

**Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology**

# **CBER Surveillance Program Biologics Effectiveness and Safety (BEST) Initiative**

## **Assessment of Effectiveness of COVID-19 Vaccination in the United States**

### **Protocol**

**3 March 2022**

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## Document History

| Editors                                       | Version   | Date             | Description                                                                                   |
|-----------------------------------------------|-----------|------------------|-----------------------------------------------------------------------------------------------|
| RTI-HS                                        | Draft 0.1 | 27 October 2021  | First draft for scientific working group review                                               |
| RTI-HS<br>FDA/CBER/OBE<br>Acumen LLC<br>Optum | Draft 0.2 | 16 November 2021 | Second draft incorporating scientific working group comments                                  |
| RTI-HS<br>FDA/CBER/OBE<br>Acumen LLC<br>Optum | Draft 0.3 | 7 December 2021  | Third draft incorporating scientific working group comments                                   |
| RTI-HS<br>FDA/CBER/OBE                        | Draft 0.4 | 4 February 2022  | Fourth draft incorporating FDA comments and updates based on preliminary feasibility analyses |
| RTI-HS<br>FDA/CBER/OBE                        | Draft 1.0 | 3 March 2022     | Final draft incorporating FDA comments and updates based on preliminary feasibility analyses  |

## List of Abbreviations

|            |                                                                                         |
|------------|-----------------------------------------------------------------------------------------|
| BEST       | Biologics Effectiveness and Safety                                                      |
| CBER       | Center for Biologics Evaluation and Research                                            |
| CDC        | Centers for Disease Control and Prevention                                              |
| CI         | confidence interval                                                                     |
| COPD       | chronic obstructive pulmonary disease                                                   |
| COVID-19   | coronavirus disease 2019                                                                |
| CPT        | <i>Current Procedural Terminology</i>                                                   |
| CVX        | Vaccine Administered codes                                                              |
| ED         | emergency department                                                                    |
| FDA        | Food and Drug Administration                                                            |
| HCPCS      | Healthcare Common Procedure Coding System                                               |
| HR         | hazard ratio                                                                            |
| ICD-10-CM  | <i>International Classification of Diseases, 10th Revision, Clinical Modification</i>   |
| ICD-10-PCS | <i>International Classification of Diseases, 10th Revision, Procedure Coding System</i> |
| IIS        | immunization information systems                                                        |
| IPT        | inverse probability of treatment                                                        |
| LTC        | long-term care                                                                          |
| mRNA       | messenger ribonucleic acid                                                              |
| NDC        | National Drug Codes                                                                     |
| Q1, Q3     | first and third quartiles                                                               |
| RCT        | randomized controlled trial                                                             |
| RD         | risk difference                                                                         |
| RR         | risk ratio                                                                              |
| RWE        | real-world evidence                                                                     |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2                                         |
| SD         | standard deviation                                                                      |
| US         | United States                                                                           |

VE

vaccine effectiveness

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## Protocol Synopsis / Executive Summary

### Background and Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic, affecting the United States (US) and countries throughout the world. Vaccines for the prevention of COVID-19 are currently available in the US through either emergency use authorization and/or licensure by US Food and Drug Administration. These vaccines are now being administered widely throughout the US in real-world settings, against predominant circulating variants different from those circulating at the time of randomized controlled trials, and in varying recommended dosing strategies (based on age, demographic characteristics, medical history, employment, and vaccine brand). Additional questions remain regarding their real-world effectiveness in the general population, in populations of special interest, against different circulating variants, and over time.

### Study Objectives

This study will explore the brand-specific effectiveness of COVID-19 vaccines in preventing medically diagnosed COVID-19 cases in any medical setting and hospital/emergency department (ED)—diagnosed COVID-19 cases in cohorts of vaccinated and unvaccinated individuals aged less than 65 years in the US. The primary objectives will evaluate the effectiveness of completion of a primary vaccine series versus being unvaccinated, overall and over time (both time since vaccination and calendar time). Secondary and exploratory objectives will evaluate subgroups of special interest, the comparative effectiveness of complete vaccine series of different vaccine brands, receipt of a single dose of a 2-dose primary series, receipt of booster/additional doses, and nonstandard vaccine exposure patterns.

### Data Sources

This study will be conducted in Optum preadjudicated commercial insurance claims linked to vaccination records from immunization information systems (IISs). Other data sources with linked IIS data may also be added.

### Study Design and Definitions

This observational cohort study within existing linked healthcare and vaccination records will describe and compare the risk of both medically diagnosed COVID-19 cases and hospital/ED—diagnosed COVID-19 cases in individuals vaccinated against COVID-19 by vaccine brand and those who have not received any COVID-19 vaccine. The primary exposure will be receiving a complete primary series of a specific COVID-19 vaccine. Vaccine administrations will be identified with procedure or pharmacy coding in insurance claims data and with vaccination records in IISs. Secondary and exploratory analyses will evaluate, as feasible due to sample size, the effectiveness of different vaccine exposure patterns, including single doses of a 2-dose primary series, booster/additional doses, and nonstandard vaccine exposure patterns (i.e., series of mixed vaccine brands or delayed administrations). The outcomes will include medically diagnosed COVID-19 in any medical setting and hospital/ED—diagnosed COVID-19 identified through *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) codes in submitted claims.

## Statistical Methods

This study will use a cohort design where vaccinated individuals are identified at the date of receiving Dose 1 of a COVID-19 vaccine series. Vaccinated individuals will be described and then matched to unvaccinated individuals on the calendar date of Dose 1, county and state, and other demographic and clinical characteristics. The cumulative incidence of COVID-19 outcomes after vaccination in each exposure group will be evaluated with Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals (CIs). Daily estimates of the risk ratio and risk difference will be estimated using the exposure group–specific daily cumulative incidence curves to describe changes in effectiveness over time. Calendar time periods representing viral variant predominance will be evaluated separately. Confounding will be addressed through matching on key characteristics and weighting using propensity score methods.

Secondary analyses will include subgroup analyses by age group, immunocompromised status, pregnancy status, and history of COVID-19 infection. Head-to-head comparisons of complete vaccine series of the various vaccine brands will be performed. Additional vaccine exposure patterns, such as a single-dose primary series, receipt of an additional or booster dose, and nonstandard vaccine exposure patterns (i.e., mixed or delayed primary series) will also be described and evaluated, if feasible.

# 1. Background and Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic, affecting the United States (US) and countries throughout the world. At the time of writing of this protocol, 3 vaccines for the prevention of COVID-19 are currently available in the US through either emergency use authorization and/or licensure by the US Food and Drug Administration (FDA)—BNT162b2 (Pfizer-BioNTech’s messenger ribonucleic acid [mRNA] COVID-19 vaccine, Comirnaty®), mRNA-1273 (Moderna’s mRNA COVID-19 vaccine, Spikevax), and JNJ-7836735 (Janssen Pharmaceutical Company’s adenovirus COVID-19 vaccine). These vaccines were evaluated in large clinical trials before authorization, and they have been demonstrated to be effective in preventing various COVID-19 outcomes, including symptomatic infection,<sup>1-3</sup> moderate-to-severe COVID-19,<sup>4</sup> severe COVID-19 illness,<sup>1-4</sup> and death due to COVID-19.<sup>4</sup> Additional vaccines and vaccine technologies may be added in the future.

Existing COVID-19 vaccines are now being administered widely throughout the US in real-world settings. Questions remain regarding the vaccines’ real-world effectiveness in the general population, in populations of special interest, in preventing different circulating variants, and over time. Specifically, questions regarding the duration of protection, the effectiveness against different circulating variants, and the effectiveness of dosing patterns different from those initially evaluated in trials are all questions that can be evaluated with real-world evidence (RWE).

The real-world effectiveness of available COVID-19 vaccines has been evaluated in numerous settings with a variety of approaches covering more recent time periods with circulating variants different from those when the pivotal randomized controlled trials (RCTs) were conducted. Many RWE studies in the US have reported vaccine effectiveness (VE) estimates comparable to those observed in RCTs<sup>5-12</sup>; however, some studies have suggested that effectiveness against any infection may wane over time in fully vaccinated individuals.<sup>3,8,11-14</sup> Other studies have demonstrated only minimal or no meaningful decreases in VE estimates over time against more severe COVID-19 or hospitalization.<sup>5-9,13</sup> Compounding the question of waning effectiveness over time since vaccination is the issue of potentially reduced effectiveness against circulating variants that became predominant in the US during the study period, including the B.1.617.2 (Delta) variant and B.1.1.529 (Omicron) variants, which contributed to large increases in COVID-19 cases among the unvaccinated<sup>1</sup> and vaccinated in the US. Other circulating variants may also become of concern.

Additional vaccination strategies continue to be introduced and authorized (i.e., additional doses for immunocompromised individuals, booster doses, heterologous vaccine series or boosters), and indicated age groups for vaccination continue to expand. 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.

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<sup>1</sup> In this protocol, “unvaccinated” means not vaccinated with any COVID-19 vaccine. An unvaccinated person may have received another type of vaccine, for example, influenza, and still be considered “unvaccinated” for the purposes of this study.

## 2. Study Objectives

This study will explore the effectiveness of COVID-19 vaccines in preventing medically diagnosed COVID-19 cases and hospital/emergency department (ED)–diagnosed COVID-19 cases over time (both time since vaccination and calendar time) by comparing vaccinated and unvaccinated individuals aged 64 years or younger in the US. It will occur in 2 phases: the descriptive and feasibility evaluation phase and the comparative analyses phase.

This protocol refers to the specific COVID-19 vaccine brands authorized or approved in the US at the time of writing of this protocol, but other vaccines may be included as they are authorized or licensed in the US and data on their use are available during the study period.

### 2.1. Descriptive and Feasibility Evaluation Phase (Phase 1) Objectives

The following objectives will be addressed by Phase 1, the initial descriptive and feasibility evaluation phase of the study:

- To describe the demographic and clinical characteristics of individuals receiving a COVID-19 vaccine
- To describe patterns of receipt of COVID-19 vaccines and primary series completion
- To estimate the incidence of medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19 in vaccinated individuals by vaccine brand.

### 2.2. Comparative Analyses Phase (Phase 2) Objectives

#### 2.2.1. Primary Objectives

The following primary objectives will be evaluated during Phase 2, the comparative analyses phase of the study:

- To assess the effectiveness of receiving a complete primary series of COVID-19 vaccination, by brand, compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19. The following vaccine exposure patterns will be 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 and potential waning effectiveness of receiving a complete primary series of COVID-19 vaccination, by brand, compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19. The following vaccine exposure patterns will be compared:
  - Complete BNT162b2 primary series versus being unvaccinated
  - Complete mRNA-1273 primary series versus being unvaccinated
  - Complete JNJ-7836735 primary series versus being unvaccinated

If additional vaccine brands are introduced during the study period, they will be included as data are available.

### 2.2.2. Secondary Objectives

The following secondary objectives will be evaluated during Phase 2 of the study:

- To assess the effectiveness of receiving a complete primary series of COVID-19 vaccination, by brand, compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19 in the following subgroups of special interest:
  - Individuals aged  $\leq 17$  years for vaccines authorized for use in this age group (further stratified as aged 5-11 and 12-17, or other relevant age groups, if feasible)
  - Women currently pregnant at the time of vaccination
  - Immunocompromised individuals
  - Individuals with a diagnosis of COVID-19 before vaccination
- To assess the comparative effectiveness of the complete primary series of each brand of COVID-19 vaccine in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19. The following vaccine exposure patterns will be 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, by brand, compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19, if feasible due to sample size. The following vaccine exposure patterns will be compared:
  - A single dose of BNT162b2 versus being unvaccinated
  - A single dose of mRNA-1273 versus being unvaccinated
- To assess the effectiveness of receiving an additional dose or booster dose compared with not receiving an additional dose or booster dose, by vaccine brand, in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19, among individuals with a complete primary series of COVID-19 vaccine, separately by immunocompromised status, if feasible due to observed sample size. The following vaccination exposure patterns will be compared among individuals receiving a complete primary series of any vaccine brand (i.e., timely receipt of 2 doses of the same brand of 2-dose series or 1 JNJ-7836735 dose):
  - BNT162b2 booster/additional dose versus not receiving a booster/additional dose
  - mRNA-1273 booster/additional dose versus not receiving a booster/additional dose
  - JNJ-7836735 booster/additional dose versus not receiving a booster/additional dose

If additional vaccine brands are introduced during the study period, they will be included as data are available as appropriate with their indicated/recommended dosing schedules.

### 2.2.3. Exploratory Objectives

The following exploratory objective may be evaluated by this study if feasible based on the descriptive results from Phase 1:

- To describe and assess the effectiveness of receiving a nonstandard primary series of COVID-19 vaccination compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19, including the following:
  - Mixed primary series of different vaccine brands versus being unvaccinated
  - Slightly delayed completion of primary series of a 2-dose BNT162b2 or mRNA-1273 primary series (received Dose 2  $\geq 7$  days after the recommended interval but  $\leq 42$  days after Dose 1) versus being unvaccinated
  - Substantially delayed completion of primary series of a 2-dose BNT162b2 or mRNA-1273 primary series (received Dose 2  $> 42$  days after the recommended interval but  $\leq 112$  days after Dose 1) versus being unvaccinated

If additional vaccine brands are introduced during the study period, they will be included as data are available as appropriate with their indicated/recommended dosing schedules.

## 3. Data Sources

This study will be conducted using commercial insurance claims databased contributing to the Biologics Effectiveness and Safety (BEST) Initiative linked to vaccination records from immunization information systems (IISs). At the time of writing this protocol, Optum administrative claims data have been linked with multiple IIS databases and will be used for the study. The study may also be implemented in other data sources within the BEST Initiative with reliable vaccine exposure information.

### 3.1. Optum Data

Optum's data sources include preadjudicated claims linked to IIS-sourced COVID-19 vaccination data from at least 12 US states. This study will be restricted to commercial insurance for individuals aged 64 years and younger. The study will be restricted to only individuals living in the catchment areas of both the linked insurance plans and IISs.

#### 3.1.1. Optum Preadjudicated Claims

The Optum data include enrollment, prescription drug, and preadjudicated hospital and physician health insurance claims. The preadjudicated claims database includes claims for privately insured enrollees. Hospital and physician claims undergo initial processing on a daily basis from a large number of providers across the US who accept patients with health insurance. Optum has established an ongoing weekly update schedule to incorporate newly processed claims into the preadjudicated claims database. This data source will be utilized to reduce the delay between the occurrence of healthcare services and their presence in the database. The preadjudicated claims have an approximately 2-month delay for 90% completeness for inpatient claims and over 70% completeness at 1 month for outpatient claims. As hospitalized COVID-19 is one of the primary study outcomes, inpatient data completeness will be prioritized, and the end of the study period will occur 2 months before the end of the available data.

### 3.1.2. Immunization Information System Data

Optum maintains a database to consolidate vaccine records for its health plan members. Since the COVID-19 outbreak, member exposure to COVID-19 vaccines has been integrated into the database. The COVID-19 vaccine database incorporates vaccine records obtained directly from IISs and is routinely refreshed. In addition to the IIS data, the database also includes a small number of Medicare claims-derived vaccine records after data cleaning, for the commercially insured population 64 years and younger that was concurrently eligible for Medicare. Also, the database includes some member self-reported vaccine administration records collected via membership online surveys and call-center interactions. These self-reported records represent less than 4% of the total vaccine records in the database and less than 1% once duplicate records already captured by claims and IIS data are removed. Due to compliance requirements, these self-reported data will not be included in this study.

## 4. Study Design and Definitions

### 4.1. Study Design

This observational cohort study within existing linked healthcare and immunization records will describe and compare the risk of medically diagnosed and hospital/ED–diagnosed COVID-19 outcomes in individuals vaccinated against COVID-19, by vaccine brand, and those who have not received any COVID-19 vaccine. The cohort approach will allow for comparisons between vaccinated and unvaccinated groups and among vaccine brands over time since vaccination, and effect measure estimates may be estimated on both the relative and absolute scales. With the widely varying incidence of COVID-19 during the study period, estimates of absolute effect measures will help contextualize any observed variation in VE measures over time.

For each comparison, the evaluation of eligibility criteria, covariate assessment, and the beginning of follow-up in both exposure groups will all be aligned at the same date (Time 0, [Section 4.2](#)), avoiding selection bias and immortal-time bias.<sup>15-18</sup> Differences between the exposure groups will be described and controlled for by matching on calendar time, county and state of residence, and other demographic or clinical factors, accounting for the changing COVID-19 incidence during the study period and phased rollout of COVID-19 vaccines. A negative outcome control analysis will be implemented to evaluate control of confounding between the exposure groups.

