NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Effectiveness of BNT162b2 formulations using state vaccine registry and insurance claims data
Protocol number	C4591065
Protocol version identifier	1.0
Date	15 November 2023
Medicinal product	Pfizer BNT162b2 formulations
Research question and objectives	**What is the real-world effectiveness of BNT162b2 formulations?** Primary objective: 1. To evaluate vaccine effectiveness (VE) of BNT162b2 formulations in non-pregnant, non-immunocompromised adults (age 18+) against medically attended COVID-19, mortality, and healthcare resource utilization by age and adapted vaccine formulation. Secondary objectives 2. To assess VE of BNT162b2 formulations in pediatrics (age < 18) against medically attended COVID-19, non-COVID-19 respiratory infections, mortality, and healthcare resource utilization by age and adapted vaccine formulation. 3. To estimate short-term (3A) and long-term (3B) healthcare resource utilization and costs associated with COVID-19 by vaccination status, age, and site of care. Exploratory objectives 4. To measure VE of BNT162b2 formulations in non-pregnant immunocompromised adults (age 18+) against medically attended COVID-19, mortality and healthcare resource utilization by age and adapted vaccine formulation. 5. To quantify differences in VE of BNT162b2 formulations in non-pregnant, non-immunocompromised adults (age 18+) when co-administered with seasonal influenza vaccines versus when each vaccine is given separately, by age groups.
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	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
aHR	Adjusted hazard ratio
aRR	Adjusted risk ratio
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CVX	Clinical Vaccines Administered code
EHR	Electronic health records
EUA	Emergency use authorization
FDA	US Food and Drug Administration
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICU	Intensive care unit
IPTW	Inverse probability of treatment weighting
KPSC	Kaiser Permanente of Southern California
OR	Odds ratio
RD	Risk differences
RSV	Respiratory syncytial virus
SMD	Standardized mean differences
TND	Test negative design
NPI	National provider identifier
VE	Vaccine effectiveness
US	United States

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4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned Date
Start of data collection	01 January 2024
End of data collection	31 March 2024
Final study report	31 May 2024

6. RATIONALE AND BACKGROUND

Administrative claims data have traditionally had limited capabilities for studying vaccinated populations. This limitation is a function of the varied settings in which vaccines may be administered to a patient and whether an individual transaction is generated. Non-medical settings (e.g., workplace, schools, public venues, etc.) and mass events (e.g., vaccination clinics, Federal Emergency Management Agency, etc.) typically only require roster billing for reimbursement. A roster claim form only records the date of vaccine administration; provider's name and national provider identifier (NPI); and patient's ID (e.g., Medicare ID, driver's license, etc.), date of birth, name, gender, and address.[1] Importantly, the roster is submitted with a modified CMS-1500 "cover" claim to capture the vaccine information, however, individual CMS-1500 claims that link the patient information to the cover claim are never generated. Since traditional claims databases capture and report the individual CMS-1500 claim form, vaccinations conducted via roster billing were lost. However, although roster billing does not generate individual CMS-1500 claims, the linkage between the roster and vaccine information are reconciled by various state entities to populate vaccine registries.

Until recently, vaccine registries were not available for de-identification and linkage to secondary claims-based databases. However, through a collaboration with HealthVerity, a leading supplier of secondary health data, the State of California and the State of Louisiana have made their vaccine registries available for linkage for research purposes. California and Louisiana deidentify the registries, using HealthVerity's software to convert each patient's protected health information to a unique HealthVerity ID which can then be linked to the full HealthVerity database to gather clinical history and outcomes. This protocol defines the utilization of HealthVerity data, linked to the State of California/Louisiana's vaccine registry, for studies of VE and uptake for populations of interest.

The ability to link the State of California/Louisiana's vaccine registry to a secondary claims-based database provides a unique opportunity to maximize the capabilities of real-world data and efficiently conduct VE studies on a variety of targeted populations and endpoints, including the updated monovalent XBB.1.5 COVID-19 vaccine formulation.

TABLE 1. TIMELINE OF KEY BNT162B2 REGULATORY MILESTONES

Vaccine formulation	Age group	Event
BNT162b2 monovalent XBB.1.5 COVID-19 vaccine	Age 12 and older	11 September 2023: U.S. Food and Drug Administration (FDA) approval[2]
	Age 6 months to 11 years	11 September 2023: FDA emergency use authorization (EUA)[2]
	N/A	15 June 2023: (FDA)'s Vaccines and Related Biological Products Advisory Committee recommended that COVID-19 vaccines for 2023-2024 be updated to a monovalent XBB.1.5 vaccine.[3]
BNT162b2 bivalent BA.4/5 COVID-19 vaccine	Age 12 and older	31 August 2022: FDA EUA[4]
	Age 5 to 11	12 October 2022: FDA EUA[5]
	Age 6 months to 4 years	08 December 2022: FDA EUA[6]
BNT162b2 wild-type booster dose(s) COVID-19 vaccine	Age 5 to 11	17 May 2022: FDA authorized first booster dose
	Age 50 and older, and immunocompromised individuals	29 March 2022: FDA authorized second booster dose
	Age 65 and older, and individuals with potentially high risk that were age 18-64	22 September 2021: FDA authorized single booster dose
BNT162b2 wild-type primary series COVID-19 vaccine	Age 6 months to 4 years	17 June 2022: FDA EUA
	Age 5 to 11	29 October 2021: FDA EUA
	Age 16 and older	23 August 2021: FDA approval
	Age 12 to 15	10 May 2021: FDA EUA
	Age 16 and older	11 December 2020: FDA EUA

This protocol is not designated as a post-approval safety study (PASS) and is not a commitment to any regulatory bodies.

7. RESEARCH QUESTION AND OBJECTIVES

What is the real-world effectiveness of BNT162b2 formulations?

This study is descriptive in nature and as such does not include any pre-specified hypotheses.

Primary objective:

1. To evaluate the VE of BNT162b2 formulations in non-pregnant, non-immunocompromised adults against medically attended COVID-19, mortality and healthcare resource utilization by age and adapted vaccine formulation.

   Main summary measure: VE = (1 – adjusted hazard ratio [aHR]) * 100, comparing vaccinated to unvaccinated persons

Secondary objectives

2. To assess VE of BNT162b2 formulations in pediatrics against medically attended COVID-19, non-COVID-19 respiratory infections, mortality and healthcare resource utilization by age and adapted vaccine formulation.

   Main summary measure: VE = (1 –aHR) * 100, comparing vaccinated to unvaccinated persons

3. To estimate short-term (3A) and long-term (3B) healthcare resource utilization and costs associated with COVID-19 by vaccination status, age, and site of care.

   Main summary measure: Inpatient healthcare expenditure comparing vaccinated to unvaccinated persons (3A); and total healthcare expenditure comparing COVID-19 to non-COVID-19 patients (3B).

Exploratory objectives

4. To measure VE of BNT162b2 formulations in non-pregnant immunocompromised adults against medically attended COVID-19, mortality and healthcare resource utilization by age and adapted vaccine formulation.

   Main summary measure: VE = (1 –aHR) * 100, comparing vaccinated to unvaccinated persons

5. To quantify differences in VE of BNT162b2 formulations in non-pregnant, non-immunocompromised adults when co-administered with seasonal influenza vaccines versus when each vaccine is given separately, by age groups.

   Main summary measure: aRR to evaluate non-inferiority, comparing people with co-administered vaccines to BNT162b2 vaccine alone for COVID-19-related outcomes

   Main summary measure: aRR to evaluate non-inferiority, comparing people with co-administered vaccines to seasonal influenza vaccine alone for influenza-related outcomes

8. RESEARCH METHODS

We will utilize a target trial emulation design in order to identify patients for follow-up based on qualifying events.[7] The target trial emulation design is a pragmatic framework that reflects real-life clinical behaviors of non-randomized exposures and subsequent outcomes (see Table 1).

A test-negative design (TND), which is a modified form of a case-control study, is commonly used in VE studies. In the TND, cases and controls are identified from persons who sought testing for a pathogen, which may increase comparability between groups as there is an association with vaccination and healthcare seeking behavior. However, for this study a retrospective cohort design was chosen over the TND for the following reasons:

1. Administrative claims data do not contain test results, which would be a necessary data element for conducting a TND study. While HealthVerity offers the option to potentially add EHR data, and separately tokenization to laboratory results through LabCorp or Quest, this is not part of the current suite of purchased data.

2. Given the end of the COVID-19 Public Health Emergency in May 2023, COVID-19 tests are no longer required to be covered by private or public insurers unless ordered by a physician.[8,9] This may create selection bias, in that persons paying out of pocket to access testing likely differ from those who are not testing.[10] A TND of those who have sought testing for COVID-19 has the potential for estimates that are different from the general population, [11] owing to distorted associations between factors related to healthcare seeking in the analysis population compared with the general population.[12]

    a. If those testing at their own expense are more likely to become diagnosed with COVID-19, such as those at higher risk of severe disease, then VE estimates would be biased towards the null.

    b. Conversely, if there was a healthy-user effect or increased uptake among higher socioeconomic position groups, VE estimates would be biased away from the null.

