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

Protocol Addendum

18 August 2022

Document History

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RTI-HS, FDA/CBER/OBPV, Acumen, Optum	Draft 0.1	2 August 2022	First draft for scientific working group review
RTI-HS	Draft 1	18 August 2022	Final draft for public posting

List of Abbreviations

BEST	Biologics Effectiveness and Safety
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
ED	emergency department
FDA	Food and Drug Administration
HR	hazard ratio
IIS	immunization information system
IPT	inverse probability of treatment
IQR	interquartile range
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
sIPT	standardized inverse probability of treatment
US	United States
VE	vaccine effectiveness

Contents

Table Shells

1. Overview

This document serves as an addendum to the protocol entitled *Assessment of Effectiveness of COVID-19 Vaccination in the United States*.[1] This addendum will describe the approach for evaluating the real-world vaccine effectiveness (VE) of COVID-19 vaccines in the pediatric population. The original protocol described an overall analysis of all COVID-19 vaccine recipients, with a subgroup analysis performed in individuals aged less than 18 years. The BNT162b2 COVID-19 vaccine was originally authorized for use in individuals aged 16 years or greater. However, subsequent vaccine authorizations for pediatric age groups younger than 16 years have resulted in increasing interest in the effectiveness of vaccination in different age subgroups in the pediatric population and across different variant eras. Therefore, the primary objectives of the comparative study described in the original protocol (Protocol Section 2.2.1[1]) will be performed only in adults aged 18 years or greater, and the pediatric population aged less than 18 years will be evaluated separately, as described in this protocol addendum.

In addition, at the time of preparing this protocol addendum, vaccine exposure data in the pediatric population are available in the study data only for the BNT162b2 vaccine in the pediatric age group 5 to 17 years; subsequent authorizations of BNT162b2 vaccine for the age group 6 months to 4 years and of mRNA-1273 vaccine for the age group 6 months to 17 years occurred on 17 June 2022.[2] Therefore, the analyses described in this addendum will initially be implemented only considering BNT162b2 in the pediatric age group aged 5 to 17 years, although it is written such that it can be applied to other age groups if needed. As data accrue for other age groups and vaccine brands, and if/when other COVID-19 vaccine brands receive authorization in the pediatric age group in the United States (US), this addendum will be applied to those age groups and vaccine brands if/when deemed necessary and feasible. Moreover, the analyses described in this current protocol addendum are being initially applied in only 1 commercial claims database because of feasibility and availability of data. If/when data from other data sources become available, the Food and Drug Administration (FDA) will decide whether it is necessary and feasible to apply this protocol to other data sources. The same decision condition will apply to availability of other data sources to supplement vaccine exposure data, such as the Immunization Information Systems (IIS).

2. Objectives

This protocol addendum will explore the effectiveness of COVID-19 vaccines in preventing medically diagnosed COVID-19 cases and hospital/emergency department (ED)–diagnosed COVID-19 in the pediatric population by comparing vaccinated and unvaccinated individuals aged 17 years or less in the US. The primary objective of this addendum is as follows:

- To assess the effectiveness of receiving a complete primary series of COVID-19 vaccination (e.g., 2 or 3 doses of a COVID-19 vaccine series, depending on age), by vaccine brand, compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in individuals aged 6 months to 17 years.

The secondary objectives of this protocol addendum include the following:

- To assess the effectiveness of receiving a complete primary series of COVID-19 vaccination, by brand, compared with being unvaccinated in preventing medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19 in relevant age subgroups corresponding to the staged authorization of vaccines and/or brand-specific dosage ranges (e.g., for BNT162b2, ages 16-17 years, 12-15 years, 5-11 years, and 6 months-4 years) as available during the study period.
- To describe/characterize the effectiveness of receiving a complete primary series of COVID-19 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, including pre-Delta, Delta, and Omicron eras.

3. Data Sources, Study Design, and Definitions

The data sources, study design, variable definitions, cohort selection and matching methodology, and exposure characterization described in the original protocol[1] for the adult population will be used for the pediatric analyses. Additional covariates adapted for the pediatric population may be included. Additional data sources, such as other commercial claims data sources or data from IIS, may be added if available and deemed feasible. This addendum clarifies the statistical analyses that will be performed in the pediatric population.