There are many potential patterns of COVID-19 vaccination receipt, both consistent with or inconsistent with current authorizations or licensure for the various available vaccines. Various patterns of vaccination receipt (“vaccine exposure patterns”) will be defined—i.e., complete primary series and unvaccinated patterns will be evaluated in primary analyses, and single doses of a 2-dose primary series and booster/additional doses will be evaluated in secondary analyses. For each comparison, the exposure pattern of interest will be defined for both exposure groups.<sup>19</sup> The primary objectives and the secondary comparative effectiveness objective will evaluate receipt of a complete primary vaccination series (either compared with being unvaccinated or compared with receipt of a different complete primary vaccination series). A primary series is dependent on the brand of vaccine received, as follows:

- Receiving 2 doses of BNT162b2 (Dose 2 is recommended 21 days after Dose 1)
- Receiving 2 doses of mRNA-1273 (Dose 2 is recommended 28 days after Dose 1)
- Receiving 1 dose of JNJ-7836735

Although the 2-dose BNT162b2 and mRNA-1273 vaccine series are recommended with spacing of 21 and 28 days, respectively, this study will allow 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 Centers for Disease Control and Prevention (CDC) recommendations for COVID-19 vaccine administration deviations.<sup>20</sup> CDC recommendations also state that receiving a second dose sooner than 4 days before the recommended interval is an invalid dose,<sup>20</sup> thus individuals receiving a vaccine sooner than 4 days before the recommended interval will be considered nonadherent to receiving the primary series. However, previous research has demonstrated very high compliance with the recommended dosing schedules.<sup>21</sup> A complete primary vaccination series will be defined as receipt of all recommended brand-specific doses of a vaccine in the initial primary series during the specified interval without receiving nonrecommended doses (Table 1).

Unvaccinated individuals will be identified and matched to vaccinated individuals on calendar date, county and state of residence, and other demographic and clinical characteristics (Section 5.1.2.1). Unvaccinated individuals will be followed in the data as long as they remain free of receipt of any COVID-19 vaccine dose (Table 1).

**Table 1. 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      | <ul style="list-style-type: none"> <li>Receipt of Dose 2 of BNT162b2 within 17 days of Dose 1</li> <li>Failure to receive Dose 2 of BNT162b2 by day 42<sup>a</sup></li> <li>Receipt of any other COVID-19 vaccine brand or unspecified brand</li> <li>Receipt of a third dose</li> </ul>   |
| mRNA-1273 complete primary series   | All eligible individuals receiving Dose 1 of mRNA-1273   | Date of Dose 1 of mRNA-1273     | <ul style="list-style-type: none"> <li>Receipt of Dose 2 of mRNA-1273 within 24 days of Dose 1</li> <li>Failure to receive Dose 2 of mRNA-1273 by day 42<sup>a</sup></li> <li>Receipt of any other COVID-19 vaccine brand or unspecified brand</li> <li>Receipt of a third dose</li> </ul> |
| JNJ-7836735 complete primary series | All eligible individuals receiving Dose 1 of JNJ-7836735 | Date of Dose 1 of JNJ-7836735   | <ul style="list-style-type: none"> <li>Receipt of any other COVID-19 vaccine dose</li> </ul>                                                                                                                                                                                               |
| Unvaccinated                        | Matched eligible unvaccinated comparator individuals     | Matched calendar date           | <ul style="list-style-type: none"> <li>Receipt of any COVID-19 vaccine dose</li> </ul>                                                                                                                                                                                                     |

COVID-19 = coronavirus disease 2019.

<sup>a</sup> A 42-day maximum time period will be considered for receiving Dose 2 of a 2-dose series; subject to revision after descriptive results from Phase 1.

Note: If additional vaccine brands are introduced during the study period, they will be included as data are available, as appropriate with their indicated/recommended dosing schedules.

Evaluations of the primary vaccination series will not consider booster/additional doses, and receipt of a booster/additional dose during follow-up will result in censoring in evaluations of the primary vaccination series, as recommendations and authorizations or licensure for the primary series and the booster/additional doses may differ. Booster/additional doses will be evaluated separately in secondary analyses ([Section 5.1.2.9](#)). Other vaccine exposure patterns will be described in secondary and exploratory analyses, including receiving a single dose of a 2-dose primary series and nonstandard vaccine exposure patterns (i.e., a primary series of 2 doses of different vaccine brands or a delayed second dose); evaluations of these exposure patterns will be conducted if feasible given the observed sample size.

## 4.2. Study Population

The study will be performed in the following 2 phases:

- Phase 1, the descriptive and feasibility evaluation phase ([Section 4.2.1](#)), will include only vaccinated individuals and will inform aspects of the approach used in the comparative analyses.
- Phase 2, the comparative analyses phase ([Section 4.2.2](#)), will include vaccinated and matched unvaccinated comparator individuals and will estimate VE measures.

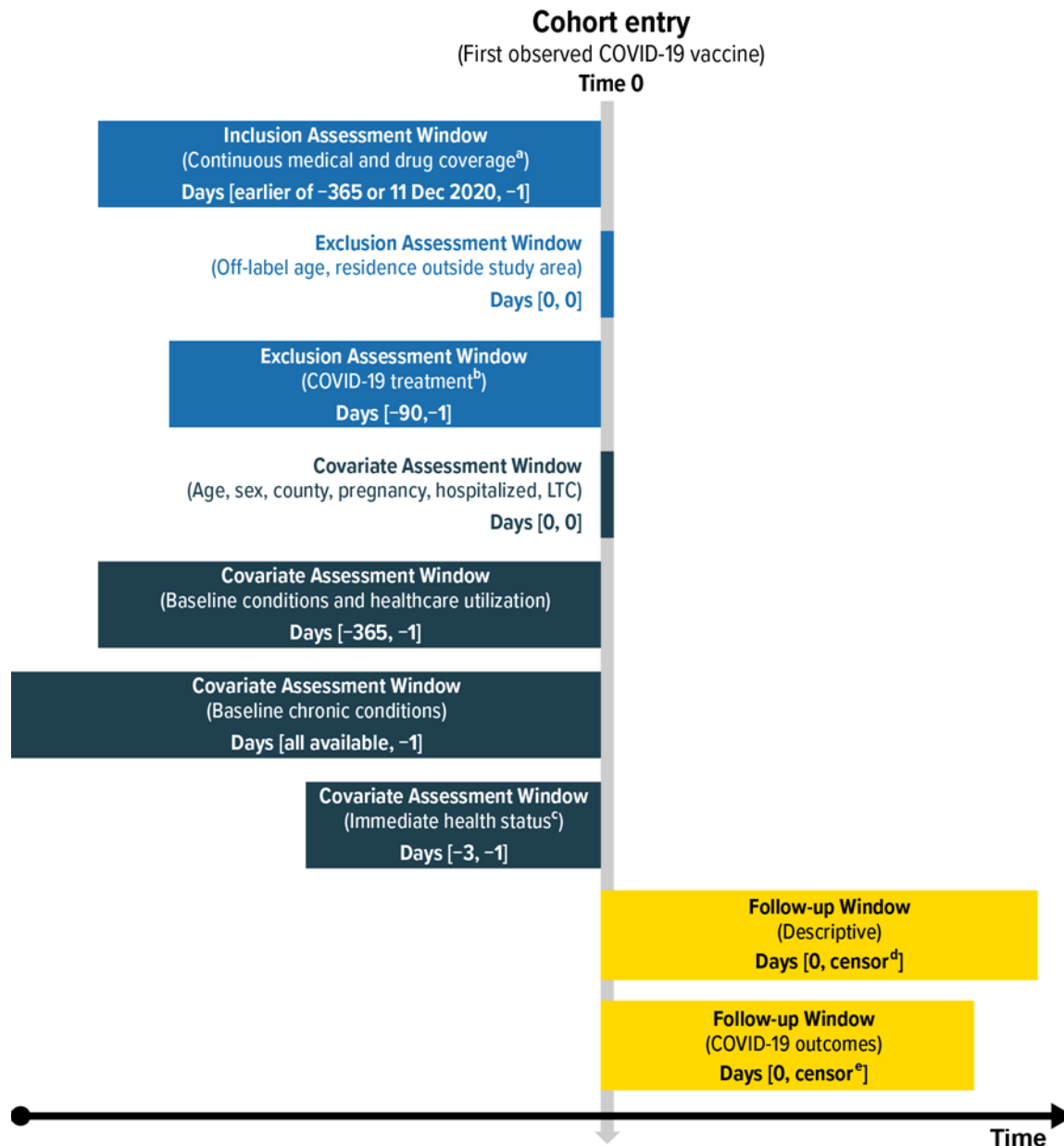
To fulfill the objectives of each phase, different populations will be included in each phase, requiring separate eligibility criteria and follow-up definitions.

### 4.2.1. Initial Descriptive and Feasibility Evaluation Phase (Phase 1)

#### 4.2.1.1. *Population*

In Phase 1, vaccinated individuals will be identified at their first COVID-19 vaccine dose recorded during the study period. The date of the first vaccine dose will be the Time 0 upon which the assessment periods for eligibility criteria, covariates, and follow-up will be defined ([Figure 1](#)). This phase will include minimal exclusion criteria to include as many real-world vaccine recipients as possible.

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



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 (1 December 2017), will be used; the duration of available data will be at least 365 days, but may vary for each individual.

<sup>a</sup> Gaps in medical and pharmacy coverage < 32 days permitted.

<sup>b</sup> COVID-19 monoclonal antibodies or convalescent plasma.

<sup>c</sup> 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.

<sup>d</sup> End of study period, end of continuous health plan enrollment, relocation out of study area.

<sup>e</sup> End of study period, end of continuous health plan enrollment, relocation out of study area, deviation from receipt of the complete primary series.

#### 4.2.1.2. Eligibility Criteria

Eligibility criteria will be evaluated relative to Time 0, the calendar date on which Dose 1 was received. Inclusion and exclusion criteria will be applied in the order shown on [Figure 1](#), from top to bottom. For the descriptive and feasibility phase, vaccinated individuals must meet the following inclusion criteria:

- Have continuous enrollment in the participating insurance plan for at least 365 days before Time 0 and that also begins 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  $\geq 16$  years, 10 May 2021 for individuals aged 12–15 years, 29 October 2021 for individuals aged 5–11 years—other modifications to be made depending on future authorizations), to characterize individual characteristics and ensure observation of all possible COVID-19 doses to accurately evaluate COVID-19 vaccination status (i.e., because some vaccine doses may be received greater than 365 days after vaccines were first available, some individuals may be required to have more than 365 days, but all must have at least 365 days).
  - Enrollment in both medical and pharmacy coverage is required.
  - Gaps in coverage of less than 32 days are permitted for continuous enrollment.

Vaccinated individuals will be excluded if any of the following exclusion criteria are met:

- Are aged outside the brand-authorized age range on the calendar date of Time 0 ([Table 2](#)).
  - The authorized ages for vaccination have varied by vaccine brand over the study period. For each calendar date of Time 0, only individuals within the authorized age range for the vaccine brand on that calendar date will be eligible.
  - If authorizations are additionally expanded during the study period, the eligibility criteria will flexibly adapt accordingly.
- Reside in a geographic region outside the catchment area of the linked IIS-claims data.
- Have 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.<sup>22</sup>

**Table 2. Authorized Age Ranges of COVID-19 Vaccines in the United States as of 21 October 2021, to Define Vaccine Brand–Specific Eligibility by Age as of 2 March 2022**

| COVID-19 vaccine | Calendar period                     | Age range       |
|------------------|-------------------------------------|-----------------|
| BNT162b2         | 11 December 2020 through 9 May 2021 | $\geq 16$ years |
| BNT162b2         | 10 May 2021 through 28 October 2021 | $\geq 12$ years |
| BNT162b2         | 29 October 2021 to the present      | $\geq 5$ years  |
| mRNA-1273        | 18 December 2020 to the present     | $\geq 18$ years |
| JNJ-7836735      | 27 February 2021 to the present     | $\geq 18$ years |

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

Note: If additional age ranges are authorized or additional vaccines are introduced during the study period, they will be included as data are available.

Source: US FDA. [23-25](#)

#### 4.2.1.3. *Follow-up*

Time 0 in vaccinated groups will be defined as the day an individual received the first dose of a COVID-19 vaccine. For descriptive analyses of individual characteristics, additional vaccine dose receipt, and series completion ([Section 5.1.1.1](#), [Section 5.1.1.2](#)), follow-up will begin at Time 0 and will consist of all available data after vaccination to observe and describe all subsequent doses. Follow-up for each individual will be censored at the first occurrence of any of the following on or after Time 0:

- Last date of the study period (i.e., end of acceptably complete claims data [[Section 3.1.1](#)] or IIS data availability)
- Last date of individual continuous eligible health plan enrollment ([Section 4.2.1.2](#))
- Date of recorded change of residence to location outside the study area (i.e., the catchment area of the linked claims-IIS data)

Phase 1 will also include an evaluation of COVID-19 cases in individuals with a complete primary vaccine series ([Section 5.1.1.3](#)). This analysis will also begin at Time 0; to avoid immortal person-time and selection bias, these analyses will not be restricted to only those who are known to complete the primary series, as that would require using future information to inform exposure status at Time 0.<sup>18</sup> For vaccines with a 2-dose primary series, all individuals receiving Dose 1 of that vaccine will begin follow-up at Time 0, because at the time of Dose 1 all individuals' behavior is consistent with receiving a complete primary series; individuals will be censored when their patterns of vaccine receipt become inconsistent with receiving a complete primary series ([Table 1](#)). For a vaccine with a 1-dose primary series, all individuals receiving Dose 1 will be considered to have completed the primary series. In addition to the general censoring criteria described above, follow-up for vaccinated individuals will also end on the date of the first occurrence of the following:

- One of the 2 COVID-19 outcomes, which will be evaluated separately ([Section 4.5](#)); an individual who experiences both outcomes may have different follow-up times for each outcome
- Censoring for deviation from receiving a complete primary vaccine series ([Table 1](#)).

#### 4.2.2. *Comparative Analyses Phase (Phase 2)*

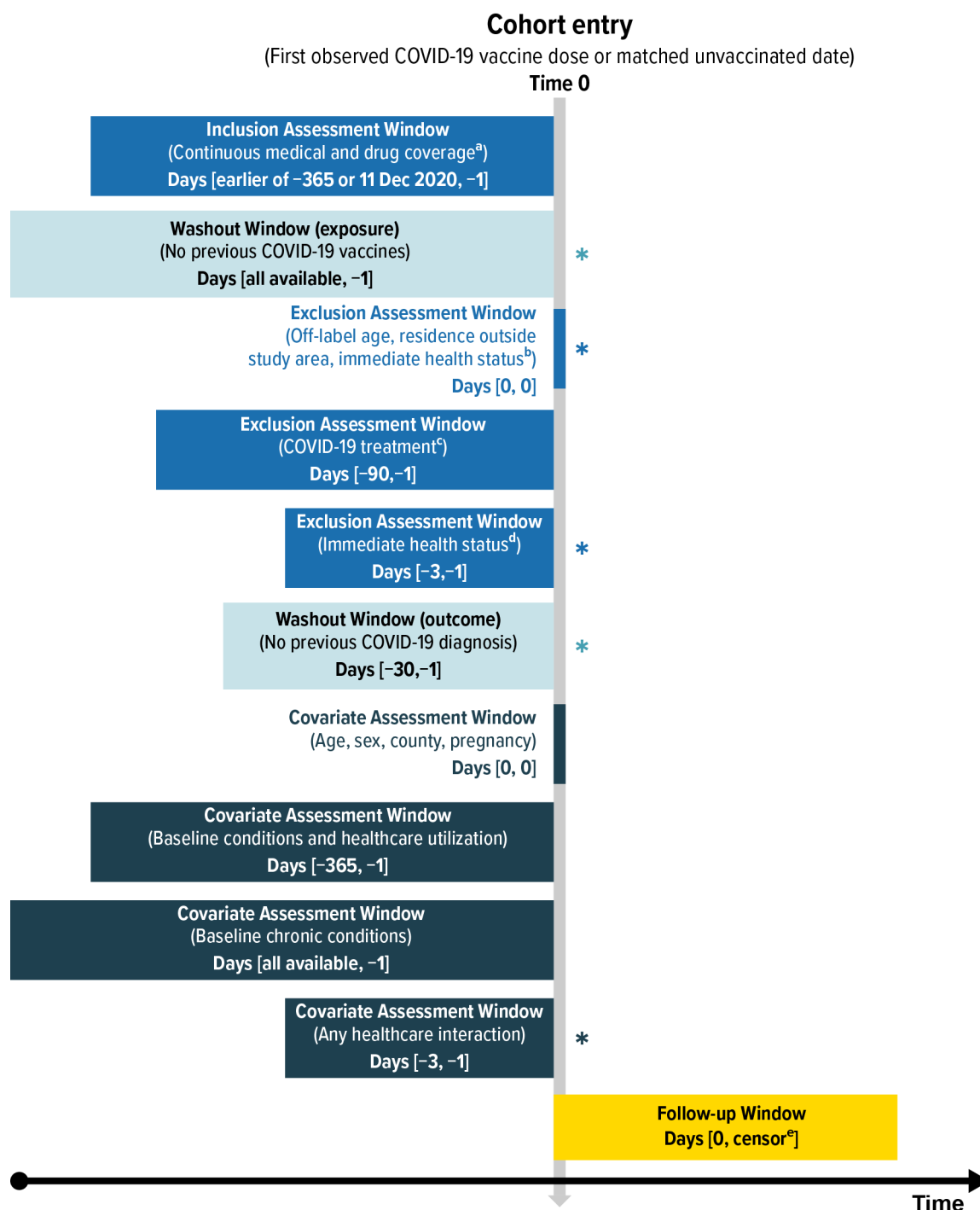
##### 4.2.2.1. *Population*

The vaccinated individuals in Phase 2—the comparative analyses phase—will constitute a subset of the vaccinated individuals included in Phase 1, the descriptive and feasibility evaluation phase. Time 0 (the date of Dose 1) will remain the same for vaccinated individuals in both phases. However, additional eligibility criteria will be applied to reduce confounding between vaccinated and unvaccinated groups by restricting analyses to more comparable exposure groups ([Figure 2](#)).