3. A key assumption of the TND is that exposure (here, COVID-19 vaccination) does not impact the probability of selection in the case (a positive test result on a COVID-19 test) or control population (a negative test result on a COVID-19 test). It is possible that vaccinated persons may be less likely to be seek testing in order to become a case than unvaccinated persons. This, if present, would create collider stratification bias via the requirement for testing in a TND, which biases estimates away from the null and may lead to overestimations of VE.[12-14]

4. Owing to the case-control nature of the design, TND allows for estimation of odds ratios (OR) but not hazard or risk ratios. OR are not directly interpretable as percentage reduction in risk, which is an easily interpretable summary measure of VE. OR with a protective direction of effect (ratio < 1) will underestimate risk, leading to underestimations of VE.[15] A cohort design allows for absolute estimates of risk such as risk differences.

The use of a retrospective cohort study allows for the adoption of design principles of randomized control trials to help mitigate some of these biases.[7]

Cohort identification will begin from the date of EUA or FDA approval for the BNT162b2 formulation. Study follow-up will occur from FDA EUA or approval date until COVID-19 diagnosis or other outcome of interest (hospitalization, emergency department visit, outpatient encounter, end of medical and/or pharmacy enrollment, or death [according to the mortality database]).

In aims 1, 2 and 4, vaccination status will be measured as a time-varying exposure. In aims 3 and 5, vaccination status will be measured as a time-fixed exposure. Exposed person-time begins 14 days after receipt of a BNT162b2 formulation. Unexposed person-time is unvaccinated person-time, as well as 0-13 days after vaccination. The unexposed group will be further stratified by previous vaccination status for relative VE: XBB.1.5 unvaccinated and BA.4/5 vaccinated; XBB.1.5 and BA.4/5 unvaccinated and at least 2 doses of mRNA vaccine (regardless of formulation); never COVID-19 vaccinated.

The full data available, from 01 December 2018, will be used as the look-back period to define patient's characteristics, clinical history, risk factors, and healthcare utilization.

TABLE 2. TARGET TRIAL AND TARGET TRIAL EMULATION

Target Trial Specification[16,17]	Target Trial Emulation
Eligibility criteria	
Inclusion criteria in trials generally reflected age-related eligibility for vaccination.	For brevity, we will not discuss each of the 5 aim's different inclusion criteria here. Throughout, we used age at time vaccine was authorized or approved by FDA for time-varying exposures, age at vaccination for time-fixed exposures to reflect age-related eligibility. We require continuous pharmacy and medical enrollment in HealthVerity prior to index date (FDA EUA date per vaccine) for follow-up. This is in order to establish pre-existing health status, which would have been queried at study entry in the clinical trials. We require continuous California/Louisiana residency to maximize pre-index capture of vaccines, as people living outside of California /Louisiana would not have prior vaccines well captured in the registry.
	Throughout, we will exclude people who are currently pregnant, using a validated

• Exclusion criteria
  ○ Pregnant
  ○ Treatment with immunosuppressive therapy or diagnosis with an immunocompromising condition
  ○ History of COVID-19
	gestational age algorithm with up to 9 months lookback.[18]
	
	Except in aim 4, where the analyses are specific to immunocompromised persons, we will exclude immunocompromised people considering claims for medications dispensed as well as and diagnosis codes.
	
	We will exclude persons with a diagnosis of COVID-19 in any setting ≤ 90 days prior to index. We are limiting to 90 days as reinfections have become more common over the pandemic and were rare during the Fall 2020 clinical trial period. We believe 90 days represents a reasonable period in which persons then can be considered to be at risk for reinfection, and also are eligible for vaccination.[19]
	
	We will exclude individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets, as these are key confounders in all analyses. Secondary deidentified data makes it impossible to reconcile differences, which would be expected to be resolved with primary data collection.

Treatment strategies	
Receive 1 dose of a BNT162b2 adapted formulation vs. no BNT162b2 formulation or other COVID-19 vaccine (XBB.1.5 or BA.4/5 depending on timing)	All persons will be considered unvaccinated from date of US Food and Drug Administration (FDA) date of vaccine authorization/approval until, where applicable, 13 days after receipt of vaccine. In order to allow for time after dose for meaningful immunologic protection to accrue, persons will be considered vaccinated 14 days after vaccination.[20,21] • For BA.4/5 vaccine in adults: FDA emergency use authorization date 31 August 2022[4] • For XBB.1.5 vaccine: FDA approval date 11 September 2023[2]

Assignment procedures	
Randomization: Eligible participants randomly assigned to receive dose of BNT162b2 XBB.1.5 vs. no BNT162b2 XBB.1.5	Adjustment for confounding factors which might influence a person's probability of exposure, using direct adjustment in time-varying exposure models and inverse probability of treatment weighting (with doubly robust adjustment, if necessary) in time-fixed exposure models.
Outcome(s)	
Confirmed COVID-19	Medically attended COVID-19, as 1. A COVID-19-related encounter, regardless of setting (primary outcome) 2. An outpatient encounter with ICD-10-CM U07.1 "COVID-19" code 3. An inpatient encounter with ICD-10-CM U07.1 "COVID-19" listed in any diagnosis position. As a sensitivity analysis, we will restrict to U07.1 in primary diagnosis field. 4. An emergency department encounter with ICD-10-CM U07.1 "COVID-19" code 5. Critical illness, defined as intensive care unit [ICU] admission, mechanical ventilation, or inpatient death. If sample size allows, we will evaluate VE against each component separately in order to support V&E models, including where possible ICU with and without mechanical ventilation. 6. An urgent care visit with ICD-10-CM U07.1 "COVID-19" code And separately, not necessarily due to COVID-19: 7. All-cause mortality within 3-months of COVID-19 encounter, regardless of setting 8. All-cause mortality within 3-months of COVID-19 outpatient encounter 9. All-cause mortality within 3-months of COVID-19 inpatient encounter

	10. All-cause mortality within 3-months of COVID-19 emergency department encounter 11. All-cause mortality within 3-months of COVID-19 critical illness 12. All-cause mortality within 3-months of urgent care encounter for COVID-19 *Note: aim 2 has additional non-COVID-19 respiratory illness outcomes and aim 5 has influenza outcomes. They are not represented here as the purpose of this chart is to demonstrate the target trial framework, and these outcomes were not assessed in clinical trials for licensure.*
Follow-up	
Analysis is limited to individuals still at risk on day 14 after vaccination/randomization	Unvaccinated follow-up time will occur from the date of FDA authorization/approval until 13 days after the receipt of vaccination, the outcome of interest, or are censored at the first of the following: 6 months of follow-up, end of medical and/or pharmacy enrollment, receipt of a non-Pfizer BioNTech vaccine or receipt of a second BNT162b2 COVID-19 vaccine dose. Vaccinated follow-up time will occur from 14 days after the receipt of vaccination until the outcome of interest or are censored at the first of the following: 6 months of follow-up, end of medical and/or pharmacy enrollment, receipt of a non-Pfizer BioNTech vaccine or receipt of a second BNT162b2 COVID-19 vaccine dose.
Causal contrasts of interest	
Per-protocol effect	Observational analog of the per-protocol effect, using sensitivity analyses and negative control outcomes to examine the quantitative impact of design and analytic assumptions.
Statistical analysis	
In BNT162b2 Fall 2020 clinical trial, VE estimated as (1-IRR)*100, comparing vaccinated with unvaccinated persons, where IRR is the incidence rate ratio per 1000 person-years.	VE estimated as (1-aHR) for aims 1, 2 and 4 (time-varying exposures), and (1-aRR) for aim 5 (time-fixed exposure).

In mRNA-1273 Fall 2020 clinical trial, (1-aHR)*100.	

8.2. Setting

Patients who were California or Louisiana residents in the HealthVerity claims database will be defined using the following hierarchical definition:

1. Persons who have their enrollment file record indicating a patient location of California or Louisiana in HealthVerity claims enrollment file.

2. Persons who have a patient state location other than California or Louisiana in HealthVerity claims enrollment but have one or more records in the California or Louisiana Immunization Registry. *Examples include people who previously lived in Texas but moved to California and received a vaccine, or persons who crossed state lines for a vaccine and remain in their non-California state in claims data.*

XBB vaccinations will be enumerated using the following hierarchical definition:

1. Any person in HealthVerity claims data who has a record in the California/Louisiana Immunization Registry with a CVX code indicating having received the BNT162b2 XBB.1.5 monovalent mRNA vaccine will be considered vaccinated 14 days after registry event date.

2. Any person in HealthVerity claims data who does not have a record in the California/Louisiana Immunization Registry but has a pharmacy claim with an NDC code indicating a BNT162b2 XBB.1.5 monovalent mRNA vaccine dose will be considered vaccinated 14 days after claim date.

3. Any person in HealthVerity claims data who does not have a record in the California/Louisiana Immunization Registry and does not have a pharmacy claim with an NDC code indicating a BNT162b2 XBB.1.5 monovalent mRNA vaccine dose but has a medical claim with a CPT code indicating a BNT162b2 XBB.1.5 monovalent mRNA vaccine dose will be considered vaccinated 14 days after claim date.

4. Any person in HealthVerity claims data who does not have a record in the California/Louisiana Immunization Registry, does not have a pharmacy claim with an NDC code indicating a BNT162b2 XBB.1.5 monovalent mRNA vaccine dose and does not have a medical claim with a CPT code indicating a BNT162b2 XBB.1.5 monovalent mRNA vaccine dose will be considered BNT162b2 XBB.1.5 unvaccinated.

