NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Investigating uptake and subsequent health outcomes associated with Pfizer-BioNTech bivalent COVID-19/Influenza vaccine concomitant administration using a claims-based real-world data source in the US
Protocol number	C4591061
Protocol version identifier	1.0
Date	26 April 2023
Active substance	J07BN01
Medicinal product	Pfizer-BioNTech BA.4/5 bivalent mRNA COVID-19 vaccine
Research question and objectives	The primary objectives are: • To describe the proportion of Pfizer-BioNTech bivalent mRNA COVID-19/influenza vaccines that are concomitantly administered, and the characteristics of patients who receive concomitant administration. • To estimate vaccine effectiveness (VE) of concomitant administration of a single dose of the mRNA Pfizer-BioNTech bivalent COVID-19 vaccine and a licensed flu vaccine versus either vaccine alone against all-cause hospitalization or acute respiratory illness requiring hospitalization, emergency department/urgent care or outpatient encounters.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
CI	Confidence interval
CDC	Centers for Disease Control and Prevention
CFR.	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CDM	Clinformatics Data Mart
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
ED	Emergency Department
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiologic Practice
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
ICD-10-CM	International Classification of Diseases, 10th revision,

Abbreviation	Definition
	Clinical Modification
IEC	Independent Ethics Committee
IPTW	Inverse Probability of Treatment Weights
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPOR-ISPE	International Society for Pharmacoeconomics and Outcomes Research – International Society for Pharmacoepidemiology
mRNA	Messenger Ribonucleic Acid
NDC	National Drug Code
NVX-CoV2373	Novavax COVID-19 vaccine
NY	New York
POS	Place of service
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCD	Sickle cell disease
SD	Standard Deviation
SIV	Seasonal Influenza Vaccine
UC	Urgent care
UK	United Kingdom
US	United States
VAERS	Vaccine adverse event reporting system

Abbreviation	Definition
VE	Vaccine effectiveness

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	05 May 2023
End of data collection	12 May 2023
Final study report	12 December 2023

7. RATIONALE AND BACKGROUND

Data suggest severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) likely follows a seasonality pattern as with other respiratory viral infections such as influenza; where activity peaks during the traditional winter viral respiratory season.[1] CDC guidance for the 2020 and 2021 flu seasons included a recommended time interval of at least 14 days between flu and COVID-19 vaccines.[2] Based on updated data, the CDC has revised their recommendations that COVID-19 vaccines may be co-administered with seasonal influenza vaccines (SIV).[3] Specifically, COVID-19 and SIV can be administered concomitantly, and routine administration of all age-appropriate doses of vaccines simultaneously is recommended for children, adolescents, and adults.[3] A systematic literature review of 30 studies revealed that when SIV and COVID-19 booster vaccines are combined, there is potential for an increase in the uptake of the COVID-19 vaccine, predominately because many individuals are accustomed to taking SIV annually.[4]

Studies have reported similar safety and immunogenicity among those who received co-administrated COVID-19 vaccine and SIV compared to those who received these vaccines separately.[5-11] Three of these studies were clinical trials comparing safety and immunogenicity between SIV and COVID-19 co-administration versus SIV or COVID-19 alone. In these three clinical trials, no safety concerns or immune interferences were found regardless of the vaccines or the age of vaccinated subjects (18-64 or 65+).[6,9-11] Hause et al in a retrospective cohort study of self-reported vaccine data found a significant increase in reports of systemic reactions 0-7 days following co-administration of a COVID-19 mRNA booster vaccines with an SIV compared to COVID-19 mRNA vaccine alone;[5] whereas results from a VAERS database[8] and the National Health Interview Survey[7] analyses found no unusual or unexpected patterns of AEs or differences in symptom severity.

Regarding efficacy/effectiveness, one study was identified and reviewed. Novavax's NVX-CoV2373 COVID-19 vaccine efficacy when co-administered with the quadrivalent influenza cell-based vaccine Flucelvax (Seqirus UK, Maidenhead) among individuals aged 18 to <65 years was 87·5% (95% CI –0·2 to 98·4); was slightly attenuated compared to when administered alone (89·8% (95% CI 79·7–95·5).[9]

Although the above studies evaluated safety, immunogenicity and efficacy, the proportion of individuals receiving concomitantly administered COVID-19/influenza vaccines in routine clinical practices is not well characterized and has the potential to be a large percentage of vaccine recipients. Further, it is unknown whether receiving COVID-19/influenza vaccines concomitantly alters subsequent health outcomes. Therefore, the aim of this study is to evaluate within the context of a large national healthcare claims database in the US the proportion of bivalent COVID-19/influenza vaccines concomitantly administered; the characteristics of patients who receive concomitant administration and subsequent health outcomes among groups defined by vaccine administration.

8. RESEARCH QUESTION AND OBJECTIVES

Primary Objective 1: To describe the proportion of Pfizer-BioNTech bivalent mRNA COVID-19/influenza vaccines that are concomitantly administered, and the characteristics of patients who receive concomitant administration.

