NON-INTERVENTIONAL STUDY FINAL REPORT ABSTRACT

Title: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Date: 08 December 2023

Names and affiliations of the main authors: Jurandir Dalle Lucca, MD, PhD, Veterans Affairs Medical Center, White River Junction, VT; Kofi Asomaning, PhD, MD, Pfizer, Inc., Collegeville, PA; Mei Sheng Duh, ScD, MPH, Analysis Group, Inc., Boston, MA

Keywords: Pfizer-BioNTech COVID-19 vaccine, emergency use authorization (EUA), rapid-cycle analysis, safety signal, Veterans Health Administration (VHA)

Rationale and background: On 11 December 2020, the United States (US) Food and Drug Administration (FDA) issued its first emergency use authorization (EUA) for a messenger ribonucleic acid (mRNA) vaccine (Pfizer-BioNTech COVID-19 vaccine) for the prevention of COVID-19 disease in individuals 16 years of age and older.[1] Pfizer, in collaboration with the US Veterans Health Administration (VHA) and Analysis Group, is conducting a study (protocol C4591012 Version 6.0 dated 31 January 2023; Annex 1. Appendix 2) for post-EUA active surveillance of safety events of interest among individuals enrolled in the VHA system. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a postmarketing commitment to the US FDA as well as a Category 3 commitment in the EU Risk Management Plan. This final report includes signal detection and evaluation analyses for the primary series, monovalent booster doses, and the Omicron BA.4/BA.5-Adapted Bivalent Vaccine Booster [i.e., bivalent booster] dose of the Pfizer-BioNTech COVID-19 vaccine using data through 30 June 2023 (end of data collection) that were locked on 13 October 2023.

Research question and objectives: What are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with Pfizer-BioNTech COVID 19 vaccine within the US VHA system overall and in sub-cohorts of interest, as compared to expected rates of those events?

Primary study objectives: To assess whether the following groups of individuals in the VHA system experience increased risk of safety events of interest following receipt of Pfizer-BioNTech COVID-19 vaccine: Individuals receiving first dose; Individuals receiving the primary series of two doses; Individuals receiving additional approved dose(s) (i.e., an additional primary series dose, a single booster dose, or additional booster doses if applicable, including the bivalent booster) of the Pfizer-BioNTech COVID-19 vaccine after the primary series of two doses.

To assess whether sub-cohorts of interest (e.g., individuals with dual coverage of VHA and Medicare, individuals with bivalent booster dose of the Pfizer-BioNTech COVID-19 vaccine) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.

Secondary study objective: To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA including estimating the proportion of individuals receiving at least one dose of the vaccine, 2-dose vaccine completion rate, additional approved dose(s) vaccine completion rate, distribution of time gaps between the first and second dose, distribution of time gaps between the second and additional approved primary or booster dose(s), demographics and health histories of recipients, overall and among the sub-cohorts of interest.

Study design: This post-EUA active safety surveillance program employed a rapid-cycle, longitudinal, observational cohort study design to provide early real-world safety information. Self-controlled risk interval (SCRI) design was used to sequentially monitor the occurrence of safety events of interest while controlling for time-invariant confounders by comparing the risk interval following Pfizer-BioNTech COVID-19 vaccination to post-vaccination control intervals in the same individual who experienced safety events of interest following vaccination. An active comparator design was used to sequentially monitor the occurrence of safety events of interest among individuals who receive Pfizer-BioNTech COVID-19 vaccinations vs. influenza vaccine during the 2014/2015 to 2018/2019 influenza seasons. Further analyses were conducted during the signal evaluation phase.

Setting: The study population consisted of VHA enrollees, which largely included veterans.

Subjects and study size: The Pfizer-BioNTech COVID-19 vaccine sample included 1,652,514 individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023 with two years of continuous enrollment in VHA benefits prior to their first Pfizer-BioNTech COVID-19 vaccination. The seasonal influenza sample included a fixed cohort of 4,104,220 historical seasonal influenza vaccine recipients across successive influenza seasons between 2014/2015 to 2018/2019 with two years of continuous enrollment in VHA benefits prior to at least one seasonal influenza vaccination.

Data source, variables, and statistical methods: The VHA is the largest integrated health care system in the US, providing comprehensive healthcare services, including primary, specialty and inpatient care and other services to over nine million veterans.[2] The study relies on secondary data from the Corporate Data Warehouse (CDW) in the National Veterans Affairs Health Care Network. The CDW data, which are updated daily, include standard electronic medical records (EMR) for all medical encounter information in the VHA system.

Descriptive statistics were used to summarize characteristics of individuals included in the study during the two-year baseline period and vaccine utilization patterns among Pfizer-BioNTech COVID-19 vaccine recipients and historical active comparators who received seasonal influenza vaccination. Standardized differences were used to compare baseline characteristics between individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine (at the time of the first Pfizer-BioNTech COVID-19 vaccine dose) and those vaccinated for seasonal influenza (at the time of their most recent seasonal influenza vaccine).

A total of 48 safety events of interest were examined, where signal detection and evaluation analyses were performed separately and on an aggregated basis for monovalent doses 1-4 and bivalent dose 1 among individuals that received at least one dose of the Pfizer-BioNTech

COVID-19 vaccine. Safety surveillance analyses for a subgroup of individuals enrolled in the VHA with dual Medicare coverage were also conducted. Additionally, a prioritized safety analysis of myocarditis/pericarditis with medical record adjudication was conducted.

1) Signal detection: The SCRI analysis included post-vaccination control intervals for certain safety events of interest that required a COVID-19 diagnosis (i.e., severe COVID-19, multisystem inflammatory syndrome in children [MIS-C]/MIS in adults [MIS-A]). To account for multiple testing, the maximized sequential probability ratio test (MaxSPRT) was applied using a binomial probability model. For comparison with individuals who received seasonal influenza vaccination, the Poisson-based MaxSPRT was applied for all other safety events of interest. Safety events of interest with a log-likelihood ratio (LLR) test statistic that exceeded the pre-specified critical value had a signal detected. When the LLR could not be calculated because the pre-specified upper limit for the number of expected events was <3, in an abundance of caution, safety events of interest were moved to signal evaluation despite no detected signal if the observed vs. expected number of events was greater in the risk interval.

2) Signal evaluation: If signals were detected, further evaluation was conducted, including comprehensive quality assurance, binomial MaxSPRT with SCRI design, multivariate Poisson regression to account for differences between Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine samples, and conditional Poisson regression with self-controlled case series (SCCS) design. Other signal evaluation and verification analyses were not performed because signals did not remain following the SCCS design analysis.

3) Prioritized safety analysis of myocarditis/pericarditis: Following CDC's 23 June 2021 investigation of myocarditis/pericarditis associated with mRNA COVID-19 vaccinations,[3] separate safety analyses with medical record adjudication were prioritized to assess the risk of myocarditis/pericarditis among Pfizer-BioNTech COVID-19 vaccinees using methods aligned with the rapid-cycle analysis performed by the Vaccine Safety Datalink (VSD).[4]

Results: The majority of the Pfizer-BioNTech COVID-19 vaccine sample was male (89.8%), with an average age of 64.0 years (median: 67.4 years), and included 59.7% white non-Hispanic, 22.0% Black, 7.3% Hispanic ethnicity of any race, and 1.5% Asian. The seasonal influenza vaccine sample consisted of 4,104,220 individuals who received at least one seasonal influenza vaccine from the 2014/2015 to 2018/2019 influenza seasons. The baseline demographic and clinical characteristics were generally similar between Pfizer-BioNTech COVID-19 and the seasonal influenza vaccine recipients (standardized differences <10%).

A total of 1,589,777 (96.2%) individuals in Pfizer-BioNTech COVID-19 vaccine sample completed the primary series of two monovalent doses. 868,181 (52.5%) individuals in the Pfizer-BioNTech COVID-19 vaccine sample received three monovalent doses, and 275,601 (16.7%) individuals received four monovalent doses. 365,972 (22.2%) individuals received a bivalent dose of the Pfizer-BioNTech COVID-19 vaccine. Among 1,960,228 individuals with their first record of Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023 and two years of continuous enrollment in VHA benefits, 6.0% received a dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the Pfizer-BioNTech primary series (i.e., heterologous booster).

Signal detection: Using the SCRI design and binomial MaxSPRT, a potential signal was detected for severe COVID-19 disease. Using the active comparator design and Poisson MaxSPRT, potential signals detected in the risk interval after any dose of the Pfizer-BioNTech COVID-19 vaccine as compared to historical seasonal influenza vaccines were cerebrovascular non-hemorrhagic stroke, other acute demyelinating disease, acute myocardial infarction (AMI), anaphylaxis, arrhythmia, coronary artery disease (CAD), myocarditis, chilblain-like lesions, pulmonary embolism (PE), optic neuritis (ON), heart failure and cardiogenic shock, acute kidney injury, stress cardiomyopathy, and DVT. Though signals were not detected for Guillain-Barré Syndrome (GBS), microangiopathy, and hemorrhagic disease, they proceeded to signal evaluation out of an abundance of caution (as the observed number of events was greater than that expected). Based on this, 18 of 48 safety events of interest warranted further investigation and were advanced to signal evaluation.

Signal evaluation: For any safety events of interest with potential signals detected that were not already analyzed during the signal detection phase using binomial MaxSPRT, this methodology was used to assess the risk of the safety event of interest during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine compared to the risk of the same safety event of interest during the post-vaccination control interval. Arrhythmia, CAD, heart failure and cardiogenic shock, DVT, and PE were the only safety events of interest with potential signals that persisted in this analysis; therefore, they proceeded to the next signal evaluation analyses (i.e., multivariate adjusted Poisson regression). However, out of an abundance of caution, the remaining 13 safety events of interest with potential signals detected also proceeded to the next signal evaluation analyses due to the small number of events observed for some safety events of interest and the consequent low power of the binomial MaxSPRT analysis.

Multivariate Poisson regression analyses were performed to compare the incidence rate of safety events of interest with potential signals detected between individuals who received the Pfizer-BioNTech COVID-19 vaccine and historical seasonal influenza comparators. Severe COVID-19 disease could not be examined through the multivariate Poisson regression analyses because the historical seasonal influenza comparator sample was evaluated prior to the COVID-19 pandemic and would not have COVID-19 diagnosis codes. After controlling for key covariates, chilblain-like lesions was the only safety event of interest that had a signal remain based on the pre-defined safety signal definition of IRR >3 and p-value <0.01, and the models did not converge when examining microangiopathy and hemorrhagic disease due to the small number of events. Therefore, microangiopathy, chilblain-like lesions, hemorrhagic stroke, and severe COVID-19 disease proceeded to the next step of signal evaluation analyses for further investigation. Conditional Poisson regression was conducted to compare the incidence of the safety event of interest during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine vs. the post-vaccination control time period using the SCCS design. No signals remained based on the pre-defined criteria of a relative incidence (RI) >3 and p-value <0.01.

Prioritized safety analysis of myocarditis/pericarditis: All individuals in the Pfizer-BioNTech COVID-19 vaccine sample (N=1,652,514) were included in this separate analysis of myocarditis/pericarditis. There was a total of 130,904 males aged 12-39 years old (population

of special interest for the CDC as myocarditis/pericarditis is most common in this group). Among individuals with at least one dose of the Pfizer-BioNTech COVID-19 vaccine, there were 52 myocarditis/pericarditis events in the codified data within the 21-day risk interval after any dose, and males had a higher incidence rate than females, with the 95% CIs overlapping between the two groups (incidence rate per million doses [95% CI]: 11.4 [8.6, 15.1] vs. 6.5 [2.1, 20.1]). In the aggregated monovalent doses 1-4 and bivalent dose 1 analyses, individuals 12-39 years old had a higher incidence rate of codified myocarditis/pericarditis events than older age groups, with overlapping 95% CIs. The rate of codified myocarditis/pericarditis events during the 21-day risk interval after the Pfizer-BioNTech COVID-19 vaccine was not significantly greater than the rate in the comparison interval across any dose (adjusted rate ratio [95% CI] for aggregated monovalent doses 1-4 and bivalent dose 1: 0.96 [0.66, 1.40]), monovalent dose 1 (1.33 [0.61, 2.91]), monovalent dose 2 (1.24 [0.56, 2.75]), monovalent dose 3 (0.73 [0.35, 1.49]), monovalent dose 4 (0.62 [0.18, 2.17]), or bivalent dose 1 (2.51 [0.48, 13.21]). Similar results were generally observed when examining the rate of myocarditis/pericarditis events during the 7-day and 42-day risk intervals after the Pfizer-BioNTech COVID-19 vaccine. While the adjusted rate ratio [95% CI] of myocarditis/pericarditis events in the 42-day risk interval after the Pfizer-BioNTech COVID-19 vaccine compared to the comparison interval for aggregated monovalent doses 1-4 and bivalent dose 1 was 1.47 [1.07, 2.01] with p-value <0.05, these results did not meet the pre-defined safety signal definition of RR >3 and p-value <0.01. Overall, based on this analysis of codified data, there was no signal detected for myocarditis/pericarditis. However, the sample size for young men may be too small to meaningfully detect rare myocarditis/pericarditis events. Of the 52 codified myocarditis/pericarditis events, 36 cases were confirmed during the 21-day risk interval (primary risk interval of interest) through chart review. These 36 cases included 34 (94.4%) individuals with pericarditis and 6 (16.7%) individuals with myocarditis. All 6 cases of myocarditis and 32 (94.1%) cases of pericarditis recovered by the end of follow-up (mean of 6.0 months).

Other analyses: Among the subgroup enrolled in the VHA with dual Medicare coverage, completion rates for monovalent doses 2, 3, 4, and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine were 97.6%, 60.3%, 22.2%, and 25.1% respectively, which were higher than the full study population's. Safety surveillance results were generally consistent, except for chilblain-like lesions that had a signal remain, which may be due to differences in clinical characteristics and health-seeking behavior between the subgroup and full study population and conducting multiple analyses with a large sample size that could increase the chance of detecting statistically significant results that are not actually clinically significant, especially as chilblain-like lesions is typically a mild, self-resolving condition. Given the association between chilblain-like lesions and COVID-19 infection, patients with COVID-19 diagnosis during the entire study period were removed, and the signal no longer remained.

Discussion: This final report presents the sample selection, baseline characteristics, and vaccine utilization patterns among individuals who received the Pfizer-BioNTech COVID-19 vaccine within the VHA system and an active comparator of a historical sample of individuals who received seasonal influenza vaccine before the COVID-19 pandemic. It also presents the safety signal analyses for the Pfizer-BioNTech COVID-19 vaccine. Most

baseline characteristics were well-balanced between the study samples, suggesting that seasonal influenza vaccine from five prior seasons is an appropriate active comparator.

Cerebrovascular non-hemorrhagic stroke, other acute demyelinating disease, AMI, anaphylaxis, arrhythmia, CAD, myocarditis, chilblain-like lesions, PE, ON, heart failure and cardiogenic shock, acute kidney injury, stress cardiomyopathy, DVT, and severe COVID-19 disease were detected as potential signals from signal detection analyses, and GBS, microangiopathy, and hemorrhagic disease were identified as warranting further evaluation. There was large variation in the signal detection results between this study and other published studies, with the CDC's Vaccine Safety Datalink study detecting signals for AMI, myocarditis/pericarditis, and venous thromboembolism out of 23 safety events of interest, and the FDA's BEST Initiative rapid surveillance study detecting signals for myocarditis/pericarditis and anaphylaxis out of 17 safety events of interest following the Pfizer-BioNTech COVID-19 vaccine.[5,6] These differences may be confounded by underlying study population differences as VHA enrollees are typically older with poorer health status than the general US population.[7] Importantly, signal detection analyses are hypothesis-generating and only indicate that further investigation is needed. Therefore, signal evaluation analyses were conducted for safety events of interest where potential signals were detected. No safety events of interest had a signal that remained following signal evaluation analyses. The monovalent and bivalent doses of the Pfizer-BioNTech COVID-19 vaccine had similar safety profiles based on a qualitative assessment that observed similar signal detection results. Among the subgroup enrolled in the VHA with dual Medicare coverage, the safety surveillance results were generally consistent. Though chilblain-like lesions had a signal remain in SCCS analyses, this signal did not remain after conducting further signal evaluation to rule out other possible explanations whereby patients with COVID-19 diagnosis prior to or during the risk interval or control time period were excluded. Since COVID-19 infection is a risk factor for chilblain-like lesions, this may explain the occurrence of this safety event of interest more than the role of the COVID-19 vaccine. Overall, no examined safety events of interest were found to be associated with the Pfizer-BioNTech COVID-19 vaccine based on the analyses conducted in this final report.

For the prioritized safety analysis of myocarditis/pericarditis, while the incidence rates of myocarditis/pericarditis were descriptively higher for males than females and for individuals 12-39 years old than older age groups, the adjusted analyses comparing events in the risk interval vs. comparison interval among Pfizer-BioNTech COVID-19 vaccine recipients detected no signals for myocarditis/pericarditis following the CDC's methodology as pre-specified in the protocol.[4] Although no signal was found linking myocarditis/pericarditis and the Pfizer-BioNTech COVID-19 vaccine, the small sample size of young men in the VHA population provided limited statistical power to detect the rare event.[3,8] After myocarditis/pericarditis case confirmation through medical chart review, results remained similar to those based on codified data, and the majority of individuals with chart-confirmed myocarditis/pericarditis after the Pfizer-BioNTech COVID-19 vaccine fully recovered, consistent with other studies.[58,9] Incidence rate estimates for myocarditis/pericarditis and other safety events of interest following the Pfizer-BioNTech COVID-19 vaccine that were reported in this final report are more stable than those described in previous reports with the accumulation of more data over time, leading to greater sample size and power.

Marketing Authorization Holder(s): BioNTech Manufacturing GmbH

Names and affiliations of principal investigators:

Name, degree(s)	Title	Affiliation	Address
Jurandir Dalle Lucca, MD, PhD	Deputy Associate Chief of Staff, Research	Veterans Affairs (VA) Medical Center	163 Veterans Drive, White River Junction, VT 05009
Caroline Korves, ScD	Epidemiologist, Clinical Epidemiology Program	Veterans Affairs (VA) Medical Center	163 Veterans Drive, White River Junction, VT 05009
Kofi Asomaning, PhD, MD	Unit Lead, Safety Surveillance Research	Pfizer, Inc.	500 Arcola Road, Collegeville, PA 19426
Mei Sheng Duh, ScD, MPH	Managing Principal and Chief Epidemiologist	Analysis Group, Inc.	111 Huntington Ave 14th Floor Boston, MA 02199
	Research Associate, Department of Biostatistics	Harvard T. H. Chan School of Public Health	677 Huntington Ave Boston, MA 02115
Maral DerSarkissian, PhD	Vice President and Senior Epidemiologist	Analysis Group, Inc.	333 South Hope Street 27th Floor Los Angeles, CA 90071
	Adjunct Assistant Professor, Department of Epidemiology	Fielding School of Public Health, University of California, Los Angeles	650 Charles E Young Drive South Los Angeles, CA 90095

References

1. U.S. Food and Drug Administration (FDA). Pfizer-BioNTech COVID-19 vaccine Biologics License Application (BLA) Approval (issued 23 Aug 2021). Available from: https://www.fda.gov/media/151710/download. Accessed on: 19 Oct 2021.
2. U.S. Department of Veteran Affairs; Veterans Health Administration. Providing health care for veterans. Available from: https://www.va.gov/health/. Accessed on: 23 Apr 2021.
3. Shimabukuro T. Center for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP): COVID-19 vaccine safety updates. 2021. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf.
4. Klein N, Donahue J, Weintraub E. Center for Disease Control (CDC): Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. 2021. Available from: https://www.cdc.gov/vaccinesafety/pdf/VSD-1342-COVID19-RCA-Protocol_FinalV1.1_508.pdf.
5. Klein N. COVID-19 Vaccine Safety Surveillance: Summary from VSD RCA. 2023. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-12/07-COVID-Klein-508.pdf.
6. Lloyd PC, Hu M, Wong H-L, et al. Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years. Vaccine. 2022;40(45):6481-88.
7. Agha Z, Lofgren RP, VanRuiswyk JV, et al. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. Arch Intern Med. 2000;160(21):3252-7.
8. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021;326(14):1390-99.
9. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021;144(6):471-84.

Document Approval Record

Document Name:	C4591012_FINAL REPORT ABSTRACT_08DEC2023
Document Title:	C4591012

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	13-Dec-2023 15:41:57	Manager Approval
De Bernardi, Barbara	14-Dec-2023 13:32:37	EUQPPV Approval

NON-INTERVENTIONAL (NI) STUDY FINAL REPORT

PASS Information

Title	Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
Protocol number	C4591012
Version identifier for the final study report	1.0
Date	08 December 2023
EU Post-Authorization Study (PAS) register number	EUPAS39779
Active substance	COVID-19 mRNA Vaccine is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine
Joint PASS	No
Research question and objectives	Research question: what are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine within the US Veterans Health Administration (VHA) system overall and in sub-cohorts of interest, as compared to expected rates of those events?

	Primary study objectives: • To assess whether the following groups of individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine: o Individuals receiving first dose; o Individuals receiving the primary series of two doses; o Individuals receiving additional approved dose(s) (i.e., an additional primary series dose, a single booster dose, or additional booster doses if applicable, including the Omicron BA.4/BA.5-Adapted Bivalent Vaccine Booster [i.e., bivalent booster]) of the Pfizer-BioNTech COVID-19 vaccine after the primary series of two doses. • To assess whether sub-cohorts of interest (e.g., individuals with dual coverage of VHA and Medicare, individuals with bivalent booster dose of the Pfizer-BioNTech COVID-19 vaccine) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. *Secondary study objective:* • To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA, including estimating the proportion of individuals receiving at least one dose of the vaccine, 2-dose vaccine completion rate, additional approved dose(s) completion rate, distribution of time gaps between the

	first and second dose, distribution of time gaps between the second and additional approved primary or booster dose(s), demographics and health histories of recipients, overall and among the sub-cohorts of interest.
Country of study	United States
Authors	Jurandir Dalle Lucca, MD, PhD Deputy Associate Chief of Staff, Research Veterans Affairs Medical Center White River Junction, VT Kofi Asomaning, PhD, MD Unit Lead, Safety Surveillance Research Pfizer Inc. Collegeville, PA Mei Sheng Duh, ScD, MPH Managing Principal and Chief Epidemiologist Analysis Group, Inc. Boston, MA

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Appendix 1. SIGNATURES

Appendix 2. PROTOCOL

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Refer to section 3 Investigators and section 5 Milestones

Appendix 4. STATISTICAL ANALYSIS PLAN

Appendix 5. SAMPLE CASE REPORT FORM (CRF)/DATA COLLECTION TOOL (DCT)

Not applicable

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Not applicable

Appendix 8. ADDITIONAL RESULTS: INCIDENCE RATES, PERSON-TIME-AT-RISK, COVID-19 SUBVARIANTS, END-OF-SURVEILLANCE, MYOCARDITIS/PERICARDITIS, SUBGROUPS

Appendix 9. ADDITIONAL DOCUMENTS: LIST OF SOURCE TABLES AND FIGURES

1. ABSTRACT (STAND-ALONE DOCUMENT)

See stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOS	Associate Chief of Staff
ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired Immunodeficiency Syndrome
AE	Adverse Event
AEM	Adverse Event Monitoring
AESI	Adverse Event of Special Interest
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CAD	Coronary Artery Disease
CBER	Center for Biologics Evaluation and Research
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
CEP	Clinical Epidemiology Program
CFR	Code of Federal Regulations
CHAMPVA	Civilian Health and Medical Program of the Department of Veterans Affairs
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
CRADA	Cooperative Research and Data Agreement
CRF	Case Report Form
DCT	Data Collection Tool
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
ED	Emergency Department
EMA	European Medicines Agency
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUA	Emergency Use Authorization
EU PAS	European Union Post-Authorization Safety
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HBV	Hepatitis B Virus
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C Virus

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRU	Healthcare Resource Utilization
ICD	Informed Consent Document
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
ICU	Intensive Care Unit
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IP	Inpatient
IQR	Interquartile Range
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
ISPE	International Society for Pharmacoepidemiology
KD	Kawasaki disease
LLR	Log-Likelihood Ratio
LOINC	Logical Observation Identifiers, Names, and Codes
MaxSPRT	Maximized Sequential Probability Ratio Test
(c)MaxSPRT	Conditional Maximized Sequential Probability Ratio Test
MenACWY	Meningococcal Conjugate
MenB	Serogroup B Meningococcal
MIS-A	Multisystem inflammatory syndrome in adults
MIS-C	Multisystem inflammatory syndrome in children
mRNA	Messenger RiboNucleic Acid
MS	Multiple Sclerosis
NDC	National Drug Code
NIS	Non-Interventional Study
NNERC VAMC	Northern New England Research Consortium Department of Veterans Affairs Medical Centers
NR	Not Reported
NSAID	Non-Steroidal Anti-Inflammatory Drugs
ON	Optic Neuritis
OP	Outpatient
OR	Odds Ratio
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCAFC	Program of Comprehensive Assistance for Family Caregivers
PE	Pulmonary Embolus
PHI	Protected Health Information

Abbreviation	Definition
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
R&D	Research and Development
RI	Relative Incidence
RR	Relative Risk
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCCS	Self-Controlled Case Series
SCRI	Self-Controlled Risk Interval
SD	Standard Deviation
SeqCURE	Sequencing Collaborations United for Research and Epidemiology
SeqFORCE	Sequencing for Research Clinical and Epidemiology
SHIELD	Science and Health Initiative to Combat Infectious and Emerging Life-threatening Diseases
SIG	SARS-CoV-2 Interagency Group
SJS	Stevens-Johnson Syndrome
SPEAC	Safety Platform for Emergency vACcines
SRSS	Subcommittee on Research Safety and Security
Std. Diff.	Standardized Difference
Td	Diphtheria and Tetanus
Tdap	Diphtheria, Tetanus and (Acellular) Pertussis
TEN	Toxic Epidermal Necrolysis
TM	Transverse Myelitis
TTS	Thrombosis with Thrombocytopenia Syndrome
US	United States
VA	Veterans Affairs
VAERS	Vaccination Adverse Event Reporting System
VAIRRS	Veterans Affairs Innovation and Research Review System
VBM	Variant Being Monitored
VHA	Veterans Health Administration
VINNE	Veteran's Institutional Review Board of Northern New England
VISN	Veterans Integrated Service Networks
VOC	Variant of Concern
VOHC	Variant of High Consequence
VOI	Variant of Interest
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolism
WHO	World Health Organization
WOC	Without Compensation

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Jurandir Dalle Lucca, MD, PhD	Deputy Associate Chief of Staff, Research	Veterans Affairs (VA) Medical Center	163 Veterans Drive, White River Junction, VT 05009
Caroline Korves, ScD	Epidemiologist, Clinical Epidemiology Program	Veterans Affairs (VA) Medical Center	163 Veterans Drive, White River Junction, VT 05009
Kofi Asomaning, PhD, MD	Unit Lead, Safety Surveillance Research	Pfizer, Inc.	500 Arcola Road, Collegeville, PA 19426
Mei Sheng Duh, ScD, MPH	Managing Principal and Chief Epidemiologist	Analysis Group, Inc.	111 Huntington Ave 14th Floor Boston, MA 02199
	Research Associate, Department of Biostatistics	Harvard T. H. Chan School of Public Health	677 Huntington Ave Boston, MA 02115
Maral DerSarkissian, PhD	Vice President and Senior Epidemiologist	Analysis Group, Inc.	333 South Hope Street 27th Floor Los Angeles, CA 90071
	Adjunct Assistant Professor, Department of Epidemiology	Fielding School of Public Health, University of California, Los Angeles	650 Charles E Young Drive South Los Angeles, CA 90095

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date
VHA CRADA execution, Determination of IRB & Research Safety and Security exemptions, Approval by Designated Member Review[1-3]	January - February 2021
Registration in the EU PAS register	5 March 2021
Start of data collection	11 May 2021[4]
Interim reports	30 June 2021 31 December 2021 30 June 2022 31 December 2022
End of data collection	30 June 2023[5]
Final study report	31 December 2023

Abbreviations: ACOS, Associate Chief of Staff; CFR, Code of Federal Regulations; COVID-19, coronavirus disease 2019; CRADA, Cooperative Research and Data Agreement; IRB, Institutional Review Board; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; NNERC VAMC, Northern New England Research Consortium VA Medical Centers; PAS, post-authorization study; R&D, Research and Development; SRSS, Subcommittee on Research Safety and Security; VA, Veterans Affairs; VAIRRS, VA Innovation and Research Review System; VINNE, Veteran's IRB of Northern New England; VHA, Veterans Health Administration; US, United States.

Notes:

[1] IRB exemption determination was granted in accordance with 38 CFR 16 by the VINNE, White River Junction VA Medical Center, White River Junction.

[2] Research Safety and Security exemption determination was granted by the SRSS, VAIRRS.

[3] Approved by Associate Chief of Staff for Research (ACOS/R) and R&D Committee of the NNERC VAMC.

[4] Start of data collection was the date for starting data extraction from the VHA system, but the actual data used for the analysis began on 11 December 2020 (the EUA authorization date by the US FDA).

[5] End of data collection was after the Pfizer-BioNTech COVID-19 vaccine exposure data reached 30 months post-EUA approval and the last day of the month during which the study was completed.

6. RATIONALE AND BACKGROUND

In March 2020, the World Health Organization (WHO) declared a global pandemic for the coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified by public health officials in China in December 2019.[1] The COVID-19 pandemic has presented an unprecedented public health crisis. As of 19 November 2022, over 98.3 million COVID-19 cases and 1.1 million deaths have been reported in the United States (US) alone.[2] To date, the cumulative incidence of COVID-19 has continued to rise, largely among the elderly and middle-aged individuals, those with comorbid conditions, and in settings with high noncompliance with public health measures.[3-5] COVID-19 is a well-adapted, highly infectious human pathogen that has evolved over time to develop multiple variants, including those associated with an increased risk of transmission and death that were first identified in late 2020.[3,6-8]

The US Food and Drug Administration (FDA) initially granted Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine two dose primary series on 11 December 2020 in individuals 16 years of age and older, and approved the vaccine for this population on 23 August 2021.[9] This vaccine, developed by Pfizer and BioNTech (BNT162b2; COMIRNATY®), contains synthetic messenger ribonucleic acid (mRNA) that instructs cells in the body to produce the virus' distinctive "spike" protein that triggers an immune response against SARS-CoV-2.[9] The EUA for the Pfizer-BioNTech COVID-19 vaccine was based on safety and efficacy data from ongoing Phase 1/2/3 trials of approximately 44,000 participants aged 12 years and older who were randomized 1:1 to receive Pfizer-BioNTech COVID-19 vaccine or saline control.[10,11] The FDA reviewed safety data from 37,586 of the participants 16 years of age and older who were followed for a median of two months after receiving their second dose, and efficacy data from 36,523 participants 12 years of age and older after day seven following vaccination with dose 2.[12] The efficacy data reviewed by the FDA indicated that the Pfizer-BioNTech COVID-19 vaccine was 95% effective in preventing symptomatic COVID-19 disease, while the safety data indicated that the most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever.[12] No severe adverse events were reported that precluded the Pfizer-BioNTech COVID-19 vaccine from meeting the criteria for EUA.[12] Based on these safety and efficacy data, as well as a review of manufacturing information regarding product quality and consistency, the FDA determined that the known and potential benefits of the vaccine outweighed the known and potential risks for the prevention of COVID-19 in individuals 16 years of age and older and therefore granted EUA for the Pfizer-BioNTech COVID-19 vaccine.[13] FDA expanded the EUA on 10 May 2021 to include children 12-15 years of age, and on 29 October 2021 to include lower-dose vaccine administration for children 5-11 years of age. The EUA was further amended on 12 August 2021 to include the administration of a third primary series dose in certain immunocompromised individuals ages 12 years or older. On 22 September 2021, a single booster dose to be administered at least six months after completion of the primary series was approved for individuals ages 65 years or older and individuals ages 18 years or older in high-risk settings or with underlying medical conditions, which was later expanded to all individuals 18 years of age or older on 19 November 2021 and then amended on 3 January 2022 to be a single booster dose at least five months after

completion of the primary series. On 29 March 2022, the FDA authorized the use of a second booster dose at least four months after receipt of the first booster dose among individuals 50 years of age and older or immunocompromised individuals.[14-19] On 31 August 2022, the FDA authorized bivalent formulations of the vaccine (i.e., Pfizer-BioNTech COVID-19 vaccine, Bivalent [Original and Omicron BA.4/BA.5]) for use as a single booster dose at least two months following primary or booster vaccination for individuals 12 years of age and older.[20]

As required by the FDA EUA,[12] post-authorization observational studies using real-world data are needed in order to assess the association between Pfizer-BioNTech COVID-19 vaccine and pre-determined safety events of interest among individuals who received the vaccine in both the population at large and in populations of interest (e.g., immunocompromised individuals, elderly, and those with specific comorbidities).[12] Such post-authorization safety evaluations are important for identifying rare, unexpected, serious safety events of interest in larger populations that may not have been detected during clinical trials (either due to sample size or selected study populations), and monitoring the benefit-risk ratio of the vaccine post-trial.

Pfizer, in collaboration with the US Veterans Health Administration (VHA) and Analysis Group, conducted a study (protocol C4591012; Annex 1. Appendix 2) for post-EUA active surveillance of safety events of interest among individuals enrolled in the VHA system. The current study included 48 safety events of interest that were primarily selected based on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project and from the preliminary list of safety events of interest presented at the 22 September 2020, meeting of Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) on the enhanced safety monitoring of COVID-19 vaccines.[21,22]

The study used data from a large-scale electronic medical record (EMR) database from the VHA to identify and evaluate rapid-cycle, near real-time safety signals (i.e., safety events of interest with signals detected [based on sequential testing of risk intervals compared to self-control intervals and active comparators receiving seasonal influenza vaccinations] that remained following signal evaluation [based on additional adjusted analyses] and signal verification through medical chart review) associated with the Pfizer-BioNTech COVID-19 vaccine. The Cooperative Research and Data Agreement (CRADA) was established between Analysis Group and White River Junction VA Medical Center and Veterans Education and Research Association of Northern New England (VINNE) for this study on 8 January 2021. Data collection regarding the Pfizer-BioNTech COVID-19 vaccine included for this study commenced on 11 December 2020 (EUA approval date by the US FDA) and continued through 30 June 2023–i.e., 30 months following the issuance of the EUA for the Pfizer-BioNTech COVID-19 vaccine.

This final report includes signal detection and signal evaluation analyses for the primary vaccination series and monovalent booster doses, as well as the bivalent dose of the Pfizer-BioNTech COVID-19 vaccine, using data on individuals identified through 30 June 2023 (end of data collection). Safety surveillance analyses were also conducted among a

subgroup of individuals enrolled in the VHA with dual Medicare coverage as identified in the Centers for Medicare & Medicaid Services (CMS) Medicare administrative claims data as well as a subgroup of individuals with the bivalent booster dose of the Pfizer-BioNTech COVID-19 vaccine. In addition, baseline characteristics and vaccine utilization patterns were described for two samples of individuals from the VHA database: individuals who received Pfizer-BioNTech COVID-19 vaccine between 11 December 2020 and 30 June 2023; and individuals who received seasonal influenza vaccine(s) during the five prior influenza seasons (2014/2015 through 2018/2019) as a fixed comparator group. Additionally, a prioritized safety analysis of myocarditis/pericarditis with signal detection, evaluation, and verification through medical record adjudication was conducted.

The data for this final report spanned from 1 January 2012 (to capture the two-year baseline period for the seasonal influenza sample starting in 2014/2015) to 30 June 2023, and the data were locked on 13 October 2023. The analyses contained in this final report were conducted pursuant to the study protocol Version 6.0 dated 31 January 2023 (Annex 1. Appendix 2).

