U.S. FOOD & DRUG ADMINISTRATION

Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance

CBER Surveillance Program Biologics Effectiveness and Safety (BEST) Initiative

Assessment of Effectiveness of BNT162b2 COVID-19 Vaccination in Children Aged 5 to 17 Years in the United States

Report

19 March 2024

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Version Control

Editors	Date	Version	Description
RTI International, FDA/CBER/OBPV, Acumen, Optum	19 March 2024	1.0	Cleared, final full report posted

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List of Tables and Figures

List of Acronyms and Abbreviations

Acronym or abbreviation	Definition
ASD	absolute standardized difference
BEST	Biologics Effectiveness and Safety
BNT162b2	Pfizer-BioNTech's messenger ribonucleic acid COVID-19 vaccine
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	Current Procedural Terminology
CVX	vaccine administered code
ED	emergency department
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HR	hazard ratio
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ICD-10-PCS	*International Classification of Diseases, 10th Revision, Procedure Coding System*
IIS	Immunization Information Systems
LTC	long-term care
mRNA	messenger ribonucleic acid
NA	not applicable
NDC	National Drug Code
Q1, Q3	first and third quartiles
RR	risk ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
sIPT	stabilized inverse probability of treatment
US	United States
VE	vaccine effectiveness

Executive Summary

Background

COVID-19 vaccines are authorized for use in children in the United States (US), and real-world assessment of vaccine effectiveness in children is needed. As part of its continued surveillance of authorized vaccines, the US Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative evaluated the real-world effectiveness of receiving a primary series of the original, monovalent BNT162b2 (Pfizer-BioNTech's messenger ribonucleic acid [mRNA] COVID-19 vaccine, Comirnaty®) in US children using national insurance claims databases supplemented with immunization information system (IIS) vaccination records to improve vaccine capture and limit misclassification bias.

Objective

To estimate the effectiveness of receiving a complete primary series of the original, monovalent BNT162b2 COVID-19 vaccine in US children aged 5–17 years.

Approach

This cohort study identified a group of children aged 5–17 years vaccinated with a first dose of BNT162b2 and a matched comparator group of unvaccinated children. Participants were identified in Optum (United Healthcare) and CVS Health (Aetna) insurance administrative claims databases supplemented with IIS COVID-19 vaccination records from 16 US jurisdictions between 11 December 2020 and 31 May 2022 (end date varied by database and IIS). Vaccinated children were followed from their first BNT162b2 dose and were matched to unvaccinated children on calendar date, US county of residence, and demographic and clinical factors. Censoring occurred if vaccinated children failed to receive a timely Dose 2 or received a third dose or if unvaccinated children received a dose. BNT162b2 vaccinations were identified using IIS vaccination records and insurance claims. Two non–mutually exclusive COVID-19 outcome definitions were evaluated: COVID-19 diagnosis in any medical setting and COVID-19 diagnosis in hospitals/emergency departments (EDs). Propensity score–weighted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with inverse probability of treatment-weighted Cox proportional hazards models, and vaccine effectiveness (VE) was estimated as 1 minus the HR. VE was estimated overall, within age subgroups, and within virus variant-specific eras. Sensitivity, negative control, and quantitative bias analyses evaluated the potential impact of various biases. Data source–specific results were meta-analyzed with fixed-effects meta-analysis models.

Results

A total of 460,473 eligible vaccinated children across both data sources were identified, and 453,655 were successfully 1-to-1 matched to unvaccinated comparators (mean age 12 years; 50% female). COVID-19 hospitalizations/ED visits were rare in children, regardless of vaccination status (Optum, 41.2 per 10,000 person-years; CVS Health, 44.1 per 10,000 person-years). Overall, vaccination with a primary series of BNT162b2 was associated with reduced incidence of any medically diagnosed COVID-19 (meta-analyzed VE = 38% [95% CI, 36%-40%]) and hospital/ED-diagnosed COVID-19 (meta-analyzed VE = 61%

[95% CI, 56%-65%]). VE estimates were lowest among children 5–11 years and during the Omicron variant era.

Conclusions

Receipt of a complete BNT162b2 vaccine primary series was associated with overall reduced medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in children. Observed VE estimates differed by age group and variant era; estimates were higher among children aged 12–17 years compared to 5–11 years, and estimates were lower during the Omicron era compared to other variant eras.

1 Background

Coronavirus disease 2019 (COVID-19), caused by the novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a global pandemic, affecting the United States (US) and countries throughout the world. Several vaccines for the prevention of COVID-19 were swiftly made available in the US through either emergency use authorization or licensure by the US Food and Drug Administration (FDA) for different age groups as either primary vaccination series or as booster/additional doses. This study focused on the original primary series of monovalent BNT162b2 (Pfizer-BioNTech's messenger ribonucleic acid [mRNA] COVID-19 vaccine, Comirnaty®), the first COVID-19 vaccine authorized in the US for use in children younger than 18 years. This vaccine was evaluated in large clinical trials in various age groups before authorization and was demonstrated to be effective in preventing COVID-19 outcomes.[1-3] However, compared with adults, there are fewer available studies on the real-world effectiveness of COVID-19 vaccination in US children.

BNT162b2 was initially authorized for use as a 2-dose primary series in individuals aged 16 years or older, and subsequent regulatory authorizations and public health recommendations expanded its use to include younger age groups. Questions remain regarding the vaccine's real-world effectiveness in the general pediatric population, in pediatric populations of special interest (e.g., immunocompromised children, in children of different age groups), and over time. Specifically, questions regarding the effectiveness against different circulating variants have arisen, as other variants emerged after the initial clinical studies were performed. These variants include the B.1.617.2 (Delta) variant and B.1.1.529 (Omicron) variants, both of which contributed to large increases in COVID-19 cases in the US. Concurrently with changes in viral variants over time, COVID-19 vaccines were authorized for use in younger groups of adolescents and children, creating a complex environment in which new viral variants, expanded age group eligibility, and changing indications for vaccination simultaneously impacted estimates of the real-world effectiveness of vaccines. Because of these overlapping factors, it is important to understand vaccine effectiveness by both variant era and age group.

This report presents the results of the pediatric analyses described in the publicly posted protocol "Assessment of Effectiveness of COVID-19 Vaccination in the United States" (dated 3 March 2022) and protocol addendum specific to pediatric analyses (dated 18 August 2022).[4,5] BNT162b2 was the only COVID-19 vaccine authorized for use in children younger than 18 during the available study period; thus, it is the only vaccine brand evaluated here. Other analyses described in the original study protocol (i.e., analyses of adults, booster doses) will be reported separately.

2 Objectives

2.1 Primary Objective

The following primary objective was evaluated in this study:

- To assess the effectiveness of receiving a complete primary series of BNT162b2 COVID-19 vaccination, compared with being unvaccinated, in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in children aged 5 to 17 years.

2.2 Secondary Objective

The following secondary objectives were evaluated in this study:

- To assess the effectiveness of receiving a complete primary series of BNT162b2, compared with being unvaccinated, in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in age subgroups corresponding to the staged authorization of vaccines or age-specific dosage ranges (i.e., BNT162b2, ages 16–17 years, 12–15 years, and 5–11 years), as available during the study period.
- To describe/characterize the effectiveness of receiving a complete primary series of BNT162b2 vaccination compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in calendar periods corresponding to different predominant circulating variants (i.e., pre-Delta, Delta, and Omicron eras).

3 Methods

3.1 Data Sources

The study was conducted using 2 US insurance claims data sources—Optum (United Healthcare) preadjudicated medical and pharmacy insurance billing claims and CVS Health (Aetna) adjudicated medical and pharmacy claims, which were supplemented with COVID-19 vaccination data sourced from immunization information systems (IISs) (Table 1).[6] This study was restricted to children with commercial insurance aged 5-17 years living in the catchment areas of both the insurance plans and the linked IISs.

Table 1. IIS Jurisdictions and Study Periods by Data Source

IIS Jurisdiction	Optum Study Period	CVS Health Study Period
1	NA	11 December 2020–31 March 2022
2	11 December 2020–31 March 2022	NA
3	NA	11 December 2020–31 March 2022
4	NA	11 December 2020–31 March 2022
5	NA	11 December 2020–31 March 2022
6	NA	11 December 2020–31 March 2022
7	11 December 2020–30 September 2021	11 December 2020–31 March 2022
8	11 December 2020–31 May 2022	11 December 2020–31 March 2022
9	11 December 2020–31 December 2021	11 December 2020–31 March 2022
10	11 December 2020–31 May 2022	11 December 2020–31 March 2022
11	11 December 2020–18 February 2022	NA
12	11 December 2020–31 March 2022	11 December 2020–31 March 2022
13	11 December 2020–31 May 2022	NA
14	11 December 2020–18 March 2022	NA
15	11 December 2020–31 May 2022	NA

IIS Jurisdiction	Optum Study Period	CVS Health Study Period
16	NA	11 December 2020–31 March 2022

IIS = immunization information system; NA = not applicable.
Note: individual state and jurisdiction names anonymized per contractual requirements to protect privacy of the linked populations.

3.1.1 Immunization Information Systems

During the COVID-19 pandemic, many COVID-19 vaccines were administered outside traditional healthcare settings (e.g., mass vaccination clinics, public health departments) and may not have resulted in submitted claims from medical providers to insurance payers for reimbursement. Thus, reliance on insurance claims alone for ascertainment of children's vaccination status may result in missing vaccine information. IIS COVID-19 vaccine administration records were used to supplement commercial claims to improve COVID-19 vaccine capture and reduce misclassification of vaccine status. States, cities, or other jurisdictions maintain registries of some administered vaccines as part of their public health functions[6,7]; each IIS is organized and maintained by the jurisdiction, and thus data structure, completeness, data access, and availability for surveillance purposes may vary across IISs. Many IISs are organized at the level of the US state, but some IISs contributing to this study were organized at jurisdictions within a state. For COVID-19 vaccines, potential vaccination providers were required to report vaccinations (usually through established IIS infrastructure) as a condition of receiving federally purchased vaccines.[8]

IIS information from each jurisdiction was evaluated for completeness and usability (process and results reported elsewhere[6]). The proportions of individuals aged younger than 65 years in each state reported as having at least 1 COVID-19 vaccine dose and who were fully vaccinated were estimated using the combined IIS data and claims data. These study-specific estimates were compared with state health department estimates, Centers for Disease Control and Prevention (CDC) estimates, and capture-recapture adjusted estimates (where the proportion of vaccinated individuals not captured with either IIS or claims data is estimated as a function of the proportion of those captured with either method alone or both[9]). To evaluate the data completeness of each IIS, a hypothetical quantitative bias analysis was then performed using the estimated vaccination status misclassification (sensitivity) for each state to evaluate the change in a hypothetical VE estimate of 70% (assuming a COVID-19 incidence of 6% among unvaccinated individuals). We assumed that an acceptable level of bias for inclusion of an IIS in the study was < 10 percentage points compared with state health department estimates for completed vaccine series. Additional considerations included the overall sample size of the state or territory, completeness of IIS data transfer, age ranges included in IIS data, the usability of IIS data (e.g., the ability to identify unique doses on specific calendar dates), and the magnitude of bias as measured by the effect of their inclusion on overall vaccine effectiveness estimates. After preliminary analyses, data from a total of 16 IISs from 14 unique US states were used (10 IIS from 10 states in Optum; 11 IIS from 9 states in CVS Health). At the time of data extraction for these pediatric analyses, there were differing levels of data completeness of the various IISs, so IIS-specific study end periods were used in the Optum linkage (ranging from 30 September 2021 to 31 May 2022); all IISs had an end date of 31 March 2022 in CVS Health (Table 1).

3.1.2 Optum Commercial Insurance Claims Supplemented With IIS Data

The Optum preadjudicated commercial claims database includes enrollment, prescription drug, and preadjudicated hospital and physician health insurance claims for privately insured enrollees. Hospital and physician claims undergo initial processing on a daily basis from a large number of providers across the US who accept patients with United Healthcare health insurance. Preadjudicated claims are updated on a weekly schedule to incorporate newly processed claims into the preadjudicated claims database. This data source was used to reduce the delay between accessing healthcare services and their recording in the database. The preadjudicated claims have an approximately 2-month delay for 90% completeness for inpatient claims. Because hospitalized COVID-19 is one of the primary study outcomes, inpatient data completeness was prioritized, and the end of the study period was defined as 2 months before the end of the available data.

Optum maintains a COVID-19 vaccine exposure database integrating COVID-19 vaccine information from insurance claims and through linkage with IISs and is routinely refreshed. Identifying information about Optum plan enrollees was sent to participating IISs, and IISs returned vaccination records for Optum enrollees within the IIS.

3.1.3 CVS Health Commercial Claims Supplemented with IIS Data

The CVS Health data include Aetna enrollment, administered vaccine claims, dispensed prescription drug claims, and adjudicated hospital and physician health insurance claims. The Aetna adjudicated claims database includes claims for Aetna commercially insured and Aetna Medicare Advantage enrollees. The adjudicated claims are 80% complete for inpatient claims at 3 months and outpatient claims at 2 months. In this analysis, the end of the study period was defined as 3 months before the end of the available data.

To enhance vaccine administration capture, the FDA requested that CVS Health collaborate with all IIS jurisdictions to obtain Aetna enrollee vaccine records that may not have been funded through Aetna health insurance. As of September 2023, CVS Health has active collaborations with 30 IISs. In this analysis, COVID-19 vaccination records from 11 IIS collaborations from 9 unique US states met data completeness criteria and were included. The IIS data collaboration sharing process involves CVS Health providing a secure person-identifiable data file on Aetna health plan enrollees to collaborating IISs, and IISs returning vaccination records for the enrollees within the IIS.

3.2 Study Period

The study period began on 11 December 2020 (the date of the first COVID-19 vaccine emergency use authorization in the US when BNT162b2 became available for use for individuals aged ≥ 16 years). Available data from before 11 December 2020—as far back as 1 December 2017—were used to define individual characteristics and eligibility criteria before Time 0 (either the day of vaccination or matched calendar date).

The study period used the most recent complete data available at the time of the data extraction, accounting for potential lag times in the accumulation of hospitalization data and linkage to IISs, as

shown in Table 1. The latest possible end date was 31 May 2022 in Optum; in CVS Health, the end date was 31 March 2022 for all IISs. During the study period, only BNT162b2 was authorized for use in children aged less than 18 years, so this study only evaluated BNT162b2.

BNT162b2 was authorized in age-specific stages, as shown in Table 2. Children were only eligible to be included in the study during calendar periods when BNT162b2 was authorized for their age group (e.g., a 13-year-old child could not be included in the vaccinated group or selected as an unvaccinated comparator before 10 May 2021, because BNT162b2 was only authorized for those aged ≥ 16 years at that time).

Table 2. Authorized Age Ranges for BNT162b2 in the United States During the Study Period, 11 December 2020–31 May 2022

Calendar period	Age range
11 December 2020 through 9 May 2021	≥ 16 years
10 May 2021 through 28 October 2021	≥ 12 years
29 October 2021 to end of study	≥ 5 years

FDA = Food and Drug Administration; US = United States.
Source: US FDA.[10]

3.3 Study Populations

This observational cohort study described and compared the risk of medically and hospital/ED-diagnosed COVID-19 outcomes among children aged 5 to 17 years vaccinated with a primary series of BNT162b2 and those who had not received any COVID-19 vaccine on a matched calendar date.

3.3.1 Cohort Entry

Vaccinated children were identified at their first recorded receipt of a COVID-19 vaccine during the study period. Children were considered for inclusion in the vaccinated or unvaccinated group during any calendar time period for which their age group was authorized to be vaccinated with BNT162b2. The date of a child's first observed BNT162b2 dose became their Time 0 in the vaccinated group (Figure 1). The evaluation of eligibility criteria, covariate assessment, and the beginning of follow-up in both the vaccinated and comparator groups were all aligned on the same date (Time 0), thus avoiding selection bias and immortal-time bias.[11-14] Unvaccinated children who met the study eligibility criteria were 1-to-1 exact matched, with replacement, to the vaccinated children, on the following characteristics:

- Calendar date
- Age, in years, in categories corresponding to the tiered authorizations (16–17 years, 12–15 years, 5–11 years)
- Sex
- County and state of residence
- Immunocompromised status
- Pregnancy status
- History of COVID-19 diagnosis

- Presence of at least 1 of the conditions identified by CDC[15] as increasing individuals' risk of severe COVID-19 (Section 3.4.3), indicating potential prioritization for primary vaccine series receipt
- Influenza vaccination receipt in previous year

The calendar date of Time 0 for the vaccinated child became the Time 0 for the matched unvaccinated comparator child who was matched on that calendar date (Figure 1).

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

Figure 1. Schematic for Assessing Eligibility, Covariates, and COVID-19 Outcomes Among BNT162b2-Vaccinated Children and Matched Unvaccinated Comparators

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

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

[a] Matching characteristics included calendar date, age group (5–11, 12–15, 16–17 years), sex, county of residence, immunocompromised status, pregnancy status, previous COVID-19 diagnosis, having a comorbidity increasing the risk of severe COVID-19,[15] and influenza vaccine receipt in the previous year.

[b] Gaps in medical and pharmacy coverage < 32 days permitted.
[c] 11 December 2020, ages ≥ 16 years; 10 May 2021, ages ≥ 12 years, 29 October 2021, ages ≥ 5 years.
[d] Hospitalization or LTC residence at Time 0.
[e] COVID-19 monoclonal antibodies or convalescent plasma.
[f] Diagnoses of general acute symptoms (fever, nausea/vomiting, rash) and healthcare utilization (hospitalization, ED visit) serving as an indicator of health status at the time of vaccination.
[g] Number of hospitalizations, number of ED visits, skilled nursing facility stay, influenza vaccination, pneumococcal vaccination, encounter for cancer screening, eye examination, colonoscopy, bone mineral density test, well-check/well-child preventive healthcare visit, arthritis, lipid abnormality, ambulance use/life support service, weakness, pregnancy completion before Time 0.
[h] Autoimmune disorders, cancer, chronic kidney disease or renal disease, chronic liver disease, chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary embolism), dementia or other neurological conditions, diabetes mellitus type 1 or 2, Down syndrome, heart conditions (e.g., heart failure, coronary artery disease, arrhythmias), hypertension, immunocompromised status, mental health conditions, obese or severely obese, sickle cell disease or thalassemia, stroke or cerebrovascular disease, tuberculosis, COVID-19 laboratory test performed (binary indicator of any test performed or none), COVID-19 diagnoses.
[i] 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).

3.3.1.1 Eligibility Criteria

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

- Continuous enrollment in the participating insurance plan for at least 365 days before Time 0 or since the first date of COVID-19 vaccine authorization in the US for each age group, whichever was earlier (i.e., 11 December 2020 for children aged ≥ 16 years, 10 May 2021 for children aged 12–15 years, and 29 October 2021 for children aged 5–11 years). The purpose of this requirement was to characterize individual characteristics and ensure observation of all possible COVID-19 doses to accurately evaluate COVID-19 vaccination status (i.e., some children may have been required to have more than 365 days of coverage to ensure observation of the first dose, but all must have had at least 365 days).
    - Enrollment in plans with both medical and pharmacy coverage was required.
    - Gaps in coverage of fewer than 32 days were permitted for continuous enrollment.

To align the health statuses of vaccinated and unvaccinated groups and control for confounding, vaccinated and unvaccinated children were excluded for any of the following criteria:

- Having received a dose of any COVID-19 vaccine brand before Time 0 (or on Time 0, for the unvaccinated comparison group).
- Being aged outside the brand-authorized age range on the calendar date of Time 0 (Table 2).
- Having an unclassifiable brand of Dose 1 (i.e., having a brand-unspecified claim for Dose 1, or claims for multiple brands on or within 3 days, Section 3.4.1.1).
- Residing in a geographic region outside the catchment area of the IIS and claims data.
- Having claims for monoclonal antibody treatment or convalescent plasma treatment for COVID-19 within the 90 days before Time 0, as individuals receiving these treatments were not recommended for COVID-19 vaccination.[16]
- Having a diagnosis of COVID-19 in any setting in the 30 days before Time 0. Children 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.[16] Thus, only a short washout window was required to differentiate new-onset cases during follow-up from continuing care for cases occurring before Time 0.

- Being hospitalized on the date of Time 0, as unvaccinated children with active illness were unlikely to be considered candidates for vaccination.
- Residing in a long-term care (LTC) facility on the date of Time 0, as factors affecting COVID-19 exposure and COVID-19 vaccination within LTC centers were highly variable and highly correlated within given LTC facilities.
- Having any of the following healthcare interactions occurring in the 3 days before Time 0, as these may be indicators of conditions or health states 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 (i.e., fever, nausea/vomiting, rash)
    - Hospitalization
    - ED visit

3.3.1.2 Follow-up

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

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

3.4 Variables and Definitions

3.4.1 COVID-19 Vaccine Exposure

3.4.1.1 COVID-19 Vaccine Dose Identification

Vaccine doses were identified in the claims and IIS databases. In the claims data, vaccines were identified in any care setting using procedure codes (*Current Procedural Terminology* [CPT®] or Healthcare Common Procedure Coding System [HCPCS]) for vaccine administration or National Drug Codes (NDC) for vaccine products.[17] Vaccine doses were also identified in collaborating IIS databases using Vaccine Administered (CVX) codes. Deduplication of individuals' vaccination records in both the IIS data and claims sources was performed because of the possibility for a single vaccination event to result in multiple claims and/or records. A record for a COVID-19 vaccine of the same brand or an unbranded COVID-19 vaccine record within the 3 days after a previous record was considered a duplicate and was ignored. If there were records for different COVID-19 brands on the same day, or if a vaccine record for

a different vaccine brand occurred within 3 days after a previous record, the first-occurring record was considered as a mixed or unclassifiable dose, and the later dose was ignored.

Some, but not all, vaccine record types indicate the dose number (e.g., Dose 1, Dose 2, additional dose, booster). Thus, the dose number was inferred from the order of observed doses within an individual's record; therefore, continuous enrollment for the entire period since the introduction of COVID-19 vaccines was required (or since the introduction of COVID-19 in specific age groups or populations). *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. Because of the inability to categorize the brand and vaccine exposure patterns of those with brand-unspecified vaccine codes, these codes were not used to define patient exposure status but were used for exclusion criteria to indicate history of vaccination or as censoring criteria if they did not occur concurrently with a brand-specific code.

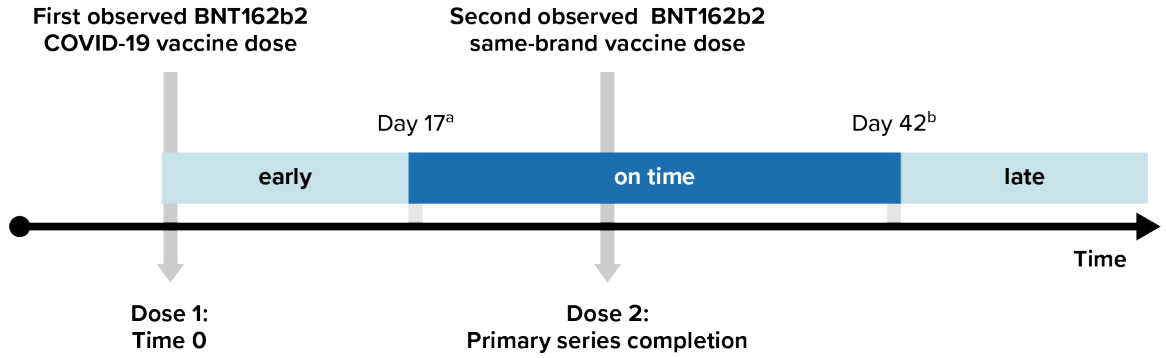
3.4.1.2 COVID-19 Vaccine Exposure Pattern Definition

All subsequent COVID-19 vaccines received by an individual after Time 0 during follow-up were identified to evaluate continuing compliance with the following patterns of vaccination receipt ("vaccine exposure patterns") assigned at Time 0:

- Receiving a complete primary series of BNT1262 (Table 3)
- Being unvaccinated (Table 3)

Vaccine exposure patterns were defined based on receipt, brand, and timing of subsequent doses after Time 0. Receiving a complete primary series required children to receive the authorized number of doses with appropriate spacing between doses without receiving extra doses or doses of a different brand (Figure 2). Although the 2-dose BNT162b2 series is recommended with spacing of 21 days, this study allowed a 42-day (inclusive) maximum time period to complete the primary series while still being considered adherent to allow for variation in real-world patterns of dose receipt, consistent with US CDC recommendations for COVID-19 vaccine administration deviations.[18] CDC recommendations also stated that receiving a second dose sooner than 4 days before the recommended interval was an invalid dose[18]; thus, children receiving a second dose of BNT162b2 sooner than day 17 (4 days before the recommended interval) were considered nonadherent to receiving the primary series and were censored. Eligible children were followed from the date of Time 0 (Dose 1 or matched unvaccinated date) and were censored when their vaccine receipt became inconsistent with receiving a complete primary series, either by failing to receive a second dose on time, receiving a second dose too early, receiving a vaccine of a different brand, or receiving another dose beyond the primary series. In the unvaccinated comparison group, children were censored if they received any COVID-19 vaccine. Complete details of these vaccine exposure patterns are given in Table 3.

