FDA Evaluation of a Preliminary Seizure Safety Signal from Rapid Surveillance of Children Ages 2 – 4/5 yrs. following COVID-19 mRNA Vaccination

CBER Surveillance Program Biologics Effectiveness and Safety Initiative (BEST)

Center for Biologics Evaluation and Research (CBER)
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LIST OF ABBREVIATIONS

FDA	Food and Drug Administration
EUA	Emergency Use Authorization
CBER	Center for Biologics Evaluation and Research
NRS	Near Real-Time Surveillance
IIS	Immunization Information System
CPT	Current Procedural Terminology
HCPCS	Healthcare Common Procedure Coding System
NDC	National Drug Codes
CVX	IIS code indicating vaccination
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IP	Inpatient
OP-ER	Outpatient Emergency Room
SCCS	Self-Controlled Case Series
SCRI	Self-Controlled Risk Interval
AR	Attributable Risk
AESI	Adverse Event of Special Interest
SE	Standard Error
CI	Confidence Interval
PPV	Positive Predictive Value
IRR	Incidence Rate Ratio

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1. Background/Introduction

On June 17, 2022 the U.S. Food and Drug Administration (FDA) granted emergency use authorization for the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines for ages 6 months through 4 years and ages 6 months through 17 years, respectively.[1] The Pfizer-BioNTech COVID-19 vaccine is administered as a primary series of three doses and the Moderna vaccine is given as a two-dose primary series. On December 8, 2022 the FDA "amended the emergency use authorizations (EUAs) of the updated (bivalent) Moderna and Pfizer-BioNTech COVID-19 mRNA vaccines to include use in children down to 6 months of age."[2]

The FDA Center for Biologics Evaluation and Research (CBER) is conducting surveillance of the Pfizer-BioNTech (BNT-162b2) and Moderna (mRNA-1273) COVID-19 vaccines and the updated bivalent vaccines using both passive and active surveillance methods to monitor vaccine safety in the pediatric population (those 6 months through 4 years of age for Pfizer-BioNTech (BNT-162b2) and 6 months through 5 years of age for Moderna (mRNA-1273)).[3] For active surveillance, the near real-time surveillance (NRS) method is being utilized.

NRS is a rapid screening method used to quickly identify preliminary statistical signals of potential elevated risk in evaluated outcomes. Given the rapid nature of the approach there is little adjustment for confounding factors or bias (such as seasonality, comorbidities, and others) that may lead to false positive signals. Accordingly, any elevated statistical signals identified in NRS must be further evaluated by FDA using a more fully-controlled, robust epidemiological study.

The NRS evaluated the risk of 19 outcomes after exposure to one of the aforementioned COVID-19 vaccines in three commercial health insurance databases. The NRS detected a statistical signal that exceeded pre-specified thresholds for the seizures/convulsions outcome across different doses in the primary series following exposure to monovalent BNT-162b2 in children aged 2-4 years and monovalent mRNA-1273 in children aged 2-5 years; however, this finding should be viewed with caution. Firstly, the number of events observed in children ages 2 to 4 or 5 years of age is extremely small and estimates reflect substantial uncertainty. At this time, no elevated signal was identified for the seizures/convulsions outcome for any other age groups. Furthermore, the statistical signal was not observed in post-hoc sensitivity analysis. Detection of a statistical signal(s) for seizures/convulsions in the NRS does not mean that it was caused by the vaccination. Thus, the COVID-19 mRNA vaccination is not necessarily associated with seizures, and further evaluation is necessary to determine a potential link between the COVID-19 vaccine(s) and outcome. Additional evaluations indicated that the background rates for seizures/convulsions were three times higher in 2022 relative to the comparator period of 2019 used in NRS,[3] which may account for the observed statistical signal. To test this hypothesis, a post-hoc sensitivity analysis was conducted using 2022 background rates to calculate expected events as the comparator in NRS. This post-hoc sensitivity analysis resulted in no statistical signal for seizures/convulsions. Finally, the outcome definition utilized in the NRS was the same definition that was used for adults and encompassed a broader set of seizures/convulsions outcomes many of which may not be relevant to vaccination in children under 5 years of age. Specifically, our NRS used a broad seizures/convulsions outcome rather than a narrower febrile seizures group, and the risk window included days 0-7 after vaccination. The seizures/convulsions outcome was chosen due to its applicability for older children up to age 18; however, febrile seizures are more common in children under age 5.[4] In the NRS, 72% of seizures identified met the definition of febrile seizures. The general

seizures/convulsions outcome used a 0-7 risk window; however, febrile seizures are more commonly seen in days 0-1 following vaccination, so outcomes observed on days 2-7 may not be associated with vaccination and may have occurred by chance. We did not see a pattern indicating that outcomes were occurring early in the risk window: of all outcomes observed in NRS, 31% occurred on days 0-1.