BA.4/5 vaccinations will be enumerated in the same manner as XBB.1.5. For influenza, herpes zoster and pneumococcal vaccinations, Pfizer has not yet licensed these specific California/Louisiana state registries; instead, we will rely wholly on NDC and CPT codes in administrative claims.

Endpoints, patient characteristics, clinical characteristics, healthcare utilization, and any variables for the analysis will be derived from the HealthVerity claims database restricted to the state of California/Louisiana. Medical settings of outpatient, ambulatory, pharmacy, emergency department, and hospital will be included in the analysis for all variables. Urgent care visits will be considered separately from emergency department visits, as differences in the populations associated with urgent care as compared to emergency department encounters are expected.

8.2.1. Inclusion Criteria

Inclusion criteria are specified by each study aim. Within each aim, patients must meet all of the following criteria to be eligible for inclusion in the study:

8.2.1.1. Aim 1 Inclusion Criteria

1) Born in 2005 or earlier (as age 18 or older in 2023, owing to the data providing year but not month or day of birth).

2) At least one year of pharmacy and medical enrollment in HealthVerity prior to index date (FDA EUA date per vaccine). A gap of up to 30 days will be allowed.

3) Have been a State of California/Louisiana resident for at least one year prior to index date (FDA EUA date per vaccine)

8.2.1.2. Aim 2 Inclusion Criteria

1) Born in 2006 or later (as age 0-17 years in 2023, owing to the data providing year but not month or day of birth)

2) At least six months of pharmacy and medical enrollment in HealthVerity prior to index date (FDA EUA date per age group vaccine). Six months was selected to allow for analysis to include children age <1 year. A gap of up to 30 days will be allowed.

3) Have been a State of California/Louisiana resident for at least six months prior to index date (FDA EUA date per age group and vaccine)

8.2.1.3. Aim 3A Inclusion Criteria

Aim 3A criteria are different based on the pediatric and adult population analyses as follows:

8.2.1.3.1. Aim 3A Adult Inclusion Criteria

1. Born in 2005 or earlier (as age 18 or older in 2023, owing to the data providing year but not month or day of birth).
2. Hospitalized for COVID-19 (an inpatient encounter with ICD-10-CM U07.1 "COVID-19" in the principal diagnosis position)
3. At least one year of continuous pharmacy and medical enrollment in HealthVerity prior to index date (i.e. hospitalization date). A gap of up to 30 days will be allowed.
4. Have been a State of California/Louisiana resident for at least one year prior to index date (i.e. hospitalization date)

8.2.1.3.2. Aim 3A Pediatric Inclusion Criteria

1. Born in 2006 or later (as age 0-17 years in 2023, owing to the data providing year but not month or day of birth)
2. Hospitalized for COVID-19 (an inpatient encounter with ICD-10-CM U07.1 "COVID-19" in the principal diagnosis position)
3. At least six months of continuous pharmacy and medical enrollment in HealthVerity prior to index date. Six months was selected to allow for analysis to include children <1yr due to patient privacy measures in HealthVerity data. A gap of up to 30 days will be allowed.
4. Have been a State of California/Louisiana resident for at least six months prior to index date

8.2.1.4. Aim 3B Inclusion Criteria

Aim 3B criteria are different based on the pediatric and adult population analyses as follows:

8.2.1.4.1. Aim 3B Adult Inclusion Criteria

1. Born in 2005 or earlier (as age 18 or older in 2023, owing to the data providing year but not month or day of birth).
2. At least one year of continuous pharmacy and medical enrollment in HealthVerity prior to index date (i.e. COVID-19 diagnosis). A gap of up to 30 days will be allowed.
3. Have been a State of California/Louisiana resident for at least one year prior to index date (i.e. COVID-19 diagnosis)

8.2.1.4.2. Aim 3B Pediatric Inclusion Criteria

1. Born in 2006 or later (as age 0-17 years in 2023, owing to the data providing year but not month or day of birth)
2. At least six months of pharmacy and medical enrollment in HealthVerity prior to index date. Six months was selected to allow for analysis to include children <1 year due to patient privacy measures in HealthVerity data. A gap of up to 30 days will be allowed
3. Have been a State of California/Louisiana resident for at least six months prior to index date

8.2.1.5. Aim 4 Inclusion Criteria

1) Born in 2005 or earlier (as age 18 or older in 2023, owing to the data providing year but not month or day of birth).

2) At least one year of pharmacy and medical enrollment in HealthVerity prior to index date. A gap of up to 30 days will be allowed.

3) Immunocompromised at the time of study index, using all-available lookback data (immunocompromised definition as per Infectious Disease Society of America Clinical Practice Guideline for Vaccination of the Immunocompromised Host)[22,23]

4) Have been a State of California/Louisiana resident for at least one year prior to index date

8.2.1.6. Aim 5 Inclusion Criteria

1) Born in 2005 or earlier (as age 18 or older in 2023, owing to the data providing year but not month or day of birth).

2) Received a BNT162b2 vaccine and/or seasonal influenza vaccine between 11 September 2023 and end of data.

3) At least one year of pharmacy and medical enrollment in HealthVerity prior to index date (earliest vaccination date is index date). A gap of up to 30 days will be allowed.

4) Have been a State of California/Louisiana resident for at least one year prior to index date

8.2.2. Exclusion Criteria

Exclusion criteria are specified by each study aim. Within each aim, patients meeting any of the following criteria will not be included in the study:

8.2.2.1. Aim 1 Exclusion Criteria

1) Currently pregnant (using a validated gestational age algorithm with up to 9 months lookback) or immunocompromised (using all-available lookback) at the time of study index[18] (code list to be listed in the appendix)

2) Individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets.

3) Persons with a diagnosis of COVID-19 in any setting ≤ 90 days prior to index (FDA EUA date per vaccine)

4) Receipt COVID-19 vaccine ≤ 90 days prior to index (FDA EUA date per vaccine)

8.2.2.2. Aim 2 Exclusion Criteria

1) Currently pregnant (using a validated gestational age algorithm with up to 9 months lookback) or immunocompromised (using all-available lookback) at the time of study index (code list to be listed in the appendix)

2) Individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets.

3) Persons with a diagnosis of COVID-19 in any setting ≤ 90 days prior to index (FDA EUA date per vaccine and age group)

4) Receipt COVID-19 vaccine ≤ 90 days prior to index (FDA EUA date per vaccine)

8.2.2.3. Aim 3A Exclusion Criteria

For each of adult and pediatric:

1. Currently pregnant (using a validated gestational age algorithm with up to 9 months lookback) or immunocompromised (using all-available lookback) at the time of study index (code list to be listed in the appendix)

2. Individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets.

3. Individuals who were vaccinated within 13 day of index.

4. Individuals who had a change in vaccination status changed during follow-up (i.e. patients who received a vaccination during hospitalization).

8.2.2.4. Aim 3B Exclusion Criteria

For each of adult and pediatric:

- Currently pregnant (using a validated gestational age algorithm with up to 9 months lookback) or immunocompromised (using all-available lookback) at the time of study index (code list to be listed in the appendix)

- Individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets.

- Individuals with a diagnosis of COVID-19 in any setting ≤ 90 days prior to index.

- Individuals who were vaccinated within 13 day of index.

- Individuals who had a change in vaccination status changed during follow-up.

8.2.2.5. Aim 4 Exclusion Criteria

1) Currently pregnant (using a validated gestational age algorithm with up to 9 months lookback) at the time of study index (code list to be listed in the appendix)

2) Individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets.

3) Persons with a diagnosis of COVID-19 in any setting ≤90 days prior to index (FDA EUA date per vaccine)

4) Receipt COVID-19 vaccine ≤ 90 days prior to index (FDA EUA date per vaccine)

8.2.2.6. Aim 5 Exclusion Criteria

1) Currently pregnant (using a validated gestational age algorithm with up to 9 months lookback) or immunocompromised (using all-available lookback) at the time of study index (code list to be listed in the appendix)

2) Individuals with discrepancies in sex and/or year of birth between HealthVerity claims and California/Louisiana immunization registry datasets.

3) Died, disenrolled, had a COVID-19 or influenza diagnosis, or received a second dose of either vaccine ≤14 days after their first dose

4) Persons with a diagnosis of COVID-19 in any setting ≤90 days prior to index (vaccination date)

5) Received influenza vaccine between August 1-September 10, 2023, as these persons are not at risk of coadministration with an XBB.1.5 monovalent vaccine given this period predates its availability.

6) Received any type of COVID-19 vaccine other than BNT162b2 XBB.1.5 on the index date

7) For patients >=65, had a standard dose influenza vaccine or unknown type influenza vaccine.

