,494	0.34 (0.32-0.37)	66% (63%-68%)
	Unvaccinated	142,153	1,668	22,057,158	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Figure C-1-Optum. Attrition of Adults Aged 18-64 Years in the Primary Adult Analytic Cohorts: Optum Preadjudicated Claims Supplemented With IIS Data, 11 December 2020 – 15 January 2022




Number of unique individuals 18-64 with commercial insurance
N = 1,599,860
Pool of individuals with at least one COVID-19 dose
N = 887,292
Remove individuals with first dose mixed or unbranded or vaccines received prior to authorization
N = 4,263
Pool of individuals with 1st dose BNT162b2, mRNA-1273, or JNJ-7836735
N = 883,029
Remove individuals aged 65 and older or under 18 at Time 0
N = 11,569
Pool of individuals aged 18-64 years with 1st dose BNT162b2, mRNA-1273, or JNJ-7836735
N = 871,460
Remove individuals with < 365 days of baseline continuous medical and drug coverage prior to Time 0
N = 248,519
Pool of individuals aged 18-64 years with 1st dose BNT162b2, mRNA-1273, or JNJ-7836735 and at least 365 days of baseline continuous medical and drug coverage
N = 622,941
Exclusions due to:
Off label age[b]
COVID-19 treatment in previous 90 days
COVID-19 in previous 30 days
Hospitalized or in long term care at Time 0
General acute symptoms, hospitalization, ED visits 3 days prior to Time 0
N = 10,816
Final eligible pool of individuals with at least one branded COVID-19 vaccine dose and no exclusions
N = 612,125
JNJ-7836735 N = 51,090
mRNA-1273 N = 210,565
BNT162b2 N = 350,470
Unmatched
JNJ-7836735 N = 1,805
mRNA-1273 N = 8,961
BNT162b2 N = 9,373
Final matched individuals 18-64 with at least one branded COVID-19 dose
JNJ-7836735 N = 49,285
mRNA-1273 N = 201,604
BNT162b2 N = 341,097
Pool of potential unvaccinated individuals
N = 1,599,860
Final eligible unvaccinated individuals[c]
JNJ-7836735 N = 49,285
JNJ-7836735 N unique individuals = 46,817
mRNA-1273 N = 201,604
mRNA-1273 N unique individuals = 171,661
BNT162b2 N = 341,097
BNT162b2 N unique individuals = 257,442
Matched 1:1

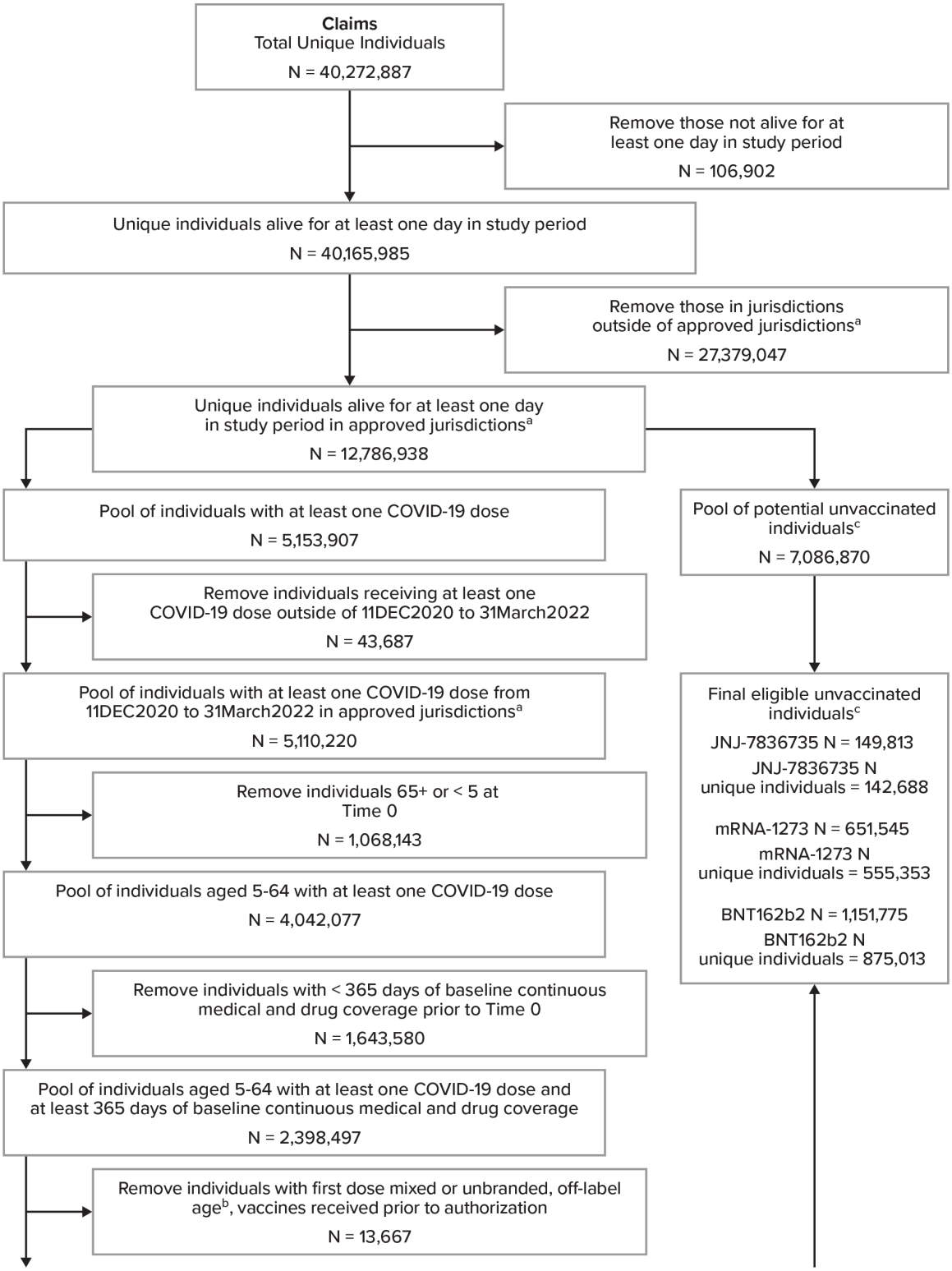
COVID-19 = coronavirus disease 2019; DOB = date of birth; ED = emergency department; IIS = immunization information system.

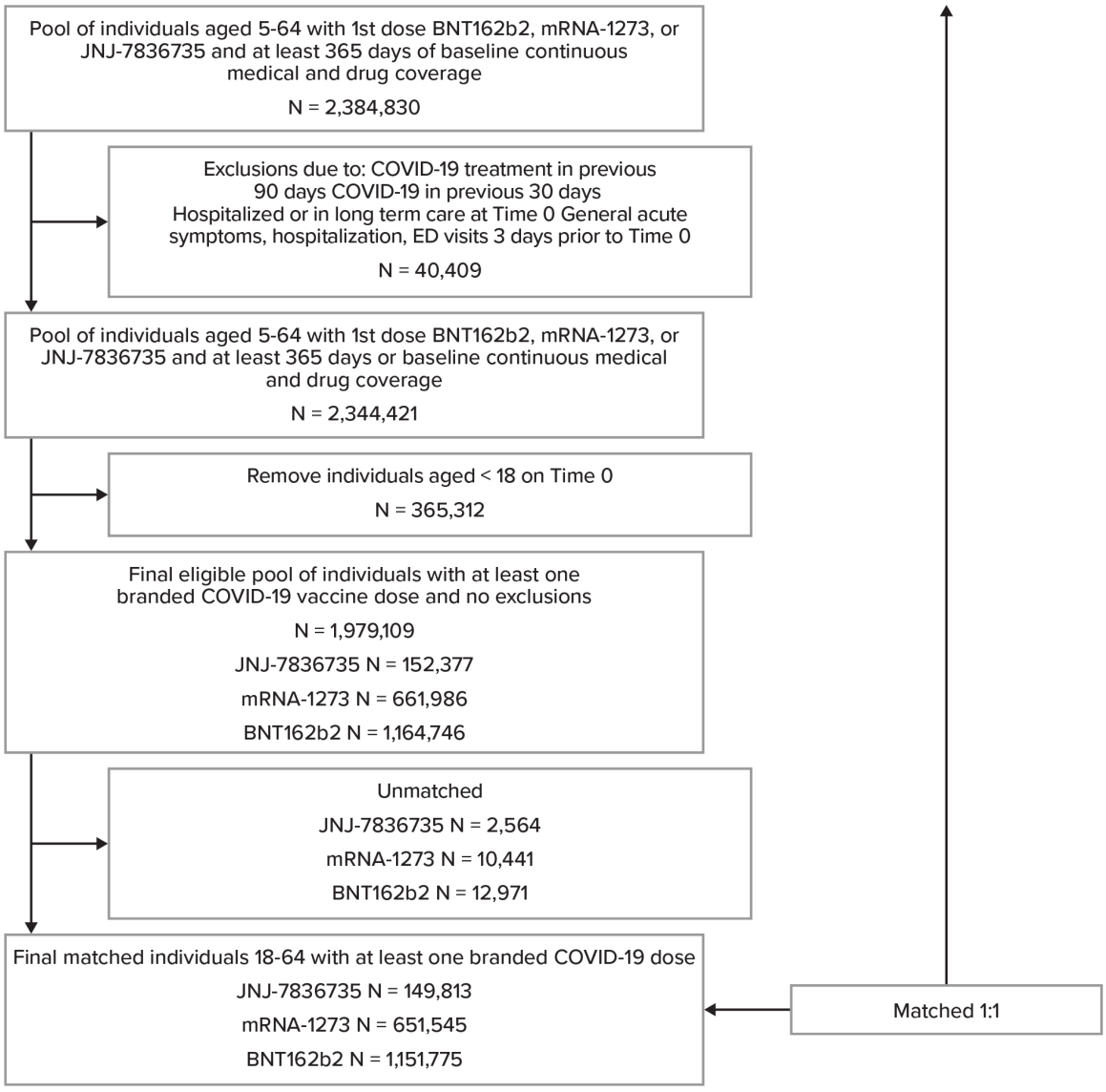
[a] 10 IISs were included from 10 unique US states.

[b] Individuals were removed if they received a COVID-19 vaccine when it was not authorized for their age group.

[c] Individuals in the unvaccinated group may also be in the vaccinated group and/or serve as matches to multiple vaccinated individuals.

Figure C-1-CVS. Attrition of Adults Aged 18-64 Years in the Primary Adult Analytic Cohorts: CVS Health Adjudicated Commercial Claims Supplemented With IIS Data, 11 December 2020 – 31 March 2022





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

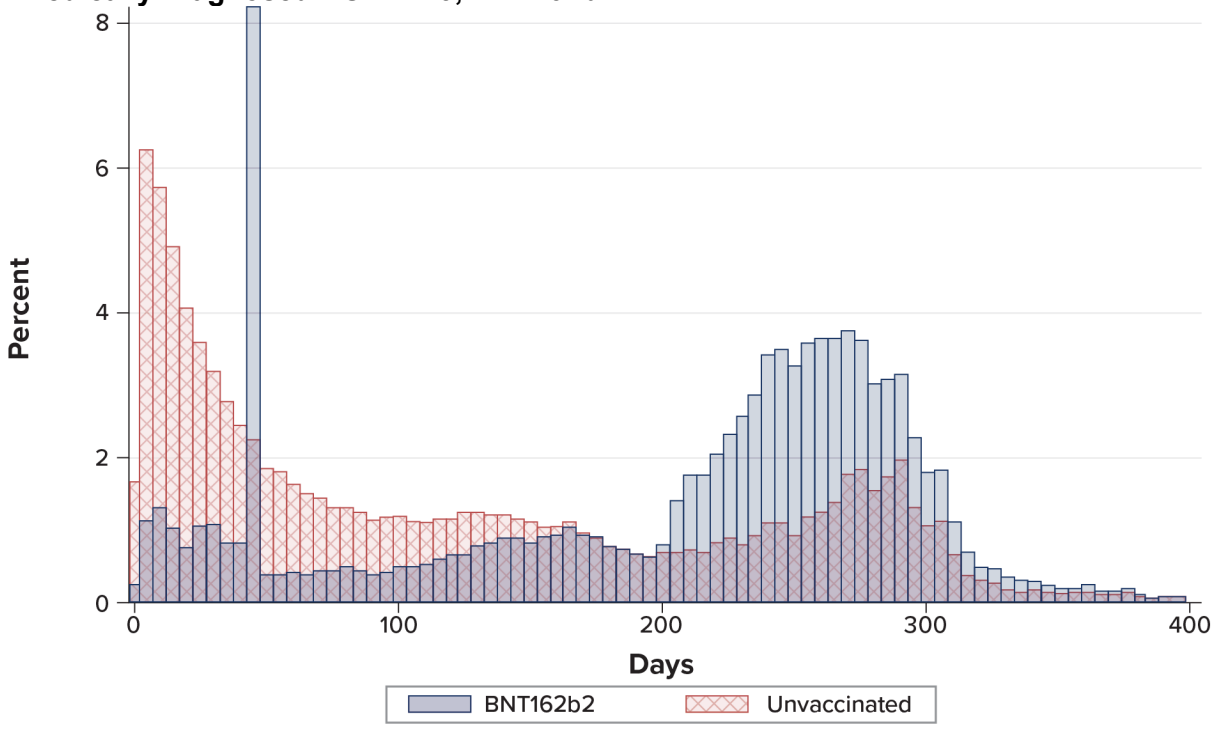
[a] 10 IISs were included from 10 unique US states.

[b] Individuals were removed if they received a COVID-19 vaccine when it was not authorized for their age group.

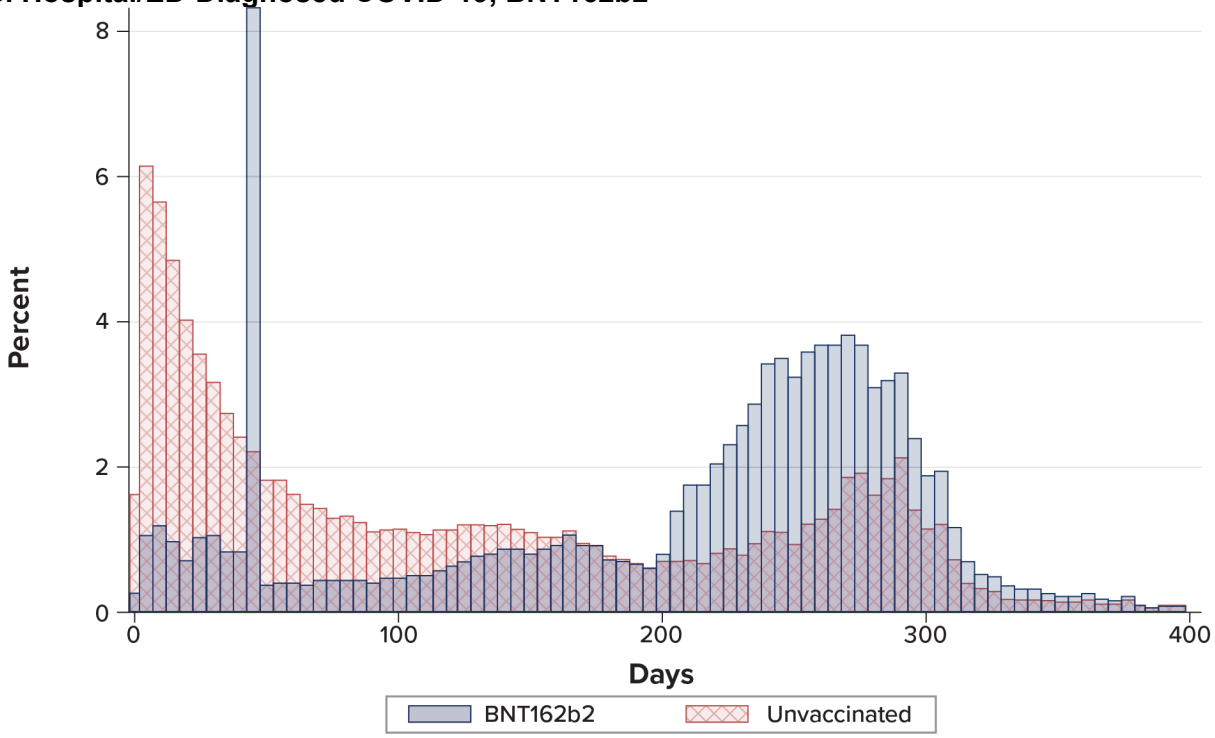
[c] Individuals in the unvaccinated group may also be in the vaccinated group and/or serve as matches to multiple vaccinated individuals.

Figure C-2-Optum. Distribution of Follow-Up Time by Vaccine Exposure Group and Outcome, Optum

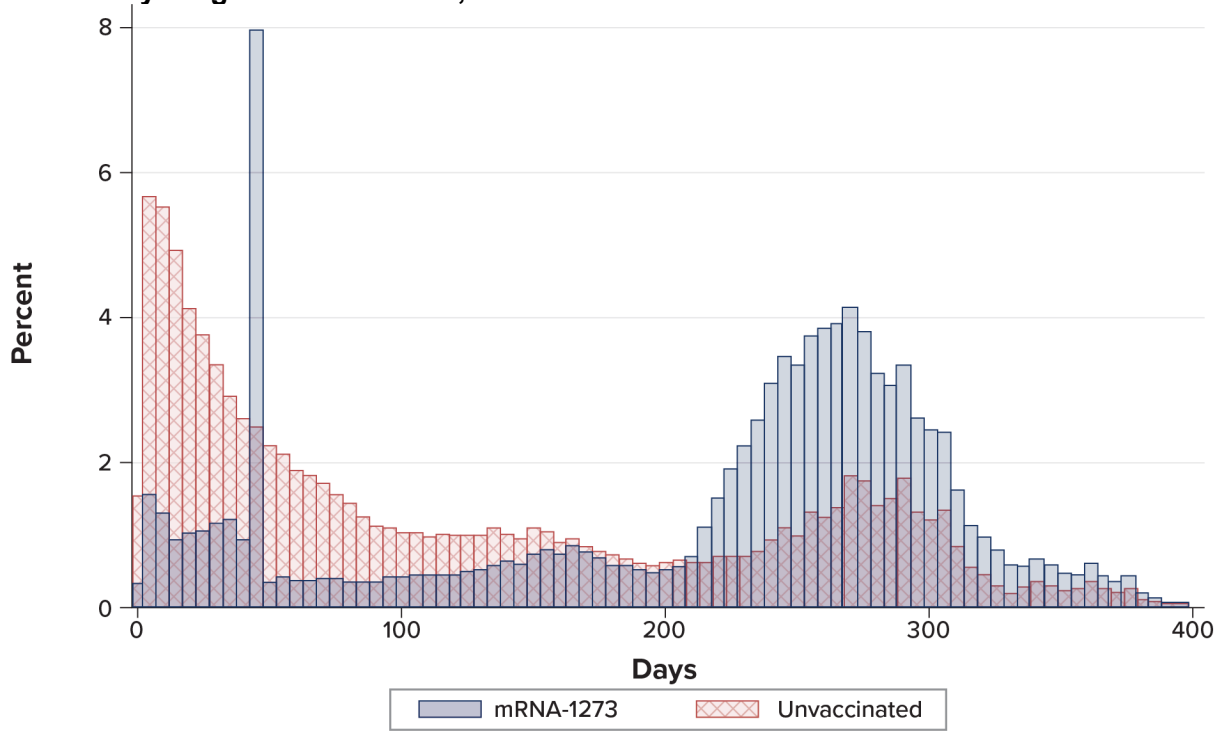
A. Medically Diagnosed COVID-19, BNT162b2



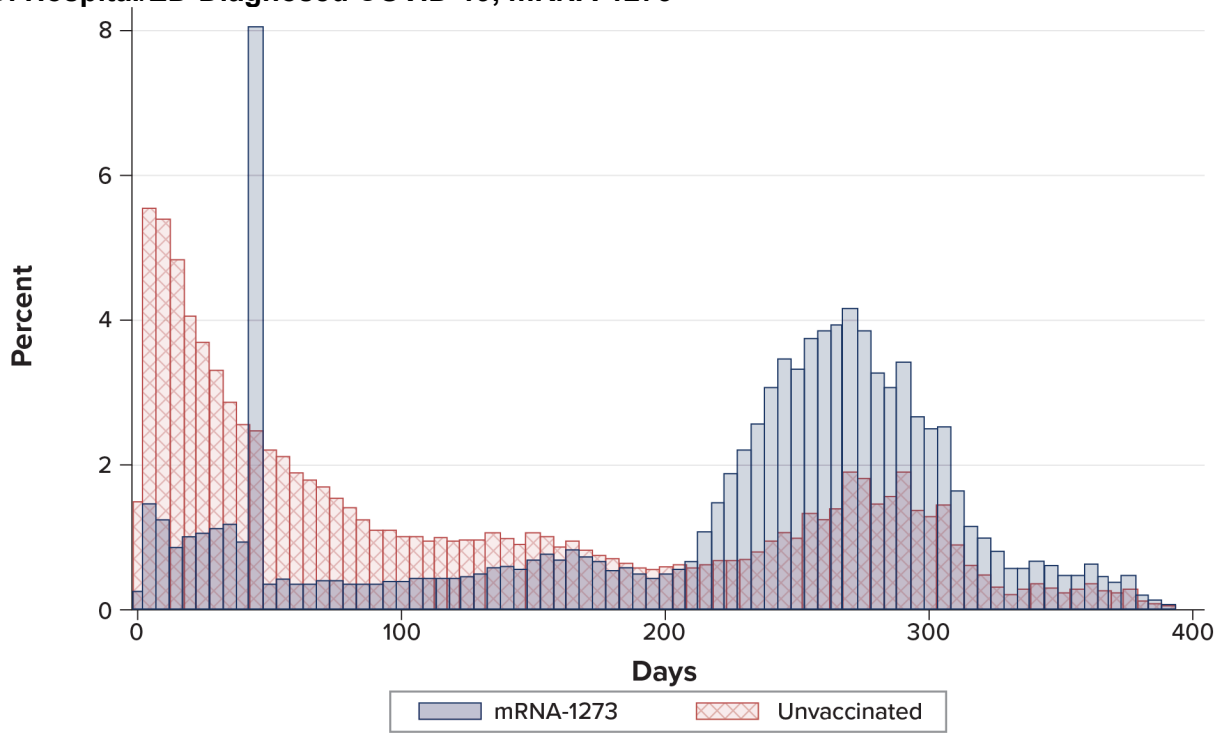
B. Hospital/ED-Diagnosed COVID-19, BNT162b2



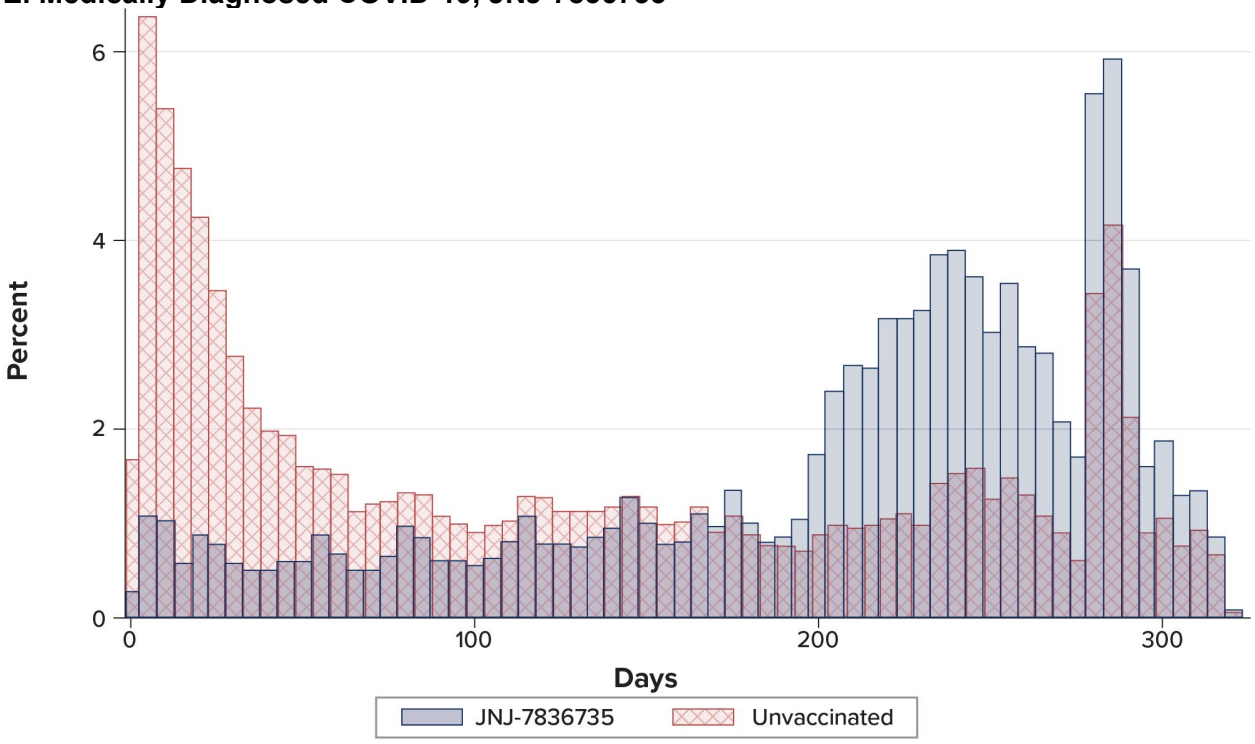
C. Medically Diagnosed COVID-19, mRNA-1273



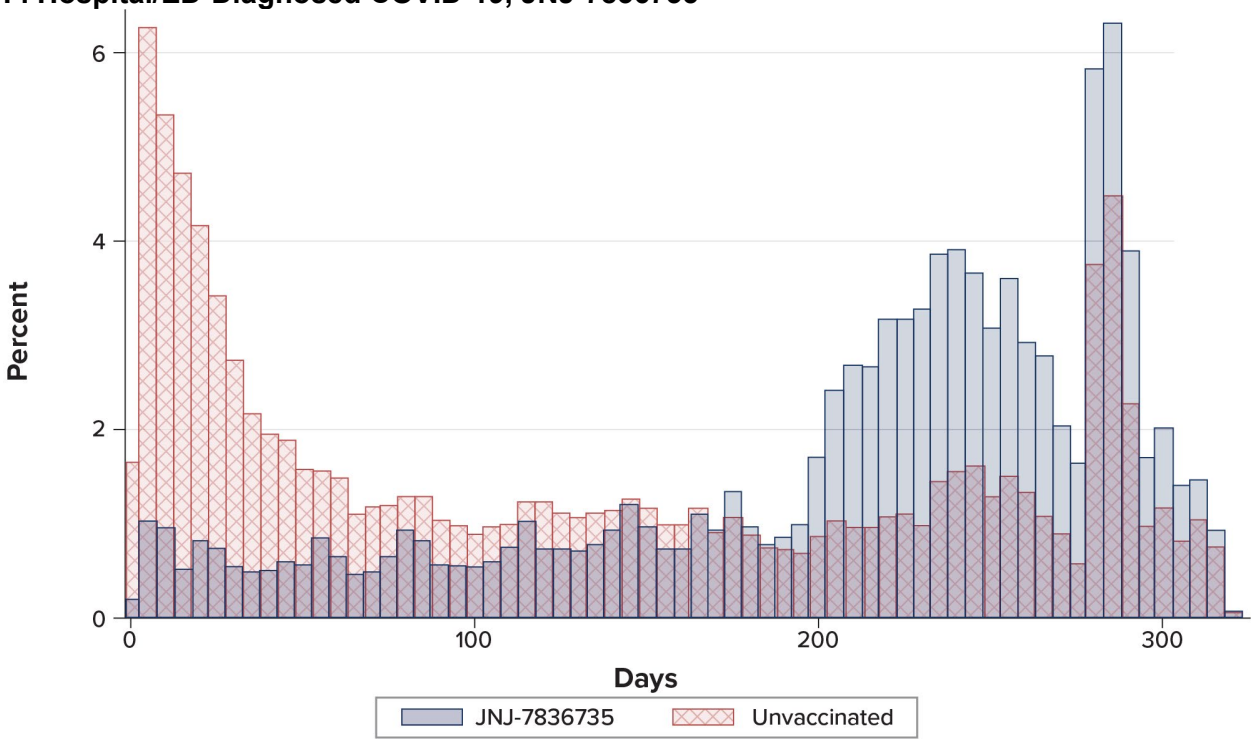
D. Hospital/ED-Diagnosed COVID-19, mRNA-1273



E. Medically Diagnosed COVID-19, JNJ-7836735



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



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

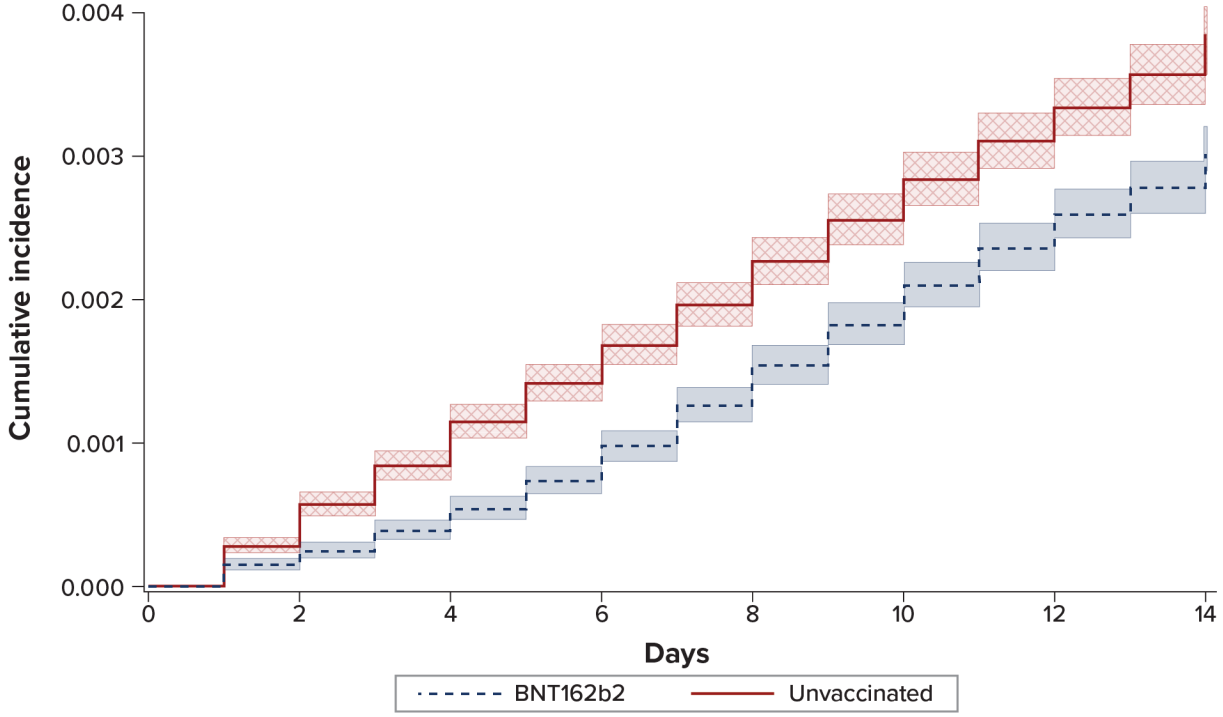
Note: For BNT162b2 and mRNA-1273 (i.e., vaccines with 2-dose primary series), a large number of vaccinated individuals' follow-up ended on day 42 when they were censored for failing to receive a second dose on time.

Figure C-2-CVS. Distribution of Follow-Up Time by vaccine Exposure Group and Outcome, CVS Health

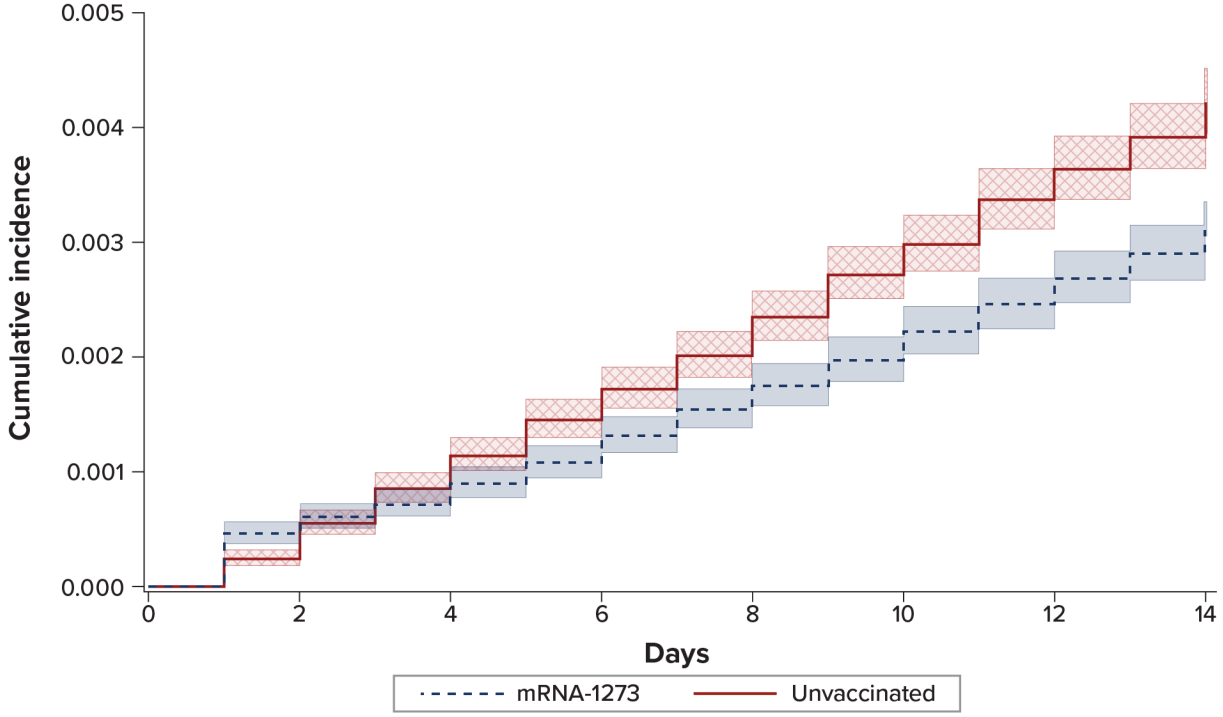
Figure was not generated for CVS Health.

Figure C-3-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Adults, 14 Days After and Including Time 0, Negative Control Outcome Analysis

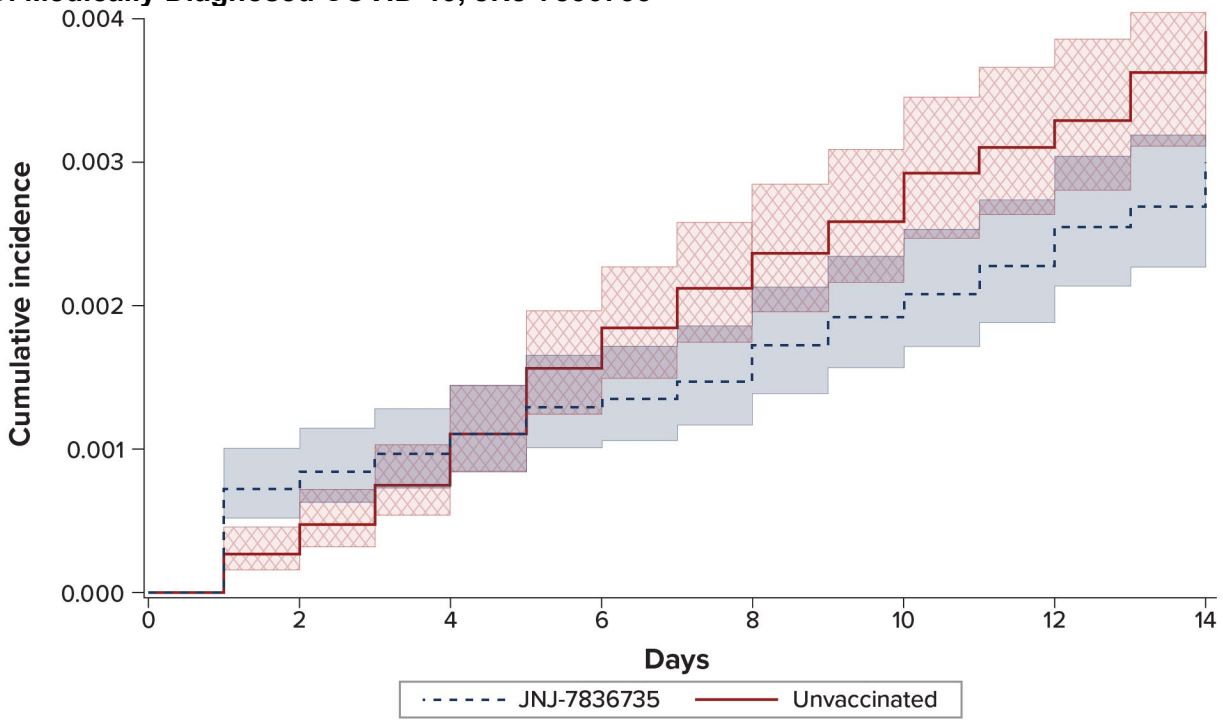
A. Medically Diagnosed COVID-19, BNT162b2



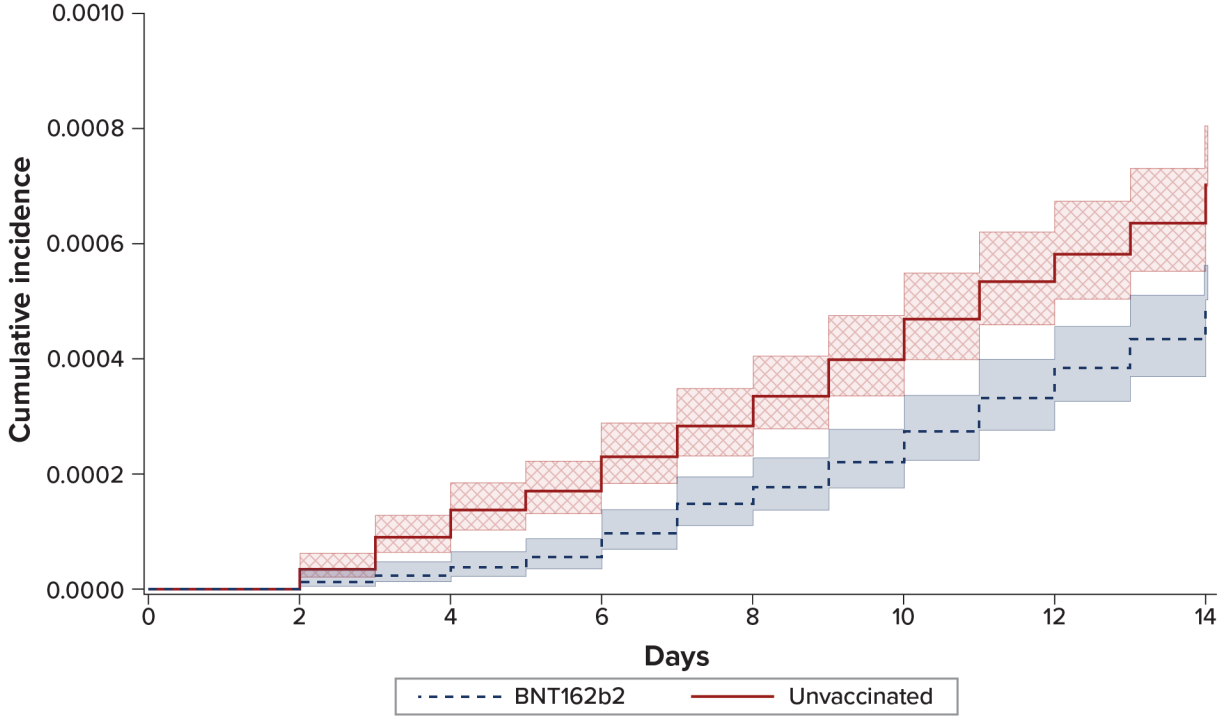
B. Medically Diagnosed COVID-19, mRNA-1273