This protocol details more rigorous study plans to further evaluate the risk of seizures/convulsions following vaccination with the BNT-162b2 vaccine in children aged 2-4 years and mRNA-1273 COVID-19 vaccine in children aged 2-5 years to more adequately characterize the safety signal.

2. Study Objectives

The primary objective of the study is to evaluate the risk of febrile seizures and seizures/convulsions after exposure to BNT-162b2 and mRNA-1273 vaccinations among 2-4/5 year olds using a self-controlled study design.

3. Data Sources

The study will include the following commercial databases: CVS Health, Optum pre-adjudicated claims, and Carelon Research. COVID-19 vaccination data from participating Immunization Information System (IIS) jurisdictions will also be used to supplement claims data in improving the capture of COVID-19 vaccine dose information. The FDA BEST Initiative, through its distributed data network, facilitated linkage of claims data with IIS data to enhance capture of vaccinations in insured populations for vaccine surveillance studies. IIS jurisdictions were solicited to share COVID-19 vaccination data that were then linked to individual-level claims records by individual commercial insurer data partners using personally identifiable information and IIS-specific linkage algorithms. Table 1 outlines the administrative claims data sources included in surveillance, and summarizes claims data characteristics by data source. IIS data characteristics are not presented in Table 1, given the variability in data characteristics by IIS jurisdiction and differences in data partner access to IIS registry data.

Table 1. Description of Administrative Claims Data Sources

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled
CVS Health†	Fully Adjudicated	Monthly	Approximately 80% data completeness in 3-4 months for inpatient claims, 2-3 months for outpatient claims, and 1-2 months for professional claims	0-4 years: > 1.1 million

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled
Optum pre-adjudicated claims†	Pre-Adjudicated	Bi-Weekly	Approximately 80% data completeness in 1-2 months for inpatient, outpatient, and professional claims	0-4 years: > 0.9 million
Carelon Research†	Fully adjudicated	Monthly	Approximately 80% data completeness in 2-3 months for inpatient claims and 1-2 months for outpatient and professional claims	0-4 years: > 1.3 million

**Data lag is based on 2020 claims delay distribution*

†Average number of annual enrollees in a given age category between 2018-2021

4. Exposure

Exposure is defined as receipt of dose 1 and/or dose 2 of the monovalent BNT162b2 COVID-19 or mRNA-1273 COVID-19 pediatric vaccines. Vaccinations will be identified in administrative claims data through vaccine-specific codes including Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Codes (NDCs) in the professional, outpatient institutional, inpatient, or prescription drug care settings, as well as CVX (vaccine administered) codes in IIS data.

Bivalent doses will be excluded from this analysis. Because the bivalent BNT162b2 and mRNA-1273 were only authorized for use in children 6 months on December 8, 2022, not enough time has elapsed to accrue the number of doses in our databases needed to evaluate the bivalent vaccines for risk of seizures/convulsions in this proposed study. Bivalent BNT162b2 and mRNA-1273 may be evaluated at later date when the data allow. Third doses of monovalent formulations of BNT162b2 and mRNA-1273 are also excluded from this analysis due to the small counts, and may be evaluated at later date.

5. Outcome

The primary adverse outcome of interest is febrile seizure; secondary analyses will be conducted for the outcome of seizures/convulsions. Though the NRS finding was identified using the more general seizures/convulsions outcome, our primary outcome will be febrile seizure as this outcome is more biologically plausible and specific in the young age groups. Outcomes will be identified with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes in any diagnosis position in the inpatient and emergency room settings.

The ICD-10 codes used to identify each febrile seizure and seizures/convulsions outcome are included in Appendix Table 2. The care settings in which each outcome will be evaluated, as well as the clean and risk windows for each are described in Table 2. The risk window is defined as an interval post-vaccination during which occurrence of the seizure outcomes may be associated with the vaccine exposure. The first qualifying occurrence of the outcome in the observation period is defined as an

incident seizure outcome only if no outcome of the same type was recorded during the preceding pre-defined clean window. The clean window is defined as a pre-specified period prior to vaccination in which individuals with an occurrence of an event during the pre-specified window are excluded because outcomes captured post-vaccination may be attributed to previous rather than incident risk. Both clean and risk windows are selected based on the literature and consultation with subject matter experts.