8.3. Variables

TABLE 3. EXPOSURE VARIABLES

Variable	Data source(s)	Operational definition
BNT162b2 XBB.1.5 mRNA vaccine after FDA authorization date and 14 or more days	California/Louisiana Immunization Registry as well as HV Claims	Vaccines will be enumerated as per section 8.2. Date of vaccination will be used to assess time-based inclusion/exclusion criteria.
BNT162b2 BA.4/5 mRNA vaccine after FDA authorization date and 14 or more days	California/Louisiana Immunization Registry as well as HV Claims	Vaccines will be enumerated as per section 8.2. Date of vaccination will be used to assess time-based inclusion/exclusion criteria.
Influenza vaccine	HV Claims	Identified using NDC or CPT code

TABLE 4. OUTCOME VARIABLES

Variable	Data source(s)	Operational definition
COVID-19 diagnosis	HV Claims	Any encounter regardless of diagnosis position or setting with ICD-10-CM code: U07.1
COVID-19 hospitalization	HV Claims	Inpatient encounter at an acute care facility with ICD-10-CM code: U07.1 "COVID-19" listed in any diagnosis position
COVID-19 emergency department visit	HV Claims	Emergency department visit with ICD-10-CM code: U07.1

Variable	Data source(s)	Operational definition
COVID-19 outpatient encounter	HV Claims	Outpatient encounter with ICD-10-CM code: U07.1
COVID-19 critical illness	HV Claims	Intensive care unit [ICU] admission, mechanical ventilation, or inpatient death
All-cause mortality	HV Mortality Database	HealthVerity ID in Mortality Database
Non-COVID-19 respiratory infections (pneumonia, RSV, rhinovirus, antibiotic prescriptions)	HV Claims	Any encounter regardless of setting with ICD-10-CM code for diagnosis or NDC codes for antibiotics (Codes in Annex)
Hospitalization length of stay (days)	HV Claims	Date of service end – date of service
ICU admission	HV Claims	As per HealthVerity's suggestion, ICU related services/inpatient stays will be found on Institutional claims, and can be identified using revenue codes (codes in Annex).
Invasive ventilation	HV Claims	CPT, HCPCS and ICD-10 (codes in Annex)
Cost of hospitalization	HV Claims	Using HealthVerity's "Proxy Financial Algorithm", based on CMS Medicare prospective payment system fee schedules
Influenza diagnosis	HV Claims	Any encounter regardless of setting with ICD-10-CM code: J09-J11
Influenza hospitalization	HV Claims	Inpatient encounter with ICD-10-CM code: J09-J11 listed as in any diagnosis position
Influenza emergency department visit	HV Claims	Emergency department visit with ICD-10-CM code: J09-J11
Influenza outpatient encounter	HV Claims	Outpatient encounter with ICD-10-CM code: J09-J11
Negative control outcome, such as accidental injury, ingrown toenail or atopic dermatitis	HV Claims	Any encounter regardless of setting, with ICD-10-CM code for negative control outcomes (codes in annex)

TABLE 5. COVARIATES

Variable	Data source(s)	Operational definition
Age	HV Claims/CAR	Age assessed at index date. Where not stratified, age will be adjusted as: For aims 1 and 4, age will be directly adjusted using indicator variables for 18-49, 50-64 and 65+. For aim 2, age will be directly adjusted using indicator variables for <5 years, 5-11 and 12-17 years. For aim 5, age will be included in the propensity score as a continuous variable.
Sex	HV Claims/CAR	Sex assessed at index date as male, female or unknown. Models will be adjusted for sex when not stratified by sex.
State of residence	HV Claims	Models will be adjusted for state (California or Louisiana), except those which are stratified by state.

CDC-defined high risk for severe COVID-19[24]	HV Claims	Assessed using all available lookback data, with high risk defined as at least one of the following: • Age ≥ 50 years • Asthma • Cancer, as hematologic malignancies • Cerebrovascular disease • Chronic kidney disease: people receiving dialysis • Chronic lung diseases: bronchiectasis, COPD, interstitial lung disease, pulmonary embolism, pulmonary hypertension • Chronic liver diseases: cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis • Cystic fibrosis • Diabetes mellitus, type 1 • Diabetes mellitus, type 2 • Disabilities, including Down syndrome • Heart conditions: heart failure, coronary artery disease, or cardiomyopathies • HIV • Mental health conditions: mood disorders including depression; Schizophrenia spectrum disorders • Neurologic conditions limited to dementia • Obesity (BMI ≥30 kg/m^2 or ≥95th percentile in children) • Physical inactivity • Primary immunodeficiencies • Smoking, current and former • Solid organ or blood stem transplantation • Tuberculosis • Use of corticosteroids or other immunosuppressive medications *Note: racial/ethnic minority status is included in the high risk definition, but not included in HealthVerity data and therefore unable to be assessed. Pregnancy is included in the high risk definition, but is an exclusion criteria for each aim in this protocol and therefore is not listed here. Given the nature of administrative claims data, obesity, physical inactivity, and smoking are likely to be undercaptured.*

Variable	Data source(s)	Operational definition
Charlson-Deyo Comorbidity Index,[25] operationalized as scores of 0, 1 or 2 using	HV Claims	Assessed using all-available lookback data. Codes are in annex, and conditions are scored as: 1 point for each of: • Myocardial infarction • CHF • Peripheral vascular disease • Cerebrovascular disease • Dementia • Chronic pulmonary disease • Connective tissue disease • Peptic ulcer disease • Mild liver disease • Diabetes mellitus without chronic complications 2 points for each of: • Hemiplegia • Moderate to severe renal disease • Diabetes with chronic complications • Cancer, including leukemia and lymphoma 3 points for moderate or severe liver disease 6 points for each of: • Metastatic carcinoma • HIV/AIDS
Receipt of skilled nursing care and/or long-term care facility stay in year prior to index	HV Claims	Codes in Annex
Wellness visit	HV Claims	Codes in Annex
Decreased functional status	HV Claims	Codes in Annex
Influenza vaccination in year prior to index	HV Claims	Vaccines will be enumerated as per section 8.2. Influenza vaccines are recommended annually, and therefore we will measure influenza vaccination in prior year.

Variable	Data source(s)	Operational definition
Pneumococcal vaccination using all-available time prior to index	HV Claims	Vaccines will be enumerated as per section 8.2. Pneumococcal vaccinations are generally not repeated events, and therefore we will use all-available lookback data to assess receipt.
Herpes zoster vaccination using all-available time prior to index	HV Claims	Vaccines will be enumerated as per section 8.2. Herpes zoster vaccinations are generally not repeated after primary series, and therefore we will use all-available lookback data to assess receipt.
Outpatient visits prior to index	HV Claims	Number of outpatient visit(s) in 180 days prior to index
Inpatient admission(s) prior to index	HV Claims	Number of inpatient admission(s) in 180 days prior to index
Telehealth visits prior to index	HV Claims	Number of telehealth encounters (CPT: 99201-99215) in 180 days prior to index
Number of documented SARS-CoV-2 tests in the 180 days prior to index	HV Claims	Number of visits in any setting with CPT: 86408, 86409, 0225U, 0226U
Prior post-COVID-19 conditions	HV Claims	Using all-available lookback data, any encounter regardless of setting with ICD-10-CM U09.9 "Post-COVID-19 condition"
For aim 5 only (coadministration): Number of documented influenza tests in the 180 days prior to index	HV Claims	Number of visits in any setting with CPT: 87400
For aim 5 only (coadministration): Lipid and/or HbA1C labs in the 180 days prior to index	HV Claims	Encounter with CPT: A56686. These labs were selected as potential measures of health system usage, as people who monitor their lipids or blood glucose may share some behaviors as vaccinations. We are able to incorporate this in propensity score adjusted analyses (aim 5) but not analyses with direct adjustment (aim 1, 2 and 4), given the need for smaller sets of covariates.
For aim 5 only (coadministration): vaccine administration setting	California /Louisiana Vaccine Registry	As pharmacy, doctor's office, or other.

8.4. Data Sources

This study will use vaccination data from the California/Louisiana Immunization Registry linked to closed claims for patients in California sourced from HealthVerity.

8.4.1. California and Louisiana Immunization Registry

The California Immunization Registry is run by the California Department of Public Health and collects nearly all records of COVID-19 vaccinations administered in the state of California. Sites exempted from reporting are the Department of Defense, Veterans Affairs and Indian Health Services; these sites are not included in the registry and will not contribute to any objective herein. In the July 2023 delivery of these data, there were 88 million COVID-19 vaccinations recorded for 32 million unique individuals. In this delivery, we identified 72.2% of persons had received at least two wild type vaccine doses (note: for non-immunocompromised persons over age 5 this represents the completion of primary vaccination series), with California's state dashboard[26] reported 72.9%. Similarly, we identified 20.9% of persons in the registry having received at least one bivalent vaccine dose, as compared to California state's estimate of 21.2%.

Data include a unique HealthVerity person identification code, vaccination event date and Clinical Vaccines Administered (CVX) code. CVX codes are unique to brand and formulation of vaccine.

Data is linked using HealthVerity's tokenization software, whereby specific patient identifiers are passed through the software and a de-identified patient ID is assigned. The same tokenization process is applied to closed claims sourced by HealthVerity, and patients can thus be linked across data sources. The tokenization process occurs outside of Pfizer, no personal identifying information will be transferred, and Pfizer will only have access to de-identified data. The data comply with Health Insurance Portability and Accountability Act (HIPAA) regulations.

The Louisiana Vaccine Registry is structured and accessed in the same way as California.

8.4.2. HealthVerity's Administrative Claims Data

HealthVerity closed claims will be limited to approximately 19 million patients residing in California and approximately 3.8 million in Louisiana. Patients who were California/Louisiana residents in the HealthVerity claims database will be defined using the following hierarchical definition:

1. Persons who have their most recent enrollment file record indicating a patient location of California or Louisiana in HealthVerity claims enrollment file.