Primary Objective 2: To estimate vaccine effectiveness (VE) of concomitant administration of a single dose of the mRNA Pfizer-BioNTech bivalent COVID-19 vaccine and a licensed flu vaccine versus either vaccine alone against all-cause hospitalization or acute respiratory illness requiring hospitalization, emergency department/urgent care or outpatient encounters.

9. RESEARCH METHODS

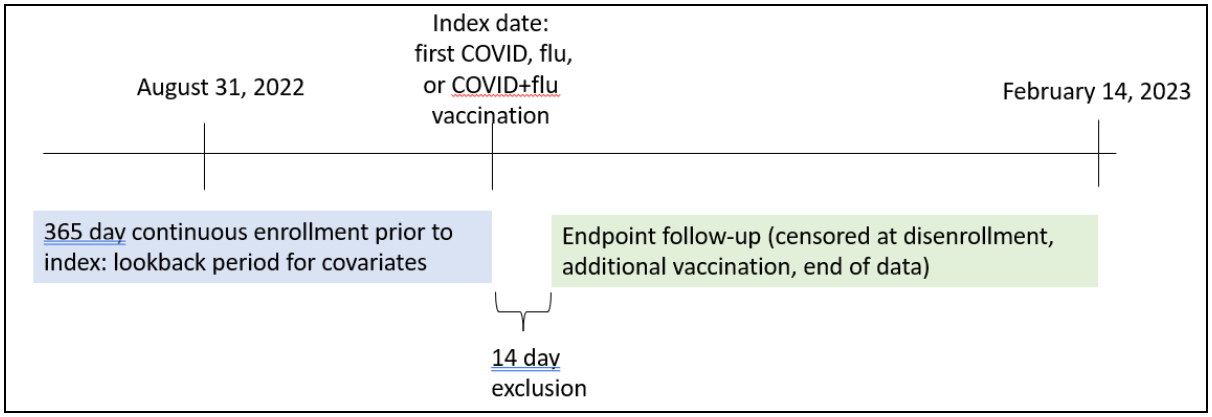
9.1. Study Design

This structured secondary data collection study will be a retrospective, cohort design to describe concomitant vaccine uptake and subsequent outcomes during one influenza vaccination season. Individuals will be indexed on the date of their first Pfizer-BioNTech mRNA bivalent COVID-19 or influenza vaccine. Exposure groups will be assigned as follows:

- Group 1: Same day (Pfizer-BioNTech mRNA bivalent COVID and flu on the same day);
- Group 2: COVID alone (Pfizer-BioNTech bivalent COVID only);
- Group 3: flu alone (influenza vaccine of any type only).
- [redacted]

A one year lookback period prior to the index vaccination will be used to identify covariates. Individuals will be followed starting 15 days after vaccination until experiencing one of the following: 1) outcome 2) disenrollment 3) receipt of a second vaccine of the same type 4) receipt of the other vaccine or any type of COVID-19 vaccine 5) end of data or 6) death. Only Pfizer-BioNTech mRNA bivalent COVID-19 vaccine will be assessed. All types of influenza vaccines recommended for the eligible population will be eligible for inclusion, but for the 65+ age group only enhanced influenza vaccines will be included.

Figure 1. Overall Study Design



9.2. Setting

The study period will be 31 August 2022 through 14 February 2023, but data will be used going back to 31 August 2021 to ascertain baseline covariates. The study population will include adults who were enrolled in the Optum Clinformatics Database as of 31 August 2022 (the date when the Pfizer-BioNTech bivalent mRNA vaccine was authorized), and have received a Pfizer-BioNTech mRNA bivalent COVID-19 or influenza vaccine during the study period.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Enrolled in Optum claims database as of 31 August 2022 (date bivalent authorized).
2. Has a Pfizer-BioNTech mRNA bivalent COVID-19 or influenza vaccine (any type) between 31 August 2022 and 30 January 2023 (earliest vaccine is index date).
3. Aged >=18 years on the index date.
4. 365 days of continuous enrolment prior to index date.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with a second dose of any type of bivalent mRNA COVID-19 or flu vaccine, disenrolled or died within 14 days following the first dose.
2. Has prior COVID-19 diagnosis (U07.1, any setting, any position) within 90 days (per CDC guidance[12] on length of time before receiving a vaccine) before and on index.
3. Has influenza vaccine between 01 August -30 August 2022 (before study period).

4. Has a COVID-19 or influenza diagnosis code in any setting within 14 days after index vaccination (excluded from all cohorts).