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and is a postmarketing commitment to the US FDA, as well as a Category 3 commitment in the European Union Risk Management Plan.

7. RESEARCH QUESTION AND OBJECTIVES

Research question: what are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine within the US VHA system overall and in sub-cohorts of interest, as compared to expected rates of those events?

Primary study objectives:

To assess whether the following groups of individuals in the VHA system experience increased risk of safety events of interest following receipt of Pfizer-BioNTech COVID-19 vaccine:

- Individuals receiving first dose;
- Individuals receiving the primary series of two doses;
- Individuals receiving additional approved dose(s) (i.e., an additional primary series dose, a single booster dose, or additional booster doses if applicable, including the Omicron BA.4/BA.5-Adapted Bivalent Vaccine Booster [i.e., bivalent booster]) of the Pfizer-BioNTech COVID-19 vaccine after the primary series of two doses.

To assess whether sub-cohorts of interest (e.g., individuals with dual coverage of VHA and Medicare, individuals with bivalent booster dose of the Pfizer-BioNTech COVID-19 vaccine) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.

Secondary study objective:

To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA including estimating the proportion of individuals receiving at least one dose of the vaccine, 2-dose vaccine completion rate, additional approved dose(s) vaccine completion rate, distribution of time gaps between the first and second dose, distribution of time gaps between the second and additional approved primary or booster dose(s), demographics and health histories of recipients, overall and among the sub-cohorts of interest.

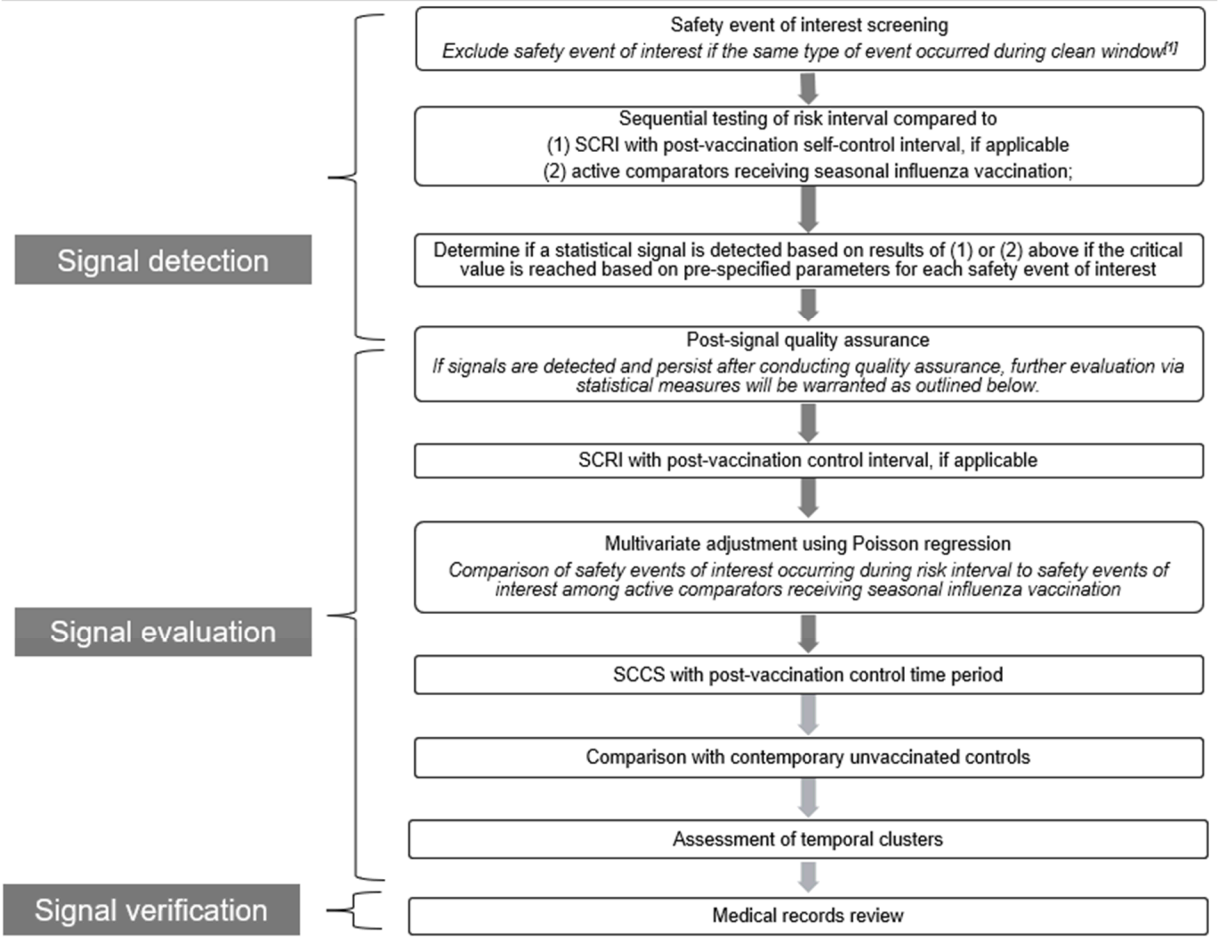
8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

A stepwise process, illustrated below, was performed for signal detection, evaluation, and verification (Figure 1). This approach was adapted from the Active Monitoring Protocol of the FDA's COVID-19 Vaccine Safety Surveillance Project.[23] Signal detection analyses identified whether potential signals were detected for certain safety events of interest that required further investigation. Signal evaluation analyses further examined safety events of interest with potential signals detected and were performed in the order described in Figure 1. Each successive analysis in the signal evaluation phase was only conducted if the signal persisted in the prior step. If signals remained following the signal evaluation phase, signals were verified through medical records review.

Figure 1. Steps in Signal Detection, Evaluation, and Verification



Notes:
[1] The risk and control intervals selected for the SCRI analysis for each safety event of interest were based on biological plausibility and precedents in the literature. Only the individual's first instance following the specified clean window (i.e., the interval used to define incident outcomes) was included. Note that only the first inpatient or outpatient occurrence of a safety event of interest following the clean window was used to identify incident events (e.g., if an inpatient safety event of interest occurs in the clean window, a repeat occurrence was not counted in the risk interval). However, event worsening was counted as a safety event of interest. For example, if an outpatient safety event of interest occurred in the clean window and an inpatient occurrence for the same type of safety event of interest occurred in the risk interval, the inpatient occurrence was counted as a safety event of interest.

9.1. Study Design

This post-EUA active safety surveillance program employed a rapid-cycle, longitudinal, observational cohort study design to provide early real-world safety information. The self-controlled risk interval (SCRI) design was used to sequentially monitor occurrence of safety events of interest while controlling for time-invariant confounders (such as sex, race, chronic illness, and state). In addition, safety events of interest in individuals who received Pfizer-BioNTech COVID-19 vaccinations were sequentially monitored and compared to individuals who received influenza vaccine in the VHA between 2014/2015 through

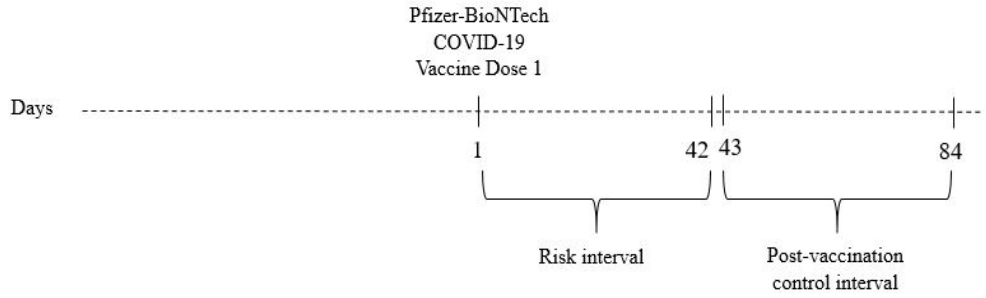
2018/2019 (active comparator design).[24,25] Separate analyses of the monovalent and bivalent doses were conducted to allow for a qualitative comparison of the safety profile of the two types of doses based on findings from the signal detection analyses.

9.1.1. SCRI Design with Post-Vaccination Control Interval (Signal Detection)

The SCRI design used data from cases (i.e., individuals who experienced safety events of interest following vaccination) to compare the risk interval following vaccination to post-vaccination non-risk intervals ("post-vaccination control interval") in the same individual.[26] A length of 42 days has been used to define the risk interval in studies using the SCRI design to ascertain the safety profile of the H1N1 vaccine and in other safety surveillance studies for the COVID-19 vaccine (including the FDA Center for Biologics Evaluation and Research [CBER] safety surveillance protocol),[23-25] therefore the same length of risk interval was used for most safety events of interest in this study. The day of vaccination (i.e., day 0) was only included in the risk interval for those safety events of interest for which a same-day occurrence is biologically plausible (e.g., anaphylaxis).

A post-vaccination control interval was used for safety events of interest for the following reasons: (1) a recent prior safety event of interest might preclude vaccination (i.e., anaphylaxis), (2) individuals might have an underlying condition that is also a contraindication for vaccination (i.e., seizure disorder), or (3) safety events of interest and vaccination may be seasonal in nature.[27] Examples of the SCRI design with a post-vaccination control interval (in an individual who only received only one vaccine dose) are presented in Figure 2 below.

Figure 2. Example of SCRI Design for Assessment of a Safety Event of Interest with a 42-day Risk Interval in an Individual who Received Only One Vaccine Dose, with Post-Vaccination Control Intervals*



*The risk interval included day 0, date of Pfizer-BioNTech COVID-19 vaccination, for some of the safety events of interest assessed (e.g., anaphylaxis). The length of the risk interval varied across each safety event of interest. Note that some individuals did not receive the complete course of vaccination, and thus only received the first dose of the vaccine.

For the general population, two doses of the Pfizer-BioNTech COVID-19 vaccine are recommended 21 days apart. On 12 August 2021, a third dose of the Pfizer-BioNTech COVID-19 vaccine was approved for immunocompromised individuals, to be administered

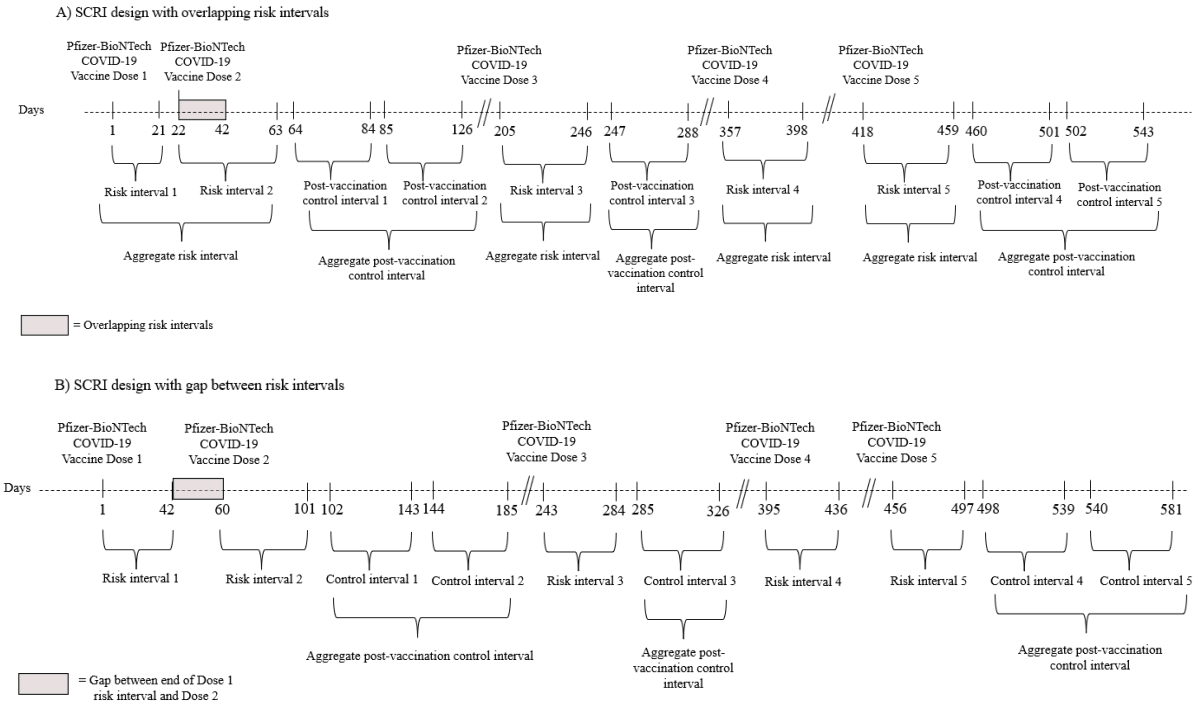
at least 28 days after dose 2. On 22 September 2021, a third dose/booster dose was approved for individuals ages 65 years or older, and individuals ages 18 years or older who live in long-term care settings or high-risk settings, work in high-risk settings, or have underlying medical conditions, and was to be administered at least six months after dose 2. The third dose/booster dose approval was later expanded to all individuals ages 18 years or older on 19 November 2021 and then updated on 3 January 2022 to be a third dose/booster dose administered at least five months after dose 2. On 29 March 2022, a fourth dose/booster dose was approved for individuals 50 years of age and older or individuals 12 years of age and older who are immunocompromised to be administered at least four months after receipt of the previous dose. On 31 August 2022, the FDA authorized a bivalent booster (i.e., fifth booster dose) that may be administered at least two months following the previous monovalent booster dose. This study program monitored safety events of interest that occurred after the primary series, monovalent booster dose(s), and bivalent dose separately and in aggregate.

In addition, heterologous boosters (i.e., a dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of two Pfizer-BioNTech vaccine doses) were described.

Given the risk intervals for specific safety events of interest range from 1 day to 90 days (Table 1 in Section 9.4.1), the time between doses 1 and 2 may be longer or shorter than the recommended risk interval for a given safety event after dose 1. See Figure 3 below for SCRI design examples where a safety event with a 42-day risk interval window (e.g., Bell's palsy; Table 1 in Section 9.4.1) was assessed in hypothetical individuals who received five doses of the Pfizer-BioNTech COVID-19 vaccine: Figure 3A shows the SCRI design with dose 2 received 21 days after dose 1 (i.e., the risk interval for dose 1 overlapped with the risk interval for dose 2), while Figure 3B shows the SCRI design with dose 2 received 60 days after dose 1 (i.e., there was a gap between the end of the risk interval for dose 1 and dose 2 initiation). For the first scenario (Figure 3A), the risk interval for dose 1 was censored at the time of dose 2. For the second scenario (Figure 3B), events were only measured during the risk intervals, ignoring the gap between the end of the risk interval for dose 1 and dose 2 initiation. In both scenarios shown below (Figure 3A and Figure 3B), a third booster dose was received 183 days following dose 2, a fourth booster dose was received 152 days after the third dose, and a fifth bivalent booster dose was received 61 days after the fourth dose. The risk intervals for dose 3, dose 4, and dose 5 are shown.

For each analysis, control intervals corresponding to the risk intervals were defined either at the end of the risk interval for dose 1 (for individuals with only one dose observed), after the risk interval for dose 2 (for individuals with two doses observed), after the risk interval for dose 3 (for individuals with three doses observed), after the risk interval for dose 4 (for individuals with four doses observed), or after the risk interval for dose 5 (for individuals with five doses observed).

Figure 3. Example of SCRI Design for Assessment of a Safety Event of Interest with a 42-day Risk Interval in an Individual who Received Five Vaccine Doses, with Post-vaccination Control Intervals



9.1.2. Active Comparator Design (Signal Detection)

In the active comparator design, the event frequency of safety events of interest among individuals who received the Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023 was compared with the event frequency among recipients of the seasonal influenza vaccination in five prior seasons, between 2014/2015 through 2018/2019. Seasonal influenza vaccination data in peri-COVID time periods from January 2020 to the present were not included in this analysis due to pandemic-associated under-utilization of health resources and under-reporting of medical events. The same risk interval length (e.g., 42 days) was used to evaluate safety events of interest following vaccination with the PfizerBioNTech COVID-19 vaccine and to assess safety events of interest occurring after vaccination for seasonal influenza in prior seasons. The observed number of safety events of interest for the Pfizer-BioNTech COVID-19 vaccine was compared to the expected number of safety events of interest based on the background rate of safety events of interest following influenza vaccine in past seasons.[24]

9.1.3. Additional Study Designs (Signal Evaluation)

Additional study designs and statistical analyses were conducted during the signal evaluation phase if a signal was detected from the analyses implemented during the signal detection phase. This included using a self-controlled case series (SCCS) design. Additionally, signal evaluation analyses were conducted for signals detected in external sources or based on

regulatory request (i.e., myocarditis/pericarditis). These analyses are further detailed in Section 9.7.3.2 and Section 9.7.3.3 in the study protocol (Annex 1. Appendix 2).

9.2. Setting

The study population consisted of VHA enrollees, which largely included veterans, and the eligibility criteria was kept as broad as possible to be representative of the real-world population at the VHA receiving the Pfizer-BioNTech COVID-19 vaccine.

The study relied on secondary data from the Corporate Data Warehouse (CDW) in the National Veterans Affairs Health Care Network. The CDW data, which are updated daily, include standard EMR for all medical encounter information in the VHA system. Information is also available on date of death, COVID-19 infection status (i.e., COVID-19 diagnosis codes, COVID-19 antigen test, COVID-19 reverse transcription-polymerase chain reaction [RT-PCR] test), and COVID-19 and seasonal influenza vaccination status.

The VHA oversees the rollout of both COVID-19 and seasonal influenza vaccination among individuals enrolled in the VHA. The VHA delivers vaccines through VHA health care facilities, community urgent care providers in the VHA's network, and community pharmacies in the VHA's network.[28] For seasonal influenza, the VHA vaccination rollout overlaps with the influenza season, which typically starts in October and ends in May of the following year.[29] For COVID-19, the VHA vaccination rollout started on 11 December 2020 and used a phased approach as follows:[28]

- *Phase 1a* included the following eligible VHA enrollees: individuals who work or live in VA community living centers and spinal cord units; who live or work in other long-term care or congregate (group living) settings and do not have access to COVID-19 vaccines in those settings; who work in cemeteries, and who work as health care personnel.

- *Phase 1b* included the following eligible VHA enrollees: veterans who are at least 75 years old; individuals who are essential frontline workers; who experience homelessness; who receive hemodialysis care; who have had a solid organ transplant or who are being considered for transplant; who have spinal cord injuries and disorders; and who receive chemotherapy treatment in a clinic or hospital.

- *Phase 1c* included the following eligible VHA enrollees: veterans who are 65 to 74 years old; who are younger than 65 years old and have certain health conditions that are deemed by the CDC to be associated with a high risk of severe illness from COVID-19; and individuals who are considered essential workers by the CDC and were not included in Phase 1b.

- *Phase 1c* was completed and COVID-19 vaccination is now offered free of charge to all veterans enrolled in the VHA, caregivers of eligible veterans under the Program of Comprehensive Assistance for Family Caregivers (PCAFC), and other eligible individuals (e.g., veteran spouses and dependents) under the Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA).[28]

As the VHA's health care delivery system is organized regionally around 18 Veterans Integrated Service Networks (VISNs) across the US, with each VISN responsible for the health care planning and resource allocation in a particular geographical region,[28] regional variations may have impacted the timing of vaccine distribution, particularly in areas where the supply of COVID-19 vaccines was not pre-planned.

9.3. Subjects

9.3.1. Inclusion Criteria

9.3.1.1. Pfizer-BioNTech COVID-19 Vaccine Sample

Individuals with at least one record of the Pfizer-BioNTech COVID-19 vaccine during the period from 11 December 2020 to 30 June 2023; and

At least two years of continuous enrollment in and no disenrollment from VHA benefits (i.e., the baseline period) prior to their first Pfizer-BioNTech COVID-19 vaccination date.

9.3.1.2. Seasonal Influenza Vaccine Sample

Individuals with records of one or more seasonal influenza vaccine from the 2014/2015 influenza season to the 2018/2019 influenza season, where the influenza season was defined as the period from 1 October of one year until 31 May of the following year; and

At least two years of continuous enrollment in and no disenrollment from VHA benefits (i.e., the baseline period) prior to at least one seasonal influenza vaccination date.

9.3.2. Exclusion Criteria

9.3.2.1. Pfizer-BioNTech COVID-19 Vaccine Sample

Individuals who received at least one dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech were excluded from the primary safety surveillance analyses (i.e., analyses conducted for individuals that met all eligibility criteria). While excluded from the study sample, these individuals were identified and described when characterizing the vaccine utilization patterns (secondary objective).

Note, individuals who received a dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of two Pfizer-BioNTech vaccine doses (i.e., a heterologous booster) were analyzed as a separate subgroup (Section 9.3.3). This subgroup did not include individuals who completed the COVID-19 vaccine primary series from a manufacturer other than Pfizer-BioNTech and then received a third dose/booster dose of the Pfizer-BioNTech COVID-19 vaccine.

9.3.2.2. Seasonal Influenza Vaccine Sample

- Individuals who had records for more than one seasonal influenza vaccine in the same influenza season were excluded from that influenza season.

9.3.3. Subgroups

In this final report, the number of individuals in each subgroup of interest was reported, and safety surveillance analyses for the subgroup of individuals enrolled in the VHA with dual Medicare coverage were conducted. Safety surveillance analyses for other subgroups were not conducted due to small sample size and/or the other subgroups having less clinical significance given the current state of the COVID-19 pandemic.

- Immunocompromised individuals, defined as individuals diagnosed with symptomatic human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), hematologic malignancy, or other immune conditions; individuals diagnosed with solid malignancy, organ transplant, or rheumatologic/inflammatory conditions, all of whom were administered chemotherapy or immune modulators; individuals diagnosed with rheumatologic/inflammatory conditions and administered systemic corticosteroids; or individuals who were administered chemotherapy, immune modulators, or systematic steroids for at least 14 days.[30]

- Different age groups, with a focus on the elderly (e.g., <12, 12 - <18, 18 - <25, 25 - <30, 30 - <40, 40 - <50, 50 - <65, ≥65 years of age at the index date).

- Individuals with specific comorbidities identified as high risk for COVID-19 by the CDC (i.e., cancer, chronic kidney disease, chronic obstruction pulmonary disease [COPD], Down Syndrome, cardiovascular conditions [e.g., heart failure, coronary artery disease, or cardiomyopathies], immunocompromised state from solid organ transplant, obesity [body mass index (BMI) of 30 kg/m^2 to <40 kg/m^2], severe obesity [BMI of ≥40 kg/m^2], sickle cell disease, smoking, type 1 and 2 diabetes mellitus).[5]

- Individuals who received only one dose of the Pfizer-BioNTech COVID-19 vaccine.

- Individuals who received additional approved doses (i.e., an additional primary series dose, a single booster dose, or additional booster doses if applicable) of the Pfizer-BioNTech COVID-19 vaccine after the primary series of two doses.

- Individuals with prior SARS-CoV-2 infection based on positive COVID-19 RT-PCR and/or antigen tests.

- Individuals with regular use of VHA medical care, defined as at least two outpatient (excluding emergency department [ED], as ED visits may not be considered regular) or inpatient encounters in the one year prior to vaccination. The encounters had to be separated by >30 days (for inpatient, by admission date), and at least one had to be within six months prior to the date of vaccination. This ensured that individuals had ongoing health care encounters, particularly near the vaccination date, and regularly received their healthcare from VHA facilities, rather than outside facilities that would not be captured in the VHA's CDW.

- Individuals who were in the VA priority group 1. These individuals had either the highest levels of service-connected disability (≥50% disabling), were considered

unemployable, or had received the Medal of Honor.[31] Individuals categorized as priority group 1 are the highest priority for VHA care and receive VHA care free of charge. This ensured that the individual was more likely to receive all of their care from a VA facility.

- Individuals enrolled in the VHA with dual coverage who were also identified in the CMS Medicare administrative claims data, which was linked to the CDW, in order to supplement CDW data for a more complete evaluation of healthcare encounters.

- Individuals who received a dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of two Pfizer-BioNTech vaccine doses (i.e., a heterologous booster; excluded from primary safety surveillance analyses but analyzed as a separate subgroup).

In addition, safety surveillance analyses of the bivalent booster dose of the COVID-19 vaccine were conducted in the following subgroups:

- Those who received the primary series of two doses of Pfizer-BioNTech COVID-19 vaccine, followed by additional approved dose(s) (i.e., an additional primary series dose, a single monovalent booster dose, or additional monovalent booster doses if applicable) from any manufacturer, and a dose of Pfizer-BioNTech COVID-19 bivalent booster

- Those who received the primary series of two doses of Pfizer-BioNTech COVID-19 vaccine, followed by additional approved dose(s) (i.e., an additional primary series dose, a single monovalent booster dose, or additional monovalent booster doses if applicable) from any manufacturer, and a dose of bivalent booster from any manufacturer

9.4. Variables

This section includes a listing of the key variables for the current study, including outcomes, exposures, and baseline characteristics. For details on the measurement of these variables in the CDW data, please see Section 9.5.2.

9.4.1. Outcomes

Outcomes included 48 safety events of interest for active safety surveillance, which were largely identified based on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's SPEAC Project, the FDA and CDC enhanced safety monitoring recommendations.[21,22] Endpoints of special interest in signal detection, as noted by the FDA and CDC's ACIP are denoted in italics.[22] See Section 9.5.2.1 for details on the measurement

of the outcome variables. The following safety events of interest were assessed in this final report:

Neurologic:

- Aseptic meningitis
- Bell's palsy
- *Cerebrovascular non-hemorrhagic stroke*
- Convulsions/seizures in individuals with controlled epilepsy
- Encephalitis/encephalomyelitis
- *Guillain-Barré Syndrome (GBS)*
- *Generalized convulsion/seizures*
- Multiple sclerosis (MS)
- Optic neuritis (ON)
- Other acute demyelinating diseases
- Transverse myelitis (TM)

Immunologic:

- Anaphylaxis
- Arthritis and arthralgia/joint pain
- Autoimmune thyroiditis
- Fibromyalgia
- *Kawasaki disease (KD)*
- *Multisystem inflammatory syndrome in children (MIS-C)/Multisystem inflammatory syndrome in adults (MIS-A)*
    - MIS-A is defined among individuals ≥21 years of age, while MIS-C is defined among individuals <21 years of age
- Vasculitides

Cardiac:

- *Acute myocardial infarction (AMI)*
- Arrhythmia
- Coronary artery disease (CAD)
- Heart failure and cardiogenic shock
- Microangiopathy
- *Myocarditis*
- *Pericarditis*
- Stress cardiomyopathy

Hematologic:

- *Cerebrovascular hemorrhagic stroke*
- Chilblain-like lesions
- *Disseminated intravascular coagulation (DIC)*
- Deep vein thrombosis (DVT)
- Hemolytic anemia
- Hemorrhagic disease
- Limb ischemia
- Pulmonary embolus (PE)
- Single organ cutaneous vasculitis
- *Thrombocytopenia*
- Thrombosis with thrombocytopenia syndrome (TTS)

Other:

- Acute kidney injury
- Appendicitis
- *Death*
- Erythema multiforme
- Glomerulonephritis
- Liver injury
- *Narcolepsy and cataplexy*
- Nephrotic syndrome
- Non-anaphylactic allergic reactions
- *Severe COVID-19 disease*
    - The associated SARS-CoV-2 subvariant lineage was assessed among individuals with this safety event of interest only
- Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)

Outpatient, ED, and/or inpatient settings were used to identify safety events of interest, depending on the type of event. The specific encounter setting considered for each safety event of interest is summarized in Table 1. Any record of death was captured, regardless of whether the individual died in a healthcare or non-healthcare setting. The risk intervals selected for each safety event of interest were based on biological plausibility and precedents in the published literature (Table 1).

Table 1. Outcome algorithms for SCRI analysis, with risk and control intervals

Safety Event of Interest	Setting (Inpatient [IP], Outpatient [OP], Emergency Department [ED])	Clean window	Risk interval (days)	Post-vaccination control interval (days)
Neurologic				
Aseptic meningitis	IP only[23]	2 years	1-42[32]	43-84[32]
Bell's palsy[23]	IP or OP	2 years	1-42	43-84
Cerebrovascular non-hemorrhagic stroke[23]	IP only	2 years	1-28	29-56
Convulsions/seizures in individuals with controlled epilepsy[33]	IP or OP-ED	2 years	1-90	91-180
Encephalitis/encephalomyelitis[23]	IP only	2 years	1-42	43-84
GBS[23]	IP, primary position on	2 years	1-42	43-84
Generalized convulsion/seizures[24]	IP or OP-ED	2 years	0-14	15-29
MS[24,25]	IP or OP	2 years	1-42	43-84
ON[24,25]	IP or OP	2 years	1-42	43-84
Other acute demyelinating diseases[24,25]	IP or OP	2 years	1-42	43-84
TM[23]	IP or OP-ED	2 years	1-42	43-84
Immunologic				
Anaphylaxis	IP or OP-ED[23]	1 month[23]	0-1[23]	7-8[24,25]
Arthritis and arthralgia/joint pain[1]	IP or OP	2 years	1-42	43-84
Autoimmune thyroiditis[1]	IP or OP	2 years	1-42	43-84
Fibromyalgia[1]	IP or OP	2 years	1-42	43-84
KD[34]	IP only	2 years	1-28	29-56
MIS-C/MIS-A[23]	IP or OP-ED	2 years	1-42	43-84
Vasculitides[2]	IP only	2 years	1-28	29-56
Cardiac				
AMI[23]	IP only	2 years	1-28	29-56
Arrhythmia[3]	IP only	2 years	1-42	43-84

Table 1. Outcome algorithms for SCRI analysis, with risk and control intervals

Safety Event of Interest	**Setting (Inpatient [IP], Outpatient [OP], Emergency Department [ED])**	**Clean window**	**Risk interval (days)**	**Post-vaccination control interval (days)**
CAD[3]	IP only	2 years	1-42	43-84
Heart failure and cardiogenic shock[3]	IP only	2 years	1-42	43-84
Microangiopathy[2]	IP only	2 years	1-28	29-56
Myocarditis[23]	IP or OP	2 years	1-42[4]	43-84
Pericarditis[23]	IP or OP	2 years	1-42[4]	43-84
Stress cardiomyopathy[3]	IP only	2 years	1-42	43-84
Hematologic				
Cerebrovascular hemorrhagic stroke[23]	IP only	2 years	1-28	29-56
Chilblain-like lesions[2]	IP or OP	2 years	1-28	29-56
DIC[23]	IP or OP-ED	2 years	1-28	29-56
DVT[23]	IP or OP	2 years	1-28	29-56
Hemolytic anemia[5]	IP or OP	2 years	1-42	43-84
Hemorrhagic disease[2]	IP only	2 years	1-28	29-56
Limb ischemia[2]	IP only	2 years	1-28	29-56
PE[23]	IP or OP	2 years	1-28	29-56
Single organ cutaneous vasculitis[2]	IP only	2 years	1-28	29-56
Thrombocytopenia[23]	IP or OP	2 years	1-42	43-84
TTS[5]	IP or OP	2 years	1-42	43-84
Other				
Acute kidney injury[6]	IP only	2 years	1-42	43-84
Appendicitis[23]	IP or OP-ED	2 years	1-42	43-84
Death	IP or OP	2 years	0-42	43-85
Erythema multiforme[7]	IP only	2 years	1-2	8-9
Glomerulonephritis	IP only	2 years	1-42	43-84
Liver injury[6]	IP or OP	2 years	1-42	43-84

Table 1. Outcome algorithms for SCRI analysis, with risk and control intervals

Safety Event of Interest	**Setting (Inpatient [IP], Outpatient [OP], Emergency Department [ED])**	**Clean window**	**Risk interval (days)**	**Post-vaccination control interval (days)**
Narcolepsy and cataplexy	IP or OP[23]	2 years	1-42[23]	43-84
Nephrotic syndrome	IP only	2 years	1-42	43-84
Non-anaphylactic allergic reactions[24,25]	IP or OP	2 years	1-2	8-9
Severe COVID-19 disease[8]	IP only	2 years	1-42	43-84
SJS/TEN[7]	IP only	2 years	1-2	8-9

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; MIS-A, multisystem inflammatory syndrome in adults; MIS-C, multisystem inflammatory syndrome in adults; MS, multiple sclerosis; ON, optic neuritis; PE, pulmonary embolus; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome.

Notes:

[1] Published setting, clean window, and risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., arthritis and arthralgia/joint pain, fibromyalgia and autoimmune thyroiditis).

[2] Published setting, clean window, and risk and control intervals for DVT, PE, and DIC were applied to other cardiovascular and hematological disorders characterized by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, limb ischemia, hemorrhagic disease, chilblain-like lesions, single organ cutaneous vasculitis and vasculitides). The published risk and control intervals for KD were applied to vasculitides given that KD is a type of medium and small-vessel vasculitis.

[3] Published setting, clean window, and risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, CAD, arrhythmia).

[4] For the prioritized safety analysis of myocarditis/pericarditis, additional risk intervals (i.e., 1-7 days and 1-21 days) were examined and described in Section 9.9.2.5.

[5] Published setting, clean window and risk and control intervals for thrombocytopenia were applied to hemolytic anemia and TTS.

[6] Risk intervals of 42 days were applied for acute kidney injury and liver injury to be consistent with other similar safety events of interest.

[7] Published setting, clean window, and risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme and SJS/TEN).

[8] As severe COVID-19 ranges from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-C/MIS-A, a 1-42 day risk interval was applied in order to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset.

9.4.2. Exposures of Interest

Vaccination with the Pfizer-BioNTech COVID-19 vaccine or seasonal influenza vaccine were the main exposures of interest. Details on the measurement of the Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine receipt in the CDW data are presented in Section 9.5.2.2.

9.4.2.1. Pfizer-BioNTech COVID-19 Vaccine Groups of Interest

While the primary vaccination group of interest consisted of all individuals receiving the Pfizer-BioNTech COVID-19 vaccine (irrespective of receipt of seasonal influenza vaccination), additional subsets of the study population were identified, similar to the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) safety surveillance program of H1N1 vaccine safety:[24] Safety surveillance analyses were conducted for Cohorts A and B+C (as both cohorts included individuals who received the Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine during the same flu season). Descriptive counts were reported for Cohort D only as there was insufficient sample size for safety surveillance analyses.

Cohort A: Individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine who did not receive the influenza vaccine during the flu season in which COVID-19 vaccination occurred;

Cohort B: Individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine who received the seasonal influenza vaccine at least 42 days prior to COVID-19 vaccination during the same flu season in which COVID-19 vaccination occurred;

Cohort C: Individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine who received the seasonal influenza vaccine within 42 days before or any time after COVID-19 vaccination during the same flu season in which COVID-19 vaccination occurred;

Cohort D: Individuals vaccinated with both the Pfizer-BioNTech COVID-19 vaccine and the seasonal influenza vaccine on the same day.

9.4.3. Baseline Characteristics

The following baseline demographic and clinical characteristics were assessed based on a two-year baseline period prior to the date of first dose of Pfizer-BioNTech COVID-19 vaccine and prior to the date of seasonal influenza vaccination for active comparators (unless otherwise specified). Operational definitions for baseline characteristics variables listed in this section are provided in Table 1 of Annex 1. Appendix 9, while measurement details are provided in Section 9.5.2.3.