Unvaccinated individuals will be matched to vaccinated individuals on calendar time, county and state of residence, and other relevant factors ([Section 5.1.2.1](#)). Matched unvaccinated individuals will be assigned Time 0 as the calendar date of Dose 1 of the vaccinated individual to whom they were matched.

Inclusion and exclusion criteria will be applied to the vaccinated and unvaccinated individuals in the order shown in [Figure 2](#) (top to bottom).

**Figure 2. Schematic for Assessing Eligibility, Covariates, and COVID-19 Outcomes of Vaccinated Individuals and Matched Unvaccinated Comparators for the Comparative Analyses Phase (Phase 2)**



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

\* Indicates that this step is unique from or modified from the Phase 1 cohort.

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 (1 December 2017), will be used; the duration of available data will be at least 365 days, but may vary for each individual.

<sup>a</sup> Gaps in medical and pharmacy coverage < 32 days permitted.

<sup>b</sup> Hospitalization or long-term care residence at Time 0.

<sup>c</sup> COVID-19 monoclonal antibodies or convalescent plasma.

<sup>d</sup> 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.

<sup>e</sup> End of study period, end of continuous health plan enrollment, relocation out of study area, deviation from the categorized vaccine exposure status (complete primary series or being unvaccinated).

#### 4.2.2.2. *Eligibility Criteria*

Eligibility criteria will be evaluated relative to Time 0—the date of Dose 1 or the matched date for the unvaccinated comparator. Vaccinated and unvaccinated individuals in Phase 2 will be required to meet the following inclusion criterion to be included:

- Have continuous enrollment in the participating insurance plan for at least 365 days before Time 0 and that also begins 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  $\geq 16$  years, 10 May 2021 for individuals aged 12-15 years, and 29 October 2021 for individuals aged 5-11 years—other modifications to be made depending on future authorizations), to characterize individual characteristics and ensure observation of all possible COVID-19 doses to accurately evaluate COVID-19 vaccination status (i.e., some individuals may be required to have more than 365 days, but all must have at least 365 days).
  - Enrollment in both medical and pharmacy coverage will be required.
  - Gaps in coverage of less than 32 days will be permitted for continuous enrollment.

To align the health statuses of vaccinated and unvaccinated individuals and control for confounding, vaccinated and unvaccinated individuals will be excluded if any of the following exclusion criteria are met:

- Are aged outside the brand-authorized age range on the calendar date of Time 0 ([Table 2](#)).
  - The authorized ages for vaccination have varied by vaccine brand over the study period. For each calendar date of Time 0, only individuals aged within the authorized age range for the vaccine brand on that calendar date will be eligible.
  - If authorizations are additionally expanded during the study period, the eligibility criteria will flexibly adapt accordingly.
- Reside in a geographic region outside the catchment area of the linked IIS-claims data.
- Have 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.<sup>22</sup>
- Have 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.<sup>22</sup> Thus, only a short washout window will be required to differentiate new-onset cases during follow-up from continuing care for cases occurring before Time 0.
- Hospitalized on the date of Time 0, as unvaccinated individuals with active illness are unlikely to be considered candidates for vaccination.
- Reside 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 are highly variable and highly correlated within given LTC facilities.

- Have 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 (e.g., fever, nausea/vomiting, rash)
  - Hospitalization
  - ED visit

All individuals meeting these eligibility criteria will be included in the comparative study cohorts. Individuals receiving a first dose of the vaccine will be classified into the vaccinated group, and individuals not receiving a first dose of the vaccine on the date they are matched will be classified into the unvaccinated comparator group. Unvaccinated individuals may be included in the comparator group with a matched Time 0 and later be censored for receiving a COVID-19 vaccine (i.e., the unvaccinated group will not be restricted to “never vaccinated” individuals to avoid immortal-time bias caused by using future information to determine current exposure status<sup>17</sup>). Unvaccinated comparator individuals would be eligible to enter the vaccinated exposure group with a new Time 0 on the day of vaccination. The matching of unvaccinated to vaccinated individuals will be performed with replacement, so an unvaccinated individual may potentially be matched to multiple vaccinated individuals, and thus the unvaccinated individual may potentially be included multiple times with multiple different Time 0s.

For each brand-specific analysis, individuals with a Dose 1 of that vaccine brand will be included, as well as the matched unvaccinated comparator individuals.

#### *4.2.2.3. Follow-up*

For both the exposure group of vaccinated individuals receiving a complete primary series and the unvaccinated comparator group, follow-up will begin on the date of Time 0 (the date of Dose 1 for the vaccinated or the matched unvaccinated comparator date for the unvaccinated [[Section 5.1.2.1](#)]). Each individual's follow-up will end on the date of the first occurrence of any of the following:

- Occurrence of one of the study COVID-19 outcomes, which will be evaluated separately ([Section 4.5](#)); an individual that experiences both outcomes may have different follow-up times for each outcome
- Censoring for any of the following:
  - Last date of the study period (i.e., end of acceptably complete claims data [[Section 3.1.1](#)] or IIS data availability)
  - Last date of individual continuous eligible health plan enrollment
  - Date of recorded change of residence to a location out of the study area (i.e., the catchment area of the linked IIS data)
  - Deviation from the categorized exposure pattern ([Table 1](#))

### **4.3. Study Period**

The study period will begin 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 will be used to define individual characteristics and eligibility criteria before Time 0. The study period will use the 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, and the end of the study period will be the date last date end of acceptably complete claims data [\[Section 3.1.1\]](#) or IIS data availability.

#### 4.4. Vaccine Exposure Characterization

This study will evaluate receipt of COVID-19 vaccines, which will be identified in existing healthcare claims databases or IISs. Each vaccine dose observed during the study period will be identified and categorized according to vaccine brand and dose number (both according to the order of the observed doses and dose number as labeled on the claim).

Vaccinated individuals will be identified on the date of the first eligible observed COVID-19 vaccine dose (“Dose 1”) during the study period and will be categorized as BNT162b2, mRNA-1273, or JNJ-7836735, based on the vaccine brand received on that day (other vaccines brands will be considered if introduced during the study period). All additional COVID-19 doses received by an individual after Dose 1 will be considered to define patterns and status of primary series completion and describe the receipt of booster/additional doses and other patterns of interest. The date of Dose 1 during the study period will be Time 0 for vaccinated exposure groups.

Unvaccinated comparators will be identified by matching to a vaccinated individual on calendar date, county and state of residence, and other demographic and clinical characteristics ([Section 5.1.2.1](#)). An individual will be considered unvaccinated if the individual does not have a record of any COVID-19 vaccine dose in the linked claims and IIS data on or before the calendar date considered. An individual will be eligible to be matched as an unvaccinated comparator on every calendar date meeting the unvaccinated eligibility criteria ([Section 4.2.2.2](#)). Matched, unvaccinated individuals will be assigned an unvaccinated Time 0 by matching to the Dose 1 date of a vaccinated individual ([Section 5.1.2.1](#)). Individuals may be matched and selected as unvaccinated comparators on one calendar date and then be vaccinated on a later calendar date (i.e., the study will not be restricted to “never vaccinated” individuals), and unvaccinated individuals may be matched and selected as unvaccinated comparators for multiple vaccinated individuals.

##### 4.4.1. Vaccine Dose Identification

Vaccine doses will be identified in linked claims and IIS databases. In the claims data, vaccines will be 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.<sup>26,27</sup> Vaccine doses will also be identified in linked IIS databases using Vaccine Administered (CVX) codes. Deduplication of individuals’ vaccination records in both the IIS data and claims sources will be performed during the data linkage.

The dose number will be inferred from the order of observed doses within an individual’s record—thus continuous enrollment for the entire time period since the introduction of vaccines will be required. In IIS data, the dose number is not specified by the CVX code itself, but dose number may be reported separately in the IIS data. Dose numbers (e.g., first, second, third, or booster) are identified with specific HCPCS administration codes, but doses identified using NDC or CPT codes are not labeled as a specific dose; thus, reliance on the dose numbering from the claims or IIS records themselves may be insufficient. The completeness and consistency of dose numbering will be evaluated in descriptive analyses in Phase 1, and the approach to considering dose number may be modified based on these results (e.g., if dose number

can be ascertained reliably from the dose number on the claims/IIS record, then requiring continuous enrollment for the entire time since vaccine introduction may not be required).

*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. Due to the inability to categorize the brand and vaccine exposure patterns of those with brand-unspecified vaccine codes, if brand-unspecified codes and any other brand-specified vaccination records occur on the same day, the brand-unspecified codes will be ignored. Brand-unspecified codes without other accompanying claims or IIS records indicating the vaccine brand will not be used to define patient exposure status but may be used for exclusion criteria to indicate history of vaccination or as censoring criteria.

#### 4.4.2. Vaccine Receipt After Time 0

All subsequent COVID-19 vaccines received by an individual after Time 0 during follow-up will be identified. The brand and timing of subsequent doses relative to Time 0 will be used to evaluate continuing adherence to the vaccine exposure patterns in different analyses considered by the study (i.e., complete primary series, single dose of a 2-dose primary series, nonstandard series) ([Table 1](#); [Table 4](#); [Appendix 1](#), [Appendix Table 1](#)). Receipt of a booster/additional doses will be identified after Time 0, but cohorts to evaluate the booster/additional doses will be identified separately and anchored on the date of receipt of the booster/additional dose, which will constitute a new Time 0 for those analyses ([Section 5.1.2.9](#)).

#### 4.5. Outcome Definition and Assessment

COVID-19 outcomes will be identified in the data sources using *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) diagnosis codes for COVID-19 (ICD-10-CM code U07.1). Medical claims with diagnosis codes for COVID-19 outcomes will be identified from inpatient, ED, outpatient, or physician billing claims. Diagnosis codes will be identified in any billing position.

To evaluate the vaccines’ effectiveness against both milder and more severe COVID-19 cases, the analyses will consider 2 sets of nested, non–mutually exclusive COVID-19 outcomes. The 2 sets of COVID-19 outcomes will be defined and analyzed separately, as follows:

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

Validation studies have reported that the ICD-10-CM code for COVID-19 has reasonably high validity, particularly for hospitalized COVID-19. [28-32](#)

An individual may have different follow-up times for the 2 outcomes. If a patient’s first COVID-19 diagnosis during follow-up was in a hospital or ED setting, then that hospitalization/ED visit would qualify for both sets of events, and the patient will have the same follow-up for both sets of outcomes. However, if a patient had nonhospitalized claims with a COVID-19 diagnosis before a hospital admission with a COVID-19 diagnosis, only the date of the hospital/ED claim will be considered for the evaluation of

hospital/ED outcomes; the date of the first nonhospitalized COVID-19 claim would be the event date for the medically diagnosed COVID-19 outcome.

#### 4.6. Covariate Definitions and Assessment

Covariates will be assessed in both study phases. In Phase 1, covariates will be used to describe the characteristics of vaccinated individuals. In Phase 2, covariates will be used 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 will be collected to identify authorized, recommended, or prioritized groups for vaccination, which may have varied across geography and over time. Healthcare utilization and data on use of preventive healthcare services will be 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.<sup>33-35</sup> Comorbidities increasing an individual's risk of severe COVID-19 will also be identified to account for differences between exposure groups.

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

- Age, in years
- Sex
- County and state of residence
  - County further categorized as US state for ease of presentation of descriptive results
- Pregnancy status at Time 0 for females
- Hospitalization at Time 0 (Phase 1 only; variable will be an exclusion criterion in Phase 2)
- LTC residence at Time 0 (Phase 1 only; variable will be an exclusion criterion in Phase 2)

The following individual characteristics will be evaluated and defined as binary indicators (unless otherwise noted) using diagnostic and procedure codes during the 365 days before and not including Time 0 to evaluate health status, access to healthcare, healthcare-seeking behavior, and indicators of frailty:<sup>36,37</sup>

- Hospitalizations (0, 1,  $\geq 2$ )
- ED visits (0, 1,  $\geq 2$ )
- Skilled nursing facility stay
- Influenza vaccination
- Pneumococcal vaccination
- Encounter for cancer screening
- Eye examination
- Colonoscopy
- Bone mineral density test
- Well-check/well-child preventive healthcare visit
- Arthritis<sup>36</sup>
- Lipid abnormality<sup>36</sup>
- Ambulance use or life support services<sup>36</sup>
- Weakness<sup>36</sup>
- Pregnancy completion before Time 0 for females (to differentiate from active pregnancy at Time 0)

The following conditions have been identified as potentially putting individuals at higher risk of severe COVID-19<sup>38</sup> and may serve as indicators of eligibility or prioritization for vaccination and/or receipt of boosters. Each characteristic will be defined individually with a binary indicator using diagnostic codes in any setting or coding position and medication use in all available baseline data before and not including Time 0. An 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 or booster dose eligibility:

- Autoimmune disorders
- Cancer<sup>39,40</sup>
- Chronic kidney disease or renal disease<sup>39,40</sup>
- Chronic liver disease<sup>39,40</sup>
- Chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, pulmonary embolism)<sup>40</sup>
- Dementia<sup>36,39,40</sup> or other neurological conditions
- Diabetes mellitus, type 1 or 2
- Down syndrome
- Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)<sup>39,40</sup>
- Hypertension<sup>40</sup>
- Immunocompromised state
- Mental health conditions<sup>36,40</sup>
- Obese or severely obese<sup>41</sup>
- Sickle cell disease or thalassemia
- Stroke or cerebrovascular disease<sup>39</sup>
- Tuberculosis

The following individual characteristics will be evaluated using diagnostic and procedure codes in all available baseline data before and not including Time 0 to describe history of COVID-19 exposure, infection, and testing behavior:

- COVID-19 laboratory test performed (binary indicator of any test performed or none)
- COVID-19 diagnoses occurring outside a hospital or ED (in Phase 1, the distribution of dates of COVID-19 diagnosis before Time 0 will be evaluated to inform a potential exclusion criterion in Phase 2 [Section 4.2.1.2], but diagnoses occurring before the washout window will serve as a covariate and subgroup-defining variable)
- Hospital/ED–diagnosed COVID-19 (the distribution of COVID-19 diagnosis dates before Time 0 will be evaluated to inform a potential exclusion criterion [Section 4.2.1.2], but diagnoses occurring before the washout window will serve as a covariate and subgroup-defining variable)

The following characteristics will be evaluated using diagnostic and procedure codes in the 3 days immediately before but not including Time 0 to evaluate individuals' immediate health status at Time 0 to inform potential exclusion criteria in Phase 2 or to be used as covariates:

- Fever
- Nausea/vomiting
- Rash
- Hospital admission
- ED visit
- Any healthcare interaction (inpatient, ED, outpatient, or physician claim)

## 5. Statistical Methods

### 5.1. Data Analysis

The data analyses will be performed in the following 2 phases:

- Phase 1, the descriptive and feasibility evaluation phase ([Section 4.2.1](#)), will describe characteristics of vaccinated individuals, patterns of vaccination receipt, and COVID-19 incidence among individuals receiving a complete primary series of a COVID-19 vaccine ([Section 5.1.1](#))
- Phase 2, the comparative analyses phase ([Section 4.2.2](#)), will evaluate the primary objectives, comparing absolute and relative measures of COVID-19 incidence between matched vaccinated and unvaccinated exposure groups overall and over time, and the secondary objectives (subgroup analyses, head-to-head comparisons of vaccine brands, single dose of a 2-dose primary series, booster/additional doses), as well as exploratory analyses (as feasible) ([Section 5.1.2](#)).

The descriptive results of Phase 1 will inform implementation of the comparative analyses in Phase 2, and any necessary modifications to the analysis plan will be documented before proceeding with Phase 2.

#### 5.1.1. Phase 1 Analyses (Descriptive and Feasibility Evaluation Phase)

All vaccinated individuals meeting the eligibility criteria at their first observed eligible COVID-19 dose, Dose 1, will be included in these descriptive analyses of vaccine dose receipt and primary series completion. The date of Dose 1 will be Time 0. No unvaccinated individuals will be included in this phase, as the results of Phase 1 will be used to refine the matching and selection criteria for unvaccinated individuals to be used in Phase 2.