5. For patients 65+, had a standard dose influenza vaccine or unknown type influenza vaccine.

6. Has Moderna mRNA bivalent COVID-19 vaccine or monovalent vaccine of any type on index date.

9.3. Variables

9.3.1. Exposure

Table 1. Vaccination Status Variables

Variable	Role	Operational definition
Group 1: Same Day (Concomitantly administered Pfizer-BioNTech COVID-19 mRNA bivalent vaccine + influenza vaccine)	Exposure	Patients meeting the following criteria will be included in the Same Day cohort: 1. NDC or CPT codes for both the Pfizer-BioNTech mRNA bivalent COVID-19 vaccine and an influenza vaccine during the study period. 2. The first Pfizer-BioNTech mRNA bivalent COVID-19 vaccine and influenza vaccine NDC or CPT codes during the study period occurred on the same date. 3. No influenza vaccine NDC or CPT code between 01 August 2022 and 30 August 2022. If the patient receives >1 mRNA bivalent COVID-19 vaccine or influenza vaccine during follow-up, the patient is censored on the date of the NDC or CPT code for the second vaccine of the same type. mRNA bivalent COVID-19 and influenza vaccine NDC and CPT codes are listed in Appendix Table 1.
Group 2: COVID alone (COVID-19 mRNA bivalent vaccine alone)	Exposure	Patients meeting the following criteria will be included in the COVID-19 alone cohort: 1. Pfizer-BioNTech mRNA bivalent COVID-19 vaccine NDC or CPT code during the study period and no influenza vaccine on that date. 2. No influenza vaccine NDC or CPT code between 01 August 2022 and 30 August 2022. If the patient receives >1 mRNA bivalent COVID-19 vaccine (any type) during follow-up or an influenza vaccine, the patient is censored on the date of the NDC or CPT code for the second mRNA bivalent COVID-19

Table 1. Vaccination Status Variables

Variable	Role	Operational definition
		vaccine/influenza vaccine. mRNA bivalent COVID-19 vaccine NDC and CPT codes are listed in Appendix Table 1.
Group 3: Flu alone (Influenza vaccine alone)	Exposure	Patients meeting the following criteria will be included in the Flu alone cohort: 1. Influenza vaccine NDC or CPT code during the study period and no mRNA bivalent COVID-19 vaccine on that date. 2. No influenza vaccine NDC or CPT code between 01 August 2022 and 30 August 2022. If the patient receives >1 influenza vaccine or an mRNA bivalent COVID-19 vaccine (any type) during follow-up, the patient is censored on the date of the NDC or CPT code for the second influenza vaccine/COVID-19 vaccine. Influenza vaccine NDC and CPT codes are listed in Appendix Table 1.
CCI [redacted]	[redacted]	[redacted]

9.3.2. Outcomes

All outcomes will be assessed starting on Day 15. All hospitalization related outcomes in the table below will be ascertained using acute facility stays only. Inpatient stays classified as skilled nursing facility or rehabilitation will not be used. COVID-19 and flu hospitalizations will be assessed in any position and in the primary position to mitigate possibility of hospitalization with the disease versus for the disease.

COVID-19 related endpoints will be identified using the following ICD-10-CM diagnosis code: U07.1.

Influenza will be identified using the following ICD-10-CM diagnosis codes: J09.X, J10.X, J11.X.

We will evaluate three negative control outcomes. These outcomes are unrelated to vaccination and likely share similar confounding patterns for health-seeking behaviors. These negative controls have been used in other studies of comparative VE of influenza vaccines or COVID-19 VE.[13-15] Urinary tract infection and accidental injury are outcomes that could differentiate patients who seek medical care versus those who do not, and is likely a better choice of outcome for younger adults. Hospitalization in the first 14 days (ie, among recently vaccinated) uses time as a negative control, in that the vaccine likely could not biologically prevent health events until adequate levels of immunity has been achieved.

Table 2. Outcome Variables

Variable	Role	Operational definition
All-cause hospitalization	Outcome	An inpatient (acute facility) claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 21. 3. Non-null confinement ID. 4. tos_cd = 'FAC_IP.ACUTE'.
Composite COVID-19 related hospitalization/ED/UC (any position)	Outcome	An inpatient (acute facility) claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 21.

Table 2. Outcome Variables

Variable	Role	Operational definition
		3. Non-null confinement ID. 4. tos_cd = 'FAC_IP.ACUTE'. 5. COVID-19 diagnosis code (ICD-10-CM: U07.1) in any position OR An ED/urgent care claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 23 or 20. 3. Confinement id = null. 4. COVID-19 diagnosis code (ICD-10-CM: U07.1) in any position
COVID-19 related hospitalization (any position)	Outcome	An inpatient (acute facility) claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 21. 3. Non-null confinement ID. 4. tos_cd = 'FAC_IP.ACUTE'. 5. COVID-19 diagnosis code (ICD-10-CM: U07.1) in any position.
CCI [redacted]	[redacted]	[redacted]

Table 2. Outcome Variables

Variable	Role	Operational definition
		[redacted]
Composite influenza-related hospitalization/ED/UC (any position)		An inpatient (acute facility) claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 21. 3. Non-null confinement ID. 4. tos_cd = 'FAC_IP.ACUTE' 5. Influenza diagnosis code (ICD-10-CM: J09.X, J10.X, J11.X) in any position. OR An ED/urgent care claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 23 or 20. 3. Confinement id = null. 4. Influenza diagnosis code (ICD-10-CM: J09.X, J10.X, J11.X) in any position.
Influenza-related hospitalization (any position)	Outcome	An inpatient (acute facility) claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 21.