Demographics:

- Age (<12, 12-<18, 18-<25, 25-<30, 30-<40, 40-<50, 50-<65, ≥65 years)
- Sex
- Race/ethnicity
- VHA service area - US region

Clinical characteristics:

- Smoking status
- BMI
- History of anaphylaxis/allergic reactions
- Previous anaphylaxis of vaccine component
- History of hospitalizations
- Charlson comorbidity index (CCI)
- Frailty index
- Selected comorbidities
    - Autoimmune disease
    - Asthma
    - Bleeding diathesis or condition associated with prolonged bleeding
    - Cancer
    - Cardiovascular conditions (e.g., heart failure, CAD, cardiomyopathies)
    - Chronic kidney disease/dialysis
    - COPD/interstitial lung disease
    - Diabetes mellitus (i.e., type 1 or type 2 diabetes)
    - Down syndrome
    - Sickle cell disease
    - Hepatitis B virus infection (HBV)
    - Hepatitis C virus infection (HCV)
    - HIV
    - Hyperlipidemia
    - Hypertension
    - Liver disease
    - Neurological disease
    - Other immune deficiencies
    - Solid organ transplant
    - Venous thromboembolism (VTE)
- Immunization history
    - Seasonal influenza (during the 2020/2021 influenza season; reported for recipients of Pfizer-BioNTech COVID-19 vaccine)
    - Tetanus diphtheria and pertussis (Tdap or Td)
    - Chickenpox (Varicella)
    - Shingles (Herpes zoster recombinant and/or live)
    - Human papillomavirus (HPV)
    - Pneumococcal conjugate
    - Pneumococcal polysaccharide
    - Hepatitis A
    - Hepatitis B
    - Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB)
    - Haemophilus influenza type b

9.4.4. Vaccine Utilization Patterns

The following vaccine utilization patterns were described for the Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine. Note, as some individuals received the bivalent vaccine as their first or second COVID-19 vaccine, "bivalent dose" terminology is used throughout this final report to refer to bivalent vaccines received as doses 1-5. "Bivalent booster dose" terminology was used to specifically refer to bivalent vaccines received after the primary series of Pfizer-BioNTech COVID-19 vaccine.

Pfizer-BioNTech COVID-19 vaccine:

- Month and year of vaccine administration
- Proportion of individuals who received monovalent dose 1, monovalent dose 2, monovalent dose 3/booster dose, monovalent dose 4/booster dose, and bivalent dose 1
- Two monovalent dose completion rate
- Three monovalent dose/booster dose completion rate
- Four monovalent dose/booster dose completion rate
- Time gaps between monovalent dose 1 and monovalent dose 2
- Time gaps between monovalent dose 2 and monovalent dose 3/booster dose
- Time gaps between monovalent dose 3/booster dose and monovalent dose 4/booster dose
- Time gaps between monovalent dose 3/booster dose and monovalent dose 4/booster dose
- Time gaps between last monovalent dose and bivalent dose 1
- Care setting where immunization was received
- COVID-19 vaccine(s) from different manufacturers in addition to the Pfizer-BioNTech COVID-19 vaccine
    - COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of two Pfizer-BioNTech vaccine doses (i.e., a heterologous booster)

Seasonal influenza vaccine:

- Month and influenza season of vaccine administration

9.5. Data Sources and Measurement

The study relied on secondary EMR data from the VHA CDW, which is a centralized data warehouse that is updated daily. For this final report, the study used data from the CDW for individuals identified through the end of data collection on 30 June 2023, and the data were locked on 13 October 2023.

9.5.1. VHA EMR Database

The VHA is the largest integrated health care system in the US, providing comprehensive healthcare services, including primary, specialty and inpatient care, rehabilitation, long-term and home care, and other services to over nine million veterans through 1,293 health care facilities, including 171 medical centers and 1,112 outpatient sites of varying care

complexity.[35] In addition to veterans, VHA enrollees may also include employees and certain categories of family members of the veterans, but these are a minority among all VHA enrollees.

The CDW consolidates data from the VHA's EMR system and contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, immunizations, and lab results. Although the VHA may have financially covered/reimbursed care provided at non-VHA facilities, the EMR system (and thus the CDW) does not capture information on visits at non-VHA facilities. The CDW stores data in separate databases based on type of clinical information (e.g., inpatient medication, inpatient admission, outpatient medication, outpatient visit). The VHA also maintains its own mortality data, in which 99% of enrollees' deaths are reported within one month of occurrence and which are based on information collected from multiple sources: family members, VHA hospitals, the National Cemetery Administration, Medicare vital status file, and the Social Security Administration. Death ascertainment from these sources in the VHA data has been shown to have 98% sensitivity.[36]

Each VHA enrollee is assigned a unique identification number in the CDW, to allow for longitudinal follow-up as well as for cross-reference across the various separate databases. For example, in each inpatient admission record, information on the primary discharge diagnosis (and as many as 15 secondary diagnoses), date of admission, date of discharge, and length of stay is available. This record can then be linked to other information pertaining to that inpatient stay located in other files, including procedures that the individual underwent during hospitalization, medical specialty of the provider, and prescriptions dispensed (inpatient and outpatient). Other files are structured similarly, and therefore can be linked together to provide comprehensive information about the individual and his/her medical encounters.

The VHA database was an appropriate data source to provide early data on potential rare safety events of interest associated with Pfizer-BioNTech COVID-19 vaccine. First, given that some groups of veterans were prioritized in the first wave of vaccinations,[28] VHA enrollees were among the first Pfizer-BioNTech COVID-19 vaccine recipients in the US, enabling early safety analyses. Second, the VHA data are refreshed daily, and thus enable rapid data analysis. Third, the VHA population is older and has more comorbid conditions than the general population,[37] thus maximizing the chance of capturing rare safety events of interest in early analyses, following the initial phases of Pfizer-BioNTech COVID-19 vaccine distribution. Since it is possible that individuals may not have all their health encounters within the VHA (especially older veterans who are also covered by Medicare), additional subgroup analyses were conducted in which the CDW data was supplemented with data from CMS, linking Medicare administrative claims data at the individual level to ensure a more comprehensive evaluation of the care an individual received. Medicare data included eligibility files and claims for services received in the inpatient and outpatient setting, as well as skilled nursing facilities, hospice, and home health agencies, and covered the US primarily among those aged 65 years or older.

Given the evolution of the SARS-CoV-2 virus and emergence of new variants and subvariants, data on subvariants collected by the VHA were also used in this study. The

VHA Sequencing for Research Clinical and Epidemiology (SeqFORCE) was founded in March 2021 to study and track variant COVID-19 strains within the VHA population.[38] Data from this source were linked to severe COVID-19 disease hospitalization, which allowed for descriptive assessment of the heterogeneous risk of severe COVID-19 disease associated with current and emerging SARS-CoV-2 variants. VHA Sequencing Collaborations United for Research and Epidemiology (SeqCURE) and Science and Health Initiative to Combat Infectious and Emerging Life-threatening Diseases (SHIELD) data sources with additional SARS-CoV-2 variant information were not included because such data could not be obtained and analyzed in time for the final report. However, the majority of the SARS-CoV-2 subvariant type information at the VHA is available in the SeqFORCE database so there may be minimal impact from not including the SeqCURE and SHIELD data sources. Note, individuals with SARS-CoV-2 subvariant strain information were not a random sample of the VHA population as certain time periods or high-risk individuals may have been prioritized for SARS-CoV-2 subvariant strain testing during the COVID-19 pandemic.

To the extent that the individuals in the VHA population are different from individuals outside of the VHA, the results may not be generalizable to the broader US population. For example, as the VHA includes predominantly men (approximately 90%), findings from this study may not be generalizable to women in the US.

9.5.2. Measurement

9.5.2.1. Outcomes

Operational definitions of the 48 safety events of interest, based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes and laboratory values, are detailed in Table 2 of Annex 1. Appendix 9.[39-43]

A safety event of interest was only counted if it could be assigned to 1) the risk interval following Pfizer-BioNTech COVID-19 vaccination (all designs), 2) the post-vaccination control interval (self-controlled designs), or 3) the risk interval for the active comparators receiving seasonal influenza vaccine (active comparator design). Events outside the intervals were not counted. Only the individual's first instance of a safety event of interest following a specified clean window (i.e., the occurrence-free baseline period used to define incident outcomes during which individuals enter the study cohort only if the safety event of interest did not occur during this period) was included; this means that if a safety event of interest was identified but the safety event of interest was also observed during the clean window, it was not counted. This approach is consistent with the FDA's COVID-19 Vaccine Safety Surveillance Project.[23]

9.5.2.2. Exposures of Interest

Administration of the Pfizer-BioNTech COVID-19 vaccine primary series, monovalent booster dose(s), and bivalent dose post-EUA approval (after 11 December 2020) and date of

immunization for each dose were identified from the CDW based on the following (Table 3 of Annex 1. Appendix 9):

- Current Procedural Terminology (CPT) codes and associated vaccine administration Healthcare Common Procedure Coding System (HCPCS) codes; or
- 10 and 11-digit National Drug Codes (NDCs) codes; or
- Immunization records that contain data on the vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization.[44]

Administration of the seasonal influenza vaccine during 2014/2015 through 2018/2019 influenza seasons and date of immunization were identified in the CDW data based on any of the following (Table 3 of Annex 1. Appendix 9):

- CPT codes and HCPCS codes; or
- 10 and 11-digit NDCs; or
- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer, lot number, injection site, and date(s) of immunization.

First, second, third/booster, fourth/booster doses, and fifth/booster doses of the Pfizer-BioNTech COVID-19 vaccine for individuals were identified by their relative dates of vaccination. Individuals' first record of Pfizer-BioNTech COVID-19 vaccination was categorized as the first dose. Among individuals with only two Pfizer-BioNTech COVID-19 vaccination records, the second vaccination record was categorized as the second dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination, the vaccination date closest to 21 days after the first vaccination dose was categorized as the second dose. Among individuals with only one Pfizer-BioNTech COVID-19 vaccination record after their second dose, that vaccination record was categorized as the third dose/booster dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination after their second dose, the next vaccination date after the second vaccination dose was categorized as the third dose/booster dose, and the vaccination date closest to five months (i.e., 152 days) after the third dose was categorized as the fourth dose/booster dose. Among individuals with only one Pfizer-BioNTech COVID-19 vaccination record after their fourth dose, that vaccination record was categorized as the fifth dose/booster dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination after their fourth dose, the vaccination date closest to two months (i.e., 61 days) after the fourth dose was categorized as the fifth dose. The bivalent dose was identified based on specific CPT/HCPCS codes and descriptions in the immunization records without relying on time intervals.

9.5.2.3. Baseline Characteristics

Operational definitions for all diagnoses, procedures, and immunizations are provided in Table 1 of Annex 1. Appendix 9. In short, diagnoses were identified by ICD-9-CM, ICD-10-CM diagnosis codes, procedures were identified by ICD-10-PCS (Procedure Coding System) codes, CPT, or HCPCS procedure codes, while vaccines were identified by NDC, CPT, and HCPCS codes, and immunization records. Baseline demographic and clinical characteristics reported in this final report were based on a two-year baseline period (unless otherwise specified), instead of one year, to account for under-utilization and hence under-detection of prior medical history during the COVID-19 pandemic period (specifically for individuals receiving Pfizer-BioNTech COVID-19 vaccine). The following baseline factors were included:

- Demographic variables included age, sex, race/ethnicity, and VHA service area. Demographic variables were extracted from the CDW data at the time of the receipt of the first dose of the Pfizer-BioNTech COVID-19 vaccine (for the Pfizer-BioNTech COVID-19 vaccine sample) and at the time of the receipt of the seasonal influenza vaccine (for the seasonal influenza vaccine sample) and were well-populated. As individuals could have multiple seasonal influenza vaccines across 2014/2015 through 2018/2019 seasons, individuals in the seasonal influenza vaccine sample had their baseline characteristics assessed both at the time of their most recent seasonal influenza vaccination and the time of each of their previous seasonal influenza vaccinations (i.e., individuals could have multiple assessments of baseline characteristics at different time points).

- BMI was extracted from the CDW based on the most recent BMI record for the individual in the two years before the receipt of the first dose of the Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine.

- History of hospitalizations included the number of hospitalizations recorded in the CDW in the two years before the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine.

- Smoking status, history of anaphylaxis/allergic reactions, previous anaphylaxis of vaccine component, comorbidities included in the CCI,[45] CCI, frailty index, and other relevant comorbidities were identified in the CDW data (based on diagnosis codes that conform with the ICD-9-CM and ICD-10-CM codes) in the two years before the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine (see Table 1 of Annex 1. Appendix 9. for more details on the specific codes used).

- Non-seasonal immunizations (i.e., all immunizations other than seasonal influenza) were measured in the two years preceding the vaccination; other immunizations were identified from the CDW based on CPT codes, HCPCS codes, and NDC codes (see Table 1 of Annex 1. Appendix 9. for more details on the specific codes used); seasonal influenza was measured only among individuals who received the Pfizer-BioNTech COVID-19 vaccine during the influenza season (i.e., from 1

October to 31 May) that overlapped or preceded with the date when the individual received their Pfizer-BioNTech COVID-19 vaccine.

9.6. Bias

Several approaches were incorporated in the study design and statistical analyses to reduce bias in this study.

First, the SCRI and active comparator designs complemented each other in mitigating bias in this study. Specifically, the SCRI design used individuals as their own controls, thus removing any potential confounding bias due to factors that did not change over short periods of time within an individual (e.g., age, sex, chronic conditions). Despite the ability to adjust for time-invariant confounders, the SCRI design may have had limited power to estimate the expected rates for very rare safety events of interest.[46] Therefore the SCRI design was complemented by an active comparator design that derived the expected rates of safety events of interest from historical controls vaccinated for seasonal influenza. To mitigate potential confounding bias in the active comparator design, historical controls only included individuals vaccinated for seasonal influenza (individuals who are open to vaccination were expected to share similarities) and additional multivariate Poisson regression models were implemented for safety events of interest that had signals detected and persisted after conducting quality assurance. However, as the multivariate Poisson regression model could only control for measured covariates, residual confounding could be present which could impact results. A SCCS design with post-vaccination control time periods was also performed for safety events of interest that had signals detected due to its increased statistical power compared to the SCRI design, which was especially useful for rare safety events of interest.

If individuals received the Pfizer-BioNTech COVID-19 vaccine or the seasonal influenza vaccine outside of a VHA facility, this information may not have been fully captured in the VHA EMR system, resulting in exposure misclassification. Veterans with secondary insurance and veterans who are 65 years of age or older who have Medicare may be more likely to receive services outside VHA. One study on VHA enrollees in seven different states found that among all individuals admitted to VHA hospitals in 2007, one-fifth also had a non-VHA hospitalization during that year.[47] To mitigate this limitation, subgroups of individuals enrolled in the VHA with dual coverage who were also identified in the CMS Medicare administrative claims data (in order to supplement CDW data for a more complete evaluation of healthcare encounters) were examined to ensure that their healthcare data was complete to the extent possible.

Further discussion of potential sources of bias in the study, including exposure misclassification, is provided in Section 11.2.

9.7. Study Size

A total of 1,652,514 individuals received at least one dose of Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023 in the VHA database. The active comparator group includes a fixed cohort of 4,104,220 historical seasonal influenza vaccine

recipients who received a total of 10,138,984 seasonal influenza vaccines across successive influenza seasons between 2014/2015 through 2018/2019.

9.7.1. Power

Power calculations for the safety signal analyses (primary objective) were conducted for each safety event of interest using the power calculation feature in the sequential R package for rapid-cycle analysis developed by Kulldorff et al.[48] As power of 80% has been used in prior power calculations for other vaccine safety surveillance studies and the FDA usually views a relative risk (RR) of ≥3 as meaningful, these values were used in the power calculations.[48,49] Table 2 presents the calculated power using the conditional Poisson maximized sequential probability ratio test (cMaxSPRT) for all safety events of interest, except for MIS-C/MIS-A and severe COVID-19 disease where binomial MaxSPRT was used. Safety events of interest that had low statistical power (<80%) to detect RR of 3 in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine among individuals that received at least one dose included convulsions/seizures in individuals with controlled epilepsy, TM, anaphylaxis, MIS-C/MIS-A, microangiopathy, chilblain-like lesions, hemorrhagic disease, and TTS.

Table 2. Statistical Power to Detect RR≥3 Comparing Risk of Each Safety Event of Interest following Pfizer-BioNTech COVID-19 Vaccine Monovalent Doses 1-4 and Bivalent Dose 1 to Seasonal Influenza Vaccine Using Conditional Poisson MaxSPRT

Safety Event of Interest	**Aggregate risk interval after Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 vaccine**	
	Number of individuals	**Statistical power to detect RR of 3[1]**
Neurologic		
Aseptic meningitis	1,652,469	0.81
Bell's palsy	1,652,395	1.00
Cerebrovascular non-hemorrhagic stroke	1,649,253	1.00
Convulsions/seizures in individuals with controlled epilepsy	1,006	0.32
Encephalitis/encephalomyelitis	1,652,470	1.00
GBS	1,652,476	0.84
Generalized convulsion/seizures	1,652,122	1.00
MS	1,652,110	1.00
ON	1,652,439	1.00
Other acute demyelinating diseases	1,652,451	1.00
TM	1,652,476	0.73
Immunologic		
Anaphylaxis	1,652,513	0.15
Arthritis and arthralgia/joint pain	1,652,484	1.00
Autoimmune thyroiditis	1,652,488	1.00

Table 2. Statistical Power to Detect RR≥3 Comparing Risk of Each Safety Event of Interest following Pfizer-BioNTech COVID-19 Vaccine Monovalent Doses 1-4 and Bivalent Dose 1 to Seasonal Influenza Vaccine Using Conditional Poisson MaxSPRT

Safety Event of Interest	Aggregate risk interval after Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 vaccine	
	Number of individuals	Statistical power to detect RR of 3[1]
Fibromyalgia	1,652,487	1.00
KD	1,652,497	-
MIS-C/MIS-A	1,645,620	0.67
Vasculitides	1,652,354	1.00
Cardiac		
AMI	1,648,707	1.00
Arrhythmia	1,646,041	1.00
CAD	1,645,062	1.00
Heart failure and cardiogenic shock	1,649,488	1.00
Microangiopathy	1,652,488	0.31
Myocarditis	1,652,471	1.00
Pericarditis	1,652,357	1.00
Stress cardiomyopathy	1,652,487	0.87
Hematologic		
Cerebrovascular hemorrhagic stroke	1,652,200	1.00
Chilblain-like lesions	1,652,497	0.31
DIC	1,652,494	1.00
DVT	1,651,744	1.00
Hemolytic anemia	1,652,478	1.00
Hemorrhagic disease	1,652,492	0.31
Limb ischemia	1,652,464	1.00
PE	1,650,589	1.00
Single organ cutaneous vasculitis	1,652,473	0.82
Thrombocytopenia	1,652,411	1.00
TTS	1,652,496	0.27
Other		
Acute kidney injury	1,648,632	1.00
Appendicitis	1,651,424	1.00
Death[2]	1,652,514	1.00
Erythema multiforme	1,652,493	-
Glomerulonephritis	1,652,454	1.00
Liver injury	1,652,055	1.00
Narcolepsy and cataplexy	1,652,496	1.00
Nephrotic syndrome	1,652,422	1.00

Table 2. Statistical Power to Detect RR≥3 Comparing Risk of Each Safety Event of Interest following Pfizer-BioNTech COVID-19 Vaccine Monovalent Doses 1-4 and Bivalent Dose 1 to Seasonal Influenza Vaccine Using Conditional Poisson MaxSPRT

Safety Event of Interest	Aggregate risk interval after Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 vaccine	
	Number of individuals	Statistical power to detect RR of 3[1]
Non-anaphylactic allergic reactions	1,651,968	1.00
Severe COVID-19 disease	1,637,996	1.00
SJS/TEN	1,652,492	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; MaxSPRT, maximized sequential probability ratio test; MIS-C/MIS-A, multisystem inflammatory syndrome in children/multisystem inflammatory syndrome in adults; MS, multiple sclerosis; ON, optic neuritis; PE, pulmonary embolus; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis thrombocytopenia syndrome.
Notes:
[1] Power was calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest. For safety events with upper limit exceeding N=1,000 events, 1.00 was used for statistical power. Power was estimated for all safety events of interest except MIS-C/MIS-A and severe COVID-19 disease using conditional Poisson MaxSPRT; for MIS-C/MIS-A and severe COVID-19 disease, binomial MaxSPRT was used to estimate power. Rows with safety events of interest that had low statistical power (<80%) to detect RR of 3 in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine were shaded purple.
[2] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine were included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death at any time (i.e., not restricted to the risk interval) or setting (i.e., healthcare or non-healthcare setting) was captured.

9.8. Data Transformation

Not applicable.

9.9. Statistical Methods

9.9.1. Main Summary Measures

9.9.1.1. Baseline Characteristics

Baseline demographics and clinical characteristics were summarized using mean, standard deviation (SD), and median (interquartile range [IQR]) values for continuous variables and frequency distributions for categorical variables. Baseline demographics and clinical characteristics were summarized and compared between the Pfizer-BioNTech COVID-19 vaccine recipients (at the time of the first dose of the Pfizer-BioNTech COVID-19 vaccine) and for active comparators who received seasonal influenza vaccination (at the time of the most recent seasonal influenza vaccine received between the 2014/2015 through 2018/2019 influenza season to facilitate comparison with the Pfizer-BioNTech COVID-19 vaccine recipients). Baseline demographics and clinical characteristics were also summarized at the

time of each seasonal influenza vaccine observed in the seasonal influenza sample from 2014/2015 through 2018/2019 influenza seasons (i.e., allowing multiple measurements per individual) as the background incidence rate of the safety events of interest were assessed in the risk intervals following all observed seasonal influenza vaccines (to increase the chance of capturing rare safety events of interest).

Standardized differences were used to compare baseline demographics and clinical characteristics between individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine (at the time of their first Pfizer-BioNTech COVID-19 vaccine dose) and those vaccinated for seasonal influenza (at the time of the most recent seasonal influenza vaccine). For a given covariate, the standardized difference scales the difference in means between the samples (if the covariate is continuous) or the difference in proportions (if the covariate is binary) by the SD of that covariate in both samples combined. Because the standardized difference is a measure of the average difference in means/proportions between two groups expressed in SD units that does not depend on sample size,[50] it is a more appropriate estimate than statistics that rely on statistical significance (e.g., t-test for continuous variables or chi-square tests for binary variables) for studies with very large samples, such as the current study.

In the current study, a standardized difference >10% was used to identify an imbalance between characteristics of recipients of the Pfizer-BioNTech COVID-19 vaccine and the seasonal influenza vaccine.[51,52] The study used a conservative threshold to indicate covariate imbalance (other authors proposed thresholds ranging from >10% to >25%)[53-56] to capture any possible differences between the study samples that should be accounted for in adjusted analyses conducted in the signal evaluation phase.

9.9.1.2. Vaccine Utilization Patterns

Descriptive statistics were used to summarize the Pfizer-BioNTech COVID-19 and seasonal influenza vaccine utilization patterns using the mean (SD) and median (IQR) values for continuous variables and frequency distributions for categorical variables. Individuals with at least one healthcare encounter in the VHA from 11 December 2020 to 30 June 2023 served as the expected number of individuals who would be eligible for the Pfizer-BioNTech COVID-19 vaccine, as they had been actively receiving care through the VHA during the time period when the Pfizer-BioNTech COVID-19 vaccine was available.

9.9.1.3. Safety Signal Analyses

In this final report, the safety signal analyses using the study designs described in Section 9.1 were performed, specifically signal detection and signal evaluation analyses, as described below.

The signal detection phase included the following analyses:

- For MIS-C/MIS-A and severe COVID-19 disease safety events of interest, these events could not use seasonal influenza vaccine as a comparator since they require a COVID-19 diagnosis code in the definitions and there was no COVID-19 in previous influenza seasons. Therefore, the SCRI design using post-vaccination control intervals, RRs and

corresponding confidence intervals (CIs) were used in the signal detection phase to compare the risk of safety events of interest during the risk interval immediately following the Pfizer-BioNTech COVID-19 vaccination and the risk of safety events of interest during the pre-specified post-Pfizer-BioNTech COVID-19 vaccination control intervals. Please see Section 9.9.2 for additional methodological details. For all other safety events of interest, the SCRI methodology was used in the signal evaluation phase, as this method requires time to accumulate during the post-vaccination control period.

- For analyses based on the active comparator design, RRs and corresponding CIs were estimated to compare the risk of safety events of interest during the risk interval immediately following the Pfizer-BioNTech COVID-19 vaccine among Pfizer-BioNTech COVID-19 vaccine recipients and the risk interval immediately following the seasonal influenza vaccine among historical seasonal influenza vaccine recipients.

The signal evaluation phase was initiated after a signal was detected, and the following analyses were then conducted sequentially:

- Post-signal quality assurance (e.g., check for possible duplications and inconsistencies of medical records).

- For safety events of interest other than MIS-C/MIS-A and severe COVID-19 disease, the SCRI design using the binomial-based MaxSPRT was applied. See Section 9.9.2 for description of the SCRI method. Incidence rate ratios (IRRs) and corresponding CIs were also calculated using a multivariate adjusted Poisson regression model to account for baseline differences between the Pfizer-BioNTech COVID-19 and seasonal influenza vaccine recipients.

- A SCCS design was used to compare the incidence of safety events occurring in the risk interval following vaccination with the incidence of safety events occurring during all other times post-vaccination (i.e., post-vaccination control time period) in the same individual until the earliest of 183 days after the Pfizer-BioNTech COVID-19 vaccination, disenrollment, death, or end of data availability. Relative incidences (RIs) and corresponding CIs were estimated using conditional Poisson regression.

- Kaplan-Meier methods were used to analyze time-to-safety event of interest, with censoring at the end of the risk interval for individuals who did not experience the safety event of interest by the end of the risk interval.

The comparison with contemporary unvaccinated controls and assessment of temporal clusters signal evaluation analyses were not conducted for this final report, pursuant to the study protocol (Annex 1. Appendix 2), because no signals of safety events of interest remained after the SCCS signal evaluation analyses.

Finally, the end-of-surveillance safety analysis (i.e., at 30 months, after the end of surveillance) was a one-time analysis conducted for safety events of interest with signals detected. Using data from the SCRI design, this analysis compared the RR for safety events

of interest with signals detected during the risk interval to the control interval, and corresponding CIs were estimated.

9.9.2. Main Statistical Methods

9.9.2.1. Safety Signal Analyses

9.9.2.1.1. Signal Detection

Signal detection utilized the SCRI design with comparison to post-vaccination control intervals for the two safety events that required COVID-19 diagnosis (i.e., severe COVID-19 disease, MIS-C/MIS-A) and comparison with seasonal influenza vaccine sample for the remaining safety events. While the active comparator design was the main analysis for signal detection because it could be performed the fastest, it could not be used for safety events that required COVID-19 diagnosis because historical seasonal influenza vaccine controls would not meet the criteria of having a COVID-19 diagnosis. Sequential analyses for each safety event of interest only commenced when at least three events occurred. This approach is consistent with the FDA's COVID-19 Vaccine Safety Surveillance Project to avoid spurious signals from a few early events.[23] The most recent signal detection results that include data up until 30 June 2023 are presented in this final report.

9.9.2.1.1.1. Sequential Testing - SCRI Design Using the Binomial-Based MaxSPRT for Comparison to Post-Vaccination Control Intervals for the Two Safety Events Requiring COVID-19 Diagnosis (i.e., MIS-C/MIS-A and Severe COVID-19)

MaxSPRT using a binomial probability model was applied, with a null hypothesis (H_0) that the risk of a safety event of interest occurring during the risk interval was equivalent to the risk of the same safety event of interest occurring during the control interval, accounting for differences in interval duration as needed; meaning a RR of 1 was specified under H_0.[25] The one-sided composite alternative hypothesis (H_a) assumed that the risk of a safety event of interest during the risk interval was greater than the risk of the same safety event of interest during the control interval, accounting for differences in interval duration (i.e., RR >1, H_a is applicable across a range of RRs).[48]

For the binomial model, the log-likelihood ratio (LLR) was calculated as the log probability of observing this distribution of events in the risk interval under H_a, divided by the probability of this occurring under H_0.[48] For each safety event of interest, critical values for LLR were calculated using the upper limit (i.e., number of expected events in the risk and control intervals based on the literature during the entire length of surveillance) and pre-specified alpha level for each safety event of interest.[57] Once the LLR test statistic reached a pre-specified critical value, a signal was detected. Specifically, H_0 was rejected if the LLR reached or exceeded the critical value. H_0 was not rejected if the LLR did not reach or exceed the critical value or if surveillance ended without reaching the upper limit.

9.9.2.1.1.2. Sequential Testing - Poisson-based MaxSPRT for Comparison to Active Comparators who Received Seasonal Influenza Vaccination for All Other Safety Events of Interest

For comparison with active comparators who received seasonal influenza vaccination, the Poisson-based MaxSPRT was applied following the same statistical approach as described above but using a Poisson probability distribution. In the Poisson MaxSPRT approach, the event frequency of safety events of interest in the risk interval after Pfizer-BioNTech COVID-19 vaccination was compared to a background rate of safety events of interest in the risk interval after seasonal influenza vaccination in five prior seasons of 2014/2015 to 2018/2019. The Poisson MaxSPRT allowed for more timely analysis using historical data, as well as increased power to detect a signal with fewer occurrences of the safety event of interest.[57] However, this method did not fully control for confounding by indication.

The critical value of the LLR for each safety event of interest was determined based on the respective upper limit and alpha level for each event. Upper limits were based on the expected number of safety events of interest under the null hypothesis, assuming the risk of the specific safety event of interest after Pfizer-BioNTech COVID-19 vaccination was no greater than the risk of the same safety event of interest after seasonal influenza vaccination. Therefore, upper limits were chosen such that they would not usually be reached. GBS was of particular interest relative to the safety profile of the Pfizer-BioNTech COVID-19 vaccine. As GBS is an extremely rare safety event of interest, the primary rapid-cycle analysis focused on Poisson MaxSPRT and applied an alpha of 0.05, while all other safety events of interest used an alpha of 0.01. This strict alpha level was selected to minimize the chances of detecting a large number of signals due to multiple outcome testing, and this approach is consistent with the FDA's BEST Initiative protocol.[23]

Conditional MaxSPRT (cMaxSPRT) was applied when the ratio of the number of observed safety events of interest among the historical active comparator population to the upper limit (i.e., expected number of safety events of interest in the risk interval following the Pfizer-COVID-19 vaccine during the entire length of surveillance) was < 2.5. cMaxSPRT was often used when examining the aggregated risk interval after doses 1-4 of the Pfizer-COVID-19 vaccine among individuals with at least one dose.[25,58] This method accounts for the variation in the estimates of the expected number of safety events of interest among the Pfizer-BioNTech COVID-19 vaccinated population under the null hypothesis and controls the type 1 error rate.[25,58] When running the sequential analyses, if there was zero or few incident events for a specific safety event of interest during a sequential test, the cMaxSPRT may not be able to generate updated LLR values. Therefore, the previous sequential test's LLR values from the cMaxSPRT may be used for that specific safety event of interest.

Safety events of interest with signals detected based on any dose analyses of the Pfizer-BioNTech COVID-19 vaccine proceeded to signal evaluation.

A qualitative assessment of the safety profiles of the monovalent and bivalent doses was conducted based on findings from the signal detection analyses. Specifically, the types of safety events of interest with signals detected for the monovalent doses and those of the

bivalent dose were identified, and the RRs calculated for respective safety events were descriptively compared (which was feasible given the same active comparators were used for both monovalent and bivalent dose analyses).

9.9.2.1.2. Signal Evaluation

When signals were detected for safety events of interest based on the analysis described above, signal evaluation was initiated to refine and test such detections. Signal evaluation analyses were conducted using the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine among individuals with at least one dose. The signal evaluation analyses were performed in the order described in the subsections below, and each successive analysis in the signal evaluation phase was only conducted if the signal persisted in the prior step. However, given the low power observed for the SCRI design using binomial MaxSPRT, all safety events of interest with signals detected proceeded to the next step of signal evaluation analyses (i.e., multivariate Poisson regression), even if the signal did not persist in the Binomial MaxSPRT analysis.

9.9.2.1.2.1. Post-Signal Quality Assurance

Quality assurance was first conducted to assess the quality of the data and analysis that produced the signal. While quality control measures were conducted during the signal detection phase, additional quality assurance (e.g., checking for possible duplications and inconsistencies of medical records) was performed during signal evaluation for this final report.

9.9.2.1.2.2. Sequential Testing - SCRI Design Using the Binomial MaxSPRT for Comparison with Post-Vaccination Control Intervals

For safety events of interest other than MIS-C/MIS-A and severe COVID-19 disease, the SCRI design using the binomial-based MaxSPRT was applied during the signal evaluation phase to allow time to accumulate during the post-vaccination control period for observation of outcomes. The same statistical methodology described above was applied.

9.9.2.1.2.3. Multivariate Adjustment Using Poisson Regression

Multivariate Poisson regression was used to compare the incidence rates of the safety events of interest occurring within the risk intervals following Pfizer-BioNTech COVID-19 vaccine vs. seasonal influenza vaccine. Analyses also adjusted for relevant baseline and/or clinical characteristics to account for baseline differences between the Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine samples (i.e., age at vaccination, age category ≥65 years old, sex, race/ethnicity, geographic region [other and unknown region were combined into one category], smoking status, BMI, history of anaphylaxis/allergic reactions, history of hospitalizations, CCI, frailty index, cancer, chronic kidney disease, COPD, cardiovascular conditions [e.g., heart failure, CAD, or cardiomyopathies], sickle cell disease, type 1 and 2 diabetes mellitus, as well as other imbalanced baseline characteristics with standardized differences >10% between the two samples).[24] For safety events of interest with few events, fewer baseline characteristics were adjusted for due to sparse data (i.e., age at vaccination, sex, race/ethnicity [white vs. non-white], geographic region [South, West, and Other], history

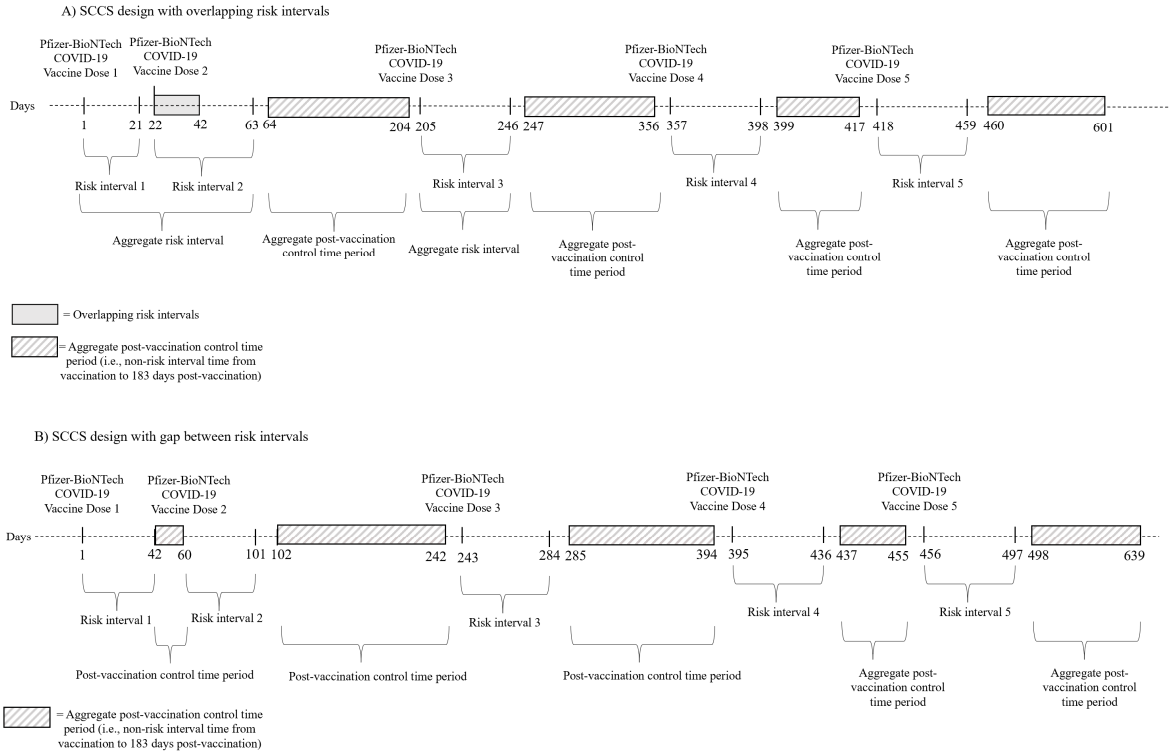
of anaphylaxis/allergic reactions, frailty index, as well as other imbalanced baseline characteristics with standardized differences >10% between the two samples). If the signal remained, based on an IRR >3 with a p-value <0.01 from the adjusted Poisson regression, further evaluation was considered via additional signal evaluation analyses. Multivariate Poisson regression analyses for safety events of interest that required a COVID-19 diagnosis could not be conducted because historical seasonal influenza vaccine comparators could not meet the criteria of having a COVID-19 diagnosis. Therefore, safety events of interest that required a COVID-19 diagnosis and had signals detected were examined through other signal evaluation analyses.