##### 5.1.1.1. *Descriptive Characteristics of Vaccinated Individuals*

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

Characteristics of all included vaccinated individuals at Time 0, regardless of their ultimate series completion, will be evaluated and described, overall and by vaccine brand. Binary or ordinal variables will be described with counts and proportions. Continuous variables will be expressed as medians and first and third quartiles (Q1, Q3) and means with standard deviations (SD). Descriptive characteristics will include prespecified demographic and subgroup-defining characteristics (pregnancy status at Time 0 for females, immunocompromised status) ([Section 4.6](#)) and a data-driven approach identifying the 100 most commonly occurring diagnosis, procedure, or medication codes occurring in the 365 days before Time 0 ([Appendix 2, Table Shell 1](#)).

The feasibility of including additional exclusion criteria in Phase 2 ([Section 4.2.1.2](#)) will be evaluated. The proportion of vaccine recipients with COVID-19 diagnoses in the 14 and 30 days before Time 0 will be described, along with a description of the distribution of time from the most recent COVID-19 diagnosis before Time 0, expressed in median, Q1 and Q3, minimum and maximum values, and the mean with SD. The prevalence of indicators of immediate health status on or immediately before Time 0 (hospitalization, LTC residence, fever, nausea/vomiting, rash, hospitalization, ED visit, any healthcare interaction [[Section 4.6](#)]) will be described ([Appendix 2, Table Shell 2](#)).

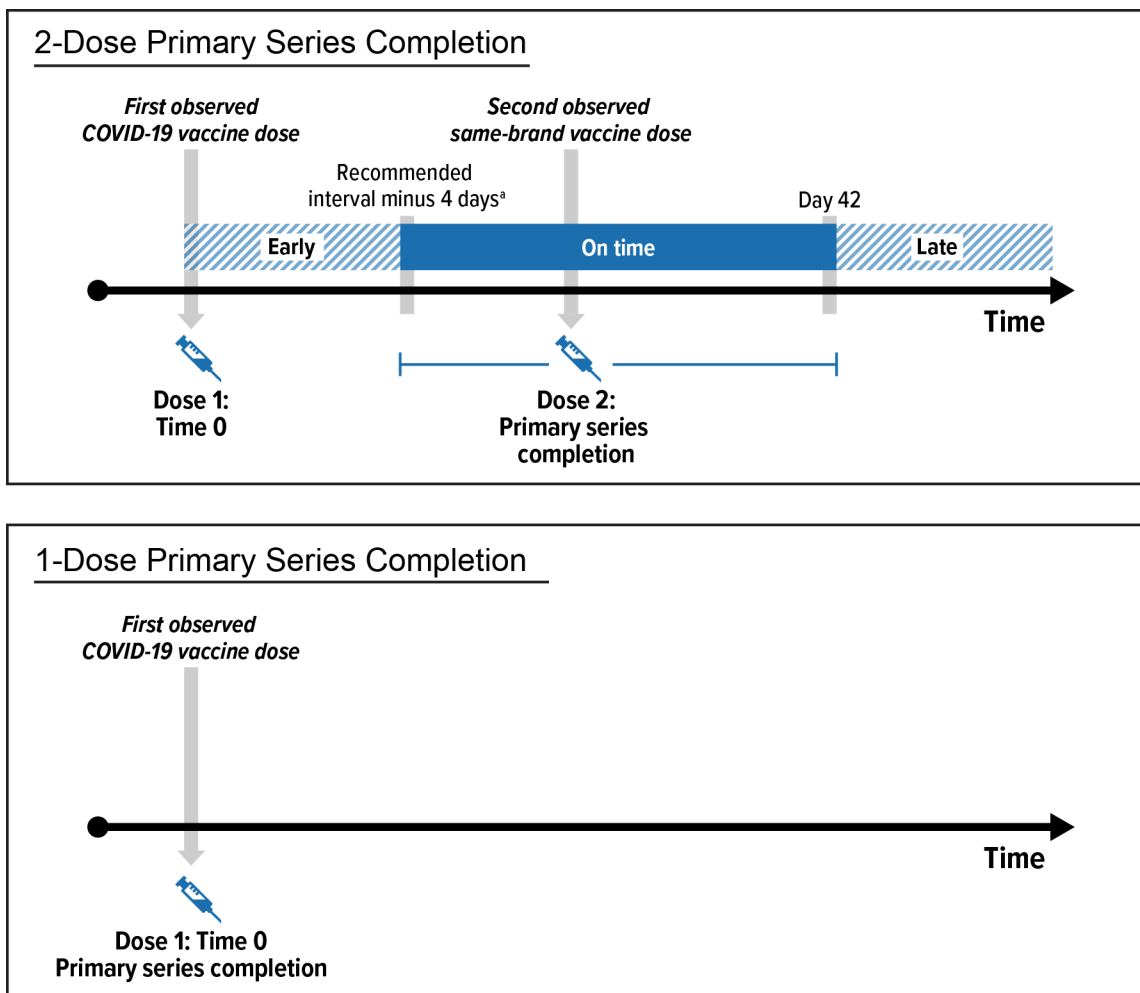
#### *5.1.1.2. Describing Vaccine Dose Receipt and Primary Series Completion*

The first day of follow-up will be Time 0, the date of Dose 1. The receipt and timing of additional COVID-19 vaccine doses during follow-up will be described. Time between doses in days, consistency of vaccine brand across doses, and adherence to recommended dosing schedules will be described ([Appendix 2, Table Shell 3](#)).

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 will be described. Completion of the 1-dose JNJ-7836735 or 2-dose primary series or other vaccine exposure pattern will be categorized based on the number of doses, vaccine brand, and timing of doses ([Appendix 2, Table Shell 3](#)). The distribution of days between Dose 1 and Dose 2 will be plotted by the brand of Dose 1.

The 2-dose BNT162b2 or mRNA-1273 series are recommended with spacing of 21 and 28 days, respectively ([Section 4.1](#)), but this study will allow 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 ([Figure 3](#)). For those with a Dose 1 of a vaccine brand with a 2-dose primary series, the distribution of times from Dose 1 and Dose 2 will be evaluated. Depending on the results of descriptive analyses, the 42-day maximum time limit may be modified in Phase 2 to match real-world patterns of vaccine receipt.

**Figure 3. Patterns of Primary Series Completion**



COVID-19 = coronavirus disease 2019.

<sup>a</sup> Day 17 for BNT162b2, day 24 for mRNA-1273.

Note: If additional vaccines are authorized during the study period, they will be included as data become available.

For vaccine brands with a 2-dose primary series, the characteristics of the subsets of individuals completing and not completing the primary series will be described ([Appendix 2, Table Shell 4](#)). Individuals who have not received Dose 2 and are censored for other reasons unrelated to their vaccine series completions (e.g., end of study period, disenrollment from study) before the end of the 42-day window to receive Dose 2 will be categorized as receiving the complete series, as their behavior at the time of censoring is consistent with receiving a complete primary series. A US study has reported that a high proportion of individuals complete the primary series on time.<sup>21</sup>

Individuals receiving only a single dose of a 2-dose primary series will be identified as those not receiving Dose 2 by day 42 (inclusive) ([Section 5.1.2.8, Figure 4](#)).

Additional vaccine doses for immunocompromised individuals<sup>42,43</sup> and booster doses<sup>23-25</sup> have been authorized and recommended, and additional modifications or additions to the vaccine schedule and recommendations may be forthcoming. The receipt and timing of booster or additional doses received after the primary series will be identified and described.

Other nonstandard permutations of the primary series—including off-label, nonrecommended, or nonauthorized patterns—will be identified ([Appendix 2, Table Shell 3](#)) and evaluated, if feasible due to sample size, including the following:

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

Detailed, operational definitions of the nonstandard vaccine exposure patterns may be found in [Appendix 1, Appendix Table 1](#).

#### *5.1.1.3. COVID-19 Outcomes in the Vaccinated*

To describe patterns of COVID-19 incidence among individuals receiving a complete primary series—over time since vaccination and calendar time—the cumulative incidence of COVID-19 outcomes will be estimated and plotted. To estimate the cumulative incidence of COVID-19 outcomes in individuals with a complete primary vaccine series, all vaccinated individuals will be followed from Time 0 until the end of follow-up ([Section 4.2.1.3](#)). COVID-19 outcomes during follow-up will be identified. The cumulative incidence of each COVID-19 outcome will be estimated in each monthly subcohort as 1 minus the Kaplan-Meier estimator.<sup>44</sup> Cumulative incidence curves will be plotted for the whole study period.

The cumulative incidence will also be estimated within mutually exclusive monthly subcohorts of vaccinated individuals defined by the calendar month of Time 0, and the monthly cumulative incidence curves will be plotted on 2 separate plots: first, with the time since Dose 1 as the time scale with the origin of each monthly subcohort curve aligned at 0; and second, with calendar month as the time scale with separate monthly subcohort curves originating at the calendar month of Time 0. Time points of relevance (e.g., the first 14 days after Dose 1 when no vaccine effect is expected; day 21 or 28 where a second dose is recommended; when the Delta variant became predominant in the US during June-July 2021; when the Omicron variant became predominant in the US during December 2021) will be overlayed on the plots. These approaches will allow visualization of COVID-19 incidence in vaccinated individuals both by time since vaccination and simultaneously considering time since vaccination and calendar time, as monthly subcohorts of vaccinated individuals will encounter key events (e.g., new variants becoming predominant) after longer or shorter periods of time since vaccination.

#### *5.1.2. Phase 2 Analyses (Comparative Analyses Phase)*

After the descriptive analyses in Phase 1, the following analyses will estimate the effectiveness of vaccine exposure patterns in comparative analyses. The results of Phase 1 will inform the following aspects of the study design for Phase 2:

- The appropriateness of a 30-day washout period for COVID-19 diagnoses before Time 0 (e.g., individuals are unlikely to be vaccinated while they have active COVID-19 or during exposure/disease quarantine periods;<sup>22</sup> the distribution between recorded COVID-19 diagnoses and COVID-19 vaccinations will be evaluated to define a washout period to identify comparable eligible unvaccinated individuals).

- The feasibility of implementing additional exclusion criteria based on immediate health status on or immediately before Time 0. If these characteristics are largely absent in vaccinated individuals, then these characteristics will be considered as exclusion criteria in Phase 2 to better align the vaccinated and unvaccinated groups.
- The appropriateness of the 42-day maximum length of time after Dose 1 during which individuals must receive Dose 2 to be categorized as having a complete vaccine series.
- The feasibility and anticipated sample sizes of analyses of secondary and exploratory objectives.

#### *5.1.2.1. Defining Exposure Groups for Comparisons*

The primary objectives will include the following vaccine exposure pattern comparisons:

- Complete BNT162b2 primary series versus being unvaccinated
- Complete mRNA-1273 primary series versus being unvaccinated
- Complete JNJ-7836735 primary series versus being unvaccinated

If additional vaccine brands are introduced during the study period, they will be included as data are available.

For each brand-specific comparison, the unvaccinated comparator group will be selected by 1:1 matching with the vaccinated group, and Time 0 for the unvaccinated will be assigned by the matching procedure. To account for rapidly changing vaccine authorizations and recommendations, vaccination priority groups (which may also vary geographically), and COVID-19 incidence, daily matching will be performed on several key demographic and clinical characteristics, allowing for flexible identification of an unvaccinated comparator group similar to the vaccinated exposure group.

Starting on the first calendar date of the study period, the following steps will be taken:

- All vaccinated individuals with an eligible Dose 1 (Time 0) on the calendar date will be identified.
- All other individuals enrolled in the data source without record of a COVID-19 vaccine on or before that calendar date will be identified.
  - Eligibility criteria for unvaccinated individuals will be evaluated on that calendar date. Those meeting eligibility criteria will be considered as potential matches.
- Unvaccinated individuals will be 1:1 exact matched, with replacement, to vaccinated individuals on the following characteristics:
  - Age, in years, in 5-year increments within age ranges corresponding to the tiered authorizations (18-64 years [16-64 for BNT162b2], 12-15 years, 5-11 years, other age groups < 64 years, if authorized)
  - Sex
  - County and state of residence
  - Immunocompromised status
  - Pregnancy status for women
  - History of COVID-19 diagnosis
  - Presence of at least one of the conditions identified by the CDC<sup>38</sup> as increasing individuals' risk of severe COVID-19 ([Section 4.6](#)) indicating potential prioritization for primary vaccine series receipt

- The vaccinated and unvaccinated individuals successfully matched on the calendar date will be selected for inclusion in the final matched cohort. The calendar date of Time 0 in the vaccinated individual will be assigned as the calendar date of the matched unvaccinated comparator.

This process will be repeated chronologically on each calendar date of the study period. Unvaccinated individuals will be matched with replacement; unvaccinated individuals who were successfully matched and selected on a previous calendar date will continue to be considered for the unvaccinated group on all future days on which they meet the eligibility criteria. Thus, an unvaccinated individual may be selected multiple times on the same date and on different dates. Unvaccinated individuals who were successfully matched on a previous calendar date who are subsequently vaccinated will be eligible for the vaccinated exposure group on the date of their first vaccination, and a new Time 0 will be assigned for the vaccination group (i.e., individuals may be included in both matched exposure groups, although at different points of calendar time). The estimation of the variance will account for the presence of repeated individuals in the study cohorts with robust variance estimators for model-based analyses or bootstrapping for nonparametric approaches.

All vaccinated and unvaccinated individuals who were successfully matched on any calendar date will be combined into the overall matched cohort with their respective Time 0 dates. Monthly subcohorts will be defined by the calendar month of Time 0 in both the vaccinated and unvaccinated groups. Additionally, Time 0s will be classified by key eras corresponding to new circulating variants (i.e., Delta, Omicron, others as identified) ([Section 5.1.2.4](#)) or by other relevant dates, as needed.

#### *5.1.2.2. Descriptive Characteristics*

For each of the brand-specific comparative cohorts, the number of individuals meeting all eligibility criteria to be included in the study cohort will be reported by exposure group. The number and proportion of vaccinated individuals excluded will also be reported for each exclusion criterion. Unvaccinated individuals will be considered as potential matches on every calendar day on which they are unvaccinated; on each considered day, they may be either excluded (potentially for different reasons on different days) or included. Thus, the attrition of the unvaccinated individuals will be described as potential matches considered and the number of potential matches excluded for each criterion. An individual may be included in the unvaccinated attrition table as a potential match more than once. The final size of the matched cohorts will be reported. The characteristics ([Section 4.6](#)) of all individuals included in an analytic cohort will be assessed relative to Time 0.

The distribution of characteristics will be described by vaccine exposure groups. Continuous variables will be described with means, SD, medians, and Q1 and Q3. Distributions of categorical variables will be described with counts and proportions. The balance of covariates between exposure groups will be evaluated with absolute standardized differences<sup>45</sup> ([Appendix 2, Table Shell 5](#)).

#### *5.1.2.3. Confounding Control*

For all comparisons, the first step to control for confounding is matching ([Section 5.1.2.1](#)), accounting for individual characteristics and local burden of COVID-19. After matching, we will further adjust for other baseline characteristics via inverse probability of treatment (IPT) weighting propensity score methods. The predicted probability of vaccine exposure (i.e., the propensity score) will be estimated via a logistic regression model with the matching factors<sup>46</sup> and the rest of the baseline characteristics identified a priori as independent variables. The model will include indicator variables for individual medical conditions that

put individuals at high risk, instead of just the overall indicator ([Section 4.6](#)). Baseline characteristics also include variables selected a priori that may be associated with both vaccination and risk of COVID-19 outcomes, including demographic characteristics, comorbidities, indicators for adherence or healthcare-seeking behavior (preventive services, other vaccinations), and COVID-19 testing behavior. The distributions of the propensity scores by vaccine exposure group will be plotted to visualize the degree of overlap between the vaccine exposure groups. The propensity score will be used to compute stabilized IPT weights<sup>47</sup> that will be applied to the analytic cohorts. The absolute standardized differences for the baseline characteristics in the IPT-weighted cohort will be evaluated to assess the balance of covariates after weighting by plotting the absolute standardized differences for each covariate before and after IPT-weighting.

A negative outcome control analysis will evaluate residual confounding in the IPT-weighted cohort ([Section 5.1.2.4](#)).

#### *5.1.2.4. Outcome Analyses*

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

Within each of the brand-specific cohorts, all individuals will be followed from Time 0 until censoring ([Section 4.2.1.3](#)) or the occurrence of the COVID-19 outcome of interest. The cumulative incidence of each COVID-19 outcome will be estimated in each IPT-weighted vaccine exposure group as 1 minus the Kaplan-Meier estimator.<sup>44</sup> Cumulative incidence curves will be plotted for the whole study period by vaccine exposure group.