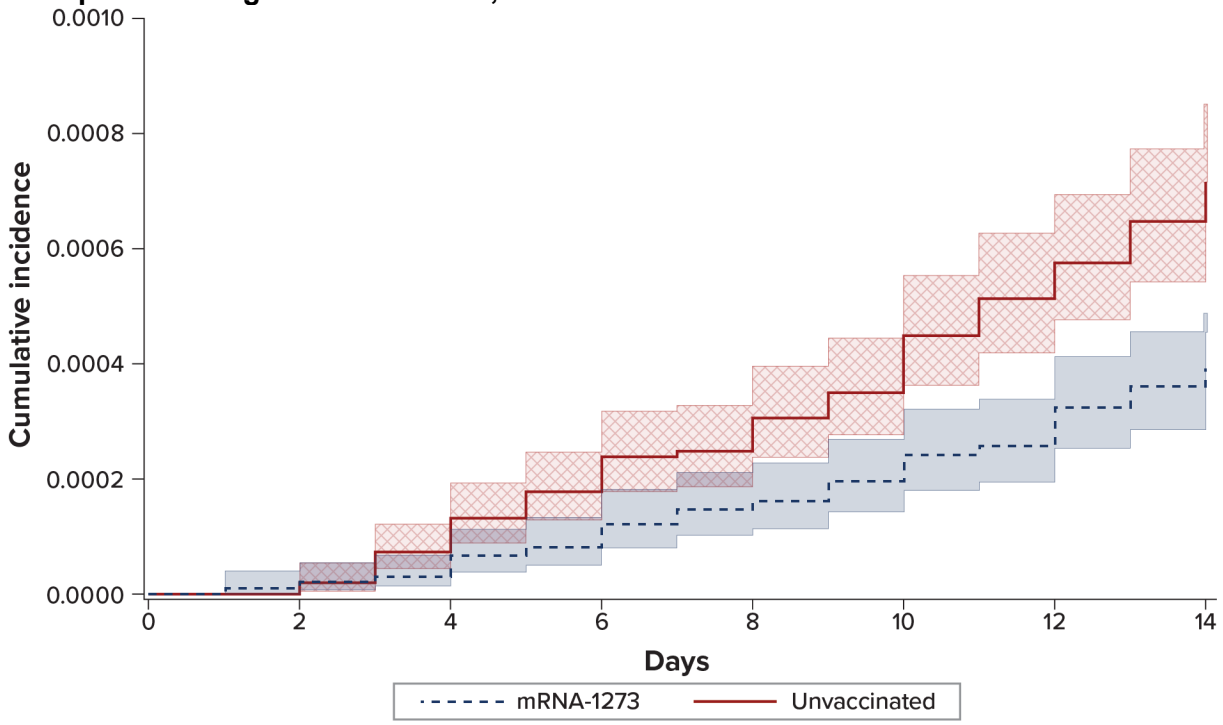
C. Medically Diagnosed COVID-19, JNJ-7836735



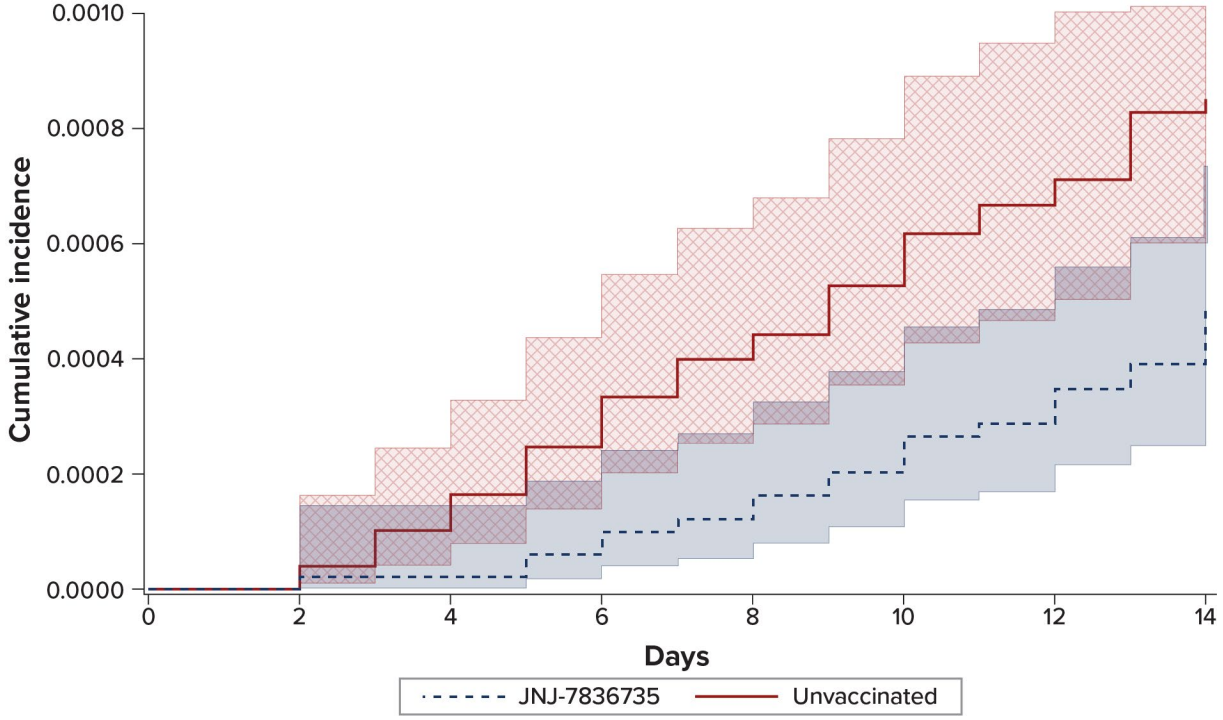
D. Hospital/ED-Diagnosed COVID-19, BNT162b2



E. Hospital/ED-Diagnosed COVID-19, mRNA-1273



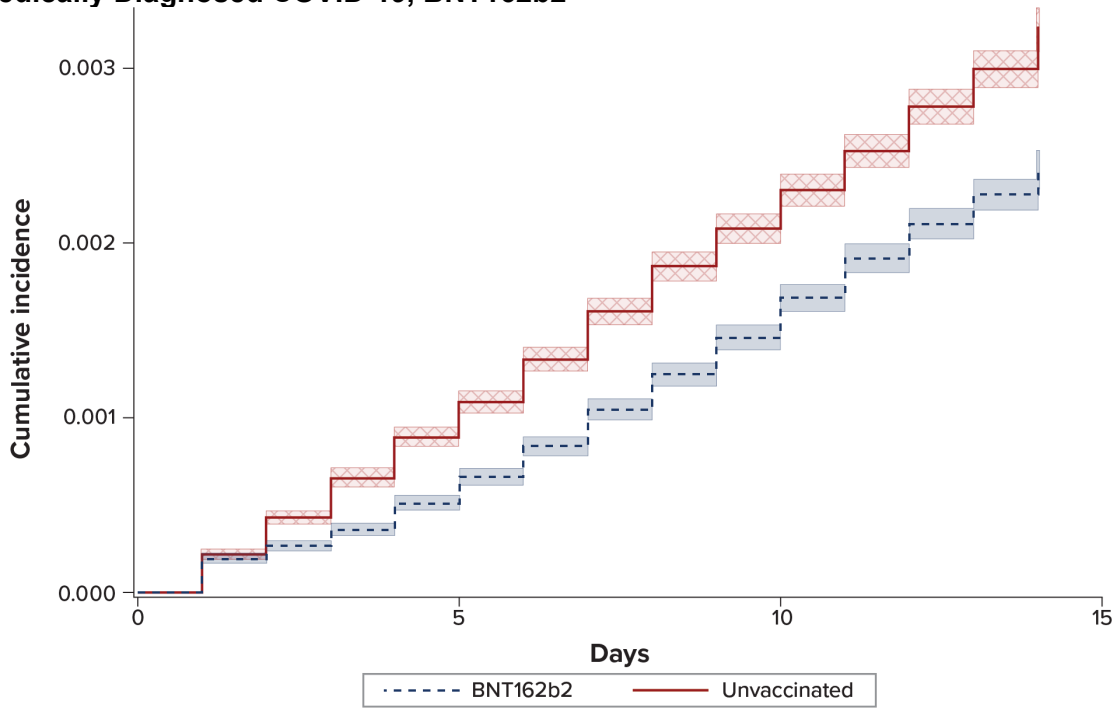
F. Hospital/ED-Diagnosed COVID-19, JNJ-7836735



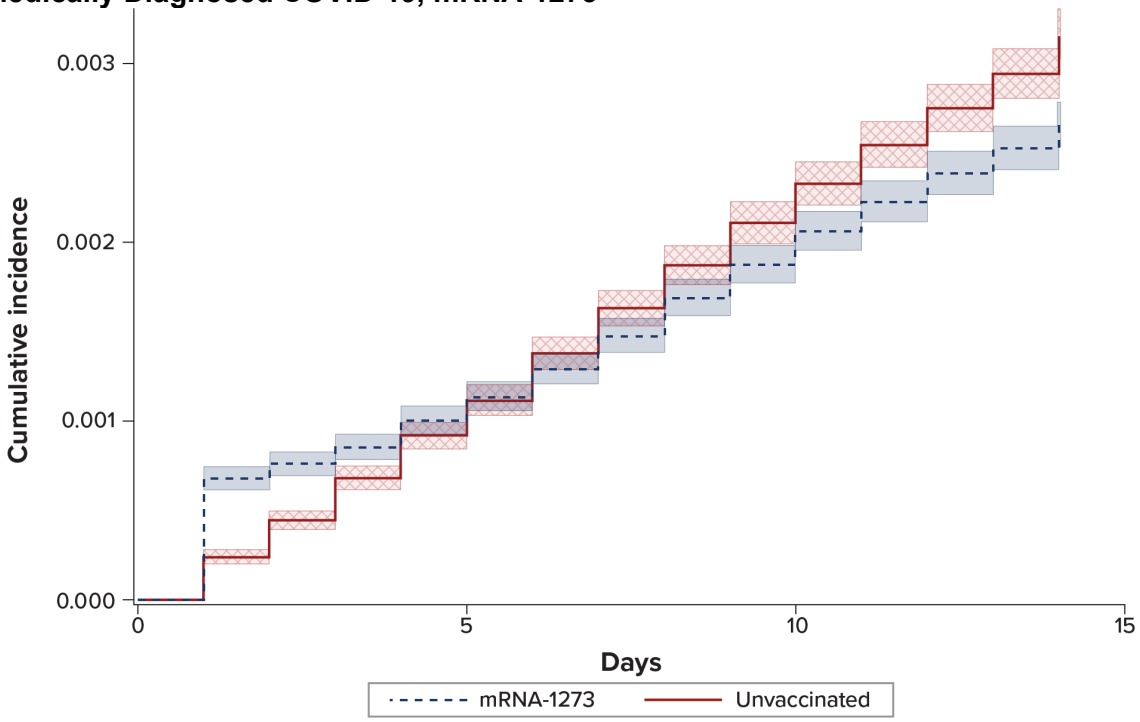
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure C-3-CVS. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Adults, 14 Days After and Including Time 0, Negative Control Outcome Analysis

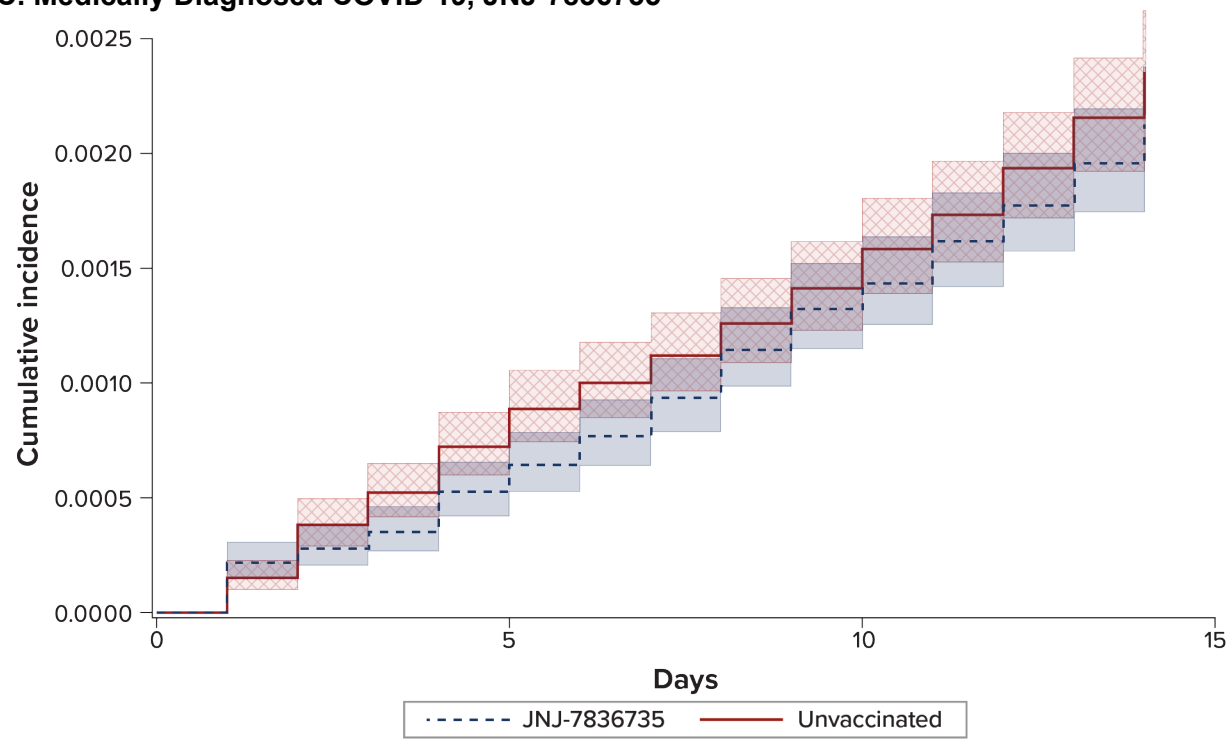
A. Medically Diagnosed COVID-19, BNT162b2



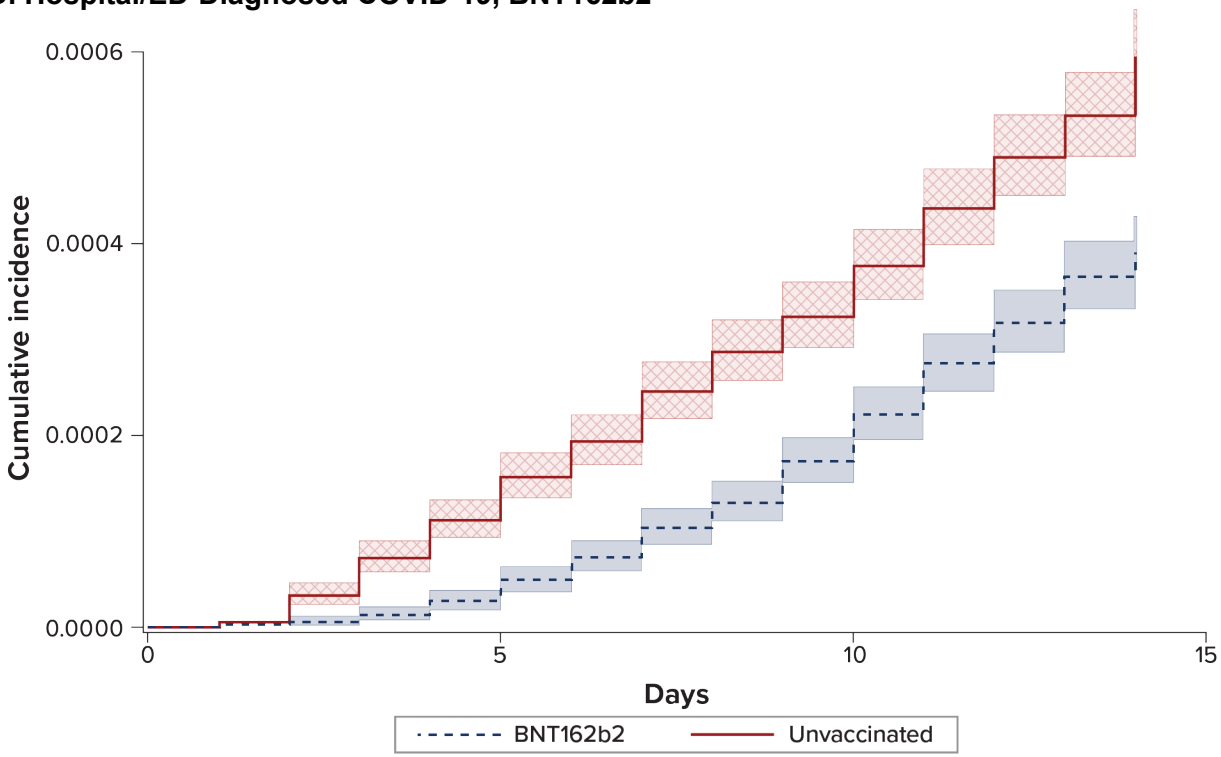
B. Medically Diagnosed COVID-19, mRNA-1273



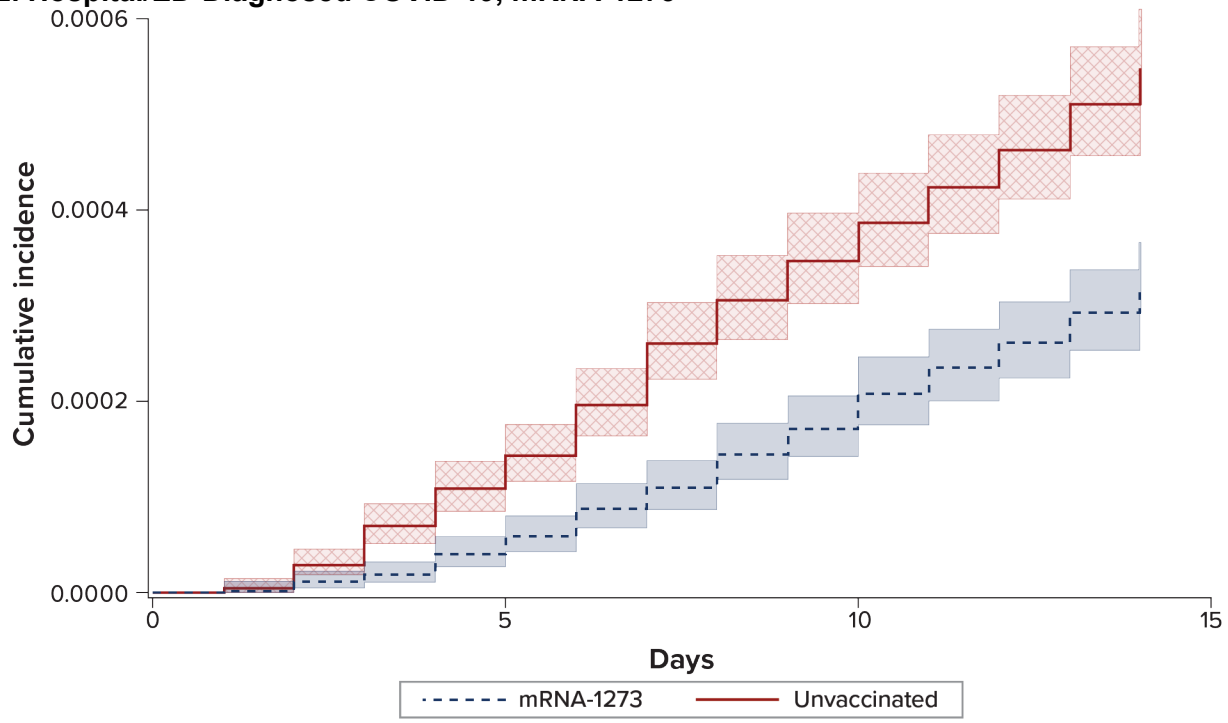
C. Medically Diagnosed COVID-19, JNJ-7836735



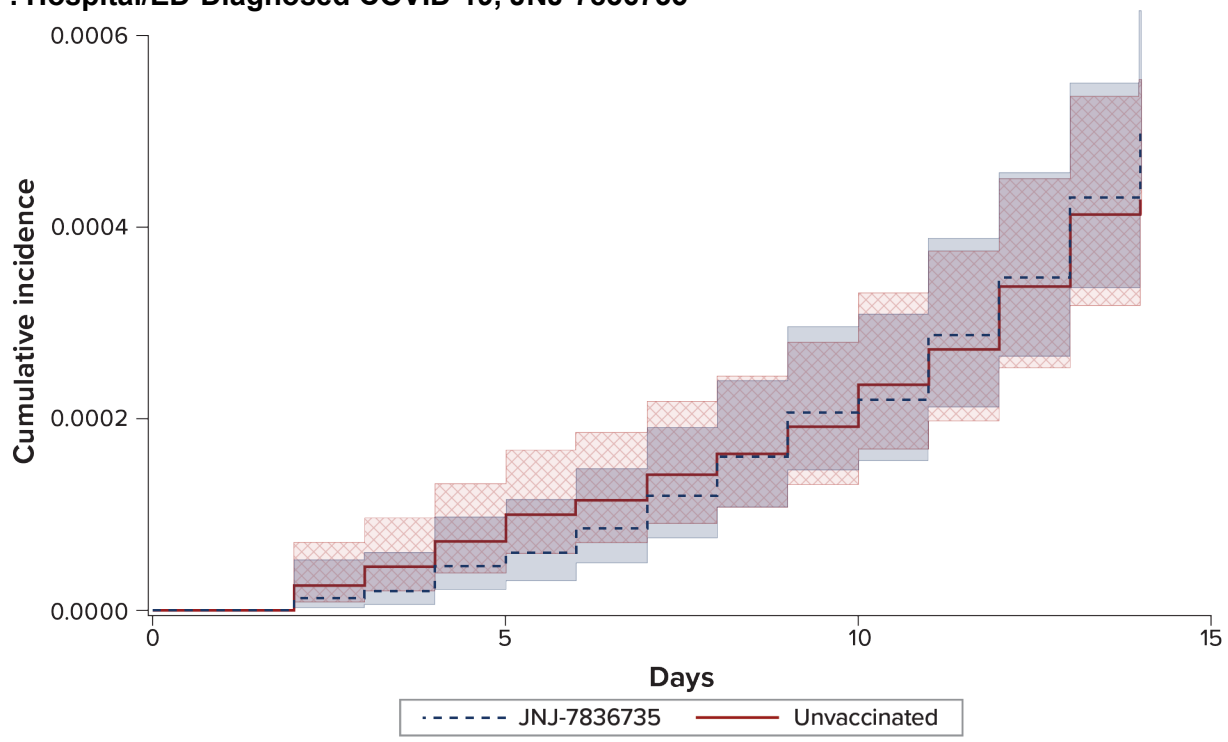
D. Hospital/ED-Diagnosed COVID-19, BNT162b2



E. Hospital/ED-Diagnosed COVID-19, mRNA-1273



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



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

Vaccine Effectiveness Over Time Analyses

Table C-12-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Over Time

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
Medically diagnosed	Day 14	Vaccinated	1,020	0.003015	0.78 (0.72-0.84)	22% (16%-28%)	−0.0008 (−0.0011 to −0.0006)
		Unvaccinated	1,213	0.003844	—	—	—
	Day 28	Vaccinated	1,362	0.004051	0.70 (0.66-0.75)	30% (25%-34%)	−0.0017 (−0.0020 to −0.0014)
		Unvaccinated	1,748	0.005762	—	—	—
	Day 42	Vaccinated	1,758	0.005261	0.57 (0.54-0.61)	43% (39%-46%)	−0.0039 (−0.0044 to −0.0035)
		Unvaccinated	2,612	0.009205	—	—	—
	Day 60	Vaccinated	2,074	0.006325	0.43 (0.41-0.45)	57% (55%-59%)	−0.0084 (−0.0089 to −0.0079)
		Unvaccinated	3,820	0.014726	—	—	—
	Day 90	Vaccinated	2,405	0.007505	0.36 (0.34-0.37)	64% (63%-66%)	−0.0135 (−0.0142 to −0.0128)
		Unvaccinated	5,010	0.021054	—	—	—
	Day 183	Vaccinated	5,433	0.019429	0.35 (0.33-0.36)	65% (64%-67%)	−0.0367 (−0.0379 to −0.0353)
		Unvaccinated	9,882	0.056098	—	—	—
	Day 270	Vaccinated	9,340	0.043553	0.44 (0.42-0.45)	56% (55%-58%)	−0.0564 (−0.0582 to −0.0544)
		Unvaccinated	13,506	0.099982	—	—	—
Hospital/ED-diagnosed	Day 14	Vaccinated	162	0.000482	0.68 (0.55-0.83)	32% (17%-45%)	−0.0002 (−0.0003 to −0.0001)
		Unvaccinated	220	0.000705	—	—	—
	Day 28	Vaccinated	212	0.000636	0.59 (0.49-0.71)	41% (29%-51%)	−0.0004 (−0.0006 to −0.0003)
		Unvaccinated	325	0.001077	—	—	—
	Day 42	Vaccinated	257	0.000777	0.43 (0.36-0.50)	57% (50%-64%)	−0.0010 (−0.0012 to −0.0008)
		Unvaccinated	506	0.001791	—	—	—
	Day 60	Vaccinated	277	0.000846	0.27 (0.23-0.32)	73% (68%-77%)	−0.0023 (−0.0025 to −0.0020)
		Unvaccinated	795	0.0031	—	—	—
	Day 90	Vaccinated	305	0.000945	0.21 (0.18-0.23)	79% (77%-82%)	−0.0036 (−0.0039 to −0.0033)

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
		Unvaccinated	1,072	0.004565	—	—	—
	Day 183	Vaccinated	524	0.001813	0.13 (0.12-0.15)	87% (85%-88%)	−0.0116 (−0.0123 to −0.0111)
		Unvaccinated	2,303	0.013443	—	—	—
	Day 270	Vaccinated	882	0.004074	0.17 (0.15-0.18)	83% (82%-85%)	−0.0202 (−0.0212 to −0.0193)
		Unvaccinated	3,191	0.024279	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

[a] Time 0 is the day of vaccination with Dose 1 in the vaccinated group, or the matched date in the unvaccinated comparator group.

Note: — denotes the reference group.

Table C-12-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Over Time

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
Medically diagnosed	Day 14	Vaccinated	2,791	0.002436	0.75 (0.72-0.79)	25% (21%-28%)	−0.0008 (−0.0009 to −0.0007)
		Unvaccinated	3,495	0.003237	—	—	—
	Day 28	Vaccinated	4,423	0.003877	0.62 (0.60-0.64)	38% (36%-40%)	−0.0024 (−0.0026 to −0.0022)
		Unvaccinated	6,338	0.006252	—	—	—
	Day 42	Vaccinated	5,282	0.004643	0.52 (0.50-0.53)	48% (47%-50%)	−0.0043 (−0.0046 to −0.0041)
		Unvaccinated	8,664	0.008985	—	—	—
	Day 60	Vaccinated	5,892	0.005252	0.44 (0.42-0.45)	56% (55%-58%)	−0.0067 (−0.0070 to −0.0065)
		Unvaccinated	11,002	0.011996	—	—	—
	Day 90	Vaccinated	7,021	0.006405	0.38 (0.36-0.39)	62% (61%-64%)	−0.0106 (−0.0109 to −0.0103)
		Unvaccinated	14,475	0.017042	—	—	—
	Day 183	Vaccinated	16,479	0.016476	0.38 (0.37-0.38)	62% (62%-63%)	−0.0272 (−0.0277 to −0.0267)
		Unvaccinated	28,036	0.043674	—	—	—
	Day 270	Vaccinated	29,331	0.036060	0.46 (0.46-0.47)	54% (53%-54%)	−0.0416 (−0.0425 to −0.0407)
		Unvaccinated	39,133	0.077682	—	—	—
Hospital/ED-diagnosed	Day 14	Vaccinated	447	0.000391	0.66 (0.58-0.75)	34% (25%-42%)	−0.0002 (−0.0003 to −0.0001)
		Unvaccinated	637	0.000596	—	—	—
	Day 28	Vaccinated	742	0.000651	0.52 (0.47-0.57)	48% (43%-53%)	−0.0006 (−0.0007 to −0.0005)
		Unvaccinated	1,261	0.001257	—	—	—
	Day 42	Vaccinated	830	0.000729	0.38 (0.35-0.42)	62% (58%-65%)	−0.0012 (−0.0013 to −0.0011)
		Unvaccinated	1,805	0.001895	—	—	—
	Day 60	Vaccinated	880	0.000779	0.30 (0.28-0.32)	70% (68%-72%)	−0.0018 (−0.0020 to −0.0017)
		Unvaccinated	2,364	0.002616	—	—	—
	Day 90	Vaccinated	977	0.000878	0.23 (0.21-0.25)	77% (75%-79%)	−0.0029 (−0.0031 to −0.0028)
		Unvaccinated	3,191	0.003816	—	—	—

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
	Day 183	Vaccinated	1,920	0.001885	0.17 (0.16-0.18)	83% (82%-84%)	−0.0090 (−0.0092 to −0.0087)
		Unvaccinated	6,765	0.010855	—	—	—
	Day 270	Vaccinated	3,314	0.004006	0.21 (0.20-0.21)	79% (79%-80%)	−0.0155 (−0.0159 to −0.0151)
		Unvaccinated	9,615	0.019530	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

[a] Time 0 is the day of vaccination with Dose 1 in the vaccinated group, or the matched date in the unvaccinated comparator group.

Note: — denotes the reference group.

Table C-13-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of mRNA-1273 COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Over Time

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
Medically diagnosed	Day 14	Vaccinated	620	0.003104	0.74 (0.66-0.82)	26% (18%-34%)	−0.0011 (−0.0015 to −0.0007)
		Unvaccinated	788	0.004217	—	—	—
	Day 28	Vaccinated	898	0.004531	0.54 (0.50-0.59)	46% (41%-50%)	−0.0038 (−0.0043 to −0.0032)
		Unvaccinated	1,448	0.00832	—	—	—
	Day 42	Vaccinated	1,048	0.005326	0.46 (0.43-0.50)	54% (50%-57%)	−0.0062 (−0.0068 to −0.0056)
		Unvaccinated	1,900	0.011515	—	—	—
	Day 60	Vaccinated	1,118	0.005738	0.37 (0.35-0.40)	63% (60%-65%)	−0.0097 (−0.0104 to −0.0090)
		Unvaccinated	2,400	0.015485	—	—	—
	Day 90	Vaccinated	1,262	0.006606	0.31 (0.29-0.33)	69% (67%-71%)	−0.0148 (−0.0157 to −0.0140)
		Unvaccinated	3,045	0.021449	—	—	—
	Day 183	Vaccinated	2,399	0.014121	0.26 (0.25-0.27)	74% (73%-75%)	−0.0404 (−0.0419 to −0.0389)
		Unvaccinated	5,701	0.054505	—	—	—
	Day 270	Vaccinated	4,281	0.03172	0.32 (0.31-0.33)	68% (67%-69%)	−0.0680 (−0.0704 to −0.0654)
		Unvaccinated	8,033	0.099753	—	—	—
Hospital/ED-diagnosed	Day 14	Vaccinated	77	0.00039	0.54 (0.41-0.71)	46% (29%-59%)	−0.0003 (−0.0005 to −0.0002)
		Unvaccinated	133	0.000716	—	—	—
	Day 28	Vaccinated	115	0.000587	0.37 (0.29-0.45)	63% (55%-71%)	−0.0010 (−0.0012 to −0.0008)
		Unvaccinated	272	0.001584	—	—	—
	Day 42	Vaccinated	127	0.000651	0.28 (0.23-0.34)	72% (66%-77%)	−0.0017 (−0.0019 to −0.0014)
		Unvaccinated	380	0.002339	—	—	—
	Day 60	Vaccinated	133	0.000691	0.21 (0.18-0.26)	79% (74%-82%)	−0.0025 (−0.0028 to −0.0022)
		Unvaccinated	491	0.003216	—	—	—
	Day 90	Vaccinated	144	0.000758	0.17 (0.14-0.20)	83% (80%-86%)	−0.0038 (−0.0041 to −0.0034)
		Unvaccinated	633	0.00452	—	—	—

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
	Day 183	Vaccinated	216	0.001236	0.09 (0.08-0.11)	91% (89%-92%)	−0.0119 (−0.0127 to −0.0112)
		Unvaccinated	1,323	0.013113	—	—	—
	Day 270	Vaccinated	382	0.002824	0.12 (0.10-0.13)	88% (87%-90%)	−0.0216 (−0.0229 to −0.0205)
		Unvaccinated	1,903	0.024429	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

[a] Time 0 is the day of vaccination with Dose 1 in the vaccinated group, or the matched date in the unvaccinated comparator group.

Note: — denotes the reference group.

Table C-13-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of mRNA-1273 COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Over Time

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
Medically diagnosed	Day 14	Vaccinated	1,721	0.002654	0.84 (0.79-0.90)	16% (10%-21%)	−0.0005 (−0.0007 to −0.0003)
		Unvaccinated	1,944	0.003162	—	—	—
	Day 28	Vaccinated	2,450	0.003793	0.61 (0.58-0.64)	39% (36%-42%)	−0.0024 (−0.0026 to −0.0022)
		Unvaccinated	3,574	0.006195	—	—	—
	Day 42	Vaccinated	2,930	0.004553	0.51 (0.49-0.53)	49% (47%-51%)	−0.0044 (−0.0047 to −0.0041)
		Unvaccinated	4,898	0.008940	—	—	—
	Day 60	Vaccinated	3,184	0.005011	0.42 (0.40-0.44)	58% (56%-60%)	−0.0069 (−0.0073 to −0.0066)
		Unvaccinated	6,211	0.011948	—	—	—
	Day 90	Vaccinated	3,585	0.005758	0.35 (0.33-0.36)	65% (64%-67%)	−0.0109 (−0.0113 to −0.0105)
		Unvaccinated	7,994	0.016618	—	—	—
	Day 183	Vaccinated	6,811	0.012016	0.29 (0.28-0.30)	71% (70%-72%)	−0.0295 (−0.0303 to −0.0288)
		Unvaccinated	15,000	0.041497	—	—	—
	Day 270	Vaccinated	12,690	0.027099	0.35 (0.34-0.36)	65% (64%-66%)	−0.0499 (−0.0510 to −0.0487)
		Unvaccinated	21,795	0.076958	—	—	—
Hospital/ED-diagnosed	Day 14	Vaccinated	206	0.000319	0.58 (0.49-0.69)	42% (31%-51%)	−0.0002 (−0.0003 to −0.0002)
		Unvaccinated	335	0.000548	—	—	—
	Day 28	Vaccinated	300	0.000465	0.38 (0.33-0.43)	62% (57%-67%)	−0.0008 (−0.0009 to −0.0007)
		Unvaccinated	703	0.001236	—	—	—
	Day 42	Vaccinated	341	0.000530	0.28 (0.25-0.31)	72% (69%-75%)	−0.0014 (−0.0015 to −0.0012)
		Unvaccinated	1,016	0.001883	—	—	—
	Day 60	Vaccinated	362	0.000568	0.22 (0.19-0.24)	78% (76%-81%)	−0.0021 (−0.0022 to −0.0019)
		Unvaccinated	1,344	0.002632	—	—	—
	Day 90	Vaccinated	394	0.000627	0.16 (0.15-0.18)	84% (82%-85%)	−0.0032 (−0.0034 to −0.0031)
		Unvaccinated	1,811	0.003858	—	—	—

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
	Day 183	Vaccinated	704	0.001230	0.11 (0.10-0.12)	89% (88%-90%)	−0.0097 (−0.0101 to −0.0093)
		Unvaccinated	3,810	0.010954	—	—	—
	Day 270	Vaccinated	1,377	0.002939	0.14 (0.13-0.15)	86% (85%-87%)	−0.0177 (−0.0183 to −0.0170)
		Unvaccinated	5,665	0.020592	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

[a] Time 0 is the day of vaccination with Dose 1 in the vaccinated group, or the matched date in the unvaccinated comparator group.

Note: — denotes the reference group.

Table C-14-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of JNJ-7836735 COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Over Time

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
Medically diagnosed	Day 14	Vaccinated	147	0.003000	0.76 (0.61-0.95)	24% (5%-39%)	−0.0009 (−0.0017 to −0.0002)
		Unvaccinated	179	0.003920	—	—	—
	Day 60	Vaccinated	341	0.007120	0.49 (0.43-0.57)	51% (43%-57%)	−0.0075 (−0.0089 to −0.0060)
		Unvaccinated	555	0.014580	—	—	—
	Day 90	Vaccinated	457	0.009720	0.45 (0.40-0.51)	55% (49%-60%)	−0.0117 (−0.0136 to −0.0099)
		Unvaccinated	753	0.021430	—	—	—
	Day 183	Vaccinated	1,163	0.027380	0.48 (0.44-0.51)	52% (49%-56%)	−0.0298 (−0.0333 to −0.0266)
		Unvaccinated	1,541	0.057210	—	—	—
	Day 270	Vaccinated	1,901	0.059790	0.58 (0.54-0.61)	42% (39%-46%)	−0.0441 (−0.0500 to −0.0388)
		Unvaccinated	2,132	0.103920	—	—	—
Hospital/ED-diagnosed	Day 14	Vaccinated	24	0.000490	0.58 (0.34-0.93)	42% (7%-66%)	−0.0004 (−0.0007 to −0.0001)
		Unvaccinated	39	0.000850	—	—	—
	Day 60	Vaccinated	59	0.001260	0.36 (0.26-0.49)	64% (51%-74%)	−0.0023 (−0.0030 to −0.0016)
		Unvaccinated	135	0.003530	—	—	—
	Day 90	Vaccinated	71	0.001520	0.30 (0.22-0.39)	70% (61%-78%)	−0.0035 (−0.0044 to −0.0027)
		Unvaccinated	180	0.005070	—	—	—
	Day 183	Vaccinated	156	0.003680	0.26 (0.21-0.31)	74% (69%-79%)	−0.0106 (−0.0124 to −0.0090)
		Unvaccinated	382	0.014300	—	—	—
	Day 270	Vaccinated	242	0.007700	0.31 (0.25-0.36)	69% (64%-75%)	−0.0175 (−0.0202 to −0.0151)
		Unvaccinated	518	0.025230	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

[a] Time 0 is the day of vaccination with Dose 1 in the vaccinated group, or the matched date in the unvaccinated comparator group.

Note: — denotes the reference group.

Table C-14-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of JNJ-7836735 COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, Over Time

COVID-19 outcome	Timepoint after Time 0[a]	Vaccine exposure group	Number of events	Cumulative incidence	sIPTW RR (95% CI)	VE (95% CI)	sIPTW RD (95% CI)
Medically diagnosed	Day 14	Vaccinated	317	0.002127	0.90 (0.76-1.05)	10% (−5% to 24%)	−0.0002 (−0.0006 to 0.0001)
		Unvaccinated	329	0.002352	—	—	—
	Day 60	Vaccinated	937	0.006372	0.61 (0.56-0.65)	39% (35%-44%)	−0.0042 (−0.0048 to −0.0035)
		Unvaccinated	1,230	0.010526	—	—	—
	Day 90	Vaccinated	1,319	0.009054	0.57 (0.53-0.61)	43% (39%-47%)	−0.0069 (−0.0077 to −0.0060)
		Unvaccinated	1,733	0.015955	—	—	—
	Day 183	Vaccinated	3,349	0.024350	0.54 (0.52-0.57)	46% (43%-48%)	−0.0204 (−0.0220 to −0.0188)
		Unvaccinated	3,823	0.044758	—	—	—
	Day 270	Vaccinated	5,572	0.050406	0.61 (0.59-0.63)	39% (37%-41%)	−0.0326 (−0.0350 to −0.0300)
		Unvaccinated	5,632	0.082978	—	—	—
Hospital/ED-diagnosed	Day 14	Vaccinated	74	0.000499	1.16 (0.78-1.68)	−16% (−68% to 22%)	0.0001 (−0.0001 to 0.0002)
		Unvaccinated	59	0.000429	—	—	—
	Day 60	Vaccinated	165	0.001116	0.45 (0.36-0.54)	55% (46%-64%)	−0.0014 (−0.0017 to −0.0010)
		Unvaccinated	287	0.002490	—	—	—
	Day 90	Vaccinated	228	0.001562	0.39 (0.32-0.45)	61% (55%-68%)	−0.0025 (−0.0029 to −0.0020)
		Unvaccinated	430	0.004034	—	—	—
	Day 183	Vaccinated	505	0.003654	0.31 (0.27-0.34)	69% (66%-73%)	−0.0083 (−0.0091 to −0.0075)
		Unvaccinated	1,005	0.011923	—	—	—
	Day 270	Vaccinated	798	0.007088	0.32 (0.29-0.35)	68% (65%-71%)	−0.0150 (−0.0162 to −0.0138)
		Unvaccinated	1,487	0.022045	—	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

[a] Time 0 is the day of vaccination with Dose 1 in the vaccinated group, or the matched date in the unvaccinated comparator group.

Note: — denotes the reference group.