Table 2. Outcomes, Settings, Clean Windows and Risk Windows

Outcome	Care Setting	Clean Window	Risk Window
Febrile seizures	IP/OP-ER	42 days	0-1 days (primary analysis); 0-7 days (secondary analysis)
Seizures/convulsions	IP/OP-ER	42 days	0-7 days (secondary analysis)

Abbreviations: IP: inpatient, OP-ER: outpatient emergency room

6. Methods

6.1 Self-Controlled Methods

The self-controlled case series (SCCS) design compares the incidence of adverse events within periods of hypothesized excess risk due to exposure (risk interval) with incidence during selected other times (control interval).[5] In SCCS, only cases (i.e., individuals with an incident outcome) occurring during the study observation period are sampled, with estimation of risk occurring within individuals rather than between individuals.[6] Created to assess the risk of acute events in clearly defined risk intervals, this design implicitly controls for measured and unmeasured time-invariant confounding as each case serves as his/her own control. To address the concern that the occurrence of the outcome may possibly affect the likelihood of subsequent vaccination, we will limit the control intervals for the primary analysis to post-vaccination only. To minimize exposure misclassification, we will restrict the study population to cases who received COVID-19 vaccines.

The self-controlled risk interval (SCRI) design is a special case of SCCS. In SCRI, a person's risk of experiencing the outcome immediately after exposure (risk interval) is compared to the same person's risk of experiencing the outcome in a discretely defined period (control interval), during which the occurrence of the outcome is deemed to be unrelated to the exposure. Unlike the standard SCCS design, the SCRI method requires defining a specific time interval within the observation period as the control interval. Compared to SCCS, SCRI may be less affected by time-varying confounding due to the shorter control interval, while the shorter control interval may reduce statistical power.

The control intervals in both designs can be defined as pre- and post-vaccination, and both have strengths and limitations. A pre-vaccination control interval can facilitate timely analyses. However, the pre-vaccination control interval is subject to bias if the occurrence of the outcome affects the probability of subsequent vaccination, biasing the relative incidence in either direction. If the event only temporarily delays vaccination or increases the probability of vaccination, a pre-exposure period can be excluded to reduce the healthy vaccinee effect. Post-vaccination control intervals will avoid such a bias of reverse causation but require additional data accrual after the post-vaccination risk window, resulting in an analysis delay; the delay of the analysis is greater for outcomes with longer risk intervals.

6.2 Overview of Study Design

The primary analysis will use the SCCS design to estimate the relative risk of febrile seizure by comparing incidence of febrile seizure in a predefined risk window of 0-1 day following COVID-19 vaccination with the incidence in a control window following COVID-19 vaccination.

6.2.1 Assumptions of SCCS Design

The SCCS design has a number of assumptions that have to be met in order to ensure valid unbiased risk estimates. These assumptions are outlined below:

I. Occurrence of an outcome does not substantially affect the probability of subsequent exposures:

The standard implementation of SCCS requires that the exposure must be external. A violation of the assumption could bias the relative incidence in either direction, thus causing reverse causation bias that would affect subsequent exposures. To address this concern, the primary analysis will be restricted to a post-vaccination control interval which will avoid a bias of reverse causation but require additional data accrual after the post-vaccination risk window.

However, given that an event observed post first dose may affect the likelihood of receiving a second dose, this assumption may not be met for the primary all dose analysis. We will include a sensitivity analysis on the all dose population which includes the adjustment described by Farrington et al.[7]

II. Occurrence of an outcome does not affect the observation length

This assumption is met for febrile seizure. Febrile seizure does not have a high case fatality rate; thus, we do not expect the observation length to be affected by outcome occurrence.

III. Outcome rates are constant within risk intervals

This assumption is met for febrile seizure. Note that fluctuations in adverse events can naturally occur based on the day of the week, with week days typically showing proportionally higher event counts than weekend days. This pattern will be investigated for febrile seizure. Seasonality will be assessed as well.