9.9.2.1.2.4. SCCS Design Using Conditional Poisson Regression for Comparison with Post-Vaccination Control Time Period

The SCCS design with post-vaccination control time period was conducted using conditional Poisson regression. Similar to the SCRI design with post-vaccination control intervals, the SCCS design with post-vaccination control time period included cases (i.e., individuals who experienced safety events of interest following vaccination with the Pfizer-BioNTech COVID-19 vaccine) to compare the incidence of safety events occurring in the risk interval following vaccination with the incidence of safety events occurring during all other times post-vaccination (i.e., post-vaccination control time period) until the earliest of 183 days after Pfizer-BioNTech COVID-19 vaccination, disenrollment, death, or end of data availability within in the same individual. The SCCS design differed from the SCRI design in that a time-varying post-vaccination control time period that included all non-risk interval time from Pfizer-BioNTech COVID-19 vaccination date until the earliest of 183 days after Pfizer-BioNTech COVID-19 vaccination, disenrollment, death, end of data availability was used rather than fixed post-vaccination control intervals of the same duration as the risk interval.[59]

See Figure 4 below for an example of an individual who receives five doses of Pfizer-BioNTech COVID-19 vaccine, where the safety event of interest has a 42-day risk interval window. Figure 4A demonstrates the SCCS design with the second dose received 21 days after the first (i.e., the risk interval for dose 1 overlaps with the risk interval for dose 2), while Figure 4B demonstrates the SCCS design with the second dose received 60 days after the first (i.e., with gaps between the end of dose 1 risk interval and dose 2). In both scenarios shown below (Figure 4A and Figure 4B), a third dose/booster dose was received 183 days following dose 2, a fourth booster dose was received 152 days following dose 3, and a fifth booster dose was received 2 months (i.e., 61 days) after dose 4. The risk intervals for dose 3, dose 4, and dose 5 are shown. The post-vaccination control time period is displayed below with shaded gray lines. In cases where a third dose/booster dose was received within the defined risk interval for dose 2, the aggregated post-vaccination control time period was defined after the risk interval for dose 3. Similarly, in cases where a fourth dose (or fifth dose) was received within the defined risk interval for dose 3, the aggregate post-vaccination control time period was defined after the risk interval for dose 4 (or dose 5).

Figure 4. Example of SCCS Design for Safety Event of Interest with a 42-day Risk Interval with Post-vaccination Control Intervals when Fifth Doses of Pfizer-BioNTech COVID-19 Vaccine are Administered



Compared to the SCRI design, the SCCS design with post-vaccination control time period has increased statistical power, which is especially useful for the study of rare safety events of interest. A conditional Poisson regression model was used to compare the rates of safety events of interest in the risk interval to the post-vaccination control time period. From this model, RI and 95% CIs were reported and interpretated as the incidence ratio for the safety event of interest in the risk interval compared to the control time period.

9.9.2.1.3. Signal Verification

Signal verification is only performed if signals persist following signal evaluation. The signal verification phase was not conducted in this final study report because no signals persisted after the signal evaluation phase. However, as the CDC investigated the occurrence of myocarditis/pericarditis associated with mRNA COVID-19 vaccinations in mid-2021, a prioritized safety analysis of myocarditis/pericarditis that included signal verification through medical record adjudication was conducted.

9.9.2.2. End-of-Surveillance Analyses

For any safety event of interest with a signal detected, an end-of-surveillance analysis (i.e., at 30 months, after the end of surveillance) was conducted. The number of events in the sum of six distinct risk intervals was compared to the control interval, adjusting for potential differences in interval length, to estimate the RR of the Pfizer-BioNTech COVID-19 vaccine

compared to the influenza vaccine. In order to monitor the safety after the first and full course of the vaccine, the number of potential safety events of interest occurring in the six separate risk intervals (P_1, P_2, P_3, P_4, P_5, P_6) was estimated. P_1 represented the risk interval after the first dose only, excluding any overlap in risk intervals with the second dose. P_2 represented the overlapping risk intervals for the first and second doses of the vaccine. P_3 represented the risk interval of the second dose of the vaccine, excluding the overlapping risk interval already captured in P_2. P_4 represented the risk interval after the third dose for individuals with a third dose. P_5 represented the risk interval after the fourth dose for individuals with a fourth dose. P_6 represented the risk interval after the fifth dose for individuals with a fifth dose. This design allowed for the assessment of risk during the appropriate periods regardless of the time interval between vaccine doses. As multiple endpoints were assessed, 99% CIs were calculated around the RR in order to ascertain whether the Pfizer-BioNTech COVID-19 vaccine was associated with any of the safety events of interest.

9.9.2.3. Subgroup Analyses

In this final report, sample sizes for each of the subgroups of interest (defined in Section 9.3.3) were reported, and separate safety surveillance analyses for subgroups of special interest (i.e., the subgroup of individuals enrolled in the VHA with dual Medicare coverage and subgroups of individuals with the bivalent booster dose of the COVID-19) were conducted. The subgroup of individuals enrolled in the VHA with dual Medicare coverage was further examined as these individuals were likely to have received services outside the VHA. Therefore, using both VHA EMR and Medicare claims data in this subgroup analysis led to more robust safety surveillance analyses by utilizing healthcare data that were as comprehensive as possible for this subgroup. The subgroups of individuals with the bivalent booster dose of the COVID-19 were further examined because, given the recent approval of the bivalent booster dose of the Pfizer-BioNTech COVID-19 vaccine, there may be less literature available regarding the safety of the bivalent booster dose. Safety surveillance analyses for other subgroups were not conducted due to small sample size and/or the other subgroups having less clinical significance given the current state of the COVID-19 pandemic.

9.9.2.4. Incidence Rates and Time to Safety Event of Interest Analysis

Incidence rates (and corresponding CIs) were calculated from signal detection analyses of the safety events of interest. Kaplan-Meier methods were used to analyze time-to-event (i.e., time to safety event of interest). If individuals did not experience the safety events of interest, they were censored at the end of the risk interval. The median time to the safety event of interest and corresponding CIs were summarized.

9.9.2.5. Prioritized Safety Analysis of Myocarditis/Pericarditis

The CDC investigated the occurrence of myocarditis/pericarditis associated with mRNA COVID-19 vaccinations in mid-2021.[60] Therefore, separate analyses were prioritized and conducted to better understand the risk of myocarditis/pericarditis among Pfizer-BioNTech COVID-19 vaccinees in the VHA. This analytical approach was intended to align with the methodology used by the Vaccine Safety Datalink (VSD) and preliminary findings of

myocarditis/pericarditis published by the ACIP on 23 June 2021.[60,61] The VSD protocol defined myocarditis/pericarditis events (ICD-10-CM codes B33.22, B33.23, I30, I40) as the first event in 60 days identified through an ED or inpatient encounter, without an individual's first diagnosis of COVID-19 (i.e., COVID-19 diagnosis code or positive RT-PCR COVID-19 lab test) in the 30 days prior to or on the day of the event. The prioritized safety analysis of myocarditis/pericarditis followed the outcome definition used in the VSD and used three distinct risk intervals following vaccination (i.e., 1-7 days, 1-21 days, and 1-42 days), with the definition and the statistical approach differing from the primary analysis described for all other safety events of interest in this final report to facilitate comparison with the results presented by the ACIP.[23,60]

This analysis included all individuals in the Pfizer-BioNTech COVID-19 vaccine sample described above in the primary safety surveillance analyses for all other safety events of interest and included outcome data on myocarditis/pericarditis up until the end of data collection (i.e., 30 June 2023). The number of myocarditis/pericarditis events in the risk interval was identified, and incidence rates per million doses summarized. Subgroup analyses were also performed, stratified by age (i.e., 12-39 years, 40-49 years, 50-64 years, ≥65 years), sex, and race/ethnicity, respectively.

In addition, concurrent vaccinated comparators were selected among individuals who received the Pfizer-BioNTech COVID-19 vaccine, and events were compared between vaccine recipients who were in their risk interval (e.g., days 1-21) and those who were concurrently, on the same calendar date, in their comparison interval (e.g., days 22-42). Poisson regression was then used to calculate IRRs and 95% CIs to compare the rate of myocarditis/pericarditis events between those individuals who were in a risk interval versus those individuals who were in a comparison interval on the same calendar day. Data were analyzed at the stratum level for each calendar day, and were further stratified by the independent variable of interest (i.e., risk vs. comparison interval) and adjustment variables (i.e., age group, sex, race/ethnicity, and VHA service area). Thus, the number of myocarditis/pericarditis events in a risk or comparison interval on a calendar day was modeled as a function of whether the stratum's vaccine recipients were in a risk versus comparison interval on that calendar day, controlling for age, sex, race/ethnicity, and VHA service area. The log of the number of individuals contributing data to each stratum on each calendar day was included as an offset term in the Poisson model.

Irrespective of whether a potential signal was detected for myocarditis/pericarditis in the codified data analysis, chart-based adjudication was planned and carried out due to the importance of understanding this safety event. Case confirmation for myocarditis/pericarditis events identified during the 21-day risk interval was conducted based on medical chart review. Myocarditis/pericarditis cases were confirmed and validated using the Brighton Collaboration's case definitions.[62] In addition, data surrounding risk factors, clinical course, and sequelae of identified myocarditis/pericarditis events up to 365 days following the event were collected and summarized. These included an examination of other possible etiologies/risk factors (i.e., prior COVID-19 infection, prior Coxsackie infection, other prior viral infections, other vaccines received, comorbid immunocompromising conditions and systemic immune-mediated diseases, demographics, and medication history); time between

Pfizer-BioNTech COVID-19 doses (first and second) and onset of myocarditis/pericarditis; echocardiogram information; lab troponin information; symptoms (e.g., chest pain, shortness of breath, weakness or fatigue, arm or shoulder pain, heart palpitations cough, swelling in abdomen or legs, fever); treatments received for myocarditis/pericarditis (e.g., non-steroidal anti-inflammatory drugs, colchicine, corticosteroids, pericardiectomy); healthcare resource utilization (HRU) following the event, and long-term sequelae for up to one year following the event (for myocarditis: recovery, sudden cardiac death, heart failure cardiogenic shock, fulminant myocarditis, inflammatory cardiomyopathy, heart transplant, arrhythmia; for pericarditis: recovery, chronic pericarditis, restrictive pericarditis, recurrent pericarditis). In addition, incidence rates of confirmed myocarditis/pericarditis cases (via chart adjudication) per million doses in the 21-day risk interval were described. Risk factor analysis were also conducted via logistic regression to estimate ORs and 95% CI among confirmed cases of myocarditis/pericarditis to further evaluate variables associated with the event. Due to the small number of chart-confirmed myocarditis/pericarditis cases, only approximately ten risk factors were examined to avoid model convergence issues, as described in the statistical analysis plan.

9.9.2.6. Analysis of Severe COVID-19 Disease Stratified by SARS-CoV-2 Subvariant Lineage

Analyses of severe COVID-19 disease stratified by SARS-CoV-2 subvariant lineages, as classified by Pango lineage designation,[63] were conducted to further examine whether the risk of severe COVID-19 disease varies across subvariant lineages. The US government SARS-CoV-2 Interagency Group (SIG) classifies SARS-CoV-2 variants into the following four groups based on the risk to public health in the US: Variant Being Monitored (VBM), Variant of Interest (VOI), Variant of Concern (VOC), Variant of High Consequence (VOHC). Currently, no VOHC are identified in the US, and no SARS-CoV-2 variants are designated as VOI. The Omicron variant was classified as a VOC due to increased transmissibility and high detection of cases, while other variants were designated as VBMs.[63]

Following the Pfizer-BioNTech COVID-19 vaccine, each severe COVID-19 disease hospitalization was linked with COVID-19 specimens collected within 14 days prior to hospital admission to 2 days after hospital discharge to identify the SARS-CoV-2 subvariant lineage associated with the COVID-19 hospitalization. If multiple specimens were observed around a COVID-19 hospitalization, the one closest to the hospital admission date was used.

SARS-CoV-2 subvariant lineage was then categorized into SIG variant classes (i.e., VBM, VOI, VOC, VOHC) and by WHO labels (e.g., Alpha, Beta, Gamma, etc.) using frequency distributions. To account for changes in SIG variant classifications over time, severe COVID-19 disease hospitalizations with an associated SARS-CoV-2 variant lineage were categorized based on the SIG variant class designated to the SARS-CoV-2 variant lineage at the time of the hospitalization. For example, based on the Delta variant being designated as VOC on 15 June 2021 and VBM on 14 April 2022; severe COVID-19 disease hospitalizations with B.1.617.2 lineage (i.e., Delta variant) that occurred between 15 June 2021 and 13 April 2022 were classified as VOC, while severe COVID-19 disease hospitalizations with the same lineage that occurred on or after 14 April 2022 were classified as VBM. In addition, the heterogeneity in the risk of severe COVID-19 disease by

SARS-CoV-2 subvariant lineage following receipt of the Pfizer-BioNTech COVID-19 vaccine was assessed. Risk of severe COVID-19 disease were analyzed separately by SIG variant classes or WHO labels, particularly in variants that posed a significant risk to public health in the US (e.g., Omicron variant).

9.9.3. Missing Values

No VHA members had missing date of birth or sex data. A very small minority of individuals had both sexes documented. Those members were categorized as "unknown" (Table 3). Individuals with missing race/ethnicity or BMI data were also categorized as "unknown" (Table 4).

9.9.4. Sensitivity Analyses

No sensitivity analyses were performed in this final report.

9.9.5. Amendments to the Statistical Analysis Plan

Not applicable.

9.10. Quality Control

For this final report, data for the study were extracted from EMR databases in the CDW of the VHA. Each data content area in the CDW was subjected to similar checks, from high-level variable name/type checks, to detailed trending comparisons. As an example, the diagnostic data was subject to the following checks:

- Checked that variables referenced in the data dictionary exist and are of appropriate length and type.
- Checked the diagnosis code type (i.e., ICD-9-CM, ICD-10-CM) was correctly matched with the codes defining specific diagnoses of interest.
- Assessed percentages and rates in light of the literature and substantive knowledge.
- Checked percentages and rates of missing data.
- Checked that both inpatient and outpatient (which include ED visits) diagnosis codes were captured.

Data retrieval was coordinated by experienced programmers/analysts. Double programming by two separate programmers/analysts was performed to program the retrieval of each data element from the electronic databases. A third programmer/analyst ran the programs on VA's servers to retrieve and analyze the data. Results/datasets were examined, and discrepancies were resolved. All tables were reviewed by the project manager and the principal investigator and evaluated for internal consistency of counts and totals. All calculated variables were checked against the component variables (cross tabs) to ensure accuracy. For example, categorical age was compared with continuous age to confirm that each category of age contained only individuals of the expected age ranges within that category.

9.11. Protection of Human Subjects

Patient Information and Consent

Protected health information (PHI) were not reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research, or for other research for which the use or disclosure of PHI was permitted by applicable regulation. The PHI obtained were the minimum necessary to conduct the research. Information regarding Institutional Review Board (IRB) exemption is provided in the below section. The project was led by the VHA, with Dr. Dalle Lucca serving as the principal investigator. The Clinical Epidemiology Program (CEP) at White River Junction VA Medical Center conducted this safety surveillance study with sponsorship from Pfizer and assistance from Analysis Group. CDW VHA data were not transferred off the VA servers to either Pfizer or Analysis Group.

All parties complied with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure personal data protection. Given the sensitive nature of healthcare data, comprehensive security measures were implemented to ensure the confidentiality, integrity, and protection of individuals enrolled in the VHA. Only VA employees, including those with WOC employee status, who have completed necessary VA training and have proper clearance accessed and analyzed data on secure VA servers and behind necessary firewalls, under the direction and supervision of Dr. Dalle Lucca. Only summary statistics based on these data were shared with study investigators who were not VA employees. Other measures included omitting individual names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

To protect the rights and freedoms of natural individuals with regard to the processing of personal data, when study data were compiled for transfer to Pfizer and other authorized parties, any individual names were removed and were replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties were identified by this single, individual-specific code. In case of data transfer, Pfizer maintained high standards of confidentiality and protection of individuals' personal data consistent with the vendor contract, and applicable privacy laws.

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

The study protocol that outlined the plan for the signal detection and signal evaluation phases of the study, including the analyses presented in this final study report, was determined on 10 February 2021 to be exempt from IRB review by the VINNE, White River Junction VA Medical Center, White River Junction, VT in accordance with 38 CFR 16. On 17 February 2021 the study protocol was reviewed and determined to be exempt from future research safety and security review by the Subcommittee on Research Safety and Security (SRSS), VA Innovation and Research Review System (VAIRRS). Finally, on 26 February 2021, the study protocol was granted approval by Designated Member Review of the Northern New England Research Consortium VA Medical Centers (NNERC VAMC) Research and Development Committee and the Associate Chief of Staff for Research (ACOS/R). All correspondence with the IRB was retained and forwarded to Pfizer.

Research Standards of the Study Conduct

The study was 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 Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE),[64] Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA),[65] International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.[66]

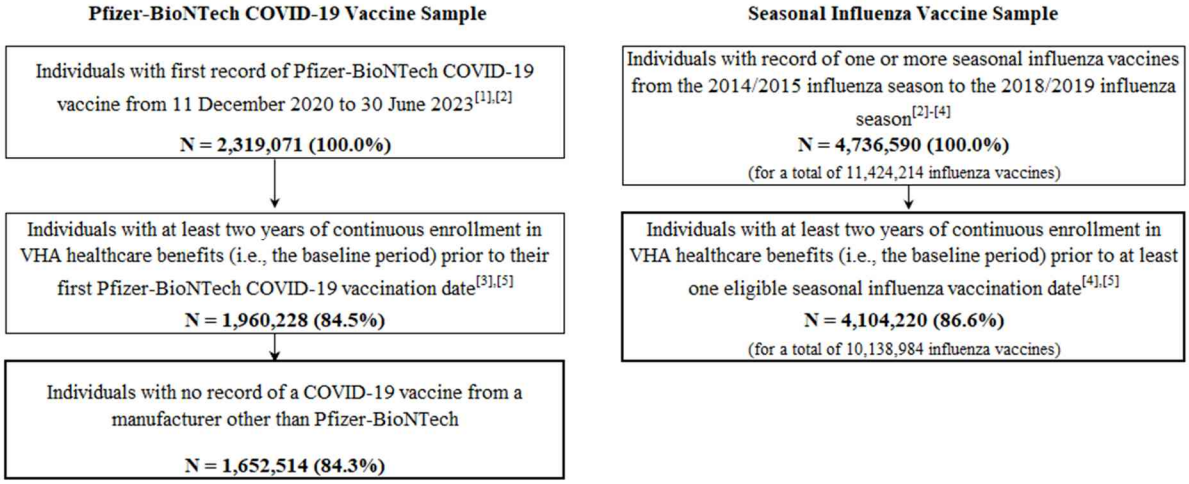
10. RESULTS

Per VHA policy, small counts (N<11) were redacted to protect patient privacy throughout this final report. However, for the chart-confirmed myocarditis/pericarditis results in Section 10.3.2.2, only small counts of N<3 were redacted given the importance of these results, and there was permission from the VHA to do this given these results were based on VHA data and no CMS data.

10.1. Participants

Figure 5 presents a summary of the sample selection for this final report. After applying all eligibility criteria, the Pfizer-BioNTech COVID-19 vaccine sample consisted of a total of 1,652,514 eligible individuals who received their first Pfizer-BioNTech COVID-19 vaccination from 11 December 2020 to 30 June 2023 (end of data collection). The seasonal influenza vaccine sample consisted of a total of 4,104,220 eligible individuals who received at least one seasonal influenza vaccine from the 2014/2015 influenza season to the 2018/2019 influenza season. Among the individuals in the seasonal influenza sample that satisfied the study eligibility criteria, a total of 10,138,984 seasonal influenza vaccinations were observed (for an average of 2.47 seasonal influenza vaccines per individual).

Figure 5. Sample Selection of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019) in the VHA Database



Abbreviations: COVID-19, coronavirus disease 2019; EUA, emergency use authorization; FDA, Food and Drug Administration; VHA, Veterans Health Administration.

Notes:

[1] 11 December 2020 was the date when the FDA issued the EUA for the Pfizer-BioNTech COVID-19 Vaccine; 30 June 2023 was the end of data collection.

[2] All data records, including vaccination records, that were observed prior to an individual's date of birth and after an individual's date of death were not included.

[3] Influenza seasons started on 1 October of one year and ended on 31 May of the next year (e.g., the 2014/2015 influenza season spanned 1 October 2014 - 31 May 2015).

[4] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.

[5] Baseline period was defined as the two years prior to (and not including) the vaccination date.

[6] To assess the timing from COVID-19 vaccination to influenza vaccination, the date of the first COVID-19 vaccination dose was used. For individuals with multiple influenza vaccination records in one influenza season, the earliest record was used.

10.2. Descriptive Data

10.2.1. Baseline Characteristics

10.2.1.1. Pfizer-BioNTech COVID-19 Vaccine Sample

Table 3 and Table 4 describe the baseline demographic and clinical characteristics, respectively, of individuals who received the Pfizer-BioNTech COVID-19 and seasonal influenza vaccines. The mean age of the Pfizer-BioNTech COVID-19 vaccine recipients from 11 December 2020 to 30 June 2023 was 64.0 years (median: 67.4 years) and the sample included 89.8% males and 59.7% white non-Hispanic, 22.0% Black, 7.3% Hispanic ethnicity any race, and 1.5% Asian individuals. Vaccine recipients resided in the South (45.5%), West (22.5%), Midwest (19.0%), and Northeast (12.5%; Table 3). Previous and current smoking status was documented in EMR records for 15.3% of individuals and 31.6% of those with a known BMI had a BMI ≥30 (obese and severe obesity; Table 4). History of anaphylaxis/allergic reactions was rare (<2%). The mean CCI score was 0.9 (median: 0.0), and 11.1% of individuals were hospitalized in the two years preceding the Pfizer-BioNTech COVID-19 vaccine. Comorbidities affecting >10% of the sample included hypertension (54.9%), hyperlipidemia (52.0%), diabetes (26.8%), cardiovascular conditions (14.6%; excludes hypertension), chronic kidney disease/dialysis (11.2%), COPD/interstitial lung disease (11.1%), and cancer (11.0%). Approximately one-third of individuals in the Pfizer-BioNTech COVID-19 vaccine sample were immunized for seasonal influenza between 1 October 2020 and the date of their first Pfizer-BioNTech COVID-19 vaccination. Non-seasonal immunizations were rare (<10% users) in the two years before Pfizer-BioNTech COVID-19 vaccine, except for the shingles vaccine which was received by 20.1% of the individuals in this sample (Table 4).

10.2.1.2. Seasonal Influenza Vaccine Sample

Baseline demographic and clinical characteristics of recipients of the seasonal influenza vaccine (at the time of their most recent seasonal influenza vaccination during the 2014/2015 through 2018/2019 influenza seasons) were generally similar to those of recipients of Pfizer-BioNTech COVID-19 vaccine at the time of their first dose (standardized difference <10%). However, a few exceptions with standardized differences ≥10% were noted, as summarized below. With respect to demographic characteristics, compared to the Pfizer-BioNTech COVID-19 vaccine sample, the seasonal influenza vaccine sample had a higher proportion of individuals age ≥65 years old (60.8% vs. 55.0%, standardized difference 11.9%), a higher proportion of males (92.7% vs. 89.8%, standardized difference 10.4%), a higher proportion of white non-Hispanic individuals (69.7% vs. 59.7%, standardized difference 21.0%), and a lower proportion of Black individuals (15.4% vs. 22.0%, standardized difference 17.0%), though similar proportions of Hispanic ethnicity, any race (6.3% vs. 7.3%, standardized difference 3.9%) and Asian individuals (1.0% vs 1.5%, standardized difference 4.9%; Table 3). With respect to clinical characteristics, the Pfizer-BioNTech COVID-19 vaccine sample had a lower proportion of individuals with known BMI and slightly lower mean CCI than the seasonal influenza vaccine sample (known BMI: 68.4% vs. 82.6%, standardized difference 33.4%; mean CCI: 0.9 vs. 1.1, standardized difference 11.2%). The Pfizer-BioNTech COVID-19 vaccine sample had comparable proportions of comorbidities with the seasonal influenza vaccine sample, with the exceptions

of hypertension, hyperlipidemia, COPD/interstitial lung disease, and HBV, which was higher among seasonal influenza vaccine recipients (hypertension: 62.8% vs 54.9%, standardized difference 16.2%; hyperlipidemia: 59.2% vs 52.0%, standardized difference 14.6%; COPD/lung disease: 16.0% vs. 11.1%, standardized difference 14.4%; HBV: 3.1% vs. 0.3%, standardized difference 22.2%;). Compared to the Pfizer-BioNTech COVID-19 vaccine sample, the seasonal influenza vaccine sample had a higher proportion of individuals immunized with pneumococcal conjugate, Tdap or Td, and pneumococcal polysaccharide vaccines and lower proportion immunized with shingles vaccine (18.4% vs. 3.8%, 16.2% vs. 9.9%, 14.5% vs. 9.1%, and 8.4% vs 20.1%, respectively; standardized differences 47.7%, 18.8%, 16.8%, and 33.9%, respectively; Table 4).

The baseline demographic and clinical characteristics assessed across all seasonal influenza vaccinations observed in the seasonal influenza vaccine sample (N=10,138,984 vaccinations) were similar to those assessed at the time of the most recent seasonal influenza vaccine for each individual in this sample (e.g., mean age: 66.2 years vs. 65.9 years; males 93.3% vs. 92.7%; white non-Hispanic: 70.7% vs. 69.7%; South VHA service area: 43.2 vs. 43.6% [Table 3]; mean BMI: 30.1 vs. 29.9; history of anaphylaxis/allergic reactions: 1.4% vs. 1.1%; hospitalization in prior two years: 13.9% vs. 14.5%, mean CCI: 1.0 vs. 1.1, respectively [Table 4]).

Table 3. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N=1,652,514 individuals	**N=4,104,220 individuals**		**N=10,138,984 vaccines (average 2.47 vaccines/individual)**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Age (years)[3], mean ± SD [median]	64.0 ± 15.6 [67.4]	65.9 ± 15.5 [68.7]	11.9%*	66.2 ± 14.1 [68.1]
Categorical, n (%)				
<12	0 (0.0)	0 (0.0)	0.0%	0 (0.0)
12–<18	0 (0.0)	<11 (<0.0)	0.1%	<11 (<0.0)
18–<25	1,629 (0.1)	NR‡	0.3%	7,787 (0.1)
25–<30	24,298 (1.5)	73,852 (1.8)	2.6%	131,084 (1.3)
30–<40	143,761 (8.7)	285,643 (7.0)	6.5%	532,705 (5.3)
40–<50	161,063 (9.7)	305,601 (7.4)	8.2%	682,598 (6.7)
50–<65	413,334 (25.0)	938,295 (22.9)	5.0%	2,501,538 (24.7)
≥65	908,429 (55.0)	2,496,409 (60.8)	11.9%*	6,283,269 (62.0)
Sex[4], n (%)				
Male	1,484,197 (89.8)	3,806,411 (92.7)	10.4%*	9,456,282 (93.3)
Race/ethnicity[5], n (%)				
White non-Hispanic	986,593 (59.7)	2,859,177 (69.7)	21.0%*	7,164,859 (70.7)
Black	363,159 (22.0)	631,076 (15.4)	17.0%*	1,516,101 (15.0)
Hispanic ethnicity, any race	120,403 (7.3)	259,117 (6.3)	3.9%	630,725 (6.2)
Asian	25,612 (1.5)	40,969 (1.0)	4.9%	92,014 (0.9)

Table 3. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	Pfizer-BioNTech COVID-19 Vaccine Sample	Seasonal Influenza Vaccine Sample	Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample	Seasonal Influenza Vaccine Sample[2]
	N=1,652,514 individuals	N=4,104,220 individuals		N=10,138,984 vaccines (average 2.47 vaccines/individual)
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Native Hawaiian or Pacific Islander	13,652 (0.8)	31,088 (0.8)	0.8%	76,837 (0.8)
American Indian or Alaskan Native	9,970 (0.6)	27,047 (0.7)	0.7%	64,241 (0.6)
Two or more races	13,452 (0.8)	29,599 (0.7)	1.1%	71,329 (0.7)
Unknown	119,673 (7.2)	226,147 (5.5)	7.1%	522,878 (5.2)
VHA service area - US region[6], n (%)				
South	752,357 (45.5)	1,788,018 (43.6)	3.9%	4,381,504 (43.2)
Midwest	313,302 (19.0)	905,928 (22.1)	7.7%	2,332,470 (23.0)
West	371,408 (22.5)	829,638 (20.2)	5.5%	2,007,404 (19.8)
Northeast	205,970 (12.5)	530,666 (12.9)	1.4%	1,272,740 (12.6)
Other	7,510 (0.5)	46,425 (1.1)	7.6%	139,780 (1.4)
Unknown	1,967 (0.1)	3,545 (0.1)	1.0%	5,086 (0.1)

Abbreviations: COVID-19, coronavirus disease 2019; NR, not reported; SD, standard deviation; Std. Diff., standardized difference; US, United States; VHA, Veterans Health Administration.

Notes:

* Denotes std. diff > 10%.

‡ Certain counts were not reported to protect patient privacy.

[1] Baseline period was defined as the two years prior to (and not including) the vaccination date.

Table 3. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N=1,652,514 individuals	**N=4,104,220 individuals**		**N=10,138,984 vaccines (average 2.47 vaccines/individual)**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*

[2] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.
[3] Age on the date of Pfizer-BioNTech COVID-19 vaccination (for Pfizer-BioNTech COVID-19 vaccine recipients) or date of seasonal influenza vaccination (for active comparators), was reported.
[4] Individuals may have had recorded unknown sex category.
[5] If multiple categories were noted in the data, individuals were classified as two or more races, with the exception of Hispanic ethnicity. If Hispanic ethnicity was recorded for any individual, they were classified as Hispanic. Individuals with both known and unknown race categories recorded in the data were classified into their known category.
[6] The region information associated with the most recent healthcare encounter prior to index date was used. Midwest included IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; Northeast included CT, ME, MA, NH, NJ, NY, PA, RI, VT; South included AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West included AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; Other included Puerto Rico.

Table 4. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	Pfizer-BioNTech COVID-19 Vaccine Sample	Seasonal Influenza Vaccine Sample[2]	Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample	Seasonal Influenza Vaccine Sample[2]
	N=1,652,514 individuals	N=4,104,220 individuals		N=10,138,984 vaccines (average 2.47 vaccines/individual)
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Smoking[3], n (%)	252,707 (15.3)	740,491 (18.0)	7.4%	1,954,250 (19.3)
BMI[4]				
BMI known, n (%)	1,130,630 (68.4)	3,388,778 (82.6)	33.4%*	8,502,441 (83.9)
BMI (kg/m^2), mean ± SD [median]	30.2 ± 5.9 [29.5]	29.9 ± 6.0 [29.2]	5.3%	30.1 ± 6.0 [29.4]
BMI category, n (%)				
Underweight (<18.5)	8,519 (0.5)	35,939 (0.9)	4.3%	69,202 (0.7)
Normal weight (18.5–<25)	195,272 (11.8)	651,926 (15.9)	11.8%*	1,509,238 (14.9)
Overweight (25–<30)	404,813 (24.5)	1,210,859 (29.5)	11.3%*	3,073,953 (30.3)
Obese (30–<40)	450,759 (27.3)	1,284,685 (31.3)	8.9%	3,319,115 (32.7)
Severe obesity (≥40)	71,267 (4.3)	205,369 (5.0)	3.3%	530,933 (5.2)
Unknown	521,884 (31.6)	715,442 (17.4)	33.4%*	1,636,543 (16.1)
History of anaphylaxis/allergic reactions[5], n (%)	18,921 (1.1)	43,197 (1.1)	0.9%	144,751 (1.4)
Previous anaphylaxis to vaccine component[5], n (%)	355 (0.0)	383 (0.0)	1.0%	752 (0.0)
History of hospitalizations				

Table 4. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	Pfizer-BioNTech COVID-19 Vaccine Sample	Seasonal Influenza Vaccine Sample[2]	Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample	Seasonal Influenza Vaccine Sample[2]
	N=1,652,514 individuals	N=4,104,220 individuals		N=10,138,984 vaccines (average 2.47 vaccines/individual)
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Individuals with at least one hospitalization, n (%)	183,614 (11.1)	593,111 (14.5)	10.0%*	1,410,548 (13.9)
Number of hospitalizations, mean ± SD [median]	0.2 ± 0.9 [0.0]	0.3 ± 1.1 [0.0]	8.4%	0.3 ± 1.0 [0.0]
CCI[5,6], mean ± SD [median]	0.9 ± 1.5 [0.0]	1.1 ± 1.6 [0.0]	11.2%*	1.0 ± 1.5 [0.0]
Frailty Index score[7], mean ± SD [median]	0.1 ± 0.5 [0.0]	0.1 ± 0.6 [0.0]	7.2%	0.1 ± 0.6 [0.1]
Frailty category[7], n (%)				
Non-frail (≤0.25)	1,088,319 (65.9)	2,605,080 (63.5)	5.0%	6,337,116 (62.5)
Frail (>0.25)	564,195 (34.1)	1,499,140 (36.5)		3,801,868 (37.5)
Comorbidities[5], n (%)				
Autoimmune disease	56,768 (3.4)	178,716 (4.4)	4.8%	559,942 (5.5)
Asthma	80,165 (4.9)	191,135 (4.7)	0.9%	502,730 (5.0)
Bleeding diathesis or condition associated with prolonged bleeding	35,766 (2.2)	110,459 (2.7)	3.4%	268,043 (2.6)
Cancer	181,048 (11.0)	535,846 (13.1)	6.5%	1,407,457 (13.9)
Cardiovascular conditions[8]	241,263 (14.6)	747,607 (18.2)	9.8%	1,732,666 (17.1)
Chronic kidney disease/dialysis	185,539 (11.2)	535,779 (13.1)	5.6%	1,321,897 (13.0)

Table 4. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N=1,652,514 individuals	**N=4,104,220 individuals**		**N=10,138,984 vaccines (average 2.47 vaccines/individual)**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
COPD/interstitial lung disease	183,233 (11.1)	656,949 (16.0)	14.4%*	1,631,855 (16.1)
Diabetes mellitus (i.e., Type 1 or 2 diabetes)	442,661 (26.8)	1,271,092 (31.0)	9.2%	3,291,354 (32.5)
Down syndrome	<11 (<0.0)	196 (0.0)	1.0%	1,148 (0.0)
Sickle cell disease	2,090 (0.1)	5,337 (0.1)	0.1%	18,838 (0.2)
HBV	4,405 (0.3)	127,547 (3.1)	22.2%*	819,018 (8.1)
HCV	29,825 (1.8)	126,222 (3.1)	8.2%	295,854 (2.9)
HIV	9,719 (0.6)	24,142 (0.6)	0.0%	67,032 (0.7)
Hyperlipidemia	859,784 (52.0)	2,431,420 (59.2)	14.6%*	6,446,770 (63.6)
Hypertension	906,723 (54.9)	2,578,040 (62.8)	16.2%*	6,665,861 (65.7)
Liver disease	80,442 (4.9)	177,094 (4.3)	2.6%	403,290 (4.0)
Neurological disease	159,272 (9.6)	463,563 (11.3)	5.4%	1,197,857 (11.8)
Other immune deficiencies[9]	9,056 (0.5)	25,154 (0.6)	0.9%	75,068 (0.7)
Solid organ transplant	303 (0.0)	535 (0.0)	0.4%	1,351 (0.0)
VTE	36,411 (2.2)	94,635 (2.3)	0.7%	227,460 (2.2)
Immunization history[10], n (%)				

Table 4. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N=1,652,514 individuals	**N=4,104,220 individuals**		**N=10,138,984 vaccines (average 2.47 vaccines/individual)**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Seasonal influenza vaccine (2020/2021, 2021/2022, or 2022/2023 influenza seasons)	570,177 (34.5)	-	-	-
Tdap or Td	164,281 (9.9)	666,502 (16.2)	18.8%*	1,896,276 (18.7)
Chickenpox (varicella)	651 (0.0)	3,914 (0.1)	2.2%	14,876 (0.1)
Shingles (herpes zoster recombinant and/or live)	332,431 (20.1)	346,001 (8.4)	33.9%*	967,210 (9.5)
HPV	3,982 (0.2)	3,814 (0.1)	3.6%	6,566 (0.1)
Pneumococcal conjugate	63,255 (3.8)	756,347 (18.4)	47.7%*	2,291,613 (22.6)
Pneumococcal polysaccharide	150,362 (9.1)	595,562 (14.5)	16.8%*	1,549,221 (15.3)
Hepatitis A	16,934 (1.0)	40,770 (1.0)	0.3%	94,394 (0.9)
Hepatitis B	22,665 (1.4)	56,889 (1.4)	0.1%	138,405 (1.4)
MenACWY and MenB	2,960 (0.2)	7,698 (0.2)	0.2%	14,065 (0.1)
Haemophilus influenza type b	584 (0.0)	1,518 (0.0)	0.1%	3,523 (0.0)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICD-9/10-CM, International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification; MenACWY, meningococcal conjugate; MenB, serogroup B meningococcal; SD, standard deviation; Std. Diff., standardized difference; TDap, diphtheria, tetanus and (acellular) pertussis; Td, diphtheria and tetanus; VTE, venous thromboembolism.