Table C-15-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, by SARS-CoV-2 Variant Era

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	sIPTW HR (95% CI)	VE (95% CI)
Pre-Delta	Medically diagnosed	BNT162b2	262,324	1,181	0.40 (0.37-0.43)	60% (57%-63%)
		Unvaccinated	262,324	2,200	—	—
		mRNA-1273	167,634	743	0.33 (0.30-0.36)	67% (64%-70%)
		Unvaccinated	167,634	1,684	—	—
		JNJ-7836735	37,705	167	0.45 (0.37-0.55)	55% (45%-63%)
		Unvaccinated	37,705	284	—	—
	Hospital/ED-diagnosed	BNT162b2	262,324	138	0.23 (0.18-0.28)	77% (72%-82%)
		Unvaccinated	262,324	444	—	—
		mRNA-1273	167,634	77	0.16 (0.12-0.21)	84% (79%-88%)
		Unvaccinated	167,634	342	—	—
		JNJ-7836735	37,705	29	0.35 (0.22-0.56)	65% (44%-78%)
		Unvaccinated	37,705	62	—	—
Delta	Medically diagnosed	BNT162b2	74,026	1,247	0.43 (0.40-0.46)	57% (54%-60%)
		Unvaccinated	74,026	2,758	—	—
		mRNA-1273	31,209	466	0.38 (0.34-0.42)	62% (58%-66%)
		Unvaccinated	31,209	1,199	—	—
		JNJ-7836735	11,234	327	0.65 (0.57-0.76)	35% (24%-43%)
		Unvaccinated	11,234	435	—	—
	Hospital/ED-diagnosed	BNT162b2	74,026	155	0.23 (0.20-0.28)	77% (72%-80%)
		Unvaccinated	74,026	645	—	—
		mRNA-1273	31,209	60	0.22 (0.17-0.29)	78% (71%-83%)
		Unvaccinated	31,209	276	—	—
		JNJ-7836735	11,234	55	0.41 (0.30-0.56)	59% (44%-70%)
		Unvaccinated	11,234	121	—	—
Omicron	Medically diagnosed	BNT162b2	4,747	44	0.90 (0.60-1.36)	9.8% (−36% to 40%)
		Unvaccinated	4,747	48	—	—
		mRNA-1273	2,761	37	1.06 (0.66-1.69)	−5.8% (−69% to 34%)
		Unvaccinated	2,761	34	—	—

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	sIPTW HR (95% CI)	VE (95% CI)
		JNJ-7836735	346	< 11	1.19 (0.37-3.86)	−19% (−286% to 63%)
		Unvaccinated	346	< 11	—	—
	Hospital/ED-diagnosed	BNT162b2	4,747	< 11	0.75 (0.30-1.86)	25% (−86% to 70%)
		Unvaccinated	4,747	11	—	—
		mRNA-1273	2,761	< 11	1.01 (0.25-4.06)	−1.3% (−306% to 75%)
		Unvaccinated	2,761	< 11	—	—
		JNJ-7836735	346	0	0.00 (0.00-0.00)	100% (100%-100%)
		Unvaccinated	346	< 11	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

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

Table C-15-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years, by SARS-CoV-2 Variant Era

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	sIPTW HR (95% CI)	VE (95% CI)
Pre-Delta	Medically diagnosed	BNT162b2	906,696	3,710	0.40 (0.38-0.41)	60% (59%-62%)
		Unvaccinated	906,696	6,961	—	—
		mRNA-1273	543,650	2,258	0.41 (0.39-0.43)	59% (57%-61%)
		Unvaccinated	543,650	4,236	—	—
		JNJ-7836735	112,783	384	0.54 (0.47-0.62)	46% (38%-53%)
		Unvaccinated	112,783	541	—	—
	Hospital/ED-diagnosed	BNT162b2	906,696	458	0.23 (0.21-0.26)	77% (74%-79%)
		Unvaccinated	906,696	1,456	—	—
		mRNA-1273	543,650	205	0.16 (0.14-0.19)	84% (81%-86%)
		Unvaccinated	543,650	922	—	—
		JNJ-7836735	112,783	61	0.38 (0.27-0.52)	62% (48%-73%)
		Unvaccinated	112,783	121	—	—
Delta	Medically diagnosed	BNT162b2	217,119	2,935	0.42 (0.41-0.44)	58% (56%-59%)
		Unvaccinated	217,119	6,219	—	—
		mRNA-1273	92,505	932	0.33 (0.31-0.36)	67% (64%-69%)
		Unvaccinated	92,505	2,648	—	—
		JNJ-7836735	34,125	788	0.62 (0.56-0.68)	38% (32%-44%)
		Unvaccinated	34,125	1,053	—	—
	Hospital/ED-diagnosed	BNT162b2	217,119	503	0.28 (0.25-0.31)	72% (69%-75%)
		Unvaccinated	217,119	1,668	—	—
		mRNA-1273	92,505	167	0.21 (0.18-0.25)	79% (75%-82%)
		Unvaccinated	92,505	760	—	—
		JNJ-7836735	34,125	138	0.39 (0.31-0.47)	61% (53%-69%)
		Unvaccinated	34,125	310	—	—
Omicron	Medically diagnosed	BNT162b2	27,960	342	0.72 (0.62-0.83)	28% (17%-38%)
		Unvaccinated	27,960	485	—	—
		mRNA-1273	15,390	185	0.63 (0.52-0.75)	37% (25%-48%)
		Unvaccinated	15,390	308	—	—

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	sIPTW HR (95% CI)	VE (95% CI)
		JNJ-7836735	2,905	32	1.18 (0.70-1.96)	−18% (−96% to 30%)
		Unvaccinated	2,905	27	—	—
	Hospital/ED-diagnosed	BNT162b2	27,960	32	0.45 (0.30-0.69)	55% (31%-70%)
		Unvaccinated	27,960	75	—	—
		mRNA-1273	15,390	29	0.77 (0.47-1.25)	23% (−25% to 53%)
		Unvaccinated	15,390	39	—	—
		JNJ-7836735	2,905	< 11	1.56 (0.49-4.91)	−56% (−391% to 51%)
		Unvaccinated	2,905	< 11	—	—

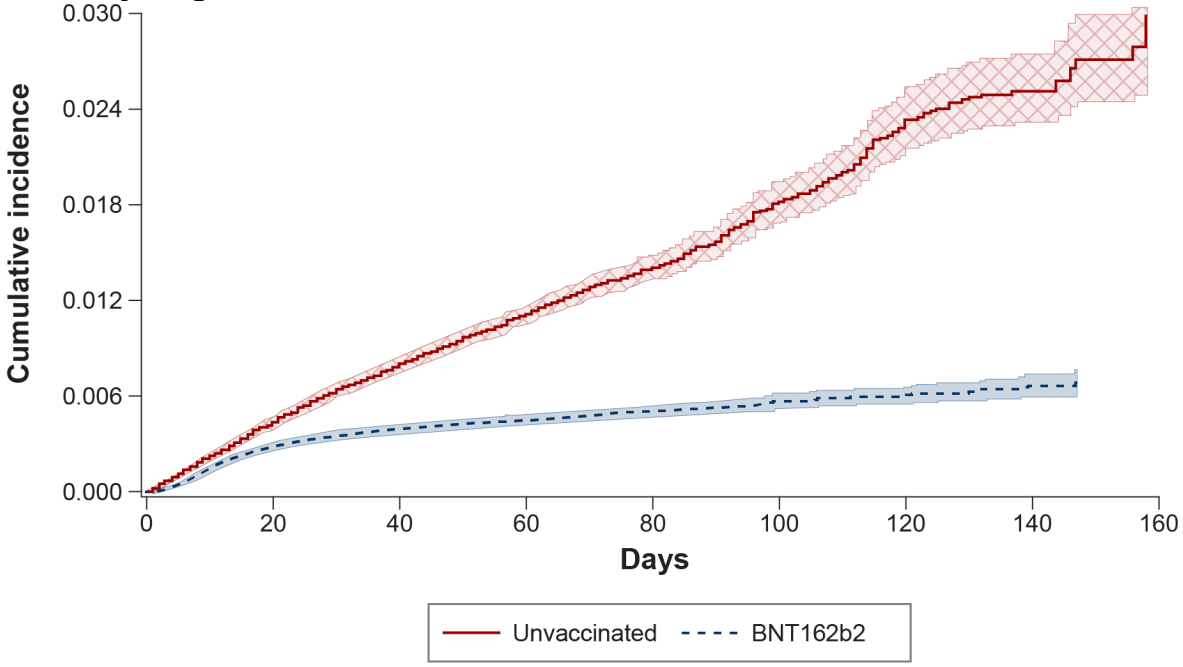
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

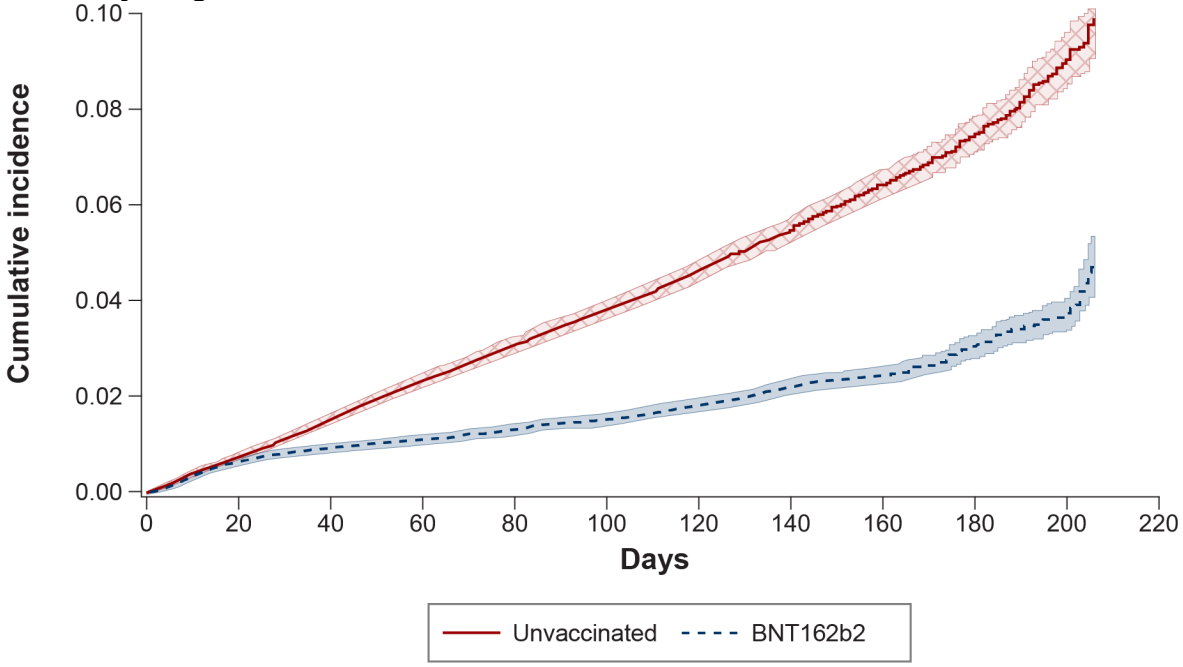
Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

Figure C-4-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Adults, by SARS-CoV-2 Variant Era

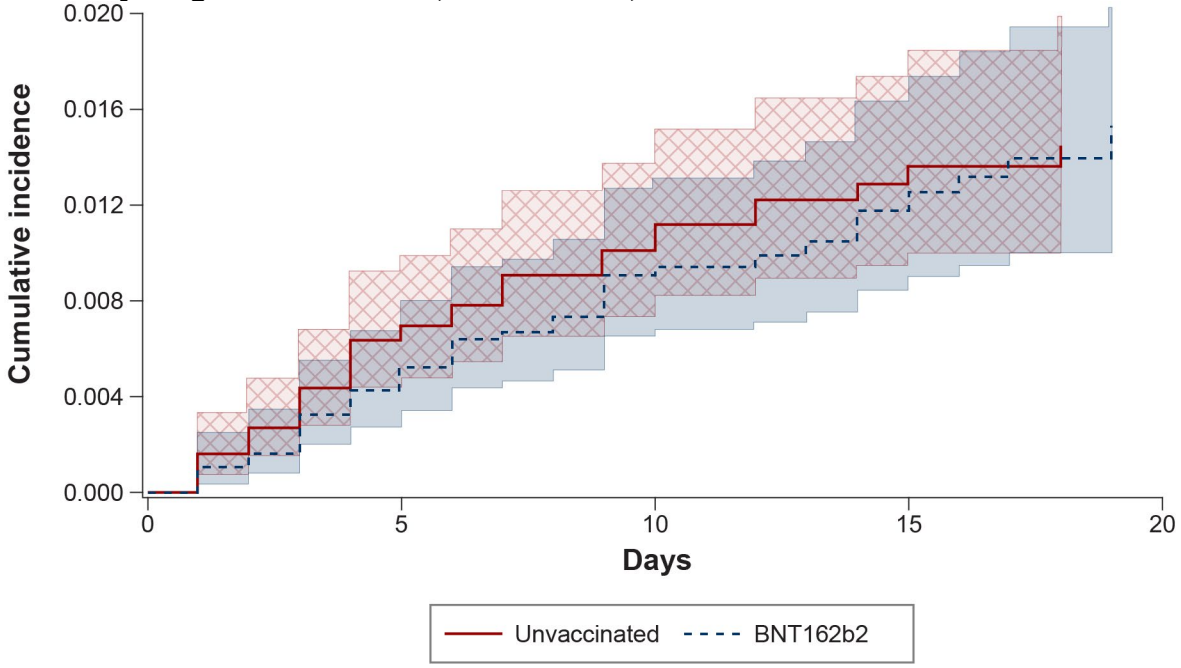
A. Medically Diagnosed COVID-19, Pre-Delta Era, BNT162b2



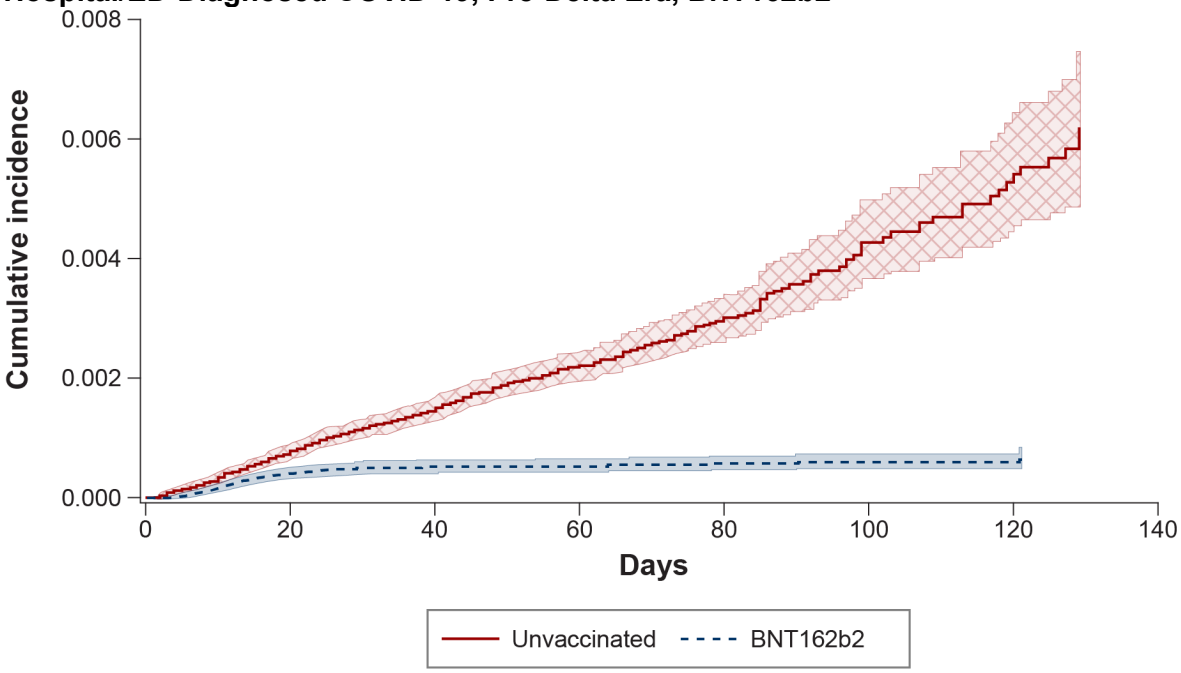
B. Medically Diagnosed COVID-19, Delta Era, BNT162b2



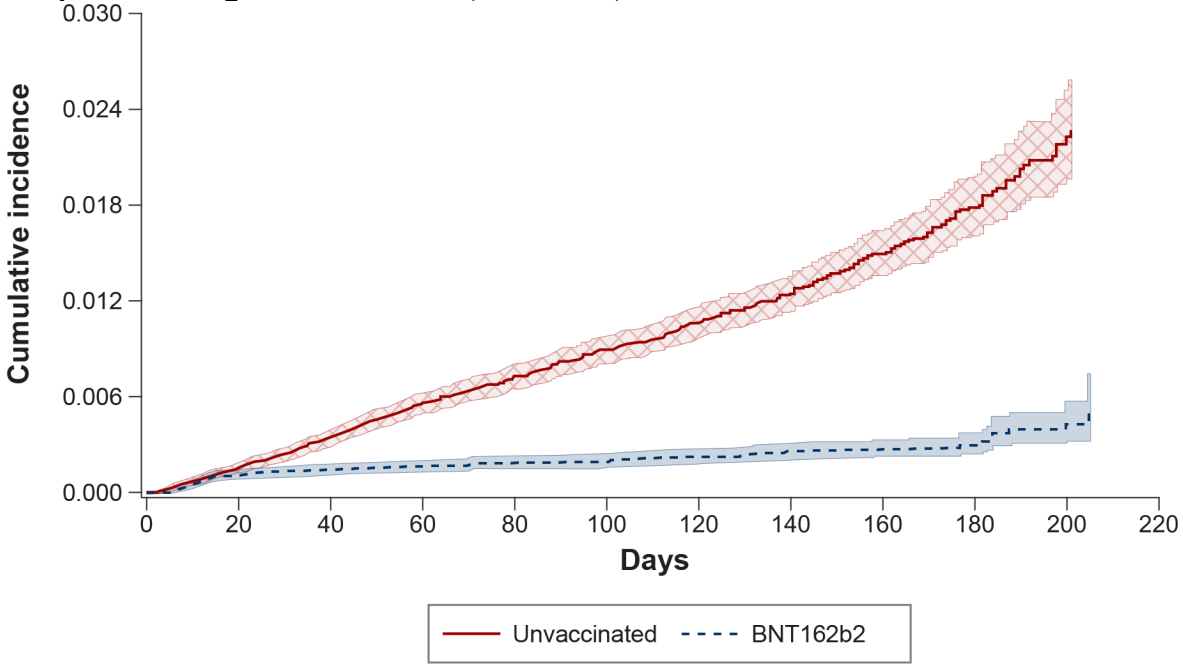
C. Medically Diagnosed COVID-19, Omicron Era, BNT162b2



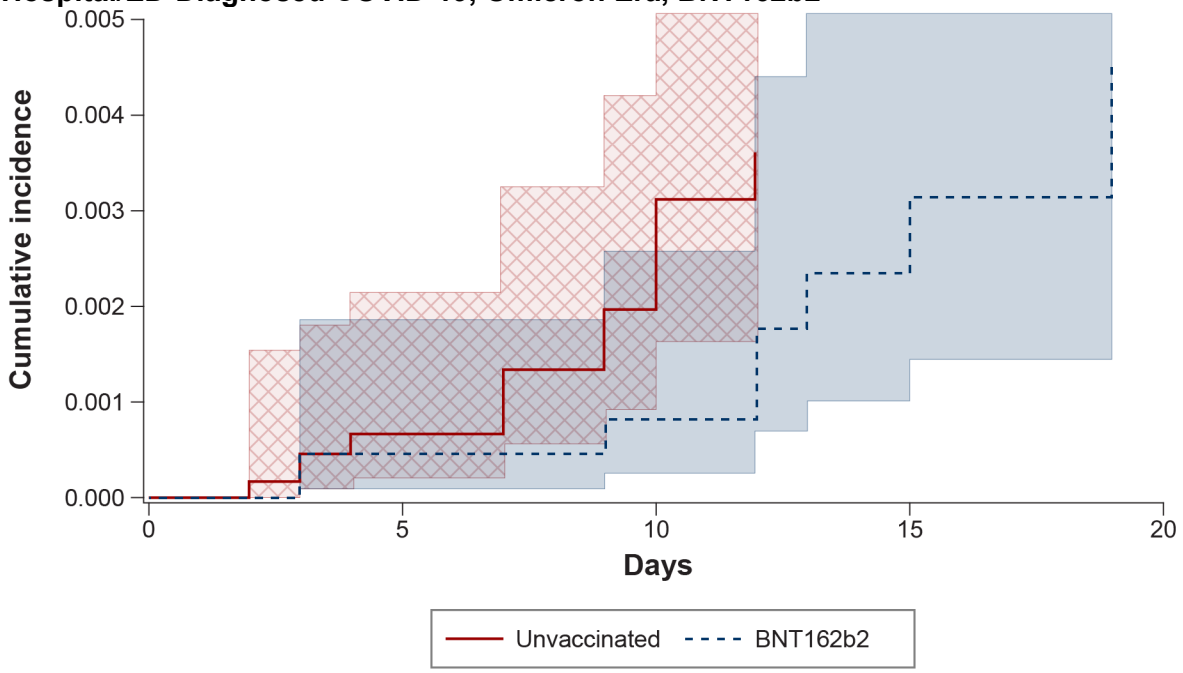
D. Hospital/ED-Diagnosed COVID-19, Pre-Delta Era, BNT162b2



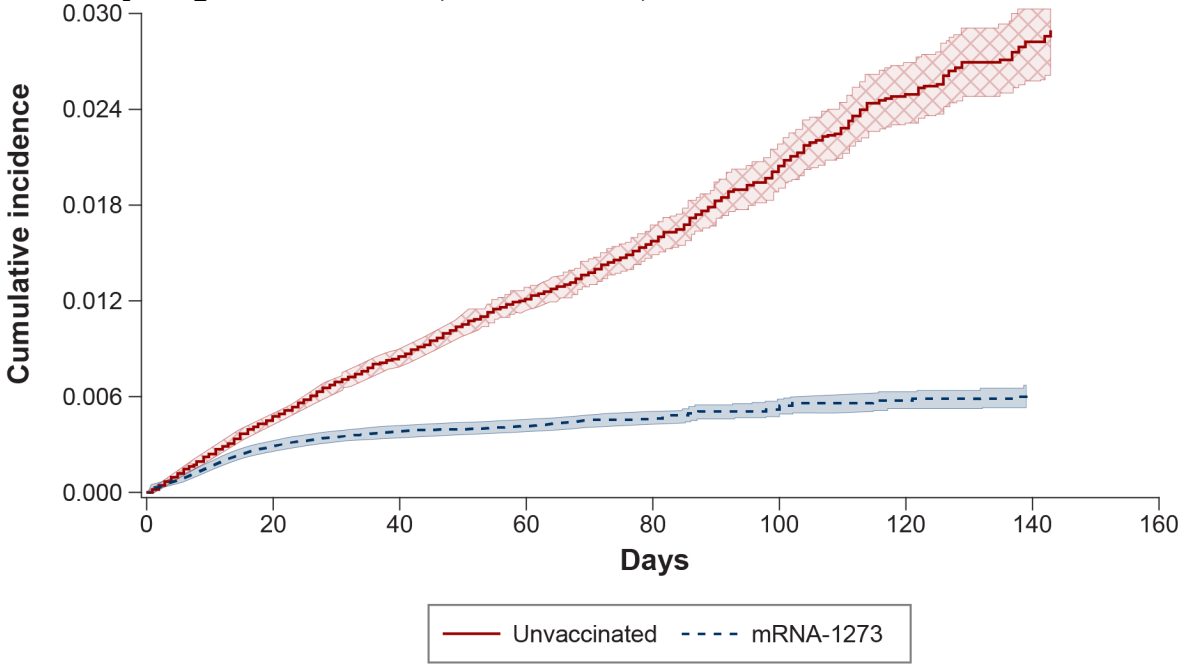
E. Hospital/ED-Diagnosed COVID-19, Delta Era, BNT162b2



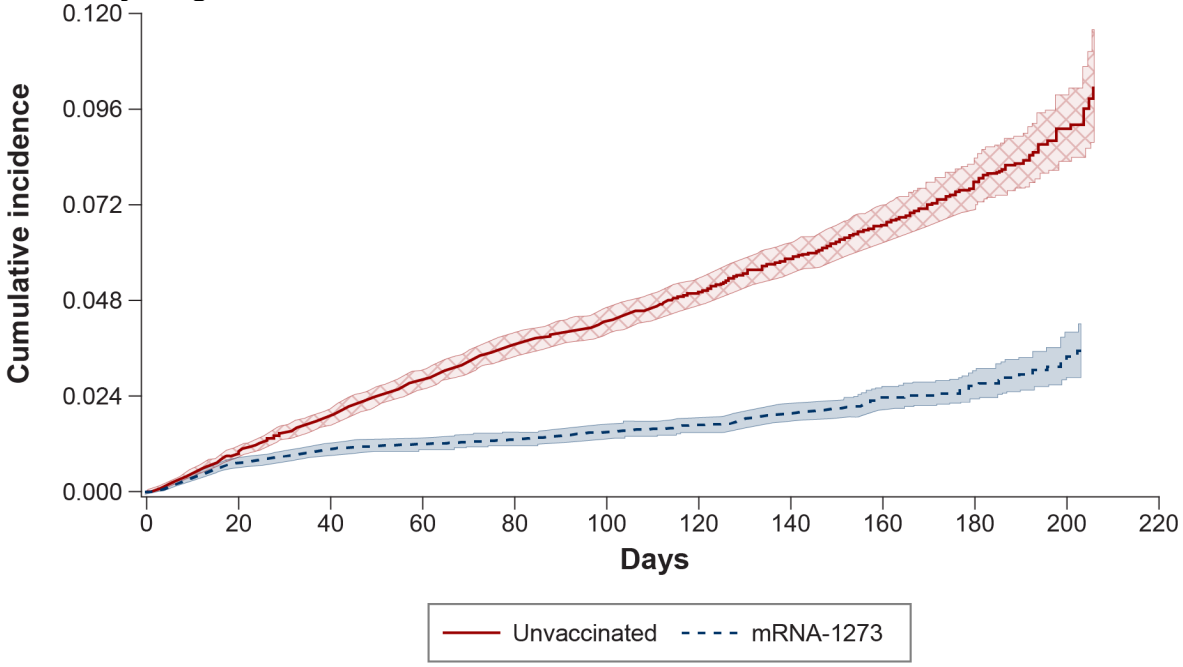
F. Hospital/ED-Diagnosed COVID-19, Omicron Era, BNT162b2



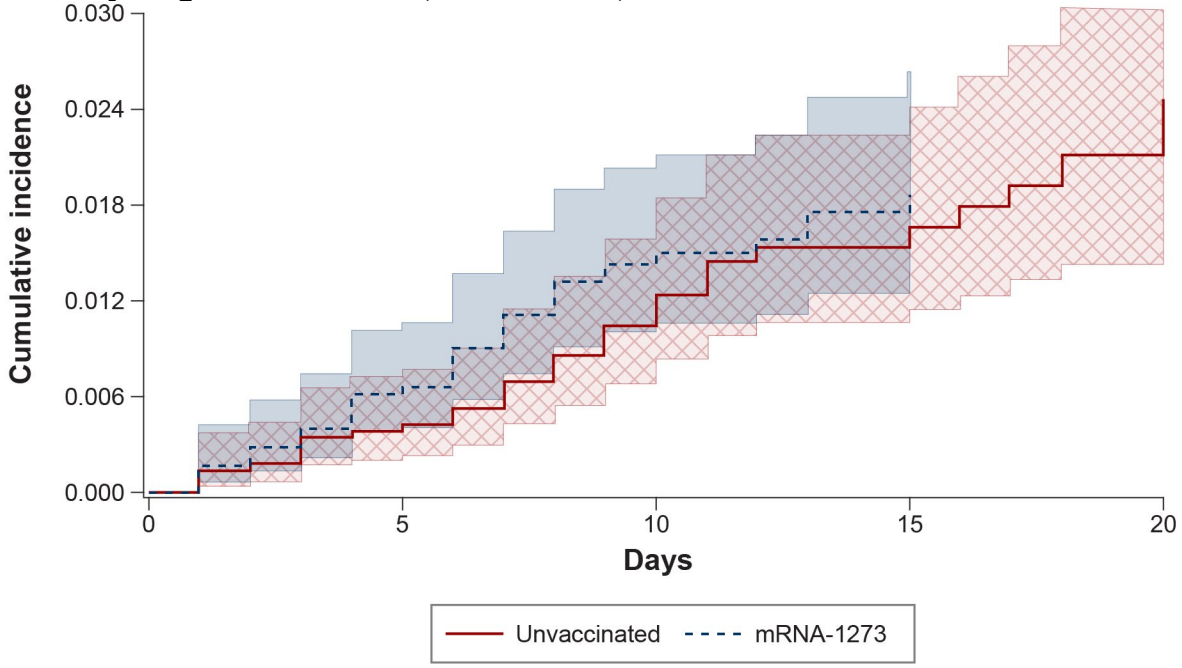
G. Medically Diagnosed COVID-19, Pre-Delta Era, mRNA-1273



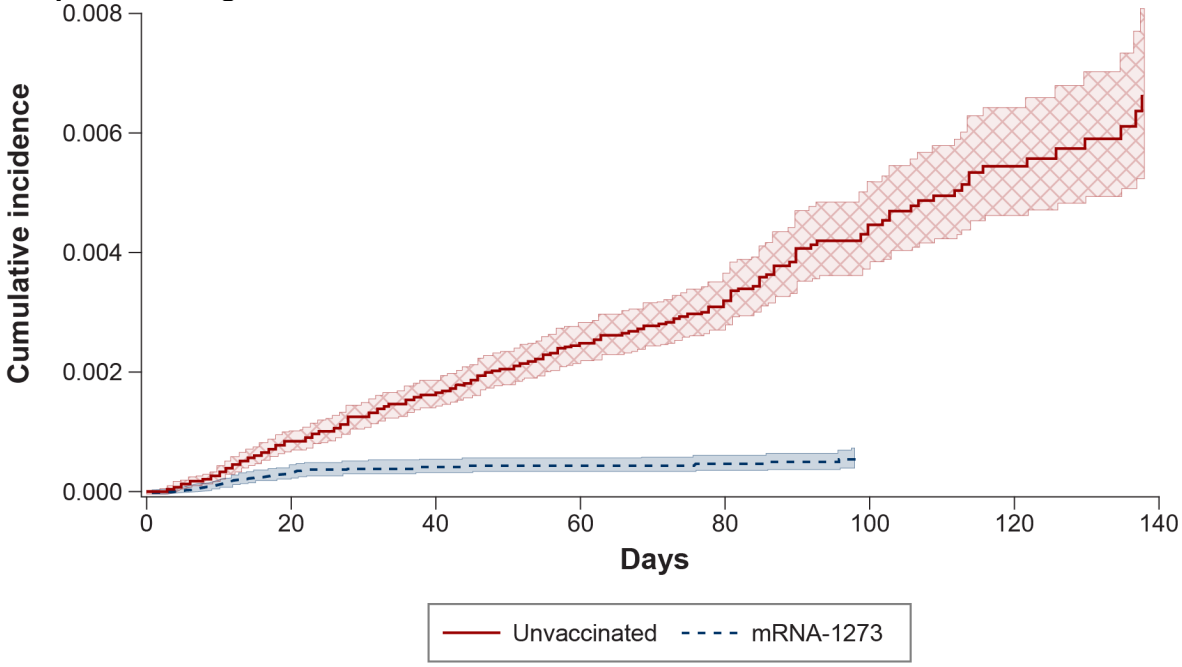
H. Medically Diagnosed COVID-19, Delta Era, mRNA-1273



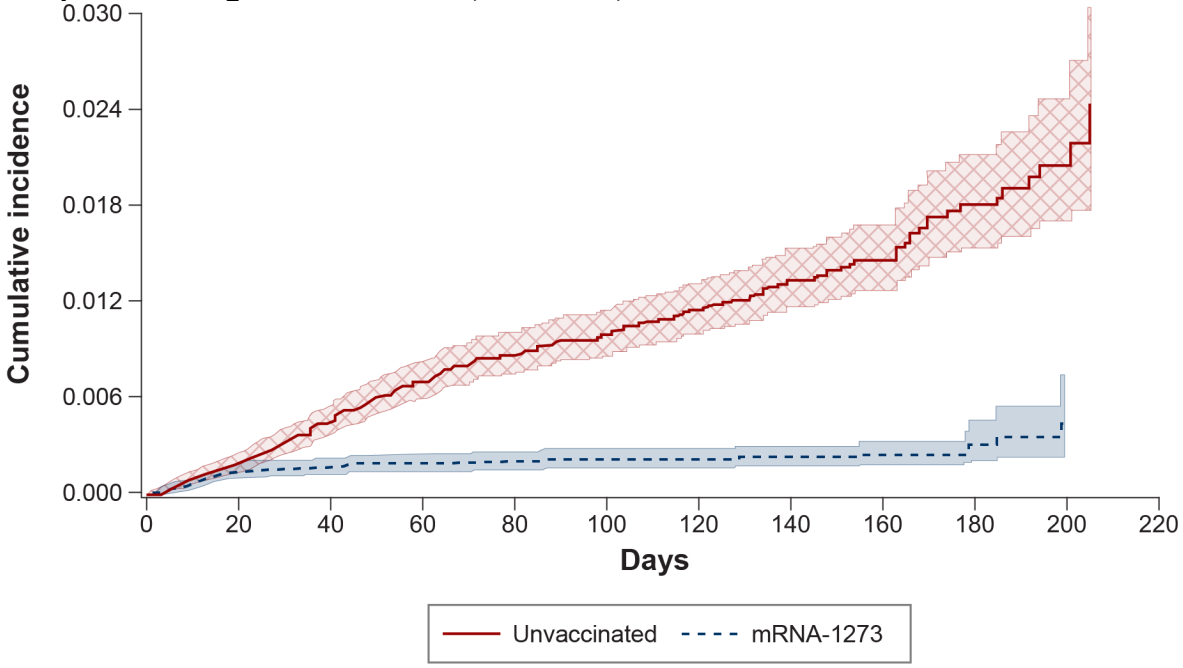
I. Medically Diagnosed COVID-19, Omicron Era, mRNA-1273



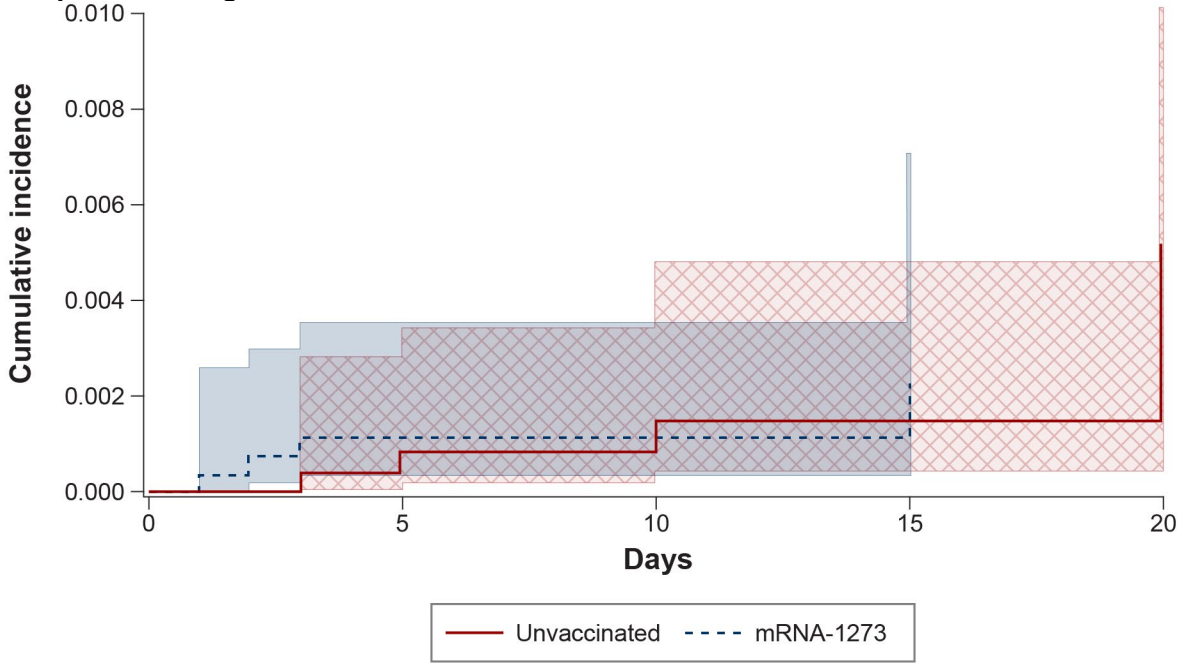
J. Hospital/ED-Diagnosed COVID-19, Pre-Delta Era, mRNA-1273



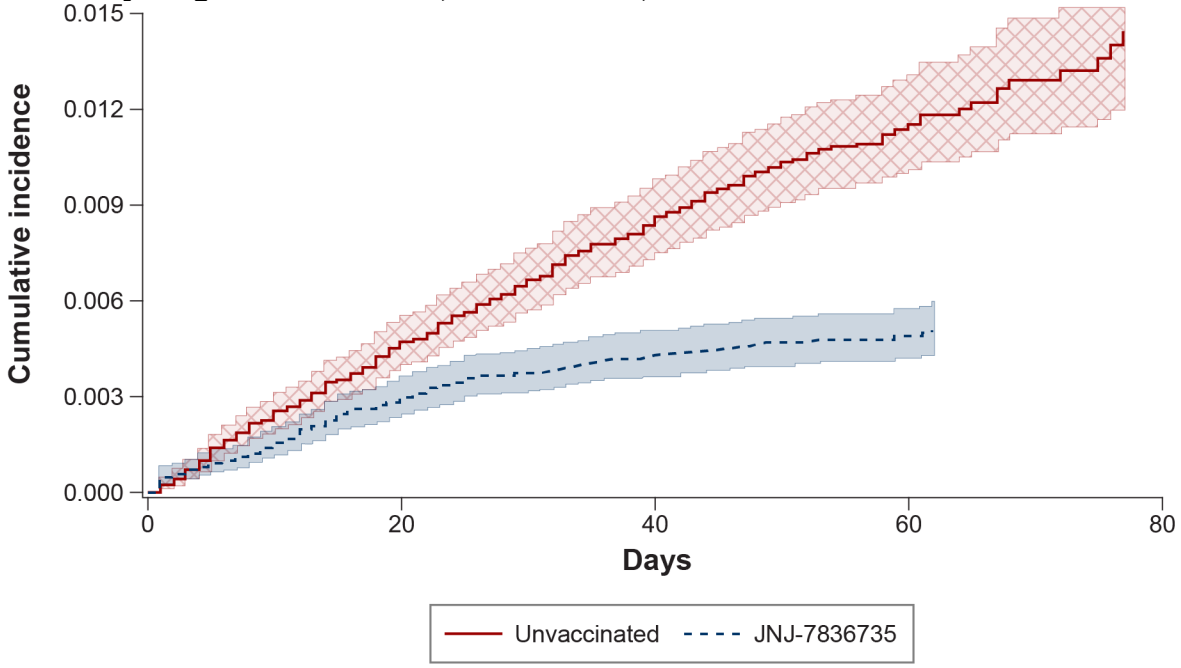
K. Hospital/ED-Diagnosed COVID-19, Delta Era, mRNA-1273



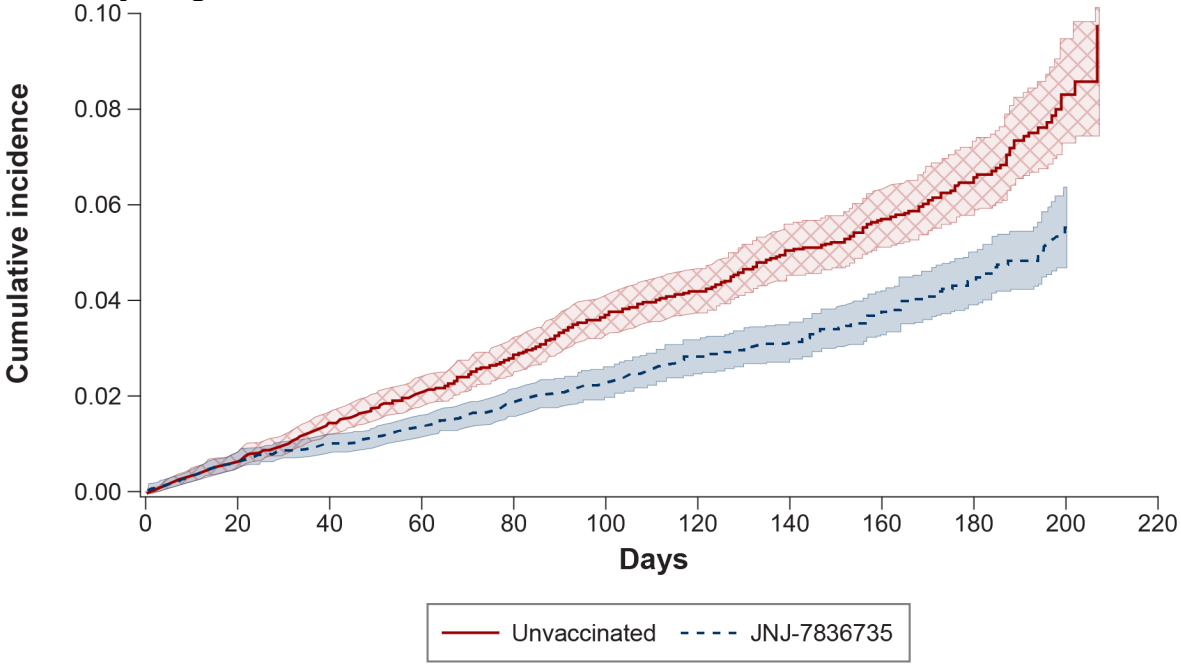
L. Hospital/ED-Diagnosed COVID-19, Omicron Era, mRNA-1273