IV. Outcomes must be independently recurrent, or non-reccurent and rare

SCCS are generally considered valid if events are non-recurrent and have a cumulative incidence <0.1 per individual over the total observation period.[8] *If the event is rare enough, we will likely see a single outcome at most for a given individual within the study window, functionally meeting the assumption of independent events.*

6.3 Study Period

The start of the study period is June 17, 2022, the date of EUA for BNT162b2 for ages 6 months-4 years and for mRNA-1273 for ages 6 months-5 years.[9]

The study period will continue through the date for which complete claims data are available for each data source at the time of data extraction.

The completeness threshold will be selected after power analyses are completed to balance the potential bias due to partially accrued observation of post-vaccination control intervals versus risk intervals, and a reasonable delay of the analysis. For instance, a 90% completeness is likely to overestimate relative risk by 10% or less. Assuming that event observation delays are accurately estimated from historical data, a 90% completeness threshold limits the difference in observation of events in risk intervals (at most 100% complete) versus control intervals (at minimum 90% complete). If the true RR is 1, the bias due to observation delay is 1-(100%/90%)=11%. However, in practice risk and control interval completeness will fall between 100% and 90% and we expect the potential bias due to claims delay to be smaller.

6.4 Study Population

For all analyses, the study population will be comprised of enrollees aged 2-4 with incident febrile seizure who received at least one dose of BNT162b2 and enrollees aged 2-5 with incident febrile seizure who received at least one dose of mRNA-1273. Febrile seizure events will be defined as incident for a subject if there are no claims for febrile seizure in the 42-day clean period preceding the seizure event date.

For attributable risk calculations, we will identify a population of all eligible vaccinations, meeting all of the inclusion and none of the exclusion criteria below.

Inclusion criteria:

(i) Receive at least one dose of a COVID-19 vaccine; and
(ii) Are aged 2-4 years at the time of BNT162b2 administration or aged 2-5 years at the time of mRNA-1273 administration; and
(iii) Are enrolled in a medical plan during the observation period and the clean window.
- Continuous enrollment will be required from 42 days prior to the vaccine dose of interest until the earlier of 63 days post-vaccination, disenrollment, administration of a subsequent COVID-19 vaccine, death or study period end.

Exclusion criteria:

(i) Does not contribute follow-up time to both risk and control intervals. If individuals disenroll, die, or reach the end of the study period during the risk window prior to accumulating any time for post-vaccination control intervals, they will be excluded. The minimum time required to contribute to the control period will range from 1-7 days and will be decided after power analyses are completed.
(ii) Had COVID-19 vaccination patterns that do not conform to expectations for the analysis of interest, e.g., doses that occur within a short time period following another dose or have a higher than expected dose number; more specific rules will be determined once more data on vaccination patterns are available.
(iii) Received different COVID-19 vaccines for the primary series.

An individual's first observed dose being ineligible (e.g., due to insufficient enrollment prior to vaccination) does not automatically exclude that individual's second observed dose. If the second observed dose meets all eligibility requirements it will be included in the all-dose analysis.

We will identify febrile seizure cases among eligible vaccinated individuals who:

(i) Have an incident event of febrile seizure during the study observation period

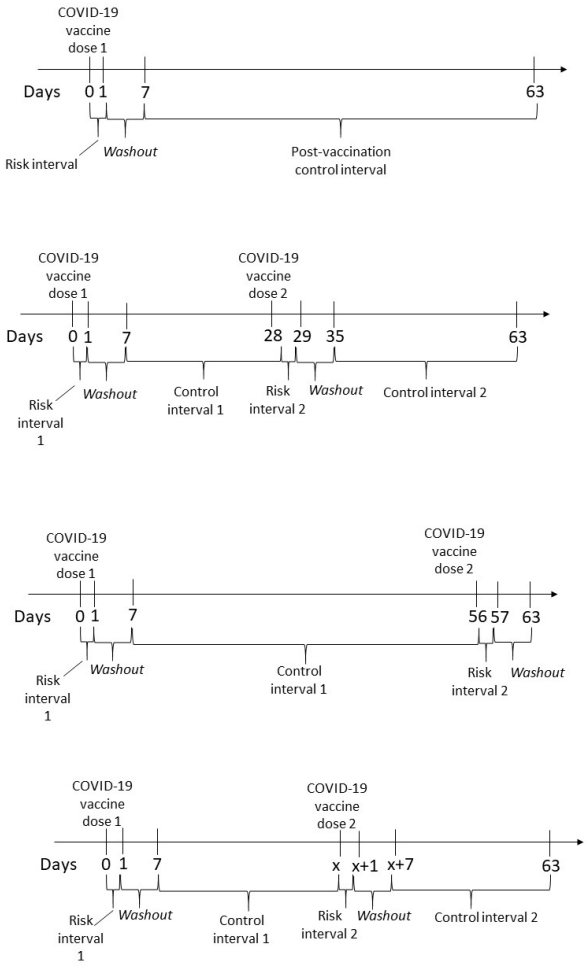
We will exclude febrile seizure cases among eligible vaccinated individuals who