Table 2. Outcome Variables

Variable	Role	Operational definition
		3. Non-null confinement ID. 4. tos_cd = 'FAC_IP.ACUTE'. 5. Influenza diagnosis code (ICD-10-CM: J09.X, J10.X, J11.X) in any position.
CCI [redacted]	[redacted]	[redacted]
COVID-19 related ED/Urgent care visit (any position)	Outcome	An ED/urgent care claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 23 or 20. 3. Confinement id = null. 4. COVID-19 diagnosis code (ICD-10-CM: U07.1) in any position.
Influenza-related ED/Urgent care visit (any position)	Outcome	An ED/urgent care claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Place of service = 23 or 20. 3. Confinement id = null.

Table 2. Outcome Variables

Variable	Role	Operational definition
		4. Influenza diagnosis code (ICD-10-CM: J09.X, J10.X, J11.X) in any position.
COVID-19related outpatient visit (any position)	Outcome	An outpatient claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Confinement id = null. 3. COVID-19 diagnosis code (ICD-10-CM: U07.1) in any position. 4. Does not meet the definition of an ED/UC/hospital visit.
Influenza-related outpatient visit (any position)	Outcome	An outpatient claim that meets the following criteria: 1. Occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period. 2. Confinement id = null. 3. Influenza diagnosis code (ICD-10-CM: J09.X, J10.X, J11.X) in any position. 4. Does not meet the definition of an ED/UC/hospital visit.
Urinary tract infection	Negative control outcome	≥1 ICD-10-CM diagnosis code in any position/any setting for a urinary tract infection (that occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period.
Accidental injury	Negative control outcome	≥1 ICD-10-CM diagnosis code in any position/any setting for accidental injury that occurs >14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period.
Hospitalization in the 14 days following vaccination (recently vaccinated) Day 1-14	Negative control outcome	An inpatient (acute facility) claim that meets the following criteria: 1. Occurs ≤14 days after the patient's first mRNA bivalent COVID-19 or influenza vaccine dose during the study period.

Table 2. Outcome Variables

Variable	Role	Operational definition
		2. Place of service = 21. 3. Non-null confinement ID.
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]

Table 2. Outcome Variables

Variable	Role	Operational definition
		within 60 days following discharge.
CCI [redacted]	[redacted]	[redacted]
Follow-up time	Outcome descriptive	Measured from day 15 through the minimum date of censoring (see follow-up time description in Section 9.3.3). Mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum, will also be summarized for the length of follow-up in each group.

9.3.3. Censoring

The censoring date will be the minimum date in follow-up (starting >14 days after vaccination) of the following variables.

Table 3. Censoring Variables

Variable	Role	Operational definition
Outcome under study	Censoring	See outcome table above. Table 2.
Disenrollment	Censoring	Date a patient disenrolls from the insurance plan, as indicated in the enrollment file.
End of data	Censoring	14 February 2023
Receipt of second vaccine of the same type	Censoring	Any kind of mRNA bivalent COVID-19 vaccine is considered as a censoring vaccine. See exposure table for vaccination definitions.
Receipt of the other vaccine type	Censoring	Any kind of mRNA bivalent COVID-19 vaccine is considered as a censoring vaccine. See exposure table for vaccination definitions.
Death	Censoring	Death date is assigned the midpoint of the month in which death is reported in the database.
Nirmatrelvir/ritonavir (sensitivity analysis for COVID-19 endpoints)	Censoring	First dispensing for Nirmatrelvir/ritonavir during follow-up using NDC codes.
Influenza treatment (sensitivity analysis for treatment endpoints)	Censoring	First dispensing of any influenza treatments (see outcome table above for definitions) during follow -up using NDC codes.

9.3.4. Covariates

Table 4. Covariates

Variable	Role	Operational definition
Age	Patient Characteristics, Subgroup	The number of years between the index date and the patient birth year. Age will be reported in the following categories: 18-64 and 65+. Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum, will also be summarized. Model specification: continuous linear
Sex	Patient Characteristics	Sex will be reported as Male ('M'), Female ('F'), and Unknown Model specification: categorical
US Geographic Region	Patient Characteristics	US geographic region will be derived from the patient state and categorized into the following: Northeast – Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Pennsylvania Midwest – Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota South – Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, Texas West – Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, Washington Other/unknown – Puerto Rico/unknown region Model specification: categorical
Charleston Comorbidity Index (CCI)	Patient Characteristics	Charleston Comorbidity Index score will be measured during the 12 month baseline period before index and will be reported in the following categories: 0, 1, and 2+. Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum, will also be summarized. Model specification: categorical (0,1,2+)
Prior Pneumonia or respiratory failure	Patient Characteristics	Any code (any setting) within the 1 year baseline for any type of pneumonia or respiratory failure
Prior heart disease	Patient Characteristics	Any code (any setting) within the 1 year baseline for heart disease
Prior asthma	Patient Characteristics	Any code (any setting) within the 1 year baseline for asthma