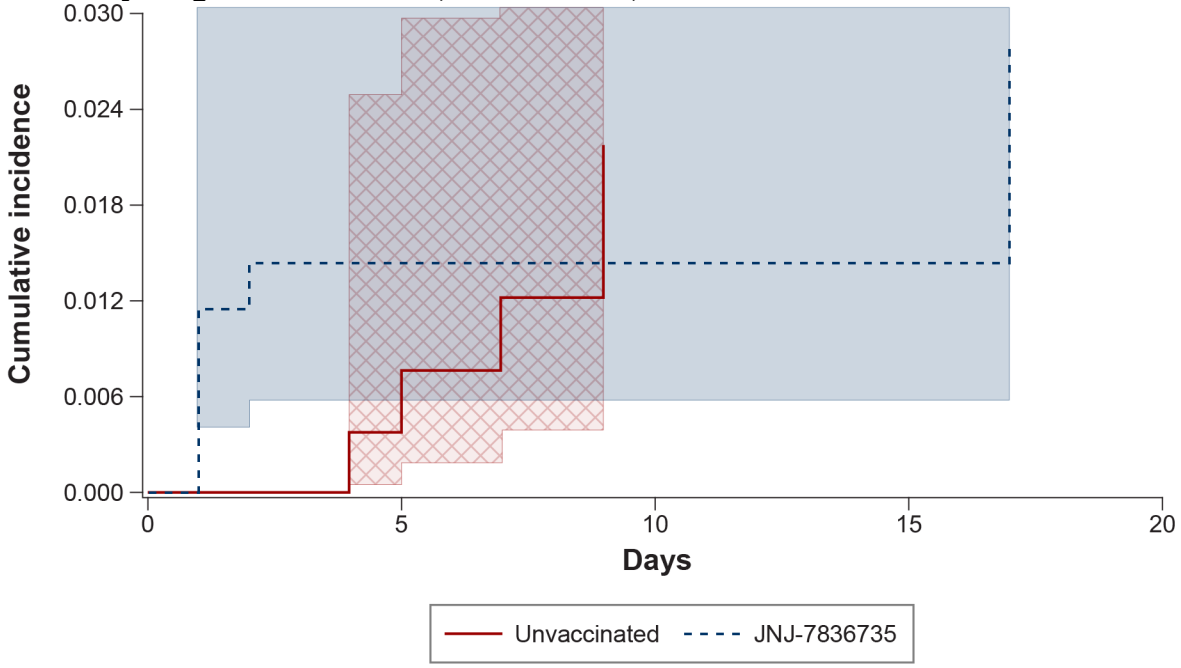
M. Medically Diagnosed COVID-19, Pre-Delta Era, JNJ-7836735



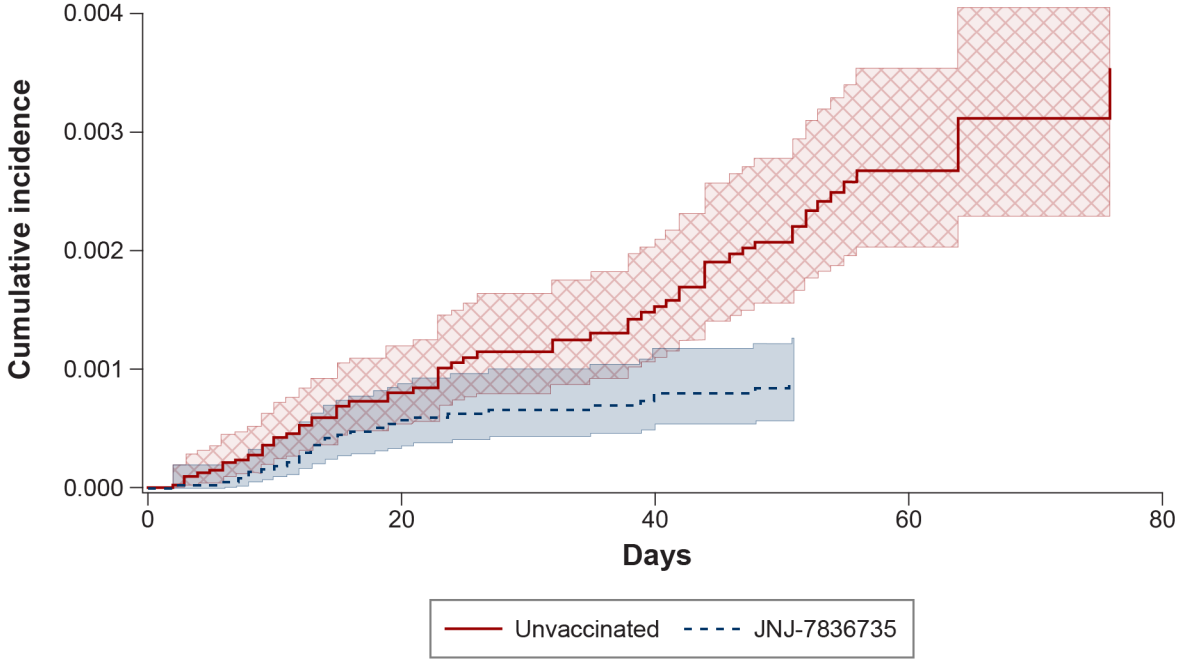
N. Medically Diagnosed COVID-19, Delta Era, JNJ-7836735



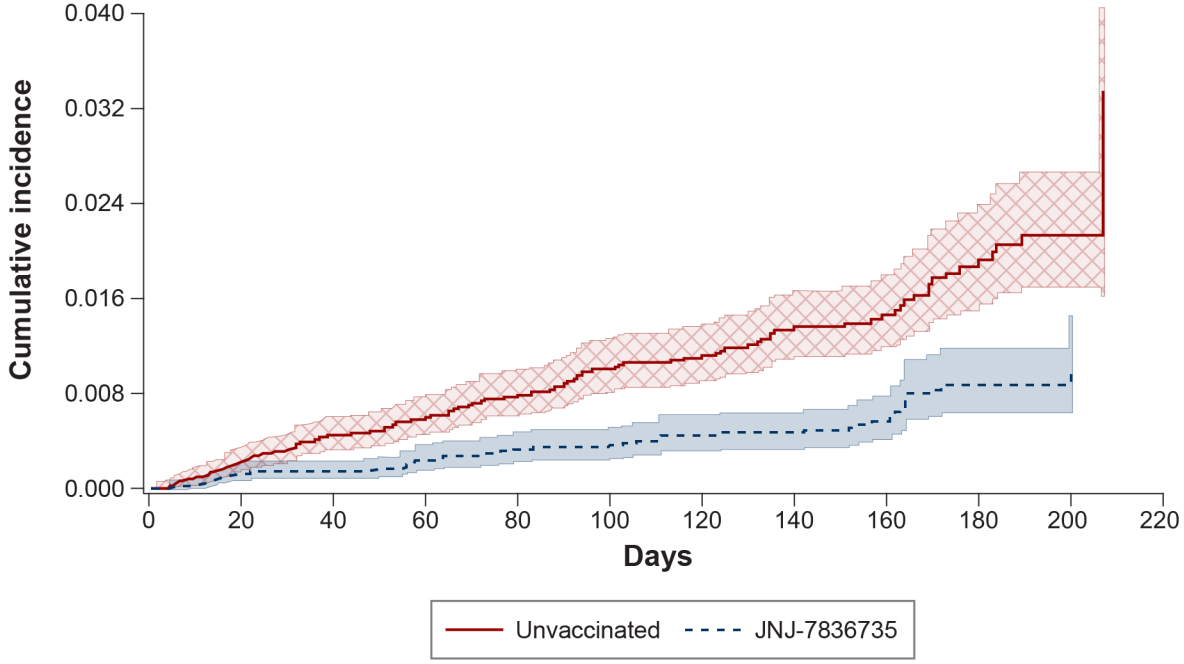
O. Medically Diagnosed COVID-19, Omicron Era, JNJ-7836735



P. Hospital/ED-Diagnosed COVID-19, Pre-Delta Era, JNJ-7836735



Q. Hospital/ED-Diagnosed COVID-19, Delta Era, JNJ-7836735



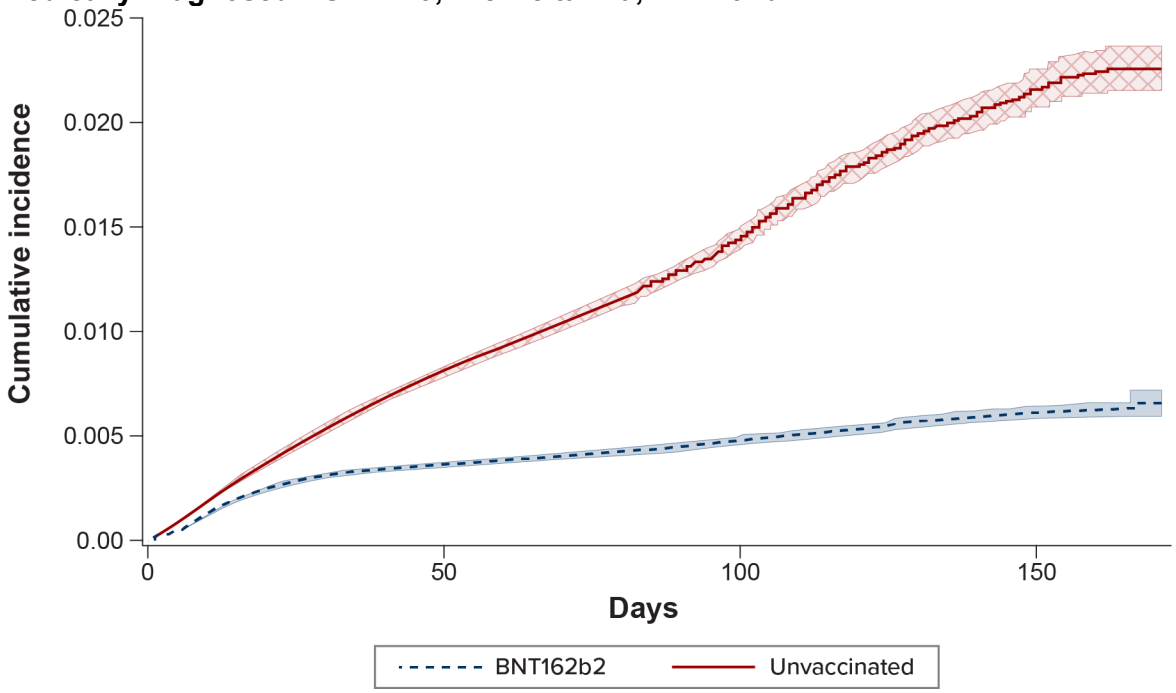
R. Hospital/ED-Diagnosed COVID-19, Omicron Era, JNJ-7836735

Figure not generated.

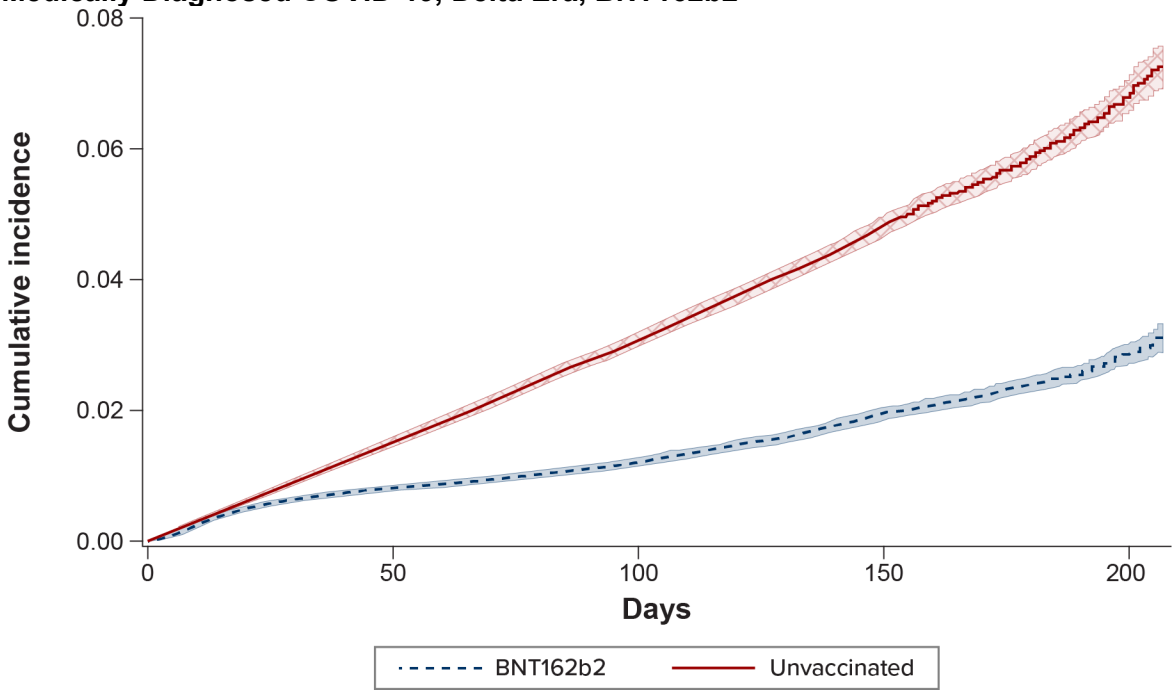
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure C-4-CVS. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Adults, by SARS-CoV-2 Variant Era

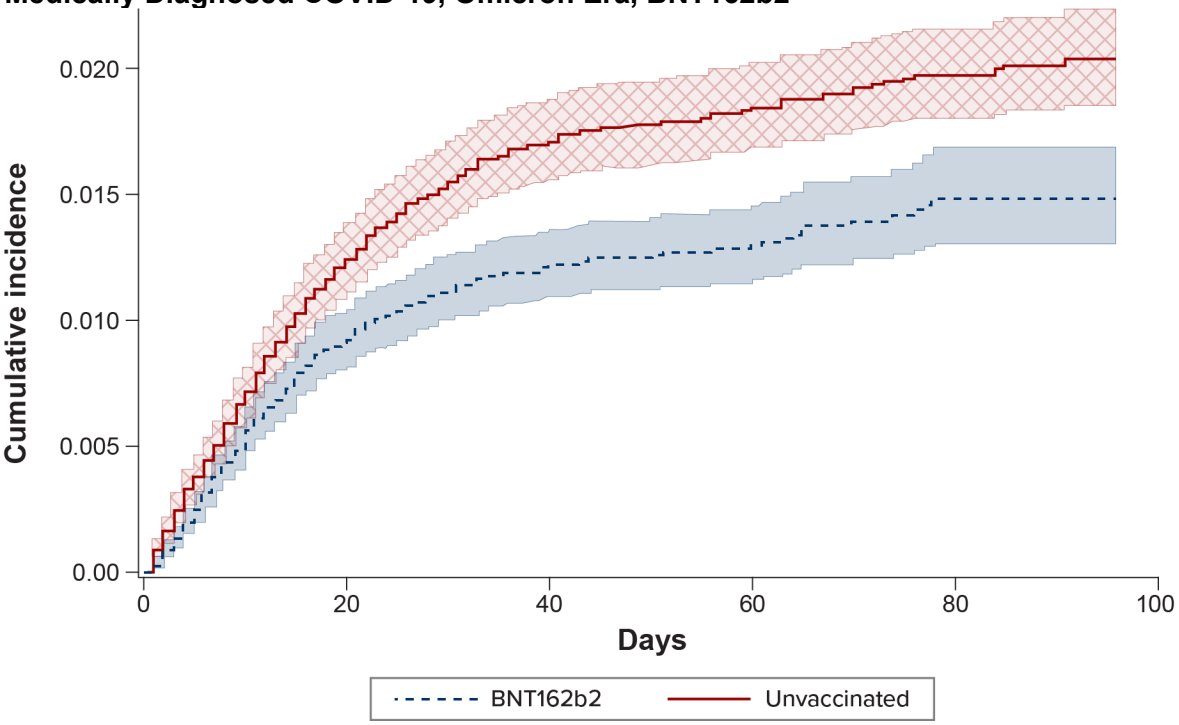
A. Medically Diagnosed COVID-19, Pre-Delta Era, BNT162b2



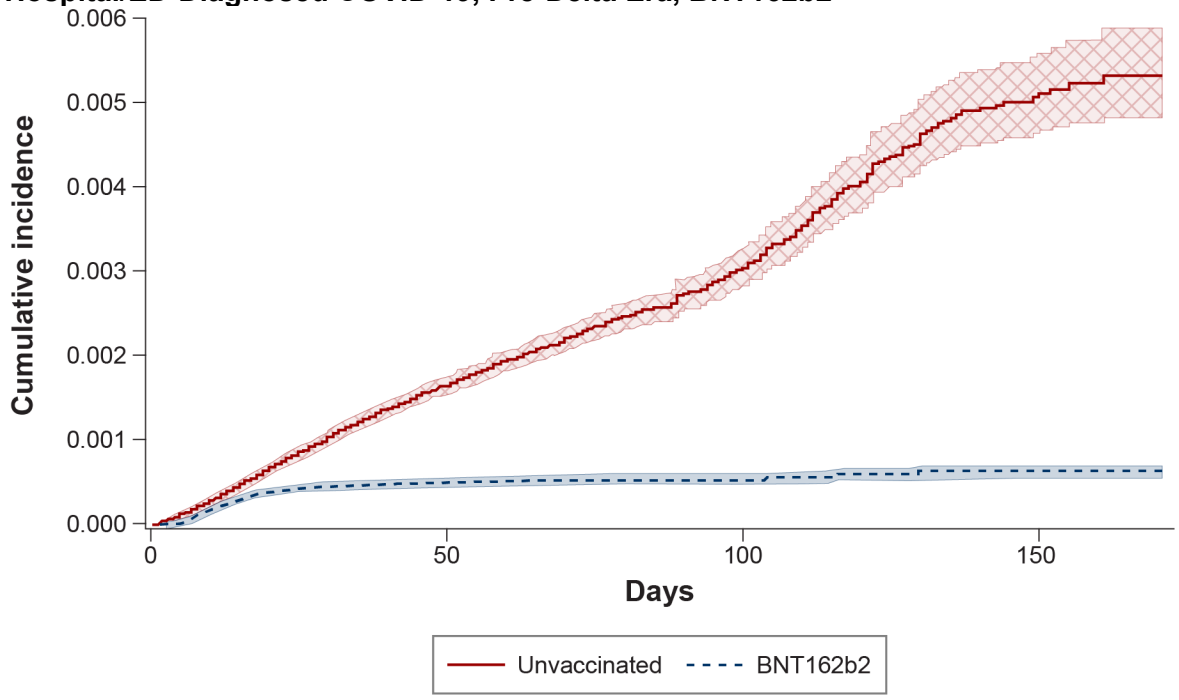
B. Medically Diagnosed COVID-19, Delta Era, BNT162b2



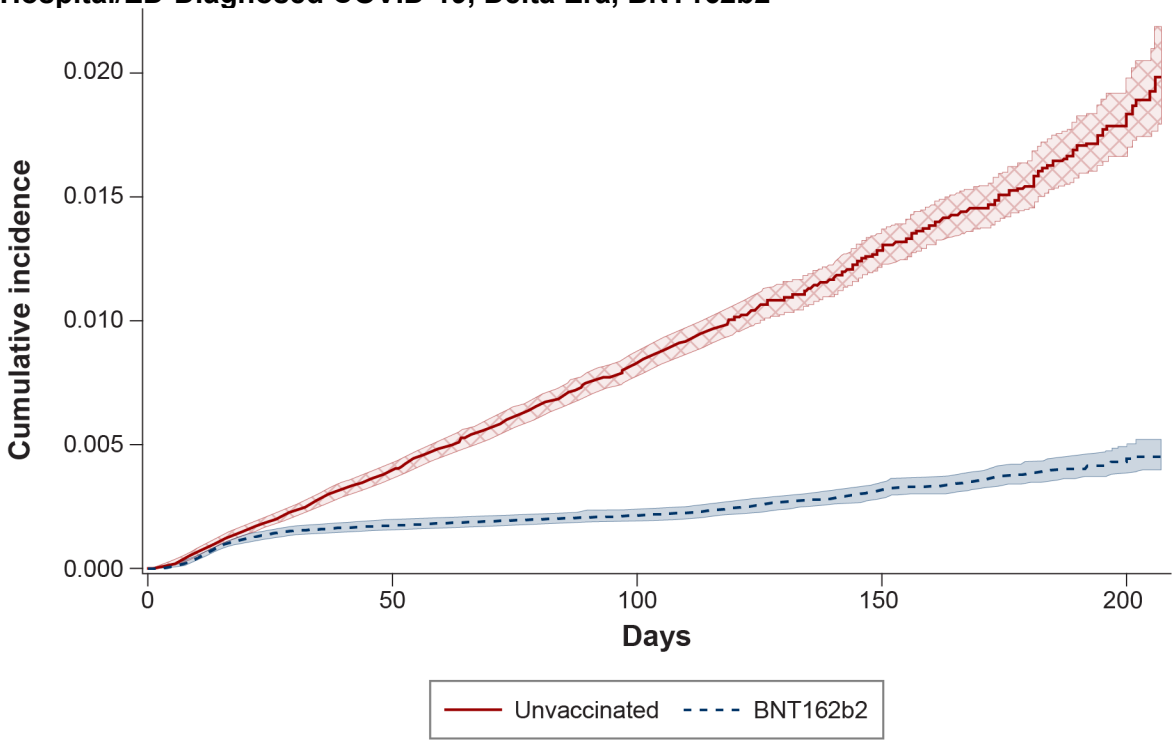
C. Medically Diagnosed COVID-19, Omicron Era, BNT162b2



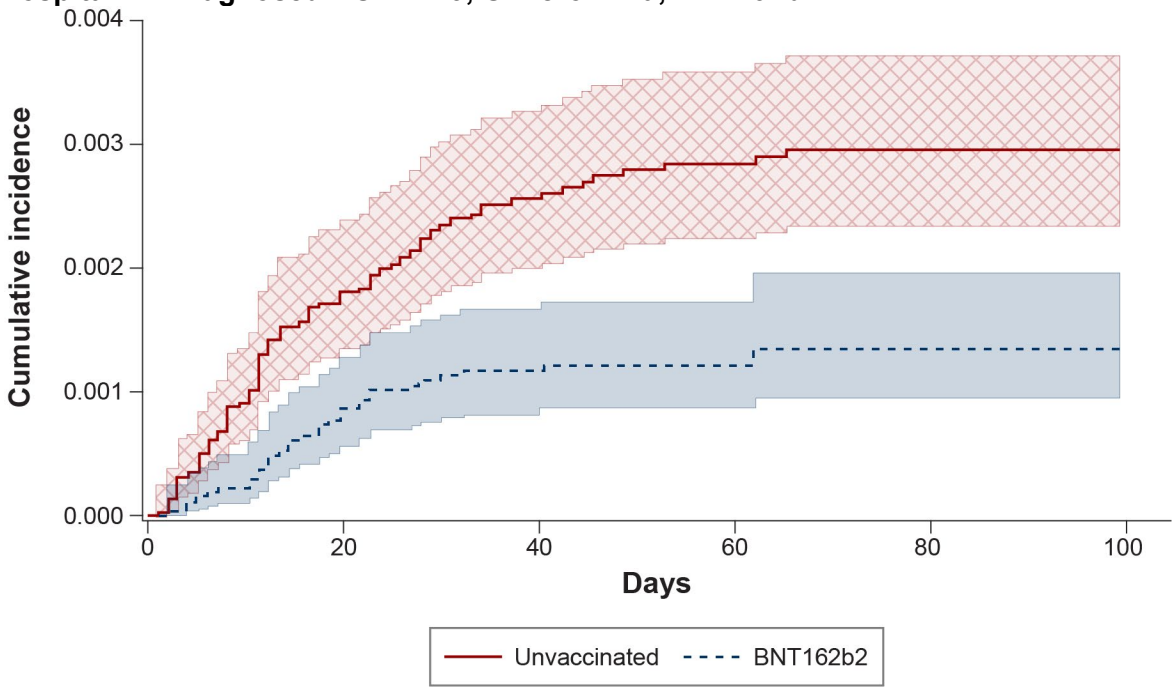
D. Hospital/ED-Diagnosed COVID-19, Pre-Delta Era, BNT162b2



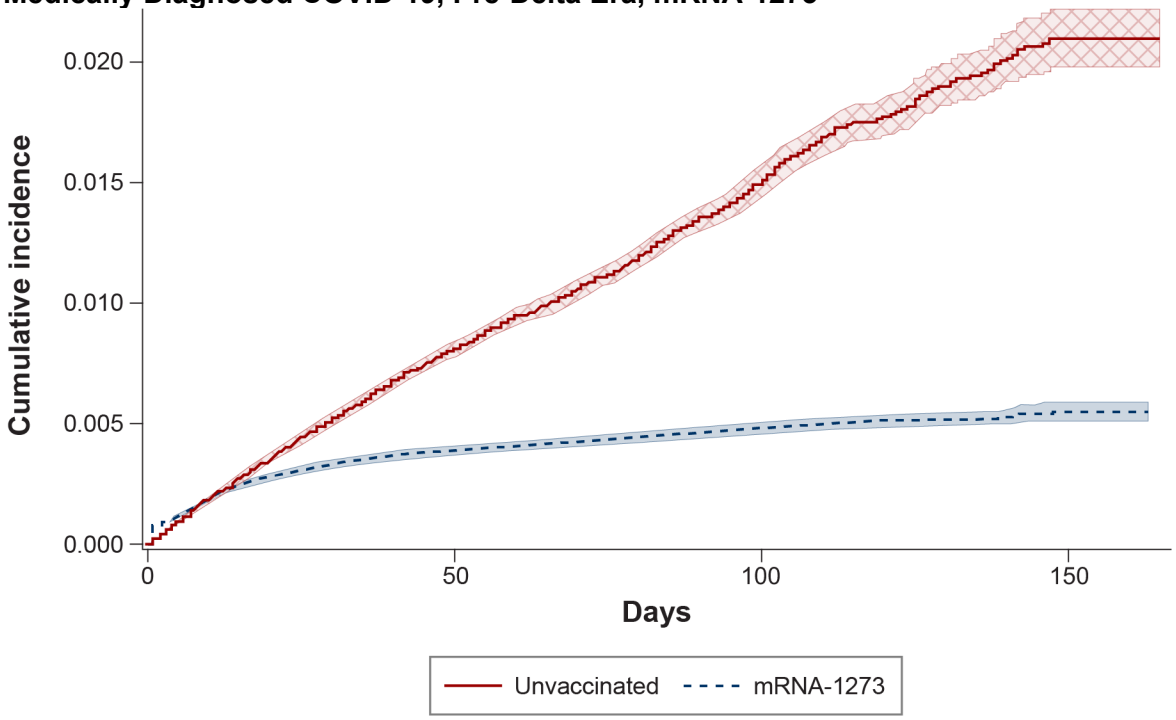
E. Hospital/ED-Diagnosed COVID-19, Delta Era, BNT162b2



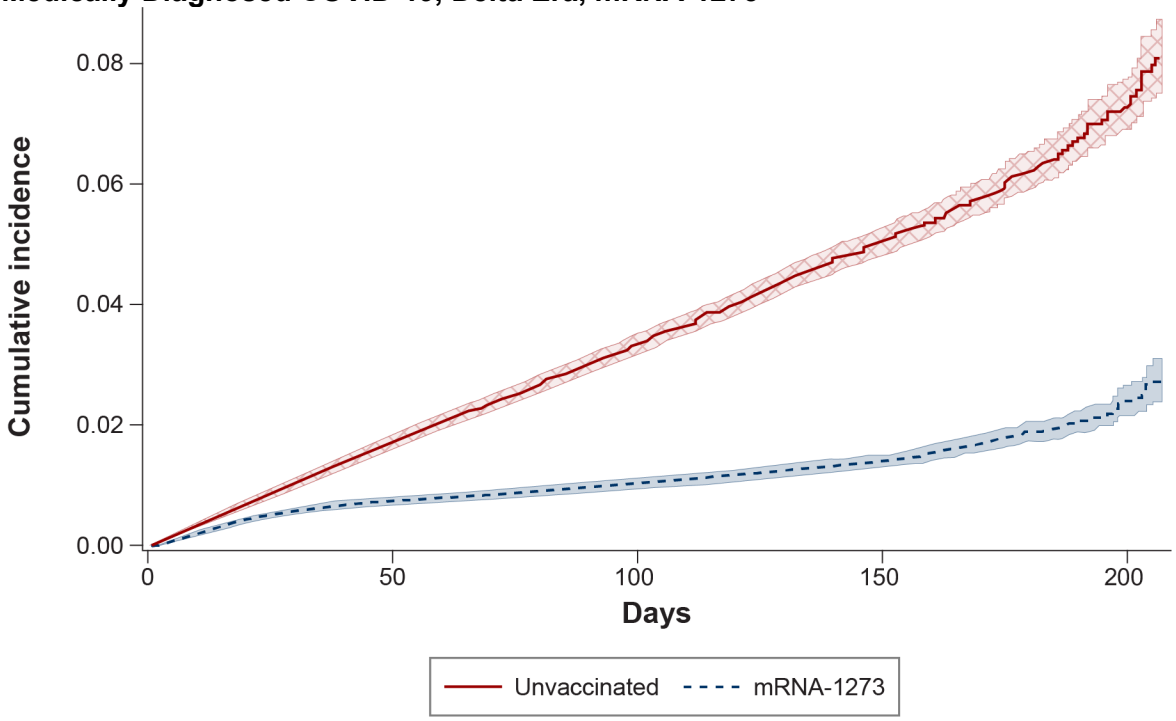
F. Hospital/ED-Diagnosed COVID-19, Omicron Era, BNT162b2



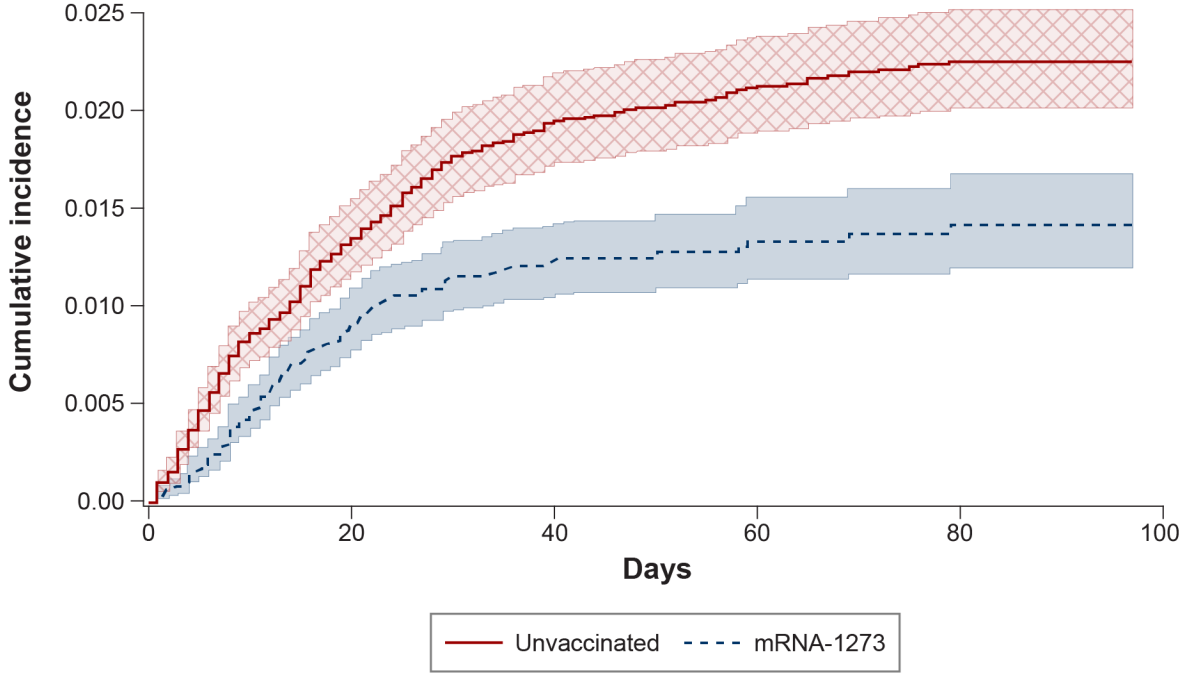
G. Medically Diagnosed COVID-19, Pre-Delta Era, mRNA-1273



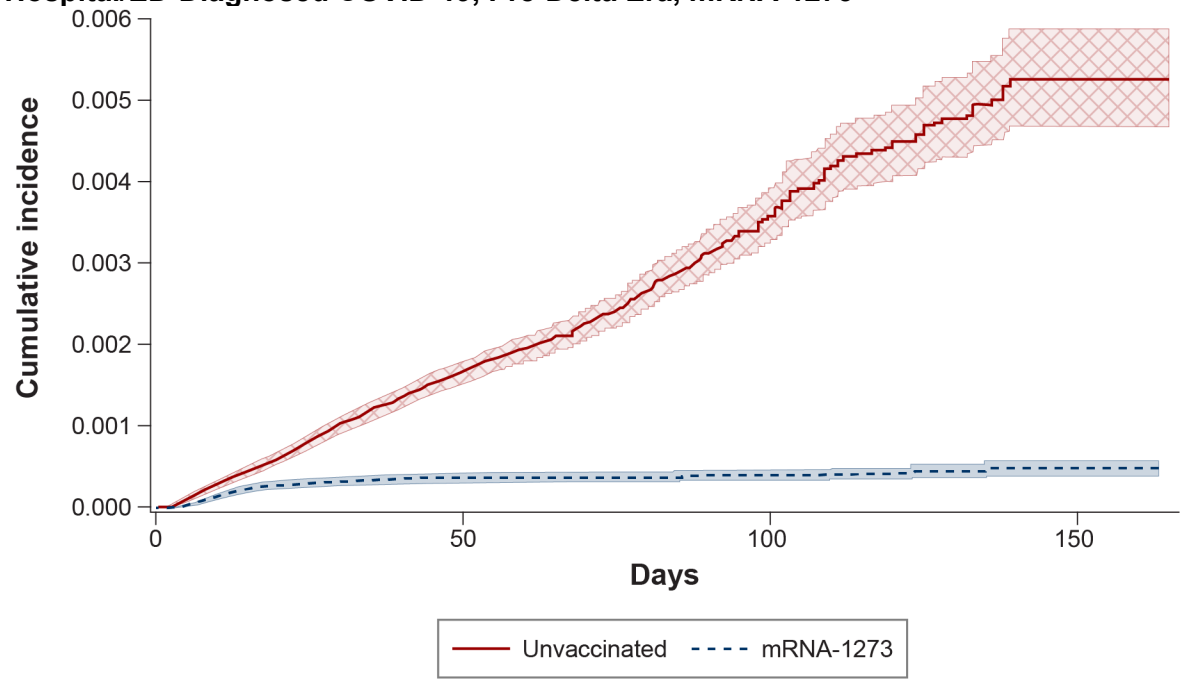
H. Medically Diagnosed COVID-19, Delta Era, mRNA-1273



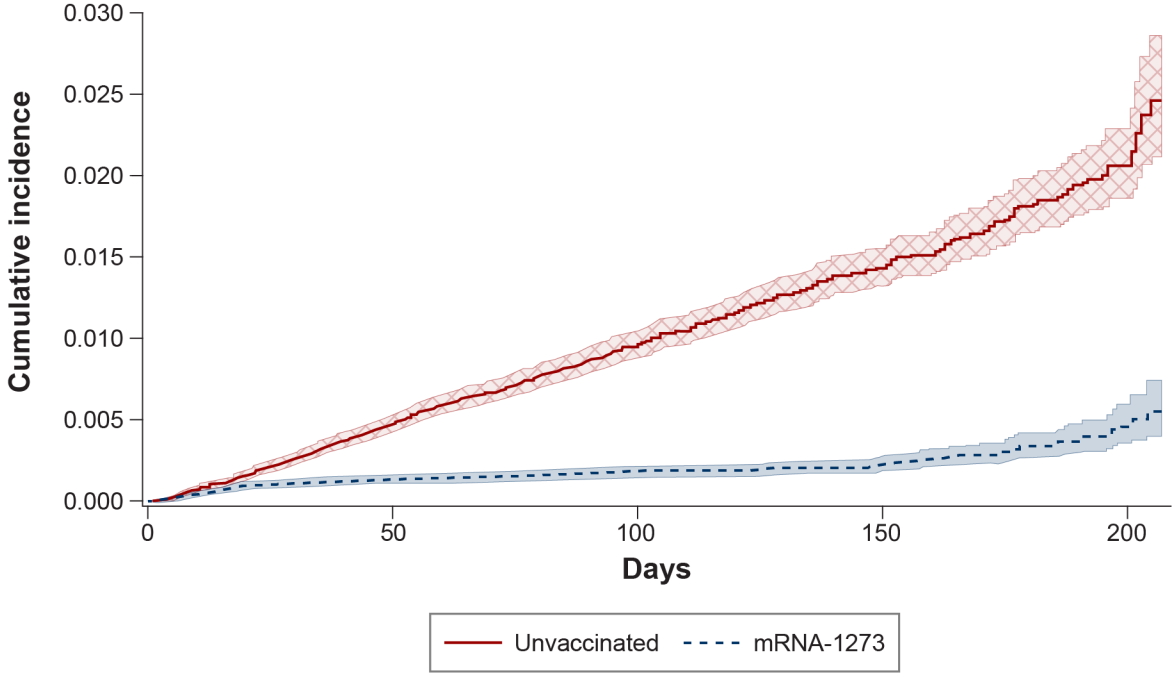
I. Medically Diagnosed COVID-19, Omicron Era, mRNA-1273



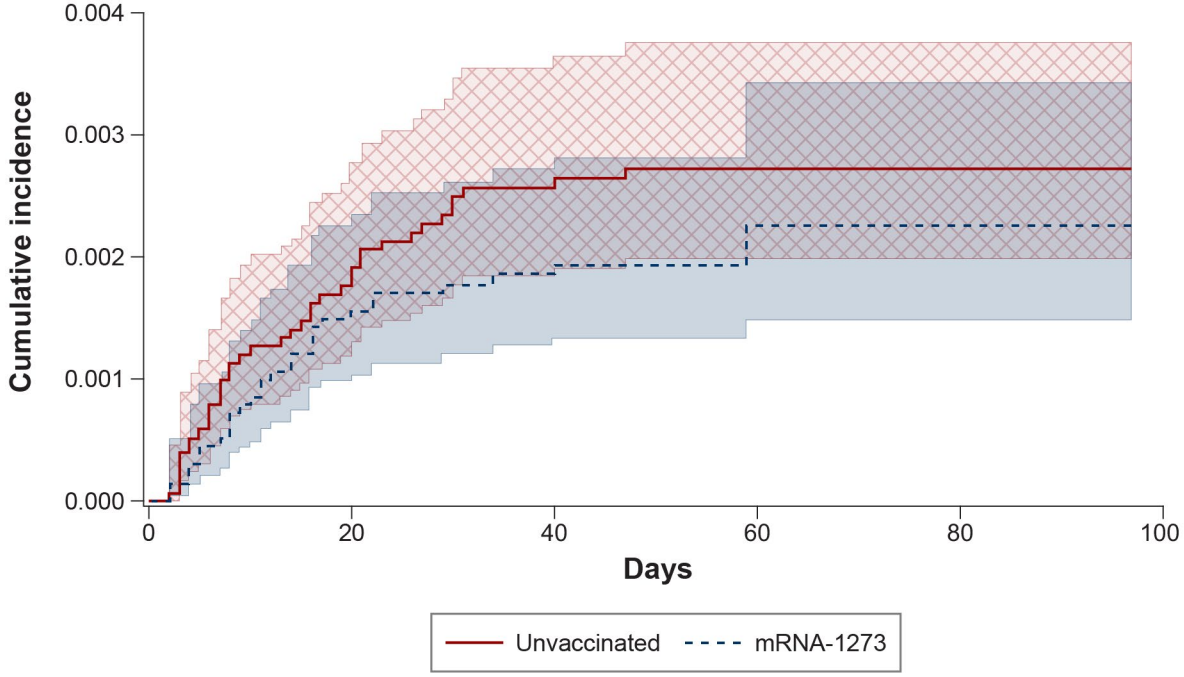
J. Hospital/ED-Diagnosed COVID-19, Pre-Delta Era, mRNA-1273