(i) Have a diagnosis of febrile seizure during the 42-day clean period (in IP/OP-ED setting)

6.5 Risk and Control Windows

The observation period will start from the vaccination date (day 0) of the first dose, if there are two doses, and extend to day 63. The risk window will be defined as days 0-1 after each dose. There will be a washout period from days 2-7 following each vaccination. The post-vaccination control interval is defined as all follow-up time during the observation period following either the first or second COVID-19 vaccine dose that is outside of the risk interval(s) and washout period(s) until day 63 post-vaccination, end of study period, disenrollment, or death, whichever occurs first; this includes any time between the end of the first dose risk window and the receipt of a second dose. Individuals who only accrued data during the risk intervals will be ineligible to be included in the analysis (Section 6.4). Figure 1 presents hypothetical design examples.

Figure 1: Hypothetical examples of SCCS design with post-vaccination control intervals for one-dose and two-dose vaccines



6.6 Statistical Analysis

Analyses will be conducted separately within each database and a meta-analysis will be performed (Section 6.6.2). The meta-analysis results will be considered primary to the database-specific results.

6.6.1 Descriptive Analysis

A descriptive analysis will be conducted summarizing counts and percentages of febrile seizure outcomes by covariates of interest such as age, sex, and U.S. region.

6.6.2 Primary Analysis

Rate Ratio (IRR) estimation

For the primary self-controlled analysis, the risk of the febrile seizure following any dose will be evaluated, without distinguishing between dose numbers. This analysis will compare the febrile seizure rates in the risk and control intervals using a conditional Poisson regression model. For multi-dose COVID-19 vaccines, the model assumes constant risk throughout each risk window, regardless of how

close together the doses may be administered. Under the assumption of constant risk, the following model will be fit:

$$\log\big(E(Y|X)\big) = \beta_1(risk\_interval) + \log(t) + strata(patient\_id)$$

$$Y = seizure$$
$$risk\_interval$$
$$= binary\ term\ indicating\ seizure\ occurrence\ in\ risk\ interval$$
$$t = time, in\ days$$
$$patient\_id = term\ identifying\ the\ patient$$

Under this model, the null and alternative hypotheses can be written as:

$$\mathrm{H}_0: e^{\beta_1} = 1 \qquad \mathrm{H}_a: e^{\beta_1} \neq 1$$

where e^{β_1} will be interpreted as the IRR for the febrile seizure in the risk interval compared to the control intervals. Thus, statistical significance of the coefficient on the risk interval variable at a pre-specified level will indicate a statistically significant association between COVID-19 vaccination and the febrile seizure. Statistical significance will be determined using 95% confidence intervals of rate ratios and two-sided p-values ($p \leq 0.05$).

Attributable Risk (AR) estimation

The study will estimate the AR (per million vaccinations). The number of excess cases due to the vaccine will be directly derived from the conditional Poisson regression model, defined as the difference between the sum of the model fitted values (i.e., model predicted number of cases), and the sum of the expected cases if there were no vaccination (i.e., all observed time is treated as control time). The unadjusted AR is the excess number of AESI cases divided by the number of eligible vaccinations (or eligible follow up dose-years). The standard error (SE) of the unadjusted AR is estimated by bootstrap resampling 10,000 times.[10] For each iteration, the study will sample the beneficiaries with AESI with replacement and repeat the AR calculation. The SE is calculated as the square root of the variance of the 10,000 AR values. The AR following COVID-19 vaccination may be compared to the AR following other vaccinations and other AESI-triggering exposures. While the unadjusted ARs are directly obtained from the primary claims-based analysis and secondary chart-confirmed analysis, they might not be truly representative of the underlying AESI risk. Thus, a positive predictive value (PPV)-adjusted AR may be calculated following the completion of the medical record review (see Section 7 for the medical record review process).