As an overall summary of the relative incidence of the COVID-19 outcomes in the vaccinated and unvaccinated groups across the entire study period, a hazard ratio (HR) for each outcome will be estimated using an IPT-weighted Cox proportional hazards model with vaccination status as the independent variable; the 95% confidence intervals (CIs) will be estimated with robust variance estimators ([Appendix 2, Table Shell 6](#)).

The cumulative incidence curves yield daily estimates of the outcome risk throughout follow-up in both exposure groups. The daily risks of COVID-19 outcomes in the exposure groups can be used to estimate both relative and absolute effect measure estimates. The time-specific risk ratio (RR) of COVID-19 outcomes can be calculated as the risk in the vaccinated exposure group on a specified day divided by the risk in the comparator group on the same day. Estimation of the 95% CI for the RR estimates requires nonparametric bootstrapping, a general method for estimating standard errors and computing CIs.<sup>48,49</sup> In this method, a random sample of the study population of the same size as the eligible population will be drawn, with replacement (“bootstrap sample”) from the source population, and the effect estimate of interest in that sample (e.g., a RR) is estimated with the same matching and weighting methods used for the original RR estimate. Then, a second bootstrap sample is drawn, and a second effect estimate is obtained. The total size of each bootstrap sample is equal, but by chance, individual bootstrap samples will generally include a different number of copies of each individual due to the random sampling with replacement and therefore will result in different effect estimates. When repeated many times (usually at least 500), the SD of all the sample-specific effect estimates consistently estimates the standard error of the effect estimate in the study population. The distribution of the bootstrapped estimates will be used to

estimate a percentile interval (i.e., the range between the 2.5th and 97.5th percentiles of the bootstrap estimates) to approximate the 95% CI.

The VE—an estimate of the proportion of expected cases avoided due to vaccination—can be estimated as 1 minus the RR.<sup>50</sup> Time period-specific RR, VE, and risk difference (RD) measures will be estimated and reported ([Appendix 2, Table Shell 7](#)) at the following timepoints:

- Day 14 (the end of the negative outcome control period)
- The recommended day to receive Dose 2 (for vaccines with 2-dose series)
  - Day 21 for BNT162b2
  - Day 28 for mRNA-1273
- 14 days after the recommended day to receive Dose 2 (for vaccines with 2-dose series) (i.e., the day individuals are considered fully vaccinated by CDC standards<sup>51</sup>)
  - Day 35 for BNT162b2
  - Day 42 for mRNA-1273
- Days 60, 90, and 183

The RR and VE values are effect measure estimates measured on the relative scale. COVID-19 incidence has varied widely during the study period<sup>52</sup>; therefore, absolute estimates of RD between exposure groups may better help contextualize changes in the relative VE over time. A time-specific RD of COVID-19 outcomes associated with receiving a complete primary series compared with being unvaccinated can be calculated as the risk in the vaccinated exposure group on a given day minus the risk in the unvaccinated comparator group on the same day. Estimation of 95% CIs will also require nonparametric bootstrapping.

Only one set of bootstrap resampling (with the associated resampling, matching, weighting, and propensity score and IPT weight re-estimation in each sample) will be required, as the weighted cumulative incidence and all the daily RR and RD estimates can be re-estimated in the same set of bootstrap samples.

### Negative Outcome Control

To evaluate the completeness of confounding control, cumulative incidence curves for the overall exposure groups will be evaluated in the first 14 days (inclusive) of follow-up. The first COVID-19 vaccine dose is not anticipated to have any preventive effect against COVID-19 immediately after vaccination, as individuals will not have mounted full immune responses to the vaccine. Previous real-world studies of the effectiveness of COVID-19 vaccines has used similar negative outcome control methods and demonstrated minimal separation of cumulative incidence curves in the time period immediately following receipt of the first COVID-19 vaccine dose.<sup>5,21,53</sup> The cumulative incidence curves of both COVID-19 outcomes during the first 14 days will be visually inspected, and the RR and RD estimates during the first 14 days will be evaluated. Minimal separation of the cumulative incidence curves and effect measure estimates with 95% CIs highly compatible with a null effect during this negative outcome control period will provide reassurance that baseline confounding has been addressed. If the negative outcome control analysis suggests residual confounding, additional approaches for confounding control will be considered, including additional adjustment variables in the propensity score models, stratification into subgroups, or application of additional exclusion criteria (such as any healthcare interaction in the 3 days before Time 0). Additional negative control outcomes may also be considered.

### Vaccine Effectiveness Over Time Since Vaccination

Changes in VE over time, both time since vaccination and calendar time (as a proxy for circulating variants, as genotyping data are typically not available in large population healthcare data), will be evaluated using the daily RR and RD estimates generated from the cumulative incidence curves in each vaccine exposure group ([Section 5.1.2.4](#)). Daily estimates of the RR (and the resulting VE) and RD can be estimated with their 95% CIs and plotted by day since Time 0 to observe changes in VE over time on the relative and absolute scales.

### Vaccine Effectiveness Over Calendar Time (Proxy for Circulating Variants or Other Events of Interest)

The Delta variant of the SARS-CoV-2 virus became dominant in the US during June and July of 2021, accounting for > 50% of cases in all regions by the beginning of July 2021.<sup>54</sup> The Omicron variant became predominant by late-December 2021.<sup>54</sup> Additional variants may become predominant during the study period, or other key events can result in other calendar periods of interest. To disentangle potential effects of changes in VE estimates over time due to waning immunity and changes due to circulating variants, the cumulative incidence and daily VE estimation analysis will be stratified and plotted as follows to observe changing incidence over comparable follow-up times after vaccination in variant-specific eras:

- Individuals with Time 0 on or before 31 May 2021, with follow-up censored on 31 May 2021
- Individuals with Time 0 on or after 1 June 2021, with follow-up censored on 11 December 2021 (Delta era)
- Individuals with Time 0 on or after 25 December 2021 (Omicron era), with follow-up censored at the end of data availability

Other eras may be added, if of interest.

In addition to the variant-specific eras, if sample size permits, daily RR and RD estimates could be estimated and plotted within monthly subcohorts defined by calendar month of Time 0 with follow-up for the entire study period.

#### 5.1.2.5. *Sensitivity Analyses*

Sensitivity analyses will be performed to evaluate the robustness of the study results against variations in the study design, including the following:

- To define vaccine exposure patterns in this study (e.g., receiving a complete vaccine series or being unvaccinated), we begin follow-up at Time 0 (Dose 1 for the vaccinated or a matched unvaccinated date for the comparators) and censor individuals when they deviate from the pattern being considered (e.g., if a vaccinated individual fails to receive a second dose during the required time period, or if an unvaccinated person receives a vaccine). We assume that, conditional on the matched covariates, uncensored individuals remaining in the cohort have a risk of the outcome similar to that of the censored individuals had they not deviated from the assigned vaccination pattern. Because much of the censoring for nonadherence to the vaccine exposure patterns occurs shortly after Time 0 in the vaccinated groups (as individuals do or do not complete the primary series within the specified time), these differences may be accounted for by the measured baseline covariates. However, to test this assumption, the primary analysis will be repeated using inverse probability of censoring weighting with time-varying covariates reassessed before the censoring to account for potential selection bias caused by differential censoring.<sup>55</sup> Inverse probability of censoring weights will be estimated and also applied to the IPT-weighted samples to estimate overall HRs and 95% CIs.
- Censoring due to deviation from the assigned vaccination pattern may introduce bias from informative censoring (e.g., if unvaccinated individuals receive a vaccination after potential COVID-19 exposure, then individuals would systematically be censored from the analysis at times of increasing risk). To account for potential informative censoring, a sensitivity analysis will amend the censoring criteria so that censoring occurs 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 a subsequent vaccine dose) instead of censoring on the day of the vaccine dose, as there would not be an expected effect of the new dose during this time.

The HR and 95% CI estimates from the sensitivity analyses will be plotted on forest plots and compared with the HR estimate from the overall primary analysis.

#### 5.1.2.6. *Secondary Subgroup Analyses*

As permitted by sample size, the following clinically meaningful subgroups will be identified for evaluation:

- Individuals aged  $\leq 17$  years at Time 0 for vaccines authorized for use in this age group (further stratified as those aged 5-11 years and 12-17 years, if feasible, or other pediatric age groups as they are authorized)
- Women currently pregnant at Time 0
- Immunocompromised individuals
- Individuals with previous diagnoses of COVID-19 before Time 0
- Individuals without previous diagnoses of COVID-19 before Time 0

These subgroup analyses would be drawn from the brand-specific matched analytic cohorts used for the primary analysis. All the subgroup-defining characteristics are included as matching factors, so the 1:1 matching of vaccinated and unvaccinated individuals will be maintained in the subgroups. The propensity score and IPT weights will be re-estimated within each subgroup, and the HR and 95% CI will be estimated within each subgroup using IPT-weighted Cox proportional hazards models and will be plotted on forest plots and compared with the overall HR from the primary analysis.

### 5.1.2.7. Secondary Comparative Effectiveness Analysis

This secondary objective will evaluate the comparative effectiveness of receiving a complete primary series of different COVID-19 vaccine brands. The following comparisons will be considered:

- Complete JNJ-7836735 primary series versus complete BNT162b2 primary series
- Complete mRNA-1273 primary series versus complete BNT162b2 primary series
- Complete JNJ-7836735 primary series versus complete mRNA-1273 primary series

If additional vaccines are introduced during the study period, they will be included as data become available.

The vaccinated individuals eligible for these comparisons would be the same as those considered for the primary vaccinated versus unvaccinated comparisons before matching, with the same Time 0 and measured covariates.

Each unique comparison between vaccine brands will require a separate analytic cohort. For each comparison, to increase comparability of exposure groups, the study period will be restricted to time periods when all vaccine brands being used in that comparison were authorized ([Table 3](#)). The latest of the authorization dates of the vaccines being considered will be the beginning of the study period for that specific comparison (e.g., the study period for a comparison of JNJ-7836735 vs. BNT162b2 would begin on 27 February 2021, as JNJ-7836735 was not available before that date). Additionally, the calendar time-specific eligibility criteria will include only the authorized age ranges for any vaccine being considered during the time period being considered ([Table 2](#)) (e.g., comparisons of other vaccines to BNT162b2 will not include individuals aged  $\leq 17$  years during time periods when those individuals were eligible to receive only BNT162b2 and not the other vaccine being considered).

**Table 3. Dates of COVID-19 Vaccine Initial Authorization and Booster or Additional Dose Authorization by Brand in the United States as of 3 February 2022**

| COVID-19 vaccine | Earliest US authorization date of the primary series | US authorization dates of booster or additional doses                                                                         |
|------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| BNT162b2         | 11 December 2020                                     | 12 August 2021 <sup>a</sup><br>22 September 2021 <sup>b</sup><br>19 November 2021 <sup>c</sup><br>3 January 2022 <sup>d</sup> |
| mRNA-1273        | 18 December 2020                                     | 12 August 2021 <sup>a</sup><br>20 October 2021 <sup>b</sup><br>19 November 2021 <sup>c</sup>                                  |
| JNJ-7836735      | 27 February 2021                                     | 20 October 2021 <sup>c</sup>                                                                                                  |

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

<sup>a</sup> For immunocompromised individuals.

<sup>b</sup> For individuals aged  $\geq 65$  years or at high risk of severe COVID-19.

<sup>c</sup> For individuals aged  $\geq 18$  years.

<sup>d</sup> For individuals aged  $\geq 12$  years.

Note: If additional vaccines are made available during the study period, or if additional booster authorizations are released, the list of dates will be updated.

Source: US FDA.<sup>23-25</sup>

For all vaccinated individuals, Time 0 will be the date of vaccine Dose 1 in each group. Follow-up for a complete primary series will be the same as that in the primary analysis ([Section 4.2.1.3](#)).

All vaccinated individuals in either exposure group with an eligible Time 0 during the comparison-specific study period will be identified. To account for variation in local COVID-19 burden between the 2 exposure groups, vaccinated individuals in both exposure groups will be 1:1 exact matched on the following characteristics:

- Calendar week of Time 0
- Age, in years, in 5-year increments within age ranges corresponding to the tiered authorizations: 18-64 years (16-64 for BNT162b2), 12-15 years, 5-11 years, other age groups if authorized
- Sex
- County and state of residence

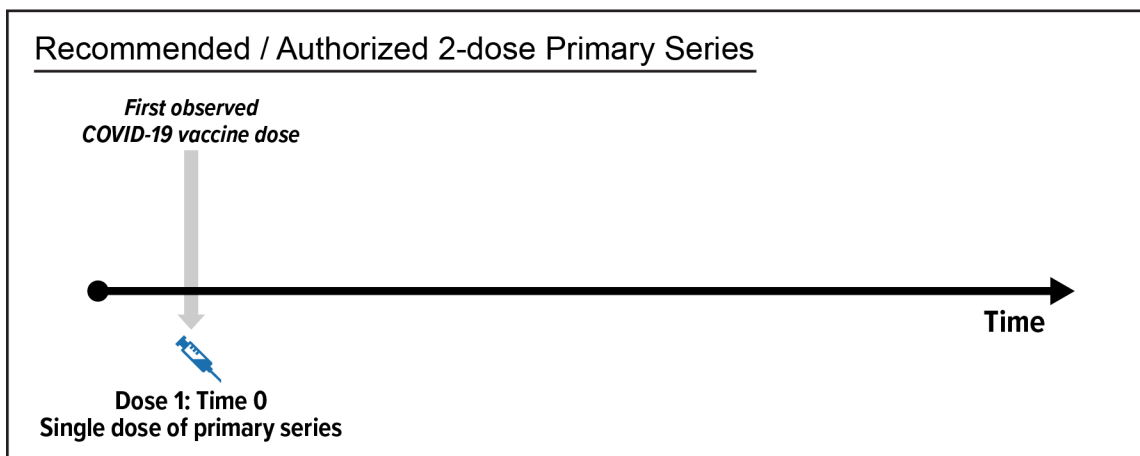
Due to the earlier introduction in the US, BNT162b2 will serve as the referent group for comparisons with mRNA-1273 and JNJ-7836735. In the comparison of JNJ-7836735 with mRNA-1273, mRNA-1273 will serve as the referent. Fewer matching criteria are used in this head-to-head analysis than in the primary analysis of vaccinated versus unvaccinated, as all vaccinated individuals in both exposure groups already have Time 0s assigned (the calendar date of Dose 1), and the extent of confounding between vaccinated groups is expected to be less than that between vaccinated and unvaccinated groups. Rather than the daily matching process used in the primary analysis of vaccinated versus unvaccinated, a single matching algorithm including all vaccinated individuals in both groups will be performed with an indicator for calendar week. All vaccinated individuals in both vaccine exposure groups who are successfully matched will be selected for inclusion in the final matched comparative cohorts. The distribution of baseline characteristics will be described ([Section 4.6](#)), and the absolute standardized differences will be estimated to evaluate exchangeability between vaccine exposure groups in each comparison ([Appendix 2, Table Shell 5](#)).

A negative outcome control analysis will be evaluated for adequacy of confounding control after matching.<sup>21</sup> If the negative outcome control analysis suggests remaining confounding after matching, other potential confounding factors may be accounted for with IPT-weighting. The propensity score and IPT weights will be re-estimated with each specific comparison. The IPT-weighted cumulative incidence curves will be plotted, and HR and 95% CI will be estimated with Cox proportional hazards models ([Appendix 2, Table Shell 6](#)).

#### *5.1.2.8. Secondary Single Dose of a 2-Dose Primary Series Analysis*

If feasible, a secondary analysis will evaluate the effectiveness of receipt of a single dose of a 2-dose primary series compared with being unvaccinated ([Figure 4](#)), by vaccine brand. JNJ-7836735 will not be included in this analysis, as its primary series consists of only a single dose.

**Figure 4. Patterns of Receiving a Single Dose of the BNT162b2 or mRNA-1273 Primary Series**



COVID-19 = coronavirus disease 2019.

The individuals included in this analysis will be 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 the unvaccinated comparator (matched unvaccinated date) will be the same, and the same 1:1 matching of vaccinated (with an eligible Dose 1 of BNT162b2 or mRNA-1273) and unvaccinated individuals will be maintained. However, as this analysis evaluates 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), the censoring criteria for deviation from the vaccine exposure pattern will differ for the vaccinated; vaccinated individuals will be censored at the receipt of an additional COVID-19 vaccine dose after Dose 1 ([Table 4](#)).

**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 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                                  |
| Unvaccinated                             | Matched eligible unvaccinated comparator individuals   | Matched calendar date           | Receipt of any COVID-19 vaccine                                             |

COVID-19 = coronavirus disease 2019.

Note: If additional vaccines with a 2-dose primary series are authorized during the study period, they will be included as data become available.

The same propensity scores and IPT weights used in the primary analysis will be used in this analysis, as the cohorts will include the same individuals with the same Time 0, but with different censoring criteria.