3.1. Analyses for All Pediatric Age Groups and Brands

Age-specific and brand-specific dates of authorization for COVID-19 vaccines in children will be used to define the study period. Authorizations of COVID-19 vaccines for pediatric use have varied over time by vaccine brand and age range. The earliest possible study period start date will be 11 December 2020 (the date the first COVID-19 vaccine [BNT162b2] was authorized in the US, including for children aged 16-17 years). Younger age groups were subsequently authorized for COVID-19 vaccination throughout the study period. Individual matching on age and calendar time, among other factors, as described in the original protocol[1] will account for the rolling vaccine authorizations during the study period. The study period will continue until the end of complete data availability, as described in the original protocol.[1] The analyses will consider all vaccine brands authorized for use among the pediatric population during the study period. If multiple COVID-19 vaccine brands are available during the study period for pediatric use, all analyses will be performed separately by vaccine brand.

3.2. Analyses for 3-dose Primary Series

All analyses described in the original protocol[1] refer to authorized 1-dose or 2-dose primary vaccine series. However, BNT162b2 was authorized for children aged 6 months to 4 years as a 3-dose primary series with Dose 2 received 3 weeks after Dose 1, and Dose 3 received 8 weeks after Dose 2.[3] Analyses of the 3-dose BNT162b2 primary series in this age group will require a modified definition of the primary series, as shown in Table 1.

Table 1. Details of Follow-up for the Complete Primary Vaccination Series Exposure Patterns With a 3-dose Primary Series

Vaccine exposure pattern	Included individuals	Time 0 (beginning of follow-up)	Deviation from vaccine exposure pattern after Time 0 resulting in censoring
BNT162b2 complete primary series (aged 6 months-4 years)	All eligible individuals receiving Dose 1 of BNT162b2	Date of Dose 1 of BNT162b2	▪ Receipt of Dose 2 of BNT162b2 within 17 days of Dose 1 ▪ Failure to receive Dose 2 of BNT162b2 by day 56[a] after Dose 1 ▪ Receipt of Dose 3 of BNT162b2 within 52 days of Dose 2 ▪ Failure to receive Dose 3 of BNT162b2 by day 77 after Dose 2 ▪ Receipt of any other COVID-19 vaccine brand or unspecified brand ▪ Receipt of a fourth dose
Unvaccinated	Matched eligible unvaccinated comparator individuals	Matched calendar date	▪ Receipt of any COVID-19 vaccine dose

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019.
Note: If additional vaccine brands are introduced during the study period, they will be included as data are available, as appropriate with their indicated/recommended dosing schedules.
[a] Immunization schedules for children allow for spacing Dose 1 and Dose 2 up to 8 weeks according to revised CDC guidance.[4]

4. Statistical Methods

The matching of vaccinated and unvaccinated children and assignment of Time 0 in the unvaccinated comparator group will be performed as described in the original protocol (Protocol Section 5.1.21).[1]

4.1. Descriptive Characteristics

The number of vaccinated and unvaccinated children meeting all eligibility criteria to be included in the study cohort will be reported by exposure group for each brand-specific comparison. The number and proportion of vaccinated children excluded will also be reported for each exclusion criterion. Unvaccinated children will be considered as potential matches on every calendar day on which they are unvaccinated; thus, the attrition of the unvaccinated children will be described as potential matches considered and the number of potential matches excluded for each criterion. The characteristics of vaccinated children who are excluded due to a failure to match will be described (Appendix 1, Table Shell 1).

The distribution of characteristics will be described by vaccine exposure groups. Continuous variables will be described with means, standard deviations, medians, and interquartile ranges. Distributions of categorical variables will be described with counts and proportions. The balance of covariates between exposure groups will be evaluated with standardized differences[5] (Appendix 1, Table Shell 1).

4.2. Confounding Control

After matching, we will adjust for baseline characteristics via inverse probability of treatment (IPT) weighting propensity score methods, as described in the original protocol (Protocol Section 5.1.2.3).[1] The distributions of the propensity scores by vaccine exposure group will be plotted to visualize the degree of overlap between the vaccine exposure groups. The propensity score will be used to compute stabilized IPT weights[6] that will be applied to the analytic cohorts. The standardized differences for the baseline characteristics in the IPT-weighted cohort will be evaluated to assess the balance of covariates after weighting by plotting the standardized differences for each covariate before and after IPT-weighting.

A negative outcome control analysis will evaluate residual confounding or other bias in the IPT-weighted cohort (Section 4.3).