Meta-Analysis

A common study protocol and a standard analytical package will be used across all three commercial claims databases that cover populations with similar demographics. A meta-analysis will be performed to pool results from all three databases to gain higher precision and statistical power using both random-effects and fixed-effect models.

The goal of the meta-analysis is to estimate the pooled result:

$$\hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k \omega_k}{\sum_{k=1}^{K} \omega_k}$$

Where $\hat{\theta}_k$ is used to represent the estimator (log of rate ratio) estimated from each data source, where k = 1,2,3 indicates the data sources — Optum, Carelon Research, CVS Health, respectively; ω is a weight assigned to each estimate.

Random-Effects Meta-Analysis

We will use random-effects meta-analysis to account for the between-study heterogeneity across multiple data sources.

The random-effects model takes the form:

$$\hat{\theta}_k = \mu + \zeta_k + \epsilon_k$$

Where μ is the global true effect of interest, ζ_k is a data source specific random error term and ϵ_k is data source specific sampling error term.

The pooled effect can be estimated by the inverse-variance method

$$\hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k \omega_k^*}{\sum_{k=1}^{K} \omega_k^*}$$

$$\omega_k^* = \frac{1}{s_k^2 + \tau^2}$$

where s_k^2 represents variance of $\hat{\theta}_k$ estimated for each study, and τ^2 is the variance of the distribution of true effect sizes.

The Paule-Mandel method will be used to estimate τ^2 as suggested by Veroniki (2016) and Bakbergenuly (2020) additionally found that the Paule-Mandel estimator is well-suited for when the number of studies is small. As a sensitivity analysis, we will use the DerSimonian-Laird and restricted maximum likelihood (RMLE) estimators for τ^2 in order to assess the variation in the estimation of τ^2 due to the small number of studies.

Fixed-Effect Meta-Analysis

To address concerns that the random-effects method may not perform well when the number of studies is small, we will additionally run a fixed-effect meta-analysis. The fixed-effects model takes the form:

$$\hat{\theta}_k = \mu + \epsilon_k$$

Where μ is the global true effect of interest, and ϵ_k is data source specific sampling error term. The pooled effect can be estimated by the inverse-variance method

$$\hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k \omega_k}{\sum_{k=1}^{K} \omega_k}$$

$$\omega_k = \frac{1}{s_k^2}$$

where s_k^2 represents variance of $\hat{\theta}_k$ estimated for each study.

Evaluating Between-Study Heterogeneity

Heterogeneity in a meta-analysis refers to the variation between studies. Evaluating the extent of heterogeneity helps determine the appropriateness of combining different studies. This section describes the methods we will use to evaluate between-study heterogeneity.

Forest Plots

Forest plots will be generated to visualize the variation of rate ratios and 95% CIs across data sources.

Cochran's Q

Cochran's *Q* is defined as a weighted sum of squares (WSS).

$$Q = \sum_{k=1}^{K} \omega_k \left(\hat{\theta}_k - \hat{\theta}\right)^2$$

We will use the value of *Q* to check if there is excess variation in our data. If there is no between-study heterogeneity, Q will approximately follow a chi-square distribution with K-1 degrees of freedom. As Q may be sensitive to the number of studies assessed, an additional complementary statistic will be assessed (further details below).

Higgins & Thompson's I^2 Statistic

We will also calculate Higgins & Thompson's I^2 statistic, which is defined as the percentage of variability in the effect sizes that is not caused by sampling error:

$$I^2 = \frac{Q - (K-1)}{Q}$$

- I^2 = 25%: low heterogeneity
- I^2 = 50%: moderate heterogeneity
- I^2 = 75%: substantial heterogeneity

The 95% CI for I^2 will also be calculated.

6.6.3 Alternate Risk Window Analysis

A secondary analysis with the 0-7 day risk window will be performed. No washout period will be used. Sensitivity analyses will be considered if significant results are found.

6.6.4 Secondary Outcome Analysis

A secondary analysis with the general seizures/convulsions outcome will be performed. A 0-7 day risk window will be used. Sensitivity analyses will be considered if significant results are found.