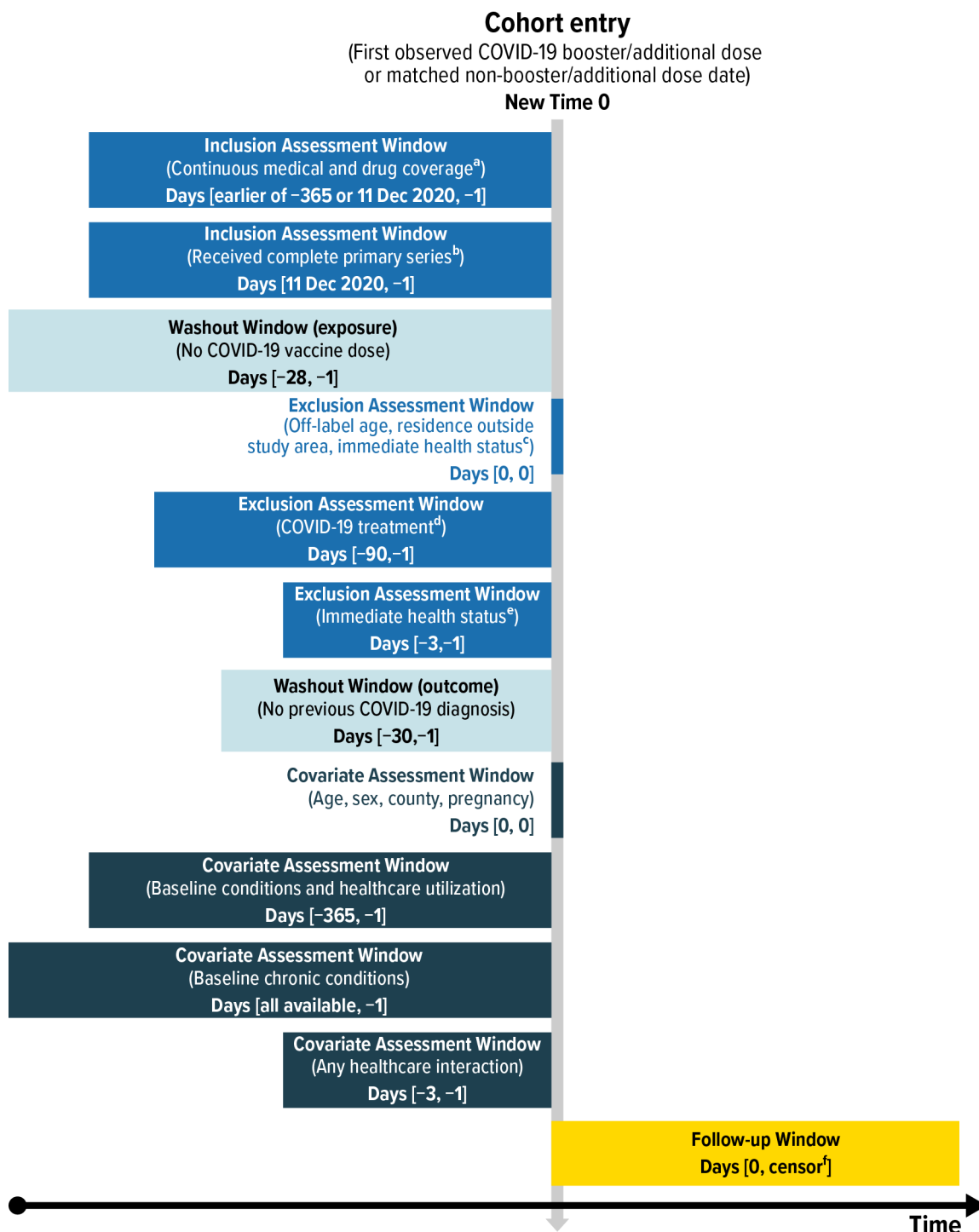
The IPT-weighted cumulative incidence curves of the COVID-19 outcomes will be plotted by exposure group, and HRs and 95% CIs will be estimated with IPT-weighted Cox proportional hazards models ([Appendix 2, Table Shell 6](#)).

#### *5.1.2.9. Secondary Booster Dose or Additional Dose Analysis*

The effectiveness of receiving a booster or additional dose of a COVID-19 vaccine after completion of the primary series will be compared with receiving a complete primary series but not receiving a booster/additional dose, stratified by immunocompromised status (if feasible due to sample size). For inclusion in this analysis, the primary series must be a “complete” series (i.e., 1 dose of JNJ-7836735 or 2 doses of BNT162b2 or mRNA-1273 with the second dose occurring on or after 17 or 24 days, respectively, and within 42 days [inclusive] of the first dose, without any additional doses), as defined in the primary analysis of the primary series ([Section 5.1.1.2, Figure 3](#)).

The study period for the booster/additional dose analyses of each brand would begin on the date of authorization for a booster/additional dose for each brand ([Table 3](#)). The analyses of booster/additional doses will use separate analytic cohorts from those evaluating primary series in the primary analysis. For these cohorts, individuals will be identified at the receipt of a booster/additional dose of a COVID-19 vaccine after completion of the primary series. The date of the booster/additional dose (or matched calendar date in the comparator group) will be the new Time 0 for this analysis, and eligibility criteria and covariates would be assessed based on this new Time 0 ([Figure 5](#)).

**Figure 5. Schematic for Assessing Eligibility, Covariates, and COVID-19 Outcomes of Individuals Receiving a Booster/Additional Dose and Matched Individuals Without a Booster/Additional Dose**



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

<sup>a</sup> Gaps in medical and pharmacy coverage < 32 days permitted.

<sup>b</sup> Primary series is 1 dose of JNJ-7836735 or 2 doses of BNT162b2 or mRNA-1273 with the second dose occurring on or after 17 or 24 days, respectively, and within 42 days (inclusive) of the first dose, without any additional doses.

<sup>c</sup> Hospitalization or LTC residence on new Time 0.

<sup>d</sup> COVID-19 monoclonal antibodies or convalescent plasma.

<sup>e</sup> 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.

<sup>f</sup> End of study period, end of continuous health plan enrollment, or deviation from the categorized vaccine exposure status (receiving a booster or not receiving a booster).

A booster/additional dose will be identified as a COVID-19 vaccine occurring after completion of a primary vaccine series. The first COVID-19 vaccine dose occurring after the authorization date of booster/additional doses per person will be identified for eligibility, and all available data before the date of that dose will be used to determine whether a complete primary series has been received and to differentiate booster/additional doses from potentially late-received primary series doses.

Booster/additional doses will be identified and categorized by the vaccine brand of the booster/additional dose. The brand of the booster/additional dose need not match the brand of the primary series, but the brand of the complete primary series will be recorded (mixed primary series will not be considered). Most of the eligibility criteria used in the primary analyses ([Section 4.2.1.2](#), [Section 4.2.2.2](#)) will be applied to these analyses, except that the new Time 0 for the variable assessment windows will be the date of booster/additional dose or matched comparison date (rather than the date of Dose 1 used in the primary analyses). Individuals will be required to have completed a primary series  $\geq 28$  days (the minimum recommended interval before an additional dose for immunocompromised individuals) before the new Time 0.

Individuals who received a primary series but who have not received a booster/additional dose at new Time 0 will be matched to those receiving a booster/additional dose on the calendar date of new Time 0 using a daily 1:1 exact matching process similar to that used in the primary analysis ([Section 5.1.2.1](#)). Matching factors will include the following:

- Age, in years, in 5-year increments within age ranges corresponding to the tiered authorizations ( $\geq 65$  years, 18-64 years [16-64 for BNT162b2], 12-15 years, other age groups as authorized)
- Sex
- County and state of residence
- Immunocompromised status
- Presence of at least one of the conditions identified by the CDC<sup>38</sup> as increasing individuals' risk of severe COVID-19 ([Section 4.6](#)) indicating potential prioritization for booster/additional dose receipt
- Brand of the complete primary series
- Time since primary series completion (14-day increments)

The same definitions of follow-up that were used in the primary analyses will apply ([Section 4.2.1.3](#), [Section 4.2.2.3](#)). The brand-specific conditions for censoring are shown in [Table 5](#).

**Table 5. Details of Follow-up for the Secondary Analysis of Booster/Additional Doses**

| <b>Vaccine exposure pattern</b>                                  | <b>Included individuals</b>                                                                                | <b>New Time 0 (beginning of follow-up)</b>     | <b>Deviation from exposure pattern after new Time 0 resulting in censoring</b>      |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------|
| Complete primary series plus BNT162b2 booster/additional dose    | All eligible individuals with a complete primary series receiving a booster/additional dose of BNT162b2    | Date of booster/additional dose of BNT162b2    | Receipt of an additional dose of any COVID-19 vaccine after booster/additional dose |
| Complete primary series plus mRNA-1273 booster/additional dose   | All eligible individuals with a complete primary series receiving a booster/additional dose of mRNA-1273   | Date of booster/additional dose of mRNA-1273   | Receipt of an additional dose of any COVID-19 vaccine after booster/additional dose |
| Complete primary series plus JNJ-7836735 booster/additional dose | All eligible individuals with a complete primary series receiving a booster/additional dose of JNJ-7836735 | Date of booster/additional dose of JNJ-7836735 | Receipt of an additional dose of any COVID-19 vaccine after booster/additional dose |
| Complete primary series without a booster/additional dose        | Matched eligible individuals with a complete primary series without receiving a booster/additional dose    | Matched calendar date                          | Receipt of any COVID-19 vaccine booster/additional dose                             |

COVID-19 = coronavirus disease 2019.

Note: If additional vaccines are authorized for booster/additional doses during the study period, they will be included as data become available.

In addition to the covariates described in the primary analysis ([Section 4.6](#)), the brand of the primary series will be identified and included as a covariate. The characteristics of the booster/additional dose and matched groups without booster/additional doses, by brand, will be described ([Appendix 2, Table Shell 5](#)). A new propensity score model will be fit in this cohort to estimate new IPT weights, as the individuals in the booster/additional dose cohorts may be different from those in the cohorts evaluating the primary series; covariates will be evaluated at the new Time 0. The cumulative incidence of the COVID-19 outcomes will be plotted in the IPT-weighted cohort, and the HR and 95% CIs will be estimated with IPT-weighted Cox proportional hazards models ([Appendix 2, Table Shell 6](#)). The first 10 days will be evaluated as a negative outcome control; this period is shorter than the 14-day negative control period of the primary analysis due to a faster response expected with a booster/additional dose (previous research has demonstrated reasonable overlap of cumulative incidence curves for the 7-10 day following receipt of a third dose of BNT162b2 vaccine<sup>56</sup>). Analyses will be performed overall by vaccine brand of the booster/additional dose, but they may also be stratified by heterologous or homologous status or specific combinations of brands, as feasible with the observed sample size.

The analyses of booster/additional doses will also be divided into variant-specific eras ([Section 5.1.2.4](#)) based on the new Time 0 of the included individuals. Era-specific HRs will be estimated to evaluate the effectiveness of the booster/additional dose within each variant-specific era.

As authorizations and recommendations for receiving an additional dose of some vaccine brands for immunocompromised individuals differ from the authorizations and recommendations for booster doses with regard to calendar date of authorization and timing of additional dose,<sup>57</sup> a subgroup analysis will also be performed among immunocompromised and nonimmunocompromised individuals, if feasible due to sample size.

#### *5.1.2.10. Exploratory Analyses*

As feasible given the observed sample sizes in the Phase 1 descriptive analyses ([Section 5.1.1](#)), the same methods used for the primary analyses of complete primary series may also be used for the following comparisons (published literature has suggested that compliance with the recommended dosing schedules is very high<sup>21</sup>). These analyses will be conducted only for vaccine brands with a 2-dose primary series:

- Receiving a mixed primary series of different vaccine brands versus being unvaccinated.
- Receiving a slightly delayed completion of a primary series versus being unvaccinated. All individuals meeting this definition of “slightly” delayed would also meet the definition of a complete vaccine series for the primary analysis. This analysis will represent a subgroup of the primary analysis.
- Receiving a substantially delayed completion of primary series versus being unvaccinated. Individuals with a substantial delay as defined here would not meet the criteria for a complete primary series in the primary analysis.

Detailed, operational definitions of the nonstandard vaccine exposure patterns may be found in [Appendix 1](#), [Appendix Table 1](#).

These exploratory analyses all begin follow-up at Dose 1 and use unvaccinated comparators. Therefore, these analyses would use the same brand-specific cohorts, matched comparator groups, Time 0, and propensity scores and IPT weights as those used in the primary analysis (complete primary vaccine series versus unvaccinated). However, the censoring criteria and follow-up time will be modified to account for the different vaccine exposure patterns ([Appendix 1](#), [Appendix Figure 1](#), [Appendix Table 1](#)). For each comparison that is deemed feasible to pursue, HRs and 95% CIs for each analysis will be estimated and reported ([Appendix 2](#), [Table Shell 6](#)).

## **5.2. Statistical Power and Sample Size Determination**

All individuals meeting the eligibility criteria will be included in the study cohorts to estimate unbiased measures of the effect of the various vaccine exposure patterns being considered using all data available at the time of analysis.<sup>58</sup>

However, the anticipated precision of the resulting VE estimates from these analyses can be estimated under varying assumptions of the expected number of included individuals in each comparison, relative size of the exposure groups, anticipated magnitude of the strength of the effect measure estimates, and risk of outcome in the unexposed group.<sup>59</sup> To estimate the precision of VE estimates (and corresponding RR estimates) for this study, the following assumptions were included in precision estimates:

- We assumed 2 conservative scenarios, VE = 80% and VE = 50%, to account for potentially reduced effectiveness over time. Pivotal randomized trial VE estimates for currently authorized/approved vaccines have reported VE estimates > 90% for the BNT162b2 and mRNA-1273 for the prevention of symptomatic infection and severe infection<sup>1-3</sup> and approximately 67% for JNJ-7836735.<sup>4</sup> Even

though some studies have reported reduced VE estimates after the Delta variant became predominant, reported VE estimates are generally still above 50%.<sup>12,60-62</sup>

- A 1:1 ratio of exposed to comparator individuals is assumed due to the 1:1 matching used for selection into the primary study cohorts for the vaccinated versus unvaccinated comparisons, with total assumed sample sizes (exposed and comparator groups combined) ranging from 200,000 to 400,000 (although unvaccinated comparators may be resampled, potentially resulting in slightly smaller actual sample sizes of unique individuals in unvaccinated comparators).
- Assumptions of the baseline risk of COVID-19 outcomes were based on a recent evaluation of US COVID-19 surveillance.<sup>61</sup> A baseline risk of hospitalized COVID-19 in the unvaccinated of 12 cases per 100,000 persons was used, as that was the reported hospitalization rate among the unvaccinated at the beginning of the study period. A baseline risk of 50 medically diagnosed COVID-19 cases per 100,000 persons was used; the surveillance study reported approximately 150 positive COVID-19 tests per 100,000 persons at the beginning of the study period, and we estimated that approximately one-third of the cases may result in a medical diagnosis.

[Table 6](#) displays the probabilities that the lower limit of the 95% CI of the VE estimate would be above 0 (a correlate of the upper bound of the underlying RR estimate being below 1, indicating a protective effect associated with the exposure) under these assumptions.

**Table 6. Precision of Vaccine Effectiveness Estimates Under an Array of Possible Sample Sizes, Underlying Risk, and Vaccine Effectiveness Magnitudes**

| Assumed VE estimate            | Ratio of unexposed to exposed | Total sample size | Risk in the unvaccinated <sup>a</sup> | Probability of VE lower 95% confidence limit being > 0 |
|--------------------------------|-------------------------------|-------------------|---------------------------------------|--------------------------------------------------------|
| Hospital/ED–diagnosed COVID-19 |                               |                   |                                       |                                                        |
| 50% (RR, 0.50)                 | 1:1                           | 200,000           | 0.00012                               | 0.28                                                   |
| 80% (RR, 0.20)                 | 1:1                           | 200,000           | 0.00012                               | 0.62                                                   |
| 50% (RR, 0.50)                 | 1:1                           | 400,000           | 0.00012                               | 0.50                                                   |
| 80% (RR, 0.20)                 | 1:1                           | 400,000           | 0.00012                               | 0.90                                                   |
| Medically diagnosed COVID-19   |                               |                   |                                       |                                                        |
| 50% (RR, 0.50)                 | 1:1                           | 200,000           | 0.0005                                | 0.81                                                   |
| 80% (RR, 0.20)                 | 1:1                           | 200,000           | 0.0005                                | > 0.99                                                 |
| 50% (RR, 0.50)                 | 1:1                           | 400,000           | 0.0005                                | 0.98                                                   |
| 80% (RR, 0.20)                 | 1:1                           | 400,000           | 0.0005                                | > 0.99                                                 |

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

<sup>a</sup> Presented as cases per person without scaling.