Table 4. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023) or Seasonal Influenza Vaccine (from 1 October 2014 to 31 May 2019)[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N=1,652,514 individuals	**N=4,104,220 individuals**		**N=10,138,984 vaccines (average 2.47 vaccines/individual)**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*

Notes:
* Denotes std. diff > 10%.
[1] Baseline period was defined as the two years prior to (and not including) the vaccination date.
[2] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.
[3] Smoking status was determined using ICD codes listed in Annex 1. Appendix 9. Smoking status represented current and/or history of smoking as documented in individuals' records during the baseline period.
[4] Most recent BMI record during the baseline period prior to vaccination date was included and was calculated based on individuals' height and weight data as dividing weight in kilograms (kg) by height in meters (m) squared. Individuals with missing BMI or those with BMI <15 or >60 were categorized as "Unknown".
[5] Identified based on ICD 9/10 diagnosis codes, as listed in the Annex 1. Appendix 9.
[6] For a full list conditions included in the CCI, and associated codes, see Annex 1. Appendix 9.
[7] Based on Segal et al. 2017, frailty index was calculated using an algorithm of 21 variables related to individuals' demographic and clinical characteristics, and a threshold of >0.25 was used to identify frail vs. non-frail individuals. Age was included in the frailty calculation as a categorical variable using 5-year increments for those 65 and older, with those younger than 65 grouped into one category.
[8] Cardiovascular conditions included heart failure, CAD, and cardiomyopathies.
[9] Other immune deficiencies included sarcoidosis, deficiency of humoral immunity, disorders of plasma protein metabolism, immunodeficiency with predominantly antibody defects, combined immunodeficiencies, immunodeficiency associated with other major defects, common variable immunodeficiency, other immunodeficiencies, and other disorders involving the immune mechanism, not elsewhere classified.
[10] Immunization history was defined as immunizations that were received during the two-year baseline period prior to receipt of Pfizer-BioNTech COVID-19 vaccination or seasonal influenza vaccination.

10.2.2. Vaccination Utilization Patterns

The month and year of first Pfizer-BioNTech COVID-19 vaccination from 11 December 2020 to 30 June 2023 were described in Section 10.2.

Table 5 presents additional details on Pfizer-BioNTech COVID-19 vaccine utilization. Individuals with at least one healthcare encounter in the VHA from 11 December 2020 to 30 June 2023 served as the expected number of individuals who would be eligible for Pfizer-BioNTech COVID-19 vaccine, as they had been actively receiving care through the VHA during the time period when Pfizer-BioNTech COVID-19 vaccine was available. Among 7,398,958 individuals with at least one healthcare encounter during the period when administration of Pfizer-BioNTech COVID-19 vaccines was assessed for this final report, 2,319,071 (31.3%) individuals received at least one Pfizer-BioNTech COVID-19 vaccine dose. Among the latter, 1,960,228 (84.5%) individuals satisfied the two years of continuous enrollment in VHA healthcare benefits eligibility criterion. Most of these individuals (N=1,652,514; 84.3%) only received the Pfizer-BioNTech COVID-19 vaccine and a minority (N=307,714; 15.7%) received COVID-19 vaccine(s) from both Pfizer-BioNTech and other manufacturer(s) (88.4% Moderna; 13.3% Johnson & Johnson; 0.2% AstraZeneca, 0.1% other vaccine manufacturers, and 0.2% unknown vaccine manufacturers [Table 5]). Among the individuals that received COVID-19 vaccine(s) from both Pfizer-BioNTech and other manufacturer(s), 107,257 (34.9%) received the Pfizer-BioNTech COVID-19 vaccine primary series followed by at least one monovalent booster dose from another manufacturer.

Table 5. Vaccine Utilization Patterns among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (From 11 December 2020 to 30 June 2023)

Individuals with at least one healthcare encounter in the VHA from 11 December 2020 to 30 June 2023	**N=7,398,958**
Individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	2,319,071 (31.3)
Individuals who satisfy the two years of continuous enrollment in VHA healthcare benefits sample eligibility criteria, n (% with at least one dose)	1,960,228 (84.5)
Individuals who received COVID-19 vaccine from Pfizer-BioNTech only, n (% with continuous enrollment)	1,652,514 (84.3)
Individuals who received COVID-19 vaccine from both Pfizer-BioNTech and another manufacturer[1], n (% with continuous enrollment)	307,714 (15.7)
Moderna, n (% with COVID-19 vaccine from multiple manufacturers)	272,033 (88.4)
Johnson & Johnson (Janssen), n (% with COVID-19 vaccine from multiple manufacturers)	40,832 (13.3)
AstraZeneca, n (% with COVID-19 vaccine from multiple manufacturers)	645 (0.2)
Other vaccines, n (% with COVID-19 vaccine from multiple manufacturers)	192 (0.1)
Unknown vaccine manufacturer, n (% with COVID-19 vaccine from multiple manufacturers)	675 (0.2)
Individuals who received Pfizer-BioNTech COVID-19 vaccine primary series followed by at least one monovalent booster dose from another manufacturer, n (% with COVID-19 vaccine from multiple manufacturers)	107,257 (34.9)
Individuals who subsequently received Pfizer-BioNTech COVID-19 vaccine bivalent booster dose, n (% who received Pfizer-BioNTech COVID-19 vaccine primary series followed by monovalent booster dose(s) from another manufacturer)	12,235 (11.4)
Individuals who subsequently received COVID-19 vaccine bivalent booster dose from another manufacturer, n (% who received Pfizer-BioNTech COVID-19 vaccine primary series followed by monovalent booster dose(s) from another manufacturer)	46,696 (43.8)

Abbreviations: COVID-19, coronavirus disease 2019; VHA, Veterans Health Administration.
Note:
[1] Individuals may have had multiple records of COVID-19 vaccines from other manufacturers, which could have been administered either before or after vaccination with Pfizer-BioNTech COVID-19 vaccine.

Table 6 describes the care setting where Pfizer-BioNTech COVID-19 vaccine doses were administered, as well as completion rates for monovalent doses (i.e., two dose, three dose/booster dose, and four dose/booster dose) and bivalent doses, and the timing of doses among Pfizer-BioNTech COVID-19 vaccine recipients. The most common care setting for the first monovalent, second monovalent, third/booster monovalent, fourth/booster monovalent, and first bivalent doses of Pfizer-BioNTech COVID-19 vaccine was outpatient clinics (55.7%, 57.7%, 57.5%, 67.2%, and 20.0%, respectively). The majority (96.2%) of individuals in the Pfizer-BioNTech COVID-19 vaccine sample received the primary series monovalent doses during the 11 December 2020 to 30 June 2023 assessment period. Of the 1,589,777 individuals who completed two monovalent Pfizer-BioNTech COVID-19 vaccine doses, 64.9% received the second dose exactly 21 days after the first dose, as recommended per the product label. A total of 868,181 (52.5%) individuals in the Pfizer-BioNTech COVID-19 vaccine sample received three monovalent doses, with a median time between the second monovalent and third monovalent dose/booster dose of 237.0 days (7.9 months). A total of 275,601 (16.7%) individuals in the Pfizer-BioNTech COVID-19 vaccine sample received four monovalent doses, among whom 68.4% received their fourth monovalent dose/booster dose 6-8 months after their third monovalent dose/booster dose of the Pfizer-BioNTech COVID-19 vaccine. A total of 365,972 (22.2%) individuals in the Pfizer-BioNTech COVID-19 vaccine sample received one bivalent dose, with a median time between the last monovalent dose and first bivalent dose of 301.0 days (10.0 months). A small proportion of individuals (<2%) received their first bivalent dose as their first or second COVID-19 vaccine dose.

Table 6. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023)

	Pfizer-BioNTech COVID-19 Vaccine Sample
	N=1,652,514
Pfizer-BioNTech COVID-19 Vaccine Monovalent Dose 1[1]	**N=1,649,168**
Care setting where first monovalent Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Outpatient clinic	920,826 (55.7)
Inpatient ward	3,325 (0.2)
Pharmacy	16 (0.0)
Unknown[2]	725,001 (43.9)
Monovalent dose completion rates	
Two dose completion rate, n (%)	
Individuals *with* two doses observed	1,589,777 (96.2)
Individuals *without* two doses observed	59,391 (3.6)
Dose 3/booster dose completion rate, n (%)	
Individuals *with* three doses observed	868,181 (52.5)
Individuals *without* three doses observed	780,987 (47.4)
Dose 4/booster dose completion rate, n (%)	
Individuals *with* four doses observed	275,601 (16.7)
Individuals *without* four doses observed	1,373,567 (83.3)
Pfizer-BioNTech COVID-19 Vaccine Monovalent Dose 2[1]	**N=1,589,777**
Care setting where second monovalent Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Outpatient clinic	916,839 (57.7)
Inpatient ward	NR‡
Pharmacy	<11 (<0.0)
Unknown[2]	671,159 (42.2)
Different settings for first and second doses[3], n (%)	1,745 (0.1)
Time gap between first monovalent and second monovalent Pfizer-BioNTech COVID-19 vaccine doses (days)	
Mean ± SD	25.6 ± 30.0
Median [IQR]	21.0 [21.0, 21.0]
Categorical[4], n (%)	
≤16 days	13,237 (0.8)
17-20 days	164,153 (10.3)
21 days	1,031,877 (64.9)
22-27 days	226,493 (14.2)

Table 6. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023)

	Pfizer-BioNTech COVID-19 Vaccine Sample
	N=1,652,514
28 days	41,245 (2.6)
29-35 days	53,955 (3.4)
36-42 days	14,414 (0.9)
≥43 days	44,403 (2.8)
Pfizer-BioNTech COVID-19 Vaccine Monovalent Dose 3/Booster Dose[5]	**N=868,181**
Care setting where third monovalent/booster Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Outpatient clinic	498,808 (57.5)
Inpatient ward	2,339 (0.3)
Pharmacy	1,003 (0.1)
Unknown[2]	366,031 (42.2)
Time gap between second monovalent and third monovalent/booster Pfizer-BioNTech COVID-19 vaccine doses (days)	
Mean ± SD	242.2 ± 60.9
Median [IQR]	237.0 [213.0, 264.0]
Categorical, n (%)	
≤30 days (month 1)	9,238 (1.1)
31-60 days (month 2)	2,251 (0.3)
61-90 days (month 3)	2,319 (0.3)
91-120 days (month 4)	3,462 (0.4)
121-150 days (month 5)	7,111 (0.8)
151-180 days (month 6)	24,915 (2.9)
181-210 days (month 7)	151,536 (17.5)
211-240 days (month 8)	272,954 (31.4)
241-270 days (month 9)	209,862 (24.2)
≥271 days (month 10)	184,533 (21.3)
Pfizer-BioNTech COVID-19 Vaccine Monovalent Dose 4/Booster Dose[6]	**N=275,601**
Care setting where fourth monovalent/booster Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Outpatient clinic	185,340 (67.2)
Inpatient ward	995 (0.4)

Table 6. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023)

	Pfizer-BioNTech COVID-19 Vaccine Sample
	N=1,652,514
Pharmacy	55 (0.0)
Unknown[2]	89,211 (32.4)
Time gap between third monovalent/booster and fourth monovalent/booster Pfizer-BioNTech COVID-19 vaccine doses (days)	
Mean ± SD	207.3 ± 53.7
Median [IQR]	203.0 [181.0, 236.0]
Categorical, n (%)	
≤30 days (month 1)	3,375 (1.2)
31-60 days (month 2)	1,338 (0.5)
61-90 days (month 3)	1,436 (0.5)
91-120 days (month 4)	3,344 (1.2)
121-150 days (month 5)	16,165 (5.9)
151-180 days (month 6)	42,565 (15.4)
181-210 days (month 7)	90,808 (32.9)
211-240 days (month 8)	55,275 (20.1)
241-270 days (month 9)	29,640 (10.8)
271-300 days (month 10)	19,715 (7.2)
301-330 days (month 11)	8,031 (2.9)
331-360 days (month 12)	2,014 (0.7)
≥361 days (month 13)	1,895 (0.7)
Pfizer-BioNTech COVID-19 Vaccine Bivalent Dose 1	**N=365,972**
Care setting where first bivalent Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Outpatient clinic	73,196 (20.0)
Inpatient ward	1,946 (0.5)
Pharmacy	47 (0.0)
Unknown[2]	290,783 (79.5)
Time gap between last monovalent and first bivalent Pfizer-BioNTech COVID-19 vaccine doses (days)[7]	
Mean ± SD	302.1 ± 149.0
Median [IQR]	301.0 [175.0, 384.0]
Categorical, n (%)	
≤30 days (month 1)	3,815 (1.0)

Table 6. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023)

	Pfizer-BioNTech COVID-19 Vaccine Sample
	N=1,652,514
31-60 days (month 2)	621 (0.2)
61-90 days (month 3)	6,546 (1.8)
91-120 days (month 4)	13,720 (3.7)
121-150 days (month 5)	27,670 (7.6)
151-180 days (month 6)	52,089 (14.2)
181-210 days (month 7)	37,503 (10.2)
211-240 days (month 8)	16,179 (4.4)
241-270 days (month 9)	11,722 (3.2)
271-300 days (month 10)	14,242 (3.9)
301-330 days (month 11)	22,650 (6.2)
331-360 days (month 12)	36,633 (10.0)
361-390 days (month 13)	38,800 (10.6)
391-420 days (month 14)	21,982 (6.0)
≥421 days (month 15)	61,800 (16.9)

Abbreviations: CDC: US Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; IQR, interquartile range; NR, not reported; SD, standard deviation; VHA, Veterans Health Administration.

Notes:

‡ Certain counts were not reported to protect patient privacy.

[1] Individuals' first record of Pfizer-BioNTech COVID-19 vaccination was categorized as the first dose. Among individuals with only two Pfizer-BioNTech COVID-19 vaccination records, the second vaccination record was categorized as the second dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination, the vaccination date closest to 21 days after the first vaccination dose was categorized as the second dose. If multiple vaccinations for the same person were observed within 3 days of each other, only the first of these was included in the analysis. 3,346 individuals received a bivalent dose as their first dose.

[2] This category included individuals with vaccination records without care setting information available or individuals who had documentation of receiving one vaccination dose in several different care settings so the care setting could not be determined.

[3] Individuals who received one of their two vaccine doses in an unknown setting were excluded from this count.

[4] According to the CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines, the second dose of the Pfizer-BioNTech COVID-19 vaccine should be administered as close to the recommended 21 days after the first dose as possible, but not earlier than 21 days. However, second doses administered within a grace period of 4 days earlier than the recommended date for the second dose are still considered valid. If it is not feasible to adhere to the recommended interval and a delay in vaccination is unavoidable, the second dose of the Pfizer-BioNTech COVID-19 vaccine may be administered up to 6 weeks (42 days) after the first dose (source: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html).

[5] Records observed after the second monovalent dose were considered the third monovalent dose/booster dose. Among individuals with only one Pfizer-BioNTech COVID-19 vaccination record after their second monovalent dose, that vaccination record was categorized as the third monovalent dose/booster dose. Among

Table 6. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from 11 December 2020 to 30 June 2023)

	Pfizer-BioNTech COVID-19 Vaccine Sample
	N=1,652,514

individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination after their second monovalent dose, the earliest vaccination record after the second monovalent dose was categorized as the third monovalent dose/booster dose. If multiple vaccinations for the same person were observed within 3 days of each other, only the first of these was included in the analysis.
[6] Records observed after the third monovalent dose/booster dose were considered the fourth monovalent dose/booster dose. Among individuals with only one Pfizer-BioNTech COVID-19 vaccination record after their third monovalent dose/booster dose, that vaccination record was categorized as the fourth monovalent dose/booster dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination after their third monovalent dose/booster dose, the vaccination record closest to 5 months after the third monovalent dose/booster dose was categorized as the fourth monovalent dose/booster dose. If multiple vaccinations for the same person were observed within 3 days of each other, only the first of these was included in the analysis.
[7] 3,346 (0.9) individuals received a bivalent dose as their first COVID-19 vaccine dose. 1,234 (0.3) individuals received a bivalent dose after monovalent dose 1; 38,067 (10.4) individuals received a bivalent dose after monovalent dose 2; 161,204 (44.0) individuals received a bivalent dose after monovalent dose 3; and 162,121 (44.3) individuals received a bivalent dose after monovalent dose 4.

10.3. Main Results

10.3.1. Safety Signal Analyses

10.3.1.1. Signal Detection

Binomial MaxSPRT with SCRI Design for Comparison to Post-Vaccination Control Intervals for the Two Safety Events Requiring COVID-19 Diagnosis

Table 7 presents signal detection results for severe COVID-19 disease and MIS-C/MIS-A where binomial MaxSPRT was conducted to compare the risk of the safety event of interest during the risk interval after the Pfizer-BioNTech COVID-19 vaccine to the risk of the same safety event of interest during the post-vaccination control interval using the SCRI design.

This included comparing the risk during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1, risk interval after monovalent dose 1, risk interval after monovalent dose 2, risk interval after monovalent dose 3, risk interval after monovalent dose 4, and risk interval after bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine to the risk during the post-vaccination control interval. Signals were detected if the LLR test statistic exceeded the pre-specified critical value. Severe COVID-19 disease was the only safety event of interest with a signal detected in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 and in the risk interval after monovalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (see green shaded rows), and therefore proceeded to signal evaluation.

Table 7. Signal Detection - Comparing Safety Events of Interest in the Aggregate and Separate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Interval using Binomial MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	N (%) of individuals with safety event	Observed events in risk interval	Risk of safety event during risk interval	Observed events in control interval	Risk of safety event during control interval	Binomial MaxSPRT[1]					
							Upper limit[2]	RR	LLR	Critical value of LLR[3]	Statistical power to detect RR of 3[3]	Signal detected based on LLR> critical value of LLR
Aggregate Monovalent Doses 1-4 and Bivalent Dose 1												
Immunologic												
MIS-C/MIS-A[4]	1,645,620	<11 (0.00)	<11	NR‡	<11	NR‡	40	2.33	0.82	4.860	0.671	no
Other												
Severe COVID-19 disease	1,637,996	1,948 (0.12)	1,142	0.586	806	0.414	1,000	1.42	29.12	5.764	1.000	yes
Monovalent Dose 1												
Immunologic												
MIS-C/MIS-A[4]	1,645,620	<11 (0.00)	<11	NR‡	<11	NR‡	40	-	-	-	-	-
Other												
Severe COVID-19 disease	1,637,996	617 (0.04)	531	0.861	86	0.139	1,000	6.10	181.19	5.764	1.000	yes
Monovalent Dose 2												
Immunologic												
MIS-C/MIS-A[4]	1,581,355	<11 (0.00)	<11	NR‡	<11	NR‡	40	-	-	-	-	-
Other												
Severe COVID-19 disease	1,573,715	319 (0.02)	154	0.483	165	0.517	1,000	0.99	0.00	5.764	1.000	no
Monovalent Dose 3												
Immunologic												

Table 7. Signal Detection - Comparing Safety Events of Interest in the Aggregate and Separate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Interval using Binomial MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	N (%) of individuals with safety event	Observed events in risk interval	Risk of safety event during risk interval	Observed events in control interval	Risk of safety event during control interval	Binomial MaxSPRT[1]					
							Upper limit[2]	RR	LLR	Critical value of LLR[3]	Statistical power to detect RR of 3[3]	Signal detected based on LLR> critical value of LLR
MIS-C/MIS-A[4]	863,776	<11 (0.00)	<11	NR‡	<11	NR‡	40	-	-	-	-	-
Other												
Severe COVID-19 disease	857,642	418 (0.05)	173	0.414	245	0.586	1,000	0.84	0.00	5.764	1.000	no
Monovalent Dose 4												
Immunologic												
MIS-C/MIS-A[4]	273,737	<11 (0.00)	<11	NR‡	<11	NR‡	40	-	-	-	-	-
Other												
Severe COVID-19 disease	271,162	266 (0.10)	110	0.414	156	0.586	1,000	0.56	0.00	5.764	1.000	no
Bivalent Dose 1												
Immunologic												
MIS-C/MIS-A[4]	273,737	<11 (0.00)	<11	NR‡	<11	NR‡	40	-	-	-	-	-
Other												
Severe COVID-19 disease	345,222	238 (0.07)	120	0.504	118	0.496	1,000	1.02	0.01	5.764	1.000	no

Table 7. Signal Detection - Comparing Safety Events of Interest in the Aggregate and Separate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Interval using Binomial MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	N (%) of individuals with safety event	Observed events in risk interval	Risk of safety event during risk interval	Observed events in control interval	Risk of safety event during control interval	Binomial MaxSPRT[1]					
							Upper limit[2]	RR	LLR	Critical value of LLR[3]	Statistical power to detect RR of 3[3]	Signal detected based on LLR> critical value of LLR

Abbreviations: COVID-19, coronavirus disease 2019; LLR, log-likelihood ratio; MaxSPRT, maximized sequential probability ratio test; MIS-A, multisystem inflammatory syndrome in adults; MIS-C, multisystem inflammatory syndrome in children; NR, not reported; RR, relative risk.

Notes:

‡ Certain counts were not reported to protect patient privacy.

[1] Some combinations of parameter values make the MaxSPRT non-applicable. In this analysis, it was not possible to calculate critical values for safety events that had incidences of <1 in any sequential test and pre-specified alpha level of 0.01. Rows with safety events of interest that had signals detected based on Binomial MaxSPRT were shaded green.

[2] The upper limit was defined as the number of expected events in the risk and control intervals based on the literature during the entire length of surveillance.

[3] Critical values and power were calculated using the upper limit and alpha level of 0.01.

[4] MIS-C/MIS-A was identified as ≥ 1 diagnosis code for COVID-19 followed by ≥1 diagnosis code for other specified systemic involvement of connective tissue or multisystem inflammatory syndrome within the same risk or control intervals.

Poisson MaxSPRT for Comparison to Active Comparators who Received Seasonal Influenza Vaccination

Table 8 presents signal detection results for all safety events (except severe COVID-19 disease and MIS-C/MIS-A) where conditional Poisson MaxSPRT was conducted to compare the risk of safety events of interest in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine to the background rate of safety events of interest in the risk interval after seasonal influenza vaccine among individuals with at least one dose. Each safety event of interest was evaluated separately and safety events of interest that had a LLR test statistic that exceeded the pre-specified critical value were determined to have a signal detected. Safety events of interest with signals detected (see green shaded rows) included cerebrovascular non-hemorrhagic stroke, other acute demyelinating diseases, anaphylaxis, AMI, arrhythmia, CAD, myocarditis, stress cardiomyopathy, chilblain-like lesions, DVT, PE, and acute kidney injury, and therefore proceeded to signal evaluation.

Table 8. Signal Detection - Comparing Safety Events of Interest in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Conditional Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR [4][5]	Statistical power to detect RR of 2[4][5]	Statistical power to detect RR of 3[4][5]	Signal detected based on LLR> critical value of LLR
Neurologic												
Aseptic meningitis[6]	1,652,469	<11	NR‡	1.3	2.2	23.1	1.00	0.00	4.71	0.33	0.81	no
Bell's palsy	1,652,395	601.0	565.6	131.1	123.4	1,277.1	1.06	0.77	6.11	1.00	1.00	no
Cerebrovascular non-hemorrhagic stroke	1,649,253	667.0	499.8	198.6	148.8	1,083.9	1.33	17.12	6.11	1.00	1.00	yes
Convulsions/seizures in individuals with controlled epilepsy	1,006	<11	NR‡	1,349.9	541.2	8.5	1.00	-	4.23	0.11	0.32	-
Encephalitis/ encephalomyelitis[6]	1,652,470	18.0	23.2	3.9	5.1	52.4	1.00	0.00	5.06	0.75	1.00	no
GBS[6]	1,652,476	<11	NR‡	1.7	1.5	16.0	1.13	0.04	2.86	0.47	0.84	no
Generalized convulsion/seizures	1,652,122	748.0	1,558.3	384.4	800.9	3,289.0	1.00	0.00	6.11	1.00	1.00	no
MS	1,652,110	338.0	298.8	73.7	65.2	674.5	1.13	1.75	5.47	1.00	1.00	no
ON	1,652,439	236.0	195.6	51.5	42.7	441.7	1.21	2.75	5.47	1.00	1.00	no
Other acute demyelinating diseases	1,652,451	149.0	100.0	32.5	21.8	225.7	1.49	7.18	5.44	1.00	1.00	yes
TM[6]	1,652,476	<11	NR‡	2.0	1.9	19.5	1.04	0.00	4.73	0.27	0.73	no
Immunologic												
Anaphylaxis	1,652,513	<11	NR‡	38.5	9.0	4.9	4.27	3.80	3.54	0.06	0.15	yes

Table 8. Signal Detection - Comparing Safety Events of Interest in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Conditional Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR [4][5]	Statistical power to detect RR of 2[4][5]	Statistical power to detect RR of 3[4][5]	Signal detected based on LLR> critical value of LLR
Arthritis and arthralgia/joint pain	1,652,484	10,185.0	12,710.8	2,229.8	2,782.7	28,798.8	1.00	0.00	6.11	1.00	1.00	no
Autoimmune thyroiditis	1,652,488	213.0	161.8	46.5	35.3	365.2	1.32	5.14	5.46	1.00	1.00	no
Fibromyalgia	1,652,487	1,317.0	1,679.3	287.4	366.5	3,792.6	1.00	0.00	6.11	1.00	1.00	no
KD	1,652,497	0.0	0.4	0.0	0.1	0.9	-	-	-	-	-	-
Vasculitides	1,652,354	109.0	98.6	32.5	29.4	213.8	1.11	0.37	5.44	1.00	1.00	no
Cardiac												
AMI[6]	1,648,707	1,350.0	1,046.5	402.1	311.7	2,270.2	1.29	27.38	6.11	1.00	1.00	yes
Arrhythmia[6]	1,646,041	5,894.0	5,082.5	1,288.2	1,110.8	11,496.1	1.16	43.58	6.11	1.00	1.00	yes
CAD	1,645,062	8,321.0	7,739.8	1,820.4	1,693.2	17,523.3	1.08	15.18	6.11	1.00	1.00	yes
Heart failure and cardiogenic shock	1,649,488	4,355.0	4,164.0	951.3	909.6	9,413.5	1.05	3.08	6.11	1.00	1.00	no
Microangiopathy[6]	1,652,488	<11	NR‡	1.2	1.2	8.4	1.03	0.00	4.22	0.11	0.31	no
Myocarditis[6]	1,652,471	71.0	33.9	15.5	7.4	76.4	2.10	10.20	5.19	0.91	1.00	yes
Pericarditis	1,652,357	204.0	174.8	44.5	38.1	394.6	1.17	1.64	5.46	1.00	1.00	no
Stress cardiomyopathy[6]	1,652,487	35.0	11.8	7.6	2.6	26.7	2.96	9.34	4.77	0.38	0.87	yes
Hematologic												
Cerebrovascular hemorrhagic stroke	1,652,200	104.0	83.0	31.0	24.7	180.0	1.25	1.67	5.43	1.00	1.00	no

Table 8. Signal Detection - Comparing Safety Events of Interest in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Conditional Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR [4][5]	Statistical power to detect RR of 2[4][5]	Statistical power to detect RR of 3[4][5]	Signal detected based on LLR> critical value of LLR
Chilblain-like lesions[6]	1,652,497	18.0	3.9	5.4	1.2	8.4	4.63	7.61	4.22	0.11	0.31	yes
DIC[6]	1,652,494	23.0	30.3	6.8	9.0	65.6	1.00	0.00	5.13	0.85	1.00	no
DVT	1,651,744	2,204.0	1,963.4	656.7	585.0	4,260.6	1.12	9.78	6.11	1.00	1.00	yes
Hemolytic anemia[6]	1,652,478	75.0	96.8	16.4	21.1	218.6	1.00	0.00	5.44	1.00	1.00	no
Hemorrhagic disease[6]	1,652,492	<11	NR‡	2.7	1.2	8.4	2.31	1.54	4.22	0.11	0.31	no
Limb ischemia[6]	1,652,464	27.0	44.5	8.0	13.3	96.6	1.00	0.00	5.26	0.97	1.00	no
PE	1,650,589	1,976.0	1,133.6	588.7	337.7	2,459.7	1.74	167.52	6.11	1.00	1.00	yes
Single organ cutaneous vasculitis[6]	1,652,473	16.0	11.2	4.8	3.3	24.4	1.42	0.60	4.73	0.34	0.82	no
Thrombocytopenia	1,652,411	198.0	154.7	43.2	33.7	349.2	1.28	3.89	5.46	1.00	1.00	no
TTS	1,652,496	0.0	3.1	0.0	0.7	7.1	-	-	4.12	0.09	0.27	-
Other												
Acute kidney injury	1,648,632	6,873.0	5,770.4	1,502.6	1,261.6	13,055.9	1.19	70.00	6.11	1.00	1.00	yes
Appendicitis	1,651,424	168.0	129.9	36.6	28.3	293.3	1.29	3.57	5.46	1.00	1.00	no
Death[7]	1,652,514	7,411.0	22,303.8	1,586.4	4,774.2	50,454.4	1.00	0.00	6.11	1.00	1.00	no
Erythema multiforme	1,652,493	0.0	0.0	0.0	0.0	0.0	-	-	-	-	-	-
Glomerulonephritis	1,652,454	56.0	46.8	12.2	10.2	105.7	1.20	0.59	5.30	0.98	1.00	no
Liver injury	1,652,055	7,253.0	7,955.8	1,585.8	1,739.4	18,001.4	1.00	0.00	6.11	1.00	1.00	no

Table 8. Signal Detection - Comparing Safety Events of Interest in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Conditional Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR [4][5]	Statistical power to detect RR of 2[4][5]	Statistical power to detect RR of 3[4][5]	Signal detected based on LLR> critical value of LLR
Narcolepsy and cataplexy	1,652,496	179.0	208.2	39.0	45.4	470.1	1.00	0.00	5.47	1.00	1.00	no
Nephrotic syndrome	1,652,422	53.0	52.7	11.6	11.5	119.1	1.00	0.00	5.33	0.99	1.00	no
Non-anaphylactic allergic reactions[6]	1,651,968	145.0	147.4	558.1	567.4	310.7	1.00	0.00	5.45	1.00	1.00	no
SJS/TEN	1,652,492	0.0	0.5	0.0	1.8	1.0	-	-	-	-	-	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; LLR, log-likelihood ratio; MaxSPRT, maximized sequential probability ratio test; MS, multiple sclerosis; NR, not reported; ON, optic neuritis; PE, pulmonary embolism; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome; VHA, Veterans Health Administration.

Notes:

‡ Certain counts were not reported to protect patient privacy.

[1] Background incidences were based on five prior influenza seasons in VHA data.

[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk interval.

[3] RR and LLR were not estimated when fewer than 3 events were observed during the risk interval or when the upper limit was fewer than 3 events (or 1 event for KD). When there was no increase in RR due to the vaccine, RR=1 and LLR=0 were reported. RR was computed manually for conditional Poisson MaxSPRT. Rows with safety events of interest with signals detected were shaded green.

[4] Critical values and power were calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest, and minimum number of events needed before the null hypothesis could be rejected were 1 for KD and 3 for all other safety events of interest. For safety events with upper limit exceeding n=1,000 events, a critical value of n=1,000 from Kulldorff 2011 was used as a conservative proxy and 1.00 was used for statistical power. Critical value and power could not be estimated when the minimum number of events exceeded the upper limit.

Table 8. Signal Detection - Comparing Safety Events of Interest in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Conditional Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR [4][5]	Statistical power to detect RR of 2[4][5]	Statistical power to detect RR of 3[4][5]	Signal detected based on LLR> critical value of LLR

[5] Based on the documentation guidance, when the upper limit was ≥50, liberal inference for the computational approach was used. When the upper limit was <50, exact inference for the computational approach was used.
[6] Some safety events of interest had zero or few incident events in the current sequential test. As a result, conditional Poisson MaxSPRT was unable to generate updated LLR values so the previous sequential iteration's LLR values were reported.
[7] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine was included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death was not restricted to the risk interval.

Table 9, Table 10, Table 11, Table 12, and Table 13 present signal detection results where Poisson MaxSPRT was conducted to compare risk of safety events of interest in the risk interval after monovalent dose 1, monovalent dose 2, monovalent dose 3, monovalent dose 4, and bivalent dose 1 respectively, of the Pfizer-BioNTech COVID-19 vaccine to the background rate of safety events of interest in the risk interval after seasonal influenza vaccinations. Safety events of interest with signals detected (see green shaded rows) included AMI and myocarditis for monovalent dose 1; none for monovalent dose 2; cerebrovascular non-hemorrhagic stroke, AMI, arrhythmia, and acute kidney injury for monovalent dose 3; cerebrovascular non-hemorrhagic stroke, ON, AMI, arrhythmia, CAD, heart failure and cardiogenic shock, PE, and acute kidney injury for monovalent dose 4; and AMI, arrhythmia, CAD, heart failure and cardiogenic shock, stress cardiomyopathy, PE, and acute kidney injury for bivalent dose 1. For safety events of interest that had a pre-specified upper limit of expected events in the risk interval that was than less than 3 (based on the background rate from the seasonal influenza vaccine sample), the LLR could not be calculated. Safety events of interest were flagged if the observed number of events was greater than the expected number of events in the risk interval and the pre-specified upper limit of expected events in the risk interval was <3, and they also moved to signal evaluation in an abundance of caution even though a signal was not detected (see blue shaded rows). Accordingly, GBS, anaphylaxis, stress cardiomyopathy, chilblain-like lesions, and hemorrhagic disease for monovalent dose 1; anaphylaxis, microangiopathy, and chilblain-like lesions for monovalent dose 2; chilblain-like lesions for monovalent dose 3; and no safety events of interest for monovalent dose 4 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine proceeded to signal evaluation.