Table 4. Covariates

Variable	Role	Operational definition
Prior chronic lung disease	Patient Characteristics	Any code (any setting) within the 1 year baseline for chronic lung disease
Prior diabetes	Patient Characteristics	Any code (any setting) within the 1 year baseline for diabetes
Prior kidney disorders	Patient Characteristics	Any code (any setting) within the 1 year baseline for kidney disorders
Month of index date	Patient Characteristics	August/September, October, November, December, January (Note: August will be combined with September as only 1 day of August will be included in the cohort). Model specification: categorical
Prior Influenza vaccination	Patient Characteristics	One claim (NDC or CPT) for influenza vaccine of any type measured between 31 August 2021 – 31 May 2022 Model specification: dichotomous (yes/no)
COVID-19 vaccination in the 1 year prior	Patient Characteristics	One claim (NCD, CPT, procedures) for COVID vaccine of any type in the 365 days before index separated into the following time periods: • Recent vaccination: ≤60 days prior to index • Older vaccination: Between 61 and 365 days prior to index • No evidence of vaccination in the prior year If there is evidence of >1 COVID vaccination in the 365 days prior to index, patients are categorized using the date of the most recent dose administered during the baseline period. Model specification: categorical (3 level)
Time from last COVID-19 vaccine dose (Due to the likelihood of misclassification, this variable will be used for descriptive table only, not for model)	Patient Characteristics	Number of days from last COVID-19 vaccine dose. Reported as categories:[17,18] <60 days, 60-179, >=180, not applicable. Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum, among those with a prior dose.
Monovalent mRNA COVID-19 vaccine in the 60 days prior to index (Note for descriptive table only, not for model due to collinearity with covid vaccine in the prior year above)	Patient Characteristics	Yes/No. One claim (NCD, CPT, procedures) for monovalent mRNA COVID-19 vaccine between 01 July 2022 – 30 August 2022

Table 4. Covariates

Variable	Role	Operational definition

Type of index influenza vaccine administered (Note for descriptive table only, not for model)	Patient Characteristics	Categories include: Enhanced/Standard/Unknown, and each specific type of vaccine
		• Standard
		  • Egg-based standard dose injection (Afluria, Fluarix, FluLaval, Fluzone Standard Dose)
		  • Fluzone intradermal
		  • Flucelvax (cell-based)
		  • FluMist
		  • Multiple
		• Enhanced
		  • Fluzone High dose (Enhanced)
		  • Flublok (recombinant/Enhanced)
		  • Fluad (adjuvanted/Enhanced)
		  • Multiple
		• Unknown
		See below for operational definition for assigning specific flu vaccines.

Concurrent Shingrix vaccination (any dose)	Patient Characteristics	NDC or CPT code for Shingrix on the same day as the index vaccination Model specification: dichotomous (yes/no)
Prior Shingrix vaccination	Patient Characteristics	NDC or CPT code for Shingrix in the 365 days prior to index • 1 prior dose • 2 prior doses (measured on unique days) Model specification: dichotomous (yes/no) (Note: number of doses used in descriptive table only)
Concurrent pneumococcal vaccination	Patient Characteristics	NDC or CPT code for polysaccharide or conjugate pneumonia vaccine on the same day as the index vaccination Model specification: dichotomous (yes/no)

Table 4. Covariates

Variable	Role	Operational definition
Prior pneumococcal vaccination	Patient Characteristics	NDC or CPT code for polysaccharide or conjugate pneumonia vaccine in the 365 days prior to index Model specification: dichotomous (yes/no)
Vaccine administration setting	Patient Characteristics	Vaccine administration setting will be determined based on the reported place of service for the claim. Prescription claims will be assumed to have occurred in the Pharmacy setting. The most common settings will be reported and patients with multiple conflicting administration setting codes on index will be classified as multiple. Model specification: pharmacy, office, other
Nursing home residence	Patient Characteristics	Any claim with care location (POS =32) of nursing home in the 365 days prior to index. Model specification: dichotomous (yes/no)
Skilled nursing facility	Patient Characteristics	Any claim with care location of SNF (POS = 31) in the 365 days prior to index. Model specification: dichotomous (yes/no)
Functional status/mobility	Patient Characteristics	A procedure code indicating decreased functional status or mobility in the 365 days prior to index. Model specification: dichotomous (yes/no)
Wellness visit	Patient Characteristics	A CPT or diagnosis code for wellness visit in the 365 days prior to index. Model specification: dichotomous (yes/no)
Immunocompromised status	Patient Characteristics	Assess this group as the following category (Yes/No): >=1 IC condition. Any code within the 1 year baseline for the following conditions: • Hematologic malignancy • HIV/AIDS • Solid organ transplant • Bone marrow transplant • Primary immunodeficiencies • Immunosuppresive medications (eg, chemotherapy, oral corticosteroids ≥20mg of prednisone or equivalent for ≥14 days). Model specification: dichotomous (yes/no)
Conditions that place or may place patients at risk of Severe COVID-19	Patient Characteristics	Assess this group as the following category (Yes/No): >=1 high risk condition. Baseline comorbid conditions that place or may place