Figure 2. Patterns of Primary Series Completion



COVID-19 = coronavirus disease 2019.
[a] 4 days before the recommended 21-day interval for BNT162b2.
[b] 6 weeks after Dose 1.

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

Vaccine exposure pattern	Included children	Time 0 (beginning of follow-up)	Deviation from vaccine exposure pattern after Time 0 resulting in censoring
BNT162b2 complete primary series	All eligible children receiving Dose 1 of BNT162b2	Date of Dose 1 of BNT162b2	• Receipt of Dose 2 of BNT162b2 < 17 days after Dose 1 • Failure to receive Dose 2 of BNT162b2 by day 42[a] • Receipt of any other COVID-19 vaccine brand or unspecified brand • Receipt of a third dose
Unvaccinated	Matched eligible unvaccinated comparator children	Matched calendar date	• Receipt of any COVID-19 vaccine dose

COVID-19 = coronavirus disease 2019.
[a] 42 days (i.e., 6 weeks) was considered the maximum allowable time period for receiving Dose 2 while remaining adherent to the primary series. Those who failed to receive Dose 2 by day 42 were censored.

3.4.2 COVID-19 Outcome Assessment

COVID-19 outcomes were identified in inpatient, ED, outpatient, or physician billing claims data using ICD-10-CM diagnosis codes for COVID-19 (ICD-10-CM code U07.1) in any billing position. To evaluate the vaccines' effectiveness against both milder and more severe COVID-19 cases, the study separately considered 2 sets of nested, non–mutually exclusive COVID-19 outcomes, as follows:

- Medically diagnosed COVID-19, identified as the first 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 was the outcome date.
- Hospital/ED-diagnosed COVID-19, identified as the first 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 was the outcome date.

Validation studies of the ICD-10-CM diagnosis code for COVID-19 have demonstrated reasonably good validity (positive predictive value estimates generally > 80%, and specificity estimates > 98%), with higher validity for hospitalized COVID-19 than for nonhospitalized settings.[19-23]

3.4.3 Covariates

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

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

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

Healthcare utilization and data on use of preventive healthcare services were collected to account for healthcare-seeking behavior, which may be associated with adherence to preventive recommendations (such as vaccination) and other behaviors resulting in better health outcomes.[24-26] The following individual characteristics were defined as binary indicators (unless otherwise noted), using the 365 days before and not including Time 0 (unless otherwise noted) to evaluate health status, access to healthcare, healthcare-seeking behavior, and indicators of frailty[27,28]:

- Hospitalizations (0, 1, ≥ 2)
- ED visits (0, 1, ≥ 2)
- Skilled nursing facility stay
- Influenza vaccination
- Pneumococcal vaccination
- Encounter for cancer screening
- Eye examination
- Colonoscopy
- Bone mineral density test
- Well-check/well-child preventive healthcare visit
- Arthritis[27]
- Lipid abnormality[27]
- Ambulance use or life support services[27]
- Weakness[27]
- Pregnancy completion before Time 0 (to differentiate from active pregnancy at Time 0)

Comorbidities increasing an individual's risk of severe COVID-19 were identified individually to account for differences between exposure groups. The following conditions have been identified as potentially putting individuals at higher risk of severe COVID-19[15] and may serve as indicators of eligibility or prioritization for vaccination. Additionally, an overall binary indicator of history of any of these conditions was defined using all available baseline data to identify children who may qualify for priority groups for vaccination:

- Autoimmune disorders
- Cancer[29,30]
- Chronic kidney disease or renal disease[29,30]
- Chronic liver disease[29,30]
- Chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, pulmonary embolism)[30]
- Dementia[27,29,30] or other neurological conditions
- Diabetes mellitus, type 1 or 2
- Down syndrome
- Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)[29,30]
- Hypertension[30]
- Immunocompromised status, defined as either of the following: (1) at least 2 diagnostic codes for HIV, hematological malignancy, immune deficiencies, solid malignancy, or rheumatological/inflammatory condition; or (2) at least 1 claim containing evidence an organ transplant in the 6 months prior to but not including Time 0
- Mental health conditions[27,30]
- Obese or severely obese[31]
- Sickle cell disease or thalassemia
- Stroke or cerebrovascular disease[29]
- Tuberculosis

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

- COVID-19 laboratory test performed (binary indicator of any test performed; test results not available)
- COVID-19 diagnoses occurring outside of a hospital or ED setting
- Hospital/ED-diagnosed COVID-19

3.5 Statistical Analysis

This analysis evaluated the effectiveness of the BNT162b2 vaccine among children aged 5 to 17 years compared with being unvaccinated. All analyses were performed separately in each data source, and then meta-analyzed. The analyses were guided by the protocol[4] and pediatric-specific protocol addendum.[5] The protocol describes a series of feasibility analyses, which were performed on the overall

study populations, and the results will be reported elsewhere, but several aspects of the analysis were informed by the results of the protocol-specified feasibility analyses.

3.5.1 Descriptive Analyses

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

The distribution of individual characteristics by vaccine exposure groups was described. Continuous variables were described with means, standard deviations (SDs), medians, and first and third quartiles (Q1, Q3). Distributions of categorical variables were described with counts and proportions. The balance of covariates between exposure groups was evaluated with absolute standardized differences (ASDs).[32]

3.5.2 Propensity Score Approach

Within each cohort, differences in the distribution of baseline characteristics were addressed via stabilized inverse probability of treatment (sIPT) weighting propensity score methods. The predicted probability of vaccine exposure (i.e., the propensity score) was estimated via a logistic regression model with the matching factors[33] and the remaining identified baseline characteristics as independent variables (Figure 3). An interaction term between a variant era indicator and the most imbalanced covariate after exact matching was included in the propensity score model. The distributions of the propensity scores by vaccine exposure group were plotted to visualize the degree of overlap between the vaccine exposure groups. To reduce the effect of potentially extreme weights, the propensity score was used to compute sIPT weights[34] that were applied to the analytic cohorts with truncation below the first percentile and above the 99th percentile of the propensity score distribution. The distribution of baseline characteristics before and after IPT weighting were evaluated and compared with ASDs.

3.5.3 Overall Vaccine Effectiveness

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

Children were followed from Time 0 until censoring (Section 3.3.1.2) or until the occurrence of the COVID-19 outcome of interest. The cumulative incidence of each COVID-19 outcome was estimated in each IPT-weighted vaccine exposure group as 1 minus the Kaplan-Meier estimator.[35] Cumulative incidence curves were plotted for the whole study period by vaccine exposure group.

As an overall summary of the relative incidence of COVID-19 outcomes in the vaccinated and unvaccinated groups across the entire study period, a hazard ratio (HR) and 95% CIs for each outcome was estimated using an IPT-weighted Cox proportional hazards model with robust sandwich variance estimators. The overall VE was estimated as 1 minus the HR.

3.5.4 Subgroup Analyses

3.5.4.1 Vaccine Effectiveness by Variant-specific Eras

To evaluate potential changes in VE over time due to circulating variants, the cumulative incidence and VE estimation were estimated separately within variant-specific eras, as follows:

- Pre-Delta era: children with Time 0 on or before 31 May 2021, with follow-up censored on 31 May 2021
- Delta era: children with Time 0 on or after 1 June 2021, with follow-up censored on 24 December 2021
- Omicron era: children with Time 0 on or after 25 December 2021, with follow-up censored at the end of data availability

These analyses were performed by restricting to children with Time 0 in each era, and the overall propensity scores and sIPT weights from the primary analyses were used. Era-specific HRs and 95% CIs with corresponding VE were estimated by censoring at the end of each era.

3.5.4.2 Vaccine Effectiveness by Age Group

To evaluate potential differences in VE among different age subgroups, the HRs and VEs were estimated in subgroups of age at Time 0, corresponding to age group–specific authorizations for BNT162b2 (Table 2), as follows:

- Aged 16–17 years
- Aged 12–15 years
- Aged 5–11 years

Within each age group, the overall propensity scores and sIPT weights from the primary analyses were used, and a separate Cox proportional hazards model was run. As both BNT162b2 authorizations for age groups and predominant circulating variants varied over time, the distribution of person-time in each variant era was described by age subgroup to provide additional context for age group estimates.

3.5.5 Additional Analyses

3.5.5.1 Negative Outcome Control

COVID-19 outcomes occurring within 14 days of Time 0 (Time 0 to day 13) were used as a negative control outcome to evaluate residual bias, as the biologic effect of vaccination would not be expected until 10 to 14 days after vaccination. The cumulative incidence of both COVID-19 outcomes during the first 14 days after (and including) Time 0 was visually inspected, and the HR and 95% CI were estimated with only 14 days of follow-up (from day 0 to day 13). To examine the negative control period more granularly in post-hoc analyses, the HRs were separately estimated in the first and second weeks of the period (days 0 to 6, and days 7 to 13). Additionally, the frequencies of procedure codes for COVID-19 laboratory testing on each day of the negative control period were evaluated by exposure group overall, and in those experiencing a COVID-19 outcome.

3.5.5.2 Quantitative Bias Analysis for Exposure Misclassification

Although vaccinations were identified in both insurance claims data and IIS data,[6] the possibility for missing vaccine information remained. Quantitative bias analyses[36,37] were performed to estimate the impact of truly vaccinated children being misclassified as unvaccinated because of missing vaccine records. No gold standard for vaccine status is available, so age-standardized estimates of statewide receipt of at least 1 COVID-19 vaccine dose among individuals aged younger than 65 years from CDC, state departments of health, and capture-recapture methods[9,38,39] were obtained at dates that matched the last date of service in the IIS data and compared with observed state-level estimates in the linked data sources[6] to estimate minimum and maximum potential sensitivities of vaccine exposure.

A simple quantitative bias analysis evaluating the impact of non-differential exposure misclassification analysis was performed, using both the minimum and maximum potential vaccine exposure sensitivities. The primary analyses estimated HRs, but for the purposes of the quantitative bias analyses, risk ratios (RRs) and 95% CIs were estimated in the weighted cohorts using a fixed 61-day follow-up time for both outcomes.

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

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

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

3.5.5.3 Sensitivity Analyses

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

3.5.5.3.1 Delayed Censoring After Vaccination

To account for potential informative censoring, we delayed censoring to occur 7 days after receipt of a censoring vaccine dose (e.g., children in the unvaccinated group receiving any vaccine, or children in the vaccinated group receiving Dose 2 too early, or receiving a third dose) instead of censoring on the day of receipt of the vaccine dose, as there would not be an expected effect of the new dose during this extended time after vaccination.

3.5.5.3.2 COVID-19 Diagnoses on the Same Day as the COVID-19 Vaccination

To address potential misclassification of COVID-19 diagnoses occurring on the same day as a COVID-19 vaccination is received (e.g., the COVID-19 diagnoses being recorded to justify need for vaccination

rather than occurrence of COVID-19 disease, or potentially recording a history of COVID-19), the following 2 sensitivity analyses were performed:

- Time 0 (i.e., the day of vaccination or matched index date) was excluded from follow-up, and follow-up began the day after vaccination.
- The end-of-follow-up criteria were reordered, so that if an individual had a COVID-19 diagnosis and a censoring COVID-19 vaccination dose occurring on the same day in follow-up, the individual would be censored on that day rather than having an outcome on that day.

3.5.6 Meta-analysis of Database-specific Results

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

4 Results

4.1 Descriptive Analyses

In the final, matched cohorts across both data sources, we identified 460,473 eligible children aged 5 through 17 years who received at least 1 dose of BNT162b2 during the study period. After matching, 453,655 vaccinated children and an equal number of unvaccinated comparators were retained. In Optum, 95,161 eligible vaccinated children were identified. After matching, 97% of vaccinated children in Optum were exact matched to an unvaccinated individual, and the pediatric analytic cohort included 92,338 vaccinated children and 92,338 unvaccinated comparators. In CVS Health, we identified 365,312 eligible vaccinated children; of these, 99% were exact matched to an unvaccinated individual, resulting in an analytic cohort of 361,317 in each exposure group. The details of the cohort attrition by application of eligibility criteria are shown in Figure B-1-Optum and Figure B-1-CVS.

Selected characteristics of the pediatric cohorts are shown by data source and vaccine exposure group in Table 4. Complete characteristics of this group are shown in Table B-1-Optum and Table B-1-CVS. Characteristics of vaccinated children who were excluded because of a failure to match are shown in Table B-2-Optum and Table B-2-CVS.

Table 4. Selected Matching Characteristics of Children Aged 5–17 Years Vaccinated With a COVID-19 Vaccine and Matched Unvaccinated Children

Characteristic	Optum, children vaccinated with BNT162b2 N = 92,338	Optum, matched unvaccinated children N = 92,338	Optum, ASD	CVS Health, children vaccinated with BNT162b2 N = 361,317	CVS Health, matched unvaccinated children N = 361,317	CVS Health, ASD
Age, years						
Median (Q1, Q3)	13 (9, 15)	13 (9, 15)		12 (9, 15)	12 (9, 15)	
Mean (SD)	12.11 (3.60)	12.08 (3.64)	0.01	11.76 (3.66)	11.71 (3.72)	0.01
Sex, N (%)						
Female	45,822 (49.62%)	45,822 (49.62%)	0.00	179,901 (49.79%)	179,901 (49.79%)	0.00
Male	46,516 (50.38%)	46,516 (50.38%)	0.00	181,416 (50.21%)	181,416 (50.21%)	0.00
Region, N (%)						
Northeast	13,051 (14.13%)	13,051 (14.13%)	0.00	64,684 (17.90%)	64,684 (17.90%)	0.00
South	12,959 (14.03%)	12,959 (14.03%)	0.00	69,202 (19.15%)	69,202 (19.15%)	0.00
Midwest	43,572 (47.19%)	43,572 (47.19%)	0.00	75,498 (20.90%)	75,498 (20.90%)	0.00
West	22,756 (24.64%)	22,756 (24.64%)	0.00	151,933 (42.05%)	151,933 (42.05%)	0.00
Characteristics in the 365 days before Time 0, N (%)						
Influenza vaccination	47,759 (51.72%)	47,759 (51.72%)	0.00	187,076 (51.78%)	187,076 (51.78%)	0.00
Pneumococcal vaccination	87 (0.09%)	77 (0.08%)	0.00	360 (0.10%)	368 (0.10%)	0.00
Well-check/well-child preventive health care visit	63,290 (68.54%)	62,515 (67.70%)	0.02	253,176 (70.07%)	246,607 (68.25%)	0.04
Characteristics assessed using all available data at or before Time 0, N (%)						
Autoimmune disorders	1,067 (1.16%)	1,049 (1.14%)	0.00	4,273 (1.18%)	3,995 (1.11%)	0.01
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	10,086 (10.92%)	10,081 (10.92%)	0.00	43,858 (12.14%)	44,283 (12.26%)	0.00

Characteristic	Optum, children vaccinated with BNT162b2 N = 92,338	Optum, matched unvaccinated children N = 92,338	Optum, ASD	CVS Health, children vaccinated with BNT162b2 N = 361,317	CVS Health, matched unvaccinated children N = 361,317	CVS Health, ASD
Dementia or other neurological conditions	3,110 (3.37%)	3,331 (3.61%)	0.01	12,075 (3.34%)	12,542 (3.47%)	0.01
Diabetes mellitus, type 1 or 2	436 (0.47%)	416 (0.45%)	0.00	1,480 (0.41%)	1,336 (0.37%)	0.01
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	3,037 (3.29%)	3,135 (3.40%)	0.01	12,537 (3.47%)	13,118 (3.63%)	0.01
Immunocompromised state	458 (0.50%)	458 (0.50%)	0.00	1,674 (0.46%)	1,674 (0.46%)	0.00
Mental health conditions	17,813 (19.29%)	16,871 (18.27%)	0.03	63,102 (17.46%)	58,900 (16.30%)	0.03
Obese or severely obese	7,750 (8.39%)	8,138 (8.81%)	0.01	35,224 (9.75%)	37,775 (10.45%)	0.02
At least 1 COVID-19 laboratory performed	36,002 (38.99%)	32,568 (35.27%)	0.08	174,485 (48.29%)	157,714 (43.65%)	0.09
COVID-19 diagnoses occurring outside of a hospital or emergency department	2,759 (2.99%)	2,751 (2.98%)	0.00	10,878 (3.01%)	10,812 (2.99%)	0.00
Hospital or emergency department-diagnosed COVID-19	116 (0.13%)	129 (0.14%)	0.00	514 (0.14%)	643 (0.18%)	0.01

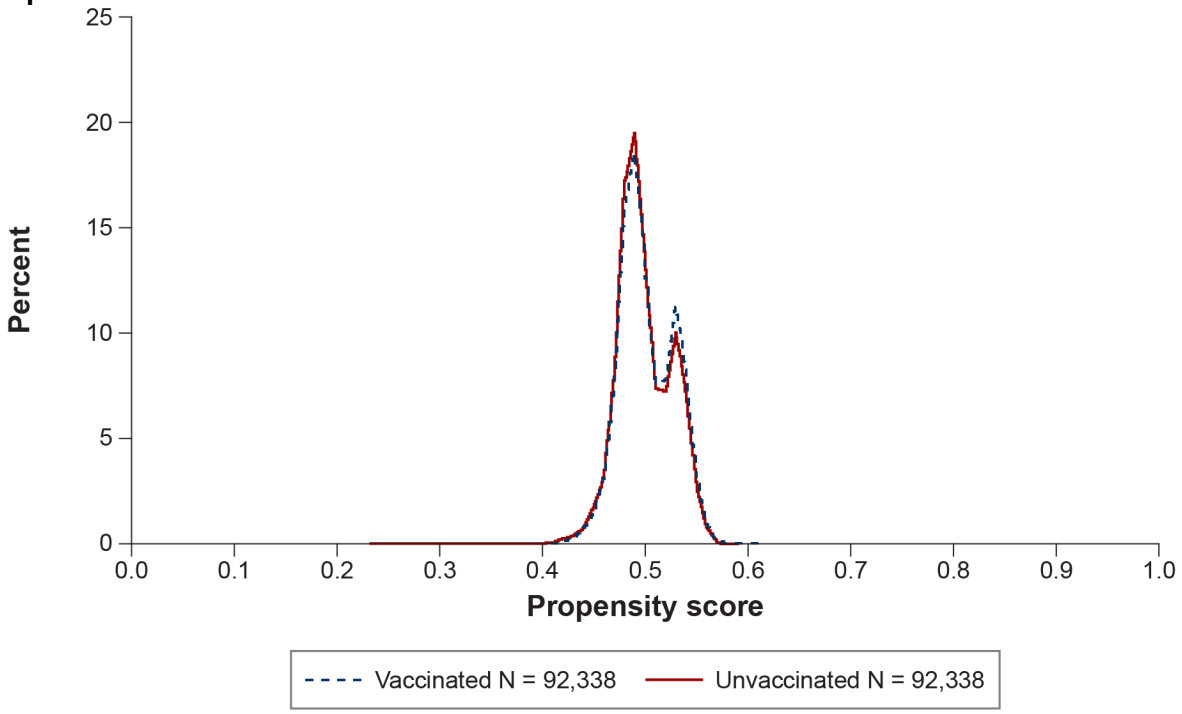
ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; Q1, Q3 = first and third quartiles; SD = standard deviation.
Source: Table B-1-Optum, Table B-1-CVS

In both data sources, the mean age in both vaccine exposure groups was approximately 12 years (SD approximately 4 years), and approximately 50% were female. The largest proportion of the Optum sample (47%) came from the US Midwest, while the largest proportion of the CVS Health sample (42%) came from the US West. Generally, this pediatric sample was relatively healthy, with most major comorbidities being very rare, except for mental health conditions (≥ 17% in both data sources), chronic lung conditions (≥ 10%), and recorded diagnoses of obesity (≥ 8%). The characteristics of the included children were very similar across both data sources; only minor differences were noted, including the following: eye examinations were more common in CVS Health than in Optum (32% vs. 22%); having a history of COVID-19 laboratory testing was less common in Optum than in CVS Health (37% vs. 46%).

In both data sources, the characteristics of the vaccinated and unvaccinated groups were very similar and well-balanced, with ASDs less than 0.1 for all measured characteristics (Table B-1-Optum, Table B-1-CVS). The distributions of the propensity scores demonstrated a high degree of overlap, suggesting comparability between the groups with regard to measured covariates (Figure 3).

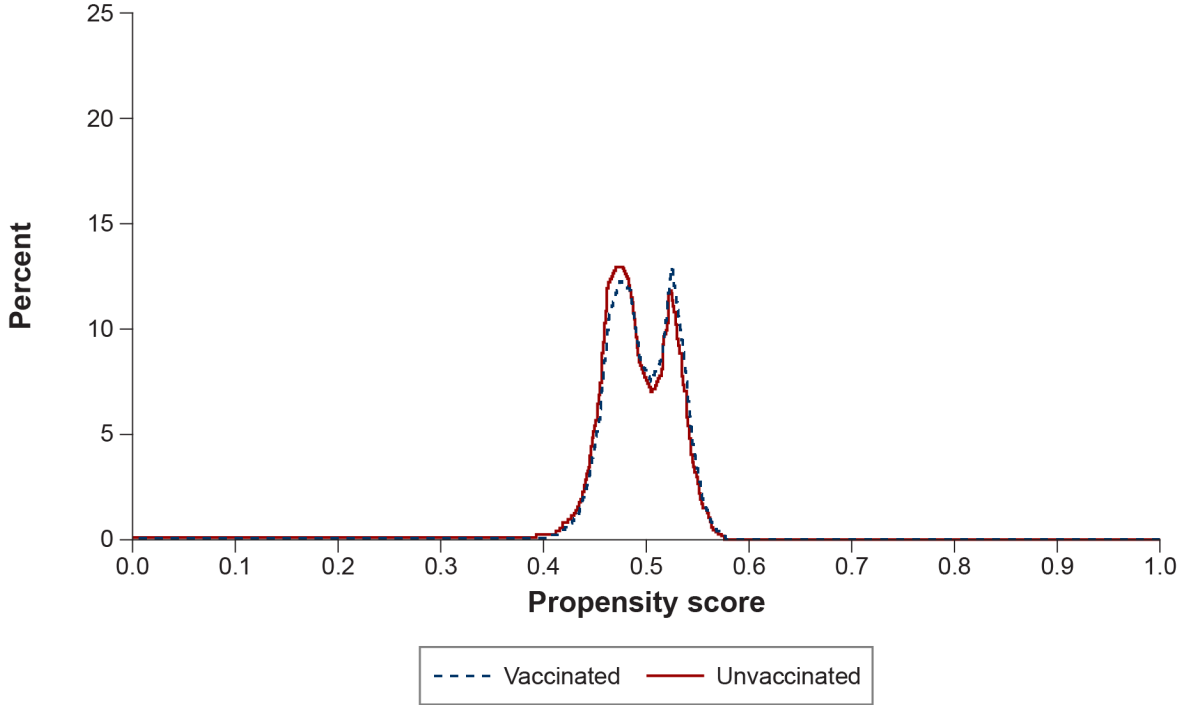
Figure 3. Propensity Score Distributions of Children Aged 5–17 Years Receiving at Least 1 Dose of BNT162b2 and Unvaccinated Comparators

A. Optum



Note: propensity score variables included the following (in binary form except where indicated otherwise): age at Time 0 (linear); sex (categorical, reference = male); state (categorical); pregnant at Time 0; hospitalizations (categorical, reference = 0); emergency department visits (categorical, reference = 0); skilled nursing facility stay; influenza vaccination; pneumococcal vaccination; encounter for cancer screening; eye examination; colonoscopy; bone mineral density test; well-check/well-child preventive healthcare visit; arthritis; lipid abnormality; ambulance use or life support services; weakness; autoimmune disorders; cancer; chronic kidney disease or renal disease; chronic liver disease; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism); dementia or other neurological conditions; diabetes mellitus, type 1 or 2; Down syndrome; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias); hypertension; immunocompromised state; mental health conditions; obese or severely obese; sickle cell disease or thalassemia; stroke or cerebrovascular disease; tuberculosis; ≥ 1 COVID-19 laboratory test performed; COVID-19 diagnosis in any setting; Delta or Omicron variant era; having ≥ 1 condition increasing risk of COVID-19; Delta/Omicron variant era * ≥ 1 COVID-19 laboratory test performed during baseline (interaction term).