2. Persons who have a patient state location other than California/ Louisiana in HealthVerity claims enrollment but have one or more records in the California/ Louisiana Immunization Registry. *Examples include people who previously lived in Texas but moved to California and received a vaccine, or persons who crossed state lines for a vaccine and remain in their non-California state in claims data.*

HealthVerity's description of their data is that they are generally representative of the age and sex distribution of the population. For our specific research context, samples created from HealthVerity claims also generally follow California's demographic patterns with respect to age & sex. However, there are several caveats to note. Our claims population is slightly more female and young people (particularly age 5-17) are overrepresented in our claims relative to other groups. Children under 5, and adults 65+, are slightly underrepresented.

The California subset of HealthVerity does not include patients in the Kaiser Permanente network. Insurers contributing to closed claims in both states include a mix of commercial payers, Medicare Advantage/Part C pains, and Medicaid Managed Care plans. Data elements include patient demographic information, inpatient/outpatient visit-level information such as diagnoses, procedures, and length of stay, hospital characteristics, and medication information. Owing to the nature of claims, the data represent the final set of diagnoses over the course of the hospitalization sent to the patient's insurer for reimbursement, with diagnosis prioritization assigned by clinicians or hospital staff. For inpatient encounters, the data will be assumed to represent the overarching events during hospitalization and may be less subject to rule out diagnosis codes than electronic health record data.

Death information is available and is sourced from over 40,000 public and private sources nationally. The coverage rate, estimated at over 90% of CDC reported deaths through present day, is based on the number of deaths in the Fact of Death Mortality Index compared to the number of deaths reported by the CDC. Due to HIPAA privacy restrictions, date of death is reported as month and year. Cause of death is not available.

8.4.3. Comparison to Other Real-World Data Sources

The results of this study may differ from those produced in other real-world datasets, for reasons including but not limited to:

- HealthVerity is an administrative claims data source.
    - Claims data contain records of all medical encounters that were billed to the insurer. Given the out-of-pocket cost that would be incurred if encounters were not billed to the insurer, it is reasonable to assume that administrative claims should capture nearly all encounters whereas a local EHR would have coverage of encounters in their hospital network but not outside.
    - Claims data contain enrollment records, which are used to implement continuous enrollment requirements in order to ascertain previous medical history more fully. Given comorbid conditions are important risk factors for severe COVID-19[24], maximal capture is crucial to begin to address potential confounding in observational research.
    - In many EHR databases, there is no way to ensure an individual is captured in the data longitudinally, except through healthcare encounters.
- The use of a retrospective cohort rather than TND allows for estimation of risk rather than odds.
- The population in the linked state vaccine registry with insurance claims data is four times the size of the Kaiser Permanente Southern California (KPSC) population (18.4 million versus 4.8 million). Having more people in the dataset means there are likely to be more events, which is particularly important given the rapid response nature of the XBB.1.5 vaccine evaluations planned.

Of note, findings are expected to be complementary (all showing protective effect of vaccination, but perhaps of varying magnitudes and statistical precision). Similar populations with a mix of commercial, Medicare Advantage and Medicaid Managed Care sources are expected in both KPSC and the combined set of California vaccine registry and insurance claims.

Thus, there is utility in potential differences between this data source and others. The potential to use claims data for VE studies will provide support for future endeavors, may result in cost savings of millions of dollars over time, and promotes Pfizer's commitment to innovation.

8.5. Study Size

Since the current study utilizes retrospective deidentified data without ability to recruit to a target, sample size calculations are not applicable. Further, this is a descriptive study without *a priori* specified hypotheses.

Initial data feasibility work has revealed approximately 19 million persons in the state of California with claims available in HealthVerity, among which approximately 25% are pediatric and 75% adult. Among these, approximately 12 million have at least one year of continuous medical and pharmacy enrollment. By end of 2023, we expect to have finished contracting to add approximately 565,000 additional persons. The proportion of these additional persons who will have 1-year continuous enrollment, and therefore the sample size estimates below have taken the conservative approach to not yet include these people.

We have identified 63% of persons in the claims data have at least one COVID-19 vaccine, and 16% received at least one bivalent dose. The claims population we have is not a random sample of Californians and may differ from the state's population in systematic ways (e.g. the age distribution). While differences may exist, we have high confidence in our ability to represent vaccination status for the individuals in our claims population.

We expect to begin to see XBB doses in data delivered in November 2023. Assuming uptake similar to that seen with the BA.4/5 vaccine, and non-differential uptake by age groups, we could anticipate in California:

(25% of 12 million are pediatric)*(16% uptake)*(60% of doses were Pfizer-BioNTech)

~ 288,000 pediatric XBB doses in California

(75% of 12 million are adult)*(16% uptake)*(60% of doses were Pfizer-BioNTech)

~ 864,000 adult XBB doses in California

Additional doses will be observed in Louisiana. In order to maintain patient de-identification, outcomes, covariates and subgroups will have at least 10 people in each category for inclusion in outputs. Throughout the protocol, this is referred to as "If sample size allows".

8.6. Data Management

Claims and vaccine registry data refreshes are delivered by HealthVerity monthly, and mortality data annually.

All HealthVerity structured data described above are stored within Pfizer's data infrastructure. Data are queried and analyzed using SAS. The HealthVerity claims, mortality, and deidentified State of California and Louisiana vaccine registries are stored as separate databases. The data are only accessible to Pfizer colleagues who have been trained and approved to access Pfizer's data warehouse.

In brief, all persons living in the state of California or Louisiana will be extracted from the national data delivery, and, where applicable, corresponding records in the California/Louisiana Immunization Registry for those HealthVerity person identification numbers will be extracted.

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

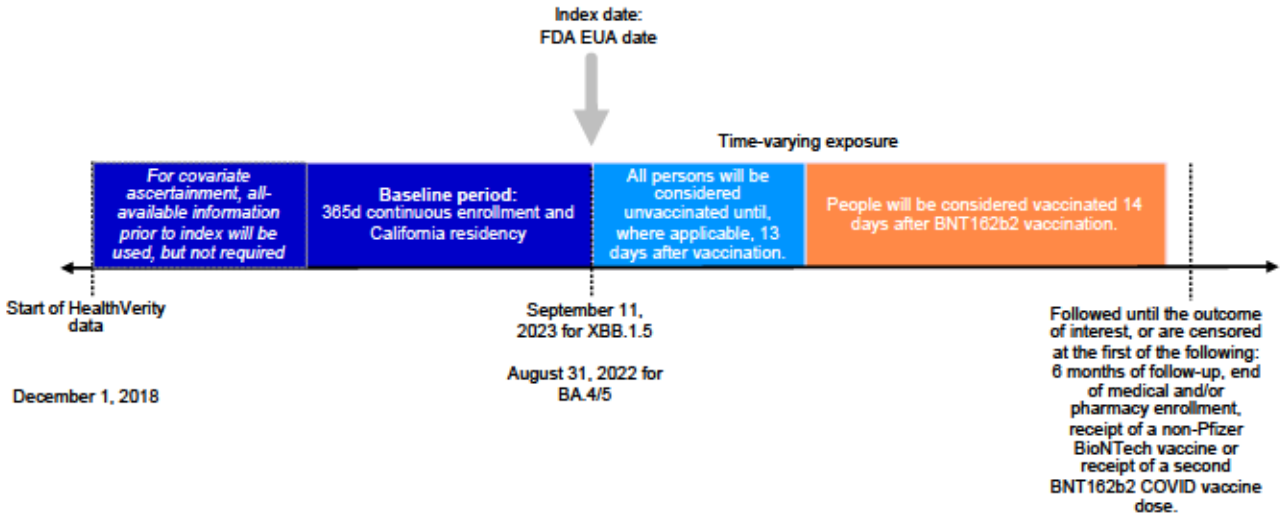
Throughout, we will use missing data indicator variables for absence of values in categorical variables (such as insurance payor) and exclude persons with missing data in continuous variables (age). Using indicator variables rather than imputation allows for the missing data patterns to be mathematically informative. Variables with data delivered of strings as 'Missing' or 'Unknown' values will be reported and analyzed as separate categories and included in the totals.

All steps will be completed using SAS version 9.4 and/or R.

8.7.1. Aim 1

To evaluate the VE of BNT162b2 formulations in non-pregnant, non-immunocompromised adults against medically attended COVID-19, mortality and healthcare resource utilization by age and adapted vaccine formulation.

Figure 1. Aim 1 study design



Exposure: time-varying exposure. All persons will be considered unvaccinated from FDA date of vaccine authorization/approval until, where applicable, 13 days after receipt of vaccine. In order to allow for time after dose for meaningful immunologic protection to accrue, persons will be considered vaccinated 14 days after vaccination (i.e. patients will be censored from the unvaccinated group).[20,21]

For XBB.1.5 vaccine: FDA approval date 11 September 2023[2]

In the event that XBB uptake is low, we will instead examine BA.4/5 VE. For BA.4/5 vaccine: FDA emergency use authorization date 31 August 2022[4]

Note: this aim pertains to adults only, and therefore does not require age-specific EUA dates.

Follow-up time: From date of FDA authorization/approval until the outcome of interest, or are censored at the first of the following: 6 months of follow-up, end of medical and/or pharmacy enrollment, receipt of a non-Pfizer BioNTech vaccine or receipt of a second BNT162b2 COVID-19 vaccine dose.