Table 4. Covariates

Variable	Role	Operational definition
		patients at risk of Severe COVID-19 will be assessed in the 12 months prior to index date. Conditions will be assess by having at least 1 ICD-10-CM code in any position in any setting. The conditions include: • Cancer history • Chronic kidney disease (CKD) at any stage • Chronic liver disease • Chronic lung diseases • Dementia or other neurological conditions • Diabetes (type 1 or type 2) • Disabilities; including Down Syndrome • Heart conditions (heart failure; coronary artery disease; or cardiomyopathies) • HIV infection • Hypertension • Immunocompromised state (primary caused by genetic defects; secondary/acquired from prolonged use of corticosteroids or other immune weakening medicines) • Mental health conditions • Overweight and obesity • Physically inactive • Sickle cell disease (SCD) or thalassemia • Smoking; current or former • Solid organ or blood stem cell transplant (includes bone marrow transplants) • Stroke or cerebrovascular disease • Substance use disorders (alcohol; opioid; or cocaine

Table 4. Covariates

Variable	Role	Operational definition
		use disorder) • Tuberculosis • Pregnancy or recent pregnancy (for at least 42 days following end of pregnancy). Model specification: dichotomous (yes/no)
Number of outpatient visits in the 180 days prior	Patient Characteristics	Count unique days with an outpatient visit in the 180 days prior to index • Dichotomous, yes/no • Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum. Model specification: number categories (0, 1, 2, 3+)
Number of hospitalizations in the 180 days prior	Patient Characteristics	Count of unique days with an acute hospital admission (POS = 21 and tos_cd = 'FAC_IP.ACUTE') in the 180 days prior to index • Dichotomous, yes/no • Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum Model specification: number categories (0, 1, 2+)
Number of prior COVID-19 tests in the prior 365 days	Patient Characteristics	Count of unique days with COVID-19 test (PCR or antigen test) ordered in the 365 days prior to index • Dichotomous, yes/no • Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum Model specification: number categories (0, 1, 2+)
Flu test in the prior 365 days	Patient Characteristics	Influenza test ordered in the 365 days prior to index • Dichotomous, yes/no Model specification: dichotomous (yes/no)
Number of prior telehealth visits in the prior 365 days	Patient Characteristics	Count of unique days with telehealth visit in the 365 days prior to index • Dichotomous, yes/no

Table 4. Covariates

Variable	Role	Operational definition
		• Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum Model specification: number categories (0, 1, 2+)
Number of labs ordered in the prior 365 days	Patient Characteristics	Count of unique days with any lab ordered in the 365 days prior to index • Dichotomous, yes/no • Continuous statistics including mean, standard deviation (SD), median (Q1 -Q3), minimum, and maximum Model specification: number categories (0, 1, 2+)
Prior COVID-19 infection	Patient Characteristics	1 ICD-10-CM code (U07.1) in the 1 year baseline in any setting (>3 months prior to reflect exclusion criteria Model specification: dichotomous (yes/no)
Prior influenza infection	Patient Characteristics	1 ICD-10-CM code for influenza in the 1 year baseline in any setting Model specification: dichotomous (yes/no)

If there are conflicting records on the type of influenza vaccine received on index, influenza vaccine category (Enhanced, Standard, Unknown) will be assigned as follows:

1. ≥1 NDC or CPT code for an enhanced flu vaccine.
2. Classified as enhanced.
3. ≥1 NDC or CPT code for a standard flu vaccine and no codes for enhanced.
4. Classified as standard.
5. ≥1 NDC or CPT code for an unknown type of flu vaccine and no codes for enhanced or standard.
    a. Classified as unknown.

For the influenza vaccine brand subcategories, patients with conflicting records will be classified as “Multiple”.

9.4. Data Sources

Optum's Clinformatics Data Mart (CDM) comes from a database of administrative health claims for members of a large national managed care company affiliated with Optum. The database includes over 73 million unique lives (2007 through 2021). Clinformatics Data Mart is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum customer data use agreements. These administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion. The Claims data comprises both commercial/employer sponsored plans and Medicare Advantage health plan data. This data covers ~30% of the national Medicare Advantage population. The population is geographically diverse, spanning all 50 states. In addition to medical claims and pharmacy claims, the Claims data includes tables with member eligibility and inpatient confinements. The Claims data also includes standard pricing for all medical claims, pharmacy claims, and inpatient confinements. Mortality is provided as month and year of death and is sourced from Centers for Medicare and Medicaid Servies, Social Security Administration Death Master File, facility claims with inpatient death, discontinuation of coverage due to death and external obituary data.

9.5. Study Size

The sample size for this study is fixed by the duration of the observation window. All subjects who meet the inclusion/exclusion criteria will be included in the analyses.

Feasibility analyses from 31 August 2022- 16 January 2023 confirmed the availability of data to identify vaccinated subjects. Table 5 below shows the estimated number of patients in each group.