B. CVS Health



Note: propensity score variables included the following (in binary form except where indicated otherwise): age (categorical, reference = 5–11 years); ambulance use of life support services; arthritis; autoimmune disorders; bone mineral density test; cancer; encounter for cancer screening; chronic kidney disease or renal disease; chronic liver disease; colonoscopy; chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism); pregnant at Time 0; COVID-19 diagnoses in any setting; hospital or emergency department–diagnosed COVID-19; ≥ 1 COVID-19 laboratory performed; COVID-19 diagnoses occurring outside of hospital or emergency department; COVID-19 vaccination index date in the Delta/Omicron era; diabetes mellitus, type 1 or 2; Down syndrome; emergency department visits (categorical, reference = 0); eye examination; influenza vaccination; heart conditions (e.g., heart failure, coronary artery disease, arrhythmias); ≥ 1 conditions which may qualify for priority groups for vaccination or booster dose eligibility; hypertension; hospitalizations (categorical, reference = 0); lipid abnormality; mental health conditions; dementia or other neurological conditions; obese or severely obese; pneumococcal vaccination; sex (categorical, reference = male); sickle cell disease or thalassemia; skilled nursing facility stay; state of residence (categorical); stroke or cerebrovascular disease; tuberculosis; immunocompromised state; pregnancy completion before Time 0; weakness; well-check/well-child preventive healthcare visit; Delta/Omicron variant era * ≥ 1 COVID-19 laboratory test performed during baseline (interaction term).

COVID-19 = coronavirus disease 2019.

4.2 Outcome Analyses

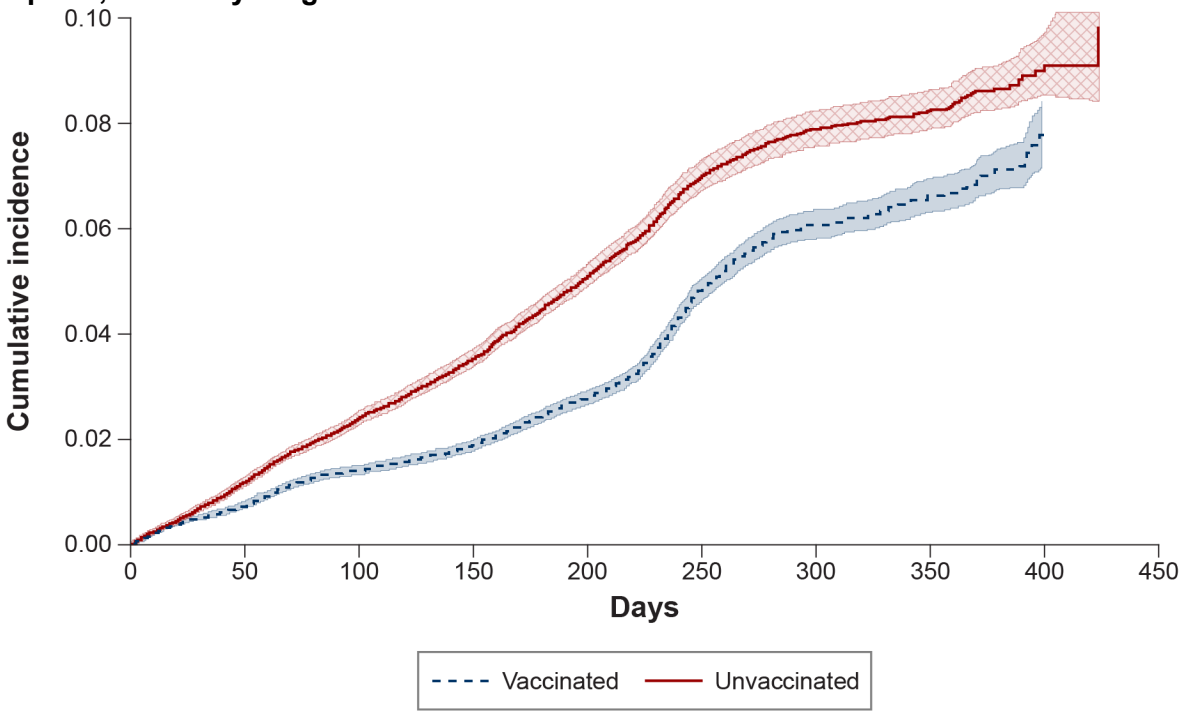
4.2.1 Outcome Incidence

The amount of follow-up time varied across data sources and analyses, but the maximum follow-up time was 529 days in Optum and 468 days in CVS Health. The median days follow-up tended to be longer for the vaccinated group in both data sources for each analysis. In Optum, the median days of follow-up (Q1, Q3) for hospital/ED-diagnosed COVID-19 was 146 (111, 251) for the vaccinated and 87 (30, 194) for the unvaccinated groups; in CVS Health, the median days of follow-up (Q1, Q3) for hospital/ED-diagnosed COVID-19 was 174 (62, 241) for the vaccinated and 87 (26, 153) for the unvaccinated groups (Table B-3-Optum, Table B-3-CVS). The cumulative incidence of COVID-19 outcomes over time by vaccination status is shown in Figure 4. Across all analyses, the number of hospital/ED-diagnosed COVID-19 cases was relatively small. As an example, in the unvaccinated group in Optum, there were 2,792 medically diagnosed COVID-19 outcomes and 186 hospital/ED-diagnosed COVID-19 events, while in the unvaccinated group CVS Health, there were 10,080 medically diagnosed COVID-19 events and 791

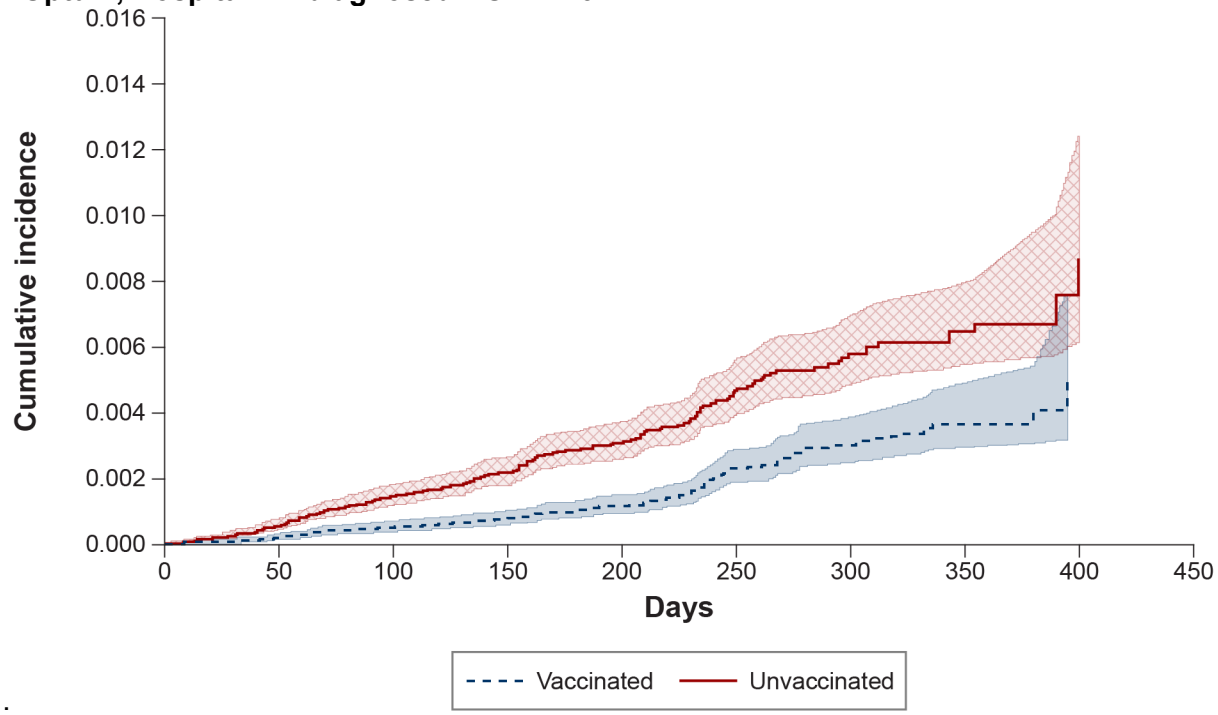
hospital/ED-diagnosed COVID-19 cases (Table B-4-Optum, Table B-4-CVS). Across all analyses in both data sources, the rates of hospital/ED-diagnosed COVID-19 cases were relatively small (Optum, 41.2 per 10,000 person-years; CVS Health, 44.1 per 10,000 person-years). For both outcomes, the risk of COVID-19 was higher in the unvaccinated than in the vaccinated group, throughout follow-up.

Figure 4. Weighted Cumulative Incidence of COVID-19 Outcomes in Children Aged 5–17 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Matched Unvaccinated Children

A. Optum, Medically Diagnosed COVID-19



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



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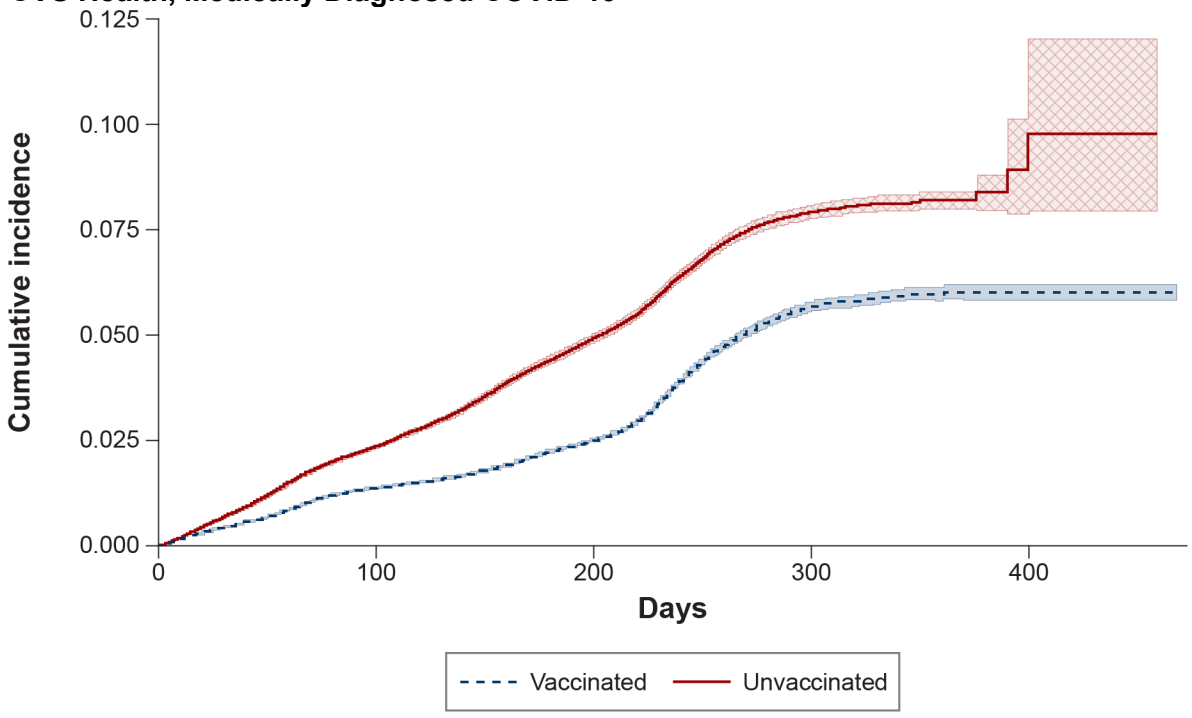
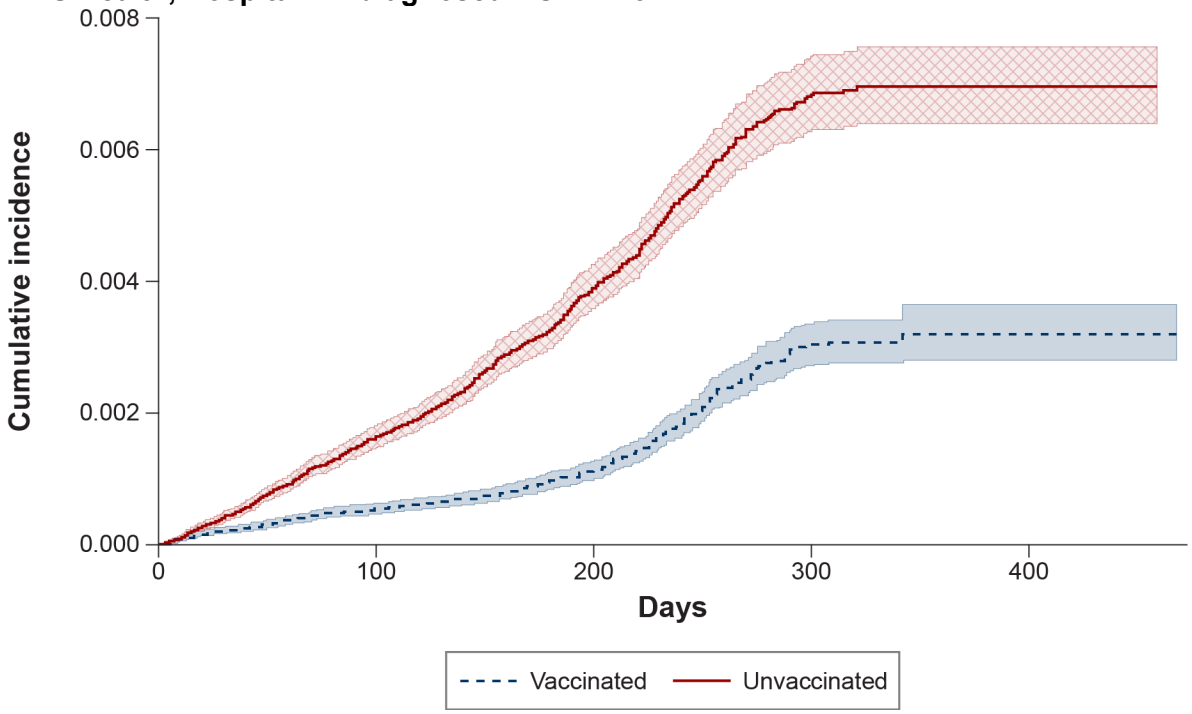
C. CVS Health, Medically Diagnosed COVID-19



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



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

4.2.2 Overall Vaccine Effectiveness

A summary of the estimated overall VE for each data source is shown in Table 5. Complete details of the estimates of the effectiveness of BNT162b2 vaccinations in children aged 5 to 17 years, overall, are shown in Table B-4-Optum and Table B-4-CVS. In both data sources, overall VE estimates across all of follow-up for any medically diagnosed COVID-19 comparing those vaccinated to unvaccinated were VE = 35% (95% CI, 31%-39%) in Optum and 39% (95% CI, 37%-41%) for CVS, with a meta-analyzed VE of 38% (95% CI, 36%-40%). For hospital/ED-diagnosed COVID-19, VE estimates were higher, with VE = 55% (95% CI, 41%-65%) in Optum and 62% (95% CI, 57%-67%) for CVS, with a meta-analyzed VE of 61% (95% CI, 56%-65%).

Table 5. Estimated Vaccine Effectiveness of a Complete Primary Series of BNT162b2 Compared With Being Unvaccinated in Children Aged 5–17 Years

Outcome	Data Source	Vaccine Exposure Group	N	Events	VE (95% CI)
Medically diagnosed	Optum	BNT162b2	92,338	2,629	35% (31%-39%)
		Unvaccinated	92,338	2,792	—
	CVS Health	BNT162b2	361,317	10,139	39% (37%-41%)
		Unvaccinated	361,317	10,080	—
	Meta-analyzed	NA	NA	NA	38% (36%-40%)
Hospital/ED-diagnosed	Optum	BNT162b2	92,338	118	55% (41%-65%)
		Unvaccinated	92,338	186	—

Outcome	Data Source	Vaccine Exposure Group	N	Events	VE (95% CI)
	CVS Health	BNT162b2	361,317	477	62% (57%-67%)
		Unvaccinated	361,317	791	—
	Meta-analyzed	NA	NA	NA	61% (56%-65%)

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; NA = not applicable; VE = vaccine effectiveness.
— indicates reference group
Source: Table B-4-Optum, Table B-4-CVS, Figure 5

4.2.3 Subgroup Analyses

A summary of the meta-analyzed VE estimates for the overall and subgroup analyses by age and variant era are given in Table 6.

Table 6. Estimated Effectiveness of BNT162b2 COVID-19 Vaccine, Overall and by Subgroup, Meta-analyzed Across Data Sources

Subgroup	COVID-19 Outcomes	Meta-analyzed VE (95% CI)	p-value[a] for heterogeneity
Overall	Medically diagnosed	38% (36%-40%)	0.08
	Hospital/ED-diagnosed	61% (56%-65%)	0.24
Age 5–11 years	Medically diagnosed	15% (11%-19%)	0.0001
	Hospital/ED-diagnosed	40% (25%-52%)	0.43
Age 12–15 years	Medically diagnosed	46% (43%-48%)	0.54
	Hospital/ED-diagnosed	64% (57%-70%)	0.09
Age 16–17 years	Medically diagnosed	51% (47%-54%)	0.61
	Hospital/ED-diagnosed	70% (62%-75%)	0.73
Pre-Delta era	Medically diagnosed	61% (52%-68%)	0.39
	Hospital/ED-diagnosed	65% (4%-87%)	0.64
Delta era	Medically diagnosed	61% (59%-64%)	0.23
	Hospital/ED-diagnosed	78% (71%-83%)	0.64
Omicron era	Medically diagnosed	9% (-1% to 19%)	0.88
	Hospital/ED-diagnosed	13% (-39% to 46%)	0.24

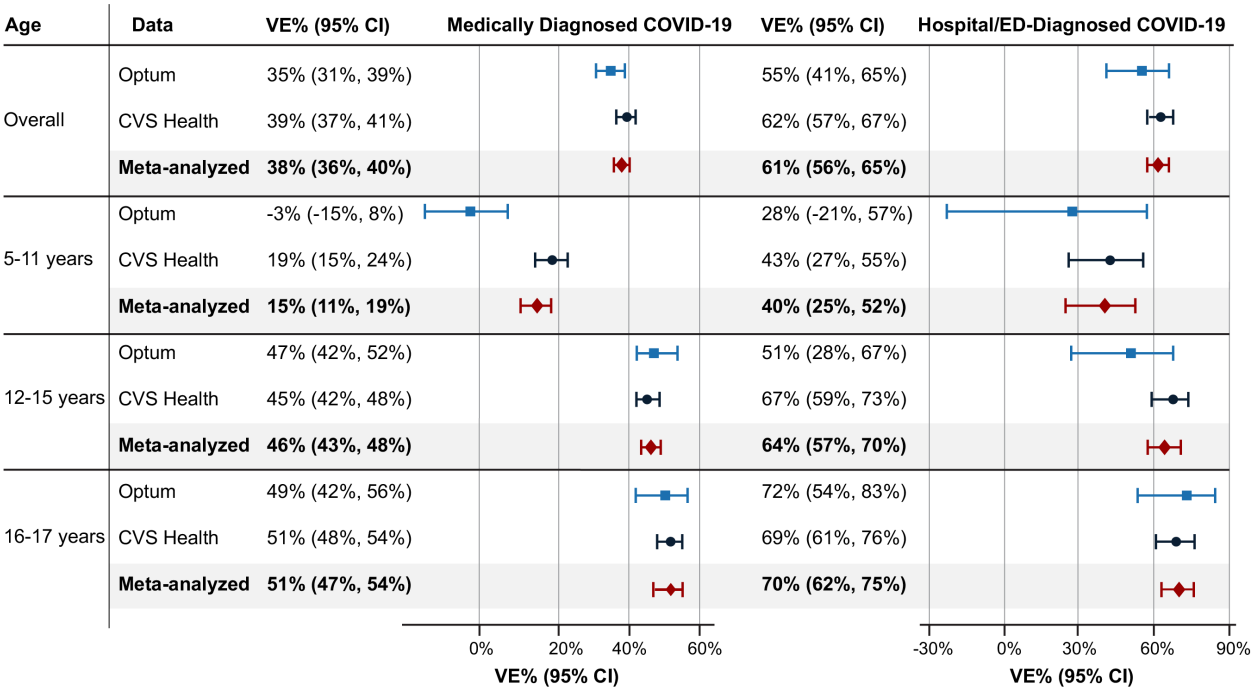
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; VE = vaccine effectiveness.
[a] *p*-values greater than 0.05 indicate a lack of statistical heterogeneity between data source–specific VE estimates.

4.2.3.1 VE by Age Subgroup

The VE estimates further evaluated by age group (ages 5–11 years, 12–15 years, 16–17 years) are shown in Figure 5 (complete details shown in Table B-6-Optum and Table B-6-CVS). When stratifying the VE estimates by age subgroup, VE estimates were always higher for hospital/ED-diagnosed COVID-19 than for medically diagnosed COVID-19, consistent with the overall analysis. However, differences were observed by age. VE estimates were generally high and similar across data sources for those aged 16 to

17 years (medically diagnosed COVID-19 meta-analyzed VE = 51% [95% CI, 47%-54%]; hospital/ED-diagnosed COVID-19 meta-analyzed VE = 70% [95% CI, 62%-75%]) and 12 to 15 years (medically diagnosed COVID-19 meta-analyzed VE = 46% [95% CI, 43%-48%]; hospital/ED-diagnosed COVID-19 meta-analyzed VE = 64% [95% CI, 57%-70%]). In both data sources, the VE estimates were lower in the 5- to 11-year-old age group; for hospital/ED-diagnosed COVID-19, the pooled VE for 5- to 11-year-olds was 40% (95% CI, 25%-52%); however, for medically diagnosed COVID-19, some heterogeneity was observed across data sources (p = 0.0001, Table 6), with an Optum VE estimate of -3% (95% CI, -15% to 8%) and a CVS Health VE estimate of 19% (95% CI, 15%-24%).