Table 9. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Neurologic												
Aseptic meningitis	1,649,132	0.0	2.3	0.0	2.2	2.6	-	-	4.34	0.15	0.47	-
Bell's palsy	1,649,058	122.0	128.3	117.4	123.4	141.9	0.97	0.00	5.59	1.00	1.00	no
Cerebrovascular non-hemorrhagic stroke[5]	1,646,396	174.0	147.4	175.7	148.8	171.1	1.19	2.43	5.64	1.00	1.00	no
Convulsions/seizures in individuals with controlled epilepsy[5]	1,006	<11	NR‡	1,393.7	541.2	0.5	-	-	3.22	0.06	0.15	-
Encephalitis/ encephalomyelitis	1,649,133	<11	NR‡	1.9	5.1	5.8	0.57	0.00	4.69	0.30	0.82	no
GBS[5]	1,649,655	<11	NR‡	2.9	1.5	1.8	-	-	2.28	0.30	0.61	-
Generalized convulsion/seizures	1,648,777	201.0	541.5	297.3	800.9	657.8	0.37	0.00	5.89	1.00	1.00	no
MS	1,648,773	59.0	67.8	56.8	65.2	74.9	0.87	0.00	5.45	1.00	1.00	no
ON	1,649,102	44.0	44.4	42.3	42.7	49.1	1.04	0.03	5.35	1.00	1.00	no
Other acute demyelinating diseases	1,649,631	36.0	22.6	34.7	21.8	25.1	1.59	3.35	5.16	0.91	1.00	no
TM	1,649,139	0.0	2.0	0.0	1.9	2.2	-	-	4.26	0.13	0.42	-
Immunologic												
Anaphylaxis[5]	1,649,676	<11	NR‡	66.4	9.0	1.0	-	-	3.82	0.08	0.23	-
Arthritis and arthralgia/joint pain	1,649,147	1,935.0	2,891.3	1,862.3	2,782.7	3,199.9	0.68	0.00	6.11	1.00	1.00	no

Table 9. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Autoimmune thyroiditis	1,649,151	35.0	36.7	33.7	35.3	40.6	1.01	0.00	5.30	0.99	1.00	no
Fibromyalgia	1,649,150	266.0	381.0	255.9	366.5	421.4	0.70	0.00	5.81	1.00	1.00	no
KD	1,649,160	0.0	0.1	0.0	0.1	0.1	-	-	4.13	0.03	0.05	-
Vasculitides	1,649,017	22.0	29.1	22.2	29.4	33.8	0.82	0.00	5.25	0.97	1.00	no
Cardiac												
AMI[5]	1,645,810	378.0	308.7	381.6	311.7	358.5	1.24	8.29	5.78	1.00	1.00	yes
Arrhythmia	1,642,709	1,036.0	1,154.4	996.9	1,110.8	1,277.3	0.91	0.00	6.11	1.00	1.00	no
CAD	1,641,735	1,422.0	1,759.5	1,368.4	1,693.2	1,947.0	0.82	0.00	6.11	1.00	1.00	no
Heart failure and cardiogenic shock	1,646,155	791.0	945.4	761.0	909.6	1,045.9	0.85	0.00	6.11	1.00	1.00	no
Microangiopathy	1,649,151	0.0	1.1	0.0	1.2	1.3	-	-	4.00	0.10	0.29	-
Myocarditis[5]	1,649,651	18.0	7.7	17.4	7.4	8.5	2.35	5.04	4.83	0.43	0.94	yes
Pericarditis	1,649,020	41.0	39.6	39.4	38.1	43.8	1.08	0.14	5.32	0.99	1.00	no
Stress cardiomyopathy[5]	1,649,667	<11	NR‡	7.7	2.6	3.0	-	-	4.41	0.17	0.53	-
Hematologic												
Cerebrovascular hemorrhagic stroke	1,648,863	26.0	24.5	26.2	24.7	28.4	1.06	0.04	5.20	0.94	1.00	no
Chilblain-like lesions[5]	1,649,677	<11	NR‡	6.1	1.2	1.3	-	-	4.00	0.10	0.29	-
DIC	1,649,157	<11	NR‡	4.0	9.0	10.4	0.45	0.00	4.90	0.52	0.97	no
DVT	1,648,408	480.0	579.9	484.2	585.0	672.7	0.84	0.00	5.90	1.00	1.00	no

Table 9. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Hemolytic anemia	1,649,141	16.0	22.0	15.4	21.1	24.3	0.73	0.00	5.16	0.89	1.00	no
Hemorrhagic disease[5]	1,649,672	<11	NR‡	5.0	1.2	1.3	-	-	4.00	0.10	0.29	-
Limb ischemia	1,649,127	<11	NR‡	7.1	13.3	15.2	0.46	0.00	5.02	0.70	1.00	no
PE	1,647,761	398.0	334.5	401.8	337.7	388.4	1.19	5.68	5.80	1.00	1.00	no
Single organ cutaneous vasculitis	1,649,136	<11	NR‡	3.0	3.3	3.8	0.90	0.00	4.53	0.21	0.65	no
Thrombocytopenia	1,649,074	30.0	35.1	28.9	33.7	38.8	0.86	0.00	5.28	0.99	1.00	no
TTS	1,649,159	0.0	0.7	0.0	0.7	0.8	-	-	3.67	0.07	0.19	-
Other												
Acute kidney injury	1,645,303	1,349.0	1,310.9	1,298.2	1,261.6	1,450.7	1.04	1.10	6.11	1.00	1.00	no
Appendicitis[5]	1,648,600	39.0	29.4	37.6	28.3	32.6	1.33	1.42	5.24	0.97	1.00	no
Death[6]	1,649,168	1,955.0	4,977.1	1,875.3	4,774.2	5,489.9	0.39	0.00	6.11	1.00	1.00	no
Erythema multiforme	1,649,156	0.0	0.0	0.0	0.0	0.0	-	-	-	-	-	-
Glomerulonephritis	1,649,117	11.0	10.6	10.6	10.2	11.7	1.04	0.01	4.94	0.57	0.99	no
Liver injury	1,648,718	1,580.0	1,807.5	1,520.5	1,739.4	2,000.2	0.88	0.00	6.11	1.00	1.00	no
Narcolepsy and cataplexy	1,649,159	42.0	47.2	40.4	45.4	52.2	0.89	0.00	5.36	1.00	1.00	no
Nephrotic syndrome	1,649,085	11.0	12.0	10.6	11.5	13.2	1.00	0.00	4.97	0.63	0.99	no
Non-anaphylactic allergic reactions	1,648,632	44.0	51.2	487.3	567.4	62.1	0.86	0.00	5.40	1.00	1.00	no
SJS/TEN	1,649,155	0.0	0.2	0.0	1.8	0.2	-	-	4.18	0.03	0.06	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; LLR, log-likelihood ratio; MaxSPRT, maximized sequential probability ratio test; MS, multiple

Table 9. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR

sclerosis; NR, not reported; ON, optic neuritis; PE, pulmonary embolism; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome; VHA, Veterans Health Administration.

Notes:

‡ Certain counts were not reported to protect patient privacy.

[1] Background incidences were based on the five prior influenza seasons in VHA data.

[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk interval.

[3] RR and LLR were not estimated when fewer than 3 events were observed during the risk interval or when the upper limit was fewer than 3 events (or 1 event for KD). When there was no increase in RR due to the vaccine, RR=1 and LLR=0 were reported. Rows with safety events of interest with signals detected were shaded green. Rows with safety events of interest where LLR could not be calculated but the observed number of events was greater than the expected number of events in the risk interval so the safety events of interest were moved to signal evaluation in an abundance of caution even though a signal was not detected were shaded blue.

[4] Critical values and power were calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest, and minimum number of events needed before the null hypothesis could be rejected were 1 for KD and 3 for all other safety events of interest. For safety events with upper limit exceeding n=1,000 events, a critical value of n=1,000 from Kulldorff 2011 was used as a conservative proxy and 1.00 was used for statistical power.

[5] For safety events where the number of observed events in the risk interval exceeded the pre-specified upper limit in the prior iteration of results, results from the prior iteration were reported.

[6] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine was included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death was not restricted to the risk interval.

Table 10. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 2 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Neurologic												
Aseptic meningitis	1,589,285	<11	NR‡	1.1	2.2	5.1	0.49	0.00	4.64	0.27	0.77	no
Bell's palsy	1,589,208	184.0	224.5	101.1	123.4	283.8	0.82	0.00	5.74	1.00	1.00	no
Cerebrovascular non-hemorrhagic stroke	1,586,188	215.0	180.8	176.9	148.8	228.2	1.22	3.96	5.69	1.00	1.00	no
Convulsions/seizures in individuals with controlled epilepsy	959	0.0	1.2	0.0	541.2	2.0	-	-	4.22	0.12	0.39	-
Encephalitis/ encephalomyelitis	1,589,283	<11	NR‡	3.8	5.1	11.7	0.76	0.00	4.93	0.57	0.99	no
GBS	1,589,291	<11	NR‡	1.6	1.5	3.6	1.07	0.01	2.65	0.42	0.82	no
Generalized convulsion/ seizures	1,589,028	175.0	522.2	268.4	800.9	657.8	0.34	0.00	5.89	1.00	1.00	no
MS	1,588,939	100.0	118.6	55.0	65.2	149.9	0.84	0.00	5.61	1.00	1.00	no
ON	1,589,253	74.0	77.7	40.7	42.7	98.1	1.04	0.07	5.51	1.00	1.00	no
Other acute demyelinating diseases	1,589,265	48.0	39.7	26.4	21.8	50.2	1.21	0.82	5.35	1.00	1.00	no
TM[5]	1,586,661	<11	NR‡	2.8	1.9	4.3	1.46	0.31	4.58	0.23	0.70	no
Immunologic												
Anaphylaxis[5]	1,586,681	<11	NR‡	34.5	9.0	1.0	-	-	3.82	0.08	0.23	-
Arthritis and arthralgia/joint pain	1,589,298	3,364.0	5,058.3	1,850.6	2,782.7	6,399.7	0.68	0.00	6.11	1.00	1.00	no

Table 10. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 2 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Autoimmune thyroiditis	1,589,302	63.0	64.2	34.6	35.3	81.2	1.01	0.00	5.47	1.00	1.00	no
Fibromyalgia	1,589,301	397.0	666.7	218.2	366.5	842.8	0.61	0.00	5.94	1.00	1.00	no
KD	1,589,311	0.0	0.2	0.0	0.1	0.2	-	-	4.18	0.03	0.06	-
Vasculitides	1,589,172	44.0	35.7	36.2	29.4	45.0	1.23	0.91	5.32	0.99	1.00	no
Cardiac												
AMI	1,585,649	398.0	378.7	327.6	311.7	477.9	1.07	0.82	5.84	1.00	1.00	no
Arrhythmia	1,583,037	1,854.0	2,020.2	1,019.4	1,110.8	2,554.7	0.95	0.00	6.11	1.00	1.00	no
CAD	1,582,084	2,751.0	3,078.5	1,513.1	1,693.2	3,894.1	0.91	0.00	6.11	1.00	1.00	no
Heart failure and cardiogenic shock	1,586,425	1,459.0	1,654.4	802.2	909.6	2,091.9	0.90	0.00	6.11	1.00	1.00	no
Microangiopathy[5]	1,586,674	<11	NR‡	4.1	1.2	1.8	-	-	4.17	0.12	0.36	-
Myocarditis[5]	1,586,658	19.0	13.4	10.5	7.4	17.0	1.49	1.40	5.05	0.75	1.00	no
Pericarditis	1,589,175	51.0	69.4	28.0	38.1	87.7	0.75	0.00	5.49	1.00	1.00	no
Stress cardiomyopathy[5]	1,586,671	<11	NR‡	3.9	2.6	5.9	1.50	0.50	4.70	0.31	0.83	no
Hematologic												
Cerebrovascular hemorrhagic stroke[5]	1,586,389	40.0	30.0	33.0	24.7	37.9	1.33	1.51	5.28	0.98	1.00	no
Chilblain-like lesions[5]	1,586,682	<11	NR‡	7.4	1.2	1.8	-	-	4.17	0.12	0.36	-
DIC	1,589,309	<11	NR‡	7.4	9.0	13.8	0.82	0.00	4.99	0.65	0.99	no
DVT	1,588,578	560.0	710.8	460.9	585.0	897.0	0.81	0.00	5.95	1.00	1.00	no
Hemolytic anemia	1,589,293	32.0	38.4	17.6	21.1	48.6	0.88	0.00	5.34	1.00	1.00	no
Hemorrhagic disease	1,589,306	<11	NR‡	0.8	1.2	1.8	-	-	4.17	0.12	0.36	-

Table 10. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 2 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Limb ischemia	1,589,278	12.0	16.1	9.9	13.3	20.3	0.74	0.00	5.10	0.83	1.00	no
PE	1,587,455	410.0	410.3	337.5	337.7	517.8	1.01	0.04	5.85	1.00	1.00	no
Single organ cutaneous vasculitis	1,589,286	<11	NR‡	3.3	3.3	5.1	1.48	0.40	4.64	0.27	0.77	no
Thrombocytopenia	1,589,225	56.0	61.4	30.8	33.7	77.6	0.94	0.00	5.46	1.00	1.00	no
TTS	1,589,310	0.0	1.2	0.0	0.7	1.6	-	-	4.10	0.11	0.32	-
Other												
Acute kidney injury	1,585,544	2,261.0	2,294.1	1,243.4	1,261.6	2,901.3	1.00	0.00	6.11	1.00	1.00	no
Appendicitis[5]	1,585,639	67.0	51.5	36.9	28.3	65.2	1.30	2.13	5.42	1.00	1.00	no
Death[6]†	1,589,388	2,608.0	8,893.6	1,400.0	4,774.2	11,241.1	1.00	0.00	6.11	1.00	1.00	no
Erythema multiforme	1,589,307	0.0	0.0	0.0	0.0	0.0	-	-	-	-	-	-
Glomerulonephritis	1,589,267	12.0	18.6	6.6	10.2	23.5	0.70	0.00	5.15	0.88	1.00	no
Liver injury	1,588,889	2,437.0	3,162.8	1,340.2	1,739.4	4,000.3	0.78	0.00	6.11	1.00	1.00	no
Narcolepsy and cataplexy	1,589,310	59.0	82.7	32.4	45.4	104.5	0.71	0.00	5.53	1.00	1.00	no
Nephrotic syndrome	1,589,240	17.0	20.9	9.3	11.5	26.5	0.81	0.00	5.18	0.92	1.00	no
Non-anaphylactic allergic reactions	1,588,800	38.0	49.4	436.7	567.4	62.1	0.77	0.00	5.40	1.00	1.00	no
SJS/TEN	1,589,306	0.0	0.2	0.0	1.8	0.2	-	-	4.18	0.03	0.06	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; LLR, log-likelihood ratio; (c)MaxSPRT, (conditional) maximized sequential probability ratio test; MS, multiple sclerosis; NR, not reported; ON, optic neuritis; PE, pulmonary embolism; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome; VHA, Veterans Health Administration.
Notes:
†cMaxSPRT used.

Table 10. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 2 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	**Number of individuals**	**Observed events in the risk interval**	**Expected events in the risk interval**	**Incidence per 100,000 person-years**	**Background incidence per 100,000 person-years[1]**	**Pre-specified upper limit of expected events in the risk interval[2]**	**RR[3]**	**LLR[3]**	**Critical value of LLR[4]**	**Statistical power to detect RR of 2[4]**	**Statistical power to detect RR of 3[4]**	**Signal detected based on LLR> critical value of LLR**

‡ Certain counts were not reported to protect patient privacy.
[1] Background incidences were based on the five prior influenza seasons in VHA data.
[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk interval.
[3] RR and LLR were not estimated when fewer than 3 events were observed during the risk interval or when the upper limit was fewer than 3 events (or 1 event for KD). When there was no increase in RR due to the vaccine, RR=1 and LLR=0 were reported. Rows with safety events of interest where the LLR could not be calculated but the observed number of events was greater than the expected number of events in the risk interval so the safety events of interest were moved to signal evaluation in an abundance of caution even though a signal was not detected were shaded blue.
[4] Critical values and power were calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest, and minimum number of events needed before the null hypothesis could be rejected were 1 for KD and 3 for all other safety events of interest. For safety events with upper limit exceeding n=1,000 events, a critical value of n=1,000 from Kulldorff 2011 was used as a conservative proxy and 1.00 was used for statistical power.
[5] For safety events where the observed events in the risk interval exceeded the pre-specified upper limit in the prior iteration of results, results from the prior iteration were reported.
[6] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine was included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death was not restricted to the risk interval.

Table 11. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 3 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Neurologic												
Aseptic meningitis	866,963	<11	NR‡	2.0	2.2	5.1	0.93	0.00	4.64	0.27	0.77	no
Bell's palsy	866,915	121.0	122.6	121.8	123.4	283.8	0.99	0.00	5.74	1.00	1.00	no
Cerebrovascular non-hemorrhagic stroke	864,793	149.0	98.7	224.7	148.8	228.2	1.51	11.07	5.69	1.00	1.00	yes
Convulsions/seizures in individuals with controlled epilepsy	789	0.0	1.0	0.0	541.2	2.0	-	-	4.22	0.12	0.39	-
Encephalitis/ encephalomyelitis	866,956	<11	NR‡	4.0	5.1	11.7	0.62	0.00	4.93	0.57	0.99	no
GBS	866,963	<11	NR‡	2.0	1.5	3.6	1.35	0.08	2.65	0.42	0.82	no
Generalized convulsion/seizures	866,806	117.0	284.9	328.9	800.9	657.8	0.41	0.00	5.89	1.00	1.00	no
MS	866,770	67.0	64.7	67.4	65.2	149.9	1.03	0.04	5.61	1.00	1.00	no
ON	866,951	51.0	42.4	51.3	42.7	98.1	1.20	0.82	5.51	1.00	1.00	no
Other acute demyelinating diseases	866,941	32.0	21.7	32.2	21.8	50.2	1.48	2.14	5.35	1.00	1.00	no
TM	866,967	<11	NR‡	2.0	1.9	4.3	1.10	0.01	4.58	0.23	0.70	no
Immunologic												
Anaphylaxis	866,995	0.0	0.4	0.0	9.0	1.0	-	-	3.82	0.08	0.23	-
Arthritis and arthralgia/joint pain	866,966	2,328.0	2,761.1	2,346.3	2,782.7	6,399.7	0.84	0.00	6.11	1.00	1.00	no
Autoimmune thyroiditis	866,971	43.0	35.1	43.3	35.3	81.2	1.23	0.84	5.47	1.00	1.00	no

Table 11. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 3 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Fibromyalgia	866,963	251.0	364.0	252.7	366.5	842.8	0.69	0.00	5.94	1.00	1.00	no
KD	866,974	0.0	0.1	0.0	0.1	0.2	-	-	4.18	0.03	0.06	-
Vasculitides	866,869	18.0	19.5	27.1	29.4	45.0	0.92	0.00	5.32	0.99	1.00	no
Cardiac												
AMI	864,489	263.0	206.7	396.6	311.7	477.9	1.29	8.05	5.84	1.00	1.00	yes
Arrhythmia	862,488	1,228.0	1,102.9	1,236.8	1,110.8	2,554.7	1.11	6.95	6.11	1.00	1.00	yes
CAD	861,996	1,694.0	1,680.7	1,706.7	1,693.2	3,894.1	1.02	0.24	6.11	1.00	1.00	no
Heart failure and cardiogenic shock	865,211	869.0	903.3	875.1	909.6	2,091.9	0.97	0.00	6.11	1.00	1.00	no
Microangiopathy	866,966	0.0	0.8	0.0	1.2	1.8	-	-	4.17	0.12	0.36	-
Myocarditis	866,963	16.0	7.3	16.1	7.4	17.0	2.18	3.81	5.05	0.75	1.00	no
Pericarditis	866,869	53.0	37.9	53.3	38.1	87.7	1.43	3.03	5.49	1.00	1.00	no
Stress cardiomyopathy	866,971	<11	NR‡	4.0	2.6	5.9	1.62	0.40	4.70	0.31	0.83	no
Hematologic												
Cerebrovascular hemorrhagic stroke	866,765	22.0	16.4	33.2	24.7	37.9	1.34	0.87	5.28	0.98	1.00	no
Chilblain-like lesions[5]	838,507	<11	NR‡	4.7	1.2	1.8	-	-	4.17	0.12	0.36	-
DIC	866,973	<11	NR‡	7.5	9.0	13.8	0.84	0.00	4.99	0.65	0.99	no
DVT	866,489	304.0	387.9	458.5	585.0	897.0	0.78	0.00	5.95	1.00	1.00	no
Hemolytic anemia	866,965	<11	NR‡	7.0	21.1	48.6	0.44	0.00	5.34	1.00	1.00	no
Hemorrhagic disease[5]	838,504	<11	NR‡	3.1	1.2	1.8	-	-	4.17	0.12	0.36	-
Limb ischemia	866,954	<11	NR‡	4.5	13.3	20.3	0.34	0.00	5.10	0.83	1.00	no

Table 11. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 3 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
PE	865,604	256.0	223.9	386.1	337.7	517.8	1.16	2.61	5.85	1.00	1.00	no
Single organ cutaneous vasculitis	866,960	<11	NR‡	6.0	3.3	5.1	1.80	0.58	4.64	0.27	0.77	no
Thrombocytopenia	866,920	47.0	33.5	47.3	33.7	77.6	1.40	2.40	5.46	1.00	1.00	no
TTS	866,974	0.0	0.7	0.0	0.7	1.6	-	-	4.10	0.11	0.32	-
Other												
Acute kidney injury	864,378	1,429.0	1,252.4	1,439.5	1,261.6	2,901.3	1.15	12.85	6.11	1.00	1.00	yes
Appendicitis	866,409	30.0	28.2	30.2	28.3	65.2	1.07	0.06	5.42	1.00	1.00	no
Death[6]†	866,995	1,576.0	4,855.9	1,549.5	4,774.2	11,241.1	1.00	0.00	6.11	1.00	1.00	no
Erythema multiforme	866,972	0.0	0.0	0.0	0.0	0.0	-	-	-	-	-	-
Glomerulonephritis	866,945	17.0	10.2	17.1	10.2	23.5	1.67	1.92	5.15	0.88	1.00	no
Liver injury	866,682	1,470.0	1,726.7	1,480.8	1,739.4	4,000.3	0.85	0.00	6.11	1.00	1.00	no
Narcolepsy and cataplexy	866,974	31.0	45.1	31.2	45.4	104.5	0.69	0.00	5.53	1.00	1.00	no
Nephrotic syndrome	866,923	<11	NR‡	8.1	11.5	26.5	0.70	0.00	5.18	0.92	1.00	no
Non-anaphylactic allergic reactions	866,596	19.0	26.9	400.2	567.4	62.1	0.71	0.00	5.40	1.00	1.00	no
SJS/TEN	866,970	0.0	0.1	0.0	1.8	0.2	-	-	4.18	0.03	0.06	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; LLR, log-likelihood ratio; (c)MaxSPRT, (conditional) maximized sequential probability ratio test; MS, multiple sclerosis; NR, not reported; ON, optic neuritis; PE, pulmonary embolism; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome; VHA, Veterans Health Administration.

Notes:

†cMaxSPRT used.

‡ Certain counts were not reported to protect patient privacy.

Table 11. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 3 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	**Number of individuals**	**Observed events in the risk interval**	**Expected events in the risk interval**	**Incidence per 100,000 person-years**	**Background incidence per 100,000 person-years[1]**	**Pre-specified upper limit of expected events in the risk interval[2]**	**RR[3]**	**LLR[3]**	**Critical value of LLR[4]**	**Statistical power to detect RR of 2[4]**	**Statistical power to detect RR of 3[4]**	**Signal detected based on LLR> critical value of LLR**

[1] Background incidences were based on the five prior influenza seasons in VHA data.
[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk interval.
[3] RR and LLR were not estimated when fewer than 3 events were observed during the risk interval or when the upper limit was fewer than 3 events (or 1 event for KD). When there was no increase in RR due to the vaccine, RR=1 and LLR=0 were reported. Rows with safety events of interest with signals detected were shaded green. Rows with safety events of interest where the LLR could not be calculated but the observed number of events was greater than the expected number of events in the risk interval so the safety events of interest were moved to signal evaluation in an abundance of caution even though a signal was not detected were shaded blue.
[4] Critical values and power were calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest, and minimum number of events needed before the null hypothesis could be rejected were 1 for KD and 3 for all other safety events of interest. For safety events with upper limit exceeding n=1,000 events, a critical value of n=1,000 from Kulldorff 2011 was used as a conservative proxy and 1.00 was used for statistical power.
[5] For safety events where the observed events in the risk interval exceeded the pre-specified upper limit in the prior iteration of results, results from the prior iteration were reported.
[6] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine was included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death was not restricted to the risk interval.

Table 12. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 4 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Neurologic												
Aseptic meningitis	274,967	<11	NR‡	3.2	2.2	5.1	1.52	1.00	4.64	0.27	0.77	no
Bell's palsy	274,951	35.0	39.0	110.9	123.4	283.8	0.92	0.00	5.74	1.00	1.00	no
Cerebrovascular non-hemorrhagic stroke	274,091	64.0	31.3	303.9	148.8	228.2	2.04	13.04	5.69	1.00	1.00	yes
Convulsions/seizures in individuals with controlled epilepsy	307	0.0	0.4	0.0	541.2	2.0	-	-	4.22	0.12	0.39	-
Encephalitis/encephalomyelitis	274,966	<11	NR‡	6.3	5.1	11.7	1.52	1.00	4.93	0.57	0.99	no
GBS	274,966	0.0	0.5	0.0	1.5	3.6	-	-	2.65	0.42	0.82	-
Generalized convulsion/seizures	274,915	52.0	90.4	460.7	800.9	657.8	0.58	0.00	5.89	1.00	1.00	no
MS	274,882	34.0	20.6	107.7	65.2	149.9	1.65	3.65	5.61	1.00	1.00	no
ON	274,958	28.0	13.5	88.7	42.7	98.1	2.08	5.96	5.51	1.00	1.00	yes
Other acute demyelinating diseases	274,952	<11	NR‡	22.2	21.8	50.2	2.20	1.95	5.35	1.00	1.00	no
TM	274,968	0.0	0.6	0.0	1.9	4.3	-	-	4.58	0.23	0.70	-
Immunologic												
Anaphylaxis[5]	242,874	<11	NR‡	75.3	9.0	1.0	-	-	3.82	0.08	0.23	-
Arthritis and arthralgia/joint pain	274,964	819.0	877.3	2,598.0	2,782.7	6,399.7	0.93	0.00	6.11	1.00	1.00	no
Autoimmune thyroiditis	274,968	20.0	11.1	63.4	35.3	81.2	1.80	2.84	5.47	1.00	1.00	no

Table 12. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 4 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Fibromyalgia	274,964	76.0	115.7	240.8	366.5	842.8	0.66	0.00	5.94	1.00	1.00	no
KD	274,969	0.0	0.0	0.0	0.1	0.2	-	-	4.18	0.03	0.06	-
Vasculitides	274,917	<11	NR‡	19.0	29.4	45.0	3.69	1.73	5.32	0.99	1.00	no
Cardiac												
AMI	273,965	107.0	65.6	508.2	311.7	477.9	1.63	10.93	5.84	1.00	1.00	yes
Arrhythmia	273,013	495.0	350.4	1,569.2	1,110.8	2,554.7	1.41	26.41	6.11	1.00	1.00	yes
CAD	272,894	730.0	533.9	2,315.1	1,693.2	3,894.1	1.37	32.27	6.11	1.00	1.00	yes
Heart failure and cardiogenic shock	274,304	354.0	287.0	1,121.9	909.6	2,091.9	1.23	7.27	6.11	1.00	1.00	yes
Microangiopathy	274,967	0.0	0.2	0.0	1.2	1.8	-	-	4.17	0.12	0.36	-
Myocarditis	274,965	<11	NR‡	15.8	7.4	17.0	2.14	1.15	5.05	0.75	1.00	no
Pericarditis	274,928	17.0	12.0	53.8	38.1	87.7	1.41	0.91	5.49	1.00	1.00	no
Stress cardiomyopathy	274,968	<11	NR‡	9.5	2.6	5.9	3.69	1.73	4.70	0.31	0.83	no
Hematologic												
Cerebrovascular hemorrhagic stroke	274,869	<11	NR‡	38.0	24.7	37.9	1.54	0.64	5.28	0.98	1.00	no
Chilblain-like lesions	274,969	0.0	0.2	0.0	1.2	1.8	-	-	4.17	0.12	0.36	-
DIC	274,967	<11	NR‡	14.2	9.0	13.8	1.52	1.00	4.99	0.65	0.99	no
DVT	274,779	129.0	123.2	612.7	585.0	897.0	1.05	0.14	5.95	1.00	1.00	no
Hemolytic anemia	274,965	<11	NR‡	19.0	21.1	48.6	0.90	0.00	5.34	1.00	1.00	no
Hemorrhagic disease	274,968	<11	NR‡	4.7	1.2	1.8	-	-	4.17	0.12	0.36	-
Limb ischemia	274,959	<11	NR‡	4.7	13.3	20.3	1.54	0.64	5.10	0.83	1.00	no
PE	274,395	107.0	71.1	508.2	337.7	517.8	1.50	7.83	5.85	1.00	1.00	yes

Table 12. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 4 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Single organ cutaneous vasculitis	274,964	<11	NR‡	14.2	3.3	5.1	1.52	1.00	4.64	0.27	0.77	no
Thrombocytopenia	274,946	16.0	10.7	50.7	33.7	77.6	1.50	1.16	5.46	1.00	1.00	no
TTS	274,969	0.0	0.2	0.0	0.7	1.6	-	-	4.10	0.11	0.32	-
Other												
Acute kidney injury	273,862	551.0	397.9	1,746.9	1,261.6	2,901.3	1.38	26.26	6.11	1.00	1.00	yes
Appendicitis	274,798	13.0	8.9	41.2	28.3	65.2	1.45	0.80	5.42	1.00	1.00	no
Death[6]†	274,976	509.0	1,543.1	1,574.8	4,774.2	11,241.1	1.00	0.00	6.11	1.00	1.00	no
Erythema multiforme	274,968	0.0	0.0	0.0	0.0	0.0	-	-	-	-	-	-
Glomerulonephritis	274,958	<11	NR‡	22.2	10.2	23.5	1.52	1.00	5.15	0.88	1.00	no
Liver injury	274,868	477.0	548.7	1,512.2	1,739.4	4,000.3	0.87	0.00	6.11	1.00	1.00	no
Narcolepsy and cataplexy	274,969	12.0	14.3	38.0	45.4	104.5	0.84	0.00	5.53	1.00	1.00	no
Nephrotic syndrome	274,947	<11	NR‡	25.3	11.5	26.5	2.20	1.95	5.18	0.92	1.00	no
Non-anaphylactic allergic reactions	274,817	13.0	8.5	863.4	567.4	62.1	1.52	1.00	5.40	1.00	1.00	no
SJS/TEN	274,968	0.0	0.0	0.0	1.8	0.2	-	-	4.18	0.03	0.06	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; LLR, log-likelihood ratio; (c)MaxSPRT, (conditional) maximized sequential probability ratio test; MS, multiple sclerosis; NR, not reported; ON, optic neuritis; PE, pulmonary embolism; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome; VHA, Veterans Health Administration.

Notes:

†cMaxSPRT used.

‡ Certain counts were not reported to protect patient privacy.

[1] Background incidences were based on the five prior influenza seasons in VHA data.

Table 12. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Monovalent Dose 4 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR

[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk interval.
[3] RR and LLR were not estimated when fewer than 3 events were observed during the risk interval or when the upper limit was fewer than 3 events (or 1 event for KD). When there was no increase in RR due to the vaccine, RR=1 and LLR=0 were reported. Rows with safety events of interest with signals detected were shaded green.
[4] Critical values and power were calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest, and minimum number of events needed before the null hypothesis could be rejected were 1 for KD and 3 for all other safety events of interest. For safety events with upper limit exceeding n=1,000 events, a critical value of n=1,000 from Kulldorff 2011 was used as a conservative proxy and 1.00 was used for statistical power.
[5] For safety events where the observed events in the risk interval exceeded the pre-specified upper limit in the prior iteration of results, results from the prior iteration were reported.
[6] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine was included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death was not restricted to the risk interval.