Table 5. Estimated Number of Patients in Each Vaccination Exposure Group

	Group 1: Same Day	Group 2: COVID-19 alone	Group 3: Flu alone	CCI [redacted]
18-64	244,864	144,695	772,418	CCI
65+	382,806	225,842	1,351,093	CCI

Composite COVID-19 hospitalizations/UC/ED

For 65+, and the Group 1 vs Group 2 comparison of the COVID-19 related composite hospitalizations/ED/UC endpoint, we assume the percentage of patients in Group 1 will be 63% and the expected percentage of patients in Group 1 and Group 2 with an event overall will be 0.56%. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 1,724 events resulting in 193,548 patients in Group 1, and 113,671 in Group 2, which meets our current estimated sample size.[19]

For 18-64, and the Group 1 vs Group 2 comparison of the COVID-related composite hospitalizations/ED/UC endpoint, we assume the percentage of patients in Group 1 will be 63% and the expected percentage of patients in Group 1 and Group 2 with an event overall will be 0.066%. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 1,638,003 in Group 1, and 962,002 in Group 2, which does not meet our current estimated sample size.

Composite influenza hospitalizations/UC/ED

For 65+ and for the Group 1 vs Group 3 comparison of the flu-related composite hospitalizations/UC/ED endpoint, we assume the percentage of patients in Group 1 will be 23% and the expected percentage of patients in Group 1 and Group 3 with the endpoint overall will be 0.3%. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 2,269 events resulting in 176,179 in Group 1, and 589,817 in Group 3, which meets our current estimated sample size.

For 18-64 and for the Group 1 vs Group 3 comparison of the flu-related composite hospitalizations/UC/ED endpoint, we assume the percentage of patients in Group 1 will be 23% and the expected percentage of patients in Group 1 and Group 3 with the endpoint overall will be 0.09%. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 574,716 in Group 1, and 1,924,050 in Group 3, which does not meet our current estimated sample size.

The inputs to the sample size calculations are based on unadjusted estimates across both exposure groups, and there is the possibility of confounding. After adjustment, it is likely that endpoint estimates may be closer together, thus increasing our power for non-inferiority analyses.

COVID-19 Outpatient Visits

For 65+, and the Group 1 vs Group 2 comparison of the COVID-19 related outpatient visits endpoint, we assume the expected percentage of patients in Group 1 and Group 2 with an event overall will be 1.77% . If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 61,218 in Group 1, and 35,954 in Group 2, which meets our current estimated sample size.

For 18-64, and the Group 1 vs Group 2 comparison of the COVID-19 related outpatient visits endpoint, we assume the expected percentage of patients in Group 1 and Group 2 with an event overall will be 1.47%. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 73,767 in Group 1, and 43,324 in Group 2, which meets our current estimated sample size.

Influenza Outpatient Visits

For 65+ and for the Group 1 vs Group 3 comparison of the flu-related outpatient visits endpoint, we assume the expected percentage of patients in Group 1 and Group 3 with the endpoint overall will be 0.47%,. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 110,467 in Group 1, and 369,822 in Group 3, which meets our current estimated sample size.

For 18-64 and for the Group 1 vs Group 3 comparison of the flu-related outpatient visits endpoint, we assume the expected percentage of patients in Group 1 and Group 3 with the endpoint overall will be 0.76%. If we use a non-inferiority margin of 1.15 for the upper bound of the 95% CI, 1-sided alpha of 0.025, and 80% power, and an expected HR of 1, then we would need 68,854 in Group 1, and 230,511 in Group 3, which meets our current estimated sample size.

9.6. Data Management

All Optum claims structured data described above are stored within Pfizer's data infrastructure. Data are queried and analyzed using SAS. The data are only accessible to Pfizer colleagues who have been trained and approved to access Pfizer's data warehouse.

9.7. Data Analysis

There is not a separate Statistical Analysis Plan document for this study. All methodology for summary and statistical analyses of data collected in this study is contained in this section. All computations and generation of tables will be performed using Statistical Analysis System (SAS) version 9.4 or higher (SAS Institute, Cary, NC, US).

All analyses will be conducted for the following age subgroups: 18-64 and 65+.

Descriptive statistics will be presented to describe baseline characteristics by vaccination exposure group. Baseline characteristics will be described by frequency distribution for categorical variables while continuous variables expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate. In general, missing or unavailable data will not be imputed and data will be analyzed as they are recorded in the database.

To account for imbalance in patient characteristics between the vaccine exposure groups, 2 separate logistic regression models will be used to create a propensity score used to calculate an inverse probability of treatment weights (IPTW). The two models will be as follows: Same day vs COVID-19 alone, and separately Same day vs Flu alone. Weights will be stabilized to avoid exertion of outliers, and we will further evaluate whether there is a need to truncate at the 1st and 99th percentile. Covariate balance before and after weighting will be assessed using standardized mean differences, separately for the same day/COVID-19 alone and Same day/flu alone comparisons. All variables listed in "Covariates" section with model specification instructions will be included in the score. If there are model convergence issues, changes in model specification may occur (eg, dropping variables with very low prevalence, categories may be collapsed further etc). Variables with residual imbalance will be included in the model for further adjustment.