Figure 5. Vaccine Effectiveness Estimates of BNT162b2 in Children, Aged 5–17 Years, Overall and by Age Group



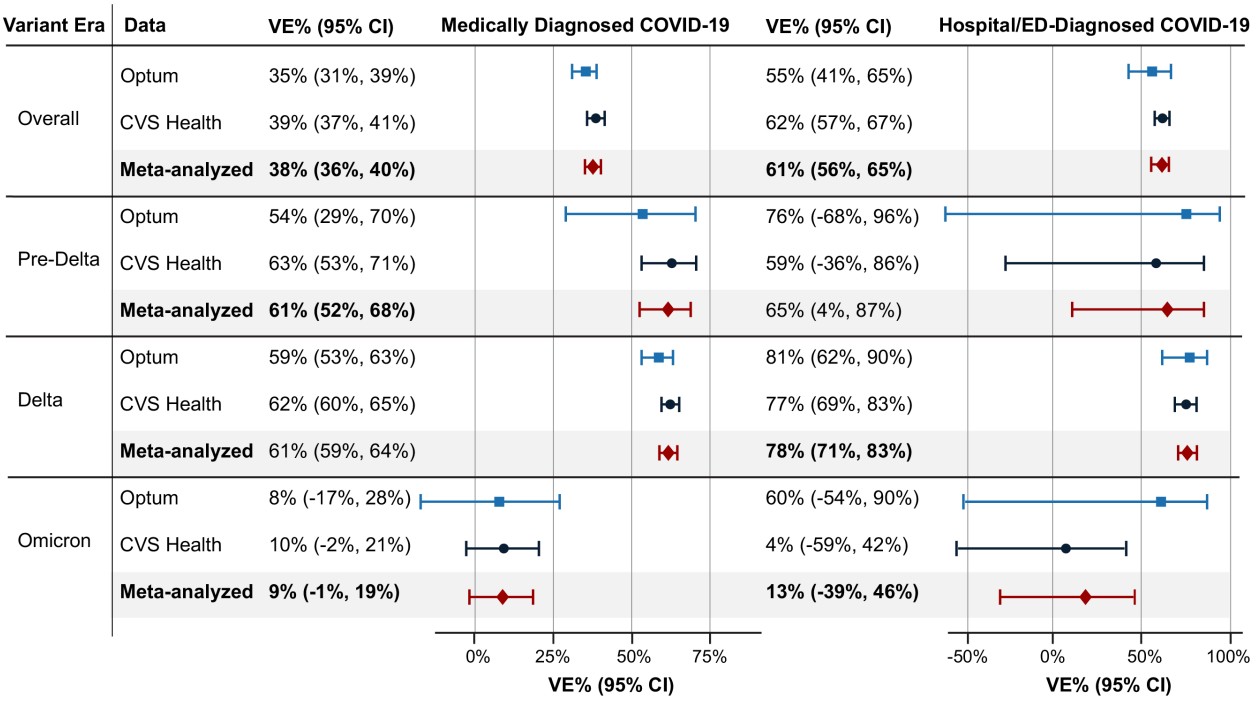
CI = confidence interval; VE = vaccine effectiveness.
Source: Table B-6-Optum, Table B-6-CVS, Table 6.

4.2.3.2 *Vaccine Effectiveness by Variant Era*

When evaluating VE by variant era, the Delta era had the largest amount of person-time available for analysis in both data sources. Variant era was strongly correlated with age group, with the largest proportion of person-time in the pre-Delta era coming from the 16- to 17-year-olds, the largest proportion of Delta era person-time coming from the 12- to 15-year-olds, and the largest portion of Omicron era person-time coming from the 5- to 11-year-olds (Table B-7-Optum, Table B-7-CVS). Cumulative incidence by variant era is shown in Figure B-4-Optum and Figure B-4-CVS. Hazard ratios and VE estimates by variant era are shown in Table B-8-Optum, Table B-8-CVS, and Figure 6. When evaluating VE by variant era, the VE estimates during the Omicron era against medically diagnosed COVID-19 (meta-analyzed VE = 9% [95% CI, -1% to 19%]) were markedly lower than the pre-Delta or Delta eras. Although there was no evidence of statistical heterogeneity between the source-specific VE estimates against hospital/ED-diagnosed COVID-19 during the Omicron era (p = 0.24), the low number of cases resulted in wide confidence intervals around the data source–specific estimates (Table 6); the

meta-analyzed VE estimate was 13% (-39% to 46%), with an Optum VE estimate of 60% (95% CI, -54% to 90%) and a CVS Health VE estimate of 4% (95% CI, -59% to 42%).

Figure 6. Vaccine Effectiveness Estimates of BNT162b2 in Children, Aged 5–17 Years, Overall and by Era of Predominant Circulating Variant



CI = confidence interval; VE = vaccine effectiveness.
Source: Table B-8-Optum, Table B-8-CVS, Table 6.

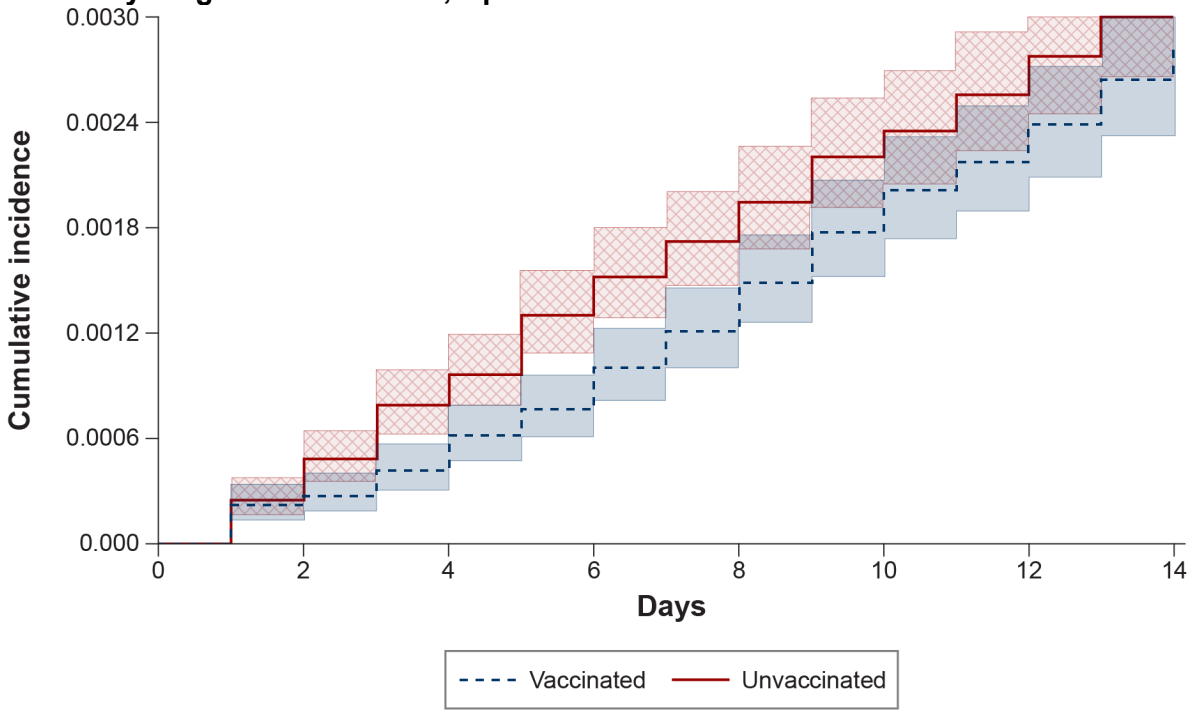
4.2.4 Additional Analyses

4.2.4.1 Negative Control Analyses

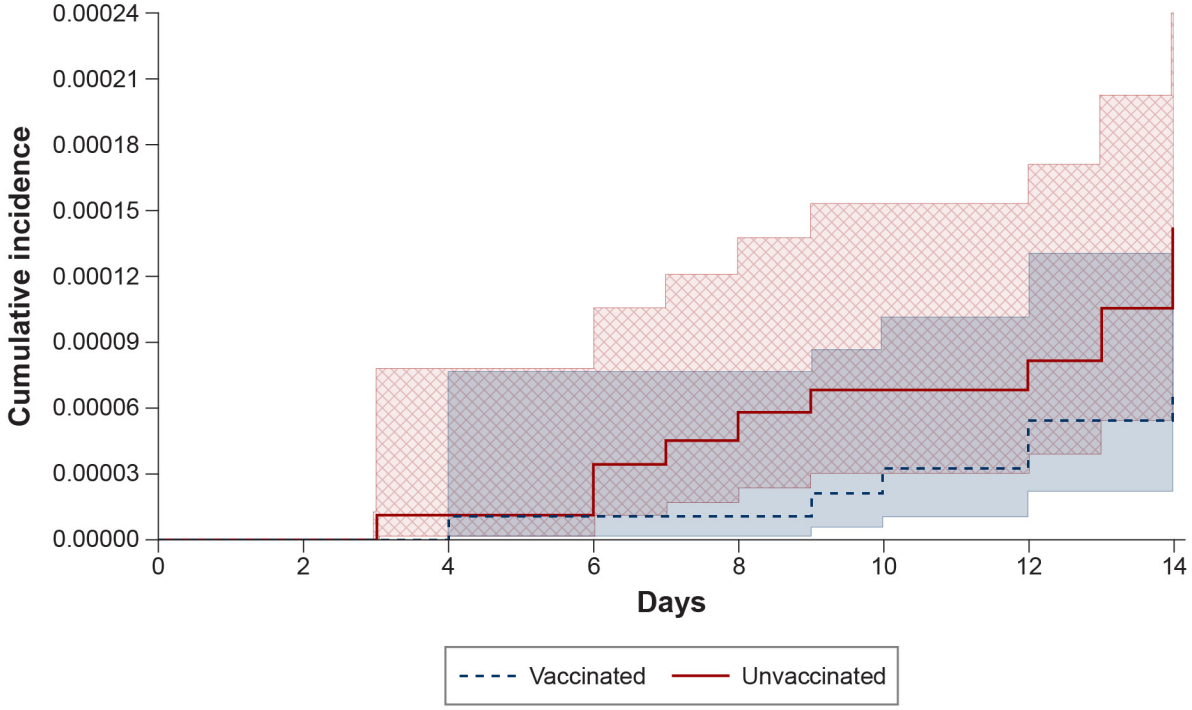
The differences between exposure groups were evaluated during the negative control period. The cumulative incidence of COVID-19 outcomes in children aged 5 to 17 years in the first 14 days following and including Time 0 is shown in Figure 7, and HRs and VEs are shown in Table B-5-Optum and Table B-5-CVS. The absolute risk of COVID-19 outcomes was very low during this period, and the absolute difference between the vaccinated and unvaccinated groups was small. However, the estimated HRs and VEs during this period indicated a non-null association of vaccination with medically diagnosed COVID-19 outcomes during this negative control period: Optum VE = 15% (95% CI, -1.7% to 28%); CVS Health VE = 25% (95% CI, 17%-32%); negative control estimates for hospital/ED-diagnosed COVID-19 were imprecise as a result of having few cases. Post hoc explorations COVID-19 diagnosis patterns over time during the negative control period suggest that incidence in the 2 groups differs primarily soon after Time 0 (as demonstrated by VE estimates above 0% in the first week of the negative control period, Table B-5-Optum), but that during the second week of the negative control period, the VE estimate is essentially null indicating no difference between the groups. Additionally, post hoc explorations of COVID-19 laboratory testing suggest that testing is more frequent in the unvaccinated group in the 3 to 4 days after Time 0 than in the vaccinated group (Figure B-2-Optum), but that testing becomes more frequent in the vaccinated group during days 4 to 13.

Figure 7. Weighted Cumulative Incidence of COVID-19 Outcomes in Children Aged 5–17 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Children, by Vaccine Exposure Group, 14 Days After and Including Time 0, Negative Control Outcome Analysis, Optum

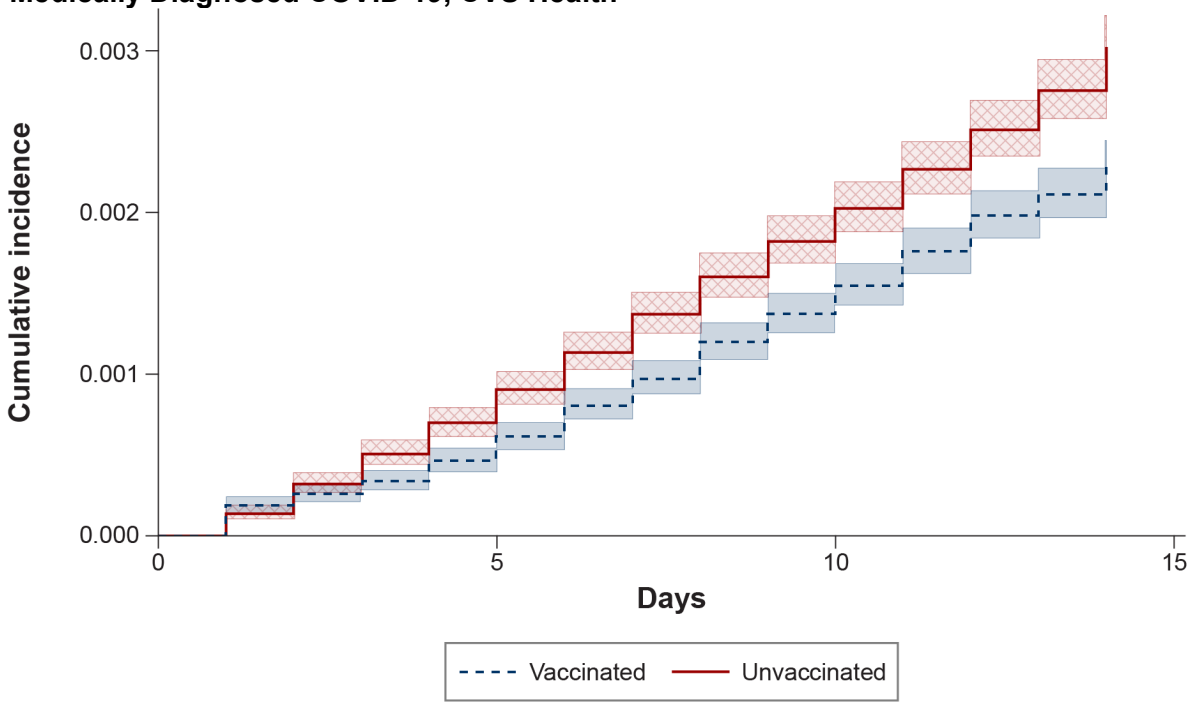
A. Medically Diagnosed COVID-19, Optum



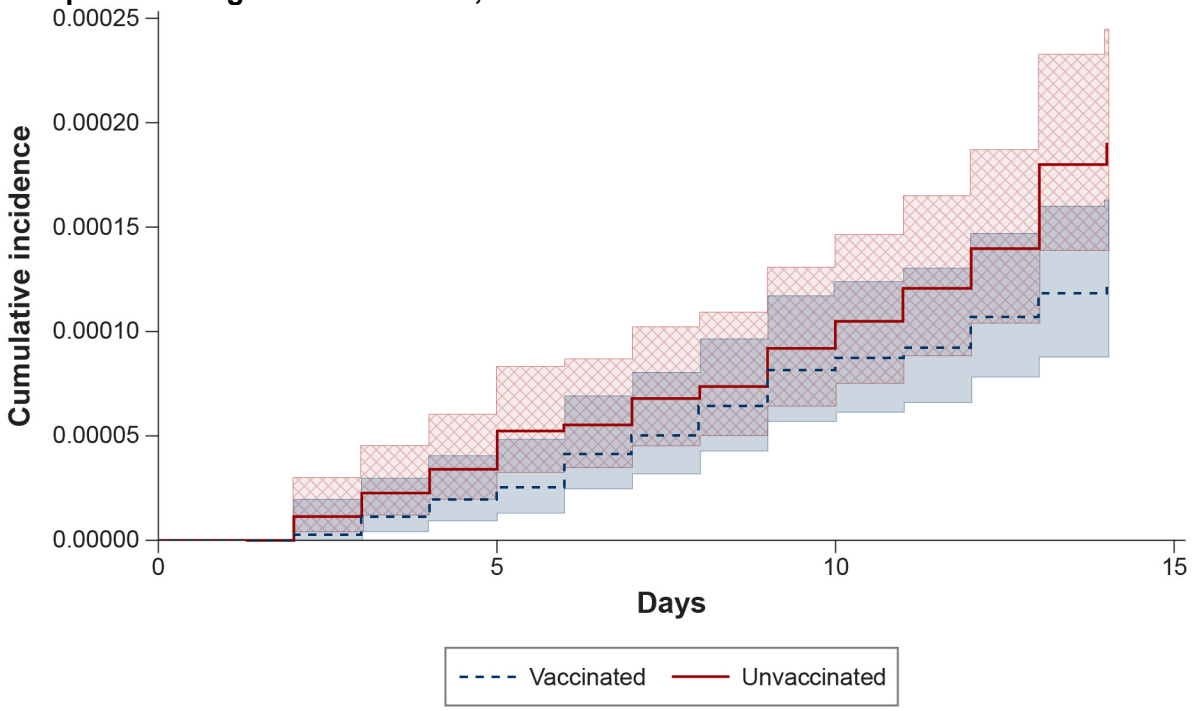
B. Hospital/ED-diagnosed COVID-19, Optum



C. Medically Diagnosed COVID-19, CVS Health



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



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

4.2.4.2 Quantitative Bias Analyses

The effect of exposure misclassification was estimated with assumed vaccine exposure classification sensitivities of 83% and 71% in Optum and 89% and 69% in CVS. The results of the quantitative bias analysis are shown in Table B-4-Optum and Table B-4-CVS and are summarized in Table 7. When considering the potential for misclassification of vaccination status, the corrected estimates VE estimates were always higher than the observed, given the assumption that some children in the

unvaccinated group may be truly vaccinated, decreasing the incidence of COVID-19 outcomes in the unvaccinated group due to misclassification. The quantitative bias analyses suggest that the observed VE estimates may underestimate the true VE by 2% to 13%, depending on the outcome.

Table 7. Estimated Vaccine Effectiveness of a Complete Primary Series of BNT162b2 in Children Aged 5–17 years, Corrected For Potentially Missing Vaccine Records

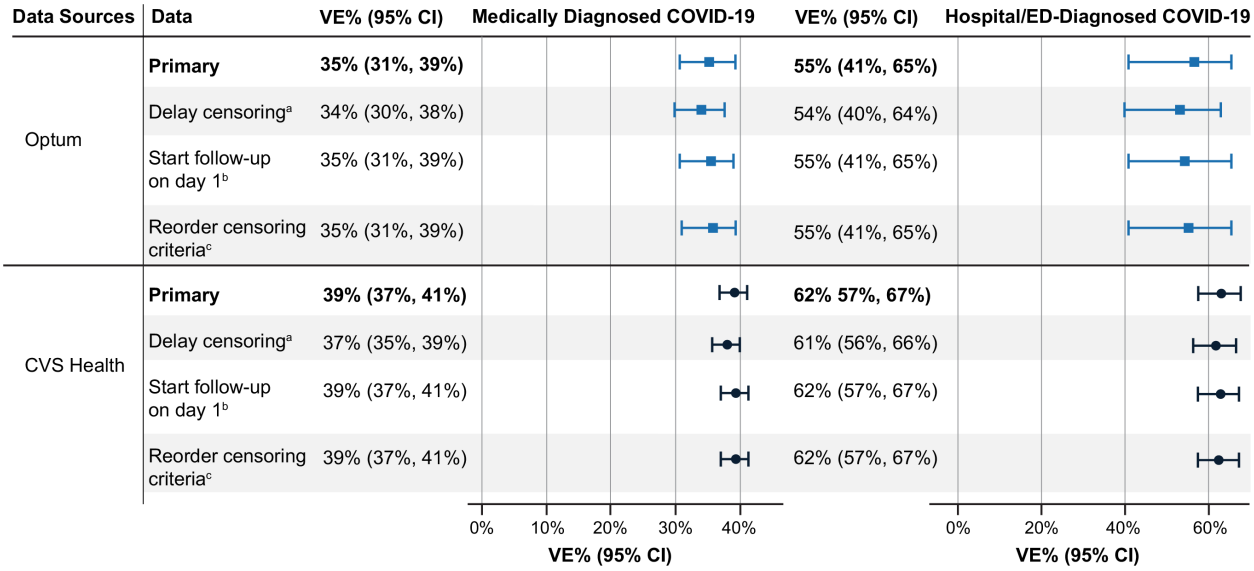
Data source	COVID-19 outcome	Hypothesized sensitivity of vaccination exposure measurement	Corrected VE (95% CI)
Optum	Medically diagnosed	100% (original, uncorrected)	35% (31%-39%)
		83%	39% (35%-43%)
		71%	45% (41%-48%)
	Hospital/ED-diagnosed	100% (original, uncorrected)	55% (41%-65%)
		83%	61% (49%-70%)
		71%	68% (58%-75%)
CVS Health	Medically diagnosed	100% (original, uncorrected)	39% (37%-41%)
		89%	41% (39%-43%)
		69%	49% (48%-51%)
	Hospital/ED-diagnosed	100% (original, uncorrected)	62% (57%-67%)
		89%	65% (60%-69%)
		69%	73% (69%-76%)

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

4.2.4.3 Sensitivity Analyses

The results of the sensitivity analysis compared with those of the overall pediatric analysis are shown in Table B-9-Optum, Figure B-3-Optum, and Table B-9-CVS and are summarized in Figure 8. All sensitivity analyses were consistent with the overall analyses.

Figure 8. Estimated Vaccine Effectiveness Estimates of BNT162b2 in Children, Aged 5–17 Years, Overall and Sensitivity Analyses



CI = confidence interval; VE = vaccine effectiveness.

Source: Table B-9-Optum, Figure B-3-Optum, Table B-9-CVS.

[a] Censoring occurred 7 days after receipt of a censoring vaccine dose (i.e., in the vaccinated group: Dose 2 received early, received Dose 2 of a different brand; received Dose 3; for unvaccinated, receipt of any dose) instead of censoring on the day of the vaccine dose.

[b] Time 0 was removed from follow-up.

[c] Censoring criteria were reordered so censoring for receipt of a censoring dose (i.e., in the vaccinated group: Dose 2 received early, received Dose 2 of a different brand; received Dose 3; for unvaccinated, receipt of any dose) was applied before identifying outcomes or other censoring criteria on each day of follow-up (e.g., if a censoring vaccine dose and an outcome occurred on the same day, the child would be censored and not have the outcome counted).

5 Discussion

5.1 Key Results and Context

This large, real-world evaluation of the effectiveness of receiving a complete, 2-dose, primary series of BNT162b2 COVID-19 vaccination in children aged 5 to 17 generally observed lower rates of medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 associated with receiving a complete primary series of BNT162b2 compared with being unvaccinated, indicating that this vaccine was effective in routine care. The observed VE estimates were generally higher for hospital/ED-diagnosed COVID-19 than for any medically diagnosed COVID-19 (consistent with other studies of pediatric COVID-19 vaccination[41,42]) across all analyses in both data sources.

Our study utilized 2 US data sources, representing commercially insured children from across the US, receiving vaccination and healthcare in a variety of treatment settings and geographic locations. The overall results and many of the age and variant subgroup results were consistent across data sources. Results from both data sources suggested lower VE in the 5- to 11-year-old age group and in the Omicron era (consistent with previous findings[42]), but there were key differences in the magnitude of the VE estimates across data sources in these groups. The 5- to 11-year-old age group was the last group receiving vaccine authorization during the study period, making it difficult to disentangle the effect of age group and variant era. Although calendar time and geography are balanced across vaccination groups within each data source (thus accounting for local differences in COVID-19 circulation and

severity), the 2 data sources cover different geographic areas and timeframes. For example, the end date for all IIS jurisdictions in CVS Health was 31 March 2022, but in Optum, the end dates varied from 30 September 2021 (before the beginning of the Omicron era) to 31 May 2022 (into the "second Omicron wave" starting in April/May 2022).[43]

The VE estimates we observed in children are generally lower than many VE estimates reported for the primary series of BNT162b2 in adults.[44-46] US children were vaccinated relatively late in the pandemic, and thus we identified vaccinated children and unvaccinated comparators after many months of potential COVID-19 exposures and infection. Many COVID-19 infections in children were relatively mild during the early pandemic,[47,48] and previous history of COVID-19 infection earlier in the pandemic before vaccination may have conveyed some level of natural immunity in both the vaccinated and unvaccinated groups, reducing the observed VE estimates.