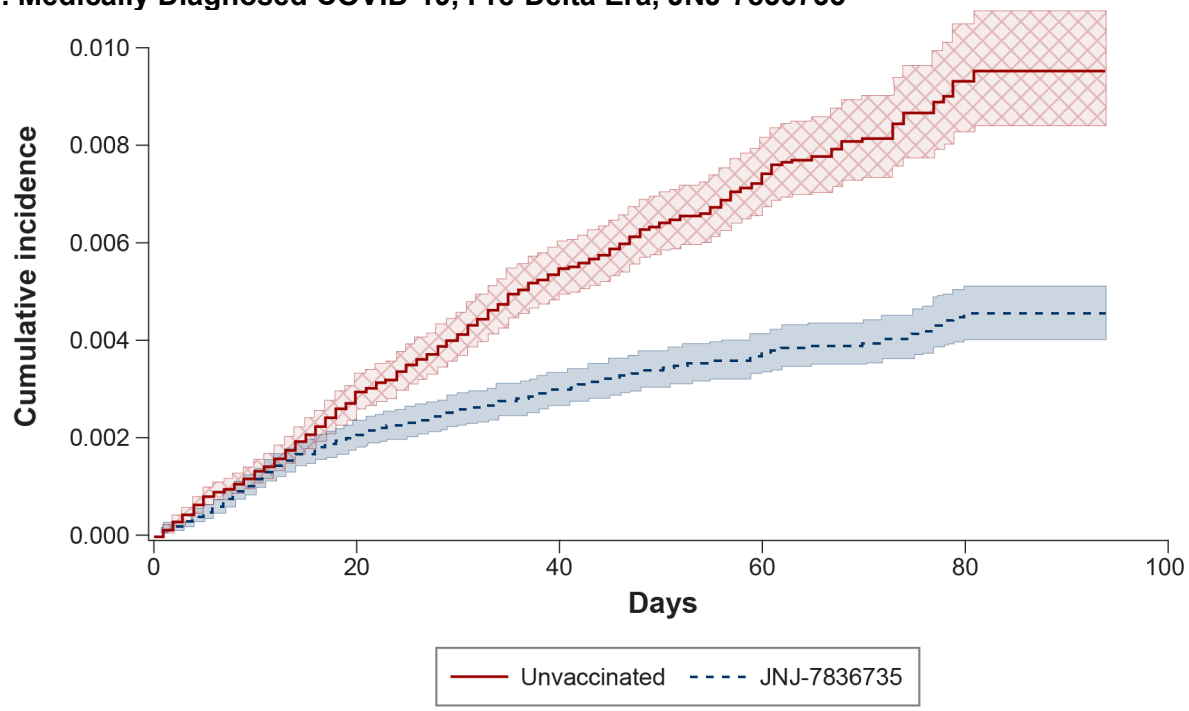
K. Hospital/ED-Diagnosed COVID-19, Delta Era, mRNA-1273



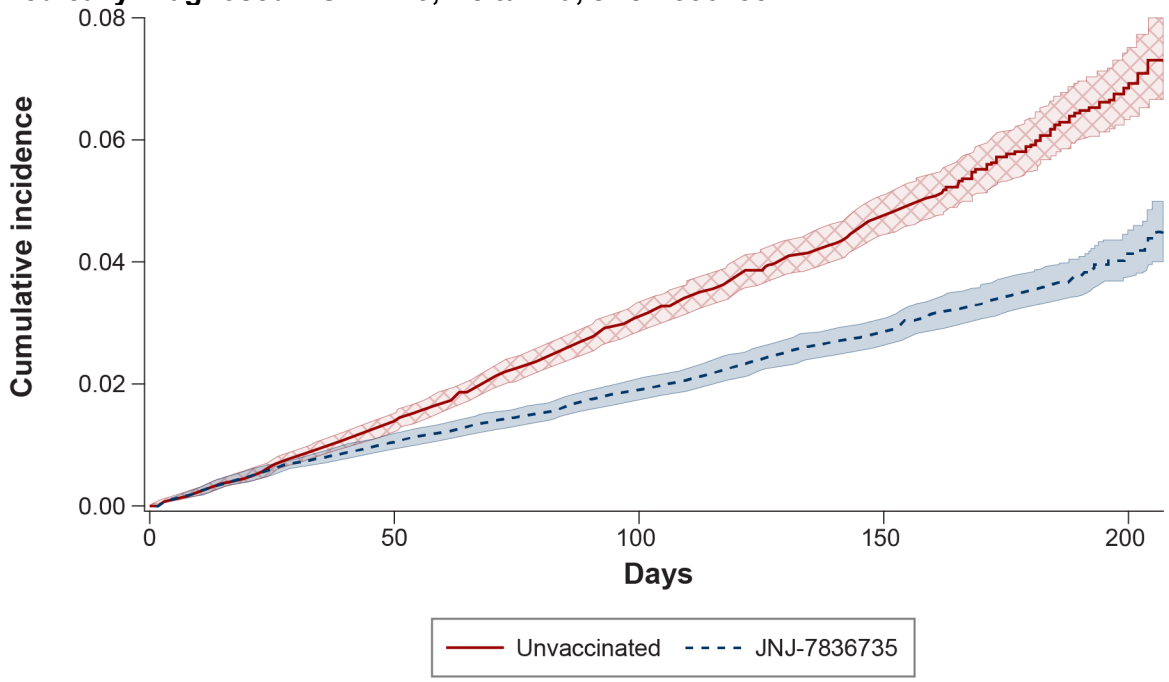
L. Hospital/ED-Diagnosed COVID-19, Omicron Era, mRNA-1273



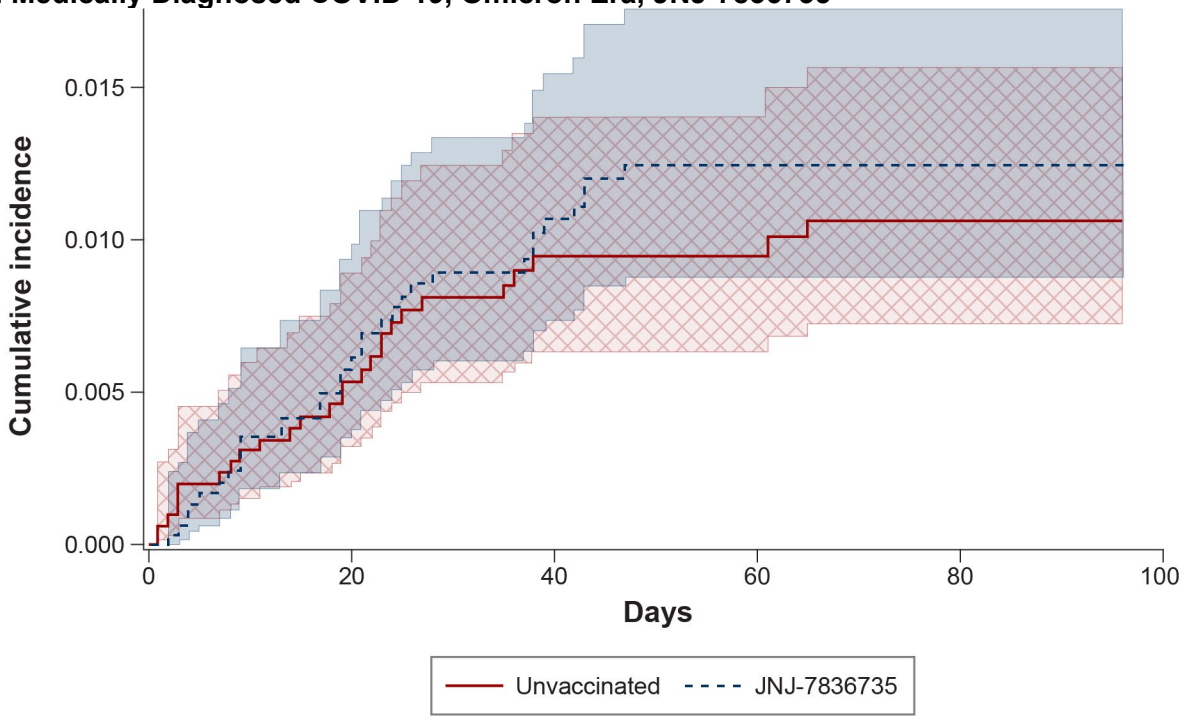
M. Medically Diagnosed COVID-19, Pre-Delta Era, JNJ-7836735



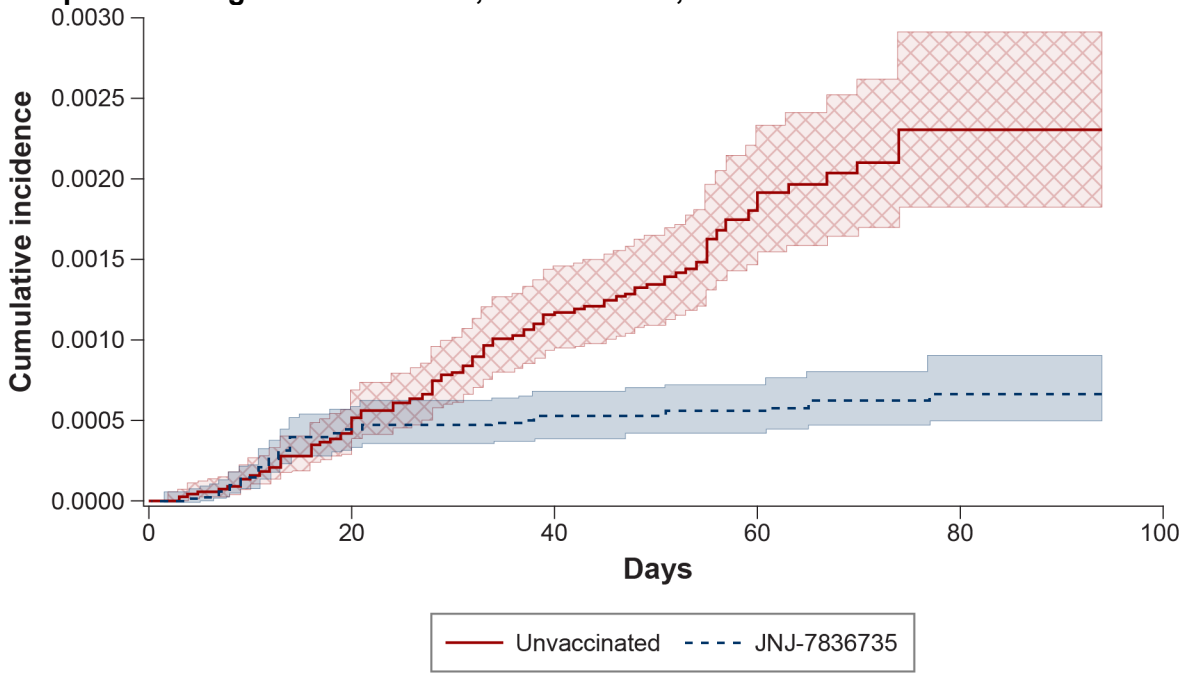
N. Medically Diagnosed COVID-19, Delta Era, JNJ-7836735



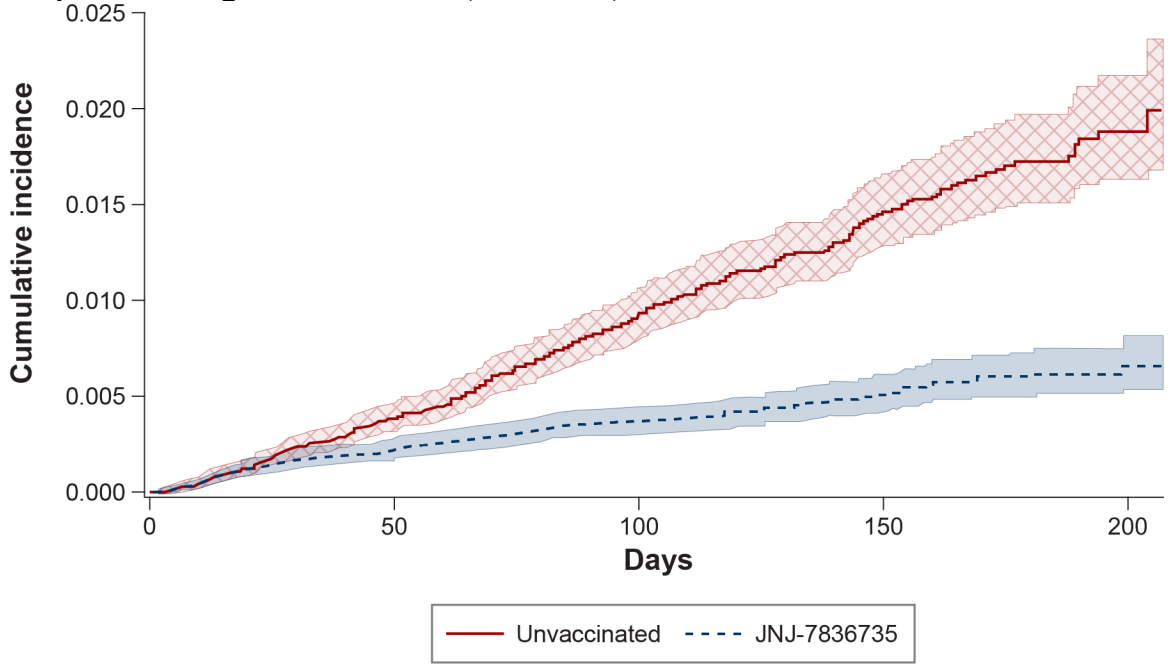
O. Medically Diagnosed COVID-19, Omicron Era, JNJ-7836735



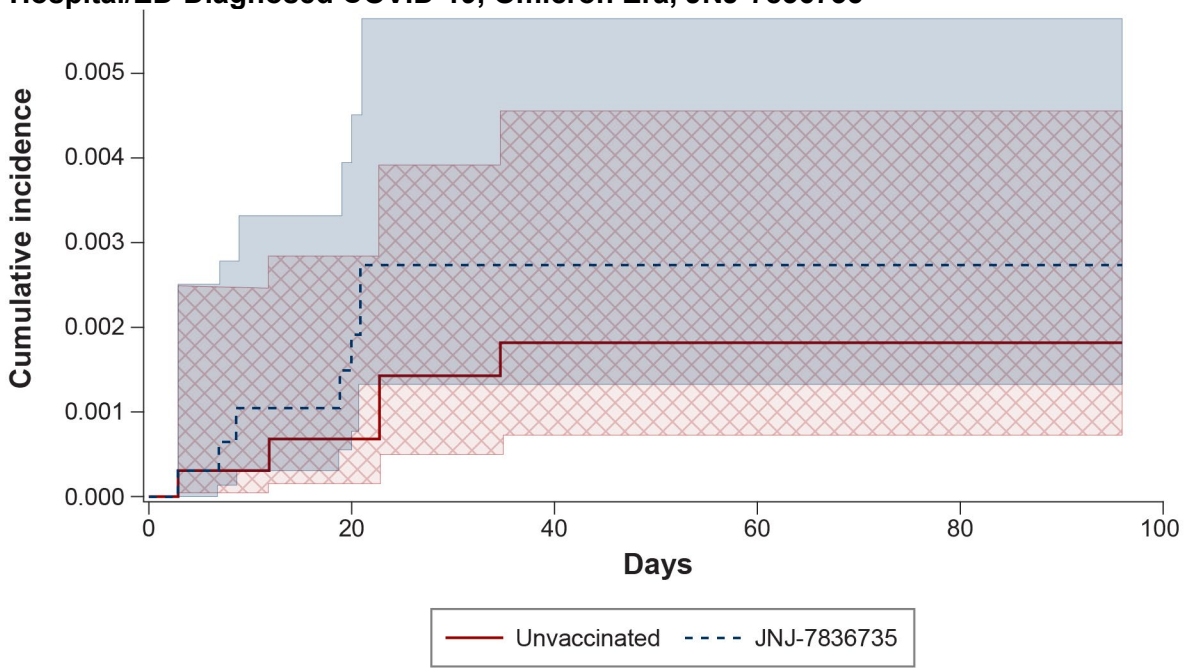
P. Hospital/ED-Diagnosed COVID-19, Pre-Delta Era, JNJ-7836735



Q. Hospital/ED-Diagnosed COVID-19, Delta Era, JNJ-7836735



R. Hospital/ED-Diagnosed COVID-19, Omicron Era, JNJ-7836735



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

Secondary Adult Comparative Effectiveness Analysis

Table C-16-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With mRNA-1273 COVID-19 Vaccine and Matched Adults Vaccinated With BNT162b2 COVID-19 Vaccine

Characteristic	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 142,771	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 142,771	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	43 (32, 54)	43 (32, 54)	
Mean (SD)	42.65 (12.93)	42.63 (12.94)	0.00
Sex, n (%)			
Male	69,470 (48.66%)	69,470 (48.66%)	0.00
Female	73,301 (51.34%)	73,301 (51.34%)	0.00
Region, n (%)			
Northeast	16,846 (11.80%)	16,846 (11.80%)	0.00
South	31,328 (21.94%)	31,328 (21.94%)	0.00
Midwest	62,887 (44.05%)	62,887 (44.05%)	0.00
West	31,710 (22.21%)	31,710 (22.21%)	0.00
Pregnant at Time 0, n (%)[a]	727 (0.51%)	831 (0.58%)	0.01
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	97,443 (68.25%)	96,336 (67.48%)	0.02
1	25,049 (17.54%)	25,649 (17.97%)	0.01
2+	20,279 (14.20%)	20,786 (14.56%)	0.01
ED visits			
0	129,215 (90.51%)	129,038 (90.38%)	0.00
1	11,068 (7.75%)	11,214 (7.85%)	0.00
2+	2,488 (1.74%)	2,519 (1.76%)	0.00
Skilled nursing facility stay	161 (0.11%)	275 (0.19%)	0.02
Influenza vaccination	62,570 (43.83%)	61,446 (43.04%)	0.02
Pneumococcal vaccination	2,288 (1.60%)	2,284 (1.60%)	0.00
Encounter for cancer screening	41,068 (28.76%)	41,688 (29.20%)	0.01
Eye examination	9,111 (6.38%)	9,441 (6.61%)	0.01
Colonoscopy	6,145 (4.30%)	6,238 (4.37%)	0.00
Bone mineral density test	1,766 (1.24%)	1,829 (1.28%)	0.00
Well-check/well-child preventive healthcare visit	61,471 (43.06%)	62,529 (43.80%)	0.01
Arthritis	18,896 (13.24%)	19,129 (13.40%)	0.00
Lipid abnormality	26,821 (18.79%)	26,349 (18.46%)	0.01
Ambulance use or life support services	2,259 (1.58%)	2,111 (1.48%)	0.01
Weakness	2,656 (1.86%)	2,797 (1.96%)	0.01
Pregnancy completion before Time 0[a]	2,681 (1.88%)	2,782 (1.95%)	0.01

Characteristic	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 142,771	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 142,771	ASD
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	6,763 (4.74%)	7,028 (4.92%)	0.01
Cancer	8,581 (6.01%)	8,922 (6.25%)	0.01
Chronic kidney disease or renal disease	2,620 (1.84%)	2,658 (1.86%)	0.00
Chronic liver disease	6,092 (4.27%)	6,250 (4.38%)	0.01
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	15,462 (10.83%)	15,388 (10.78%)	0.00
Dementia or other neurological conditions	9,614 (6.73%)	9,507 (6.66%)	0.00
Diabetes mellitus, type 1 or 2	11,085 (7.76%)	10,980 (7.69%)	0.00
Down syndrome	27 (0.02%)	37 (0.03%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	18,883 (13.23%)	19,020 (13.32%)	0.00
Hypertension	30,587 (21.42%)	30,528 (21.38%)	0.00
Immunocompromised state	7,140 (5.00%)	7,477 (5.24%)	0.01
Mental health conditions	41,265 (28.90%)	39,825 (27.89%)	0.02
Obese or severely obese	29,290 (20.52%)	28,740 (20.13%)	0.01
Sickle cell disease or thalassemia	334 (0.23%)	359 (0.25%)	0.00
Stroke or cerebrovascular disease	2,145 (1.50%)	2,173 (1.52%)	0.00
Tuberculosis	108 (0.08%)	85 (0.06%)	0.01
≥ 1 COVID-19 laboratory test performed	51,738 (36.24%)	52,744 (36.94%)	0.01
COVID-19 diagnoses occurring outside a hospital or ED setting	7,818 (5.48%)	7,931 (5.56%)	0.00
Hospital/ED-diagnosed COVID-19	1,178 (0.83%)	1,256 (0.88%)	0.01

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-16-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With mRNA-1273 COVID-19 Vaccine and Matched Adults Vaccinated With BNT162b2 COVID-19 Vaccine

Characteristic	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 515,403	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 515,403	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	43 (32, 54)	43 (32, 54)	0.00
Mean (SD)	42.65 (13.39)	42.63 (13.4)	0.00
Sex, n (%)			
Male	248,944 (48.30%)	248,944 (48.30%)	0.00
Female	266,459 (51.70%)	266,459 (51.70%)	0.00
Region, n (%)			
Northeast	105,781 (20.52%)	105,781 (20.52%)	0.00
South	86,711 (16.82%)	86,711 (16.82%)	0.00
Midwest	81,020 (15.72%)	81,020 (15.72%)	0.00
West	241,891 (46.93%)	241,891 (46.93%)	0.00
Pregnant at Time 0, n (%)[a]	2,476 (0.48%)	2,895 (0.56%)	0.01
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	370,254 (71.84%)	369,535 (71.70%)	0.00
1	78,774 (15.28%)	78,024 (15.14%)	0.00
2+	66,375 (12.88%)	67,844 (13.16%)	0.01
ED visits			
0	466,787 (90.57%)	468,100 (90.82%)	0.01
1	39,160 (7.60%)	38,122 (7.40%)	0.01
2+	9,456 (1.83%)	9,181 (1.78%)	0.00
Skilled nursing facility stay	419 (0.08%)	444 (0.09%)	0.00
Influenza vaccination	192,183 (37.29%)	187,339 (36.35%)	0.02
Pneumococcal vaccination	8,068 (1.57%)	7,728 (1.50%)	0.01
Encounter for cancer screening	137,931 (26.76%)	139,280 (27.02%)	0.01
Eye examination	39,958 (7.75%)	40,900 (7.94%)	0.01
Colonoscopy	21,442 (4.16%)	21,407 (4.15%)	0.00
Bone mineral density test	7,573 (1.47%)	7,532 (1.46%)	0.00
Well-check/well-child preventive healthcare visit	198,430 (38.50%)	200,433 (38.89%)	0.01
Arthritis	72,444 (14.06%)	71,192 (13.81%)	0.01
Lipid abnormality	104,311 (20.24%)	102,780 (19.94%)	0.01
Ambulance use or life support services	8,659 (1.68%)	8,065 (1.56%)	0.01
Weakness	9,313 (1.81%)	9,269 (1.80%)	0.00
Pregnancy completion before Time 0[a]	9,247 (1.79%)	9,519 (1.85%)	0.00

Characteristic	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 515,403	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 515,403	ASD
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	26,600 (5.16%)	26,232 (5.09%)	0.00
Cancer	33,136 (6.43%)	33,514 (6.50%)	0.00
Chronic kidney disease or renal disease	12,771 (2.48%)	12,184 (2.36%)	0.01
Chronic liver disease	26,645 (5.17%)	26,326 (5.11%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	61,198 (11.87%)	59,185 (11.48%)	0.01
Dementia or other neurological conditions	39,199 (7.61%)	37,752 (7.32%)	0.01
Diabetes mellitus, type 1 or 2	43,746 (8.49%)	41,855 (8.12%)	0.01
Down syndrome	225 (0.04%)	202 (0.04%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	75,040 (14.56%)	74,672 (14.49%)	0.00
Hypertension	115,598 (22.43%)	113,110 (21.95%)	0.01
Immunocompromised state	25,271 (4.90%)	24,675 (4.79%)	0.01
Mental health conditions	149,297 (28.97%)	143,850 (27.91%)	0.02
Obese or severely obese	112,180 (21.77%)	108,544 (21.06%)	0.02
Sickle cell disease or thalassemia	1,642 (0.32%)	1,745 (0.34%)	0.00
Stroke or cerebrovascular disease	10,339 (2.01%)	10,040 (1.95%)	0.00
Tuberculosis	459 (0.09%)	530 (0.10%)	0.00
≥ 1 COVID-19 laboratory test performed	233,092 (45.23%)	232,393 (45.09%)	0.00
COVID-19 diagnoses occurring outside a hospital or ED setting	23,394 (4.54%)	23,277 (4.52%)	0.00
Hospital/ED-diagnosed COVID-19	3,970 (0.77%)	4,020 (0.78%)	0.00

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-17-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With JNJ-7836735 COVID-19 Vaccine and Matched Adults Vaccinated With BNT162b2 COVID-19 Vaccine

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 40,012	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 40,012	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (32, 54)	44 (32, 54)	
Mean (SD)	42.60 (12.89)	42.61 (12.86)	0.00
Sex, n (%)			
Male	22,207 (55.50%)	22,207 (55.50%)	0.00
Female	17,805 (44.50%)	17,805 (44.50%)	0.00
Region, n (%)			
Northeast	4,391 (10.97%)	4,391 (10.97%)	0.00
South	8,033 (20.08%)	8,033 (20.08%)	0.00
Midwest	18,539 (46.33%)	18,539 (46.33%)	0.00
West	9,049 (22.62%)	9,049 (22.62%)	0.00
Pregnant at Time 0, n (%)[a]	82 (0.20%)	205 (0.51%)	0.08
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	28,405 (70.99%)	27,731 (69.31%)	0.04
1	6,743 (16.85%)	7,002 (17.50%)	0.02
2+	4,864 (12.16%)	5,279 (13.19%)	0.03
ED visits			
0	36,368 (90.89%)	36,180 (90.42%)	0.02
1	3,008 (7.52%)	3,106 (7.76%)	0.01
2+	636 (1.59%)	726 (1.81%)	0.02
Skilled nursing facility stay	27 (0.07%)	23 (0.06%)	0.00
Influenza vaccination	14,500 (36.24%)	16,299 (40.74%)	0.09
Pneumococcal vaccination	469 (1.17%)	578 (1.44%)	0.02
Encounter for cancer screening	10,964 (27.40%)	11,052 (27.62%)	0.00
Eye examination	2,399 (6.00%)	2,610 (6.52%)	0.02
Colonoscopy	1,598 (3.99%)	1,722 (4.30%)	0.02
Bone mineral density test	442 (1.10%)	419 (1.05%)	0.01
Well-check/well-child preventive healthcare visit	16,456 (41.13%)	16,555 (41.38%)	0.01
Arthritis	5,287 (13.21%)	5,240 (13.10%)	0.00
Lipid abnormality	6,791 (16.97%)	7,277 (18.19%)	0.03
Ambulance use or life support services	624 (1.56%)	613 (1.53%)	0.00
Weakness	773 (1.93%)	767 (1.92%)	0.00
Pregnancy completion before Time 0[a]	505 (1.26%)	641 (1.60%)	0.04

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 40,012	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 40,012	ASD
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	1,839 (4.60%)	1,830 (4.57%)	0.00
Cancer	2,345 (5.86%)	2,359 (5.90%)	0.00
Chronic kidney disease or renal disease	679 (1.70%)	749 (1.87%)	0.01
Chronic liver disease	1,540 (3.85%)	1,666 (4.16%)	0.02
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	4,013 (10.03%)	4,127 (10.31%)	0.01
Dementia or other neurological conditions	2,551 (6.38%)	2,619 (6.55%)	0.01
Diabetes mellitus, type 1 or 2	2,595 (6.49%)	3,014 (7.53%)	0.04
Down syndrome	< 11	< 11	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	4,896 (12.24%)	5,263 (13.15%)	0.03
Hypertension	8,060 (20.14%)	8,583 (21.45%)	0.03
Immunocompromised state	1,755 (4.39%)	1,950 (4.87%)	0.02
Mental health conditions	11,050 (27.62%)	11,035 (27.58%)	0.00
Obese or severely obese	7,521 (18.80%)	7,990 (19.97%)	0.03
Sickle cell disease or thalassemia	62 (0.15%)	79 (0.20%)	0.01
Stroke or cerebrovascular disease	553 (1.38%)	572 (1.43%)	0.00
Tuberculosis	17 (0.04%)	24 (0.06%)	0.01
≥ 1 COVID-19 laboratory test performed	14,522 (36.29%)	14,512 (36.27%)	0.00
COVID-19 diagnoses occurring outside a hospital or ED setting	2,484 (6.21%)	2,326 (5.81%)	0.02
Hospital/ED-diagnosed COVID-19	357 (0.89%)	381 (0.95%)	0.01

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

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

Table C-17-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With JNJ-7836735 COVID-19 Vaccine and Matched Adults Vaccinated With BNT162b2 COVID-19 Vaccine

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 131,597	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 131,597	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (32, 54)	44 (32, 54)	0.00
Mean (SD)	42.76 (13.3)	42.74 (13.31)	0.00
Sex, n (%)			
Male	71,900 (54.64%)	71,900 (54.64%)	0.00
Female	59,697 (45.36%)	59,697 (45.36%)	0.00
Region, n (%)			
Northeast	26,325 (20.00%)	26,325 (20.00%)	0.00
South	22,222 (16.89%)	22,222 (16.89%)	0.00
Midwest	22,031 (16.74%)	22,031 (16.74%)	0.00
West	61,019 (46.37%)	61,019 (46.37%)	0.00
Pregnant at Time 0, n (%)[a]	295 (0.22%)	628 (0.48%)	0.04
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	98,249 (74.66%)	96,119 (73.04%)	0.04
1	18,691 (14.20%)	19,296 (14.66%)	0.01
2+	14,657 (11.14%)	16,182 (12.30%)	0.04
ED visits			
0	119,998 (91.19%)	119,424 (90.75%)	0.02
1	9,482 (7.21%)	9,835 (7.47%)	0.01
2+	2,117 (1.61%)	2,338 (1.78%)	0.01
Skilled nursing facility stay	81 (0.06%)	83 (0.06%)	0.00
Influenza vaccination	41,263 (31.36%)	44,764 (34.02%)	0.06
Pneumococcal vaccination	1,495 (1.14%)	1,769 (1.34%)	0.02
Encounter for cancer screening	33,161 (25.20%)	34,074 (25.89%)	0.02
Eye examination	9,527 (7.24%)	9,901 (7.52%)	0.01
Colonoscopy	5,256 (3.99%)	5,519 (4.19%)	0.01
Bone mineral density test	1,630 (1.24%)	1,719 (1.31%)	0.01
Well-check/well-child preventive healthcare visit	48,300 (36.70%)	49,795 (37.84%)	0.02
Arthritis	18,298 (13.90%)	18,022 (13.69%)	0.01
Lipid abnormality	24,076 (18.30%)	25,899 (19.68%)	0.04
Ambulance use or life support services	2,043 (1.55%)	2,077 (1.58%)	0.00
Weakness	2,295 (1.74%)	2,322 (1.76%)	0.00
Pregnancy completion before Time 0[a]	1,543 (1.17%)	2,053 (1.56%)	0.03

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 131,597	Individuals vaccinated with BNT162b2 COVID-19 vaccine N = 131,597	ASD
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	6,041 (4.59%)	6,518 (4.95%)	0.02
Cancer	7,769 (5.90%)	7,903 (6.01%)	0.00
Chronic kidney disease or renal disease	2,823 (2.15%)	3,115 (2.37%)	0.01
Chronic liver disease	5,949 (4.52%)	6,691 (5.08%)	0.03
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	14,134 (10.74%)	14,710 (11.18%)	0.01
Dementia or other neurological conditions	9,294 (7.06%)	9,360 (7.11%)	0.00
Diabetes mellitus, type 1 or 2	9,104 (6.92%)	10,381 (7.89%)	0.04
Down syndrome	44 (0.03%)	48 (0.04%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	17,252 (13.11%)	18,426 (14.00%)	0.03
Hypertension	26,685 (20.28%)	28,691 (21.80%)	0.04
Immunocompromised state	5,251 (3.99%)	5,839 (4.44%)	0.02
Mental health conditions	36,628 (27.83%)	35,876 (27.26%)	0.01
Obese or severely obese	25,721 (19.55%)	27,284 (20.73%)	0.03
Sickle cell disease or thalassemia	330 (0.25%)	396 (0.30%)	0.01
Stroke or cerebrovascular disease	2,173 (1.65%)	2,501 (1.90%)	0.02
Tuberculosis	89 (0.07%)	105 (0.08%)	0.00
≥ 1 COVID-19 laboratory test performed	59,670 (45.34%)	58,645 (44.56%)	0.02
COVID-19 diagnoses occurring outside a hospital or ED setting	6,680 (5.08%)	6,457 (4.91%)	0.01
Hospital/ED-diagnosed COVID-19	974 (0.74%)	1,178 (0.90%)	0.02

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-18-Optum. Characteristics of Adults Aged 18-64 Years Vaccinated With JNJ-7836735 COVID-19 Vaccine and Matched Adults Vaccinated With mRNA-1273 COVID-19 Vaccine

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 33,274	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 33,274	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (33, 54)	44 (33, 54)	
Mean (SD)	42.79 (12.84)	42.81 (12.82)	0.00
Sex, n (%)			
Male	18,101 (54.40%)	18,101 (54.40%)	0.00
Female	15,173 (45.60%)	15,173 (45.60%)	0.00
Region, n (%)			
Northeast	3,639 (10.94%)	3,639 (10.94%)	0.00
South	6,835 (20.54%)	6,835 (20.54%)	0.00
Midwest	14,957 (44.95%)	14,957 (44.95%)	0.00
West	7,843 (23.57%)	7,843 (23.57%)	0.00
Pregnant at Time 0, n (%)[a]	64 (0.19%)	152 (0.46%)	0.07
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	23,465 (70.52%)	23,225 (69.80%)	0.02
1	5,684 (17.08%)	5,632 (16.93%)	0.00
2+	4,125 (12.40%)	4,417 (13.27%)	0.03
ED visits			
0	30,278 (91.00%)	30,179 (90.70%)	0.01
1	2,471 (7.43%)	2,521 (7.58%)	0.01
2+	525 (1.58%)	574 (1.73%)	0.01
Skilled nursing facility stay	23 (0.07%)	14 (0.04%)	0.01
Influenza vaccination	12,433 (37.37%)	13,980 (42.01%)	0.10
Pneumococcal vaccination	398 (1.20%)	505 (1.52%)	0.03
Encounter for cancer screening	9,197 (27.64%)	9,221 (27.71%)	0.00
Eye examination	2,015 (6.06%)	2,021 (6.07%)	0.00
Colonoscopy	1,364 (4.10%)	1,424 (4.28%)	0.01
Bone mineral density test	378 (1.14%)	360 (1.08%)	0.01
Well-check/well-child preventive healthcare visit	13,714 (41.22%)	13,716 (41.22%)	0.00
Arthritis	4,388 (13.19%)	4,446 (13.36%)	0.01
Lipid abnormality	5,793 (17.41%)	6,309 (18.96%)	0.04
Ambulance use or life support services	536 (1.61%)	538 (1.62%)	0.00
Weakness	651 (1.96%)	616 (1.85%)	0.01
Pregnancy completion before Time 0[a]	413 (1.24%)	519 (1.56%)	0.04
Characteristics assessed using all available data before Time 0, n (%)			

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 33,274	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 33,274	ASD
Autoimmune disorders	1,553 (4.67%)	1,549 (4.66%)	0.00
Cancer	2,005 (6.03%)	1,902 (5.72%)	0.01
Chronic kidney disease or renal disease	565 (1.70%)	625 (1.88%)	0.01
Chronic liver disease	1,308 (3.93%)	1,443 (4.34%)	0.02
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	3,365 (10.11%)	3,497 (10.51%)	0.01
Dementia or other neurological conditions	2,091 (6.28%)	2,115 (6.36%)	0.00
Diabetes mellitus, type 1 or 2	2,240 (6.73%)	2,538 (7.63%)	0.03
Down syndrome	< 11	< 11	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	4,169 (12.53%)	4,291 (12.90%)	0.01
Hypertension	6,811 (20.47%)	7,281 (21.88%)	0.03
Immunocompromised state	1,478 (4.44%)	1,548 (4.65%)	0.01
Mental health conditions	9,167 (27.55%)	9,438 (28.36%)	0.02
Obese or severely obese	6,237 (18.74%)	6,711 (20.17%)	0.04
Sickle cell disease or thalassemia	46 (0.14%)	72 (0.22%)	0.02
Stroke or cerebrovascular disease	477 (1.43%)	500 (1.50%)	0.01
Tuberculosis	13 (0.04%)	24 (0.07%)	0.01
≥ 1 COVID-19 laboratory test performed	12,016 (36.11%)	11,896 (35.75%)	0.01
COVID-19 diagnoses occurring outside a hospital or ED setting	2,005 (6.03%)	1,880 (5.65%)	0.02
Hospital/ED-diagnosed COVID-19	298 (0.90%)	298 (0.90%)	0.00

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

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

Table C-18-CVS. Characteristics of Adults Aged 18-64 Years Vaccinated With JNJ-7836735 COVID-19 Vaccine and Matched Adults Vaccinated With mRNA-1273 COVID-19 Vaccine

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 117,170	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 117,170	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	44 (32, 54)	44 (32, 54)	0.00
Mean (SD)	42.97 (13.34)	42.98 (13.34)	0.00
Sex, n (%)			
Male	63,808 (54.46%)	63,808 (54.46%)	0.00
Female	53,362 (45.54%)	53,362 (45.54%)	0.00
Region, n (%)			
Northeast	23,611 (20.15%)	23,611 (20.15%)	0.00
South	19,143 (16.34%)	19,143 (16.34%)	0.00
Midwest	18,415 (15.72%)	18,415 (15.72%)	0.00
West	56,001 (47.79%)	56,001 (47.79%)	0.00
Pregnant at Time 0, n (%)[a]	253 (0.22%)	454 (0.39%)	0.03
Characteristics assessed in the 365 days before Time 0, n (%)			
Hospitalizations			
0	87,539 (74.71%)	85,844 (73.26%)	0.03
1	16,628 (14.19%)	17,128 (14.62%)	0.01
2+	13,003 (11.10%)	14,198 (12.12%)	0.03
ED visits			
0	106,908 (91.24%)	105,981 (90.45%)	0.03
1	8,445 (7.21%)	9,053 (7.73%)	0.02
2+	1,817 (1.55%)	2,136 (1.82%)	0.02
Skilled nursing facility stay	78 (0.07%)	100 (0.09%)	0.01
Influenza vaccination	37,388 (31.91%)	41,472 (35.39%)	0.07
Pneumococcal vaccination	1,378 (1.18%)	1,665 (1.42%)	0.02
Encounter for cancer screening	29,674 (25.33%)	30,181 (25.76%)	0.01
Eye examination	8,538 (7.29%)	8,780 (7.49%)	0.01
Colonoscopy	4,694 (4.01%)	4,941 (4.22%)	0.01
Bone mineral density test	1,503 (1.28%)	1,547 (1.32%)	0.00
Well-check/well-child preventive healthcare visit	42,920 (36.63%)	43,286 (36.94%)	0.01
Arthritis	16,317 (13.93%)	16,310 (13.92%)	0.00
Lipid abnormality	21,844 (18.64%)	23,763 (20.28%)	0.04
Ambulance use or life support services	1,795 (1.53%)	2,069 (1.77%)	0.02
Weakness	2,014 (1.72%)	2,144 (1.83%)	0.01
Pregnancy completion before Time 0[a]	1,339 (1.14%)	1,758 (1.50%)	0.03

Characteristic	Individuals vaccinated with JNJ-7836735 COVID-19 vaccine N = 117,170	Individuals vaccinated with mRNA-1273 COVID-19 vaccine N = 117,170	ASD
Characteristics assessed using all available data before Time 0, n (%)			
Autoimmune disorders	5,480 (4.68%)	5,547 (4.73%)	0.00
Cancer	7,015 (5.99%)	7,145 (6.10%)	0.00
Chronic kidney disease or renal disease	2,564 (2.19%)	2,997 (2.56%)	0.02
Chronic liver disease	5,350 (4.57%)	5,976 (5.10%)	0.02
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	12,686 (10.83%)	13,445 (11.47%)	0.02
Dementia or other neurological conditions	8,242 (7.03%)	8,470 (7.23%)	0.01
Diabetes mellitus, type 1 or 2	8,321 (7.10%)	9,864 (8.42%)	0.05
Down syndrome	41 (0.03%)	50 (0.04%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	15,513 (13.24%)	16,654 (14.21%)	0.03
Hypertension	24,151 (20.61%)	26,406 (22.54%)	0.05
Immunocompromised state	4,745 (4.05%)	5,300 (4.52%)	0.02
Mental health conditions	32,576 (27.80%)	33,028 (28.19%)	0.01
Obese or severely obese	22,969 (19.60%)	25,096 (21.42%)	0.04
Sickle cell disease or thalassemia	288 (0.25%)	348 (0.30%)	0.01
Stroke or cerebrovascular disease	1,987 (1.70%)	2,284 (1.95%)	0.02
Tuberculosis	86 (0.07%)	96 (0.08%)	0.00
≥ 1 COVID-19 laboratory test performed	52,803 (45.07%)	52,313 (44.65%)	0.01
COVID-19 diagnoses occurring outside a hospital or ED setting	5,818 (4.97%)	5,471 (4.67%)	0.01
Hospital/ED-diagnosed COVID-19	861 (0.73%)	963 (0.82%)	0.01

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

[a] Pregnancy percentages are calculated using the entire population (males and females) as the denominator.