Primary outcome:

1. A COVID-19-related encounter, regardless of setting

Secondary outcomes:

1. An outpatient encounter with ICD-10-CM U07.1 "COVID-19" code
2. An inpatient encounter with ICD-10-CM U07.1 "COVID-19" listed in any diagnosis position. As a sensitivity analysis, we will restrict to U07.1 in primary diagnosis field.
3. An emergency department encounter with ICD-10-CM U07.1 "COVID-19" code
4. COVID-19 critical illness, defined as intensive care unit [ICU] admission, mechanical ventilation, or inpatient death. If sample size allows, we will evaluate VE against each component separately in order to support V&E models.

5. Negative control outcomes such as accidental injury, ingrown toenail or atopic dermatitis

Exploratory outcomes:

1. An urgent care encounter with ICD-10-CM U07.1 "COVID-19" code
2. All-cause mortality within 3-months of COVID-19 encounter, regardless of setting
3. All-cause mortality within 3-months of COVID-19 outpatient encounter
4. All-cause mortality within 3-months of COVID-19 inpatient encounter
5. All-cause mortality within 3-months of COVID-19 emergency department encounter
6. All-cause mortality within 3-months of COVID-19 critical illness
7. All-cause mortality within 3-months of COVID-19 urgent care encounter

Measures of absolute and relative VE: For each outcome above, results will be calculated as:

1. Absolute VE comparing vaccinated to unvaccinated persons, regardless of prior vaccination
2. Relative VE will be calculated for each of the following mutually exclusive subgroups.
    a. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who received BA.4/5 bivalent vaccine.
    b. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who did not receive BA.4/5 bivalent vaccine but did receive at least 2 doses of mRNA vaccine (regardless of formulation).
    c. XBB.1.5 vaccinated vs never COVID-19 vaccinated.

Stratifications: Results will be stratified by age group (overall, age 18-49, 50-64, 65+) as well as by calendar time (BA.4/5 versus XBB.1.5 vaccine available eras).

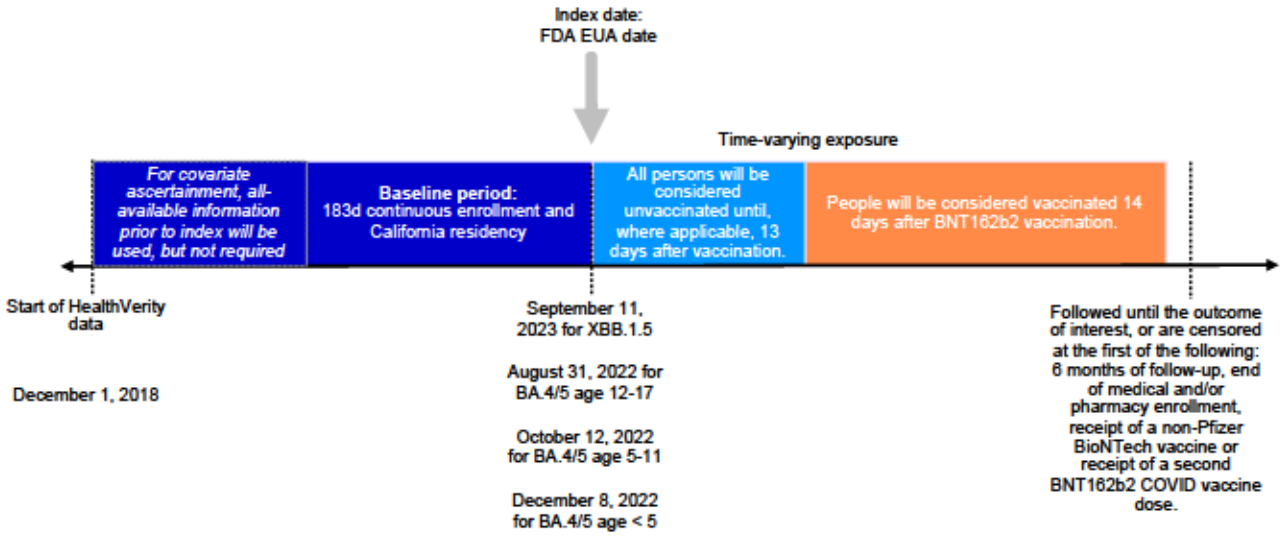
Statistical methods: All analyses will be pooled across California and Louisiana. To consider the potential for effect measure modification, we will additionally stratify by state, rather than adjust, for the primary endpoint. Descriptive statistics will be used to summarize patient characteristics, with mean (standard deviation) or median (25^{th} percentile – 75^{th} percentile) for continuous variables and counts (percentages) for categorical variables. Time-dependent Cox proportional hazards models will be used to estimate the risk of each outcome of interest with time-varying exposure and time-fixed covariates, resulting in aHR and 95% confidence intervals (95% CI). VE will be defined as (1 – aHR)*100. We will further use incidence of the COVID-19 endpoint in unvaccinated persons and apply VE estimates to estimate the number of cases averted.

Models will be adjusted for covariates listed in "Table 5: Covariates". Negative control outcomes will be used to quantify residual and unmeasured confounding. In the event aHR for negative control outcomes have a significant effect (95% CI do not include null value of 1), then the set of confounders will be adjusted to allow for calibration. Sensitivity analyses will consider the impact of study design and analytic assumptions, such as varying the exposure definition to 7 days post vaccination rather than 14 days.

8.7.2. Aim 2

To assess VE of BNT162b2 formulations in pediatrics against medically attended COVID-19, non-COVID-19 respiratory infections, mortality and healthcare resource utilization by age and adapted vaccine formulation.

Figure 2. Aim 2 study design



Exposure: time-varying exposure. All persons will be considered unvaccinated FDA date of vaccine authorization/approval until, where applicable, 13 days after receipt of vaccine. In order to allow for time after dose for meaningful immunologic protection to accrue, persons will be considered vaccinated 14 days after vaccination.

For BA.4/5 vaccine: FDA emergency use authorization date 31 August 2022[4] for age 12-17, 12 October 2022 for ages 5-11,[5] and 08 December 2022 for ages 6 months to 4 years[6]

For XBB.1.5 vaccine: FDA approval date 11 September 2023 regardless of age[3]

Follow-up time: From date of FDA authorization/approval until the outcome of interest, or are censored at the first of the following: 6 months of follow-up, end of medical and/or pharmacy enrollment, receipt of a non-Pfizer BioNTech vaccine or receipt of a second BNT162b2 COVID-19 vaccine dose.

Primary outcome:

1. A COVID-19-related encounter, regardless of setting (primary outcome)

Secondary outcomes:

1. An outpatient encounter with ICD-10-CM U07.1 "COVID-19" code
2. An inpatient encounter with ICD-10-CM U07.1 "COVID-19" listed in any diagnosis position. As a sensitivity analysis, we will restrict to U07.1 in primary diagnosis field.

3. An emergency department encounter with ICD-10-CM U07.1 "COVID-19" code

4. COVID-19 critical illness, defined as intensive care unit [ICU] admission, mechanical ventilation, or inpatient death. If sample size allows, we will evaluate VE against each component separately in order to support V&E models.

5. Non-COVID-19 respiratory infection: diagnosis of any of pneumonia, respiratory syncytial virus (RSV), rhinovirus and/or receipt of antibiotic prescription. If sample size allows, we will evaluate VE against each component separately in order to support V&E models.
6. Negative control outcomes such as accidental injury, ingrown toenail or atopic dermatitis

Exploratory outcomes:

1. An urgent care encounter with ICD-10-CM U07.1 "COVID-19" code
2. All-cause mortality within 3-months of COVID-19 encounter, regardless of setting
3. All-cause mortality within 3-months of COVID-19 outpatient encounter
4. All-cause mortality within 3-months of COVID-19 inpatient encounter
5. All-cause mortality within 3-months of COVID-19 emergency department encounter
6. All-cause mortality within 3-months of COVID-19 critical illness
7. All-cause mortality within 3-months of COVID-19 urgent care encounter

Measures of absolute and relative VE: For each outcome above, results will be calculated as:

1. Absolute VE comparing vaccinated to unvaccinated persons, regardless of prior vaccination
2. Relative VE will be calculated for each of the following mutually exclusive subgroups.
    a. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who received BA.4/5 bivalent vaccine.
    b. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who did not receive BA.4/5 bivalent vaccine but did receive at least 2 doses of mRNA vaccine (regardless of formulation).
    c. XBB.1.5 vaccinated vs never COVID-19 vaccinated.

Stratifications: Results will be stratified by age group (overall, age 6 months – 4 years, 5-11, 12-17) as well as by calendar time (BA.4/5 versus XBB.1.5 vaccine available eras).

Statistical Methods: All analyses will be pooled across California and Louisiana. To consider the potential for effect measure modification, we will additionally stratify by state, rather than adjust, for the primary endpoint. Descriptive statistics will be used to summarize patient characteristics, with mean (standard deviation) or median (25^{th} percentile – 75^{th} percentile) for continuous variables and counts (percentages) for categorical variables. Time-dependent Cox proportional hazards models will be used to estimate the risk of each outcome of interest with time-varying exposure and time-fixed covariates, resulting in aHR and 95% confidence intervals (95% CI). VE will be defined as (1 – aHR)*100. We will further use incidence of the COVID-19 endpoint in unvaccinated persons and apply VE estimates to estimate the number of cases averted.