6.6.5 Concomitant Vaccines Analysis

COVID-19 vaccines may be given at the same time as other vaccinations. Vaccines recommended by the CDC to be administered to children from 6 months through 6 years of age include[11]:

(i) **Hepatitis B**, third dose: *6-18 months of age*
(ii) **Rotavirus**, third dose: *6 months of age*
(iii) **Diphtheria, tetanus, & acellular pertussis (DTaP)**, third, fourth, and fifth doses (brand dependent): *6 months, 15-18 months, 4-6 years of age, respectively*
(iv) **Haemophilus influenzae type b (Hib),** third, fourth doses (brand dependent): *6 months, 12-15 months, respectively*
(v) **Pneumococcal conjugate (PCV13, PCV15),** third, fourth doses (brand dependent): *6 months, 12-15 months, respectively*
(vi) **Inactivated polio virus (IPV)**, third, fourth doses: *6 and 18 months and 4-6 years of age, respectively*
(vii) **Influenza** (annually)
(viii) **Measles, Mumps, & Rubella (MMR)** first and second dose: *12-15 months, 4-6 years of age, respectively*
(ix) **Varicella**, first and second dose: *12-15 months, 4-6 years of age, respectively*
(x) **Hepatitis A** 2-dose series: *between 12 and 23 months of age*

There was a potential risk of febrile seizures following the Measles, Mumps, and Rubella (MMR) and Measles, Mumps, Rubella, and Varicella (MMRV) vaccines in the 5 to 12 days after vaccination.[4] FDA additionally identified an increased risk of febrile seizure when the inactivated influenza vaccine is given at the same visit as the PCV13 or the DTaP vaccine.[12] Though an increased risk was identified for febrile seizure following the influenza vaccine alone in the 2010-2011 season,[13] no independent risk of febrile seizure (i.e., without concomitant vaccination) was identified in later seasons.[14] No independent risk of febrile seizure has been identified following DTaP vaccination. There may be a small increased risk of febrile seizure when PCV13 (pneumococcal) vaccine is administered alone.[4]

We will conduct a subgroup analysis on concomitant vaccination, considering the MRR/MMRV, PCV13, DTAP, and influenza vaccines. Specifications will be determined following a descriptive analysis assessing the timing and frequency of concomitant vaccinations.

6.6.6 Sensitivity Analysis

Sensitivity analyses will include seasonality adjustment, event dependent exposure adjustment, and adjustment for the positive predictive value (PPV) determined from medical record review.

Seasonality Adjustment

To evaluate potential time-varying confounding given the length of the observation period, the study will assess the association of time-varying risk factors with the seizure outcomes and adjust for the changing risk of the seizure outcomes, namely that seizure may exhibit seasonal trends. Baseline seizure outcomes risk will be estimated from the within-study background rates of seizure and will be included as an offset term in the Poisson regression model.

Farrington Adjustment

An all-dose analysis containing the event dependent exposure adjustment proposed by Farrington will be conducted.[7] This analysis will address concerns that the primary analysis may violate the assumption that events will not influence subsequent exposures, given that individuals who experience seizure may not receive a subsequent dose. The modified SCCS analysis adjusting for censored, perturbed or curtailed post-event exposures allows us to estimate the rate ratio of all doses after adjusting exposures whose occurrence is influenced by the event (i.e., second doses of the COVID-19 vaccination).

PPV-Adjusted Analysis

In the case of significant results in the primary analysis, we may also conduct an analysis adjusting for the PPV of the febrile seizure definition using quantitative bias analysis to reflect the uncertainty in the claims-identified cases (i.e., "QBA-imputed" analysis). We will use the PPV resulting from the medical record review process. This adjustment will be used to assess results robustness by using the claims-based febrile seizure definition. Quantitative bias analysis may be conducted by creating multiple datasets where the status of claims-identified febrile seizure cases is imputed by assigning them the status of "chart-confirmed" with probability equal to the PPV. The PPV is calculated as the number of chart-confirmed febrile seizure cases over the total number of charts returned via the medical record review process; cases with "insufficient evidence" are not considered as chart-confirmed. A PPV will be calculated from cases identified during the risk window. Analyses conducted on each of the individual imputed datasets can be combined using a rule developed by Schenker and Rubin.[15] Assuming normality of the coefficient estimates, the p-values for the imputed analyses are found by dividing the coefficient estimate by the model's standard error to generate the z-statistic. We may additionally produce figures displaying distribution of the risk ratios from the imputed datasets resulting from our positive predictive value adjustment.