Table C-19-Optum. Estimated Relative Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Receiving a Complete Primary Series of a Different COVID-19 Vaccine in Adults Aged 18-64 Years

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	HR (95% CI)	RVE (95% CI)
Medically diagnosed	mRNA-1273	142,771	3,915	29,984,509	0.83 (0.80-0.87)	17% (13%-20%)
	BNT162b2	142,771	4,610	30,180,791	—	—
	JNJ-7836735	40,012	1,767	8,558,403	1.35 (1.26-1.45)	−35% (−45% to −26%)
	BNT162b2	40,012	1,270	8,282,776	—	—
	JNJ-7836735	33,274	1,455	7,263,729	1.60 (1.47-1.74)	−60% (−74% to −47%)
	mRNA-1273	33,274	882	6,896,381	—	—
Hospital/ED-diagnosed	mRNA-1273	142,771	342	30,232,139	0.80 (0.70-0.93)	20% (7.2%-30%)
	BNT162b2	142,771	422	30,478,538	—	—
	JNJ-7836735	40,012	209	8,671,831	1.80 (1.43-2.26)	−80% (−126% to −43%)
	BNT162b2	40,012	113	8,358,030	—	—
	JNJ-7836735	33,274	169	7,359,591	2.22 (1.69-2.92)	−122% (−192% to −69%)
	mRNA-1273	33,274	74	6,948,391	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; RVE = relative vaccine effectiveness.
Note: — denotes the reference group.

Table C-19-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of a COVID-19 Vaccine Compared With Adults Receiving a Complete Primary Series of a Different COVID-19 Vaccine in Adults Aged 18-64 Years

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	RVE (95% CI)
Medically diagnosed	mRNA-1273	515,403	14,602	120,571,724	0.84 (0.82-0.86)	16% (14%-18%)
	BNT162b2	515,403	16,918	121,218,538	—	—
	JNJ-7836735	131,597	5,808	32,322,131	1.25 (1.2-1.3)	−25% (−30% to −20%)
	BNT162b2	131,597	4,327	30,077,023	—	—
	JNJ-7836735	117,170	5,159	29,060,125	1.47 (1.41-1.54)	−47% (−54% to −41%)
	mRNA-1273	117,170	3,302	26,790,088	—	—
Hospital/ED-diagnosed	mRNA-1273	515,403	1,556	121,939,485	0.81 (0.76-0.87)	19% (13%-24%)
	BNT162b2	515,403	1,852	122,785,433	—	—
	JNJ-7836735	131,597	791	32,882,139	1.50 (1.34-1.67)	−50% (−67% to −34%)
	BNT162b2	131,597	504	30,463,776	—	—
	JNJ-7836735	117,170	718	29,559,008	2.00 (1.76-2.27)	−100% (−127% to −76%)
	mRNA-1273	117,170	351	27,100,842	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; RVE = relative vaccine effectiveness; sIPTW = stabilized inverse probability of treatment weighted.

Note: — denotes the reference group.

Table C-20-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Receiving a Complete Primary Series of a Different COVID-19 Vaccine in Adults Aged 18-64 Years, 14 Days After Time 0, Negative Control Analysis

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	mRNA-1273	142,771	417	1,967,735	1.20 (1.04-1.38)	−20% (−38% to −3.9%)
	BNT162b2	142,771	351	1,975,374	—	—
	JNJ-7836735	40,012	114	553,996	1.07 (0.82-1.40)	−7.5% (−40% to 18%)
	BNT162b2	40,012	106	555,462	—	—
	JNJ-7836735	33,274	99	460,746	1.12 (0.84-1.49)	−12% (−49% to 16%)
	mRNA-1273	33,274	88	460,380	—	—
Hospital/ED-diagnosed	mRNA-1273	142,771	57	1,970,249	1.14 (0.78-1.66)	−14% (−66% to 22%)
	BNT162b2	142,771	51	1,977,229	—	—
	JNJ-7836735	40,012	17	554,716	0.91 (0.47-1.75)	9.2% (−75% to 53%)
	BNT162b2	40,012	19	555,953	—	—
	JNJ-7836735	33,274	14	461,383	1.83 (0.77-4.38)	−83% (−338% to 23%)
	mRNA-1273	33,274	< 11	460,968	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

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

Table C-20-CVS. Estimated Relative Effectiveness of Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Receiving a Complete Primary Series of a Different COVID-19 Vaccine in Adults Aged 18-64 Years, 14 Days After Time 0, Negative Control Analysis

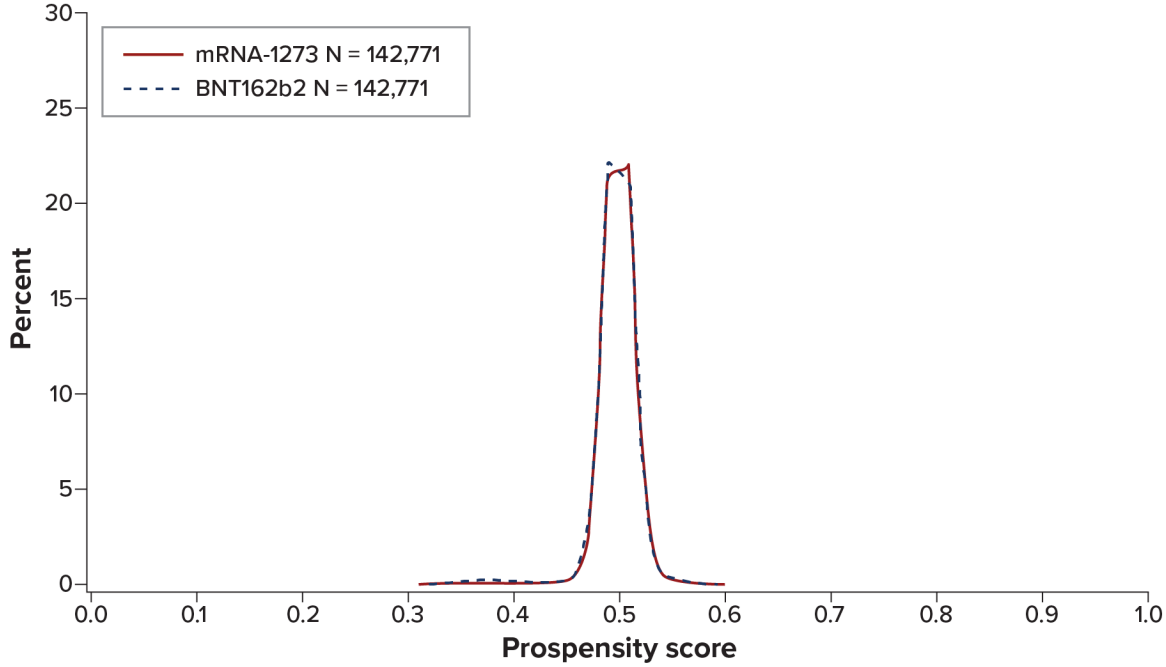
COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	RVE (95% CI)
Medically diagnosed	mRNA-1273	515,403	1,352	7,168,898	1.24 (1.14-1.34)	−24% (−34% to −14%)
	BNT162b2	515,403	1,088	7,178,063	—	—
	JNJ-7836735	131,597	254	1,833,689	0.90 (0.76-1.07)	10% (−7% to 24%)
	BNT162b2	131,597	286	1,834,012	—	—
	JNJ-7836735	117,170	231	1,632,654	0.74 (0.62-0.88)	26% (12%-38%)
	mRNA-1273	117,170	319	1,630,997	—	—
Hospital/ED-diagnosed	mRNA-1273	515,403	151	7,178,682	0.93 (0.74-1.16)	7% (−16% to 26%)
	BNT162b2	515,403	159	7,184,126	—	—
	JNJ-7836735	131,597	51	1,835,101	1.00 (0.68-1.47)	0% (−47% to 32%)
	BNT162b2	131,597	52	1,835,552	—	—
	JNJ-7836735	117,170	51	1,633,902	1.63 (1.05-2.52)	−63% (−152% to −5%)
	mRNA-1273	117,170	33	1,633,653	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; RVE = relative vaccine effectiveness; sIPTW = stabilized inverse probability of treatment weighted.

Note: — denotes the reference group.

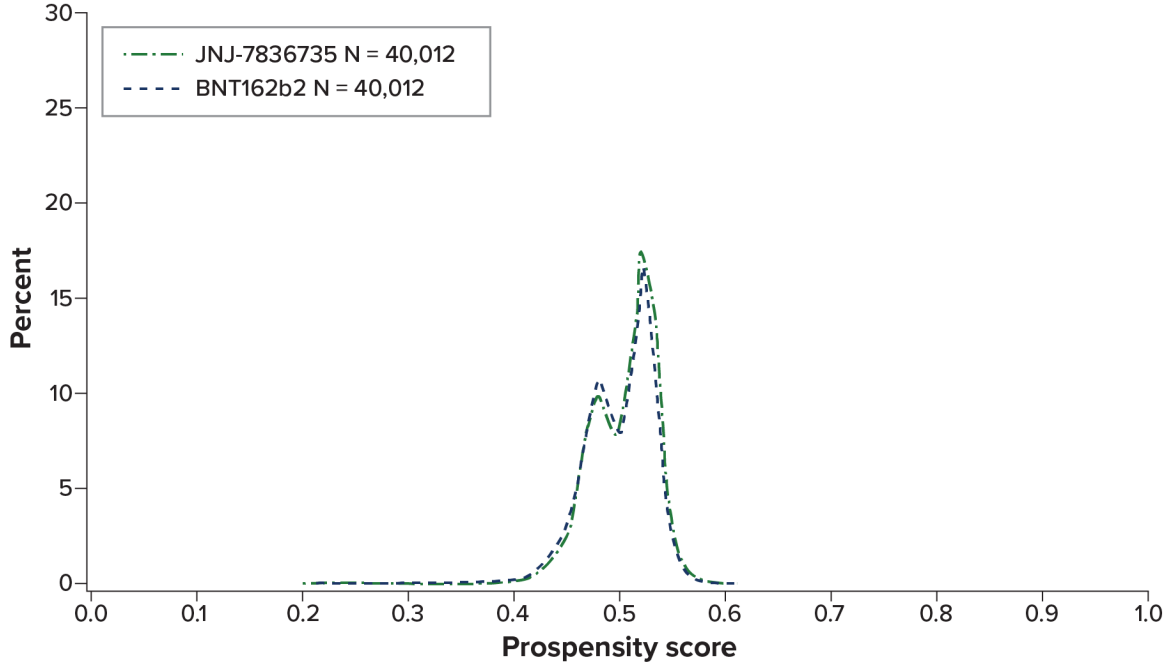
Figure C-5-Optum. Propensity Score Distributions by COVID-19 Vaccine Exposure Group for Comparative Effectiveness Analyses

A. mRNA-1273 vs. BNT162b2



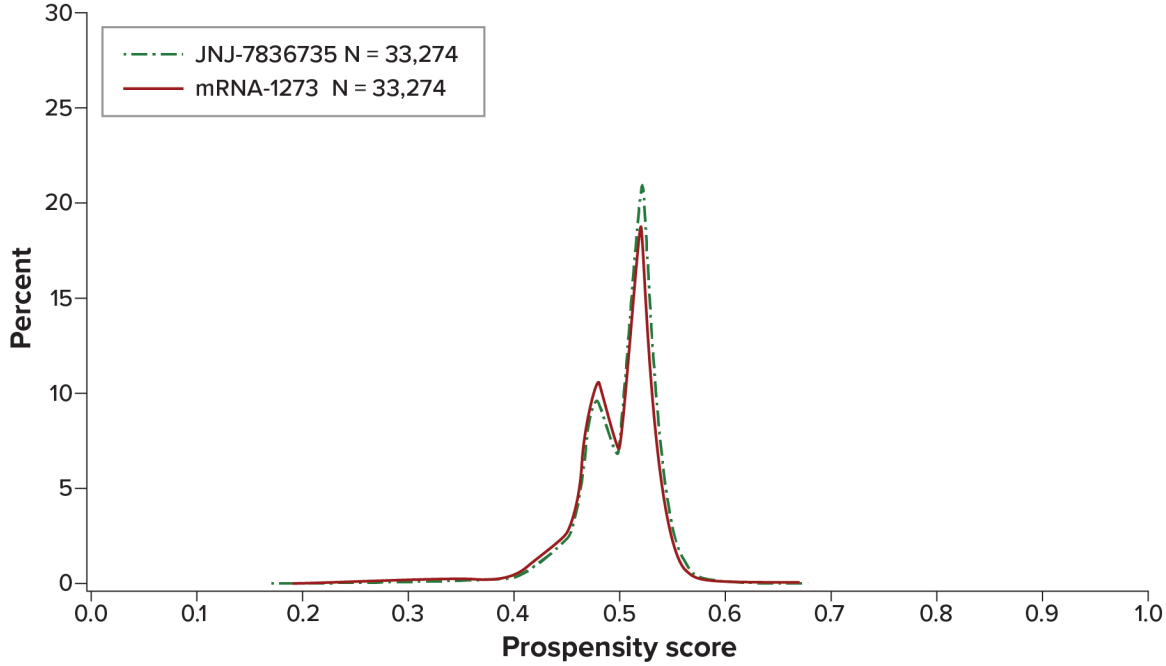
Note: Propensity score variables included the following: age at index date (linear); female sex indicator; state indicator (categorical with indicator variables); pregnant at Time 0; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); ED visits (categorical with indicator variables: 2+, 1, reference = 0); skilled nursing facility stay indicator; influenza vaccination indicator; pneumococcal vaccination indicator; encounter for cancer screening indicator; eye examination indicator; colonoscopy indicator; bone mineral density test indicator; well-check/well-child preventive healthcare visit indicator; arthritis indicator; lipid abnormality indicator; ambulance use or life support services indicator; weakness indicator; autoimmune disorders indicator; cancer indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; dementia or other neurological conditions indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; hypertension indicator; immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies) indicator; mental health conditions indicator; obese or severely obese indicator; sickle cell disease or thalassemia indicator; stroke or cerebrovascular disease indicator; tuberculosis indicator; at least 1 COVID-19 laboratory performed indicator; COVID-19 diagnosis in any setting indicator; Delta or Omicron variant era indicator; increased risk of COVID-19 indicator; interaction term of Delta/Omicron era indicator and mental health conditions indicator.

B. JNJ-7836735 vs. BNT162b2



Note: Propensity score variables included the following: age at index date (linear); female sex indicator; state indicator (categorical with indicator variables); pregnant at Time 0; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); ED visits (categorical with indicator variables: 2+, 1, reference = 0); skilled nursing facility stay indicator; influenza vaccination indicator; pneumococcal vaccination indicator; encounter for cancer screening indicator; eye examination indicator; colonoscopy indicator; bone mineral density test indicator; well-check/well-child preventive healthcare visit indicator; arthritis indicator; lipid abnormality indicator; ambulance use or life support services indicator; weakness indicator; autoimmune disorders indicator; cancer indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; dementia or other neurological conditions indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; hypertension indicator; immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies) indicator; mental health conditions indicator; obese or severely obese indicator; sickle cell disease or thalassemia indicator; stroke or cerebrovascular disease indicator; tuberculosis indicator; at least 1 COVID-19 laboratory performed indicator; COVID-19 diagnosis in any setting indicator; Delta or Omicron variant era indicator; increased risk of COVID-19 indicator; interaction term of Delta/Omicron era indicator and flu vaccine indicator.

C. JNJ-7836735 vs. mRNA-1273

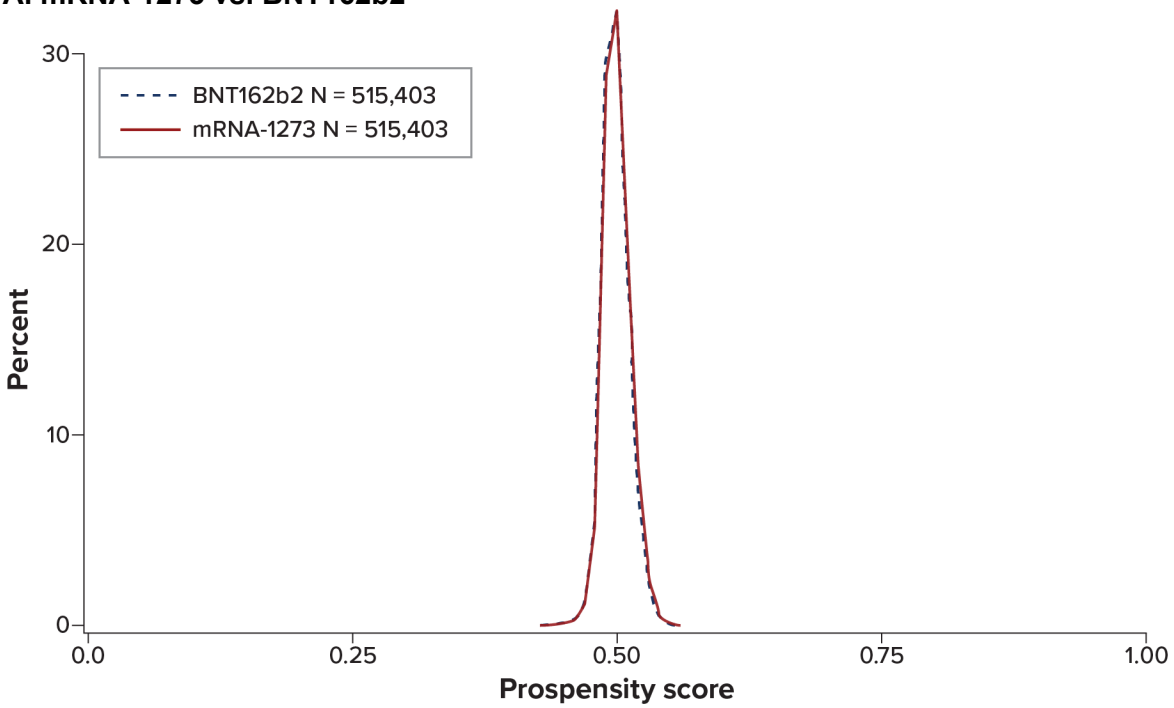


Note: Propensity score variables included the following: age at index date (linear); female sex indicator; state indicator (categorical with indicator variables); pregnant at Time 0; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); ED visits (categorical with indicator variables: 2+, 1, reference = 0); skilled nursing facility stay indicator; influenza vaccination indicator; pneumococcal vaccination indicator; encounter for cancer screening indicator; eye examination indicator; colonoscopy indicator; bone mineral density test indicator; well-check/well-child preventive healthcare visit indicator; arthritis indicator; lipid abnormality indicator; ambulance use or life support services indicator; weakness indicator; autoimmune disorders indicator; cancer indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; dementia or other neurological conditions indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; hypertension indicator; immunocompromised state (identified through diagnoses of immunocompromising conditions and use of immunosuppressive therapies) indicator; mental health conditions indicator; obese or severely obese indicator; sickle cell disease or thalassemia indicator; stroke or cerebrovascular disease indicator; tuberculosis indicator; at least 1 COVID-19 laboratory performed indicator; COVID-19 diagnosis in any setting indicator; Delta or Omicron variant era indicator; increased risk of COVID-19 indicator; interaction term of Delta/Omicron era indicator and flu vaccine indicator.

COVID-19 = coronavirus disease 2019.

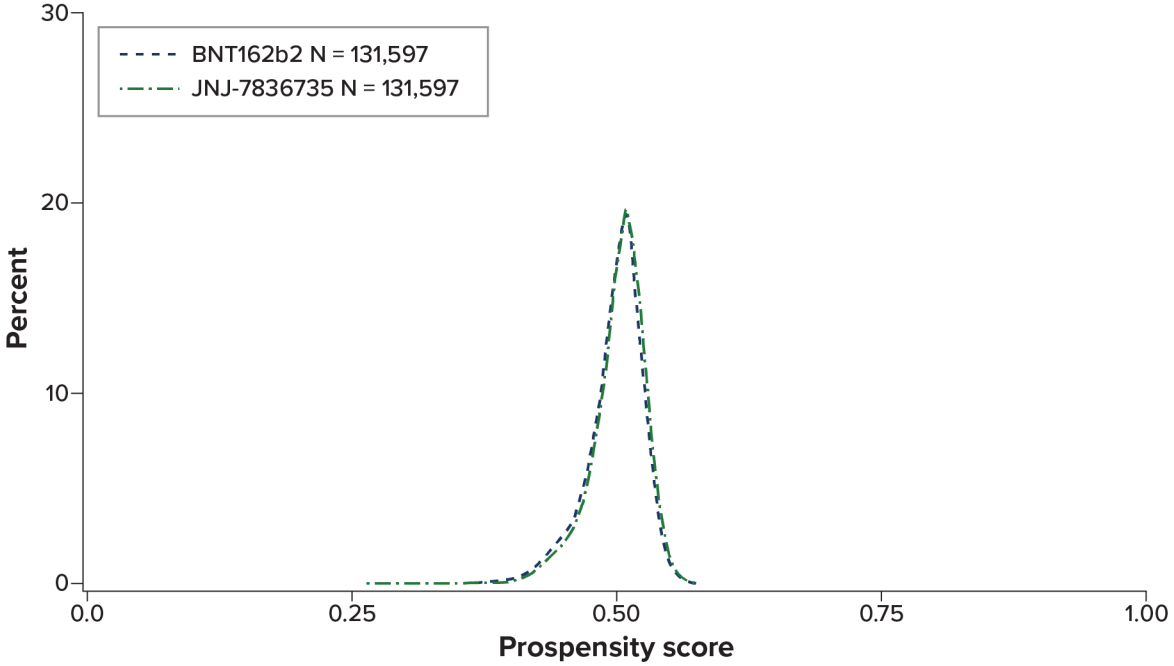
Figure C-5-CVS. Propensity Score Distributions by COVID-19 Vaccine Exposure Group for Comparative Effectiveness Analyses

A. mRNA-1273 vs. BNT162b2



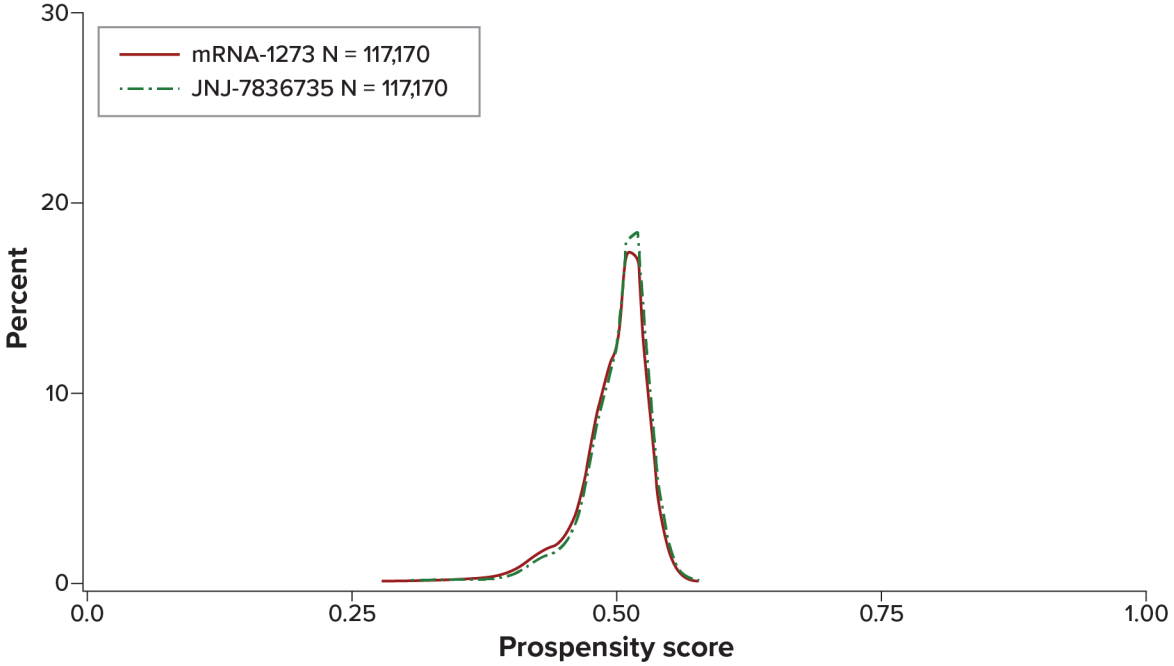
Note: Propensity score variables included the following: age (categorical with indicator variables: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years); ambulance use of life support services indicator; arthritis indicator; autoimmune disorders indicator; bone mineral density test indicator; cancer indicator; encounter for cancer screening indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; colonoscopy indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; county FIPS codes (categorical with indicator variables); pregnant at Time 0 indicator; COVID-19 diagnoses in any setting indicator; hospitalization or emergency department-diagnosed COVID-19 indicator; at least 1 COVID-19 laboratory performed indicator, COVID-19 diagnoses occurring outside of hospital or ED indicator; COVID-19 vaccination index date in the Delta/Omicron era indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; ED visits (categorical with indicator variables: 2+, 1, reference = 0); eye examination indicator; influenza vaccination indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; overall binary indicator of the presence of any of these conditions will be defined to identify individuals who may qualify for priority groups for vaccination eligibility; hypertension indicator; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); lipid abnormality indicator; mental health conditions indicator; dementia or other neurological conditions indicator; obese or severely obese indicator; pneumococcal vaccination indicator; female indicator; male indicator; sickle cell disease or thalassemia indicator; skilled nursing facility stay indicator; IIS jurisdiction (categorical with indicator variables); stroke or cerebrovascular disease indicator; tuberculosis indicator; immunocompromised state indicator; pregnancy completion before Time 0 indicator; weakness indicator; well-check/well-child preventive healthcare visit indicator.

B. JNJ-7836735 vs. BNT162b2



Note: Propensity score variables included the following: age (categorical with indicator variables: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years); ambulance use of life support services indicator; arthritis indicator; autoimmune disorders indicator; bone mineral density test indicator; cancer indicator; encounter for cancer screening indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; colonoscopy indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; county FIPS codes (categorical with indicator variables); pregnant at Time 0 indicator; COVID-19 diagnoses in any setting indicator; hospitalization or emergency department-diagnosed COVID-19 indicator; at least 1 COVID-19 laboratory performed indicator, COVID-19 diagnoses occurring outside of hospital or ED indicator; interaction term of COVID-19 vaccination after 31 May 2021 and received influenza vaccination; COVID-19 vaccination index date in the Delta/Omicron era indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; ED visits (categorical with indicator variables: 2+, 1, reference = 0); eye examination indicator; influenza vaccination indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; overall binary indicator of the presence of any of these conditions will be defined to identify individuals who may qualify for priority groups for vaccination eligibility; hypertension indicator; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); lipid abnormality indicator; mental health conditions indicator; dementia or other neurological conditions indicator; obese or severely obese indicator; pneumococcal vaccination indicator; female indicator; male indicator; sickle cell disease or thalassemia indicator; skilled nursing facility stay indicator; IIS jurisdiction (categorical with indicator variables); stroke or cerebrovascular disease indicator; tuberculosis indicator; immunocompromised state indicator; pregnancy completion before Time 0 indicator; weakness indicator; well-check/well-child preventive healthcare visit indicator.

C. JNJ-7836735 vs. mRNA-1273

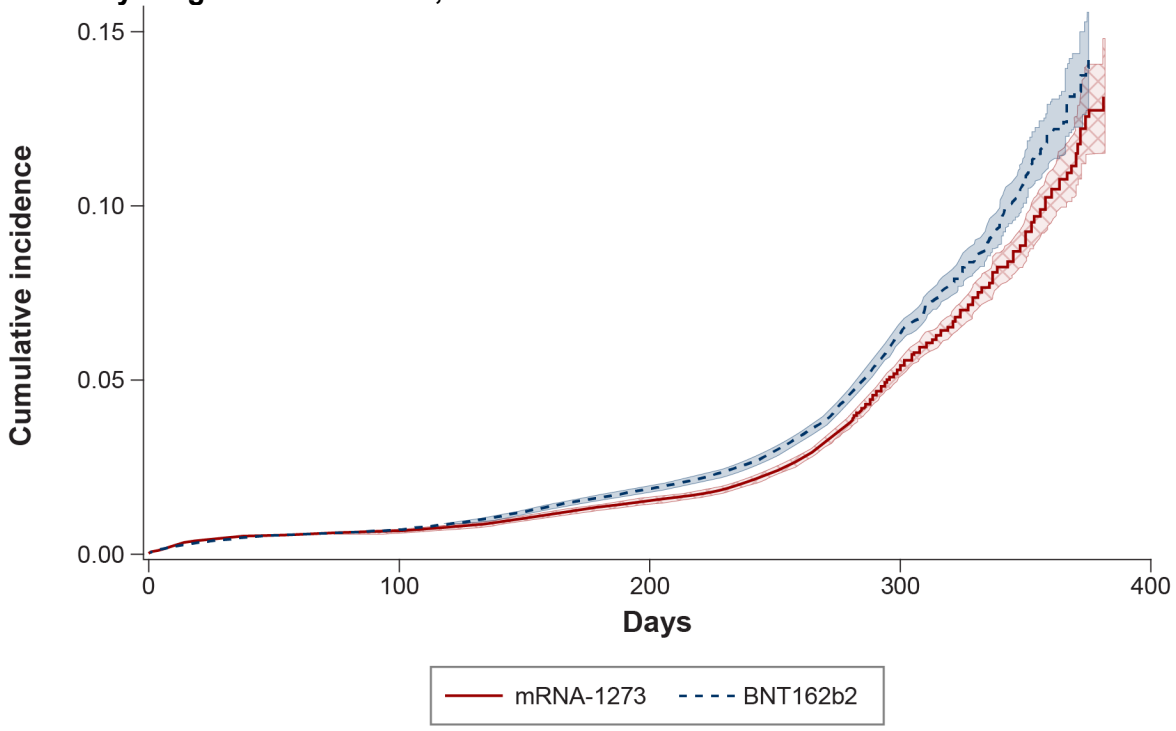


Note: Propensity score variables included the following: age (categorical with indicator variables: 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years); ambulance use of life support services indicator; arthritis indicator; autoimmune disorders indicator; bone mineral density test indicator; cancer indicator; encounter for cancer screening indicator; chronic kidney disease or renal disease indicator; chronic liver disease indicator; colonoscopy indicator; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism) indicator; county FIPS codes (categorical with indicator variables); pregnant at Time 0 indicator; COVID-19 diagnoses in any setting indicator; hospitalization or emergency department-diagnosed COVID-19 indicator; at least 1 COVID-19 laboratory performed indicator, COVID-19 diagnoses occurring outside of hospital or ED indicator; interaction term of COVID-19 vaccination after 31 May 2021 and received influenza vaccination; COVID-19 vaccination index date in the Delta/Omicron era indicator; diabetes mellitus, type 1 or 2 indicator; Down syndrome indicator; ED visits (categorical with indicator variables: 2+, 1, reference = 0); eye examination indicator; influenza vaccination indicator; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias) indicator; overall binary indicator of the presence of any of these conditions will be defined to identify individuals who may qualify for priority groups for vaccination eligibility; hypertension indicator; hospitalizations (categorical with indicator variables: 2+, 1, reference = 0); lipid abnormality indicator; mental health conditions indicator; dementia or other neurological conditions indicator; obese or severely obese indicator; pneumococcal vaccination indicator; female indicator; male indicator; sickle cell disease or thalassemia indicator; skilled nursing facility stay indicator; IIS jurisdiction (categorical with indicator variables); stroke or cerebrovascular disease indicator; tuberculosis indicator; immunocompromised state indicator; pregnancy completion before Time 0 indicator; weakness indicator; well-check/well-child preventive healthcare visit indicator.

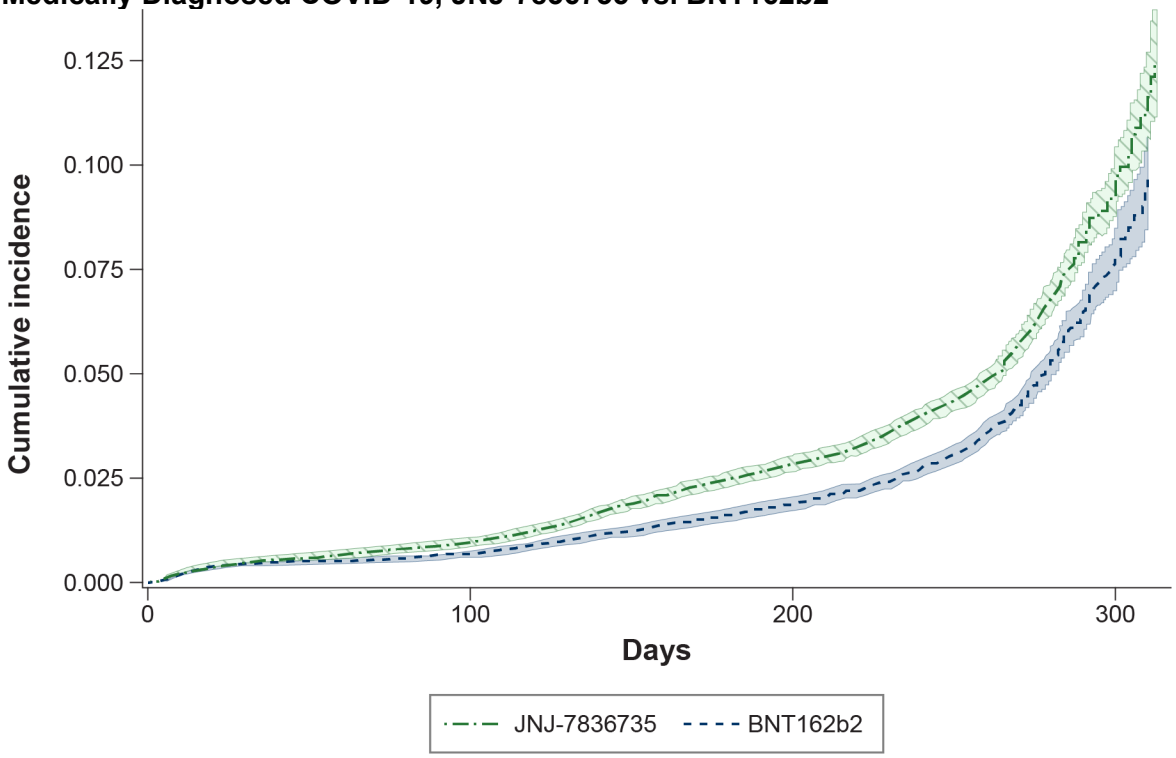
COVID-19 = coronavirus disease 2019.