4.3. Outcome Analyses

All outcome analyses will be performed separately for the 2 COVID-19 outcomes: medically diagnosed COVID-19 and hospital/ED-diagnosed COVID-19, as defined in the original protocol (Protocol Section 4.5).[1]

Within each of the brand-specific cohorts, all individuals will be followed from Time 0 until censoring (as described in the original protocol [Protocol Section 4.2.2.3][1] or 2-dose primary series, or in Table 1 for 3-dose primary series) or the occurrence of the COVID-19 outcome of interest. The cumulative incidence of each COVID-19 outcome will be estimated in each IPT-weighted vaccine exposure group as 1 minus the Kaplan-Meier estimator.[7] Cumulative incidence curves will be plotted for the whole study period by vaccine exposure group.

As an overall summary of the relative incidence of the COVID-19 outcomes in the vaccinated and unvaccinated groups across the entire study period, a hazard ratio (HR) for each outcome will be estimated using an IPT-weighted Cox proportional hazards model with vaccination status as the independent variable; the 95% confidence intervals (CIs) will be estimated with robust variance estimators (Appendix 1, Table Shell 2).

The HR and VE estimates will be estimated in the entire overall pediatric population, as well as separately in age subgroups (e.g., 16-17 years, 12-15 years, 5-11 years, 6 months-4 years, as available) (Appendix 1, Table Shell 3). Within each age group, a separate propensity score model and separate standardized inverse probability of treatment (sIPT) weights will be estimated, and a separate Cox proportional hazards model will run.

Negative Outcome Control

To evaluate the completeness of confounding control, cumulative incidence curves for the overall exposure groups will be evaluated in the first 14 days (inclusive) of follow-up. The cumulative incidence curves of both COVID-19 outcomes during the first 14 days will be visually inspected, and a HR will be estimated with a Cox proportional hazards model restricted to the first 14 days of follow-up. Minimal separation of the cumulative incidence curves and effect measure estimates with 95% CIs highly compatible with a null effect during this negative outcome control period will provide reassurance that baseline confounding has been addressed. The risk difference rather than the HR may be considered to estimate absolute difference during the negative control period. If the negative outcome control analysis suggests residual confounding, additional approaches for confounding control will be considered, including additional adjustment variables in the propensity score models, stratification into subgroups, or application of additional exclusion criteria. Additional negative control outcomes may also be considered.

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

The Delta variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus became dominant in the US during June and July of 2021, accounting for > 50% of cases in all regions by the beginning of July 2021.[8] The Omicron variant became predominant by late December 2021.[8] Additional variants may become predominant during the study period, or other key events can result in other calendar periods of interest. To evaluate changes in VE due to circulating variants, subgroup analyses by calendar time will be performed as follows:

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

Other variant eras may be added, if of interest.

Cox proportional hazards models will be used to estimate era-specific HRs and corresponding VE estimates (Appendix 1, Table Shell 4).

4.3.1. Sensitivity Analyses

A sensitivity analysis will be performed to evaluate the robustness of the study results against variations in the study design. To account for potential informative censoring, the censoring criteria will be amended so that censoring occurs 7 days after receipt of a censoring vaccine dose (e.g., individuals in the unvaccinated group receiving any vaccine, or individuals in the vaccinated group receiving a subsequent vaccine dose) instead of censoring on the day of the vaccine dose, as there would not be an expected effect of the new dose during this time.

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

4.4. Quantitative Bias Analysis

To evaluate the potential impacts of misclassification of vaccine exposure status, quantitative bias analysis methods[9,10] will be applied to comparisons of vaccinated versus unvaccinated individuals.

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

vaccination rate in the study divided by the external vaccination rate will yield an estimate of the sensitivity of the vaccination measure.

Quantitative bias analysis will be employed to estimate the potential change in observed effect measure estimates for the range of estimated exposure misclassification levels. Effect measure estimates and the resulting VE estimates will be estimated with bias correction factors for exposure misclassification based on the external vaccination coverage rate and the estimated sensitivity and specificity of the study vaccination measure.[11] The results of the bias analysis using the highest and lowest vaccination coverage estimates will be presented as sensitivity analyses to the primary results to inform the impact of potential exposure misclassification (Appendix 1, Table Shell 2).

5. Limitations

All the limitations described in the original protocol[1] also apply to this protocol addendum. Additional pediatric-specific limitations may also apply.

Because of the staged authorization of vaccines for different age subgroups, studies may be unable to evaluate specific age subgroups in different variant eras (e.g., only pediatric individuals aged 16-17 years were authorized to be vaccinated until nearly the end of the pre-Delta era). Even when combining all pediatric groups and evaluating VE in variant-specific eras, the results may not be generalizable to all age groups.