Models will be adjusted for covariates listed in "Table 5: Covariates". Negative control outcomes will be used to quantify residual and unmeasured confounding. In the event aHR for negative control outcomes have a significant effect (95% CI do not include null value of 1), then the set of confounders will be adjusted to allow for calibration. Sensitivity analyses will consider the impact of study design and analytic assumptions, such as varying the exposure definition to 7 days post vaccination rather than 14 days.

8.7.3. Aim 3A

To estimate short-term healthcare resource utilization and costs associated with COVID-19 by vaccination status, age, and site of care.

Exposure: Persons will be considered vaccinated if they received the XBB.1.5 dose 14 or more days prior to admission. Persons will be considered unvaccinated if they had not received a dose.

Study Period: September 2023 – January 2024

Follow-up time: From admission (index date) to discharge.

Outcomes of interest: Similar to those in Somani, Firestone, Donnelley et al (2023)[22]

1. Cost of hospitalization
2. Average length of stay, in days
3. ICU admission
4. Receipt of high-flow oxygen or mechanical ventilation
5. Inpatient Mortality
6. Use of antiviral treatment

Statistical Methods: All analyses will be pooled across California and Louisiana, and stratified by state. Descriptive statistics will be used to summarize patient characteristics, with mean (standard deviation) or median (25^{th} percentile – 75^{th} percentile) for continuous variables and counts (percentages) for categorical variables. Logistic regression will be used to estimate odds ratios (OR, with 95% CI) of ICU admission comparing vaccinated persons to unvaccinated persons. Linear regression with analysis of covariance (ANCOVA) will be used to compare costs of hospitalization for vaccinated and unvaccinated persons, and will be adjusted for age, and baseline characteristics. Results will be stratified by age groups.

8.7.4. Aim 3B

To estimate long-term healthcare resource utilization and costs associated with COVID-19 by vaccination status, age, and site of care.

Exposure: Persons will be considered a COVID-19 patient if they experienced a COVID-19-related encounter, regardless of setting (cases). COVID-19 patients (cases) will be matched to 4 patients

without a COVID-19 diagnosis (controls) using the matched index date. Controls may or may not have had health care encounters during the study period. Cases and controls will be matched based on age, sex, insurance type, previous Charlson Comorbidity Index (CCI), number of previous hospitalizations, and follow-up time. The CCI and number of hospitalizations were calculated by using diagnoses during pre-index. For stratification/subgroup analyses, adult persons will be considered vaccinated if they received the BA.4.5 dose 14 or more days prior to index, persons will be considered unvaccinated if they had not received any COVID-19 vaccination doses. Children will be considered vaccinated if they received the any COVID-19 vaccination dose 14 or more days prior to index and will be considered unvaccinated if they had not received any COVID-19 vaccination doses.

Study Period (data including pre-index and follow-up): 01 June 2021 – 31 August 2023

Patient identification (index) window: June 2022 – November 2022

Follow-up time: starting 30 days after first COVID-19 diagnosis (index date) with follow-ups of 1 month, 3 months, 6 month, and 9 months.

Outcomes of interest: Similar to those in Pike et al, 2023

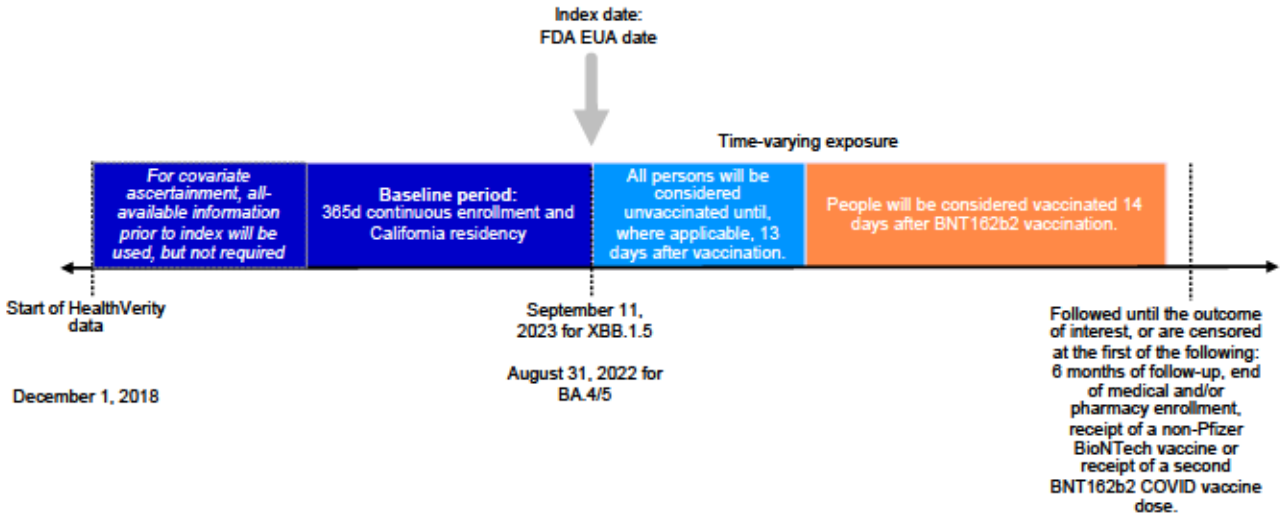
1. All-cause direct healthcare costs (medical and pharmacy)
2. All-cause Healthcare resource utilization
3. COVID-19-related hospitalization (for cases only)

Statistical Methods: All analyses will be pooled across California and Louisiana, and stratified by state. Descriptive statistics will be used to summarize patient characteristics, with mean (standard deviation) or median (25^{th} percentile – 75^{th} percentile) for continuous variables and counts (percentages) for categorical variables. A regression model will be developed that adjusts for age, sex, and baseline comorbidities. We will stratify outcomes by vaccination status, healthcare cost (medical and pharmacy), and sites of care (inpatient, outpatient, etc.).

8.7.5. Aim 4

To measure VE of BNT162b2 formulations in non-pregnant immunocompromised adults against medically attended COVID-19, mortality and healthcare resource utilization by age and adapted vaccine formulation.

Figure 3. Aim 4 study design



Note: for this aim, the inclusion criteria will additionally restrict the population to immunocompromised adults.

Exposure: time-varying exposure. All persons will be considered unvaccinated from FDA date of vaccine authorization/approval until, where applicable, 13 days after receipt of vaccine. In order to allow for time after dose for meaningful immunologic protection to accrue, persons will be considered vaccinated 14 days after vaccination.

For BA.4/5 vaccine: FDA emergency use authorization date 31 August 2022

For XBB.1.5 vaccine: FDA approval date 11 September 2023

Note: this aim pertains to adults only, and therefore does not require age-specific EUA dates.

Follow-up time: From date of FDA authorization/approval until the outcome of interest, or are censored at the first of the following: 6 months of follow-up, end of medical and/or pharmacy enrollment, receipt of a non-Pfizer BioNTech vaccine or receipt of a second BNT162b2 COVID-19 vaccine dose.

Primary outcome:

1. A COVID-19-related encounter, regardless of setting (primary outcome)

Secondary outcomes:

1. An outpatient encounter with ICD-10-CM U07.1 "COVID-19" code
2. An inpatient encounter with ICD-10-CM U07.1 "COVID-19" listed in any diagnosis position. As a sensitivity analysis, we will restrict to U07.1 in primary diagnosis field.
3. An emergency department encounter with ICD-10-CM U07.1 "COVID-19" code

4. COVID-19 critical illness, defined as intensive care unit [ICU] admission, mechanical ventilation, or inpatient death. If sample size allows, we will evaluate VE against each component separately in order to support V&E models.
5. Negative control outcomes such as accidental injury, ingrown toenail or atopic dermatitis

Exploratory outcomes:

1. An urgent care encounter with ICD-10-CM U07.1 "COVID-19" code
2. All-cause mortality within 3-months of COVID-19 encounter, regardless of setting
3. All-cause mortality within 3-months of COVID-19 outpatient encounter
4. All-cause mortality within 3-months of COVID-19 inpatient encounter
5. All-cause mortality within 3-months of COVID-19 emergency department encounter
6. All-cause mortality within 3-months of COVID-19 critical illness
7. All-cause mortality within 3-months of COVID-19 urgent care encounter

Measures of absolute and relative VE: For each outcome above, results will be calculated as:

1. Absolute VE comparing vaccinated to unvaccinated persons, regardless of prior vaccination
2. Relative VE will be calculated for each of the following mutually exclusive subgroups.
    a. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who received BA.4/5 bivalent vaccine.
    b. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who did not receive BA.4/5 bivalent vaccine but did receive at least 2 doses of mRNA vaccine (regardless of formulation).
    c. XBB.1.5 vaccinated vs never COVID-19 vaccinated.

Stratifications: Results will be stratified by age group (overall, age 18-49, 50-64, 65+) as well as by calendar time (BA.4/5 versus XBB.1.5 vaccine available eras) and level of immunosuppression.

Statistical Methods: All analyses will be pooled across California and Louisiana. To consider the potential for effect measure modification, we will additionally stratify by state, rather than adjust, for the primary endpoint. Descriptive statistics will be used to summarize patient characteristics, with mean (standard deviation) or median (25^{th} percentile – 75^{th} percentile) for continuous variables and counts (percentages) for categorical variables. Time-dependent Cox proportional hazards models will be used to estimate the risk of each outcome of interest with time-varying exposure and time-fixed covariates, resulting in aHR and 95% confidence intervals (95% CI). Absolute VE will be defined as (1 – aHR)*100, comparing vaccinated to unvaccinated persons regardless of prior vaccinations. We will further use incidence of the COVID-19 endpoint in unvaccinated persons and apply VE estimates to estimate the number of cases averted.