Table 13. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Neurologic												
Aseptic meningitis	364,573	<11	NR‡	2.4	2.2	5.1	1.08	0.00	4.64	0.27	0.77	no
Bell's palsy	364,540	49.0	51.3	117.8	123.4	283.8	0.95	0.00	5.74	1.00	1.00	no
Cerebrovascular non-hemorrhagic stroke	363,327	50.0	41.4	179.8	148.8	228.2	1.21	0.84	5.69	1.00	1.00	no
Convulsions/seizures in individuals with controlled epilepsy	438	0.0	0.6	0.0	541.2	2.0	-	-	4.22	0.12	0.39	-
Encephalitis/encephalomyelitis	364,569	<11	NR‡	2.4	5.1	11.7	0.47	0.00	4.93	0.57	0.99	no
GBS	364,572	0.0	0.6	0.0	1.5	3.6	-	-	2.65	0.42	0.82	-
Generalized convulsion/seizures	364,605	70.0	119.6	468.6	800.9	657.8	0.59	0.00	5.89	1.00	1.00	no
MS	364,476	36.0	27.1	86.5	65.2	149.9	1.33	1.32	5.61	1.00	1.00	no
ON	364,560	17.0	17.8	40.9	42.7	98.1	0.96	0.00	5.51	1.00	1.00	no
Other acute demyelinating diseases	364,558	<11	NR‡	16.8	21.8	50.2	0.77	0.00	5.35	1.00	1.00	no
TM	364,577	<11	NR‡	2.4	1.9	4.3	1.27	0.03	4.58	0.23	0.70	no
Immunologic												
Anaphylaxis	364,718	0.0	0.2	0.0	9.0	1.0	-	-	3.82	0.08	0.23	-
Arthritis and arthralgia/joint pain	364,570	1,021.0	1,156.2	2,457.4	2,782.7	6,399.7	0.88	0.00	6.11	1.00	1.00	no
Autoimmune thyroiditis	364,575	16.0	14.7	38.5	35.3	81.2	1.09	0.06	5.47	1.00	1.00	no

Table 13. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Fibromyalgia	364,575	114.0	152.4	274.0	366.5	842.8	0.75	0.00	5.94	1.00	1.00	no
KD	364,578	0.0	0.0	0.0	0.1	0.2	-	-	4.18	0.03	0.06	-
Vasculitides	364,523	<11	NR‡	36.0	29.4	45.0	1.22	0.19	5.32	0.99	1.00	no
Cardiac												
AMI	363,314	130.0	86.7	467.4	311.7	477.9	1.50	9.36	5.84	1.00	1.00	yes
Arrhythmia	362,086	613.0	461.8	1,474.5	1,110.8	2,554.7	1.33	22.41	6.11	1.00	1.00	yes
CAD	361,783	931.0	703.6	2,240.3	1,693.2	3,894.1	1.32	33.31	6.11	1.00	1.00	yes
Heart failure and cardiogenic shock	363,894	506.0	378.2	1,217.0	909.6	2,091.9	1.34	19.50	6.11	1.00	1.00	yes
Microangiopathy	364,576	0.0	0.3	0.0	1.2	1.8	-	-	4.17	0.12	0.36	-
Myocarditis	364,574	<11	NR‡	9.6	7.4	17.0	1.30	0.13	5.05	0.75	1.00	no
Pericarditis	364,519	15.0	15.9	36.1	38.1	87.7	0.95	0.00	5.49	1.00	1.00	no
Stress cardiomyopathy	364,575	<11	NR‡	21.6	2.6	5.9	8.40	11.22	4.70	0.31	0.83	yes
Hematologic												
Cerebrovascular hemorrhagic stroke	364,482	<11	NR‡	18.0	24.7	37.9	0.73	0.00	5.28	0.98	1.00	no
Chilblain-like lesions	364,578	<11	NR‡	7.2	1.2	1.8	-	-	4.17	0.12	0.36	-
DIC	364,578	<11	NR‡	3.6	9.0	13.8	0.40	0.00	4.99	0.65	0.99	no
DVT	364,310	169.0	162.7	607.7	585.0	897.0	1.04	0.12	5.95	1.00	1.00	no
Hemolytic anemia	364,573	<11	NR‡	16.8	21.1	48.6	0.80	0.00	5.34	1.00	1.00	no
Hemorrhagic disease	364,578	0.0	0.3	0.0	1.2	1.8	-	-	4.17	0.12	0.36	-
Limb ischemia	364,567	<11	NR‡	14.4	13.3	20.3	1.08	0.01	5.10	0.83	1.00	no
PE	363,858	147.0	93.9	528.6	337.7	517.8	1.56	12.77	5.85	1.00	1.00	yes

Table 13. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR
Single organ cutaneous vasculitis	364,572	<11	NR‡	3.6	3.3	5.1	1.07	0.00	4.64	0.27	0.77	no
Thrombocytopenia	364,552	19.0	14.0	45.7	33.7	77.6	1.35	0.79	5.46	1.00	1.00	no
TTS	364,578	0.0	0.3	0.0	0.7	1.6	-	-	4.10	0.11	0.32	-
Other												
Acute kidney injury	363,057	798.0	524.4	1,919.9	1,261.6	2,901.3	1.52	61.47	6.11	1.00	1.00	yes
Appendicitis	364,304	14.0	11.8	33.6	28.3	65.2	1.19	0.20	5.42	1.00	1.00	no
Death[5]†	364,719	771.0	2,034.0	1,809.7	4,774.2	11,241.1	1.00	0.00	6.11	1.00	1.00	no
Erythema multiforme	364,578	0.0	0.0	0.0	0.0	0.0	-	-	-	-	-	-
Glomerulonephritis	364,563	<11	NR‡	14.4	10.2	23.5	1.41	0.32	5.15	0.88	1.00	no
Liver injury	364,468	668.0	723.1	1,607.0	1,739.4	4,000.3	0.92	0.00	6.11	1.00	1.00	no
Narcolepsy and cataplexy	364,578	18.0	18.9	43.3	45.4	104.5	0.95	0.00	5.53	1.00	1.00	no
Nephrotic syndrome	364,555	<11	NR‡	12.0	11.5	26.5	1.04	0.00	5.18	0.92	1.00	no
Non-anaphylactic allergic reactions	364,368	<11	NR‡	501.0	567.4	62.1	0.88	0.00	5.40	1.00	1.00	no
SJS/TEN	364,576	0.0	0.0	0.0	1.8	0.2	-	-	-	-	-	-

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; KD, Kawasaki disease; LLR, log-likelihood ratio; (c)MaxSPRT, (conditional) maximized sequential probability ratio test; MS, multiple sclerosis; NR, not reported; ON, optic neuritis; PE, pulmonary embolism; RR, relative risk; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TM, transverse myelitis; TTS, thrombosis with thrombocytopenia syndrome; VHA, Veterans Health Administration.

Notes:

†cMaxSPRT used.

‡ Certain counts were not reported to protect patient privacy.

[1] Background incidences were based on the five prior influenza seasons in VHA data.

Table 13. Signal Detection - Comparing Safety Events of Interest in the Risk Interval After Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Background Rate in the Risk Interval After Seasonal Influenza Vaccine using Poisson MaxSPRT through 30 June 2023

Safety Event of Interest	Number of individuals	Observed events in the risk interval	Expected events in the risk interval	Incidence per 100,000 person-years	Background incidence per 100,000 person-years[1]	Pre-specified upper limit of expected events in the risk interval[2]	RR[3]	LLR[3]	Critical value of LLR[4]	Statistical power to detect RR of 2[4]	Statistical power to detect RR of 3[4]	Signal detected based on LLR> critical value of LLR

[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk interval.
[3] RR and LLR were not estimated when fewer than 3 events were observed during the risk interval or when the upper limit was fewer than 3 events (or 1 event for KD). When there was no increase in RR due to the vaccine, RR=1 and LLR=0 were reported. Rows with safety events of interest with signals detected were shaded green.
[4] Critical values and power were calculated using the upper limit, alpha level of 0.05 for GBS and 0.01 for all other safety events of interest, and minimum number of events needed before the null hypothesis could be rejected were 1 for KD and 3 for all other safety events of interest. For safety events with upper limit exceeding n=1,000 events, a critical value of n=1,000 from Kulldorff 2011 was used as a conservative proxy and 1.00 was used for statistical power.
[5] For each individual, only the last influenza vaccine and/or the Pfizer-BioNTech COVID-19 vaccine was included in the analysis. Death was only counted once after their Pfizer-BioNTech COVID-19 vaccine, or if they did not receive the Pfizer-BioNTech COVID-19 vaccine, after their last influenza vaccine. Death was not restricted to the risk interval.

Based on the sequential signal detection results above, cerebrovascular non-hemorrhagic stroke, ON, other acute demyelinating disease, GBS, anaphylaxis, AMI, arrhythmia, CAD, heart failure and cardiogenic shock, myocarditis, stress cardiomyopathy, microangiopathy, chilblain-like lesions, DVT, hemorrhagic disease, PE, acute kidney injury, and severe COVID-19 disease warranted further evaluation to refine and test such detections through signal evaluation.

10.3.1.2. Signal Evaluation

Binomial MaxSPRT with SCRI Design for Safety Events of Interest with Signals Detected

For any safety events of interest with signals detected that were not already analyzed using binomial MaxSPRT methodology during the signal detection phase, Table 14 presents the signal evaluation results where binomial MaxSPRT was conducted to compare the risk of the safety event of interest during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine to the risk of the same safety event of interest during the post-vaccination control interval using the SCRI design. Signals were considered to persist if the LLR test statistic exceeded the pre-specified critical value (green shaded rows). Given the lower power of the SCRI design using binomial MaxSPRT, all safety events of interest with signals detected from the signal detection phase proceeded to the next step of signal evaluation analyses (i.e., multivariate Poisson regression analysis).

Table 14. Signal Evaluation - Comparing Safety Events of Interest in the Aggregate Risk Intervals After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Interval using Binomial MaxSPRT

Safety Event of Interest with Signal Detected	Number of individuals	N (%) of individuals with safety event	Observed events in risk interval	Risk of safety event during risk interval	Observed events in control interval	Risk of safety event during control interval	Binomial MaxSPRT[1]					
							Upper limit[2]	RR	LLR	Critical value of LLR[3]	Statistical power to detect RR of 3[3]	Signal remains based on LLR> critical value of LLR
Neurologic												
Cerebrovascular non-hemorrhagic stroke	1,644,419	1,245 (0.08)	642	0.516	603	0.484	1,000	1.06	0.611	5.764	1.000	No
GBS	1,645,600	13 (0.00)	<11	NR‡	<11	NR‡	32	1.60	0.349	3.391	0.754	No
ON	1,645,563	414 (0.03)	236	0.570	178	0.430	883	1.33	4.076	5.731	1.000	No
Other acute demyelinating diseases	1,645,575	272 (0.02)	150	0.551	122	0.449	451	1.23	1.444	5.545	1.000	No
Immunologic												
Anaphylaxis	1,652,211	14 (0.00)	<11	NR‡	<11	NR‡	10	1.80	0.579	4.159	0.133	No
Cardiac												
AMI	1,643,895	2,566 (0.16)	1,267	0.494	1,299	0.506	1,000	0.98	0.000	5.764	1.000	No
Arrhythmia	1,639,302	10,937 (0.67)	5,742	0.525	5,195	0.475	1,000	1.11	13.684	5.764	1.000	Yes
CAD	1,638,272	15,093 (0.92)	8,136	0.539	6,957	0.461	1,000	1.17	46.096	5.764	1.000	Yes
Heart failure and cardiogenic shock	1,642,746	8,042 (0.49)	4,193	0.521	3,849	0.479	1,000	1.09	7.360	5.764	1.000	Yes
Microangiopathy	1,647,611	11 (0.00)	<11	NR‡	<11	NR‡	17	0.38	0.000	4.852	0.251	No
Myocarditis	1,645,595	122 (0.01)	70	0.574	52	0.426	153	1.35	1.333	5.468	1.000	No

Table 14. Signal Evaluation - Comparing Safety Events of Interest in the Aggregate Risk Intervals After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Interval using Binomial MaxSPRT

Safety Event of Interest with Signal Detected	**Number of individuals**	**N (%) of individuals with safety event**	**Observed events in risk interval**	**Risk of safety event during risk interval**	**Observed events in control interval**	**Risk of safety event during control interval**	**Binomial MaxSPRT[1]**					
							Upper limit[2]	**RR**	**LLR**	**Critical value of LLR[3]**	**Statistical power to detect RR of 3[3]**	**Signal remains based on LLR> critical value of LLR**
Stress cardiomyopathy	1,645,611	61 (0.00)	34	0.557	27	0.443	53	1.26	0.403	4.883	0.825	No
Hematologic												
Chilblain-like lesions	1,647,620	27 (0.00)	NR‡	NR‡	<11	NR‡	17	1.70	0.918	4.852	0.251	No
Hemorrhagic disease	1,647,615	13 (0.00)	<11	NR‡	<11	NR‡	17	1.17	0.039	4.852	0.251	No
DVT	1,646,874	3,907 (0.24)	2,164	0.554	1,743	0.446	1,000	1.24	22.727	5.764	1.000	Yes
PE	1,645,737	3,246 (0.20)	1,937	0.597	1,309	0.403	1,000	1.48	61.134	5.764	1.000	Yes
Other												
Acute kidney injury	1,641,847	12,977 (0.79)	6,610	0.509	6,367	0.491	1,000	1.04	2.275	5.764	1.000	No

Table 14. Signal Evaluation - Comparing Safety Events of Interest in the Aggregate Risk Intervals After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Interval using Binomial MaxSPRT

Safety Event of Interest with Signal Detected	**Number of individuals**	**N (%) of individuals with safety event**	**Observed events in risk interval**	**Risk of safety event during risk interval**	**Observed events in control interval**	**Risk of safety event during control interval**	**Binomial MaxSPRT[1]**					
							Upper limit[2]	**RR**	**LLR**	**Critical value of LLR[3]**	**Statistical power to detect RR of 3[3]**	**Signal remains based on LLR> critical value of LLR**

Abbreviations: AMI, acute myocardial infarction; CAD: coronary artery disease; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; GBS, Guillain-Barré Syndrome; LLR, log-likelihood ratio; MaxSPRT, maximized sequential probability ratio test; NR, not reported; ON, optic neuritis; PE: pulmonary embolism; RR, relative risk; VHA, Veterans Health Administration.

Notes:

‡ Certain counts were not reported to protect patient privacy.

[1] Some combinations of parameter values make the MaxSPRT non-applicable. In this analysis, it was not possible to calculate critical values for safety events that had incidences of <1 and upper limit <7. Rows with safety events of interest that had signals that persisted based on binomial MaxSPRT were shaded green.

[2] The upper limit was calculated by multiplying the background incidence of each safety event of interest in the risk interval by the total estimated number of Pfizer-BioNTech COVID-19 vaccines administered in the VHA. According to correspondence with the VHA, the total estimated number of dose 1 Pfizer-BioNTech COVID-19 vaccines was 2 million. Therefore, the upper limit was defined as the expected number of events in the risk and control intervals, and was rounded to the nearest whole number. Upper limits larger than 1,000 were capped at 1,000 based on binomial MaxSPRT documentation.

[3] Critical values and power were calculated using the upper limit, and alpha level of 0.05 for GBS and 0.01 for all other safety events of interest.

Multivariate Adjustment using Poisson Regression

Table 15 describes the incidence rates per 100,000 person-years [95% CI] for all safety events of interest that proceeded to signal evaluation. Incidence rates during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 among individuals who were administered at least one dose of the Pfizer-BioNTech COVID-19 vaccine and the background incidence rate among the seasonal influenza vaccine sample are described.

Among the Pfizer-BioNTech COVID-19 vaccine sample and seasonal influenza vaccine sample, respectively, the unadjusted incidence rate per 100,000 person-years [95% CI] for chilblain-like lesions was 5.36 [3.38, 8.51] and 1.16 [0.60, 2.23]; for anaphylaxis was 38.49 [20.71, 71.53] and 9.01 [3.75, 21.64]; for myocarditis was 15.49 [12.27, 19.54] and 7.38 [5.98, 9.12]; and for stress cardiomyopathy was 7.63 [5.48, 10.63] and 2.58 [1.80, 3.68]. The incidence rate per 100,000 person-years [95% CI] for severe COVID-19 disease was 474.57 [455.03, 494.94] for the Pfizer-BioNTech COVID-19 vaccine sample.

The multivariate Poisson regression adjusted for relevant baseline and/or clinical characteristics and imbalanced baseline characteristics with standardized differences >10% between the two samples, which included HBV, hyperlipidemia, hypertension, Tdap or Td vaccination, shingles vaccination, pneumococcal conjugate vaccination, and pneumococcal polysaccharide vaccination. For safety events of interest with few events, fewer imbalanced baseline characteristics were adjusted for due to sparse data; these were restricted to hyperlipidemia, hypertension, Tdap or Td vaccination, shingles vaccination, pneumococcal conjugate vaccination, and pneumococcal polysaccharide vaccination. Based on this analysis, chilblain-like lesions met the pre-defined safety signal definition (i.e., IRR >3 and p <0.01) with an adjusted IRR [95% CI] of 3.60 [1.48, 8.77] with p-value <0.01. Myocarditis and stress cardiomyopathy did not meet the pre-defined safety signal definition with adjusted IRR [95% CI] (p-value) 2.22 [1.59, 3.10] (<0.01) and 2.89 [1.71, 4.87] (<0.01), respectively. Anaphylaxis nearly met the pre-defined safety signal definition and had a signal that remained with an adjusted IRR [95% CI] (p-value) of 4.54 [1.29, 16.01] (0.019). The multivariate Poisson regression models did not converge when examining microangiopathy and hemorrhagic disease due to the small number of events, and Poisson regression models could not be used to further examine severe COVID-19 disease. Therefore, microangiopathy, chilblain-like lesions, hemorrhagic disease, and severe COVID-19 disease proceeded to the next step of signal evaluation analyses for further investigation.

Table 15. Signal Evaluation - Multivariate Adjusted Comparison of Incidence Rates for Safety Events of Interest Occurring in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine and Background Incidence Rates among the Seasonal Influenza Vaccine Sample[1]

Safety Events of Interest with Signal Detected	Incidence per 100,000 person-years (95% CI) among Pfizer-BioNTech COVID-19 Vaccine Sample	Background incidence per 100,000 person-years (95% CI)[2] among Seasonal Influenza Vaccine Sample	IRR[3][4]	95% CI	p-value	Signal remains (i.e., IRR>3 and p-value <0.01)
	Number of doses = 1,652,514	Number of doses = 10,138,984				
Neurologic						
Cerebrovascular non-hemorrhagic stroke	198.65 (184.13, 214.31)	148.84 (140.50, 157.67)	1.38	(1.24, 1.54)	<0.001*	No
GBS[4]	1.75 (0.87, 3.49)	1.55 (0.97, 2.45)	1.61	(0.63, 4.08)	0.320	No
ON	51.48 (45.32, 58.49)	42.68 (39.08, 46.60)	1.33	(1.12, 1.59)	0.001*	No
Other acute demyelinating diseases[4]	32.50 (27.68, 38.16)	21.81 (19.29, 24.66)	1.54	(1.23, 1.92)	<0.001*	No
Immunologic						
Anaphylaxis[4]	38.49 (20.71, 71.53)	9.01 (3.75, 21.64)	4.54	(1.29, 16.01)	0.019	No
Cardiac						
AMI	402.14 (381.25, 424.17)	311.72 (299.55, 324.39)	1.39	(1.29, 1.49)	<0.001*	No
Arrhythmia	1,288.20 (1,255.73, 1,321.51)	1,110.84 (1,091.85, 1,130.15)	1.30	(1.25, 1.34)	<0.001*	No
CAD	1,820.36 (1,781.67, 1,859.90)	1,693.22 (1,669.74, 1,717.03)	1.24	(1.21, 1.28)	<0.001*	No
Heart failure and cardiogenic shock	951.32 (923.48, 979.99)	909.60 (892.43, 927.09)	1.14	(1.09, 1.18)	<0.001*	No
Microangiopathy[4]	1.19 (0.45, 3.17)	1.16 (0.60, 2.23)	-†	-	-	-
Myocarditis[4]	15.49 (12.27, 19.54)	7.38 (5.98, 9.12)	2.22	(1.59, 3.10)	<0.001*	No
Stress cardiomyopathy[4]	7.63 (5.48, 10.63)	2.58 (1.80, 3.68)	2.89	(1.71, 4.87)	<0.001*	No
Hematologic						
Chilblain-like lesions[4]	5.36 (3.38, 8.51)	1.16 (0.60, 2.23)	3.60	(1.48, 8.77)	0.005*	Yes
DVT	656.72 (629.87, 684.72)	585.03 (568.26, 602.29)	1.23	(1.16, 1.30)	<0.001*	No
Hemorrhagic disease[4]	2.68 (1.39, 5.15)	1.16 (0.60, 2.23)	-†	-	-	-
PE	588.72 (563.33, 615.26)	337.74 (325.06, 350.92)	1.77	(1.65, 1.89)	<0.001*	No
Other						
Acute kidney injury	1,502.60 (1,467.49, 1,538.54)	1,261.55 (1,241.31, 1,282.13)	1.25	(1.21, 1.29)	<0.001*	No
Severe COVID-19 disease[5]	474.57 (455.03, 494.94)	-	-	-	-	-

Table 15. Signal Evaluation - Multivariate Adjusted Comparison of Incidence Rates for Safety Events of Interest Occurring in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine and Background Incidence Rates among the Seasonal Influenza Vaccine Sample[1]

Safety Events of Interest with Signal Detected	Incidence per 100,000 person-years (95% CI) among Pfizer-BioNTech COVID-19 Vaccine Sample	Background incidence per 100,000 person-years (95% CI)[2] among Seasonal Influenza Vaccine Sample	IRR[3][4]	95% CI	p-value	Signal remains (i.e., IRR>3 and p-value <0.01)
	Number of doses = 1,652,514	Number of doses = 10,138,984				

Abbreviations: AMI, acute myocardial infarction; BMI, Body Mass Index; CAD: coronary artery disease; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; GBS, Guillain-Barré Syndrome; HBV, hepatitis B virus; IRR, incidence rate ratio; ON, optic neuritis; PE: pulmonary embolism; Td, diphtheria and tetanus; Tdap, diphtheria, tetanus and (acellular) pertussis; VHA, Veterans Health Administration.
Notes:
* Denotes p-values <0.01.
† Models did not converge due to small number of events.
[1] All individuals in each sample were included in the unadjusted incidence rate (95% CI) calculation. Less than seven individuals (i.e., 21 doses; 14 doses from Pfizer-BioNTech COVID-19 vaccine sample and seven doses from seasonal influenza vaccine sample) with unknown gender were excluded from the multivariate Poisson regression analysis.
[2] Background incidences were based on events that occurred in the risk interval after the seasonal influenza vaccine during five prior influenza seasons (i.e., 2014/2015 to 2018/2019) in VHA data.
[3] IRR was estimated using a multivariate Poisson regression model, adjusting for age at vaccination, age category ≥65, sex, race/ethnicity, geographic region (other and unknown region were combined into one category), smoking status, BMI, history of anaphylaxis/allergic reactions, history of hospitalizations, CCI, frailty index, cancer, chronic kidney disease, COPD, cardiovascular conditions [e.g., heart failure, CAD, or cardiomyopathies], sickle cell disease, type 1 and 2 diabetes mellitus, as well as other imbalanced baseline characteristics with standardized differences >10% between the two samples, which include HBV, hyperlipidemia, hypertension, Tdap or Td vaccination, shingles vaccination, pneumococcal conjugate vaccination, and pneumococcal polysaccharide vaccination. Rows with safety events of interest that had signals that persisted were shaded green.
[4] For these safety events of interest, IRR was estimated using a multivariate Poisson regression model, adjusting for fewer covariates, due to sparse data. The following covariates were adjusted for: age at vaccination, sex, race/ethnicity (white vs. non-white), geographic region (South, West, and Other), history of anaphylaxis/allergic reactions, frailty index, as well as other imbalanced baseline characteristics with standardized differences >10% between the two samples, which include hyperlipidemia, hypertension, Tdap or Td vaccination, shingles vaccination, pneumococcal conjugate vaccination, and pneumococcal polysaccharide vaccination.
[5] Multivariate Poisson regression was not run for severe COVID-19 disease, as there was no historical incidence of severe COVID-19 in the seasonal influenza vaccine comparator cohort.

SCCS Design using Conditional Poisson Regression for Comparison with Post-Vaccination Control Time Period

Table 16 presents signal evaluation results where conditional Poisson regression was conducted to compare the incidence of microangiopathy, chilblain-like lesions, hemorrhagic disease, and severe COVID-19 disease during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine to the incidence of the same safety event of interest during the post-vaccination control time period using the SCCS design.

Signals remained if RI>3 and the p-value <0.01. Microangiopathy and severe COVID-19 disease both had RI<1. Chilblain-like lesions and hemorrhagic disease had RI>1; however, p-values were not <0.01 (RI [95% CI] (p-value): 1.49 [0.86, 2.59] (0.06) and 1.22 [0.54, 2.76] (0.63), respectively). Therefore, no signals remained based on the conditional Poisson regression with SCCS design as no safety events met the pre-defined safety signal definition.

Table 16. Signal Evaluation - Comparing Safety Events of Interest in the Aggregate Risk Interval After Monovalent Doses 1-4 and Bivalent Dose 1 of the Pfizer-BioNTech COVID-19 Vaccine to the Post-Vaccination Control Time Period using Conditional Poisson Regression with SCCS Design

Safety Event of Interest with Signals Detected	**Number of individuals**	**N (%) of individuals with safety event**	**Observed events in risk interval**	**Observed events in control time period**	**RI**	**95% CI**	**p-value**	**Signal remains (i.e., RI>3 and p-value <0.01)**
Cardiac								
Microangiopathy[1]	1,652,505	36 (0.00)	<11	NR‡	0.41	(0.14, 1.17)	0.10	No
Hematologic								
Chilblain-like lesions[1]	1,652,514	66 (0.00)	18	48	1.49	(0.86, 2.59)	0.06	No
Hemorrhagic disease[1]	1,652,509	32 (0.00)	<11	NR‡	1.22	(0.54, 2.76)	0.63	No
Other								
Severe COVID-19 disease	1,644,767	4,234 (0.00)	1,214	3,020	0.94	(0.88, 1.01)	0.07	No

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; RI, relative incidence; SCCS, self-controlled case series.
Notes:
‡ Certain counts were not reported to protect patient privacy.
[1] Firth correction was used due to small event counts in risk and control intervals.

Overall, for the safety events of interest for which signals were detected following the Pfizer-BioNTech COVID-19 vaccine, none had signals remained based on the signal evaluation analyses. Accordingly, no safety events of interest proceeded to the next signal evaluation analyses or signal verification through chart review.

10.3.2. Prioritized Safety Analysis of Myocarditis/Pericarditis

10.3.2.1. Analysis of Myocarditis/Pericarditis Events based on Codified Data

Based on the analysis of the codified data, there was no signal detected for myocarditis/pericarditis. However, the sample size of young men of 12-39 years of age (N=130,904; population of special interest based on CDC as myocarditis/pericarditis is most common in this group of young males) may have been too small to meaningfully detect rare myocarditis/pericarditis events.

10.3.2.1.1. Codified Myocarditis/Pericarditis Incidence Rates in 21-Day Risk Interval

Table 17 presents descriptive incidence rates of codified myocarditis/pericarditis events in the 21-day risk interval (the primary risk interval of interest as defined by the VSD) after the Pfizer-BioNTech COVID-19 vaccine stratified by sex, age (i.e., 12-39 years, 40-49 years, 50-64 years, ≥65 years), and race/ethnicity. Among all individuals receiving at least one dose, there were a total of 52 myocarditis/pericarditis events in the 21-day risk intervals after monovalent dose 1, monovalent dose 2, monovalent dose 3, monovalent dose 4, or bivalent dose 1.

Sex

Males had a higher incidence rate than females overall with the 95% CIs overlapping between the two groups (incidence rate per million doses [95% CI]: 11.4 [8.6, 15.1] vs. 6.5 [2.1, 20.1]). A similar trend was observed among individuals that were 12-39 years old, whereby the incidence rate in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 was higher for males than females with overlapping 95% CIs (incidence rate per million doses [95% CI]: 20.4 [9.2, 45.4] vs. 11.3 [1.6, 80.1]). No females had any myocarditis/pericarditis events after monovalent dose 1, monovalent dose 2, or bivalent dose 1, however females had higher incidence rates than males after monovalent dose 3 (25.1 [6.3, 100.5] vs. 15.2 [8.7, 26.8]) and monovalent dose 4 (47.9 [6.7, 339.9] vs. 11.8 [3.8, 36.6]), with overlapping 95% CIs.

Age

In the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 among individuals with at least one dose, individuals 12-39 years old had higher incidence rates with overlapping 95% CIs of myocarditis/pericarditis events than older age groups. A similar trend was seen among males after monovalent doses 1 and 2.

Dose

Among male individuals, a possible dose-response effect was observed with an increasing myocarditis/pericarditis risk from monovalent dose 1 (incidence rate per million doses [95% CI]: 10.1 [6.1, 16.8]) and monovalent dose 2 (9.8 [5.8, 16.5]) to monovalent dose 3 (15.2 [8.7, 26.8]), with overlapping 95% CI; although the risk decreased slightly in the risk interval after monovalent dose 4 with a wider confidence interval (11.8 [3.8, 36.6]). A similar trend was observed among male individuals ≥65 years old, but no dose-response effect was

seen in male individuals 12-39 years old. Bivalent dose 1 had an incidence rate per million doses [95% CI] of 15.1 [6.3, 36.3].

Race/Ethnicity

In the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 among males, other race/ethnicity (which included Asian, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, and those with two or more races) had a higher incidence rate per million doses [95% CI] of 19.3 [6.2, 59.9] than white non-Hispanic (12.6 [9.0, 17.7]), Black (10.9 [5.9, 20.3]), and Hispanic ethnicity, any race (10.0 [3.2, 30.9]) with overlapping 95% CIs. A similar trend was observed in the risk interval after monovalent dose 1 and bivalent dose 1. There were no clear patterns or differences in myocarditis/pericarditis incidence rate per million doses between race/ethnicity categories after monovalent doses 2-4.

Table 17. Myocarditis/Pericarditis Rates Based on ICD-10 Coded Events in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Female events[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male events[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Aggregate Monovalent Doses 1-4 and Bivalent Dose 1[5]						
Overall	<11	NR‡	6.5 (2.1, 20.1)	NR‡	NR‡	11.4 (8.6, 15.1)
Age (years)[6]						
12-39	<11	NR‡	11.3 (1.6, 80.1)	<11	NR‡	20.4 (9.2, 45.4)
12-17	0	0	-	0	0	-
18-24	0	1,287	-	0	2,168	-
25-29	0	13,558	-	0	39,168	-
30-39	<11	NR‡	13.5 (1.9, 96.2)	<11	NR‡	23.7 (10.7, 52.8)
40-49	0	88,104	-	<11	NR‡	6.6 (1.6, 26.2)
50-64	<11	NR‡	5.4 (0.8, 38.0)	12	NR‡	12.1 (6.9, 21.3)
⩾65	<11	NR‡	10.1 (1.4, 72.0)	29	NR‡	10.8 (7.5, 15.5)
Race/ethnicity[7], n (%)						
White non-Hispanic	<11	NR‡	9.6 (2.4, 38.2)	33	2,618,915	12.6 (9.0, 17.7)
Black	0	NR‡	-	<11	NR‡	10.9 (5.9, 20.3)
Hispanic ethnicity, any race	0	NR‡	-	<11	NR‡	10.0 (3.2, 30.9)
Other[8]	0	23,055	-	<11	NR‡	19.3 (6.2, 59.9)
Unknown	<11	NR‡	31.0 (4.4, 219.9)	0	295,040	-
Monovalent Dose 1						
Overall	0	167,957	-	15	1,481,209	10.1 (6.1, 16.8)
Age (years)[6]						
12-39	0	38,704	-	<11	NR‡	23.0 (7.4, 71.2)
12-17	0	0	-	0	0	-
18-24	0	595	-	0	1,030	-
25-29	0	6,138	-	0	18,102	-
30-39	0	31,971	-	<11	NR‡	26.9 (8.7, 83.4)
40-49	0	35,177	-	<11	NR‡	15.9 (4.0, 63.7)
50-64	0	NR‡	-	<11	NR‡	14.3 (6.0, 34.4)
⩾65	0	NR‡	-	<11	NR‡	5.7 (2.4, 13.7)

Table 17. Myocarditis/Pericarditis Rates Based on ICD-10 Coded Events in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Female events[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male events[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Race/ethnicity[7], n (%)						
White non-Hispanic	0	NR‡	-	<11	NR‡	7.7 (3.7, 16.1)
Black	0	58,090	-	<11	NR‡	16.4 (6.8, 39.5)
Hispanic ethnicity, any race	0	13,949	-	<11	NR‡	9.4 (1.3, 66.8)
Other[8]	0	8,455	-	<11	NR‡	37.0 (9.3, 148.0)
Unknown	0	12,153	-	0	107,239	-
Monovalent Dose 2						
Overall	0	160,055	-	14	1,429,331	9.8 (5.8, 16.5)
Age (years)[6]						
12-39	0	35,737	-	<11	NR‡	24.8 (8.0, 76.9)
12-17	0	0	-	0	0	-
18-24	0	531	-	0	918	-
25-29	0	5,603	-	0	16,487	-
30-39	0	29,603	-	<11	NR‡	29.0 (9.3, 89.9)
40-49	0	33,195	-	0	118,603	-
50-64	0	61,195	-	<11	NR‡	8.9 (2.9, 27.7)
⩾65	0	29,928	-	<11	NR‡	9.4 (4.7, 18.7)
Race/ethnicity[7], n (%)						
White non-Hispanic	0	72,327	-	NR‡	NR‡	14.8 (8.6, 25.4)
Black	0	54,778	-	<11	NR‡	3.4 (0.5, 24.4)
Hispanic ethnicity, any race	0	13,245	-	0	102,277	-
Other[8]	0	8,099	-	0	52,206	-
Unknown	0	11,606	-	0	103,314	-
Monovalent Dose 3						
Overall	<11	NR‡	25.1 (6.3, 100.5)	NR‡	NR‡	15.2 (8.7, 26.8)
Age (years)[6]						
12-39	<11	NR‡	94.8 (13.4, 673.3)	0	32,131	-
12-17	0	0	-	0	0	-

Table 17. Myocarditis/Pericarditis Rates Based on ICD-10 Coded Events in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Female events[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male events[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
18-24	0	120	-	0	178	-
25-29	0	1,390	-	0	3,545	-
30-39	<11	NR‡	110.7 (15.6, 785.9)	0	28,408	-
40-49	0	13,763	-	0	NR‡	-
50-64	<11	NR‡	28.2 (4.0, 200.0)	<11	NR‡	16.7 (5.4, 51.8)
⩾65	0	19,799	-	NR‡	NR‡	16.9 (8.8, 32.5)
Race/ethnicity[7], n (%)						
White non-Hispanic	<11	NR‡	27.7 (3.9, 196.9)	<11	NR‡	16.7 (8.3, 33.4)
Black	0	28,617	-	<11	NR‡	17.1 (5.5, 52.9)
Hispanic ethnicity, any race	0	5,778	-	<11	NR‡	18.5 (2.6, 131.6)
Other[8]	0	3,971	-	0	28,362	-
Unknown	<11	NR‡	192.5 (27.1, 1,366.5)	0	50,035	-
Monovalent Dose 4						
Overall	<11	NR‡	47.9 (6.7, 339.9)	<11	NR‡	11.8 (3.8, 36.6)
Age (years)[6]						
12-39	0	530	-	0	1,313	-
12-17	0	0	-	0	0	-
18-24	0	NR‡	-	0	<11	-
25-29	0	NR‡	-	0	NR‡	-
30-39	0	475	-	0	1,174	-
40-49	0	1,324	-	0	3,568	-
50-64	0	10,856	-	<11	NR‡	19.8 (2.8, 140.6)
≥65	<11	NR‡	122.3 (17.2, 868.3)	<11	NR‡	10.1 (2.5, 40.2)
Race/ethnicity[7], n (%)						
White non-Hispanic	<11	NR‡	101.1 (14.2, 717.8)	<11	NR‡	13.0 (3.2, 51.8)
Black	0	7,721	-	<11	NR‡	16.8 (2.4, 119.5)
Hispanic ethnicity, any race	0	1,078	-	0	16,054	-
Other[8]	0	838	-	0	8,782	-

Table 17. Myocarditis/Pericarditis Rates Based on ICD-10 Coded Events in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Female events[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male events[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Unknown	0	1,359	-	0	15,443	-
Bivalent Dose 1						
Overall	0	NR‡	-	<11	NR‡	15.1 (6.3, 36.3)
Age (years)[6]						
12-39	0	3,156	-	0	9,201	-
12-17	0	0	-	0	0	-
18-24	0	35	-	0	41	-
25-29	0	378	-	0	896	-
30-39	0	2,743	-	0	8,264	-
40-49	0	4,645	-	0	14,211	-
50-64	0	15,681	-	0	75,417	-
⩾65	0	NR‡	-	<11	NR‡	21.5 (9.0, 51.7)
Race/ethnicity[7], n (%)						
White non-Hispanic	0	NR‡	-	<11	NR‡	15.4 (5.0, 47.6)
Black	0	NR‡	-	0	NR‡	-
Hispanic ethnicity, any race	0	2,164	-	<11	NR‡	45.0 (6.3, 319.3)
Other[8]	0	NR‡	-	<11	NR‡	84.1 (11.8, 597.0)
Unknown	0	1,971	-	0	19,009	-

Table 17. Myocarditis/Pericarditis Rates Based on ICD-10 Coded Events in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Female events[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male events[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ICD-10, International Classification of Disease, 10th Revision; NR, not reported.

Notes:

‡ Certain counts were not reported to protect patient privacy.

[1] Individuals with unknown gender were excluded from this analysis.

[2] The end of observation for each dose was defined as the earliest of first disenrollment from the Veterans Health Administration, end of the risk interval, date of monovalent dose 2 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 1 analyses only), date of monovalent dose 3 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 2 analyses only), date of monovalent dose 4 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 3 analyses only), date of bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 4 analyses only), date of death, or end of data collection (i.e., 30 June 2023).

[3] Myocarditis/pericarditis events were identified by the following ICD-10 codes: B33.22, B33.23, I30.*, I40.*. In order to be considered an incident event, the diagnosis must be the first incidence in the inpatient or emergency department setting in 60 days. The event was not counted if the individual's first ever COVID-19 diagnosis code or COVID-19 positive lab test was present in the last 30 days prior to the event.