6.7 Statistical Power and Sample Size

To ensure sufficient sample size, a power analysis will be conducted to evaluate the minimum detectable IRR for each of the seizure outcomes following COVID-19 vaccination, at varying power levels and a two-sided alpha of 0.05. A minimum detectable IRR will be calculated at various data cutoff dates for the study, and the study cutoff data date will be determined based on an assessment of minimum risk detection at varied timeframes. Varying data completeness thresholds (90%, 85%, 90%) at the

specified data cutoff date to reduce differences in data accrual and the likelihood of observing events during risk relative to control intervals. Minimum control time of 1 day and 7 days will also be assessed.

7. Medical Record Review

We will conduct medical record review of claims-identified cases in the risk and control windows. Records will be adjudicated using the Brighton collaboration definition for seizure, which will be further modified to differentiate febrile from non-febrile seizures.[16] The study will identify appropriate clinical reviewers to review the redacted medical records and adjudicate the cases.

A sample size of up to 50 adjudicated cases for each safety outcome will result in precision within 15% to estimate a positive predictive value (PPV) of 0.8. The PPV is defined as the likelihood that a person with the diagnosis code recorded in administrative claims data within a prespecified period actually has the disease (as defined by clinical adjudication).

8. References

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9. Appendix

9.1 COVID-19 Monovalent Dose Vaccine Administration Code List

Appendix Table 1 presents COVID-19 monovalent vaccine administration codes available in CPT, HCPCS, NDC diagnosis and medical service coding vocabularies as of October 3, 2022.

Appendix Table 1. COVID-19 Monovalent Vaccine Administration Codes in Claims and IIS data

Manufacturer	Name	Code Type	Code	Dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	CVX Codes (IIS-Specific)	208	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	CVX Codes (IIS-Specific)	217	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	CVX Codes (IIS-Specific)	218	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	CVX Codes (IIS-Specific)	219	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	HCPCS/CPT Code	91300	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	HCPCS/CPT Code	91305	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	HCPCS/CPT Code	91307	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	HCPCS/CPT Code	91308	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0001A	1st dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0051A	1st dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0071A	1st dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0081A	1st dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0002A	2nd dose

Manufacturer	Name	Code Type	Code	Dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0052A	2nd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0072A	2nd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0082A	2nd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0003A	3rd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0053A	3rd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0073A	3rd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0083A	3rd dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0004A	Booster dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0054A	Booster dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	Vaccine Administration Code	0074A	Booster dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	00069-2025-01	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	00069-2025-10	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	00069-2025-25	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-0078-01	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-0078-02	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-0078-04	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1000-01	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1000-02	Non-Specific

Manufacturer	Name	Code Type	Code	Dose
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1000-03	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1025-01	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1025-02	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1025-03	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1025-04	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1055-01	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1055-02	Non-Specific
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	59267-1055-04	Non-Specific
Moderna	Moderna COVID-19 Vaccine	CVX Codes (IIS-Specific)	207	Non-Specific
Moderna	Moderna COVID-19 Vaccine	HCPCS/CPT Code	91301	Non-Specific
Moderna	Moderna COVID-19 Vaccine	HCPCS/CPT Code	91306	Non-Specific
Moderna	Moderna COVID-19 Vaccine	HCPCS/CPT Code	91309	Non-Specific
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0011A	1st dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0091A	1st dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0012A	2nd dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0092A	2nd dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0013A	3rd dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0093A	3rd dose

Manufacturer	Name	Code Type	Code	Dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0064A	Booster dose
Moderna	Moderna COVID-19 Vaccine	Vaccine Administration Code	0094A	Booster dose
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	61434-0043-00	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	61434-0043-01	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0100-11	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0100-98	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0100-99	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0277-05	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0279-05	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0273-10	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0273-99	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0273-15	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0273-98	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0275-05	Non-Specific
Moderna	Moderna COVID-19 Vaccine	NDC 11 Labeler Product ID (Vial)	80777-0275-99	Non-Specific

9.2 ICD-10 Codes for Febrile Seizures and Related Disorders

Appendix Table 2 includes the ICD-10 codes used to identify the outcomes of interest.

Appendix Table 2. ICD-10-CM for Febrile Seizures and Related Disorders

Code	Description	Primary Outcome: Febrile Seizure	Secondary Outcome: Seizures/Convulsions	Code Type
R56.00	Simple febrile convulsions	Yes	Yes	ICD-10-CM
R56.01	Complex febrile convulsions	Yes	Yes	ICD-10-CM
R56.9	Unspecified convulsions	No	Yes	ICD-10-CM