Models will be adjusted for covariates listed in "Table 5: Covariates". Negative control outcomes will be used to quantify residual and unmeasured confounding. In the event aHR for negative control outcomes have a significant effect (95% CI do not include null value of 1), then the set of confounders will be adjusted to allow for calibration. Sensitivity analyses will consider the impact of

study design and analytic assumptions, such as varying the exposure definition to 7 days post vaccination rather than 14 days.

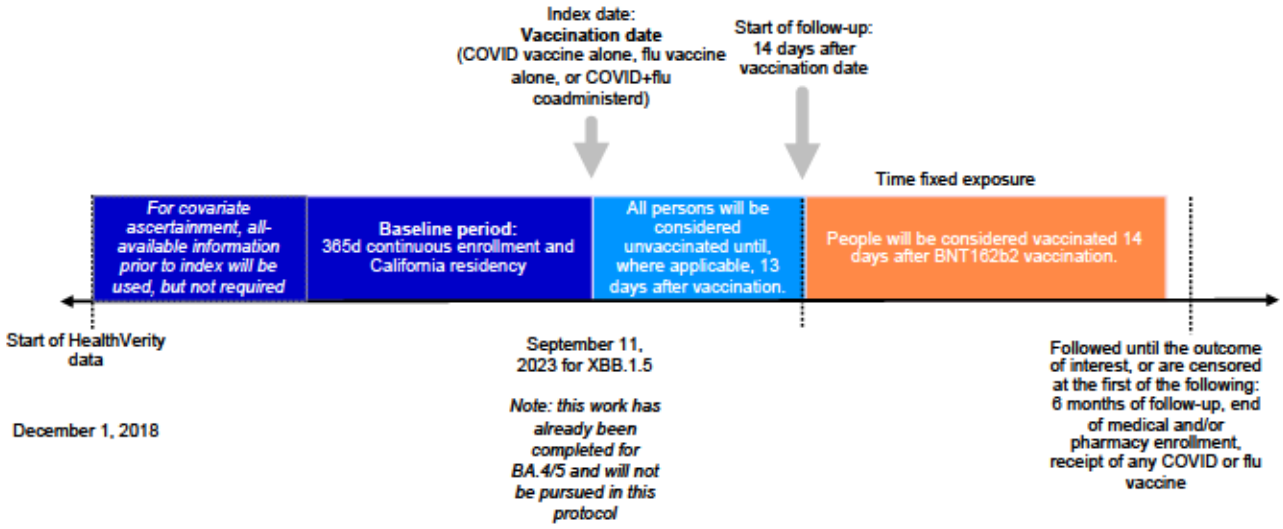
8.7.6. Aim 5

To quantify differences in VE of BNT162b2 formulations in non-pregnant, non-immunocompromised adults when co-administered with seasonal influenza vaccines versus when each vaccine is given separately, by age groups.

Main summary measure: aRR to evaluate non-inferiority, comparing people with co-administered vaccines to BNT162b2 vaccine alone for COVID-19-related outcomes

Main summary measure: aRR to evaluate non-inferiority, comparing people with co-administered vaccines to seasonal influenza vaccine alone for influenza-related outcomes

Figure 4. Aim 5 study design



Exposure: Co-administration will be defined as same-day receipt of BNT162b2 vaccine and any formulation of seasonal influenza vaccine (for individuals 65+, only enhanced influenza vaccines).

Follow-up time: From 14 days after vaccination (index date). until the outcome of interest, or are censored at the first of the following: 6 months of follow-up, end of medical and/or pharmacy enrollment, receipt of any post-index COVID-19 or influenza date vaccine.

Outcomes of interest, for co-administered vaccines versus BNT1621b2 XBB.1.5 monovalent alone:

Primary outcome:

1. A COVID-19-related encounter, regardless of setting (primary outcome)

Secondary outcomes:

1. An outpatient encounter with ICD-10-CM U07.1 "COVID-19" code

2. An inpatient encounter with ICD-10-CM U07.1 "COVID-19" listed in any diagnosis position. As a sensitivity analysis, we will restrict to U07.1 in primary diagnosis field.
3. An emergency department encounter with ICD-10-CM U07.1 "COVID-19" code
4. All-cause mortality
5. Negative control outcomes such as accidental injury, ingrown toenail or atopic dermatitis.

Exploratory outcome:

1. An urgent care encounter with ICD-10-CM U07.1 "COVID-19" code

Outcomes of interested, for co-administered vaccines versus seasonal influenza vaccine alone:

Primary outcome:

1. A flu-related encounter, regardless of setting (primary outcome)

Secondary outcomes:

1. An outpatient encounter with ICD-10-CM code indicating influenza
2. An inpatient encounter with influenza. Note, influenza will not be required to be the principal diagnosis as there is less concern about incidental findings and previous experience from the flu team suggests primary diagnosis coding in influenza hospitalizations might prioritize complications rather than the infection.
3. An emergency department encounter with ICD-10-CM code indicating influenza
4. All-cause mortality
5. Negative control outcomes such as accidental injury, ingrown toenail or atopic dermatitis.

Exploratory outcome:

1. An urgent care encounter with ICD-10-CM code indicating influenza

Measures of absolute and relative VE: For each outcome above, results will be calculated as:

1. Absolute VE comparing vaccinated to unvaccinated persons, regardless of prior vaccination
2. Relative VE will be calculated for each of the following mutually exclusive subgroups.
    a. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who received BA.4/5 bivalent vaccine.
    b. XBB.1.5 vaccinated vs XBB.1.5 unvaccinated persons who did not receive BA.4/5 bivalent vaccine but did receive at least 2 doses of mRNA vaccine (regardless of formulation).
    c. XBB.1.5 vaccinated vs never COVID-19 vaccinated.

Stratifications: Results will be stratified by age group (overall, age 18-49, 50-64, 65+) as well as by calendar time (BA.4/5 versus XBB.1.5 vaccine available eras).

Statistical Methods: All analyses will be pooled across California and Louisiana. To consider the potential for effect measure modification, we will additionally stratify by state, rather than adjust, for the primary endpoint. Descriptive statistics will be used to summarize patient characteristics, with

mean (standard deviation) or median (25th percentile – 75th percentile) for continuous variables and counts (percentages) for categorical variables. Standardized mean differences (SMD) will be used to compare covariate balance in cohorts before and after inverse probability of treatment weighting (IPTW).[27,28] Variables with SMD > 0.10 after weighting will be included in models for doubly robust adjustment.[29]

Stabilized IPTW, trimmed at the 1st and 99th percentile if necessary after examining the distribution of weights to avoid exertion of outliers,[30] will be calculated as the probability of coadministered vaccines given the covariates outlined in *McGrath, Malhotra, Miles et al (2023, JAMA Network Open)* which are listed in "Table 5: Covariates". Sensitivity analyses will consider the impact of study design and analytic assumptions, such as varying the exposure definition to 7 days post vaccination rather than 14 days.

Weighted survival functions will be used to estimate aRR with 95% CI and risk differences (RD), separately for coadministration as compared to COVID-19 vaccine alone and for coadministration as compared to flu vaccine alone. Given the time fixed exposure definition, RR and RD will be used for this aim rather than HR, as the proportional hazards assumption required to fit aHR may be violated.

8.8. Quality Control

Data in HealthVerity's database are provided monthly in an electronic format. HealthVerity employs its foundational product to match patients between different data sources with high accuracy. All analyses will be performed internally and according to Pfizer analytic standards, including double programming to ensure quality control.

8.9. Limitations of the Research Methods

- This analysis is from two states and thus may not generalize to other areas of the country. California is the largest and most populous state in the US (approximately the size of Canada), which afford unique opportunities with study population size. Louisiana represents a different geographical region of the country, where there may be varying patterns of individual health characteristics and health seeking behaviors.
- We do not have laboratory confirmation of the COVID-19 diagnosis, therefore it is possible that some patients are being diagnosed with symptoms alone or that we are missing positive cases due to at-home testing.
- The results from this study may differ from those of VE studies using other data sources, such as Kaiser Permanente of Southern California.
- Exposed patients may have varying times since vaccination, and VE may wane over the 6 months of follow-up, which could bias the results towards the null.
- Attempts to address confounding may not be able to fully account for confounders.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

This study uses de-identified data. As such this study will be submitted to an IRB for exemption under category 4, pursuant to the terms of the US Department of Health and Human Service's Policy for Protection of human Subjects at 45 C.F.R 46.104(d).

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in CT24-WI-GL02-RF04 including Guidelines for Good Pharmacoepidemiologic Practices (GPP) and the European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves the use of databases which consist of data that existed as structured data at the time that the study started. In this data, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For all publications relating to the study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

This study is not a PASS protocol submitted in the EU/EEA or UK, and thus this annex is not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	C4591065_RAVEN_Protocol_FINAL_15Nov2023
Document Title:	Effectiveness of BNT162b2 formulations using state vaccine registry and insurance claims data

Signed By:	Date(GMT)	Signing Capacity
PPD	17-Nov-2023 18:20:11	Manager Approval