The literature on changes in vaccine effectiveness with BNT162b2 in children from the Delta era to the Omicron era suggests that VE decreased between these 2 periods, although there is significant variation in reported VE due to differences in methodological approaches, data sources, populations, and end points. Reported effectiveness against Delta-associated infection in adolescents ages 12 to 15 years ranges from just over 60%[42] to between 80% and 95% in 12- to 18-year-olds.[49] VE against Omicron-associated infection is consistently lower, although also varied across the literature. Reported VE estimates ranged from 20% in 5- to 11-year-olds[50] to as high as 54.9% in 12- to 18-year-olds,[51] with reported VE estimates varying within this range.[42,52,53] A systematic review and meta-analysis estimated that overall vaccine effectiveness against infection across ages 5 to 18 years was 63% for Delta-associated infection and 33% for Omicron-associated infection.[42] There is also some indication that in adolescents and children, VE wanes over time. One study of 12- to 16-year-olds in Israel found that during the Delta wave, 2-dose VE against infection fell from 85% at 14 to 89 days after vaccination to 58% 150 to 180 days after vaccination.[54] During the Omicron era, a similar trend was seen in a younger age group of 5- to 11-year-olds in South Korea, although during that era the 2-dose VE against infection fell from 57.6% at 30 days after vaccination to 41.2% at 90 days after vaccination.[55] Additional studies have also demonstrated waning of the vaccines' effectiveness over time since vaccination.[44,49] Thus, many older children vaccinated earlier in the pre-Delta or Delta eras may have experienced some natural waning by the time they entered the Omicron eras, even further complicating the entanglement between age group and variant era. The variation between these studies illustrates the challenges of interpreting the literature on this subject; data across COVID-19 strain eras and age groups are inconsistent and difficult to compare across studies.

In examining differences in VE by age group, it is important to consider that vaccines were not made available to all age groups at once. In the US, adolescents 16 years and older could be vaccinated with BNT162b2 starting December 2020, adolescents 12 years and older in May 2021, and adolescents 5 years and older starting October 2021.[10] One prospective cohort study in the US described 2-dose VE for both older children (ages 12 to 15 years) and younger children (ages 5 to 11 years) and found that for the older age group, VE against infection decreased from 87% in the Delta period to 59% in the Omicron period. In the younger age group, VE was reported as 31% during the Omicron period.[56] Vaccines were

made available to this younger age group in the same relative time that Omicron was designated a variant of concern.[57]

Studies assessing vaccine effectiveness in children have primarily relied on test-negative case-control study designs of SARS-CoV-2 infection, although cohort studies (both retrospective and prospective) have also been used. National cohort or population-based cohort studies were often based in non-US settings, including Denmark, Israel, Singapore, and South Korea.[52,58-63] Few US-based cohort studies were identified in the literature, but those that were identified used 2 methodologies to identify vaccinated individuals and subsequent COVID-19 infections. One method was to collect vaccination status from participants via electronic survey and verify vaccination status through vaccine cards, electronic medical records, or state vaccination registries.[56,64] These studies also used self-administered nasal swabs to conduct COVID-19 testing. Other US-based cohort studies linked multiple health databases to compile vaccination and COVID-19 testing data. Some studies linked state- or city-level COVID-19 surveillance systems that collected laboratory-confirmed COVID-19 test results with immunization registries to create their datasets.[49,65] As 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, it is important to use methods accounting for time since vaccination, variants, calendar time, and confounding between exposure groups to evaluate the real-world effectiveness of these vaccines in the US population, while avoiding the selection bias common to many studies comparing different lengths of exposure.

5.2 Strengths and Limitations

This study has a number of strengths including a large sample size, inclusion of multiple US geographic regions, robust methodology, and multiple sources of vaccination information. This study used health insurance administrative claims data and IIS records from several jurisdictions in the US to include a large sample of children being vaccinated and receiving care in a variety of settings. Pandemic conditions varied widely in the US over time and across geography, and thus we granularly matched vaccinated and unvaccinated children on calendar day and US county of residence to account for these differences. The eligibility and matching criteria were designed to identify vaccinated and unvaccinated children who were eligible for vaccination on each calendar day, avoiding selection bias. Starting follow-up on Time 0 without considering future vaccination behaviors avoided immortal person-time bias.[66]

The combination of vaccine administration claims to IIS data supplemented the vaccine exposure data and reduced vaccine exposure misclassification from vaccine doses not recorded in claims data. However, some vaccine administrations may still be missed. The study used external estimates of vaccine coverage for those under the age of 65 years to quantify potential residual exposure misclassification and applied quantitative bias analysis to correct VE estimates. Younger children were vaccinated later in the study period when mass vaccination clinics (without reimbursement by health insurance) were less common, and younger children may have lower levels of vaccination compared with adults[67]; thus, we may have overestimated the extent of exposure misclassification. However, any degree of vaccine exposure misclassification caused by missing vaccination claims would result in our observed VE estimates being underestimates of the true VE.

Because of the timing of authorizations for different age groups, it was difficult to disentangle the effects of age group from those of variant eras. For example, only children aged 16–17 years were authorized to be vaccinated until nearly the end of the pre-Delta era, and no 5- to 11-year-olds were vaccinated during the pre-Delta era. Conversely, very few 16- to 17-year-olds were vaccinated during the later Omicron era.

This real-world study is subject to many limitations common to observational research using existing data sources (e.g., key study elements may be misclassified or missing, the observed VEs may be subject to confounding by unmeasured characteristics, and these results may not be generalizable to other populations). Laboratory-confirmed COVID-19 status was not available, so we relied on recorded diagnoses of COVID-19. Although diagnosis codes for COVID-19 have shown reasonable validity for hospitalized cases,[19-23,68] many COVID-19 cases may never be formally diagnosed in a healthcare setting, and the dynamics of COVID-19 testing and diagnosis have changed over time during the study period. We evaluated hospital/ED-diagnosed COVID-19 separately from any medically diagnosed COVID-19 as a proxy for more severe COVID-19 disease, but diagnosis codes are unable to convey information about disease severity. COVID-19 may be incidentally diagnosed while patients sought care for other conditions.

Despite matching on demographic and clinical characteristics and propensity score weighting, residual confounding may remain. Comparisons of vaccinated and unvaccinated children may be confounded by difficult-to-measure behavioral characteristics such as access to healthcare, healthcare-seeking behavior, adherence to guidelines or recommendations, and pandemic-related risk tolerance. The negative control analysis suggested a potential difference between the exposure groups during the time when vaccines are assumed to have no biologic effect for 10-14 days after vaccination while the body mounts an antibody response to a novel antigen. However, the post hoc analysis further exploring the differences in the first 14 days demonstrated decreased COVID-19 testing and diagnoses in the vaccinated children in the 3-4 days after Time 0, as recently vaccinated individuals may not seek COVID-19 testing, attributing symptoms to vaccine side effects, as has been noted in other studies.[69] This difference in testing and diagnosis behavior appeared to resolve after day 5 through the rest of the negative control period. However, longer term differences in healthcare-seeking behavior cannot be ruled out.

5.3 Generalizability

This study was conducted in the data of 2 national commercial insurers combined with IIS data from multiple jurisdictions around the US. The large number and national representation of children should result in the results being generally applicable to commercially insured children in the US during the study period. These study results may not be applicable to uninsured children or those with Medicaid without commercial insurance.

This study only considered the original, monovalent primary series (2 doses) of BNT162b2 among children aged 5-17 years during the study period ending May 2022. However, subsequent authorizations have been made for additional vaccine brands, dosing schedules, and pediatric age groups; thus, these results may not be applicable to the entire pediatric population. Immunocompromised children aged 5

years or greater are recommended to receive an additional dose as part of a primary series,[70] and BNT162b2 is now authorized for children aged 6 months to 4 years as a 3-dose primary series.[71]

5.4 Conclusion

Vaccination with a complete primary series of BNT162b2 was associated with reduced COVID-19 incidence in the pediatric population, especially for hospital/ED-diagnosed COVID-19. However, the observed VE estimates differed by age group and variant era. In the rapidly changing dynamics of the COVID-19 pandemic, additional real-world studies and surveillance activities are needed to evaluate vaccine effectiveness as authorizations and recommendations for boosters and additional brands in children have changed over time. COVID-19 vaccines play an important role in reducing COVID-19 disease burden in the pediatric population.

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

Protocol section(s)	Change	Rationale
2.2.1, 2.2.2, 4.2.2.1	A secondary objective was added evaluating children aged 6 months to ≤ 17 separately from adults. The other primary and secondary analyses will be performed in adults aged 18-64 years (further described in the protocol addendum). The following analyses were performed in the pediatric analysis: • Descriptive characteristics • Overall HR and VE estimation • Quantitative bias analysis for exposure misclassification	Subsequent consideration of authorizations of COVID-19 vaccines for children increased the regulatory and scientific interest in vaccine effectiveness among children.
3.0, 5.0	The study was conducted using CVS Health commercial claims data supplemented with IIS data, in addition to Optum data. Analyses were performed separately by data source, and database-specific estimates were combined using meta-analytic methods.	At the time the protocol was written, Optum was the only available participating data source with successful IIS linkage. The protocol provided the option to include additional data sources with reliable vaccine exposure information to increase sample size and geographic coverage; CVS Health also successfully incorporated IIS data during the conduct of the study.
4.1	The 42-day period after Dose 1 to receiving Dose 2 while still being considered adherent to the primary series was retained.	Feasibility evaluations demonstrated that most individuals received Dose 2 within the 42-day period.
4.2.2.2	Exclusion criterion for COVID-19 diagnosis assessed in any setting in the 30 days before Time 0 was retained.	Feasibility evaluations demonstrated that very few vaccinated individuals had recorded diagnoses of COVID-19 in the 30 days before vaccination.
4.2.2.2	Any healthcare interaction in the 3 days before the index date was not used as an exclusion criterion, nor was it added as a covariate in propensity score models.	It was concluded that application of this nonspecific exclusion criterion would exclude too many vaccinated individuals.
4.2.2.2	Exclusion criteria for having the following healthcare interactions in the 3 days before Time 0 were retained: • Fever • Nausea/vomiting • Rash • Hospitalization • Emergency department visit	Feasibility evaluations demonstrated that very few vaccinated individuals had these characteristics in the 3 days before Time 0, thus making them appropriate for exclusion criteria to ensure equivalent health status between vaccinated and unvaccinated individuals.

Protocol section(s)	Change	Rationale
4.2.2.2, 4.4.1	Individuals with claims for 2 different branded vaccines on Time 0, or with a different vaccine brand within 3 days of Time 0, were excluded.	The vaccine brand of the initial vaccination with closely spaced records of 2 different brands could not be accurately classified.
5.1.2.1	An additional matching criterion was added: influenza vaccination in the 365 days before Time 0.	To further reduce differences in healthcare-seeking behaviors between vaccine exposure groups.
5.1.2.3	Propensity scores were truncated below the 1st percentile and above the 99th percentile of the distribution of all propensity scores.	To reduce the influence of extreme weights.
5.1.2.4	The end of the Delta variant era was defined as 24 Dec 2021.	To correct an error in the protocol draft and align the end of the Delta era with the beginning of the Omicron era.
5.1.2.4	A post hoc analysis was performed describing the distribution of person-time within different variant era/age groups.	To better understand potential differences in results between age group-specific subgroup results.
5.1.2.4	A post hoc analysis was performed further evaluating the negative control outcome by using 2 separate time periods—day 0-6 and 7-13—and evaluating COVID-19 testing patterns in days 0-13.	To investigate the potential causes of non-null negative control results.
5.1.2.5	The following additional sensitivity analyses were performed: • Time 0 was excluded from follow-up, and follow-up began on Day 1. • The censoring criteria were reordered, so if an individual had a COVID-19 outcome and a censoring vaccine dose on the same day, they were censored rather being counted as an event.	Exploratory analyses indicated that some individuals had diagnoses for COVID-19 on the same day as a COVID-19 vaccine was received.
5.1.2.5	Clarification that a “censoring dose” consists of children in the unvaccinated group receiving any vaccine, or children in the vaccinated group receiving Dose 2 too early, Dose 2 of a different brand, or receiving a third dose.	To clarify all potential censoring doses, including those not explicitly mentioned in the protocol.
5.1.2.6	For subgroup analyses, the overall propensity scores from the primary analyses were used for the subgroups.	The differences in approaches was assumed to be minimal.

COVID-19 = coronavirus disease 2019; HR = hazard ratio; VE = vaccine effectiveness.

Appendix B. Supplementary Tables and Figures

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

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

Optum

CVS Health

Supplementary Tables

Table B-1-Optum. Characteristics of Children Aged 5–17 Years Receiving a BNT162b2 COVID-19 Vaccine and Matched Unvaccinated Children, Optum

Characteristic	Vaccinated N = 92,338	Unvaccinated N = 92,338	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	13 (9, 15)	13 (9, 15)	
Mean (SD)	12.11 (3.60)	12.08 (3.64)	0.01
Sex, N (%)			
Male	46,516 (50.38%)	46,516 (50.38%)	0.00
Female	45,822 (49.62%)	45,822 (49.62%)	0.00
Region, N (%)			
Northeast	13,051 (14.13%)	13,051 (14.13%)	0.00
South	12,959 (14.03%)	12,959 (14.03%)	0.00
Midwest	43,572 (47.19%)	43,572 (47.19%)	0.00
West	22,756 (24.64%)	22,756 (24.64%)	0.00
Pregnant at Time 0, N (%)	< 11	< 11	0.00
Characteristics in the 365 days before Time 0, N (%)			
Hospitalizations			
0	78,015 (84.49%)	77,519 (83.95%)	0.01
1	9,757 (10.57%)	10,098 (10.94%)	0.01
2+	4,566 (4.94%)	4,721 (5.11%)	0.01
Emergency department visits			
0	85,807 (92.93%)	85,029 (92.08%)	0.03
1	5,665 (6.14%)	6,254 (6.77%)	0.03
2+	866 (0.94%)	1,055 (1.14%)	0.02
Skilled nursing facility stay	11 (0.01%)	< 11	0.00
Influenza vaccination	47,759 (51.72%)	47,759 (51.72%)	0.00
Pneumococcal vaccination	87 (0.09%)	77 (0.08%)	0.00
Encounter for cancer screening	194 (0.21%)	220 (0.24%)	0.01
Eye examination	20,534 (22.24%)	20,462 (22.16%)	0.00
Colonoscopy	114 (0.12%)	114 (0.12%)	0.00
Bone mineral density test	57 (0.06%)	54 (0.06%)	0.00
Well-check/well-child preventive healthcare visit	63,290 (68.54%)	62,515 (67.70%)	0.02
Arthritis	6,683 (7.24%)	6,943 (7.52%)	0.01

Characteristic	Vaccinated N = 92,338	Unvaccinated N = 92,338	ASD
Lipid abnormality	787 (0.85%)	795 (0.86%)	0.00
Ambulance use or life support services	856 (0.93%)	956 (1.04%)	0.01
Weakness	1,126 (1.22%)	1,127 (1.22%)	0.00
Pregnancy completion before Time 0 for females	15 (0.03%)	39 (0.09%)	0.02
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	1,067 (1.16%)	1,049 (1.14%)	0.00
Cancer	193 (0.21%)	213 (0.23%)	0.00
Chronic kidney disease or renal disease	194 (0.21%)	185 (0.20%)	0.00
Chronic liver disease	209 (0.23%)	205 (0.22%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	10,086 (10.92%)	10,081 (10.92%)	0.00
Dementia or other neurological conditions	3,110 (3.37%)	3,331 (3.61%)	0.01
Diabetes mellitus, type 1 or 2	436 (0.47%)	416 (0.45%)	0.00
Down syndrome	113 (0.12%)	119 (0.13%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	3,037 (3.29%)	3,135 (3.40%)	0.01
Hypertension	389 (0.42%)	413 (0.45%)	0.00
Immunocompromised state	458 (0.50%)	458 (0.50%)	0.00
Mental health conditions	17,813 (19.29%)	16,871 (18.27%)	0.03
Obese or severely obese	7,750 (8.39%)	8,138 (8.81%)	0.01
Sickle cell disease or thalassemia	142 (0.15%)	137 (0.15%)	0.00
Stroke or cerebrovascular disease	97 (0.11%)	97 (0.11%)	0.00
Tuberculosis	< 11	< 11	0.00
At least 1 COVID-19 laboratory performed	36,002 (38.99%)	32,568 (35.27%)	0.08
COVID-19 diagnoses occurring outside of a hospital or emergency department	2,759 (2.99%)	2,751 (2.98%)	0.00
Hospital or emergency department–diagnosed COVID-19	116 (0.13%)	129 (0.14%)	0.00

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

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

Table B-1-CVS. Characteristics of Children Aged 5–17 Years Receiving a BNT162b2 COVID-19 Vaccine and Matched Unvaccinated Children, CVS Health

Characteristic	Vaccinated N = 361,317	Unvaccinated N = 361,317	ASD
Characteristics assessed at Time 0			
Age, years			
Median (Q1, Q3)	12 (9, 15)	12 (9, 15)	0.00
Mean (SD)	11.76 (3.66)	11.71 (3.72)	0.01
Sex, N (%)			
Male	181,416 (50.21%)	181,416 (50.21%)	0.00
Female	179,901 (49.79%)	179,901 (49.79%)	0.00
Region, N (%)			
Northeast	64,684 (17.90%)	64,684 (17.90%)	0.00
South	69,202 (19.15%)	69,202 (19.15%)	0.00
Midwest	75,498 (20.90%)	75,498 (20.90%)	0.00
West	151,933 (42.05%)	151,933 (42.05%)	0.00
Pregnant at Time 0, N (%)	< 11	< 11	0.00
Characteristics in the 365 days before Time 0, N (%)			
Hospitalizations			
0	310,325 (85.89%)	308,799 (85.46%)	0.01
1	34,669 (9.60%)	36,038 (9.97%)	0.01
2+	16,323 (4.52%)	16,480 (4.56%)	0.00
Emergency department visits			
0	337,110 (93.30%)	333,776 (92.38%)	0.04
1	21,207 (5.87%)	23,725 (6.57%)	0.03
2+	3,000 (0.83%)	3,816 (1.06%)	0.02
Skilled nursing facility stay	47 (0.01%)	36 (0.01%)	0.00
Influenza vaccination	187,076 (51.78%)	187,076 (51.78%)	0.00
Pneumococcal vaccination	360 (0.10%)	368 (0.10%)	0.00
Encounter for cancer screening	676 (0.19%)	610 (0.17%)	0.00
Eye examination	117,681 (32.57%)	114,902 (31.80%)	0.02
Colonoscopy	463 (0.13%)	430 (0.12%)	0.00
Bone mineral density test	256 (0.07%)	196 (0.05%)	0.01
Well-check/well-child preventive healthcare visit	253,176 (70.07%)	246,607 (68.25%)	0.04
Arthritis	23,131 (6.40%)	23,328 (6.46%)	0.00
Lipid abnormality	4,352 (1.20%)	3,936 (1.09%)	0.01

Characteristic	Vaccinated N = 361,317	Unvaccinated N = 361,317	ASD
Ambulance use or life support services	3,014 (0.83%)	3,554 (0.98%)	0.02
Weakness	3,678 (1.02%)	3,480 (0.96%)	0.01
Pregnancy completion before Time 0 for females	56 (0.02%)	114 (0.03%)	0.01
Characteristics assessed using all available data, N (%)			
Autoimmune disorders	4,273 (1.18%)	3,995 (1.11%)	0.01
Cancer	800 (0.22%)	907 (0.25%)	0.01
Chronic kidney disease or renal disease	1,065 (0.29%)	1,149 (0.32%)	0.00
Chronic liver disease	730 (0.20%)	747 (0.21%)	0.00
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	43,858 (12.14%)	44,283 (12.26%)	0.00
Dementia or other neurological conditions	12,075 (3.34%)	12,542 (3.47%)	0.01
Diabetes mellitus, type 1 or 2	1,480 (0.41%)	1,336 (0.37%)	0.01
Down syndrome	396 (0.11%)	386 (0.11%)	0.00
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	12,537 (3.47%)	13,118 (3.63%)	0.01
Hypertension	1,531 (0.42%)	1,568 (0.43%)	0.00
Immunocompromised state	1,674 (0.46%)	1,674 (0.46%)	0.00
Mental health conditions	63,102 (17.46%)	58,900 (16.30%)	0.03
Obese or severely obese	35,224 (9.75%)	37,775 (10.45%)	0.02
Sickle cell disease or thalassemia	712 (0.20%)	773 (0.21%)	0.00
Stroke or cerebrovascular disease	509 (0.14%)	597 (0.17%)	0.01
Tuberculosis	58 (0.02%)	44 (0.01%)	0.00
At least 1 COVID-19 laboratory performed	174,485 (48.29%)	157,714 (43.65%)	0.09
COVID-19 diagnoses occurring outside of a hospital or emergency department	10,878 (3.01%)	10,812 (2.99%)	0.00
Hospital or emergency department–diagnosed COVID-19	514 (0.14%)	643 (0.18%)	0.01

ASD = absolute standardized difference; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; IQR = interquartile range; SD = standard deviation.