Figure C-6-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine

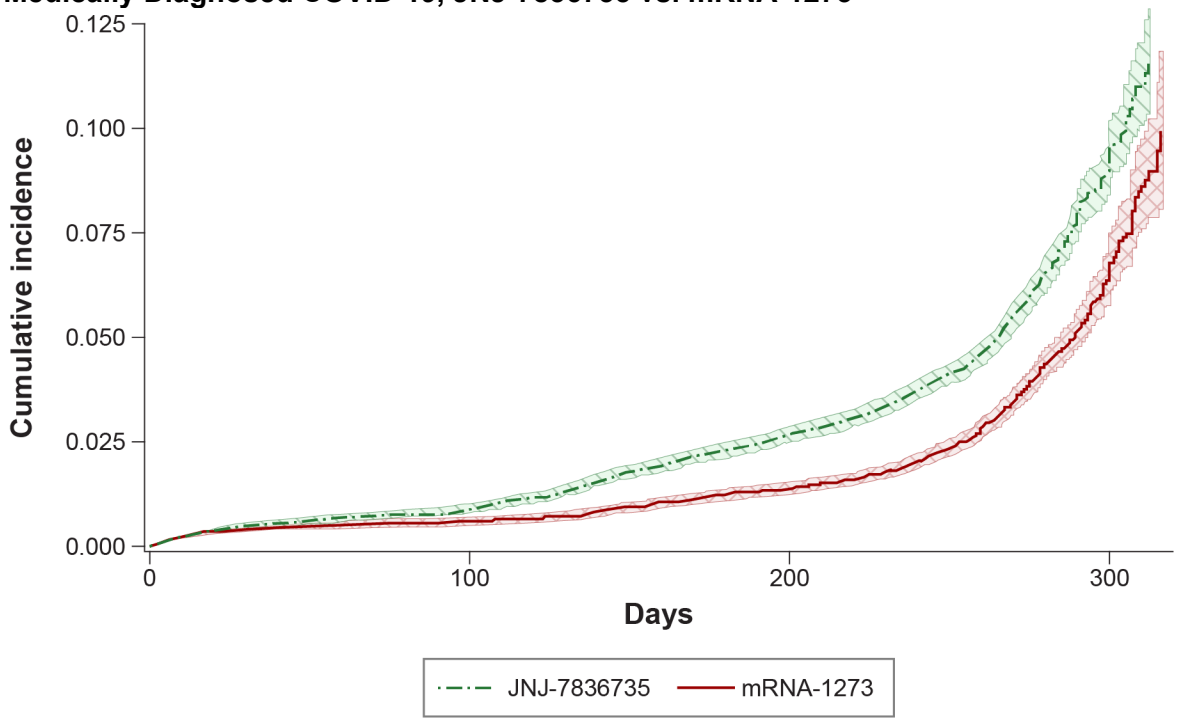
A. Medically Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



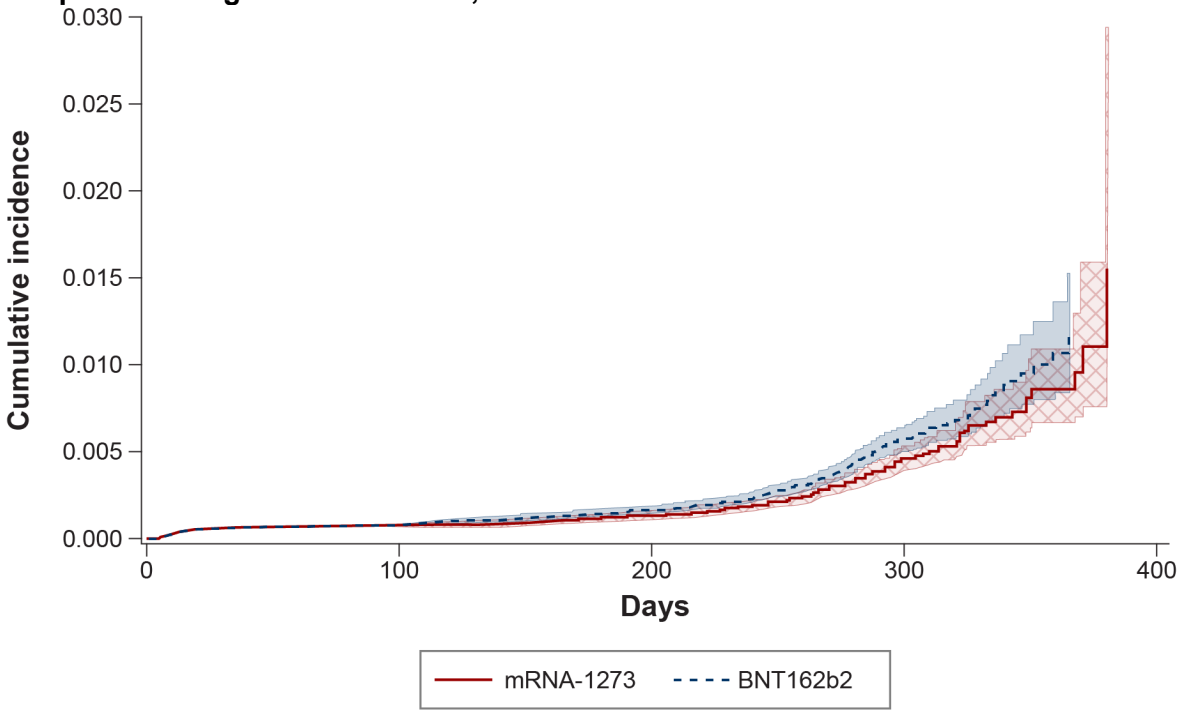
B. Medically Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



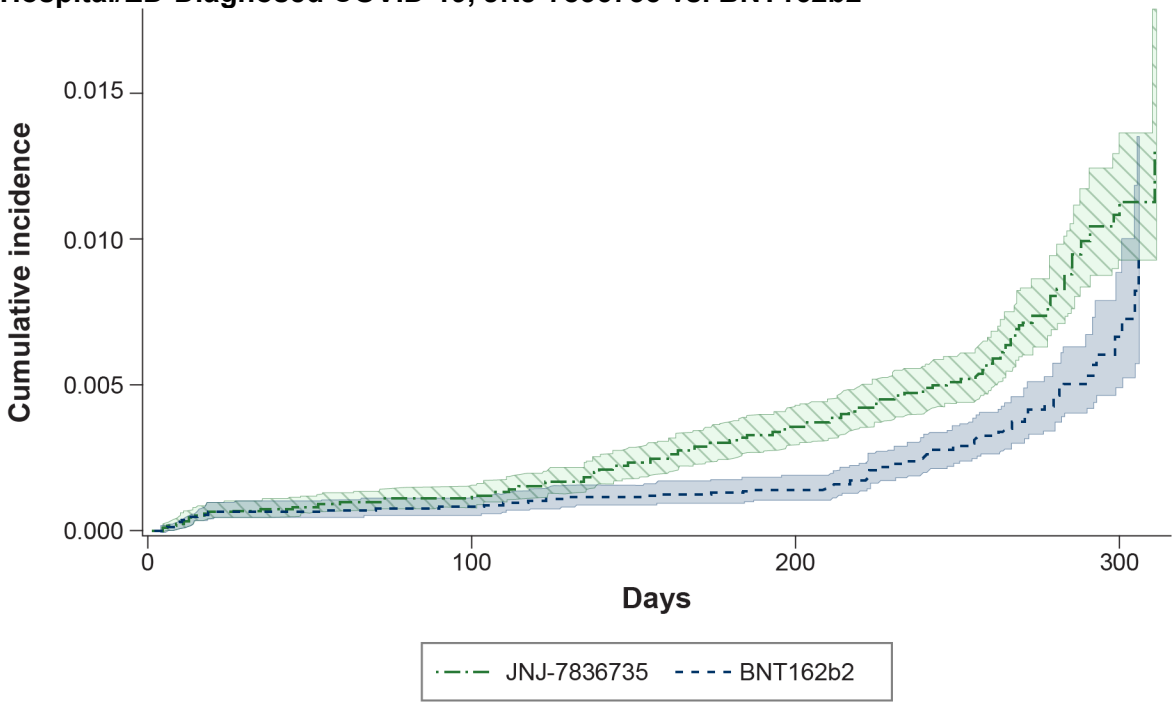
C. Medically Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



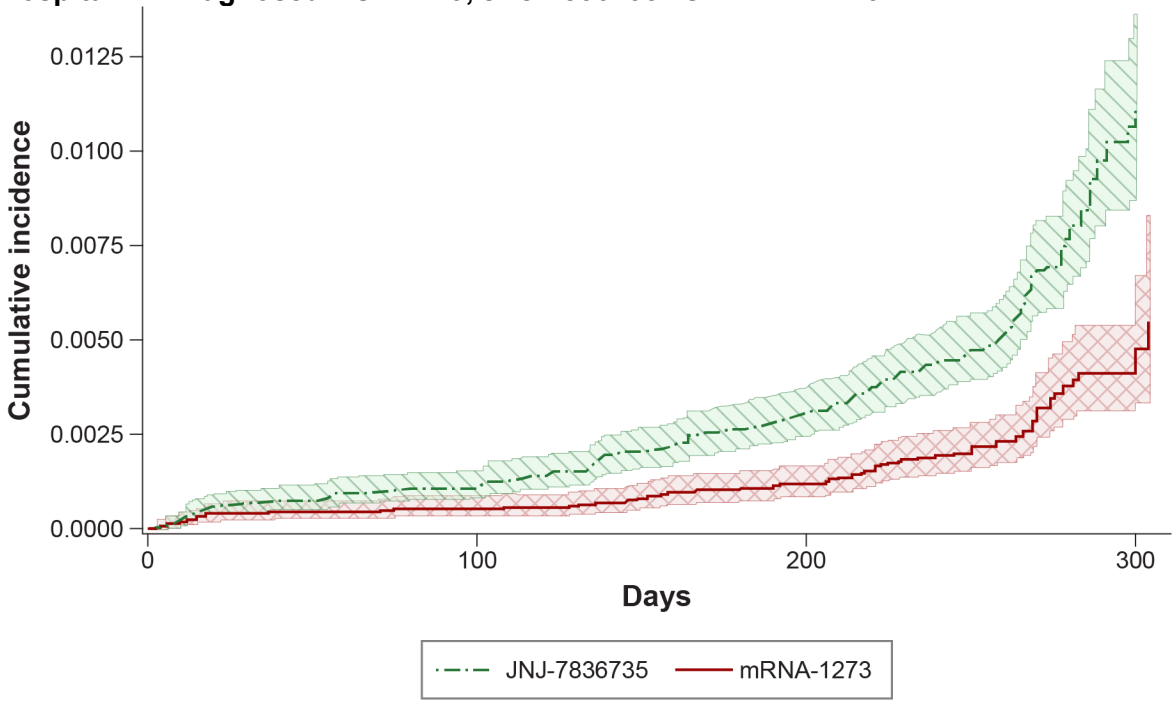
D. Hospital/ED-Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



E. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



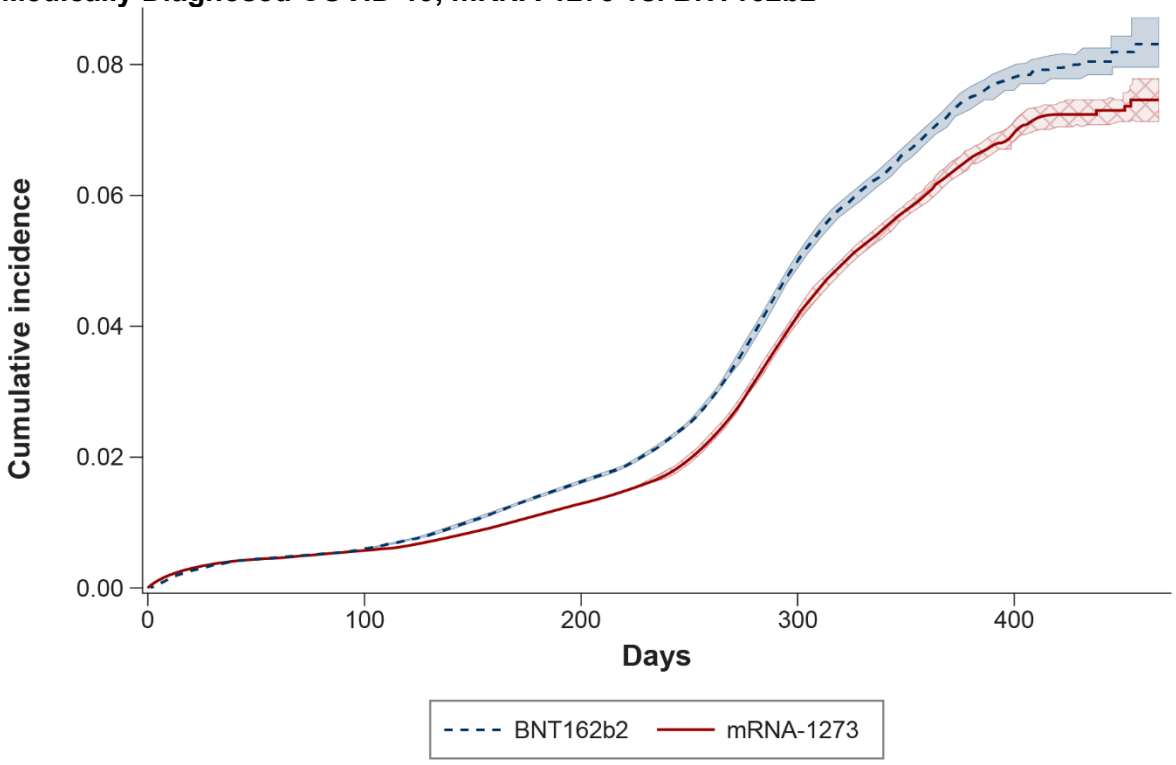
F. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



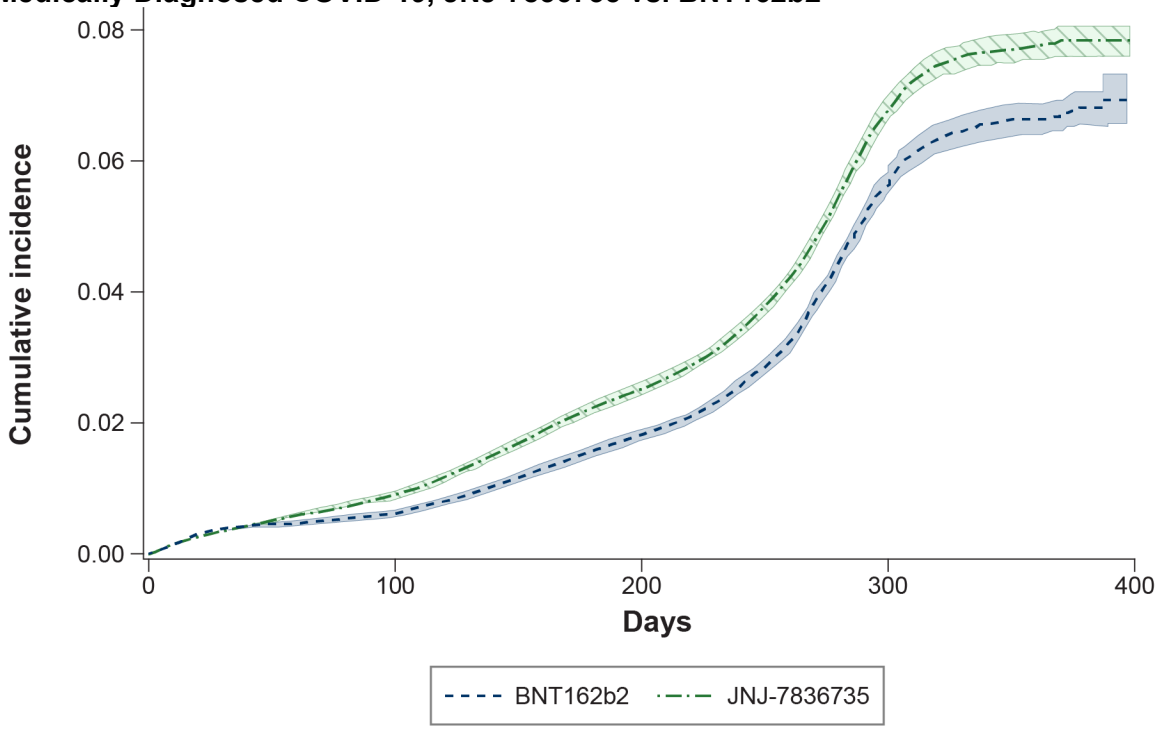
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure C-6-CVS. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine, by Vaccine Exposure Group

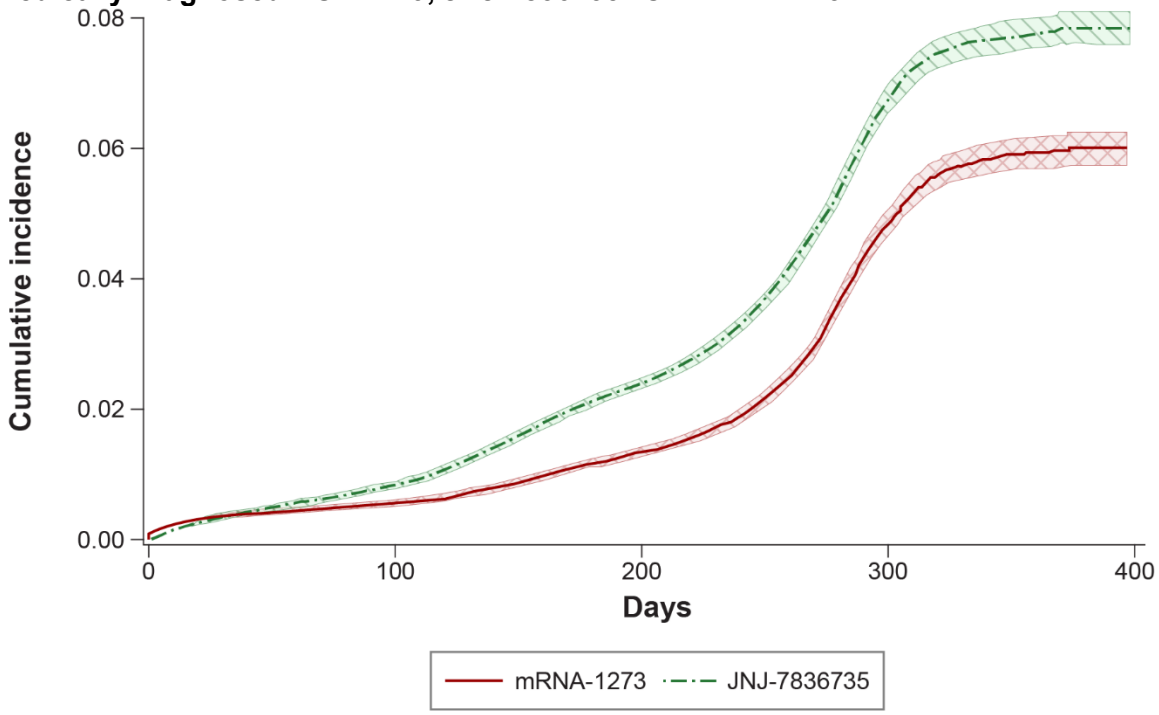
A. Medically Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



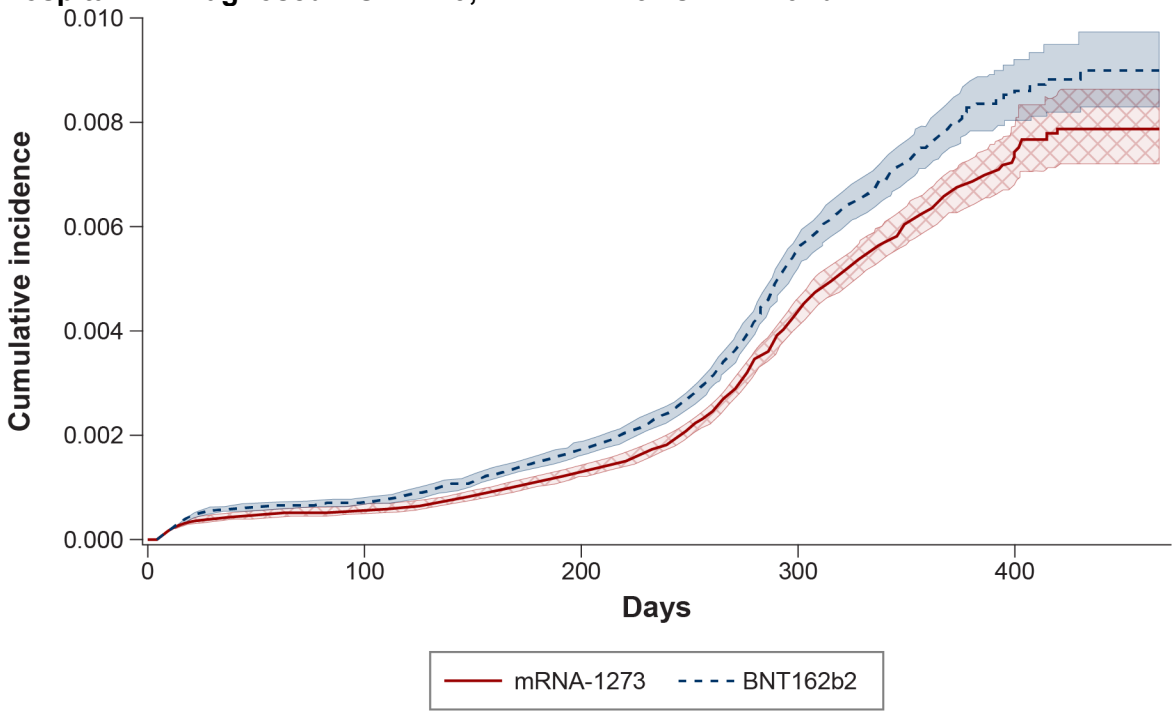
B. Medically Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



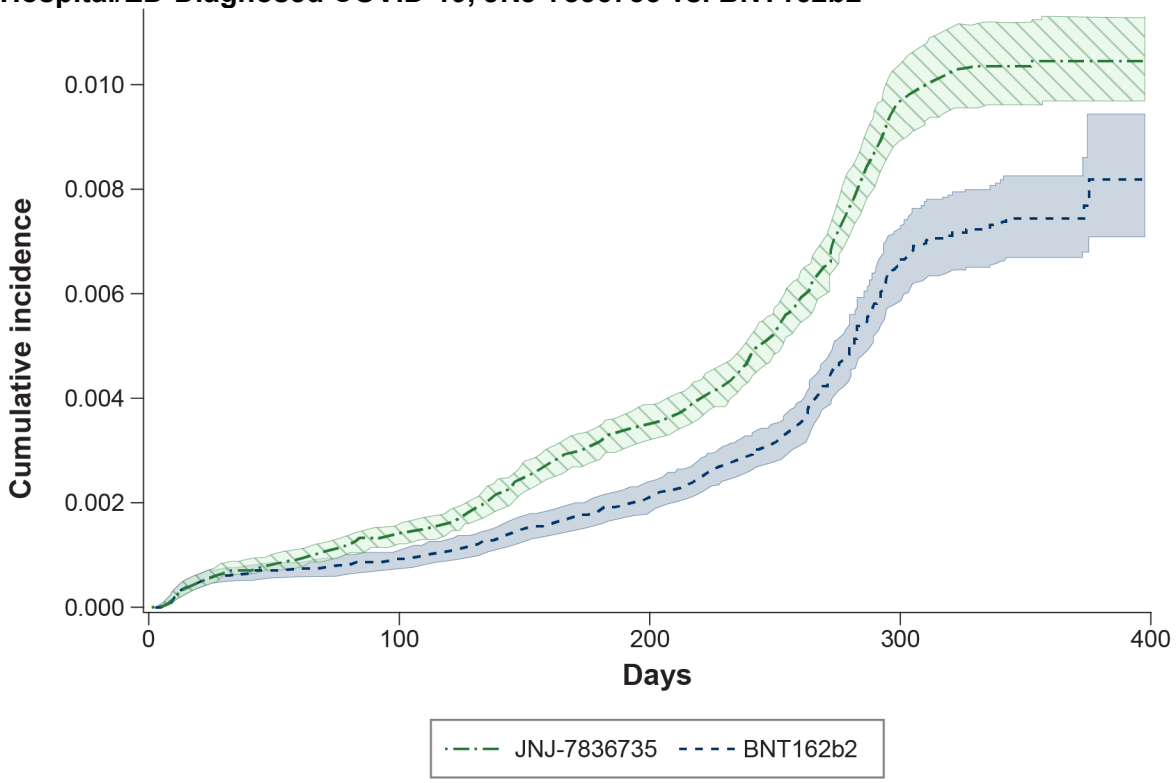
C. Medically Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



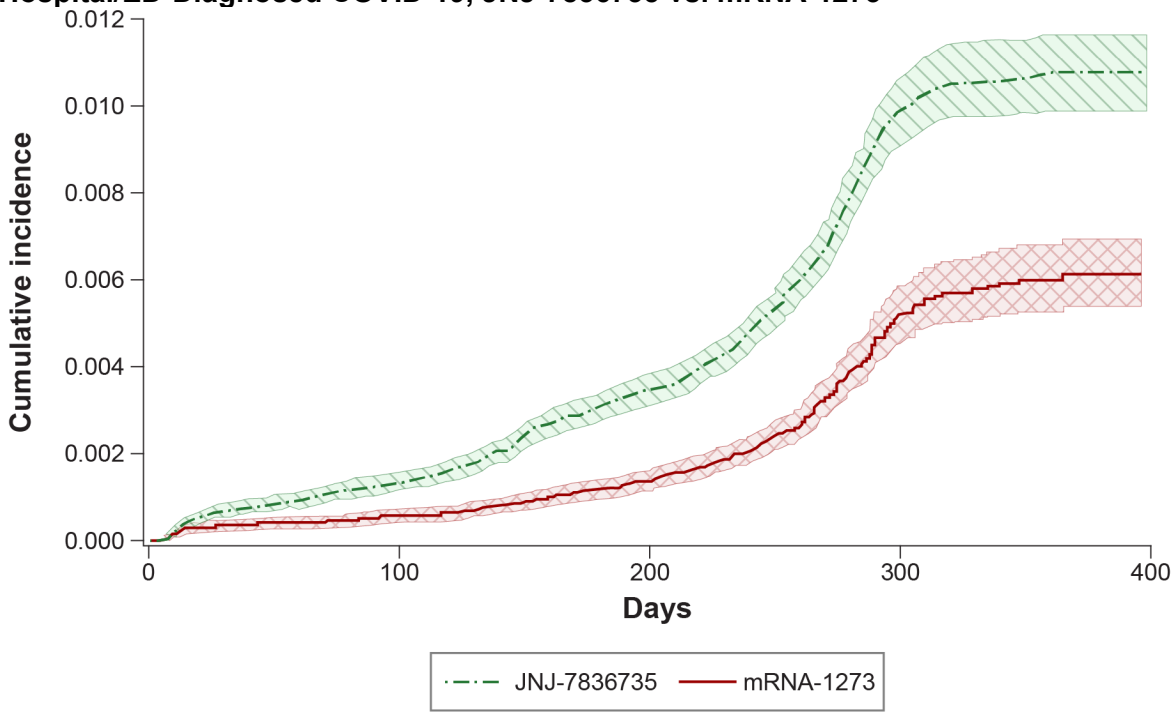
D. Hospital/ED-Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



E. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



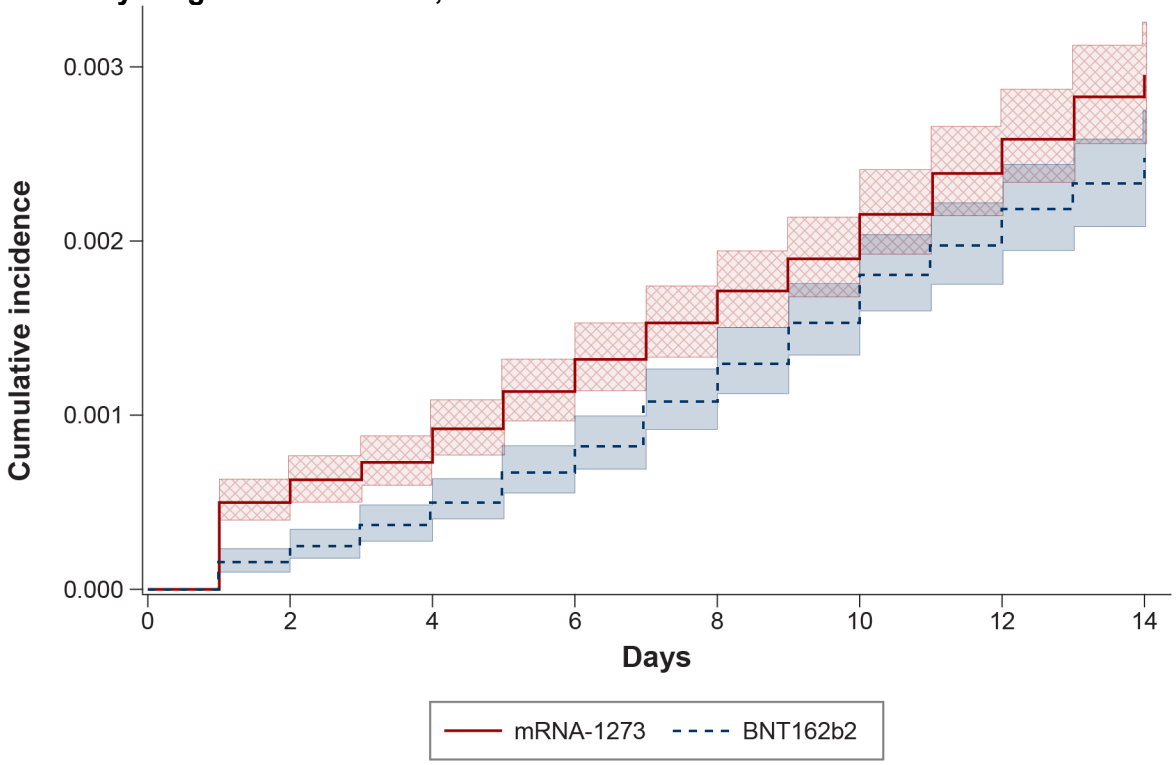
F. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



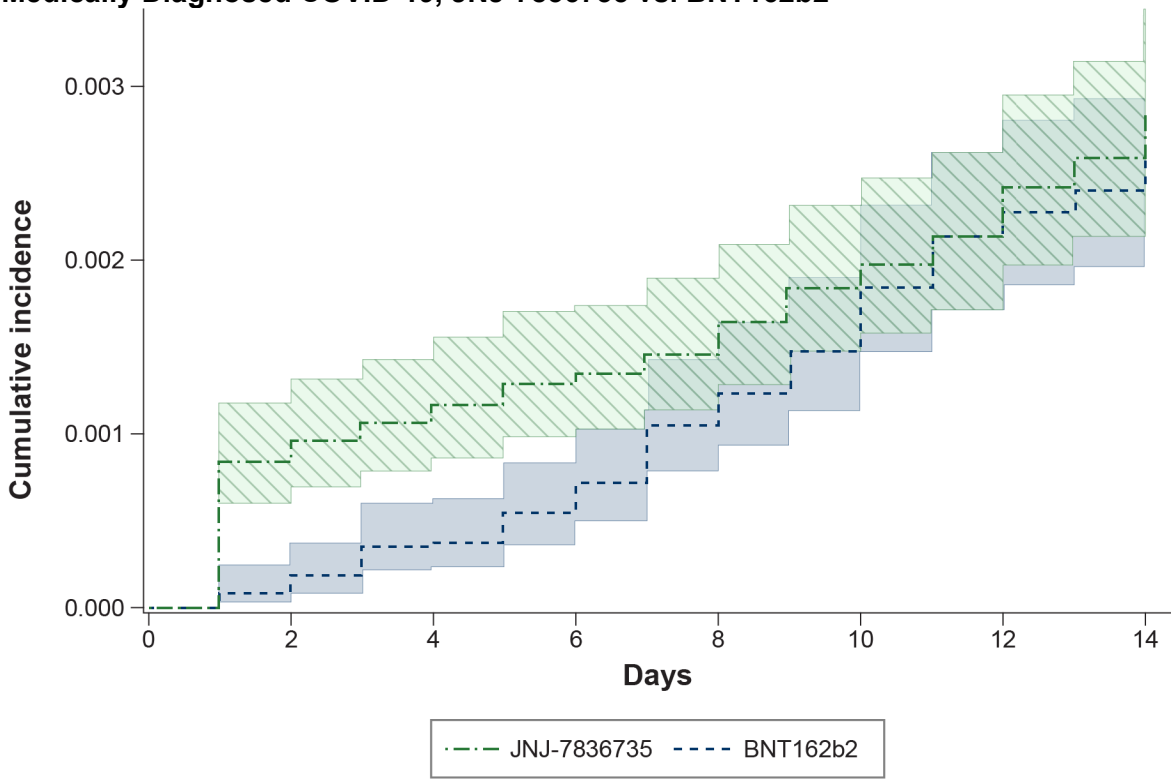
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure C-7-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine, 14 Days After and Including Time 0, Negative Control Outcome Analysis

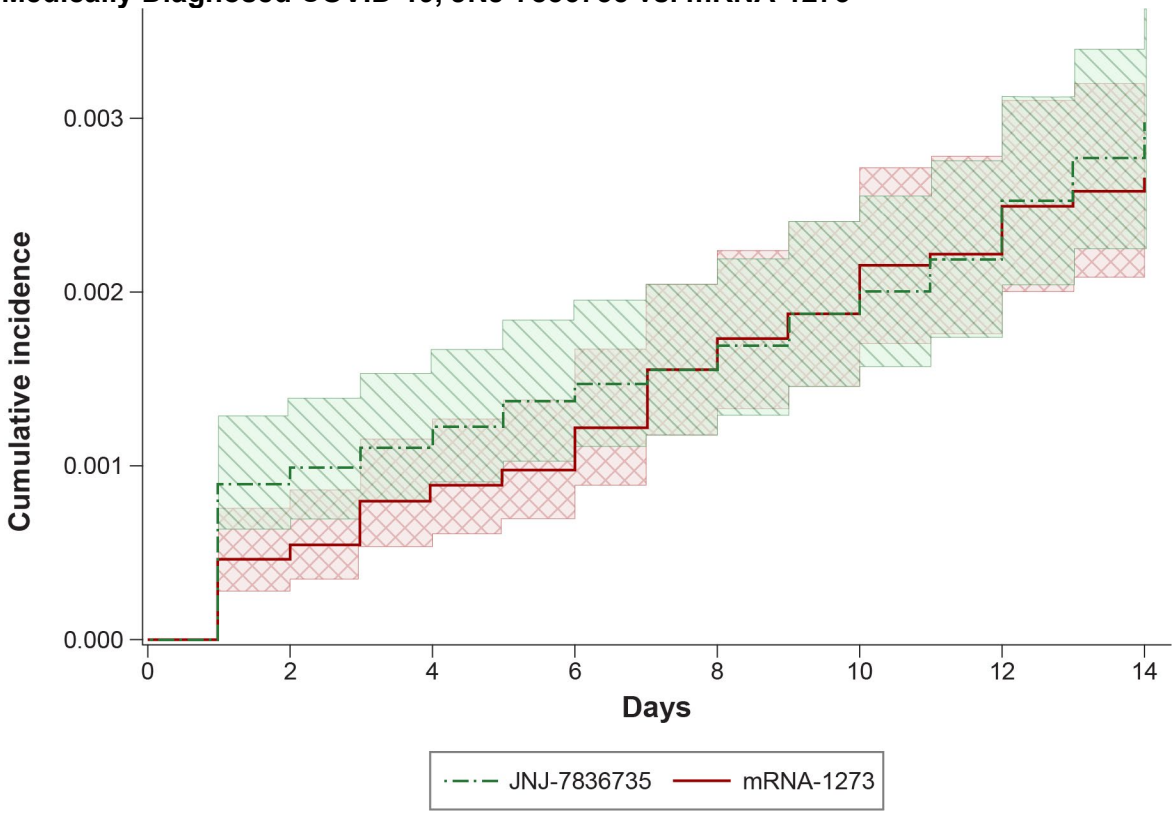
A. Medically Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



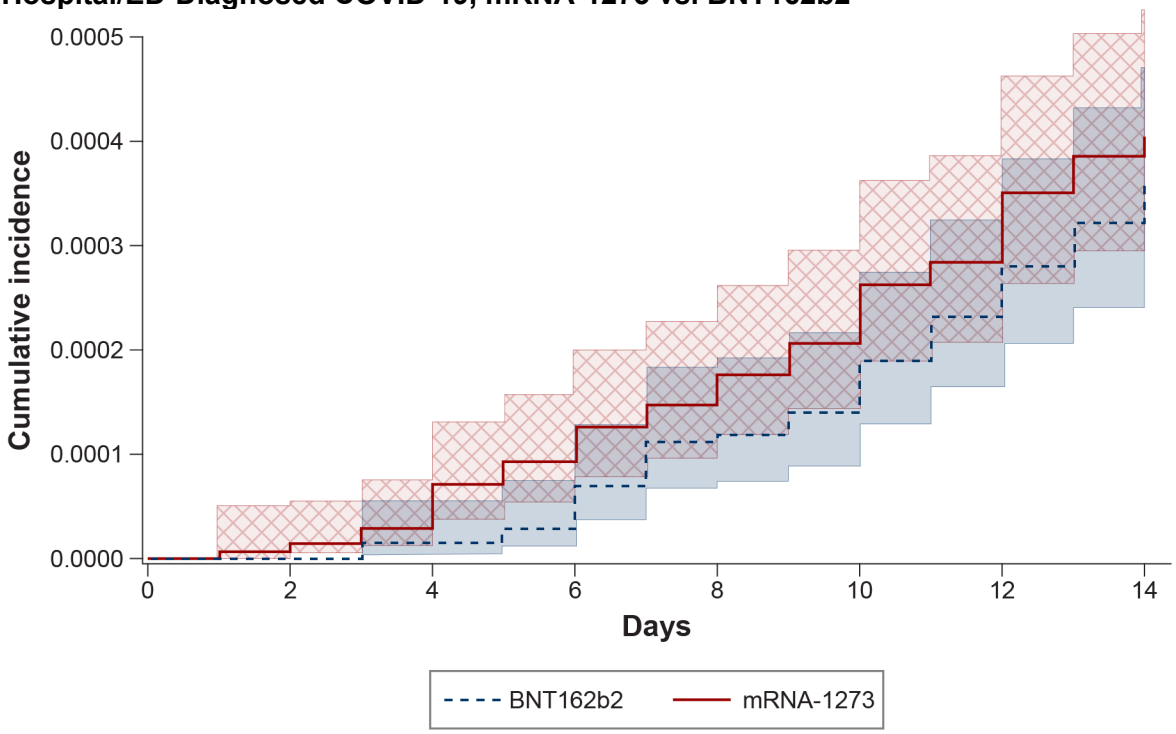
B. Medically Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



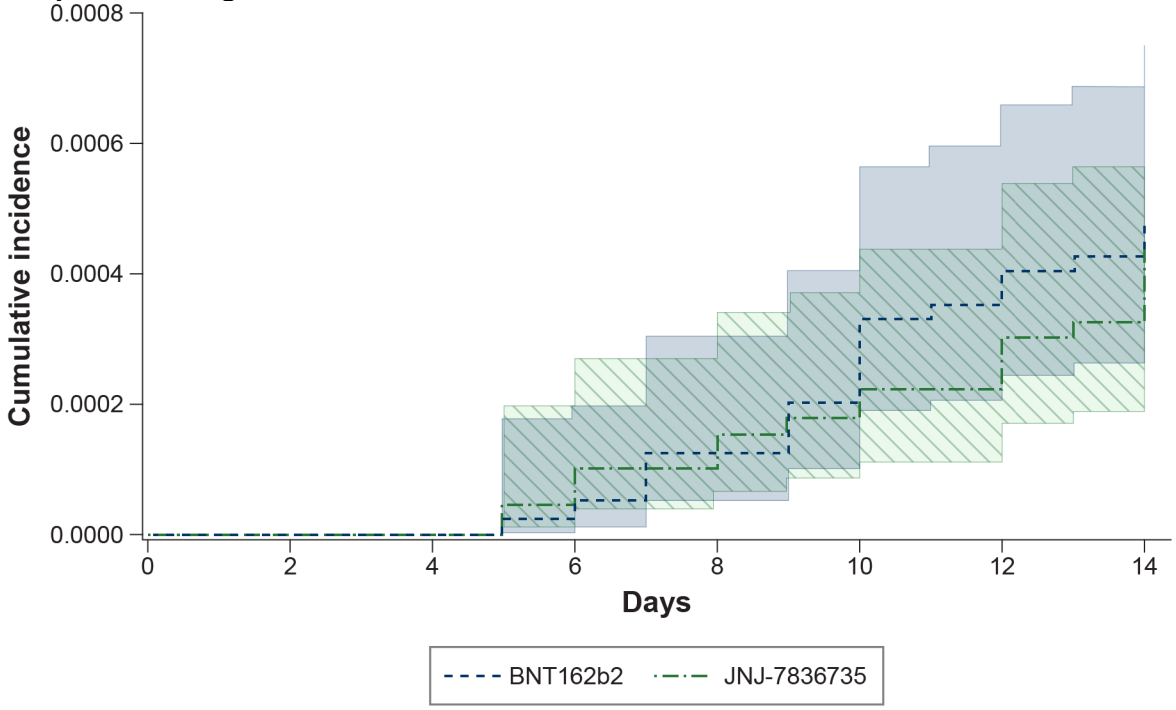
C. Medically Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



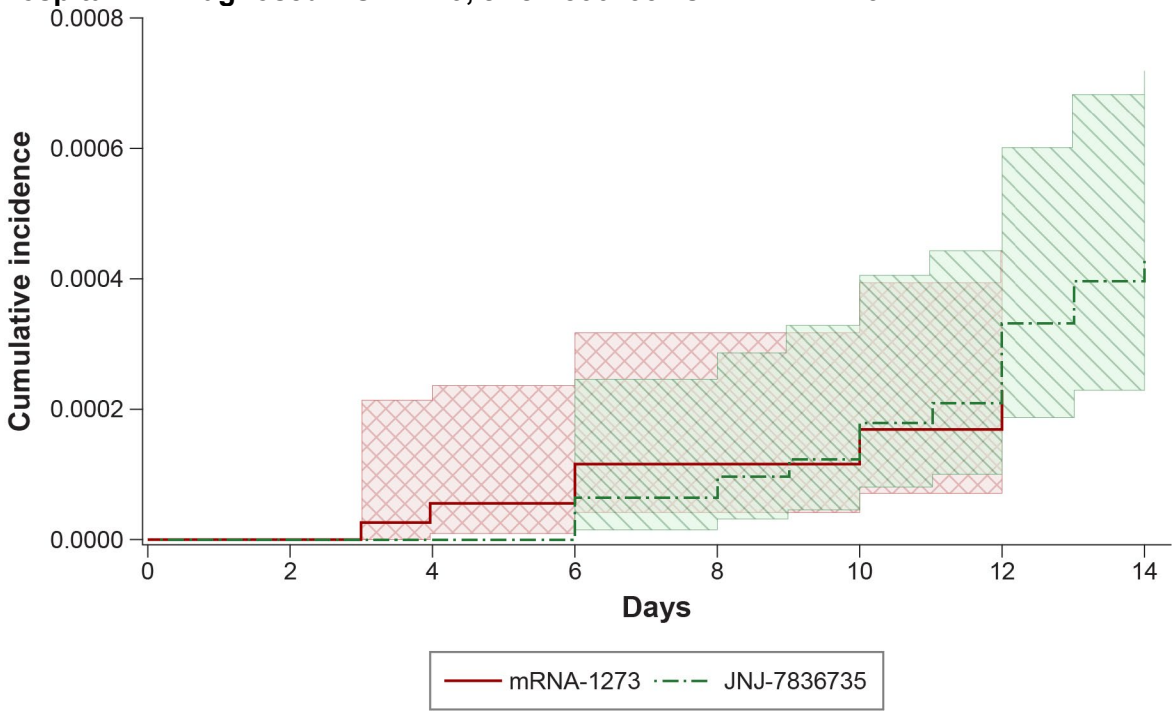
D. Hospital/ED-Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



E. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



F. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273

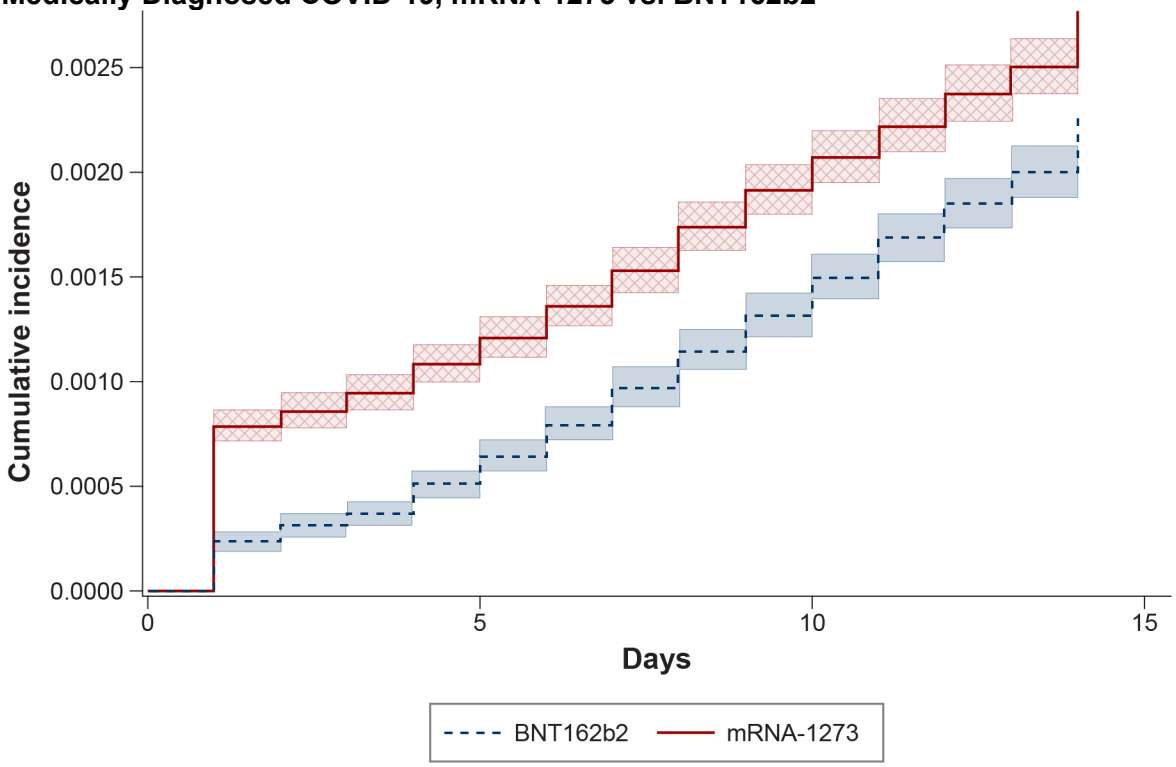


COVID-19 = coronavirus disease 2019; ED = emergency department.