Under expected conditions and with conservative assumptions, the study is anticipated to yield reasonably precise estimates of VE between vaccinated and unvaccinated individuals. Initial explorations of the Optum data have identified over 500,000 unique individuals with at least 1 eligible dose of BNT162b2, over 260,000 for mRNA-1273, and approximately 60,000 for JNJ-7836735. Following additional accumulation of data over time and with the addition of new claims-IIS linkages, the sample size is anticipated to increase at the time of the conduct of the study. Comparisons of different vaccine brands, subgroups, or exploratory analyses may result in smaller sample sizes, baseline risks, or magnitude of VE

estimates, resulting in less precise effect measure estimates for some analyses, as would additional statistical adjustment.

## 6. Quantitative Bias Analysis

This study will define numerous vaccine exposure patterns based on the presence of records for COVID-19 vaccine doses. Despite the use of both claims and IIS data to identify vaccine doses, some vaccine administrations may not be accurately captured in either system, resulting in exposure misclassification where truly vaccinated individuals may be misclassified as unvaccinated. To evaluate the potential impacts of misclassification of vaccine exposure status, quantitative bias analysis methods<sup>63,64</sup> will be applied to comparisons of vaccinated versus unvaccinated individuals.

The extent of potential exposure misclassification will be estimated by comparing the observed vaccination rate in the included data sources against external estimates of state-level vaccination coverage (e.g., reported estimates from state or federal public health agencies), or utilizing capture-recapture methods to estimate the proportion of vaccination records that are absent from either claims or IIS data. As there may be considerable variation in the estimation of state-level vaccination coverage from different sources (e.g., some sources may lack the granularity to differentiate boosters or second doses from initial doses, thus overestimating counts of those with first doses and underestimating those with complete primary series or booster/additional doses), the highest and lowest estimate of state vaccine coverage for those aged less than 65 years from the various sources will be considered as the high and low bounds of coverage. Under the assumption that no truly unvaccinated individual is labeled by either claims or IIS data as being vaccinated (i.e., specificity = 100%), the observed vaccination rate in the study divided by the external vaccination rate will yield an estimate of the sensitivity of the vaccination measure.

Quantitative bias analysis will be employed to estimate the potential change in observed effect measure estimates for the range of estimated exposure misclassification levels. Effect measure estimates and the resulting VE estimates will be estimated with bias correction factors for exposure misclassification based on the external vaccination coverage rate and the estimated sensitivity and specificity of the study vaccination measure.<sup>65</sup> The results of the bias analysis using the highest and lowest vaccination coverage estimates will be presented as sensitivity analyses to the primary results to inform the impact of potential exposure misclassification.

Published validation studies have suggested a reasonably high validity of COVID-19 diagnosis codes,<sup>28-32</sup> but misclassification of COVID-19 outcomes may result in biased effect measure estimates, particularly if the validity of COVID-19 diagnoses coding varies differentially by vaccination status.<sup>63</sup> Quantitative bias analysis methods will be implemented to investigate the potential impact of differential outcome misclassification.<sup>65</sup> If published validity measures of COVID-19 diagnosis by vaccination status are available, they will be used to estimate corrected VE estimates; if validity measures by vaccination status are not available, a range of plausible differential misclassification scenarios based on published overall validity estimates will be considered to determine the extent of misclassification necessary to substantively alter the study results.

## 7. Limitations

This study will be subject to biases common to all observational studies based in existing healthcare data. Insurance billing claims are generated for reimbursement purposes rather than research; thus, some information may be unavailable or may be subject to misclassification.

This real-world study will not be able to evaluate effectiveness against overall COVID-19 infection. Many cases of COVID-19 are mild or even asymptomatic and do not require medical attention; thus, medical claims for these infections would not be generated and recorded in healthcare databases. Laboratory test results are not contained in the administrative claims data used for this study, so the identified COVID-19 outcomes will be identified using recorded diagnoses rather than laboratory test results. Additionally, routine testing for COVID-19 may occur outside traditional medical care settings (e.g., employer-based, mass testing clinics, home testing kits), and results of these tests may not be documented in administrative claims data sources. Testing behavior also may be associated with vaccination status through personal health beliefs or behaviors (e.g., adherence to vaccination and testing recommendations) or policy (e.g., increased testing requirements for unvaccinated individuals). Therefore, the association of vaccination with identification of mild or asymptomatic cases relying on test results alone may be strongly confounded. Additionally, accurate cause of death information is not available in the utilized administrative claims data; therefore, COVID-19–related death may not be a viable outcome. Therefore, the outcomes for this study will be restricted to those most likely to be accurately captured in claims data: medically diagnosed COVID-19 and hospital/ED–diagnosed COVID-19 cases. However, it is possible that some medically diagnosed or hospital/ED–diagnosed COVID-19 cases are not accurately captured in the included data sources, resulting in misclassification. Similarly, history of COVID-19 laboratory tests will be identified as a covariate, but only tests submitted for reimbursement by payers may be identified in the data sources. Additionally, some mild or asymptomatic COVID-19 cases may be identified and diagnosed when a patient sought care for an unrelated issue, and these incidental diagnoses may not be reflective of severity, even when diagnosed in hospital or ED settings. Incidental COVID-19 diagnoses may be more common in later time periods (e.g., the Omicron era) once vaccines were widely available.

COVID-19 vaccines in the US were provided without charge to the public during the study period, and not all institutions administering vaccines submitted claims for reimbursement to health insurance payers. Linked claims data from health insurance companies and IIS data from certain jurisdictions will be used to identify vaccine doses and categorize individuals as vaccinated or unvaccinated. While the addition of IIS vaccination data will substantially improve the accuracy of vaccine exposure information, it is possible that some vaccination information will not be recorded in either database, and the potential for missing or misclassified vaccine doses remains (e.g., unreimbursed vaccine doses received in an IIS jurisdiction other than a person's residence and vaccines received in clinical trials). Missing dose information may result in misclassifying truly vaccinated individuals as unvaccinated, complete primary series as incomplete, booster dose recipients as nonrecipients, or assigning incorrect Time 0 (or new Time 0) or timing of second or booster doses. Some coding systems for vaccination data include information about the dose number, but generally, the observed order of the vaccination records in the data will be used to define the dose number. Missing doses may result in incorrect assignment of the dose number or timing between doses. Further evaluations of the validity of vaccine exposure information are ongoing, and the results of those findings will guide the interpretation of the results of this study, including the potential for formal statistical exploration or quantitative bias analysis of exposure misclassification.<sup>65</sup> It is unlikely that a true

“gold standard” for vaccination status will be identified, and as those enrolled in the selected data sources will not be a true random sample of all residents in a state, the true vaccination coverage rate in the data source may not be the same as the overall state coverage level; thus, a range of potential coverage options will be considered.

This study will consider the “per-protocol” effects of vaccination, defining and evaluating vaccine exposure patterns with individual’s adherence to the recommended number, brand, and spacing of vaccine doses. Some individuals may have experienced severe adverse events after the receipt of vaccine doses, contraindicating the receipt of subsequent doses by these individuals.<sup>20</sup> Although these individuals may be adherent to current recommendations by not receiving subsequent doses,<sup>55</sup> this study will define adherence to vaccine exposure patterns and the per-protocol effect solely on receipt of all doses in the recommended series; the pivotal trials of both BNT162b2 and mRNA-1273 included only individuals receiving both doses in the primary series in the per-protocol analysis sets.<sup>1,2</sup>

The absence of a diagnosis in an individual’s claims will be interpreted as the individual not having that condition, but not all conditions are routinely or accurately captured within billing data. Key variables may be inconsistently recorded or underrecorded in claims data. Smoking status, overweight/obesity status, or substance abuse may all be COVID-19 risk factors used to define priority vaccination populations and/or eligibility for booster doses but are less likely to be reliably recorded in claims data. Minor health complaints or symptoms may lead to delaying vaccination, and these characteristics may be useful as exclusion criteria to identify appropriate unvaccinated comparators on specific calendar dates; however, minor symptoms not requiring medical attention are often not recorded in clinical or claims databases. Lastly, pregnant women are a key subgroup of interest. Pregnancy status on a particular calendar date may be identified in administrative claims data using information about pregnancy outcomes (events occurring and captured in future dates) and prenatal care. However, not all pregnancy outcomes may be captured in the data if women change insurance during pregnancy or if pregnancy outcomes occur after the end of available data; thus, identification of pregnancy status at Time 0 may rely on pregnancy-related encounters before or after Time 0. Healthcare utilization has changed over the course of the pandemic, with sharp declines in healthcare encounters across a variety of settings and populations early in the pandemic.<sup>66,67</sup> Recorded diagnoses of medical conditions may be decreased during the covariate assessment periods compared with other time periods. For many chronic conditions, all available data without requiring continuous enrollment will be used to identify specified covariates.

Observational studies evaluating changes in the vaccines’ effectiveness over time or during eras of differing variant circulation may inadvertently introduce time-related bias due to study design. Studies of waning effectiveness over time may be subject to selection bias. For example, if a study design defines exposure groups as those with longer event-free times since vaccination compared with those with shorter event-free times since vaccination, the differential requirements for event-free survival before inclusion in the study may result in a highly selected exposure group with very different baseline risk than the general population of vaccinated individuals.<sup>15</sup> Additionally, observed waning of VE estimates over time may be the result of study designs introducing bias due to depletion of susceptibles. Studies considering only time periods long after vaccination require long periods of event-free survival in both the vaccinated and unvaccinated groups. These studies exclude individuals who were infected with COVID-19 early in the study period (individuals who may have been at higher risk of developing COVID-19 due to high-risk conditions, employment exposure, or personal preventive behaviors), leaving a cohort with very little risk of developing COVID-19, whether vaccinated or not. If the unvaccinated individuals who have

remained free of COVID-19 for longer periods of time are the only comparator individuals included, the vaccine's effectiveness may appear to wane over time.<sup>68</sup> The design of the current study is specifically intended to avoid selection bias by aligning the assignment of exposure status, the beginning of follow-up, and the evaluation of baseline variables between the exposure groups at Time 0.

Confounding is among the largest threats to the validity of the current study. Vaccine effectiveness studies have been shown to be highly subject to residual confounding, even after implementation of a variety of methods for confounding control.<sup>69-75</sup> Vaccine receipt is highly correlated with behavioral characteristics that are very difficult to measure and account for in existing healthcare data (e.g., healthcare-seeking behavior, healthcare access, adherence to recommendations, frailty). Proxies for these measures will be used as adjustment variables, and a negative outcome control analysis will be used to evaluate the control of baseline confounding. Individuals whose probabilities of exposure and vaccination are too variable to be adjusted more in analyses (e.g., individuals in LTC) will be excluded from the study as a form of confounding control.

The vaccine exposure patterns evaluated in this study are sustained over time, and we implement censoring to assign the observed person-time to each pattern. Such postbaseline censoring can introduce bias in the presence of treatment-confounder feedback (i.e., if some postbaseline variables are affected by prior vaccination status, affect the probability of subsequent vaccination, and are associated with the probability of the outcome). In this study, we assume that, conditional on the matched baseline covariates, uncensored individuals in the IPT-weighted population have a risk of the outcome similar to that of the censored individuals had they not deviated from the assigned vaccination pattern. This assumption will be evaluated in sensitivity analyses.

## 8. Ethical Evaluation

This surveillance activity is conducted as part of the FDA public health surveillance mandate.

## 9. Quality Assurance and Control

The study will be carried out according to Optum Epidemiology's internal standard operating procedures, which are consistent with the International Society for Pharmacoepidemiology's *Guidelines for Good Pharmacoepidemiology Practices*<sup>76</sup> as well as the FDA's *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*<sup>77</sup> and FDA's *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance*, September 2021.<sup>78</sup> In particular, the standard operating procedures prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

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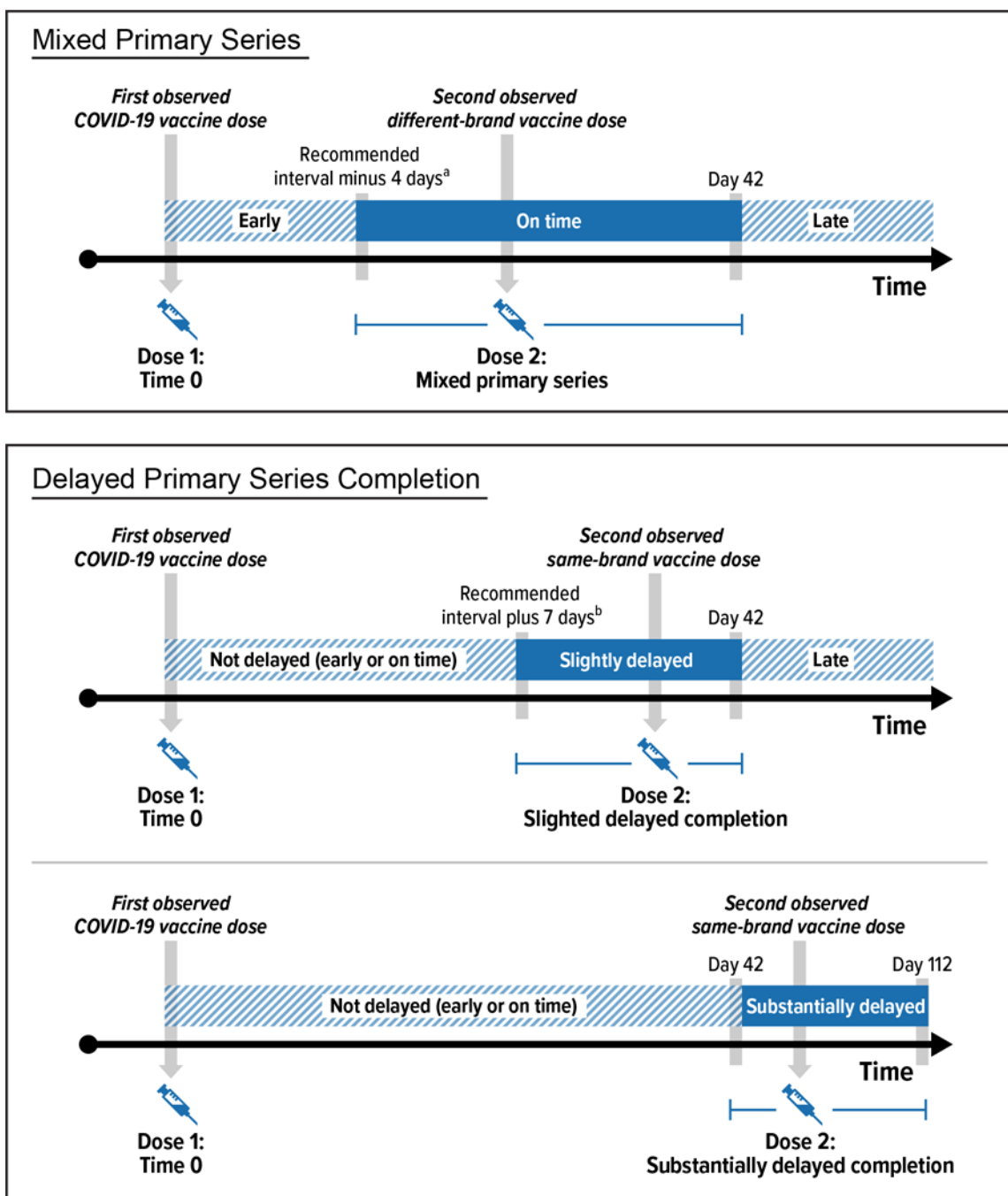
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## Appendices

### Appendix 1. Defining Nonstandard Vaccine Exposure Patterns for Exploratory Analyses

Appendix Figure 1. Patterns of Nonstandard Primary Series Completion



<sup>a</sup> Day 17 for BNT162b2, day 24 for mRNA-1273.

<sup>b</sup> Day 28 for BNT162b2, day 35 for mRNA-1273.

Note: delayed primary series completion will only be identified for individuals with Dose 1 of a vaccine with a recommended 2-dose primary series.