Each outcome will be assessed separately. Experiencing one disease specific outcome is not a censoring criteria for the other disease (ie, having a COVID-19 outpatient diagnosis is not a censoring event for the influenza endpoints). Weighted cumulative incidence curves will be used to describe the occurrence of each outcome separately over the entire follow-up period. Given the relatively short follow-up time, we expect small numbers of deaths. Therefore, regular Cox proportional hazards models will be used to estimate HRs and 95% CI for each outcome separately. If we find that death is more common than anticipated, we will consider using Fine and Gray's proportional subdistribution hazards models to account for the competing risk of death. Models for the following vaccine group/outcome combinations will be assessed:

- Same day/COVID-19 only:
    - All-cause hospitalization, composite COVID-19 hospitalization/ED/UC (any position), COVID-19 hospitalization (any position, primary position), COVID-19 ED/UC, COVID-19 outpatient
- Same day/Flu only:
    - All-cause hospitalization, composite flu-hospitalization/ED/UC (any position), flu-hospitalization (any position, primary position), flu ED/UC, flu outpatient.

CCI [redacted]

Sensitivity Analysis

For disease specific endpoints, we will conduct a sensitivity analysis whereby an additional censoring criteria will be applied. For COVID-19 specific endpoints, we will censor for Paxlovid dispensing. For influenza specific endpoints, we will censor for any of the following influenza treatment dispensing (Oseltamivir phosphate, Zanamivir, Peramivir, Baloxavir marboxil).

9.8. Quality Control

Data in Optum's claims database are collected monthly in an electronic format. Analyses are programmed according to the specifications in the protocol and documented in a programming plan. All analyses will be performed internally and according to Pfizer analytic standards, including double programming to ensure quality control. All quality checks are documented in the programming plan.

9.9. Limitations of the Research Methods

There are several limitations associated with this study. This analysis is from one insurer that provides employer-sponsored and Medicare Advantage coverage and thus may not generalize to other populations, such as traditional Medicare fee-for-service, other government insurance or uninsured. It is possible that some vaccines may be missing if patients received vaccine in a setting where an insurance claim was not filed (ie employer sponsored clinic or paid out of pocket). This may be more problematic for influenza vaccine for younger ages. This will only impact the singular vaccine groups (ie, COVID-19 alone or influenza alone). The healthcare claims data are collected for billing purposes and may be subject to misclassification, misdiagnosis, and underreporting. Additionally, for our medically attended COVID-19 endpoints, 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.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

10.2. Patient Consent

As this study involves 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.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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).

10.4. 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 Guidelines for Good Pharmacoepidemiologic Practices (GPP),[20] Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[21] and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.[22]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, 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.

12. 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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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2 ADDITIONAL INFORMATION

Appendix Table 1. Excel File Containing all Bivalent mRNA Codes and Influenza Codes

Appendix Table 2. COVID-19 Variant Proportions in the US

Collection Week End Date	Predominant Variant[1]	% of Viral Lineages among Infections[2]
03 Sep 2022	BA.4/BA.5	97.6%
10 Sep 2022	BA.4/BA.5	96.8%
17 Sep 2022	BA.4/BA.5	95.5%
24 Sep 2022	BA.4/BA.5	93.9%
01 Oct 2022	BA.4/BA.5	91.6%
08 Oct 2022	BA.4/BA.5	86.7%
15 Oct 2022	BA.4/BA.5	81.5%
22 Oct 2022	BA.4/BA.5	76.4%
29 Oct 2022	BA.4/BA.5	65.8%
05 Nov 2022	BA.4/BA.5	58.3%
12 Nov 2022	BA.4/BA.5	49.6%
19 Nov 2022	BQ.1/BQ.1.1	42.8%
26 Nov 2022	BQ.1/BQ.1.1	47.6%
03 Dec 2022	BQ.1/BQ.1.1	52.8%
10 Dec 2022	BQ.1/BQ.1.1	57.1%
17 Dec 2022	BQ.1/BQ.1.1	58.9%
24 Dec 2022	BQ.1/BQ.1.1	59.3%
31 Dec 2022	BQ.1/BQ.1.1	58.5%
07 Jan 2023	BQ.1/BQ.1.1	53.0%

Collection Week End Date	Predominant Variant[1]	% of Viral Lineages among Infections[2]
14 Jan 2023	BQ.1/BQ.1.1	47.5%
21 Jan 2023	XBB	45.7%
28 Jan 2023	XBB	55.1%
04 Feb 2023	XBB	64.7%
11 Feb 2023	XBB	71.5%
18 Feb 2023	XBB	78.1%

1. The predominant variant was defined as the variant representing highest estimated percent of viral lineages among infections in a given week. Variant sublineage proportions were combined with the parent lineages.

2. The percent of viral lineages among infections was calculated using weekly weighted estimates from the CDC's national genomic surveillance system. The CDC's weighted estimates are based on empirical (observed) genomic sequencing data from the National SARS-CoV-2 Strain Surveillance (NS3) program, commercial or academic laboratories contracted by CDC, and state/local public health laboratories. Estimated percentages were calculated using data as of 14 April 2023.

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