The extent of vaccination completeness and exposure misclassification will be estimated using estimates from the entire population aged less than 65 years. Due to staged authorizations by age group, much of the pediatric population may be vaccinated later in the study period, and changing distribution patterns of vaccination throughout the pandemic may result in more pediatric vaccinations being recorded in pharmacy or medical claims from pediatricians, rather than mass vaccination clinics or public health settings. Therefore, the extent of misclassification may be overestimated by the quantitative bias analyses.

6. References

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Appendices

Appendix 1. Table Shells

Table Shell 1. Characteristics of Individuals Aged 17 Years or Younger Vaccinated With <<COVID-19 vaccine brand >> and Matched Unvaccinated Individuals

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

COVID-19 = coronavirus disease 2019; IQR = interquartile range; SD = standard deviation.

Notes: This table will be created separately for each COVID-19 vaccine brand, if multiple brands are present in the study period.

This table will be recreated without the columns for the unvaccinated group and the standardized difference to describe the characteristics of the vaccinated individuals who failed to match.

Table Shell 2. Association of COVID-19 Outcomes With Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated Among Individuals Aged 17 Years or Younger, Inverse Probability of Treatment–Weighted Vaccine Exposure Groups, Overall and Quantitative Bias Analyses Accounting for Potentially Missing Vaccine Records Resulting in Exposure Misclassification

COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)	Quantitative bias analysis assuming <<XX>>% exposure misclassification VE (95% CI)	Quantitative bias analysis assuming <<XX>>% exposure misclassification VE (95% CI)
Medically diagnosed	BNT162b2							
Medically diagnosed	Unvaccinated				—	—	—	—
Hospital/ED-diagnosed	BNT162b2							
Hospital/ED-diagnosed	Unvaccinated				—	—	—	—

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

Note: Additional vaccine exposure groups may be added, if available during the study period.

Table Shell 3. Association of COVID-19 Outcomes With Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated Among Individuals Aged 17 Years or Younger, Inverse Probability of Treatment–Weighted Vaccine Exposure Groups

Age group	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
16-17 years	Medically diagnosed	BNT162b2					
16-17 years	Medically diagnosed	Unvaccinated				—	—
16-17 years	Hospital/ED-diagnosed	BNT162b2					
16-17 years	Hospital/ED-diagnosed	Unvaccinated				—	—
12-15 years	Medically diagnosed	BNT162b2					
12-15 years	Medically diagnosed	Unvaccinated				—	—
12-15 years	Hospital/ED-diagnosed	BNT162b2					
12-15 years	Hospital/ED-diagnosed	Unvaccinated				—	—
5-11 years	Medically diagnosed	BNT162b2					
5-11 years	Medically diagnosed	Unvaccinated				—	—
5-11 years	Hospital/ED-diagnosed	BNT162b2					
5-11 years	Hospital/ED-diagnosed	Unvaccinated				—	—

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

Note: Additional vaccine exposure groups may be added, if available during the study period.

Table Shell 4. Association of COVID-19 Outcomes With Receiving a Complete Primary Series of COVID-19 Vaccine Compared With Being Unvaccinated in Calendar Periods of Different Predominant Circulating Variants Among Individuals Aged 17 Years or Younger in the US, Inverse Probability of Treatment–Weighted Vaccine Exposure Groups

Variant era	COVID-19 outcome	Vaccine exposure group	N	Events	Person-time (days)	HR (95% CI)	VE (95% CI)
Pre-delta	Medically diagnosed	BNT162b2					
Pre-delta	Medically diagnosed	Unvaccinated				—	—
Pre-delta	Hospital/ED-diagnosed	BNT162b2					
Pre-delta	Hospital/ED-diagnosed	Unvaccinated				—	—
Delta	Medically diagnosed	BNT162b2					
Delta	Medically diagnosed	Unvaccinated				—	—
Delta	Hospital/ED-diagnosed	BNT162b2					
Delta	Hospital/ED-diagnosed	Unvaccinated				—	—
Omicron	Medically diagnosed	BNT162b2					
Omicron	Medically diagnosed	Unvaccinated				—	—
Omicron	Hospital/ED-diagnosed	BNT162b2					
Omicron	Hospital/ED-diagnosed	Unvaccinated				—	—

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

Note: Additional variant eras and vaccine exposure groups may be added, if available during the study period.