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

Table B-2-Optum. Characteristics of Children Aged 5–17 Years Receiving a BNT162b2 COVID-19 Vaccine Who Were Excluded From the Analytic Cohort Due to Failing to Match, Optum

Characteristic	Unmatched vaccinated children N = 2,823
Characteristics assessed at Time 0	
Age, years	
Median (Q1, Q3)	15 (12, 16)
Mean (SD)	13.73 (3.14)
Sex, N (%)	
Male	1,332 (47.18%)
Female	1,491 (52.82%)
Region, N (%)	
Northeast	428 (15.16%)
South	632 (22.39%)
Midwest	1,314 (46.55%)
West	449 (15.91%)
Pregnant at Time 0, N (%)	< 11
Characteristics in the 365 days before Time 0, N (%)	
Hospitalizations	
0	1,914 (67.80%)
1	478 (16.93%)
2+	431 (15.27%)
Emergency department visits	
0	2,446 (86.65%)
1	302 (10.70%)
2+	75 (2.66%)
Skilled nursing facility stay	< 11
Influenza vaccination	1,865 (66.06%)
Pneumococcal vaccination	23 (0.81%)
Encounter for cancer screening	17 (0.60%)
Eye examination	569 (20.16%)
Colonoscopy	39 (1.38%)
Bone mineral density test	< 11
Well-check/well-child preventive healthcare visit	1,804 (63.90%)
Arthritis	363 (12.86%)
Lipid abnormality	35 (1.24%)

Characteristic	Unmatched vaccinated children N = 2,823
Ambulance use or life support services	61 (2.16%)
Weakness	69 (2.44%)
Pregnancy completion before Time 0 for females	0 (0.00%)
Characteristics assessed using all available data, N (%)	
Autoimmune disorders	170 (6.02%)
Cancer	51 (1.81%)
Chronic kidney disease or renal disease	28 (0.99%)
Chronic liver disease	25 (0.89%)
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	462 (16.37%)
Dementia or other neurological conditions	201 (7.12%)
Diabetes mellitus, type 1 or 2	42 (1.49%)
Down syndrome	< 11
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	209 (7.40%)
Hypertension	39 (1.38%)
Immunocompromised state	410 (14.52%)
Mental health conditions	787 (27.88%)
Obese or severely obese	370 (13.11%)
Sickle cell disease or thalassemia	< 11
Stroke or cerebrovascular disease	< 11
Tuberculosis	0 (0.00%)
At least 1 COVID-19 laboratory performed	1,570 (55.61%)
COVID-19 diagnoses occurring outside of a hospital or emergency department	926 (32.80%)
Hospital or emergency department–diagnosed	50 (1.77%)

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

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

Table B-2-CVS. Characteristics of Children Aged 5–17 Years Receiving a BNT162b2 COVID-19 Vaccine Who Were Excluded From the Analytic Cohort Due to Failing to Match, CVS Health

Characteristic	Unmatched vaccinated children N = 3,995
Age, years	
Median (IQR)	14 (12, 16)
Mean (SD)	13.45 (3.38)
Sex, N (%)	
Male	1,903 (47.63%)
Female	2,089 (52.29%)
Region, N (%)	
Northeast	1,675 (41.93%)
South	375 (9.39%)
Midwest	1,088 (27.23%)
West	857 (21.45%)
Pregnant at Time 0, N (%)	18 (0.45%)
Characteristics assessed in the 365 days before Time 0, N (%)	
Hospitalizations	
0	2,647 (66.26%)
1	613 (15.34%)
2+	735 (18.40%)
Emergency department visits	
0	3,389 (84.83%)
1	452 (11.31%)
2+	154 (3.85%)
Skilled nursing facility stay	< 11
Influenza vaccination	2,685 (67.21%)
Pneumococcal vaccination	38 (0.95%)
Encounter for cancer screening	21 (0.53%)
Eye examination	1,040 (26.03%)
Colonoscopy	77 (1.93%)
Bone mineral density test	17 (0.43%)
Well-check/well-child preventive healthcare visit	2,643 (66.16%)
Arthritis	434 (10.86%)
Lipid abnormality	71 (1.78%)
Ambulance use or life support services	95 (2.38%)

Characteristic	Unmatched vaccinated children N = 3,995
Weakness	82 (2.05%)
Pregnancy completion before Time 0	< 11
Characteristics assessed using all available data before Time 0, N (%)	
Autoimmune disorders	295 (7.38%)
Cancer	97 (2.43%)
Chronic kidney disease or renal disease	72 (1.80%)
Chronic liver disease	74 (1.85%)
Chronic lung diseases (e.g., asthma, COPD, cystic fibrosis, pulmonary embolism)	681 (17.05%)
Dementia or other neurological conditions	219 (5.48%)
Diabetes mellitus, type 1 or 2	49 (1.23%)
Down syndrome	13 (0.33%)
Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias)	363 (9.09%)
Hypertension	84 (2.10%)
Immunocompromised state	665 (16.65%)
Mental health conditions	1,139 (28.51%)
Obese or severely obese	595 (14.89%)
Sickle cell disease or thalassemia	16 (0.40%)
Stroke or cerebrovascular disease	17 (0.43%)
Tuberculosis	< 11
At least 1 COVID-19 laboratory test performed	2,619 (65.56%)
COVID-19 diagnoses occurring outside a hospital or emergency department setting	1,452 (36.35%)
Hospital or emergency department–diagnosed COVID-19	128 (3.20%)

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

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

Table B-3-Optum. Distribution of Follow-up Person-time by Vaccination Group and Outcome, Optum

COVID-19 Outcome	Vaccine Exposure Group	N	Sum of person-days	Mean person-days (SD)	Median person-days (Q1, Q3)	Min, max person-days
Medically diagnosed	BNT162b2	92,338	15,334,736	166 (103)	169 (58, 240)	1, 512
	Unvaccinated	92,338	11,114,593	120 (107)	93 (29, 191)	1, 503
Hospital/ED-diagnosed	BNT162b2	92,338	15,566,203	169 (104)	174 (62, 241)	1, 512
	Unvaccinated	92,338	11,400,524	123 (109)	97 (30, 194)	1, 529

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

Table B-3-CVS. Distribution of Follow-up Person-time by Vaccination Group and Outcome, CVS Health

COVID-19 Outcome	Vaccine Exposure Group	N	Sum of person-days	Mean person-days (SD)	Median person-days (Q1, Q3)	Min, max person-days
Medically diagnosed	BNT162b2	361,317	63,030,324	174 (92.48)	146 (107, 249)	1, 468
	Unvaccinated	361,317	40,140,782	111 (100.3)	84 (25, 147)	1, 459
Hospital/ED-diagnosed	BNT162b2	361,317	63,794,102	177 (92.51)	146 (111, 251)	1, 468
	Unvaccinated	361,317	41,115,760	114 (101.82)	87 (26, 153)	1, 459

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

Table B-4-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, Overall, and Sensitivity Analyses Accounting for Vaccine Exposure Misclassification, Optum

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)	VE (95% CI) assuming 83% exposure measurement sensitivity	VE (95% CI) assuming 71% exposure measurement sensitivity
Medically diagnosed	BNT162b2	92,338	2,629	15,334,736	0.65 (0.61-0.69)	35% (31%-39%)	39% (35%-43%)	45% (41%-48%)
	Unvaccinated	92,338	2,792	11,114,593	—	—	—	—
Hospital/ED-diagnosed	BNT162b2	92,338	118	15,566,203	0.45 (0.35-0.59)	55% (41%-65%)	61% (49%-70%)	68% (58%-75%)
	Unvaccinated	92,338	186	11,400,524	—	—	—	—

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

Note: — indicates the reference group.

Table B-4-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, Overall, and Sensitivity Analyses Accounting for Vaccine Exposure Misclassification, CVS Health

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)	Sensitivity analysis assuming 89% sensitivity of exposure classification VE (95% CI)	Sensitivity analysis assuming 69% sensitivity of exposure classification VE (95% CI)
Medically diagnosed	BNT162b2	361,317	10,139	63,030,324	0.61 (0.59-0.63)	39% (37%-41%)	41% (39%-43%)	49% (48%-51%)
	Unvaccinated	361,317	10,080	40,140,782	—	—	—	—
Hospital/ED-diagnosed	BNT162b2	361,317	477	63,794,102	0.38 (0.33-0.43)	62% (57%-67%)	65% (60%-69%)	73% (69%-76%)
	Unvaccinated	361,317	791	41,115,760	—	—	—	—

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

Note: — indicates the reference group.

Table B-5-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, 14 Days After and Including Time 0, Negative Control Outcome Analysis, Optum

Time period	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
Overall (Time 0 through day 13)	Medically diagnosed	BNT162b2	92,338	263	1,275,410	0.85 (0.72-1.02)	15% (-2% to 28%)
		Unvaccinated	92,338	278	1,188,068	—	—
	Hospital/ED-diagnosed	BNT162b2	92,338	< 11	1,276,957	0.46 (0.17-1.26)	54% (-26% to 83%)
		Unvaccinated	92,338	12	1,189,854	—	—
Time 0 through day 6	Medically diagnosed	BNT162b2	92,338	114	643,295	0.70 (0.55-0.90)	30% (10%-45%)
		Unvaccinated	92,338	152	622,480	—	—
	Hospital/ED-diagnosed	BNT162b2	92,338	< 11	643,599	0.24 (0.03-2.20)	76% (-120% to 97%)
		Unvaccinated	92,338	< 11	622,932	—	—
Day 7 through day 13	Medically diagnosed	BNT162b2	92,224	149	1,274,920	1.03 (0.81-1.32)	-3% (-32% to 19%)
		Unvaccinated	92,186	126	1,187,480	—	—
	Hospital/ED-diagnosed	BNT162b2	92,337	< 11	1,276,953	0.57 (0.17-1.83)	43% (-83% to 83%)
		Unvaccinated	92,334	< 11	1,189,832	—	—

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

Note: — indicates the reference group.

Note: Optum privacy rules prohibit displaying cells sizes < 11.

Table B-5-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, 14 Days After and Including Time 0, Negative Control Outcome Analysis, CVS Health

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
Medically diagnosed	BNT162b2	361,317	828	5,027,773	0.75 (0.68-0.83)	25% (17%-32%)
	Unvaccinated	361,317	974	4,601,077	—	—
Hospital/ED-diagnosed	BNT162b2	361,317	43	5,032,434	0.64 (0.43-0.95)	36% (5%-57%)
	Unvaccinated	361,317	61	4,606,708	—	—

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

Note: — indicates the reference group.

Table B-6-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, by Age Subgroup, Optum

Age group	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
5–11 years	Medically diagnosed	BNT162b2	33,423	1,002	3,746,047	1.03 (0.92-1.15)	-3% (-15% to 8%)
		Unvaccinated	33,423	764	2,950,100	—	—
	Hospital/ED-diagnosed	BNT162b2	33,423	34	3,828,835	0.72 (0.43-1.21)	28% (-21% to 57%)
		Unvaccinated	33,423	37	3,014,593	—	—
12–15 years	Medically diagnosed	BNT162b2	39,560	1,090	7,556,338	0.53 (0.48-0.58)	47% (42%-52%)
		Unvaccinated	39,560	1,322	5,274,074	—	—
	Hospital/ED-diagnosed	BNT162b2	39,560	54	7,654,311	0.49 (0.33-0.72)	51% (28%-67%)
		Unvaccinated	39,560	76	5,422,148	—	—
16–17 years	Medically diagnosed	BNT162b2	19,355	537	4,032,351	0.51 (0.44-0.58)	49% (42%-56%)
		Unvaccinated	19,355	706	2,890,419	—	—
	Hospital/ED-diagnosed	BNT162b2	19,355	30	4,083,057	0.28 (0.17-0.46)	72% (54%-83%)
		Unvaccinated	19,355	73	2,963,783	—	—

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

Note: — indicates the reference group.

Table B-6-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, by Age Subgroup, CVS Health

Age group	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
5–11 years	Medically diagnosed	BNT162b2	152,460	3,650	16,280,047	0.81 (0.76-0.85)	19% (15%-24%)
		Unvaccinated	152,460	3,135	10,846,098	—	—
	Hospital/ED-diagnosed	BNT162b2	152,460	144	16,513,481	0.57 (0.45-0.73)	43% (27%-55%)
		Unvaccinated	152,460	183	11,056,080	—	—
12–15 years	Medically diagnosed	BNT162b2	138,492	4,256	30,119,067	0.55 (0.52-0.58)	45% (42%-48%)
		Unvaccinated	138,492	4,341	18,919,212	—	—
	Hospital/ED-diagnosed	BNT162b2	138,492	199	30,450,710	0.33 (0.27-0.41)	67% (59%-73%)
		Unvaccinated	138,492	351	19,378,583	—	—
16–17 years	Medically diagnosed	BNT162b2	70,365	2,233	16,631,210	0.49 (0.46-0.52)	51% (48%-54%)
		Unvaccinated	70,365	2,604	10,375,472	—	—
	Hospital/ED-diagnosed	BNT162b2	70,365	134	16,829,911	0.31 (0.24-0.39)	69% (61%-76%)
		Unvaccinated	70,365	257	10,681,097	—	—

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

Note: — indicates the reference group.

Table B-7-Optum. Distribution of Person-time of Observable Follow-up for Analyses of Medically Diagnosed COVID-19 Stratified by Vaccination Status, Age Groups, and Variant Era, Optum

COVID-19 outcome	Vaccine exposure group	Age group	Person-years in pre-Delta era	Person-years in Delta era	Person-years in Omicron era	Overall person-years in all variant eras
Medically diagnosed	BNT162b2	Overall	769,372 (100%)	3,699,202 (100%)	709,984 (100%)	5,178,558 (100%)
		5–11 years	0 (0%)	901,696 (24%)	555,117 (78%)	1,456,813 (28%)
		12–15 years	245,740 (32%)	2,191,191 (59%)	110,646 (16%)	2,547,577 (49%)
		16–17 years	523,632 (68%)	606,315 (16%)	44,221 (6%)	1,174,168 (23%)
	Unvaccinated	Overall	614,292 (100%)	3,179,877 (100%)	809,064 (100%)	4,603,233 (100%)
		5–11 years	0 (0%)	726,740 (23%)	594,804 (74%)	1,321,544 (29%)
		12–15 years	203,137 (33%)	1,882,309 (59%)	148,528 (18%)	2,233,974 (49%)
		16–17 years	411,155 (67%)	570,828 (18%)	65,732 (8%)	1,047,715 (23%)
Hospital/ED-diagnosed	BNT162b2	Overall	770,390 (100%)	3,713,632 (100%)	717,802 (100%)	5,201,824 (100%)
		5–11 years	0 (0%)	905,166 (24%)	561,458 (78%)	1,466,624 (28%)
		12–15 years	245,824 (32%)	2,199,665 (59%)	111,279 (16%)	2,556,768 (49%)
		16–17 years	524,566 (68%)	608,801 (16%)	45,065 (6%)	1,178,432 (23%)
	Unvaccinated	Overall	615,697 (100%)	3,219,630 (100%)	819,005 (100%)	4,654,332 (100%)
		5–11 years	0 (0%)	729,776 (23%)	602,159 (74%)	1,331,935 (29%)
		12–15 years	203,261 (33%)	1,911,495 (59%)	150,313 (18%)	2,265,069 (49%)
		16–17 years	412,436 (67%)	578,359 (18%)	66,533 (8%)	1,057,328 (23%)

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

Table B-7-CVS. Distribution of Person-time of Observable Follow-up for Analyses of Medically Diagnosed COVID-19 Stratified by Vaccination Status, Age Groups, and Variant Era, CVS Health

COVID-19 outcome	Vaccine exposure group	Age group	Person-years in pre-Delta era	Person-years in Delta era	Person-years in Omicron era	Person-years in all variant eras
Medically diagnosed	BNT162b2	Overall	3,058,485 (100%)	14,616,762 (100%)	2,412,356 (100%)	20,087,603 (100%)
		5–11 years	0 (0%)	4,230,331 (29%)	1,934,714 (80%)	6,165,045 (31%)
		12–15 years	935,058 (31%)	8,181,097 (56%)	349,760 (14%)	9,465,915 (47%)
		16–17 years	2,123,427 (69%)	2,205,334 (15%)	127,882 (5%)	4,456,643 (22%)
	Unvaccinated	Overall	2,336,820 (100%)	11,694,986 (100%)	2,403,331 (100%)	16,435,137 (100%)
		5–11 years	0 (0%)	3,170,004 (27%)	1,868,530 (78%)	5,038,534 (31%)
		12–15 years	759,766 (33%)	6,596,854 (56%)	381,401 (16%)	7,738,021 (47%)
		16–17 years	1,577,054 (67%)	1,928,128 (16%)	153,400 (6%)	3,658,582 (22%)
Hospital/ED-diagnosed	BNT162b2	Overall	3,061,916 (100%)	14,665,396 (100%)	2,435,520 (100%)	20,162,832 (100%)
		5–11 years	0 (0%)	4,239,598 (29%)	1,954,605 (80%)	6,194,203 (31%)
		12–15 years	935,276 (31%)	8,210,262 (56%)	352,165 (14%)	9,497,703 (47%)
		16–17 years	2,126,640 (69%)	2,215,536 (15%)	128,750 (5%)	4,470,926 (22%)
	Unvaccinated	Overall	2,343,319 (100%)	11,837,049 (100%)	2,433,893 (100%)	16,614,261 (100%)
		5–11 years	0 (0%)	3,181,710 (27%)	1,893,113 (78%)	5,074,823 (31%)
		12–15 years	760,047 (32%)	6,693,946 (57%)	385,957 (16%)	7,839,950 (47%)
		16–17 years	1,583,272 (68%)	1,961,393 (17%)	154,823 (6%)	3,699,488 (22%)

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

Table B-8-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, by Variant-specific Era, Optum

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
Pre-Delta	Medically diagnosed	BNT162b2	31,050	36	769,372	0.46 (0.30-0.71)	54% (29%-70%)
		Unvaccinated	31,050	66	614,292	—	—
	Hospital/ED-diagnosed	BNT162b2	31,050	< 11	770,390	0.24 (0.04-1.68)	76% (-68% to 96%)
		Unvaccinated	31,050	< 11	615,697	—	—
Delta	Medically diagnosed	BNT162b2	51,892	446	3,699,202	0.41 (0.37-0.47)	59% (53%-63%)
		Unvaccinated	51,892	904	3,179,877	—	—
	Hospital/ED-diagnosed	BNT162b2	51,892	11	3,713,632	0.19 (0.10-0.38)	81% (62%-90%)
		Unvaccinated	51,892	48	3,219,630	—	—
Omicron	Medically diagnosed	BNT162b2	9,396	130	709,984	0.92 (0.72-1.17)	8.2% (-17% to 28%)
		Unvaccinated	9,396	145	809,064	—	—
	Hospital/ED-diagnosed	BNT162b2	9,396	< 11	717,802	0.40 (0.10-1.54)	60% (-54% to 90%)
		Unvaccinated	9,396	< 11	819,005	—	—

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

Note: — indicates the reference group.

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

Table B-8-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, by Variant-specific Era, CVS Health

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
Pre-Delta	Medically diagnosed	BNT162b2	118,851	119	3,058,485	0.37 (0.29-0.47)	63% (53%-71%)
		Unvaccinated	118,851	245	2,336,820	—	—
	Hospital/ED-diagnosed	BNT162b2	118,851	< 11	3,061,916	0.41 (0.12-1.36)	59% (-36% to 88%)
		Unvaccinated	118,851	< 11	2,343,319	—	—
Delta	Medically diagnosed	BNT162b2	203,051	1,318	14,616,762	0.38 (0.35-0.40)	62% (60%-65%)
		Unvaccinated	203,051	2,733	11,694,986	—	—
	Hospital/ED-diagnosed	BNT162b2	203,051	60	14,665,396	0.23 (0.17-0.31)	77% (69%-83%)
		Unvaccinated	203,051	212	11,837,049	—	—
Omicron	Medically diagnosed	BNT162b2	39,415	509	2,412,356	0.90 (0.79-1.02)	10% (-2% to 21%)
		Unvaccinated	39,415	534	2,403,331	—	—
	Hospital/ED-diagnosed	BNT162b2	39,415	31	2,435,520	0.96 (0.58-1.59)	4% (-59% to 42%)
		Unvaccinated	39,415	32	2,433,893	—	—

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

Note: — indicates the reference group.

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

Table B-9-Optum. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, Sensitivity Analyses, Optum

Analysis	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
Start follow-up on day 1	Medically diagnosed	BNT162b2	92,338	2,609	15,242,398	0.65 (0.61-0.69)	35% (31%-39%)
		Unvaccinated	92,338	2,769	11,022,255	—	—
	Hospital/ED-diagnosed	BNT162b2	92,338	118	15,473,865	0.45 (0.35-0.59)	55% (41%-65%)
		Unvaccinated	92,338	186	11,308,186	—	—
Reorder censoring criteria[a]	Medically diagnosed	BNT162b2	92,338	2,617	15,334,736	0.65 (0.61-0.69)	35% (31%-39%)
		Unvaccinated	92,338	2,778	11,114,593	—	—
	Hospital/ED-diagnosed	BNT162b2	92,338	118	15,566,203	0.45 (0.35-0.59)	55% (41%-65%)
		Unvaccinated	92,338	186	11,400,524	—	—

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

[a] Application of censoring criteria reordered, so censoring for a censoring dose on a particular day occurred before the identification of an outcome on the same day.

Note: — indicates the reference group.

Note: Results for the sensitivity analysis delaying censoring for 7 days after a censoring dose are shown in Figure B-3-Optum.

Table B-9-CVS. Estimated Effectiveness of Receiving a Complete Primary Series of BNT162b2 COVID-19 Vaccine Compared With Being Unvaccinated in Children Aged 5–17 Years, Sensitivity Analyses, CVS Health

Analysis	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	sIPTW HR (95% CI)	sIPTW VE (95% CI)
Censor 7 days after censoring dose	Medically diagnosed	BNT162b2	361,317	10,307	63,577,242	0.63 (0.61-0.65)	37% (35%-39%)
		Unvaccinated	361,317	10,080	41,225,307	—	—
	Hospital/ED-diagnosed	BNT162b2	361,317	484	64,353,602	0.38 (0.34-0.44)	62% (56%-66%)
		Unvaccinated	361,317	791	42,209,270	—	—
Start follow-up on day 1	Medically diagnosed	BNT162b2	361,079	10,071	62,669,007	0.61 (0.59-0.63)	39% (37%-41%)
		Unvaccinated	361,053	10,029	39,779,465	—	—
	Hospital/ED-diagnosed	BNT162b2	361,147	477	63,432,785	0.38 (0.33-0.43)	62% (57%-67%)
		Unvaccinated	361,104	791	40,754,443	—	—
Reorder censoring criteria[a]	Medically diagnosed	BNT162b2	361,317	10,123	63,030,324	0.61 (0.59-0.63)	39% (37%-41%)
		Unvaccinated	361,317	10,080	40,140,782	—	—
	Hospital/ED-diagnosed	BNT162b2	361,317	477	63,794,102	0.38 (0.33-0.43)	62% (57%-67%)
		Unvaccinated	361,317	791	41,115,760	—	—

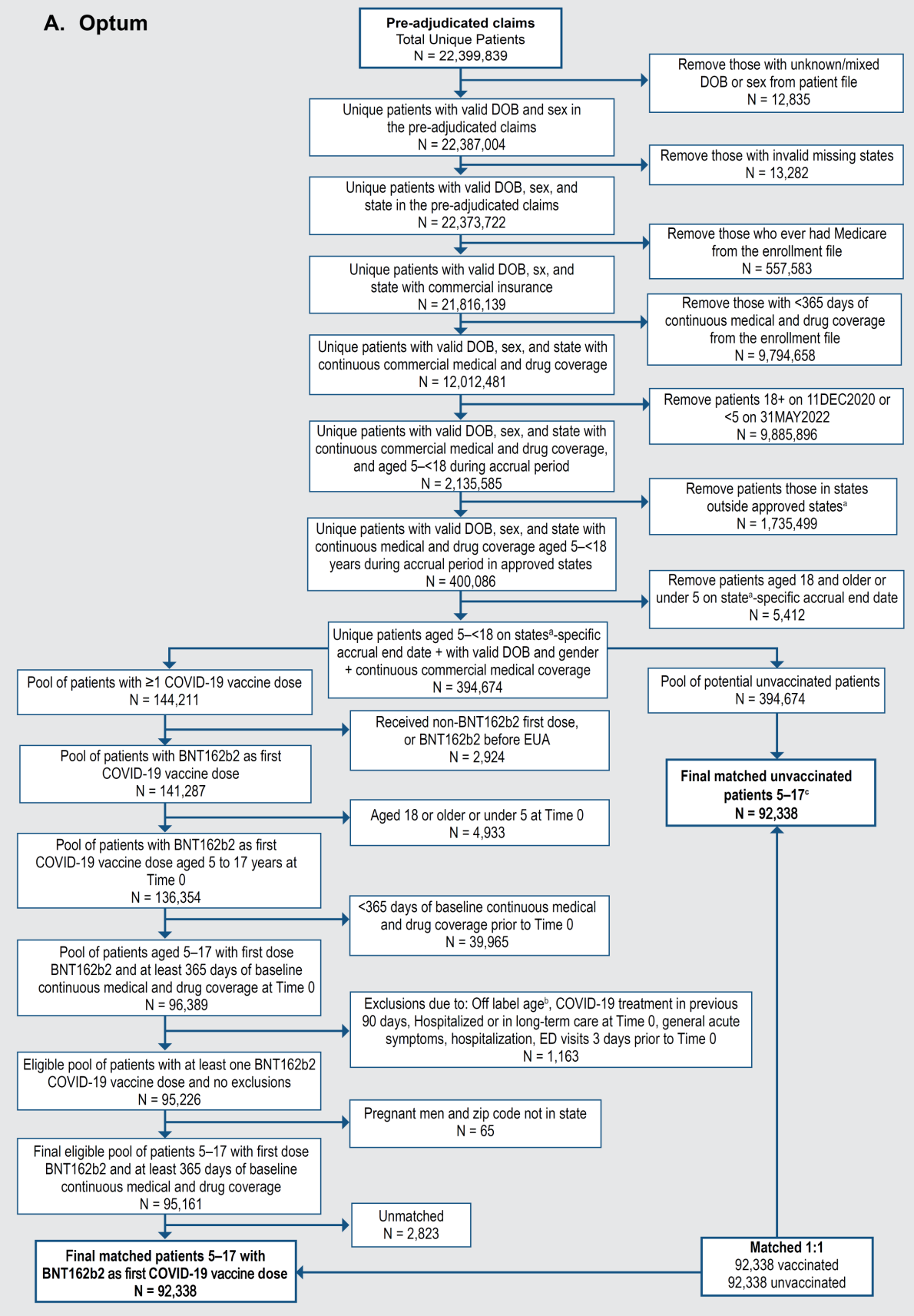
CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; VE = vaccine effectiveness.

[a] Application of censoring criteria reordered, so censoring for a censoring dose on a particular day occurred before the identification of an outcome on the same day.

Note: — indicates the reference group.