**Appendix Table 1. Details of Follow-up for the Exploratory Analysis of Atypical Primary Series**

| <b>Vaccine exposure pattern</b>                                   | <b>Included individuals</b>                                       | <b>Time 0 (beginning of follow-up)</b> | <b>Deviation from vaccine exposure pattern after Time 0 resulting in censoring</b>                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mixed primary series                                              | All eligible individuals receiving Dose 1 of any COVID-19 vaccine | Date of Dose 1 of any COVID-19 vaccine | <ul style="list-style-type: none"> <li>▪ Receipt of any other COVID-19 vaccine as Dose 2 within 17 days of Dose 1 (BNT162b2) or within 24 days of Dose 1 (mRNA-1273)</li> <li>▪ Failure to receive any other brand of COVID-19 vaccine as Dose 2 by day 42</li> <li>▪ Receipt of Dose 2 of the same brand as Dose 1 or unspecified brand</li> <li>▪ Receipt of a third dose</li> </ul> |
| Slightly delayed BNT162b2 primary series completion <sup>a</sup>  | All eligible individuals receiving Dose 1 of BNT162b2             | Date of Dose 1 of BNT162b2             | <ul style="list-style-type: none"> <li>▪ Receipt of Dose 2 of BNT162b2 within 27 days of Dose 1</li> <li>▪ Failure to receive Dose 2 of BNT162b2 by day 42</li> <li>▪ Receipt of any other COVID-19 vaccine brand or unspecified brand</li> <li>▪ Receipt of a third dose</li> </ul>                                                                                                   |
| Slightly delayed mRNA-1273 primary series completion <sup>a</sup> | All eligible individuals receiving Dose 1 of mRNA-1273            | Date of Dose 1 of mRNA-1273            | <ul style="list-style-type: none"> <li>▪ Receipt of Dose 2 of mRNA-1273 within 34 days of Dose 1</li> <li>▪ Failure to receive Dose 2 of mRNA-1273 by day 42</li> <li>▪ Receipt of any other COVID-19 vaccine brand or unspecified brand</li> <li>▪ Receipt of a third dose</li> </ul>                                                                                                 |
| Substantially delayed BNT162b2 primary series completion          | All eligible individuals receiving Dose 1 of BNT162b2             | Date of Dose 1 of BNT162b2             | <ul style="list-style-type: none"> <li>▪ Receipt of Dose 2 of BNT162b2 within 42 days of Dose 1</li> <li>▪ Failure to receive Dose 2 of BNT162b2 by day 112</li> <li>▪ Receipt of any other COVID-19 vaccine brand or unspecified brand</li> <li>▪ Receipt of a third dose</li> </ul>                                                                                                  |
| Substantially delayed mRNA-1273 primary series completion         | All eligible individuals receiving Dose 1 of mRNA-1273            | Date of Dose 1 of mRNA-1273            | <ul style="list-style-type: none"> <li>▪ Receipt of Dose 2 of mRNA-1273 within 42 days of Dose 1</li> <li>▪ Failure to receive Dose 2 of mRNA-1273 by day 112</li> <li>▪ Receipt of any other COVID-19 vaccine brand or unspecified brand</li> <li>▪ Receipt of a third dose</li> </ul>                                                                                                |

COVID-19 = coronavirus disease 2019.

<sup>a</sup> This vaccine exposure pattern is a subset of the primary analysis of complete primary series; all individuals with slightly delayed primary series completions would also meet the criteria for completion of the primary series.

Appendix 2. Table Shells

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

| Characteristic                                                    | Overall<br>N = | BNT162b2<br>N = | mRNA-1273<br>N = | JNJ-7836735<br>N = | Unknown<br>N = |
|-------------------------------------------------------------------|----------------|-----------------|------------------|--------------------|----------------|
| Age, years                                                        |                |                 |                  |                    |                |
| Median (Q1, Q3)                                                   |                |                 |                  |                    |                |
| Mean (SD)                                                         |                |                 |                  |                    |                |
| Sex, n, %                                                         |                |                 |                  |                    |                |
| Male                                                              |                |                 |                  |                    |                |
| Female                                                            |                |                 |                  |                    |                |
| Region, n, %                                                      |                |                 |                  |                    |                |
| Northeast                                                         |                |                 |                  |                    |                |
| South                                                             |                |                 |                  |                    |                |
| Midwest                                                           |                |                 |                  |                    |                |
| West                                                              |                |                 |                  |                    |                |
| Characteristics assessed during 365-day baseline period, n, %     |                |                 |                  |                    |                |
| Pregnancy <sup>a</sup>                                            |                |                 |                  |                    |                |
| Top 100 drugs, diagnoses, and procedures                          |                |                 |                  |                    |                |
| ...                                                               |                |                 |                  |                    |                |
| Characteristics assessed during all available baseline time, n, % |                |                 |                  |                    |                |
| Immunocompromised status <sup>b</sup>                             |                |                 |                  |                    |                |

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.

<sup>a</sup> Pregnancy at Time 0 to be defined as presence of an ICD-10-CM Z3A code and no delivery code during a 365-day baseline period.

<sup>b</sup> Defined using diagnosis codes and use of immunocompromising medications.

**Table Shell 2. Phase 1: Descriptive Exploration of Characteristics of Vaccinated Individuals Relative to the Date of the First Vaccine Dose, Which May Inform the Design of the Comparative Vaccine Effectiveness Study**

| Characteristic                                                       | Overall<br>N = | BNT162b2<br>N = | mRNA-1273<br>N = | JNJ-7836735<br>N = | Unknown<br>N = |
|----------------------------------------------------------------------|----------------|-----------------|------------------|--------------------|----------------|
| COVID-19 diagnosis in any setting at any point before Dose 1, %      |                |                 |                  |                    |                |
| 14 days before Dose 1                                                |                |                 |                  |                    |                |
| 30 days before Dose 1                                                |                |                 |                  |                    |                |
| Days since most recent COVID-19 diagnosis (Q1, Q3) <sup>a</sup>      |                |                 |                  |                    |                |
| Median (Q1, Q3)                                                      |                |                 |                  |                    |                |
| Minimum, maximum                                                     |                |                 |                  |                    |                |
| Mean (SD)                                                            |                |                 |                  |                    |                |
| Indicators of immediate health status at Time 0, %                   |                |                 |                  |                    |                |
| Hospitalized                                                         |                |                 |                  |                    |                |
| Long-term care resident                                              |                |                 |                  |                    |                |
| Indicators of immediate health status in the 3 days before Time 0, % |                |                 |                  |                    |                |
| Fever                                                                |                |                 |                  |                    |                |
| Nausea/vomiting                                                      |                |                 |                  |                    |                |
| Rash                                                                 |                |                 |                  |                    |                |
| Hospital admission                                                   |                |                 |                  |                    |                |
| ED visit                                                             |                |                 |                  |                    |                |
| Any healthcare interaction                                           |                |                 |                  |                    |                |

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

<sup>a</sup> Only among those with a COVID-19 diagnosis in any setting at any point before Dose 1.

**Table Shell 3. Phase 1: Characteristics of Vaccine Dose Receipt and Vaccine Exposure Patterns, Overall and by Vaccine Brand**

| Characteristic                                                                       | Overall | BNT162b2 | mRNA-1273 | JNJ-7836735 | Unknown |
|--------------------------------------------------------------------------------------|---------|----------|-----------|-------------|---------|
| Individuals with an eligible first observed COVID-19 vaccine dose <sup>a</sup>       |         |          |           |             |         |
| Vaccine dose number according to vaccine record; n, %                                |         |          |           |             |         |
| Labeled as Dose 1                                                                    |         |          |           |             |         |
| Labeled as Dose 2                                                                    |         |          |           |             |         |
| Labeled as Dose 3                                                                    |         |          |           |             |         |
| Labeled as booster                                                                   |         |          |           |             |         |
| Labeled dose number unspecified                                                      |         |          |           |             |         |
| Individuals with an observed second dose <sup>b</sup> , %                            |         |          |           | NA          |         |
| Vaccine dose number according to vaccine record; n, %                                |         |          |           | NA          |         |
| Labeled as Dose 1                                                                    |         |          |           | NA          |         |
| Labeled as Dose 2                                                                    |         |          |           | NA          |         |
| Labeled as Dose 3                                                                    |         |          |           | NA          |         |
| Labeled as booster                                                                   |         |          |           | NA          |         |
| Labeled dose number unspecified                                                      |         |          |           | NA          |         |
| Days between first and second doses, median (Q1, Q3)                                 | NA      |          |           | NA          |         |
| Vaccine brand of Dose 2 matches Dose 1, % yes                                        | NA      |          |           | NA          |         |
| Status of primary series completion; n, %                                            |         |          |           |             |         |
| Complete primary series <sup>c</sup>                                                 |         |          |           |             |         |
| Slightly delayed primary series completion <sup>d</sup>                              | NA      |          |           | NA          |         |
| Nonstandard primary series <sup>e</sup>                                              | NA      |          |           | NA          |         |
| Single dose of primary series (Dose 2 not received before end of recommended window) | NA      |          |           | NA          |         |
| Substantially delayed primary series completion <sup>f</sup>                         | NA      |          |           | NA          |         |
| Dose 2 received too early                                                            | NA      |          |           | NA          |         |
| Mixed series (Dose 2 different brand than Dose 1)                                    | NA      |          |           | NA          |         |

| Characteristic                                                                        | Overall | BNT162b2 | mRNA-1273 | JNJ-7836735 | Unknown |
|---------------------------------------------------------------------------------------|---------|----------|-----------|-------------|---------|
| Individuals with an observed booster/additional dose; n, %                            |         |          |           |             |         |
| Vaccine record labeled as Dose 1                                                      |         |          |           |             |         |
| Vaccine record labeled as Dose 2                                                      |         |          |           | NA          |         |
| Vaccine record labeled as Dose 3                                                      |         |          |           | NA          |         |
| Vaccine record labeled as booster                                                     |         |          |           |             |         |
| Vaccine record dose number unspecified                                                |         |          |           |             |         |
| Booster/additional dose after complete primary series <sup>g</sup>                    |         |          |           |             |         |
| Booster/additional dose same brand as complete primary series                         |         |          |           |             |         |
| Booster/additional dose occurs after nonstandard primary series                       |         |          |           |             |         |
| Booster/additional dose occurs after mixed primary series                             |         |          |           |             |         |
| Booster/additional dose occurs after Dose 2 received too early                        |         |          |           |             |         |
| Booster/additional dose occurs after substantially delayed Dose 2                     |         |          |           |             |         |
| Days between last dose of primary series and booster/additional dose; median (Q1, Q3) |         |          |           |             |         |

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

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

<sup>b</sup> Dose 2 of primary series is the same brand as Dose 1; those with Dose 1 of JNJ-7836735 not considered, as they are considered to have completed the primary series, and any subsequent dose after Dose 1 would be considered a booster/additional dose.

<sup>c</sup> Complete primary series defined as either Dose 1 of JNJ-7836735 or Dose 1 and Dose 2 of same brand of either BNT162b2 or mRNA-1273.

<sup>d</sup> Slightly delayed primary series defined as receiving Dose 2  $\geq 7$  days after recommended interval but  $\leq 42$  days after Dose 1.

<sup>e</sup> Nonstandard primary series defined as mixed series, Dose 2 received too early, or substantially delayed primary series completion.

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

<sup>g</sup> Booster/additional dose does not need to be the same brand as the first and second doses.

**Table Shell 4. Phase 1: Characteristics of Individuals With Complete and Incomplete Primary Series of the <<COVID-19 vaccine >>**

| Characteristic                                                | Individuals with a complete primary series<br>N = | Individuals with an incomplete primary series<br>N = |
|---------------------------------------------------------------|---------------------------------------------------|------------------------------------------------------|
| Age, years                                                    |                                                   |                                                      |
| Median (Q1, Q3)                                               |                                                   |                                                      |
| Mean (SD)                                                     |                                                   |                                                      |
| Sex, n, %                                                     |                                                   |                                                      |
| Male                                                          |                                                   |                                                      |
| Female                                                        |                                                   |                                                      |
| Region, n, %                                                  |                                                   |                                                      |
| Northeast                                                     |                                                   |                                                      |
| South                                                         |                                                   |                                                      |
| Midwest                                                       |                                                   |                                                      |
| West                                                          |                                                   |                                                      |
| Characteristics assessed during 365-day baseline period, n, % |                                                   |                                                      |
| ...                                                           |                                                   |                                                      |

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

*Note: Characteristics given in [Section 4.6](#).*

*Note: This table will be created separately for each COVID-19 vaccine having a primary series of > 1 dose.*

**Table Shell 5. Phase 2: Characteristics of Individuals Vaccinated With <<COVID-19 vaccine >> and Matched Unvaccinated Individuals**

| Characteristic                                                | Individuals vaccinated with <<COVID-19 vaccine brand>><br>N = | Matched unvaccinated individuals<br>N = | Absolute standardized difference |
|---------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------|----------------------------------|
| Age, years                                                    |                                                               |                                         |                                  |
| Median (Q1, Q3)                                               |                                                               |                                         |                                  |
| Mean (SD)                                                     |                                                               |                                         |                                  |
| Sex, n, %                                                     |                                                               |                                         |                                  |
| Male                                                          |                                                               |                                         |                                  |
| Female                                                        |                                                               |                                         |                                  |
| Region, n, %                                                  |                                                               |                                         |                                  |
| Northeast                                                     |                                                               |                                         |                                  |
| South                                                         |                                                               |                                         |                                  |
| Midwest                                                       |                                                               |                                         |                                  |
| West                                                          |                                                               |                                         |                                  |
| Characteristics assessed during 365-day baseline period, n, % |                                                               |                                         |                                  |
| ...                                                           |                                                               |                                         |                                  |

COVID-19 = coronavirus disease 2019; IQR = interquartile range; Q1, Q3 = first and third quartiles; SD = standard deviation.

*Note: Characteristics given in [Section 4.6](#).*

*Note: This table will be created separately for each COVID-19 vaccine brand ([Section 5.1.2.2](#)).*

*Note: This table shell will also be used (with modifications to the vaccine exposure group column headings and the title) for the secondary comparisons of COVID-19 brands compared with each other ([Section 5.1.2.7](#)), and booster/additional doses compared with not receiving booster/additional doses ([Section 5.1.2.9](#)).*

**Table Shell 6. Phase 2: Association of COVID-19 Outcomes With Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated, Inverse Probability of Treatment–Weighted Vaccine Exposure Groups, Overall and Sensitivity Analyses Accounting for Potentially Missing Vaccine Records Resulting in Exposure Misclassification**

| COVID-19 outcome      | Vaccine exposure group | N | Events | HR (95% CI) | VE (95% CI) | Sensitivity analysis assuming <<XX>>% exposure misclassification VE (95% CI) | Sensitivity analysis assuming <<XX>>% exposure misclassification VE (95% CI) |
|-----------------------|------------------------|---|--------|-------------|-------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Medically diagnosed   | BNT162b2               |   |        |             |             |                                                                              |                                                                              |
|                       | Unvaccinated           |   |        | —           | —           | —                                                                            | —                                                                            |
|                       | mRNA-1273              |   |        |             |             |                                                                              |                                                                              |
|                       | Unvaccinated           |   |        | —           | —           | —                                                                            | —                                                                            |
|                       | JNJ-7836735            |   |        |             |             |                                                                              |                                                                              |
|                       | Unvaccinated           |   |        | —           | —           | —                                                                            | —                                                                            |
| Hospital/ED–diagnosed | BNT162b2               |   |        |             |             |                                                                              |                                                                              |
|                       | Unvaccinated           |   |        | —           | —           | —                                                                            | —                                                                            |
|                       | mRNA-1273              |   |        |             |             |                                                                              |                                                                              |
|                       | Unvaccinated           |   |        | —           | —           | —                                                                            | —                                                                            |
|                       | JNJ-7836735            |   |        |             |             |                                                                              |                                                                              |
|                       | Unvaccinated           |   |        | —           | —           | —                                                                            | —                                                                            |

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

*Note: This table shell will also be used (with modifications to the vaccine exposure group labels and the title) for the secondary comparisons of COVID-19 vaccines compared with each other ([Section 5.1.2.7](#)), single doses of 2-dose vaccine series compared with being unvaccinated ([Section 5.1.2.8](#)), booster/additional doses compared with not receiving booster/additional doses ([Section 5.1.2.9](#)), and exploratory analyses of nonstandard vaccine exposure patterns (if performed) ([Section 5.1.2.10](#)).*

**Table Shell 7. Association of COVID-19 Outcomes With Receiving a Complete Primary Series of <<COVID-19 vaccine >> Compared With Being Unvaccinated Over Time, Inverse Probability of Treatment–Weighted Vaccine Exposure Groups**

| COVID-19 outcome      | Timepoint           | Vaccine exposure group | Events | Cumulative incidence | RR (95% CI) | VE (95% CI) | RD (95% CI) |
|-----------------------|---------------------|------------------------|--------|----------------------|-------------|-------------|-------------|
| Medically diagnosed   | Day 14              | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 21 <sup>a</sup> | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 35 <sup>b</sup> | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 60              | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 90              | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 183             | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
| Hospital/ED–diagnosed | Day 14              | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 21 <sup>a</sup> | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 60              | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 90              | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 35 <sup>b</sup> | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |
|                       | Day 183             | Vaccinated             |        |                      |             |             |             |
|                       |                     | Unvaccinated           |        |                      | —           | —           | —           |

— indicates the reference group; CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; RD = risk difference; RR = risk ratio; VE = vaccine effectiveness.

<sup>a</sup> Day of recommended receipt of Dose 2 in the primary series. [NOTE: Day will be modified to 28 for mRNA-1273; this row will be dropped for JNJ-7836735]

<sup>b</sup> 14 days after recommended day of receipt of Dose 2 in the primary series. [NOTE: Day will be modified to 42 for mRNA-1273; this row will be dropped for JNJ-7836735]

*Note: this table will be created separately for each COVID-19 vaccine.*