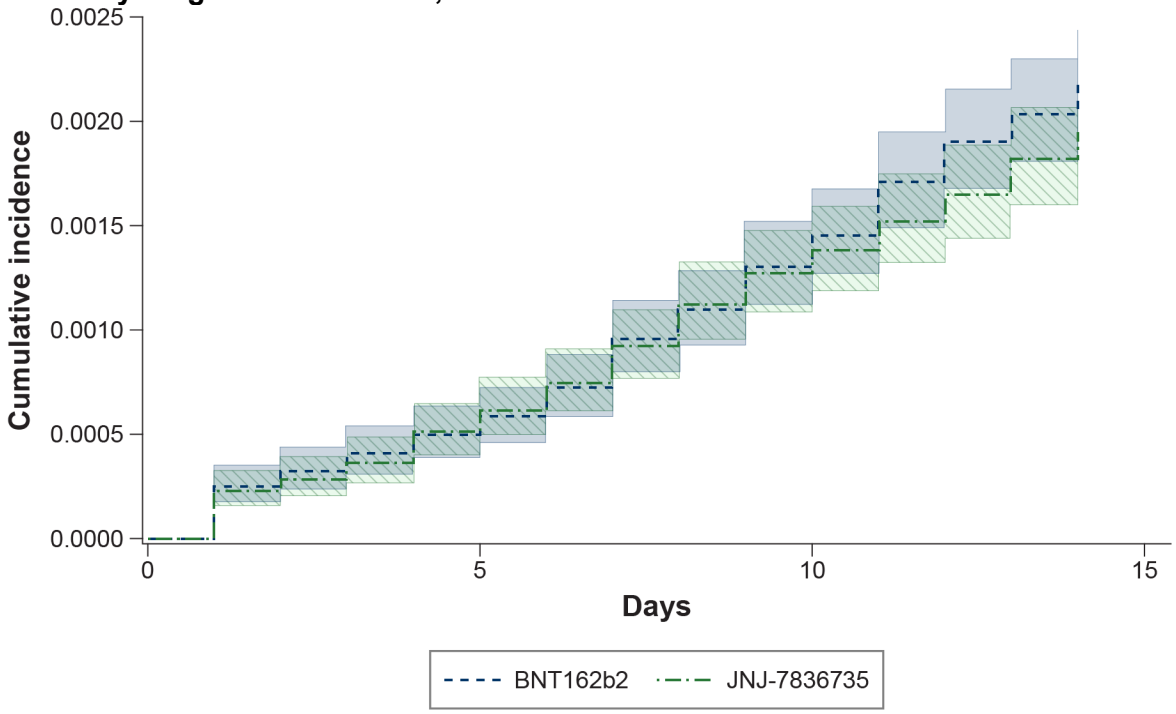
Note: The study Time 0 (date of vaccination) is the first day of follow-up, and it labelled as day 1 in the cumulative incidence figures.

Figure C-7-CVS. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving a Complete Primary Series of COVID-19 Vaccine, 14 Days After and Including Time 0, Negative Control Outcome Analysis

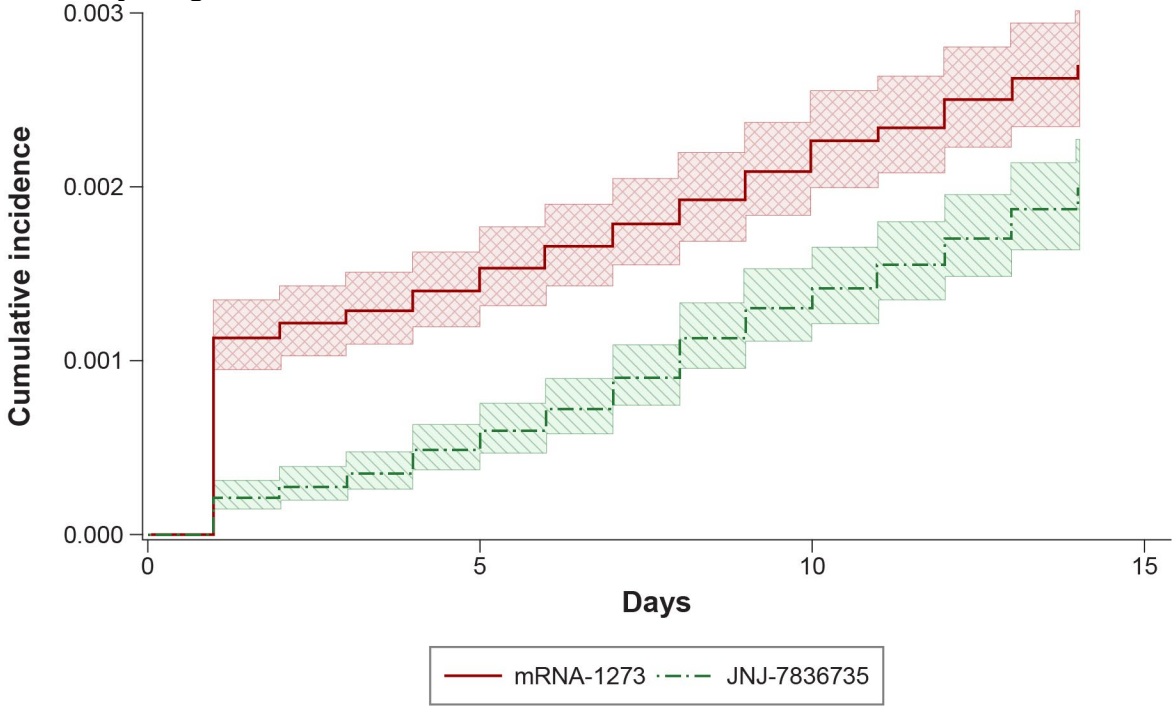
A. Medically Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



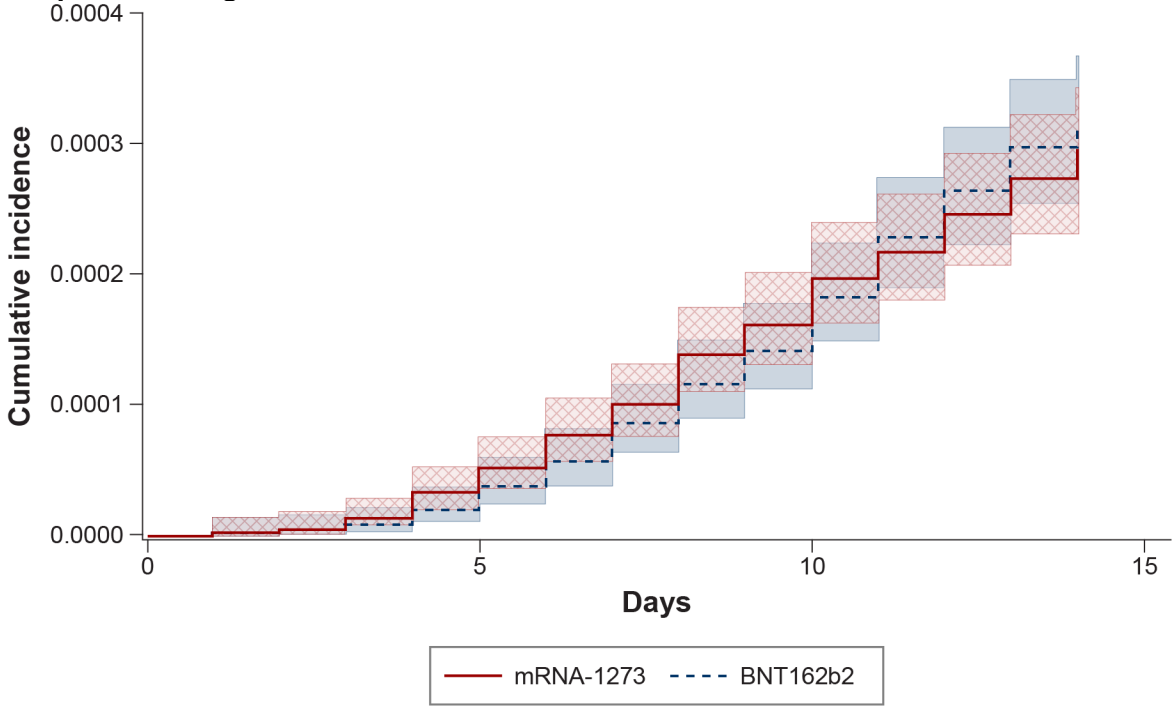
B. Medically Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



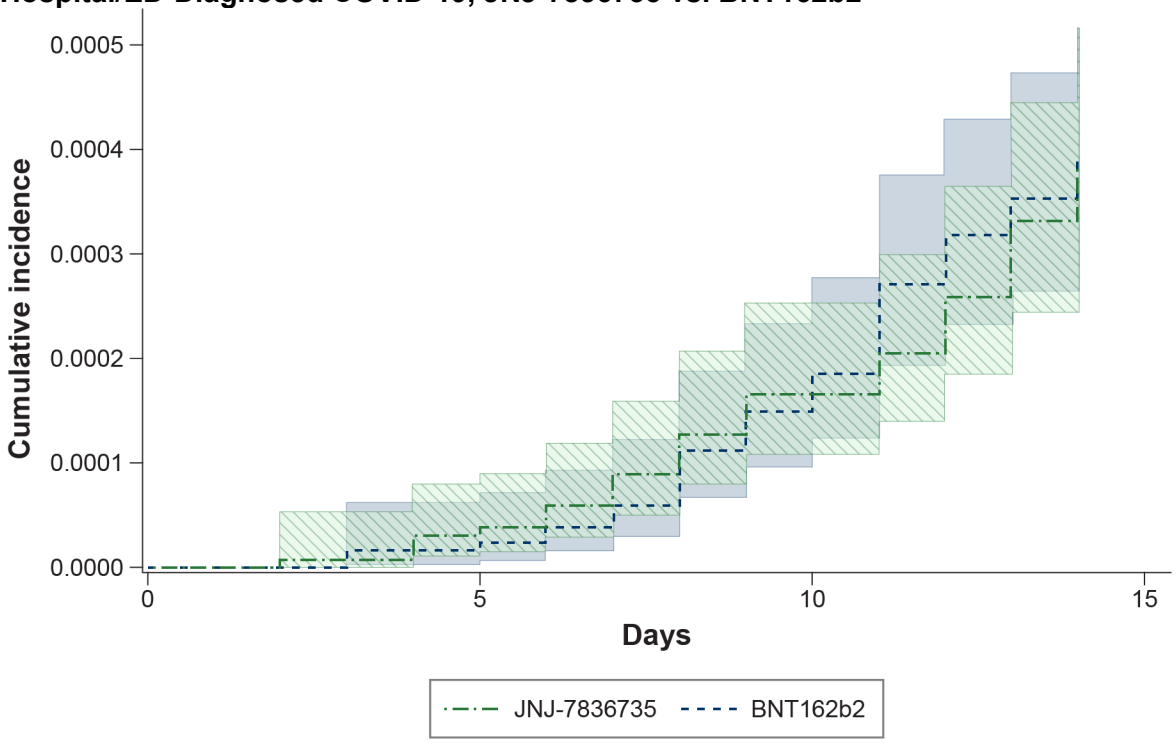
C. Medically Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



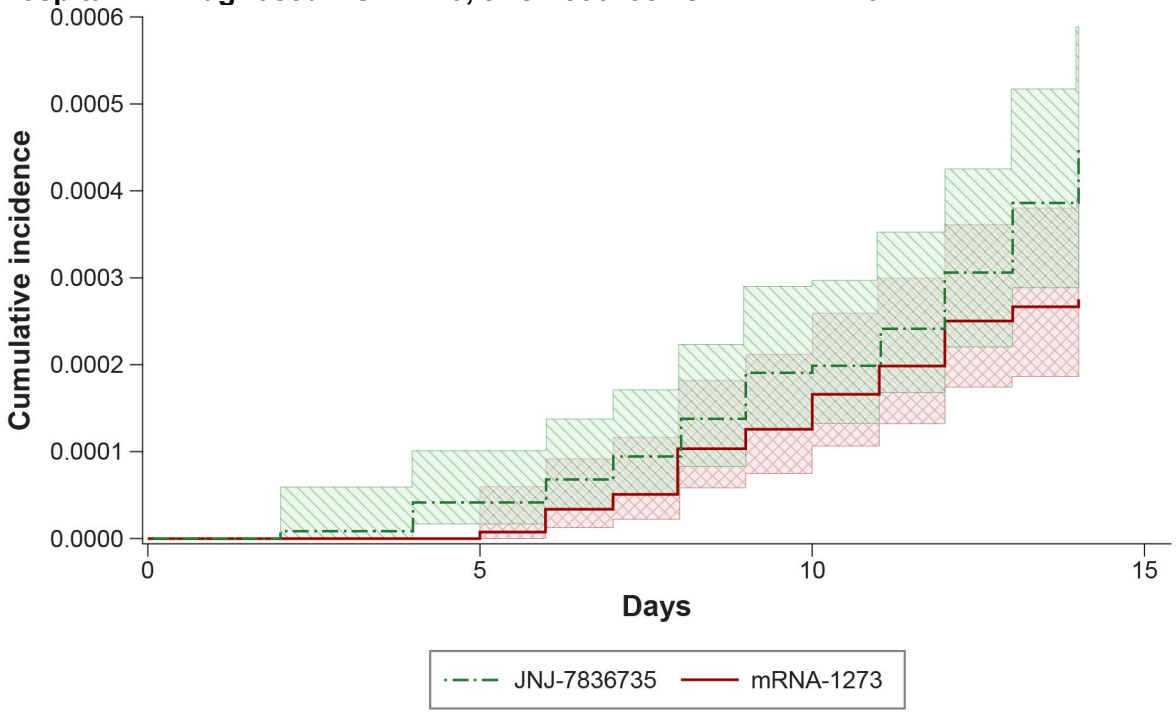
D. Hospital/ED-Diagnosed COVID-19, mRNA-1273 vs. BNT162b2



E. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. BNT162b2



F. Hospital/ED-Diagnosed COVID-19, JNJ-7836735 vs. mRNA-1273



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

Secondary Adult One-Dose Analyses

Table C-21-Optum. Estimated Effectiveness of Receiving Only 1 Dose of a 2-Dose Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years

COVID-19 outcome	Vaccine exposure group	N	Events	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	341,097	2,315	0.69 (0.66-0.73)	31% (27%-34%)
	Unvaccinated	341,097	15,007	—	—
	mRNA-1273	201,604	1,349	0.58 (0.54-0.62)	42% (38%-46%)
	Unvaccinated	201,604	9,122	—	—
Hospital/ED-diagnosed	BNT162b2	341,097	305	0.42 (0.37-0.48)	58% (52%-63%)
	Unvaccinated	341,097	3,470	—	—
	mRNA-1273	201,604	159	0.33 (0.28-0.39)	67% (61%-72%)
	Unvaccinated	201,604	2,131	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

Note: — denotes the reference group.

Table C-21-CVS. Estimated Effectiveness of Receiving Only 1 Dose of a 2-Dose Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Adults Aged 18-64 Years

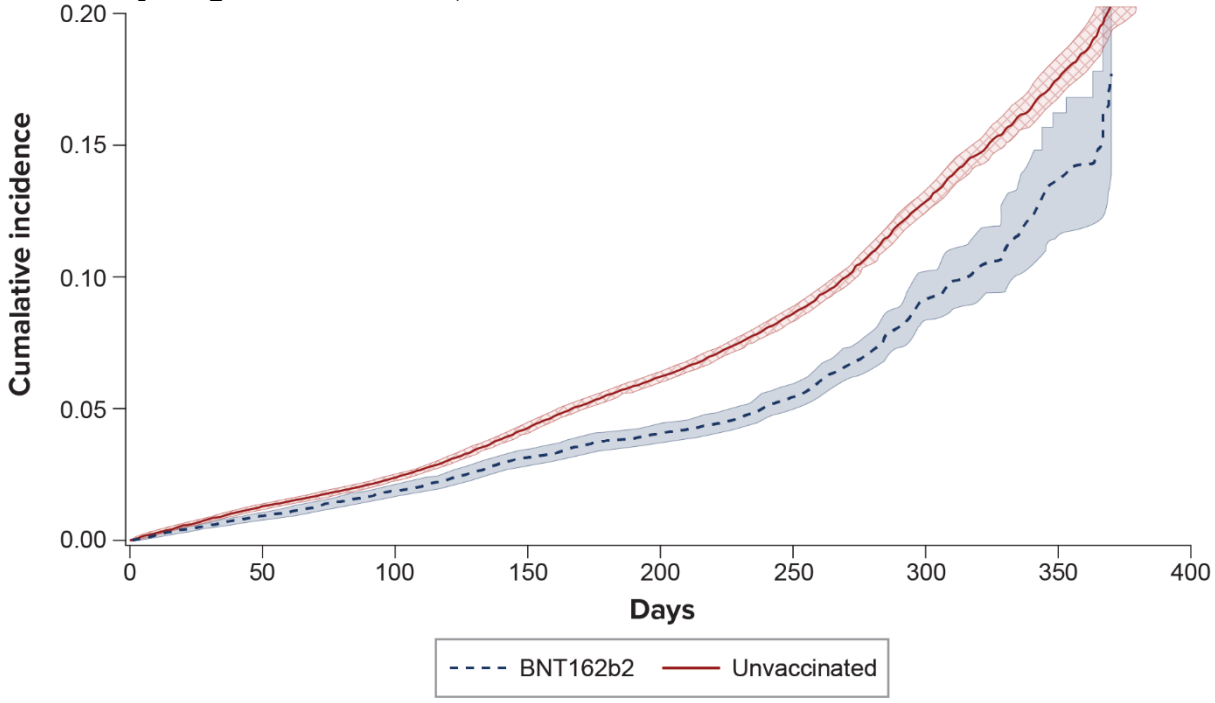
COVID-19 outcome	Vaccine exposure group	N	Events	sIPTW HR (95% CI)	VE (95% CI)
Medically diagnosed	BNT162b2	1,151,775	7,344	0.67 (0.66-0.69)	33% (31%-34%)
	Unvaccinated	1,151,775	47,292	—	—
	mRNA-1273	651,545	4,748	0.62 (0.60-0.64)	38% (36%-40%)
	Unvaccinated	651,545	27,079	—	—
Hospital/ED-diagnosed	BNT162b2	1,151,775	1,065	0.43 (0.40-0.46)	57% (54%-60%)
	Unvaccinated	1,151,775	11,464	—	—
	mRNA-1273	651,545	530	0.30 (0.27-0.33)	70% (67%-73%)
	Unvaccinated	651,545	6,884	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted; VE = vaccine effectiveness.

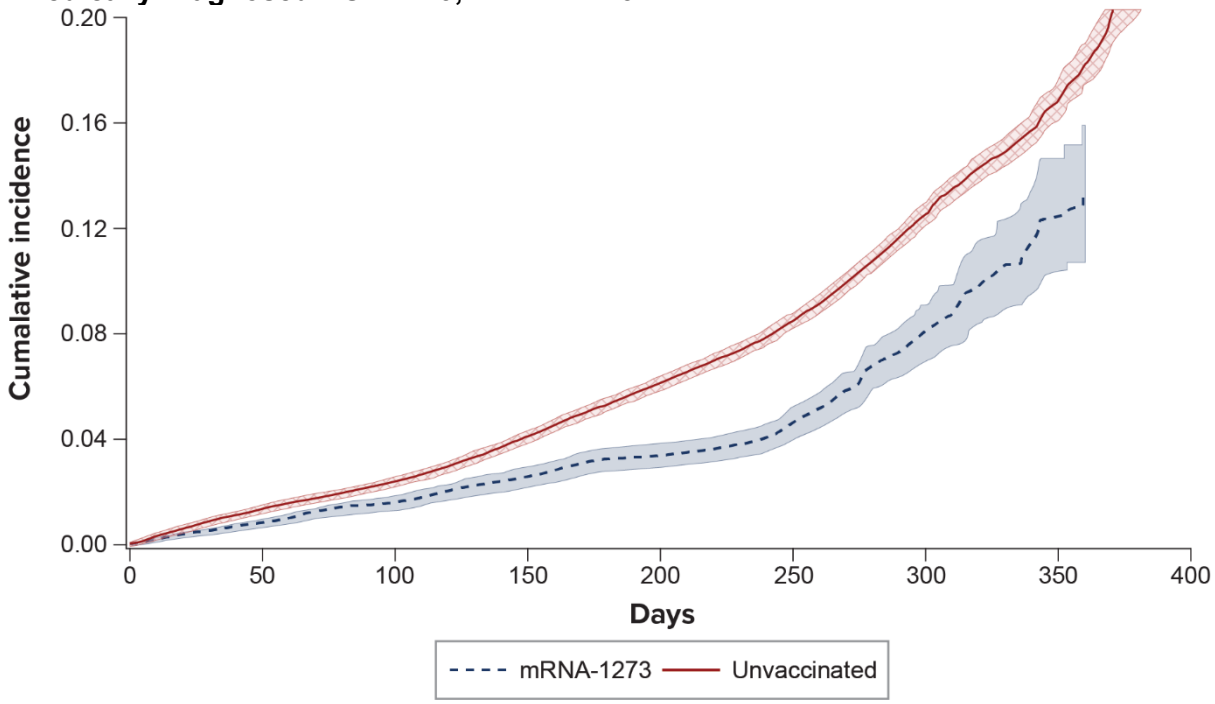
Note: — denotes the reference group.

Figure C-8-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving Only 1 Dose of a 2-Dose Primary Series of COVID-19 Vaccine and Unvaccinated Adults

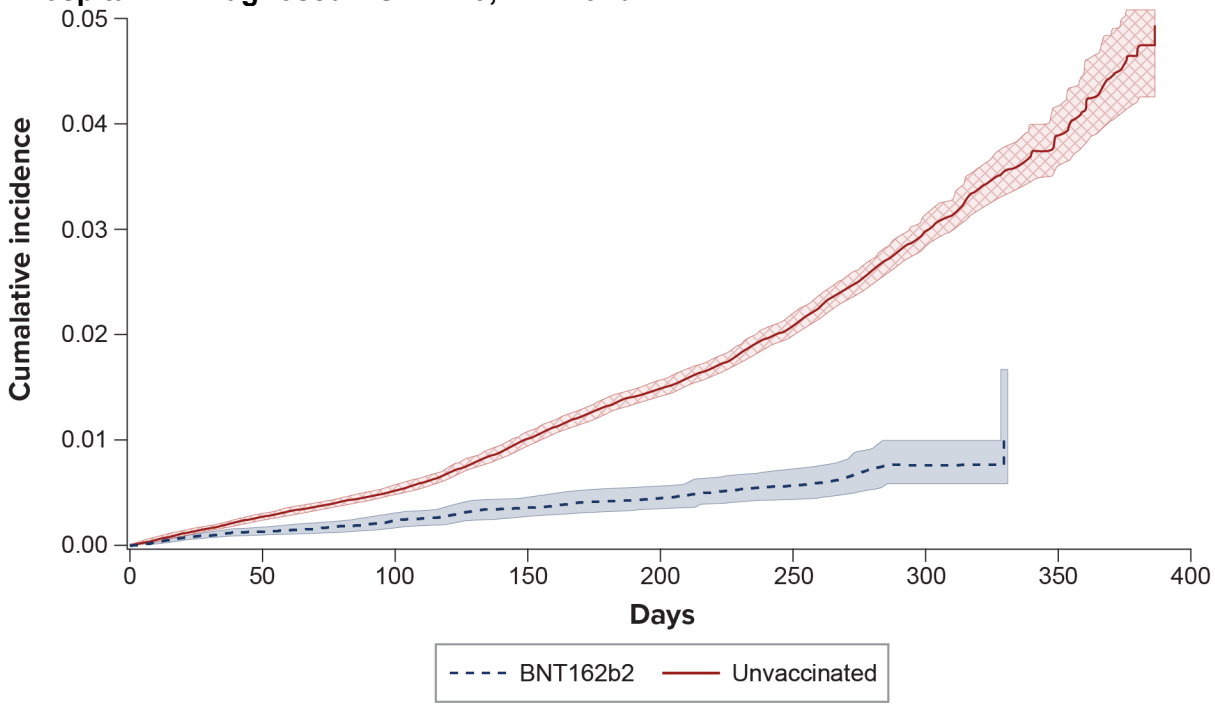
A. Medically Diagnosed COVID-19, BNT162b2



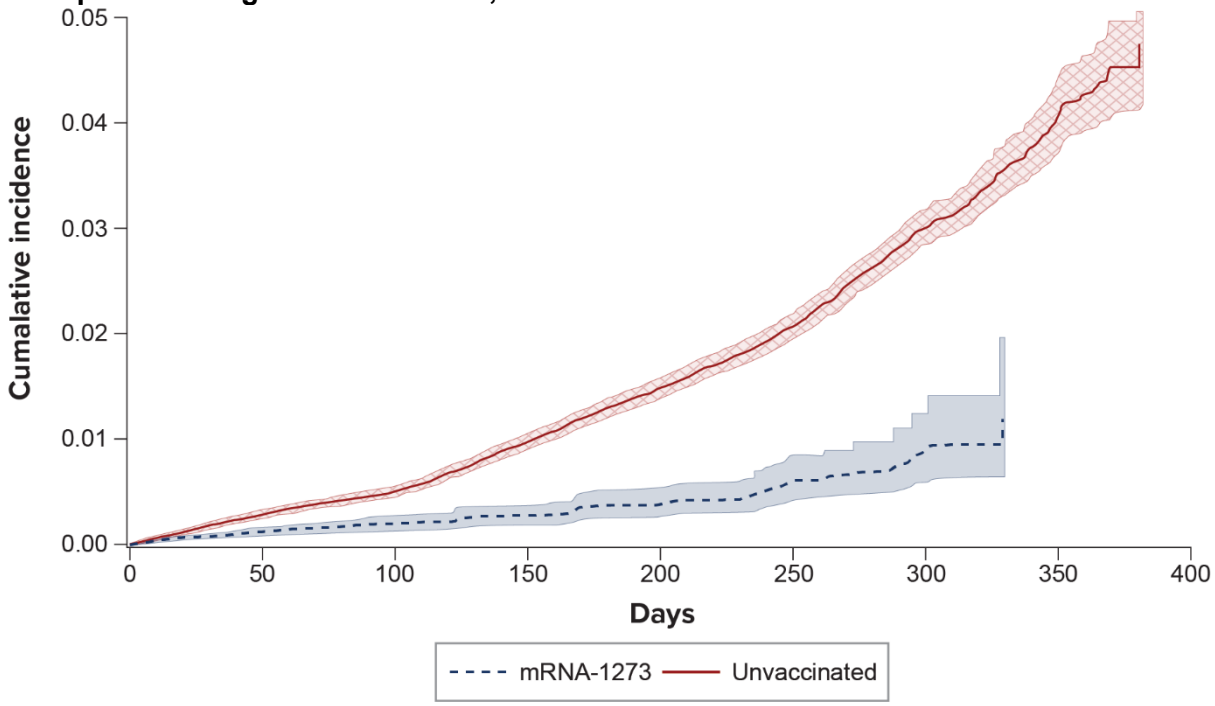
B. Medically Diagnosed COVID-19, mRNA-1273



C. Hospital/ED-Diagnosed COVID-19, BNT162b2



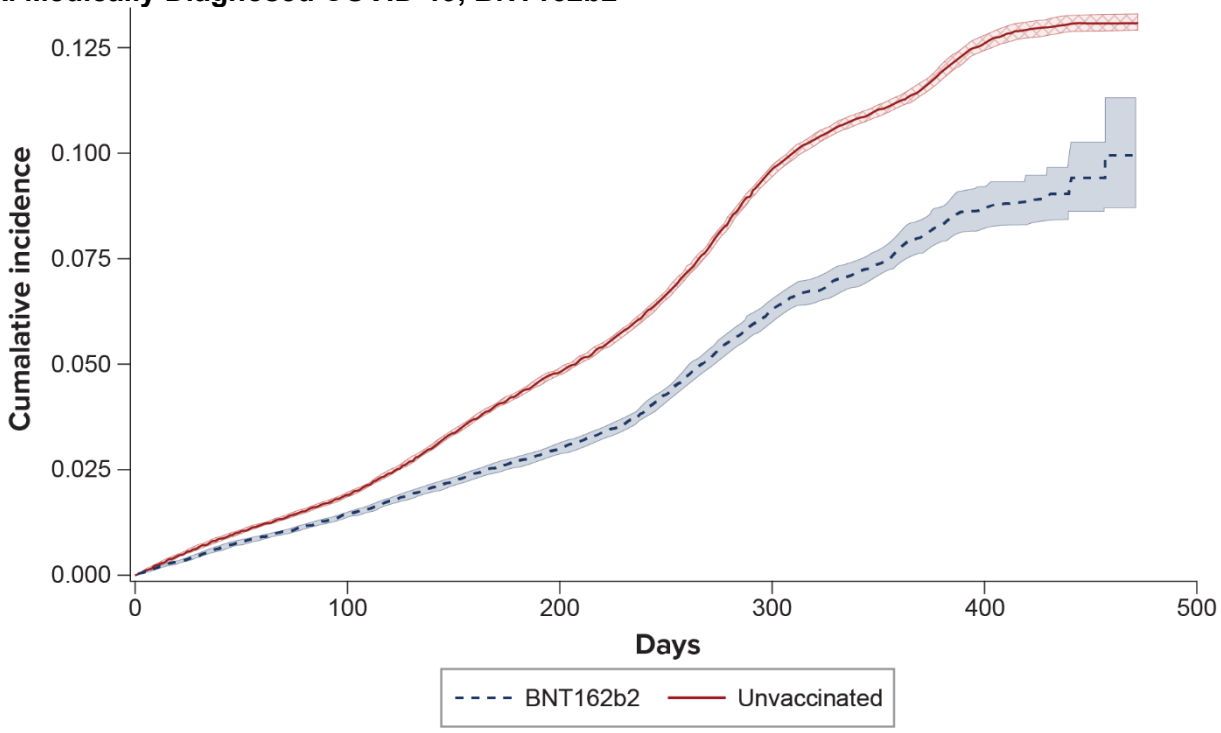
D. Hospital/ED-Diagnosed COVID-19, mRNA-1273



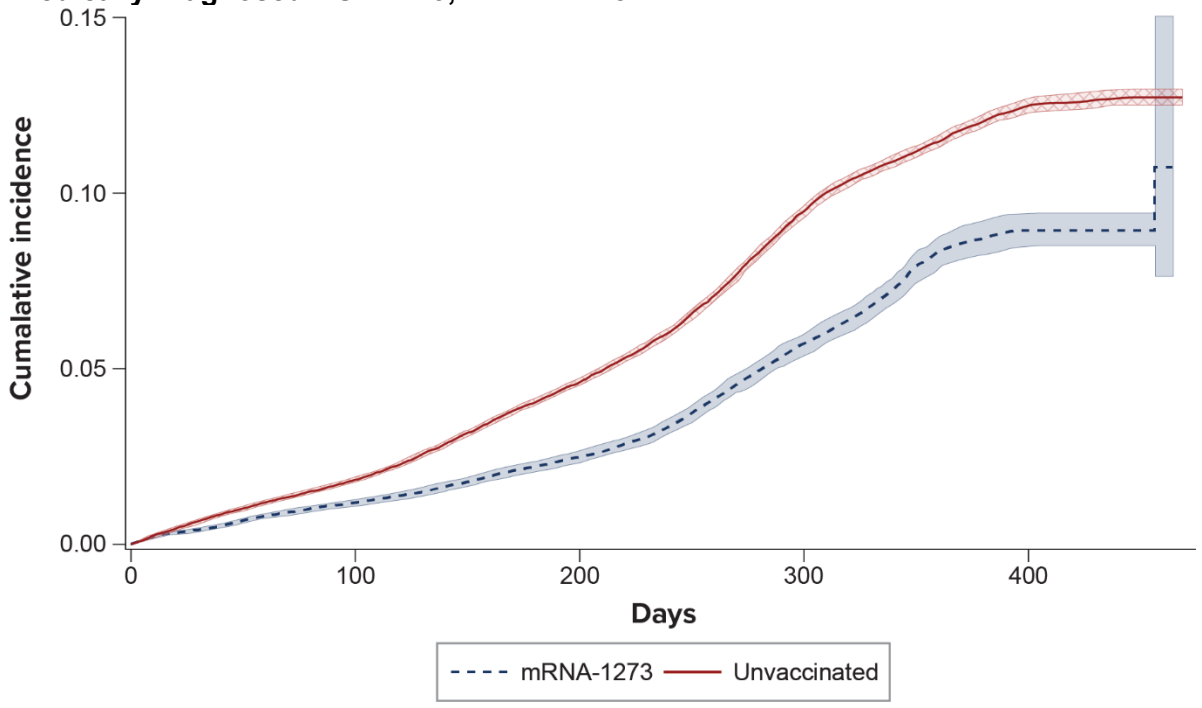
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure C-8-CVS. Weighted Cumulative Incidence of COVID-19 Outcomes in Adults Aged 18-64 Years Receiving Only 1 Dose of a 2-Dose Primary Series of COVID-19 Vaccine and Unvaccinated Adults

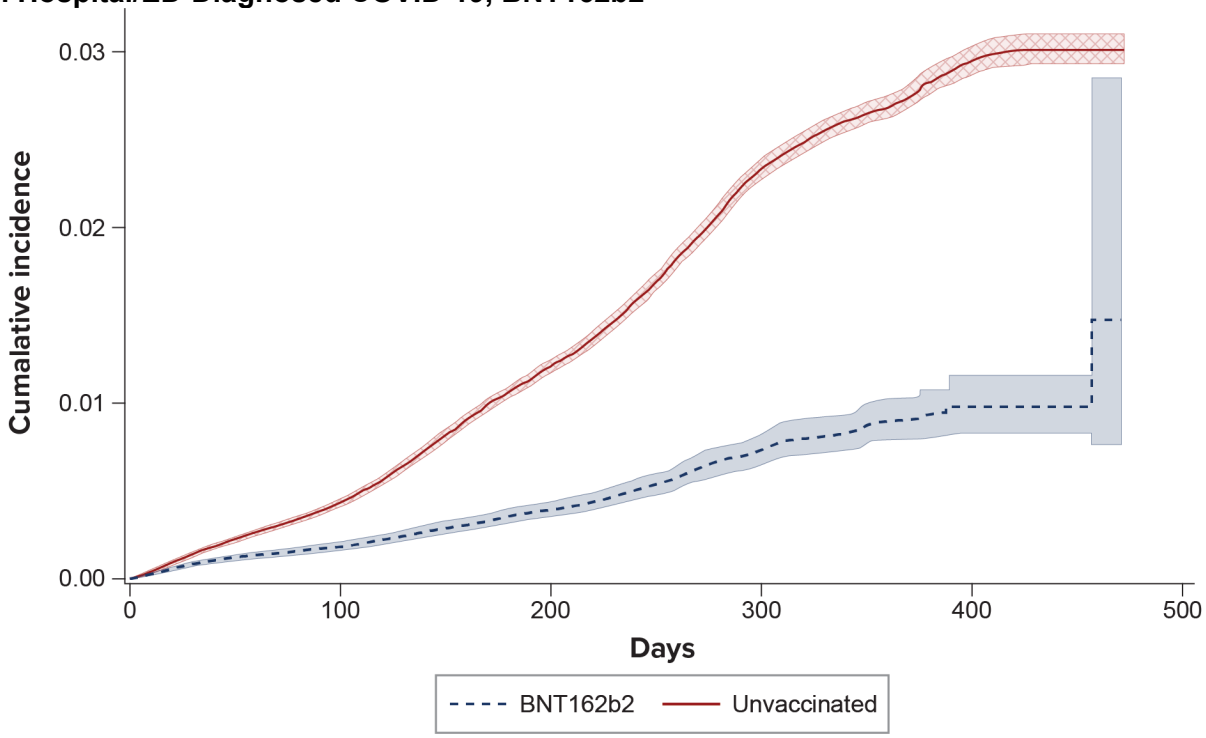
A. Medically Diagnosed COVID-19, BNT162b2



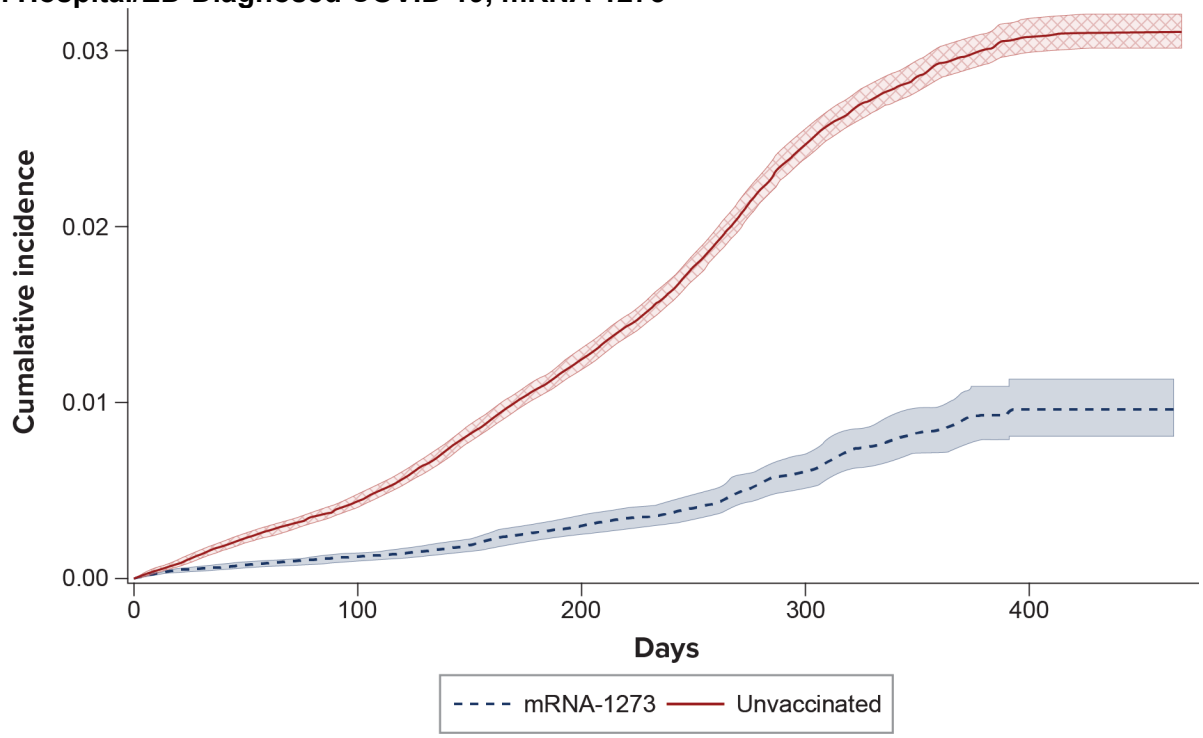
B. Medically Diagnosed COVID-19, mRNA-1273



C. Hospital/ED-Diagnosed COVID-19, BNT162b2



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



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