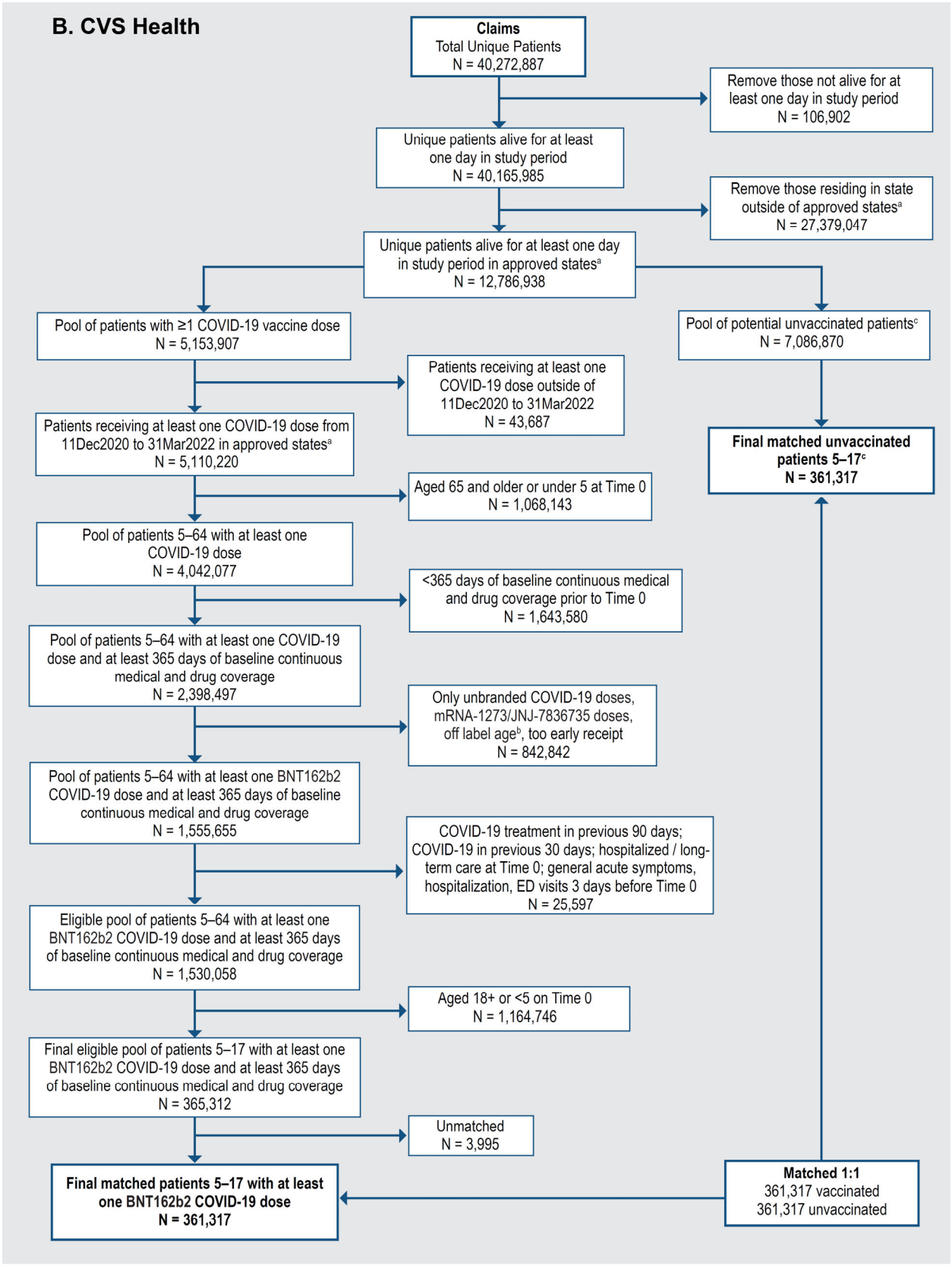
Supplementary Figures

Figure B-1-Optum. Attrition Flowchart of Children Aged 5–17 Years in the Pediatric Primary Analysis Cohort: Optum Preadjudicated Claims Supplemented With IIS Data, 11 December 2020–31 May 2022, Optum



DOB = date of birth; ED = emergency department; IIS = immunization information system; US = United States.
[a] 10 IIS from 10 US states were included.
[b] Children were excluded if they received a COVID-19 vaccine when it was not authorized for their age group.
[c] Children in the vaccinated group may also appear in the unvaccinated comparator group.

Figure B-1-CVS. Attrition Flowchart of Children Aged 5–17 Years in the Pediatric Primary Analysis Cohort: Adjudicated Claims Data Supplemented With IIS Data, 11 December 2020–31 March 2022, CVS Health

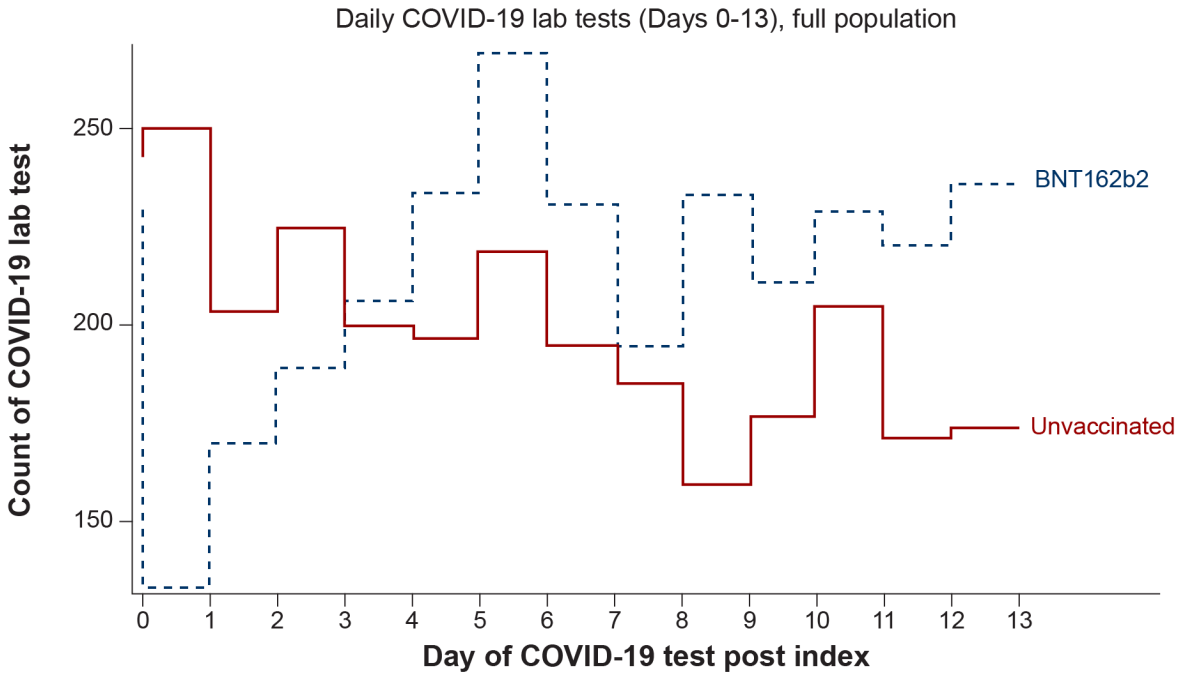


DOB = date of birth; ED = emergency department; IIS = immunization information system; US = United States.

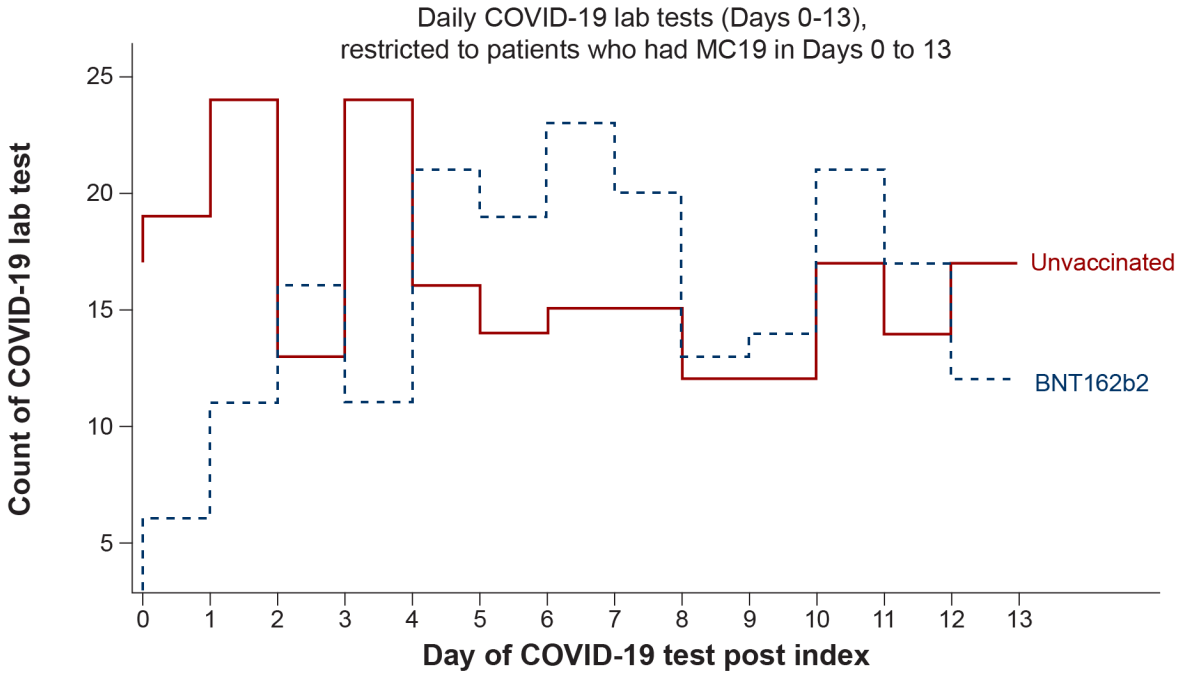
[a] 11 IIS from 9 US states were included.
[b] Children were excluded if they received a COVID-19 vaccine when it was not authorized for their age group.
[c] Children in the vaccinated group may also appear in the unvaccinated comparator group.

Figure B-2-Optum. Daily Covid-19 Lab Tests Stratified by Vaccine Status in the First 14 Days of Follow-Up, Optum

A. Overall



B. Among Those With Medically Diagnosed COVID-19 Outcomes in Days 0 through 13



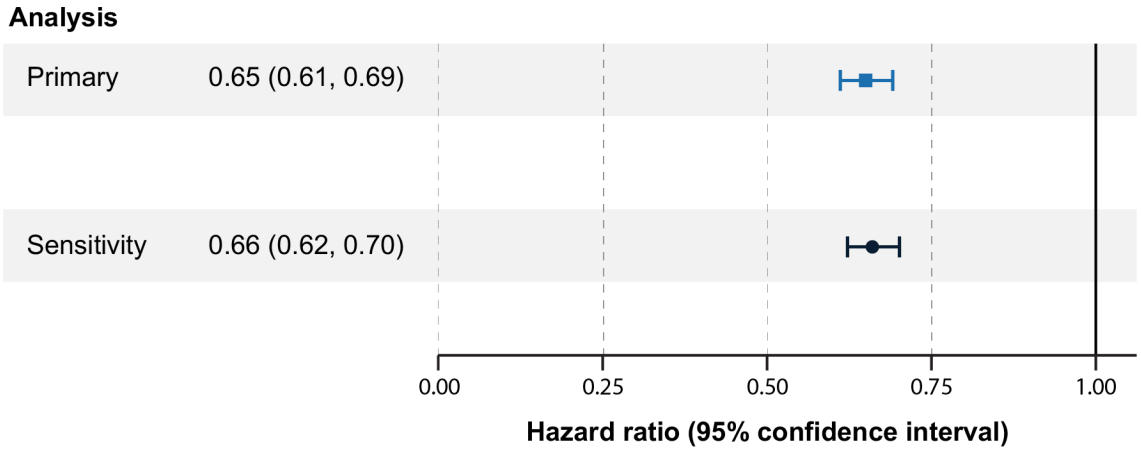
COVID-19 = coronavirus disease 2019.

Figure B-2-CVS. Daily Covid-19 Lab Tests Stratified by Vaccine Status in the First 14 Days of Follow-Up, CVS Health

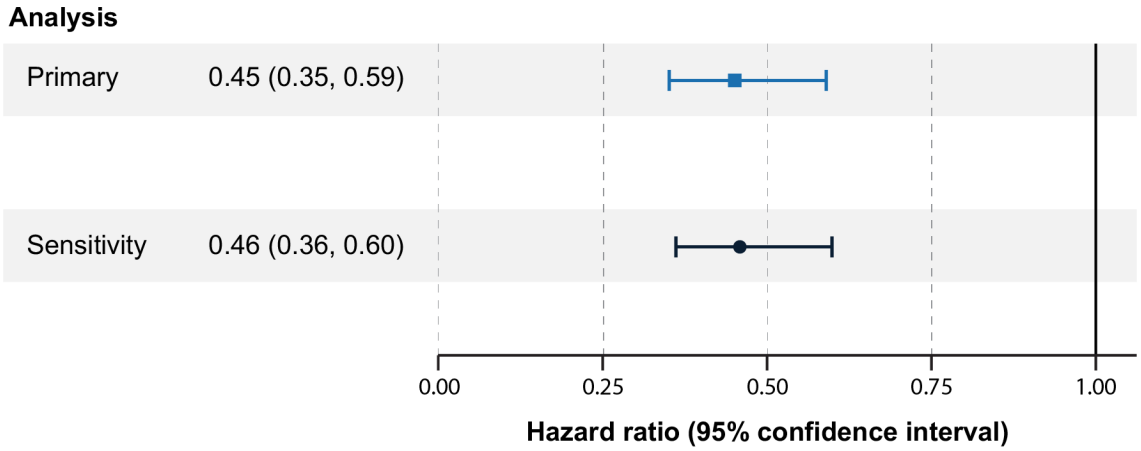
This ad hoc analysis was not performed in CVS Health data.

Figure B-3-Optum. Sensitivity Analysis of COVID-19 Outcomes Among Children Aged 5–17 Years With Extended Censoring Criteria After Subsequent Receipt of Another COVID-19 Vaccine, Optum

A. Medically Diagnosed COVID-19



B. Hospital/ED-diagnosed COVID-19



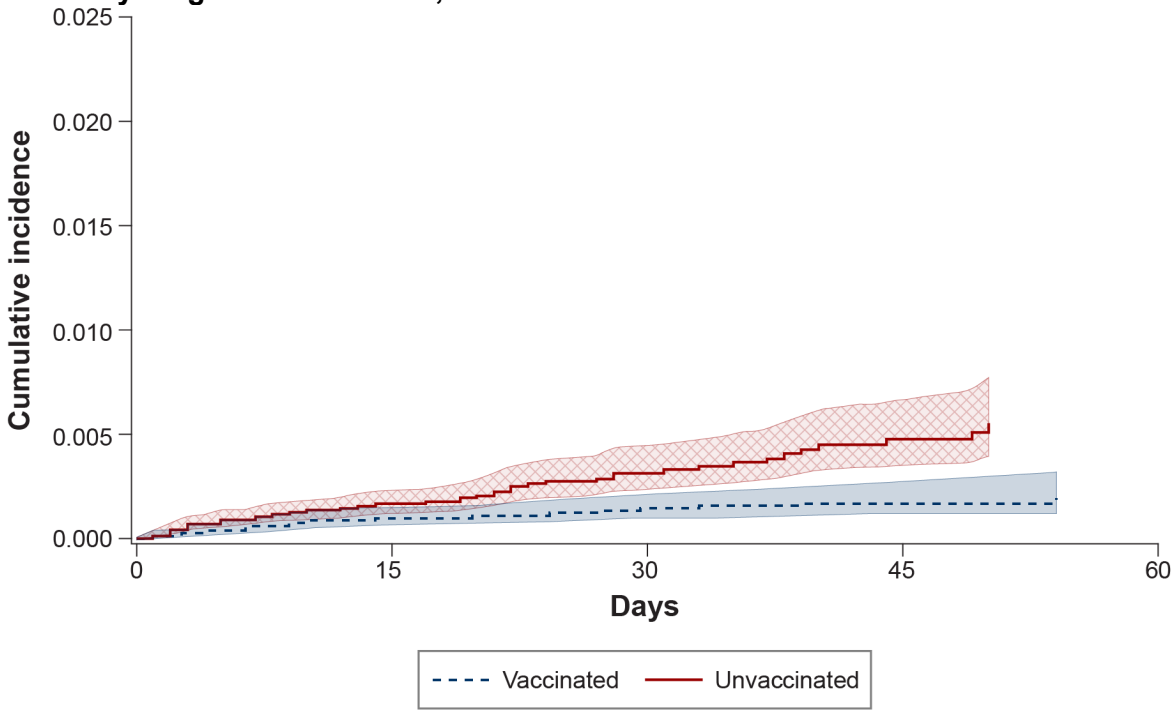
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure B-3-CVS. Sensitivity Analysis of COVID-19 Outcomes Among Children Aged 5–17 Years With Extended Censoring Criteria After Subsequent Receipt of Another COVID-19 Vaccine, CVS Health

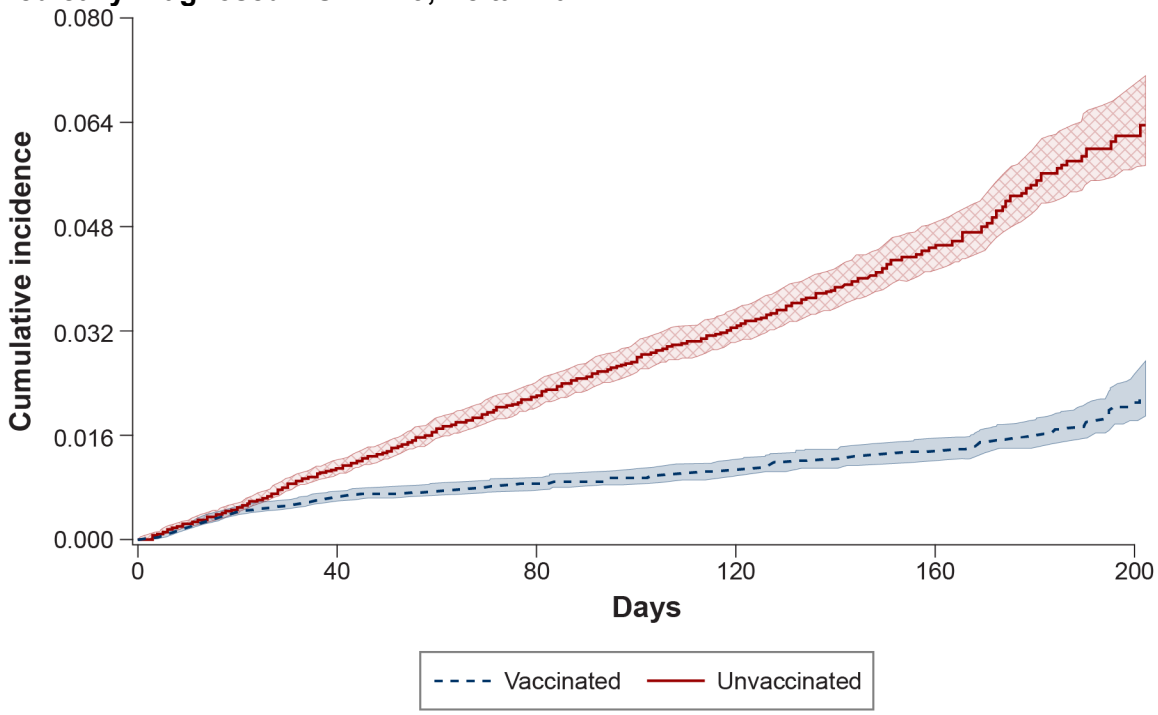
This figure was not generated in CVS Health data; results of this analyses are presented in Table B-9-CVS.

Figure B-4-Optum. Weighted Cumulative Incidence of COVID-19 Outcomes in Children Aged 5–17 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Children, by Vaccine Exposure Group, by Variant-specific Era, Optum

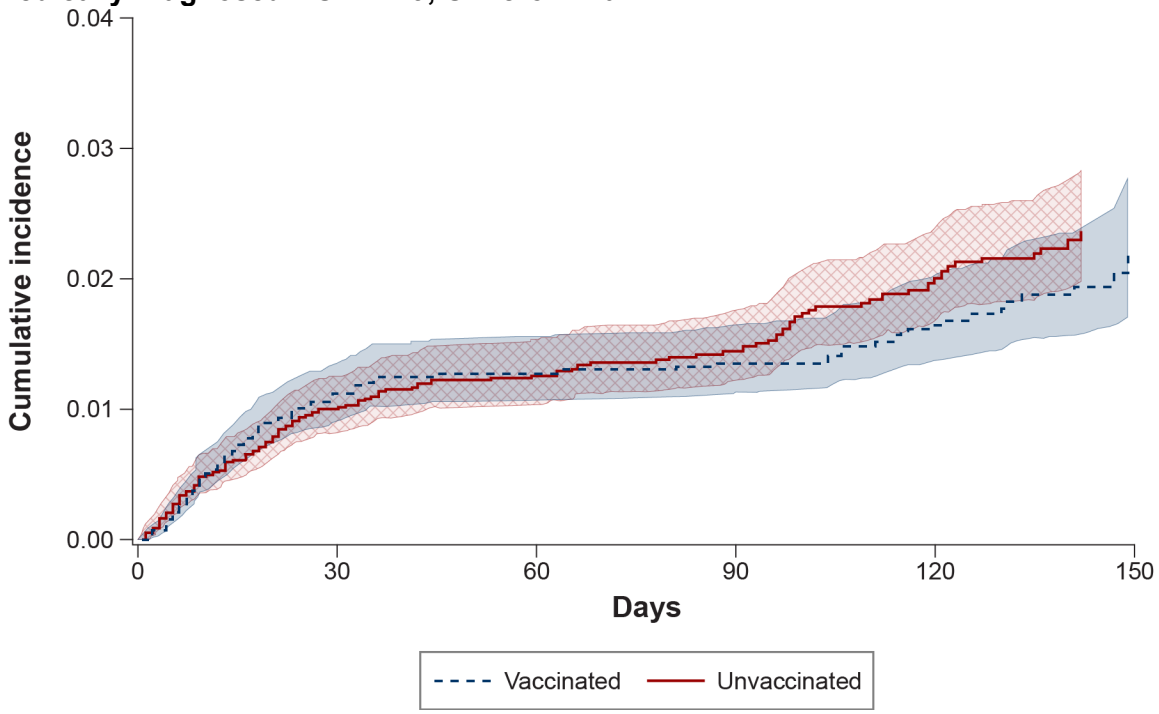
A. Medically Diagnosed COVID-19, Pre-Delta Era



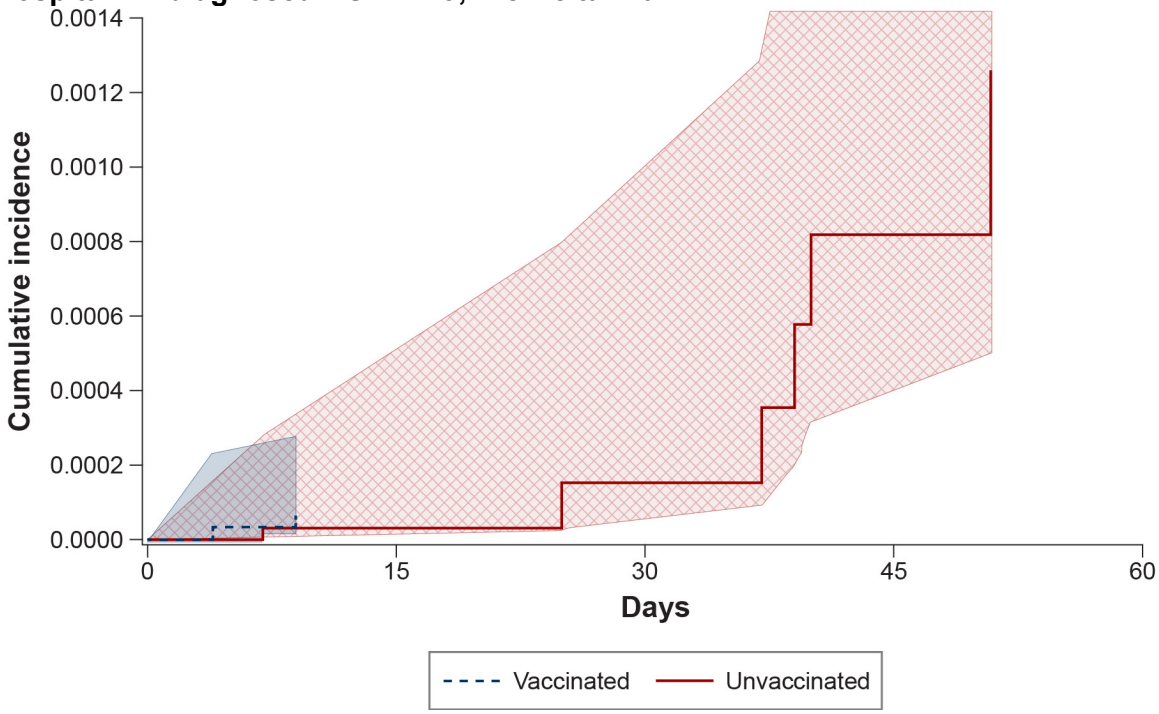
B. Medically Diagnosed COVID-19, Delta Era



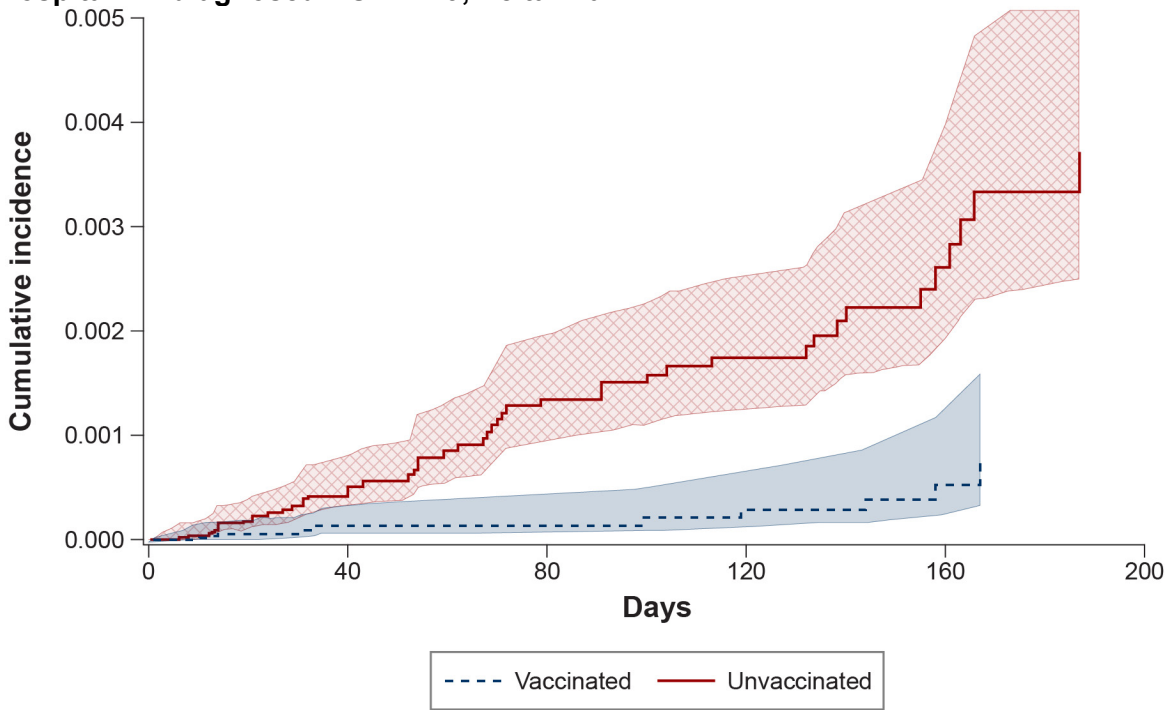
C. Medically Diagnosed COVID-19, Omicron Era



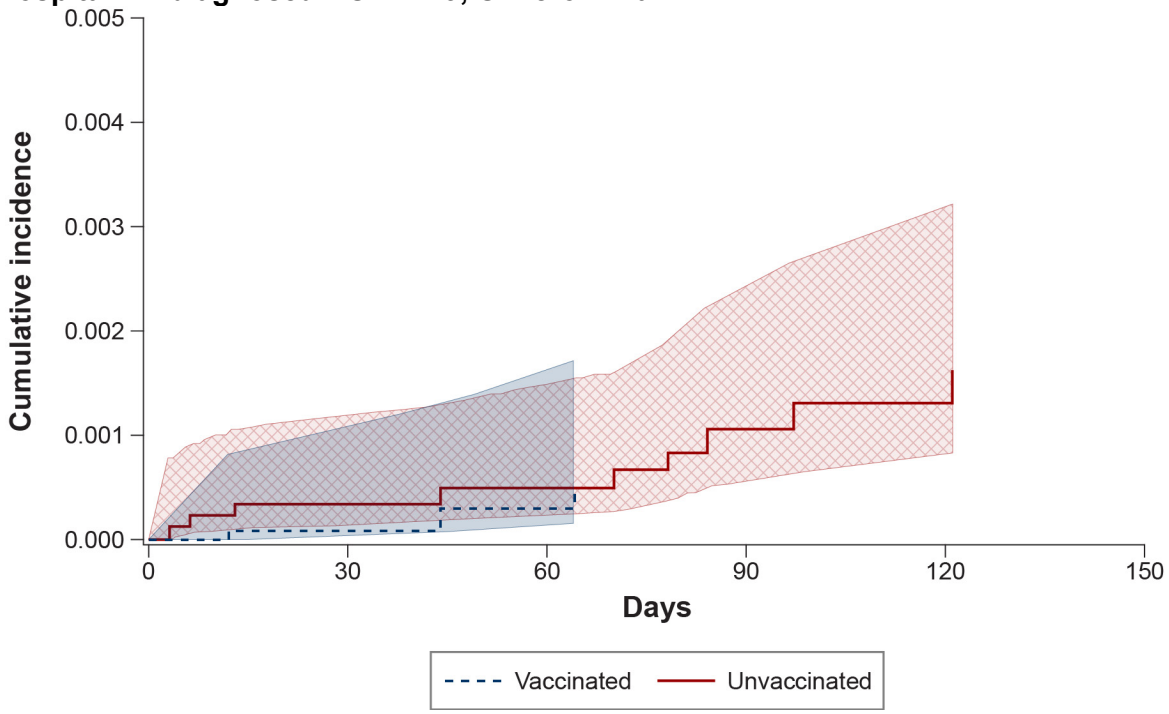
D. Hospital/ED-diagnosed COVID-19, Pre-Delta Era



E. Hospital/ED-diagnosed COVID-19, Delta Era



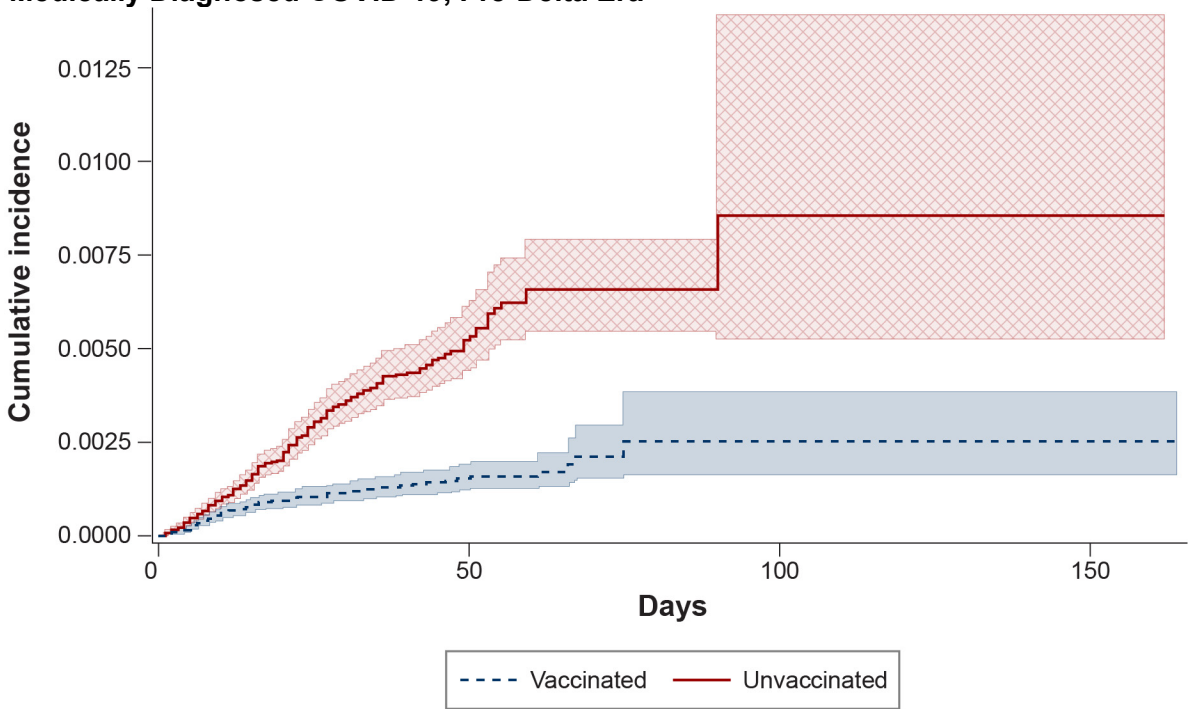
F. Hospital/ED-diagnosed COVID-19, Omicron Era



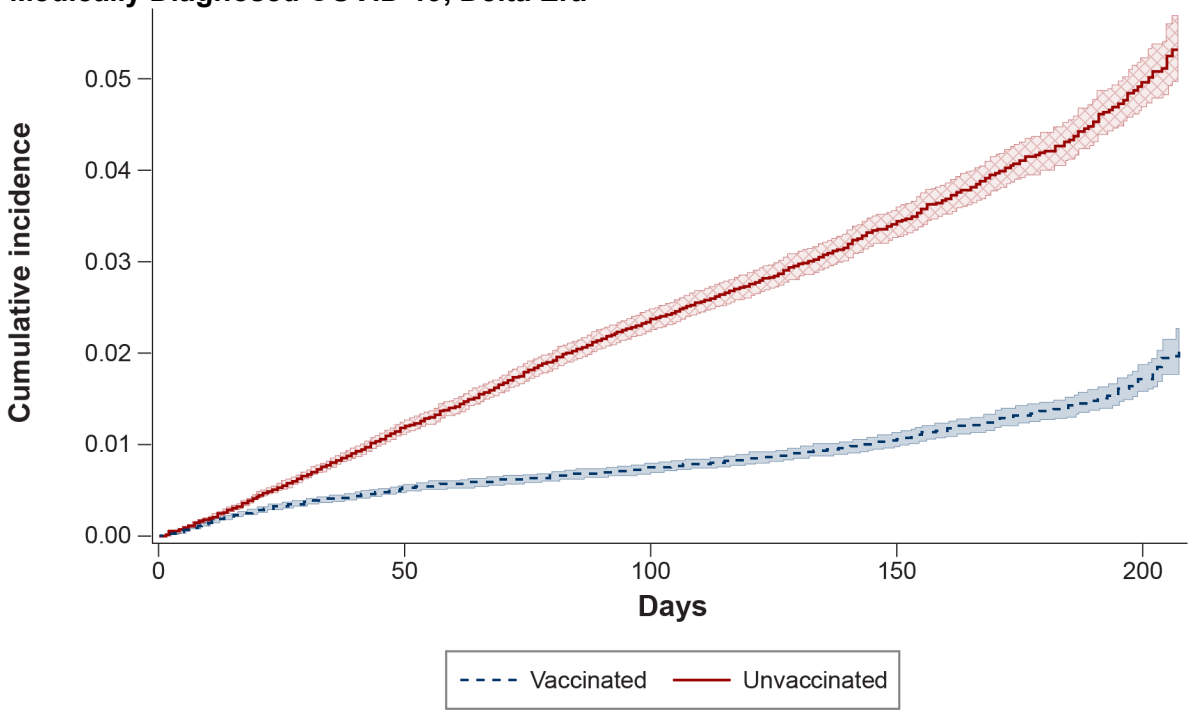
COVID-19 = coronavirus disease 2019; ED = emergency department.

Figure B-4-CVS. Weighted Cumulative Incidence of COVID-19 Outcomes in Children Aged 5–17 Years Receiving a Complete Primary Series of COVID-19 Vaccine and Unvaccinated Children, by Vaccine Exposure Group, by Variant-specific Era, CVS Health

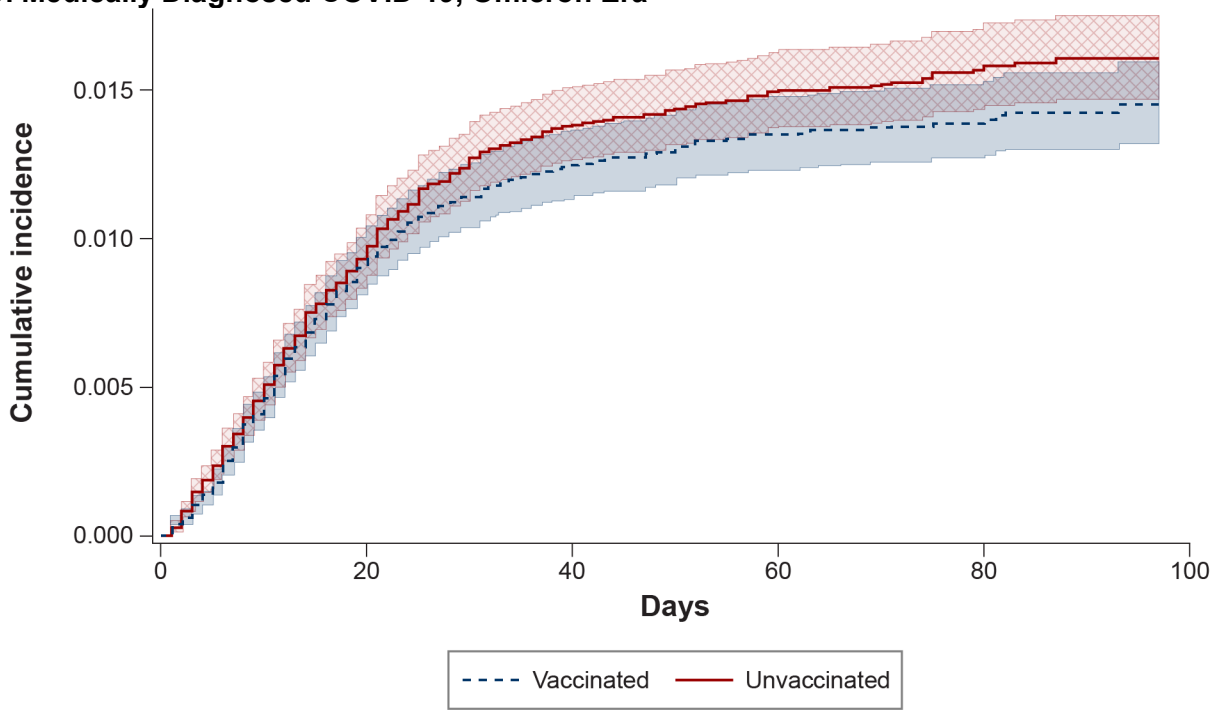
A. Medically Diagnosed COVID-19, Pre-Delta Era



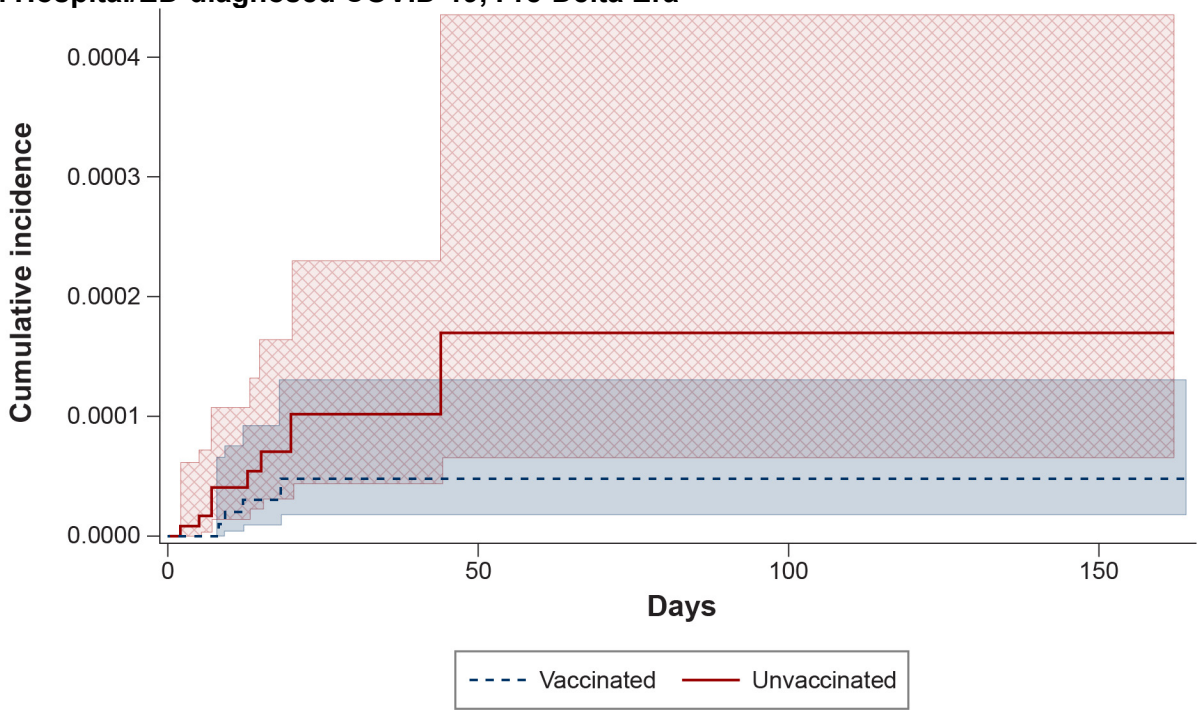
B. Medically Diagnosed COVID-19, Delta Era



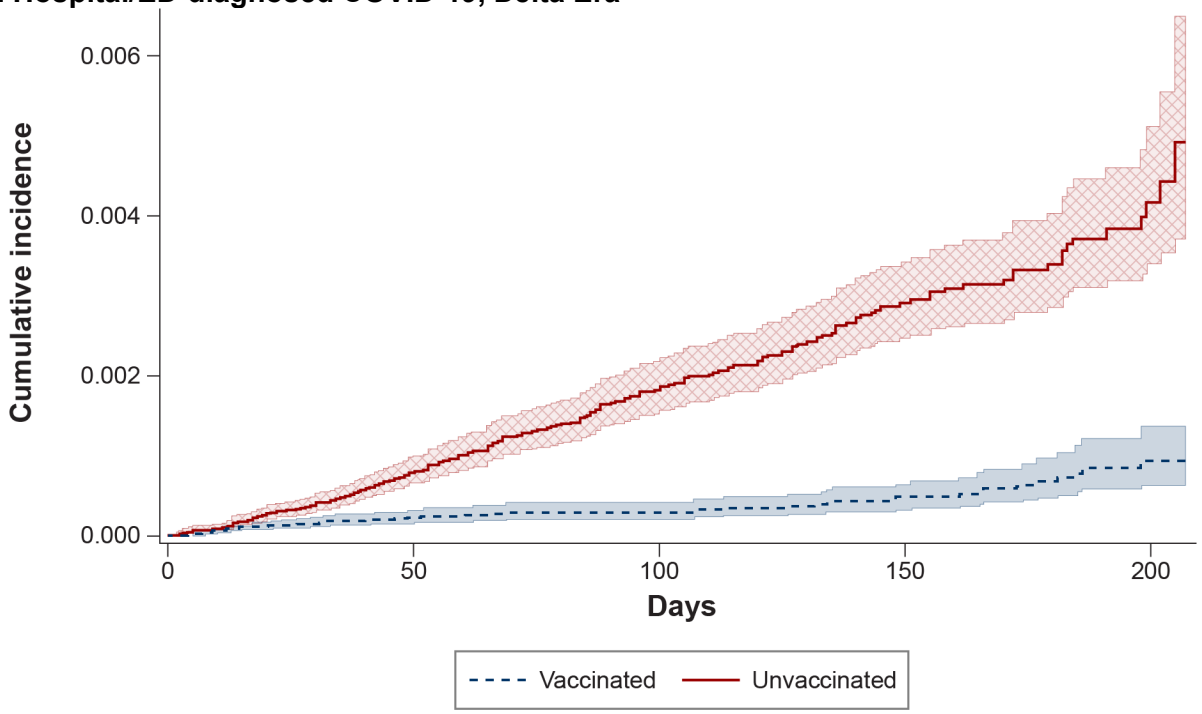
C. Medically Diagnosed COVID-19, Omicron Era



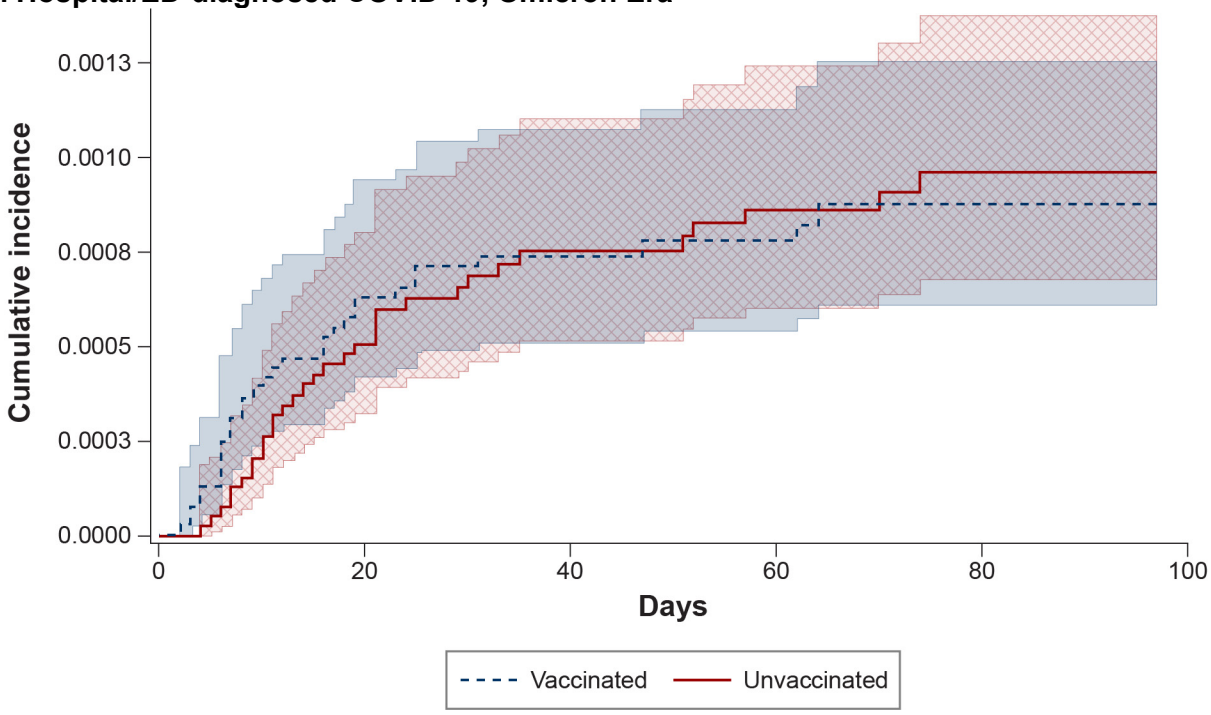
D. Hospital/ED-diagnosed COVID-19, Pre-Delta Era



E. Hospital/ED-diagnosed COVID-19, Delta Era



F. Hospital/ED-diagnosed COVID-19, Omicron Era



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