[4] Myocarditis/pericarditis rates were calculated as the number of events divided by the number of doses administered, which were then standardized to a per-million doses basis. Rates and associated 95% CI were obtained from the GENMOD procedure in SAS.

[5] Individuals with any dose of the Pfizer-BioNTech COVID-19 vaccine were included in this analysis.

[6] Age on the date of the first Pfizer-BioNTech COVID-19 vaccination was reported.

[7] If multiple categories were noted in the data, individuals were classified as two or more races, with the exception of Hispanic ethnicity. If Hispanic ethnicity was recorded for any individual, they were classified as Hispanic. Individuals with both known and unknown race categories recorded in the data were classified into their known category.

[8] Other races included Asian, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, and those with two or more races.

10.3.2.1.2. Concurrent Vaccinated Comparator Analysis

Table 18 reports adjusted rate ratios calculated by comparing myocarditis/pericarditis events during the risk intervals (i.e., 7-day, 21-day, and 42-day) after the Pfizer-BioNTech COVID-19 vaccine to those occurring in the corresponding comparison interval among concurrent Pfizer-BioNTech COVID-19 vaccinated comparators on the same calendar days. The rate of myocarditis/pericarditis events during the 21-day risk interval after the Pfizer-BioNTech COVID-19 vaccine was not significantly different during the comparison interval for aggregated monovalent doses 1-4 and bivalent dose 1 (adjusted rate ratio [95% CI]: 0.96 [0.66, 1.40]), monovalent dose 1 (1.33 [0.61, 2.91]), monovalent dose 2 (1.24 [0.56, 2.75]), monovalent dose 3 (0.73 [0.35, 1.49]), monovalent dose 4 (0.62 [0.18, 2.17]), or bivalent dose 1 (2.51 [0.48, 13.21]) of the Pfizer-BioNTech COVID-19 vaccine. Similar results were observed when examining the rate of myocarditis/pericarditis events during the 7-day and 42-day risk interval after the Pfizer-BioNTech COVID-19 vaccine, except for the adjusted rate ratio [95% CI] of myocarditis/pericarditis events in the 42-day risk interval after the Pfizer-BioNTech COVID-19 vaccine compared to the comparison interval for aggregated monovalent doses 1-4 and bivalent dose 1 was 1.47 [1.07, 2.01]. However, these results did not meet the pre-defined safety signal definition of RR >3 and p <0.01. Overall, based on this analysis of the codified data, there was no signal detected for myocarditis/pericarditis. However, the sample size of men of 12-39 years of age may be too small to meaningfully detect rare myocarditis/pericarditis events.

Table 18. Myocarditis/Pericarditis Events Based on ICD-10 Codes in the Risk Interval after the Pfizer-BioNTech COVID-19 Vaccine Compared with Events in Concurrent Vaccinated Comparators on the Same Calendar Days[1-3]

		Events in risk interval	Adjusted rate ratio[4]	95% CI	p-value	Signal detected (i.e., rate ratio >3 and p-value <0.05)
Any dose [5,6]						
7-day risk interval	(N=1,652,495)	<11	0.37	[0.17, 0.78]	0.010*	no
21-day risk interval	(N=1,652,480)	52	0.96	[0.66, 1.40]	0.818	no
42-day risk interval	(N=1,652,324)	94	1.47	[1.07, 2.01]	0.018*	no
Monovalent Dose 1 [5]						
7-day risk interval†	(N=1,649,158)	<11	0.48	[0.12, 1.97]	0.308	no
21-day risk interval	(N=1,649,142)	15	1.33	[0.61, 2.91]	0.472	no
42-day risk interval	(N=1,648,867)	20	1.06	[0.55, 2.06]	0.854	no
Monovalent Dose 2 [5]						
7-day risk interval†	(N=1,589,309)	<11	0.30	[0.06, 1.51]	0.144	no
21-day risk interval	(N=1,589,304)	14	1.24	[0.56, 2.75]	0.599	no
42-day risk interval	(N=1,589,250)	25	0.87	[0.50, 1.51]	0.621	no
Monovalent Dose 3 [5]						
7-day risk interval†	(N=866,972)	<11	0.28	[0.06, 1.35]	0.113	no
21-day risk interval†	(N=866,972)	14	0.73	[0.35, 1.49]	0.381	no
42-day risk interval†	(N=866,972)	31	1.73	[0.91, 3.26]	0.093	no
Monovalent Dose 4 [5]						
7-day risk interval†	(N=274,967)	<11	0.35	[0.04, 3.36]	0.362	no
21-day risk interval†	(N=274,967)	<11	0.62	[0.18, 2.17]	0.458	no
42-day risk interval†	(N=274,967)	NR‡	1.63	[0.60, 4.46]	0.340	no
Bivalent Dose 1						
7-day risk interval†	(N=364,577)	<11	0.45	[0.04, 5.07]	0.522	no
21-day risk interval†	(N=364,577)	<11	2.51	[0.48, 13.21]	0.277	no
42-day risk interval†	(N=364,513)	<11	0.91	[0.25, 3.29]	0.887	no

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ICD-10, International Classification of Disease, 10th Revision; NR, not reported; VHA, Veterans Health Administration.

Notes:

* Denotes p-values <0.05.

† Models did not converge due to small number of events.

‡ Certain counts were not reported to protect patient privacy.

[1] Myocarditis/pericarditis events were identified by the following ICD-10 codes: B33.22, B33.23, I30.*, I40.*. In order to be considered an incident event, the diagnosis must be the first incidence in the inpatient or emergency department setting in 60 days. The event was excluded if the individual's first ever COVID-19 diagnosis code or COVID-19 positive lab test was present in the last 30 days prior to the event.

[2] The end of observation for each dose was defined as the earliest of first disenrollment from the Veterans Health Administration, end of the risk interval, date of monovalent dose 2 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 1 analyses only), date of monovalent dose 3 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 2 analyses only), date of monovalent dose 4 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 3 analyses only), date of bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 4 analyses only), date of death, or end of data collection (i.e., 30 June 2023).

[3] Individuals with unknown gender were excluded from this analysis.

[4] Poisson regression was used to compare outcome incidence during risk intervals to outcome incidence during comparison intervals. The log of the expected count of events in a risk or comparison interval in a stratum on a calendar day

Table 18. Myocarditis/Pericarditis Events Based on ICD-10 Codes in the Risk Interval after the Pfizer-BioNTech COVID-19 Vaccine Compared with Events in Concurrent Vaccinated Comparators on the Same Calendar Days[1-3]

	Events in risk interval	Adjusted rate ratio[4]	95% CI	p-value	Signal detected (i.e., rate ratio >3 and p-value <0.05)

was modeled as a function of whether the stratum's vaccinees were in a risk versus a comparison interval on that day. The analysis was adjusted for age group, sex, race-ethnicity, VHA service area, as well as calendar date. Calendar dates that had individuals only in a risk or a comparison interval were excluded from the analysis.
[5] If the date of Pfizer-BioNTech COVID-19 vaccine monovalent dose 2 or bivalent dose 1 overlapped with the risk interval of monovalent dose 1, the risk interval of monovalent dose 1 was censored on the date of monovalent dose 2 or bivalent dose 1, and the comparison interval of monovalent dose 1 was shortened to match the length of the risk interval of monovalent dose 1. If the date of Pfizer-BioNTech COVID-19 vaccine monovalent dose 3 or bivalent dose 1 overlapped with the risk interval of monovalent dose 2, the risk interval of monovalent dose 2 was censored on the date of monovalent dose 3 or bivalent dose 1, and the comparison interval of monovalent dose 2 was shortened to match the length of the risk interval of monovalent dose 2. If the date of Pfizer-BioNTech COVID-19 vaccine monovalent dose 4 or bivalent dose 1 overlapped with the risk interval of monovalent dose 3, the risk interval of monovalent dose 3 was censored on the date of monovalent dose 4 or bivalent dose 1, and the comparison interval of monovalent dose 3 was shortened to match the length of the risk interval of monovalent dose 3. If the date of Pfizer-BioNTech COVID-19 vaccine bivalent dose 1 overlapped with the risk interval of monovalent dose 4, the risk interval of monovalent dose 4 was censored on the date of bivalent dose 1, and the comparison interval of monovalent dose 4 was shortened to match the length of the risk interval of monovalent dose 4.
[6] Individuals with any dose of the Pfizer-BioNTech COVID-19 vaccine were included in this analysis.

10.3.2.2. Analysis of Chart-Confirmed Myocarditis/Pericarditis Cases

A total of 52 codified myocarditis/pericarditis events that occurred in the 21-day risk interval (the primary risk interval of interest as defined by the VSD) after any dose of the Pfizer-BioNTech COVID-19 vaccine were reviewed for case confirmation through medical chart examination. A physician examined relevant medical chart data from one year prior to the myocarditis/pericarditis event date to the end of follow-up (i.e., earliest of one year after the event date, death, disenrollment from VHA benefits, lost to follow-up, or database end date [30 June 2023]) for adjudication. Chart review data from 47 myocarditis/pericarditis events included in prior interim reports were reused for this final report so these 47 previously examined myocarditis/pericarditis events did not undergo chart review again.

Of the 52 cases, 36 were confirmed as myocarditis/pericarditis events that occurred within the 21-day risk interval (Table 19). Of these, 34 (94.4%) individuals had pericarditis and 6 (16.7%) individuals had myocarditis, with 4 individuals having both myocarditis and pericarditis.

For these 36 confirmed cases that occurred following a Pfizer-BioNTech COVID-19 vaccine, <3 (<8.3%) case(s) was noted as vaccine-related by the adjudicator team; <3 (<8.3%) cases were possibly vaccine-related with influences of confounding factors such as flare of rheumatologic condition and coexisting pneumonia; 19 (52.8%) cases were likely not

vaccine-related, including 13 (36.1%) cases that were likely procedure-related (e.g., ablation procedures, pacemaker placement, percutaneous coronary intervention, drain placed to treat an enlarging chronic pericardial effusion, stent for non-ST-elevation myocardial infarction) and 6 (16.7%) likely due to other reasons (e.g., pre-existing conditions, viral or idiopathic pericarditis); the remaining 14 (38.9%) cases did not have a clearly defined cause although there was no evidence that they were vaccine-related.

In addition to the 36 confirmed cases occurring during the 21-day risk interval, 3 events were confirmed as cases but occurred after the 21-day risk interval and were thus excluded from the analysis. These events included possible vaccine-related events with influences from other factors such as presence of lung cancer, recent radiation therapy, and use of the immunomodulator pembrolizumab, and procedure-related cases (e.g., pericardial window, pacemaker placement).

Of the 52 total codified myocarditis/pericarditis events, 13 events were not confirmed as cases through chart review. Reasons for non-confirmation included absence of evidence of myocarditis/pericarditis in medical charts, cases were determined to be pericardial effusion, and individual having experienced the event in years prior.

Table 19. Case Confirmation of Codified Myocarditis/Pericarditis Events through Chart Review among Individuals who Received the Pfizer-BioNTech COVID-19 Vaccine

	Myocarditis/pericarditis events identified by ICD-10 codes in the 21-day risk interval[1] (N=52)
Number of chart-confirmed myocarditis/pericarditis cases, n (%)	36 (69.2)
Adjudication results, n (%)[2]	
Any myocarditis	6 (16.7)
Any pericarditis	34 (94.4)

Abbreviations: COVID-19, coronavirus disease 2019; ICD-10, International Classification of Disease, 10th Revision; VHA, Veterans Health Administration.
Notes:
[1] Of the 52 cumulative myocarditis/pericarditis events, 26 events were previously observed and adjudicated for the second interim report, 17 events were previously observed and adjudicated for the third interim report, 4 events were previously observed and adjudicated for the fourth interim report, and 5 events were newly identified. Note, the second interim report included 29 codified myocarditis/pericarditis events in the 21-day risk interval that were adjudicated, however 3 of those events are no longer included in the final report due to individuals with the event no longer meeting eligibility criteria or updates to the VHA database. Reasons for ineligibility included no longer meeting the continuous enrollment criterion prior to vaccination date and receipt of other manufacturer's vaccine.
[2] Four individuals had both myocarditis and pericarditis.

10.3.2.2.1. Chart-Confirmed Myocarditis/Pericarditis Rates in 21-Day Risk Interval

Table 20 describes incidence rates for the 36 chart-confirmed myocarditis/pericarditis cases in the 21-day risk interval stratified by age (i.e., 12-39 years old, 40-49 years old, 50-64 years old, ⩾65 years old), sex, and race/ethnicity. Overall incidence rates for chart-confirmed myocarditis/pericarditis cases (not stratified by sex) are also presented to facilitate comparison with preliminary findings on myocarditis/pericarditis following COVID-19 vaccination published by ACIP on 23 June 2021.[60]

Sex

Among individuals with at least one dose, males had a higher incidence rate than females, with the 95% CIs overlapping between the two groups (incidence rate per million doses [95% CI]: 7.9 [5.7, 11.1] vs. 4.3 [1.1, 17.3]). This pattern remained for monovalent doses 1 and 2 and bivalent dose 1 but reversed for monovalent doses 3 and 4, though 95% CI overlapped between the two groups.

Among individuals 12-39 years old, the incidence rate in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 was lower for males than females with overlapping 95% CIs (incidence rate per million doses [95% CI]: 10.2 [3.3, 31.6] vs. 11.3 [1.6, 80.1]). In the risk interval after monovalent dose 1 and dose 2, 12-39 year old males had an incidence rate per million doses [95% CI] of 15.3 [3.8, 61.2] and 8.3 [1.2, 58.7], respectively, and no females had any confirmed myocarditis/pericarditis. In the risk interval after dose 3, the 12-39 year old females had an incidence rate per million doses [95% CI]: 94.8 [13.4, 673.3], and no 12-39 year old males had any confirmed myocarditis/pericarditis cases. Neither 12-39 year old males nor females had any confirmed myocarditis/pericarditis cases after monovalent dose 4 and bivalent dose 1.

Age

In the aggregated monovalent doses 1-4 and bivalent dose 1 analyses, individuals 12-39 years old had higher incidence rates of myocarditis/pericarditis than older age groups with overlapping 95% CIs. This trend was not observed for monovalent doses 1 and 2 but was seen for monovalent dose 3. In the risk interval after monovalent dose 4 and bivalent dose 1, no 12-39 years old had any confirmed myocarditis/pericarditis.

Dose

There was no clear dose-response trend among all male individuals and male individuals 12-39 years old. Among male individuals ≥65 years old, a possible dose-response effect was observed with an increasing myocarditis/pericarditis risk from monovalent dose 1 (incidence rate per million doses [95% CI]: 4.6 [1.7, 12.2]) to monovalent dose 2 (7.0 [3.2, 15.6]) to monovalent dose 3 (13.2 [6.3, 27.6]), with overlapping 95% CIs; though incidence decreased slightly in the risk interval after monovalent dose 4 with a wider confidence interval (10.1 [2.5, 40.2]) and the incidence was 17.2 [6.5, 45.8] in the risk interval after bivalent dose 1.

Race/Ethnicity

In the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 among males, incidence rates per million doses [95% CI] were similar between the race/ethnicity categories (i.e., white non-Hispanic: 9.5 [6.5, 14.1]; Hispanic ethnicity, any races: 10.0 [3.2, 30.9]; other race/ethnicity: 6.4 [0.9, 45.7]; Black: 5.5 [2.3, 13.2]). The only female cases were white non-Hispanic.

Table 20. Chart-Confirmed Myocarditis/Pericarditis Rates Regardless of Etiology Based on Adjudication Results in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Cases[3]*	*Doses*	*Rates per million doses (95% CI)[4]*	*Female cases[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male cases[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Aggregated Monovalent Doses 1-4 and Bivalent Dose 1[5]									
Overall	NR‡	NR‡	7.6 (5.5, 10.5)	<3	NR‡	4.3 (1.1, 17.3)	NR‡	NR‡	7.9 (5.7, 11.1)
Age (years)[6]									
12-39	NR‡	NR‡	10.4 (3.9, 27.8)	<3	NR‡	11.3 (1.6, 80.1)	NR‡	NR‡	10.2 (3.3, 31.6)
12-17	0	0	-	0	0	-	0	0	-
18-24	0	3,455	-	0	1,287	-	0	2,168	-
25-29	0	52,726	-	0	13,558	-	0	39,168	-
30-39	NR‡	NR‡	12.2 (4.6, 32.6)	<3	NR‡	13.5 (1.9, 96.2)	NR‡	NR‡	11.9 (3.8, 36.8)
40-49	<3	NR‡	5.1 (1.3, 20.3)	0	88,104	-	<3	NR‡	6.6 (1.6, 26.2)
50-64	NR‡	NR‡	5.1 (2.3, 11.3)	0	NR‡	-	NR‡	NR‡	6.1 (2.7, 13.5)
≥65	NR‡	NR‡	8.6 (5.8, 12.8)	<3	NR‡	10.1 (1.4, 72.0)	NR‡	NR‡	8.5 (5.7, 12.8)
Race/ethnicity[7], n (%)									
White non-Hispanic	NR‡	NR‡	9.5 (6.5, 13.9)	<3	NR‡	9.6 (2.4, 38.2)	NR‡	NR‡	9.5 (6.5, 14.1)
Black	5	1,074,646	4.7 (1.9, 11.2)	0	NR‡	-	5	NR‡	5.5 (2.3, 13.2)
Hispanic ethnicity, any race	3	336,929	8.9 (2.9, 27.6)	0	NR‡	-	NR‡	NR‡	10.0 (3.2, 30.9)
Other[8]	<3	NR‡	5.6 (0.8, 39.8)	0	23,055	-	<3	NR‡	6.4 (0.9, 45.7)
Unknown	0	327,324	-	0	NR‡	-	0	295,040	-
Monovalent Dose 1									
Overall	11	1,649,166	6.7 (3.7, 12.0)	0	167,957	-	11	1,481,209	7.4 (4.1, 13.4)
Age (years)[6]									
12-39	<3	NR‡	11.8 (3.0, 47.2)	0	38,704	-	<3	NR‡	15.3 (3.8, 61.2)
12-17	0	0	-	0	0	-	0	0	-
18-24	0	1,625	-	0	595	-	0	1,030	-

Table 20. Chart-Confirmed Myocarditis/Pericarditis Rates Regardless of Etiology Based on Adjudication Results in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Cases[3]*	*Doses*	*Rates per million doses (95% CI)[4]*	*Female cases[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male cases[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
25-29	0	24,240	-	0	6,138	-	0	18,102	-
30-39	<3	NR‡	13.9 (3.5, 55.7)	0	31,971	-	<3	NR‡	17.9 (4.5, 71.7)
40-49	<3	NR‡	12.4 (3.1, 49.8)	0	35,177	-	<3	NR‡	15.9 (4.0, 63.7)
50-64	3	412,396	7.3 (2.3, 22.6)	0	NR‡	-	3	NR‡	8.6 (2.8, 26.7)
≥65	4	906,750	4.4 (1.7, 11.8)	0	NR‡	-	4	NR‡	4.6 (1.7, 12.2)
Race/ethnicity[7], n (%)									
White non-Hispanic	7	984,741	7.1 (3.4, 14.9)	0	NR‡	-	7	NR‡	7.7 (3.7, 16.1)
Black	<3	NR‡	5.5 (1.4, 22.1)	0	58,090	-	<3	NR‡	6.6 (1.6, 26.3)
Hispanic ethnicity, any race	<3	NR‡	8.3 (1.2, 59.1)	0	13,949	-	<3	NR‡	9.4 (1.3, 66.8)
Other[8]	<3	NR‡	16.0 (2.3, 113.6)	0	8,455	-	<3	NR‡	18.5 (2.6, 131.4)
Unknown	0	119,392	-	0	12,153	-	0	107,239	-
Monovalent Dose 2									
Overall	8	1,589,386	5.0 (2.5, 10.1)	0	160,055	-	8	1,429,331	5.6 (2.8, 11.2)
Age (years)[6]									
12-39	<3	NR‡	6.4 (0.9, 45.3)	0	35,737	-	<3	NR‡	8.3 (1.2, 58.7)
12-17	0	0	-	0	0	-	0	0	-
18-24	0	1,449	-	0	531	-	0	918	-
25-29	0	22,090	-	0	5,603	-	0	16,487	-
30-39	<3	NR‡	7.5 (1.1, 53.3)	0	29,603	-	<3	NR‡	9.7 (1.4, 68.6)
40-49	0	151,798	-	0	33,195	-	0	118,603	-
50-64	<3	NR‡	2.5 (0.4, 17.9)	0	61,195	-	<3	NR‡	3.0 (0.4, 21.2)
≥65	6	884,135	6.8 (3.0, 15.1)	0	NR‡	-	6	NR‡	7.0 (3.2, 15.6)

Table 20. Chart-Confirmed Myocarditis/Pericarditis Rates Regardless of Etiology Based on Adjudication Results in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Cases[3]*	*Doses*	*Rates per million doses (95% CI)[4]*	*Female cases[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male cases[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Race/ethnicity[7], n (%)									
White non-Hispanic	NR‡	NR‡	7.3 (3.5, 15.4)	0	72,327	-	NR‡	NR‡	8.0 (3.8, 16.7)
Black	<3	NR‡	2.9 (0.4, 20.5)	0	54,778	-	<3	NR‡	3.4 (0.5, 24.4)
Hispanic ethnicity, any race	0	115,522	-	0	13,245	-	0	102,277	-
Other[8]	0	60,305	-	0	8,099	-	0	52,206	-
Unknown	0	114,920	-	0	11,606	-	0	103,314	-
Monovalent Dose 3									
Overall	NR‡	NR‡	10.4 (5.4, 20.0)	<3	NR‡	12.6 (1.8, 89.2)	NR‡	NR‡	10.2 (5.1, 20.3)
Age (years)[6]									
12-39	<3	NR‡	23.4 (3.3, 166.4)	<3	NR‡	94.8 (13.4, 673.3)	0	32,131	-
12-17	0	0	-	0	0	-	0	0	-
18-24	0	298	-	0	120	-	0	178	-
25-29	0	4,935	-	0	1,390	-	0	3,545	-
30-39	<3	NR‡	26.7 (3.8, 189.6)	<3	NR‡	110.7 (15.6, 785.9)	0	28,408	-
40-49	0	NR‡	-	0	13,763	-	0	NR‡	-
50-64	<3	NR‡	4.7 (0.7, 33.0)	0	NR‡	-	<3	NR‡	5.6 (0.8, 39.5)
≥65	NR‡	NR‡	12.7 (6.0, 26.6)	0	19,799	-	NR‡	NR‡	13.2 (6.3, 27.6)
Race/ethnicity[7], n (%)									
White non-Hispanic	NR‡	NR‡	13.6 (6.5, 28.5)	<3	NR‡	27.7 (3.9, 196.9)	6	NR‡	12.5 (5.6, 27.9)
Black	<3	NR‡	4.9 (0.7, 34.8)	0	28,617	-	<3	NR‡	5.7 (0.8, 40.4)

Table 20. Chart-Confirmed Myocarditis/Pericarditis Rates Regardless of Etiology Based on Adjudication Results in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Cases[3]*	*Doses*	*Rates per million doses (95% CI)[4]*	*Female cases[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male cases[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Hispanic ethnicity, any race	<3	NR‡	16.7 (2.4, 118.9)	0	5,778	-	<3	NR‡	18.5 (2.6, 131.6)
Other[8]	0	32,333	-	0	3,971	-	0	28,362	-
Unknown	0	NR‡	-	0	NR‡	-	0	50,035	-
Monovalent Dose 4									
Overall	NR‡	NR‡	14.5 (5.5, 38.8)	<3	NR‡	47.9 (6.7, 339.9)	3	NR‡	11.8 (3.8, 36.6)
Age (years)[6]									
12-39	0	1,843	-	0	530	-	0	1,313	-
12-17	0	0	-	0	0	-	0	0	-
18-24	0	7	-	0	NR‡	-	0	<3	-
25-29	0	187	-	0	NR‡	-	0	NR‡	-
30-39	0	1,649	-	0	475	-	0	1,174	-
40-49	0	4,892	-	0	1,324	-	0	3,568	-
50-64	<3	NR‡	16.3 (2.3, 115.8)	0	10,856	-	<3	NR‡	19.8 (2.8, 140.6)
≥65	3	206,909	14.5 (4.7, 45.0)	<3	NR‡	122.3 (17.2, 868.3)	<3	NR‡	10.1 (2.5, 40.2)
Race/ethnicity[7], n (%)									
White non-Hispanic	3	164,294	18.3 (5.9, 56.6)	<3	NR‡	101.1 (14.2, 717.8)	<3	NR‡	13.0 (3.2, 51.8)
Black	<3	NR‡	14.9 (2.1, 105.8)	0	7,721	-	<3	NR‡	16.8 (2.4, 119.5)
Hispanic ethnicity, any race	0	17,132	-	0	1,078	-	0	16,054	-
Other[8]	0	9,620	-	0	838	-	0	8,782	-
Unknown	0	16,802	-	0	1,359	-	0	15,443	-

Table 20. Chart-Confirmed Myocarditis/Pericarditis Rates Regardless of Etiology Based on Adjudication Results in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Cases[3]*	*Doses*	*Rates per million doses (95% CI)[4]*	*Female cases[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male cases[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*
Bivalent Dose 1									
Overall	4	364,718	11.0 (4.1, 29.2)	0	NR‡	-	4	NR‡	12.1 (4.5, 32.2)
Age (years)[6]									
12-39	0	12,357	-	0	3,156	-	0	9,201	-
12-17	0	0	-	0	0	-	0	0	-
18-24	0	76	-	0	35	-	0	41	-
25-29	0	1,274	-	0	378	-	0	896	-
30-39	0	11,007	-	0	2,743	-	0	8,264	-
40-49	0	18,856	-	0	4,645	-	0	14,211	-
50-64	0	91,098	-	0	15,681	-	0	75,417	-
≥65	4	242,407	16.5 (6.2, 44.0)	0	NR‡	-	4	NR‡	17.2 (6.5, 45.8)
Race/ethnicity[7], n (%)									
White non-Hispanic	NR‡	NR‡	14.2 (4.6, 44.1)	0	NR‡	-	NR‡	NR‡	15.4 (5.0, 47.6)
Black	0	94,908	-	0	NR‡	-	0	NR‡	-
Hispanic ethnicity, any race	<3	NR‡	41.0 (5.8, 291.0)	0	2,164	-	<3	NR‡	45.0 (6.3, 319.3)
Other[8]	0	13,583	-	0	NR‡	-	0	NR‡	-
Unknown	0	20,980	-	0	1,971	-	0	19,009	-

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ED, emergency department; ICD-10, International Classification of Disease, 10th Revision; IP, inpatient; NR, not reported; VHA, Veterans Health Administration.

‡ Certain counts were not reported to protect patient privacy.

Notes:

[1] Individuals with unknown gender were excluded from this analysis.

[2] The end of observation for each dose was defined as the earliest of first disenrollment from the VHA, end of the risk interval, date of monovalent dose 2 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 1 analyses only), date of monovalent dose 3 or bivalent dose 1 of the Pfizer-

Table 20. Chart-Confirmed Myocarditis/Pericarditis Rates Regardless of Etiology Based on Adjudication Results in the 21-Day Risk Interval among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine[1,2]

Subgroups	*Cases[3]*	*Doses*	*Rates per million doses (95% CI)[4]*	*Female cases[3]*	*Female doses*	*Female rates per million doses (95% CI)[4]*	*Male cases[3]*	*Male doses*	*Male rates per million doses (95% CI)[4]*

BioNTech COVID-19 vaccine (for monovalent dose 2 analyses only), date of monovalent dose 4 or bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 3 analyses only), date of bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine (for monovalent dose 4 analyses only), date of death, or end of data collection (i.e., 30 June 2023).

[3] Each myocarditis/pericarditis event identified by the ICD-10 codes (B33.22, B33.23, I30.*, I40.*) was reviewed by one physician. Only the first incident event was included in the analysis. In order to be considered an incident event, the diagnosis must have been the first incidence in the IP or ED setting in 60 days. The event was excluded if the individual's first ever COVID-19 diagnosis code or COVID-19 positive lab test was present in the last 30 days prior to the event. An event was considered chart-confirmed if the physician determined the event was present.

[4] Myocarditis/pericarditis rates were calculated as the number of events divided by the number of doses administered, which were then standardized to a per-million doses basis. Rates and associated 95% CI were obtained from the GENMOD procedure in SAS.

[5] Individuals with any dose of the Pfizer-BioNTech COVID-19 vaccine were included in this analysis.

[6] Age on the date of first Pfizer-BioNTech COVID-19 vaccination was reported.

[7] If multiple categories were noted in the data, individuals were classified as two or more races, with the exception of Hispanic ethnicity. If Hispanic ethnicity was recorded for any individual, they were classified as Hispanic. Individuals with both known and unknown race categories recorded in the data were classified into their known category.

[8] Other races included Asian, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, and those with two or more races.

10.3.2.2.2. Risk Factors, Clinical Course, and Sequalae of Chart-Confirmed Myocarditis/Pericarditis Rates

Table 21 describes the risk factors, clinical course, and sequelae of the 36 confirmed myocarditis/pericarditis cases. With regard to etiologies/risk factors evaluated in the 365 days prior to the occurrence of chart-confirmed myocarditis/pericarditis, 7 (19.4%) individuals had other vaccines (including influenza, zoster, TDAP, and tetanus); 6 (16.7%) individuals had other prior viral infections (including SARS-CoV-2 viral infection, upper respiratory infection and rhinovirus); and 7 (19.4%) individuals had comorbid immunocompromising conditions and systemic immune-mediated disease. The mean times between monovalent doses and bivalent dose of the Pfizer-BioNTech COVID-19 vaccine to onset of myocarditis/pericarditis were 10-15 days and 15.3 days, respectively.

During the myocarditis/pericarditis episode, individuals experienced chest pain (91.7%) and shortness of breath (44.4%), although the majority had symptom resolution. The most common treatments received for myocarditis/pericarditis included colchicine (83.3%) and non-steroidal anti-inflammatory drugs (NSAIDs; 66.7%). From myocarditis/pericarditis onset to the end of follow-up (mean of 6.0 months), 30.6% individuals had at least one ED visit, 30.6% had at least one outpatient visit, and 33.3% had at least one hospitalization. All 6 (100%) individuals with chart-confirmed myocarditis and 32 (94.1%) individuals with chart-confirmed pericarditis had recovered by the end of follow-up; individuals with pericarditis who had not recovered by the end of follow-up had chronic pericarditis.

Table 21. Descriptive Analysis of Risk Factors, Clinical Course, and Sequelae of Chart-Confirmed Myocarditis/Pericarditis Cases among Individuals who Received the Pfizer-BioNTech COVID-19 Vaccine

	Individuals with chart-confirmed myocarditis/pericarditis (N=36)
Etiologies/risk factors for myocarditis/pericarditis evaluated in the 365 days prior to event, n (%)	
Other vaccines[1]	7 (19.4)
Prior viral infections[2]	6 (16.7)
Prior SARS-CoV-2 viral infection[3]	4 (11.1)
Comorbid immunocompromising conditions and systemic immune-mediated diseases[4]	7 (19.4)
None of the above	19 (52.8)
Onset of myocarditis/pericarditis after first monovalent dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	**11 (30.6)**
Time between first monovalent dose and onset of myocarditis/pericarditis (days)	
Mean ± SD	11.8 ± 6.8
Median (IQR)	12.0 (8.0, 19.0)
Onset of myocarditis/pericarditis after second monovalent dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	**8 (22.2)**
Time between second monovalent dose and onset of myocarditis/pericarditis (days)	
Mean ± SD	14.5 ± 5.3
Median (IQR)	15.0 (9.5, 19.0)
Onset of myocarditis/pericarditis after third monovalent dose/booster dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	**NR‡**
Time between third monovalent dose/booster dose and onset of myocarditis/pericarditis (days)	
Mean ± SD	9.7 ± 7.0
Median (IQR)	8.0 (4.0, 14.0)
Onset of myocarditis/pericarditis after fourth monovalent dose/booster dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	**NR‡**
Time between fourth monovalent dose/booster dose and onset of myocarditis/pericarditis (days)	
Mean ± SD	10.5 ± 3.1
Median (IQR)	11.5 (8.5, 12.5)

Table 21. Descriptive Analysis of Risk Factors, Clinical Course, and Sequelae of Chart-Confirmed Myocarditis/Pericarditis Cases among Individuals who Received the Pfizer-BioNTech COVID-19 Vaccine

	Individuals with chart-confirmed myocarditis/pericarditis (N=36)
Onset of myocarditis/pericarditis after first bivalent dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	**4 (11.1)**
Time between first bivalent dose and onset of myocarditis/pericarditis (days)	
Mean ± SD	15.3 ± 5.3
Median (IQR)	15.5 (11.0, 19.5)
Symptoms experienced during the myocarditis/pericarditis episode, n (%)	
Chest pain	**33 (91.7)**
Resolved	23 (69.7)
Ongoing	0 (0.0)
Unknown	10 (30.3)
Shortness of breath	**16 (44.4)**
Resolved	9 (56.3)
Ongoing	<3 (<18.8)
Unknown	NR‡
Weakness or fatigue	**5 (13.9)**
Resolved	<3 (<60.0)
Ongoing	NR‡
Unknown	3 (60.0)
Fever	**4 (11.1)**
Resolved	<3 (<75.0)
Ongoing	0 (0.0)
Unknown	<3 (<75.0)
Heart palpitations[5]	**<3 (<8.3)**
Resolved	NR‡
Ongoing	NR‡
Unknown	NR‡
Cough[5]	**<3 (<8.3)**
Resolved	NR‡
Ongoing	NR‡
Unknown	NR‡
Arm or shoulder pain[5]	**<3 (<8.3)**
Resolved	NR‡
Ongoing	NR‡
Unknown	NR‡

Table 21. Descriptive Analysis of Risk Factors, Clinical Course, and Sequelae of Chart-Confirmed Myocarditis/Pericarditis Cases among Individuals who Received the Pfizer-BioNTech COVID-19 Vaccine

	Individuals with chart-confirmed myocarditis/pericarditis (N=36)
Orthopnea[5]	**<3 (<8.3)**
Resolved	NR‡
Ongoing	NR‡
Unknown	NR‡
Hypotension[5]	**<3 (<8.3)**
Resolved	NR‡
Ongoing	NR‡
Unknown	NR‡
Treatments received for myocarditis/pericarditis, n (%)	
Colchicine	30 (83.3)
NSAIDs	24 (66.7)
Corticosteroids	5 (13.9)
Other[6]	5 (13.9)
Length of follow-up after myocarditis/pericarditis event onset (months), mean ± SD [median]	6.0 ± 2.0 [6.4]
Healthcare resource utilization from myocarditis/pericarditis onset to the end of follow-up[7]	
Individuals with ≥1 ED visit, n (%)	11 (30.6)
Number of ED visits, per month, mean ± SD [median]	0.2 ± 0.1 [0.1]
Individuals with ≥1 hospitalization, n (%)	12 (33.3)
Number of hospitalizations, per month, mean ± SD [median]	0.2 ± 0.1 [0.2]
Length of hospitalization stay (days), per stay, mean ± SD [median]	1.5 ± 0.9 [1.4]
Individuals with ≥1 ICU admissions, n (%)	<3 (<8.3)
Number of ICU admissions, per month, mean ± SD [median]	0.3 ± 0.2 [0.3]
Individuals with ≥1 outpatient visit, n (%)	11 (30.6)
Number of outpatient visits, per month, mean ± SD [median]	1.0 ± 0.8 [0.8]
Recovered by the end of follow-up, n (%)	
Myocarditis (n=6)	6 (100.0)
Pericarditis (n=34)[8]	32 (94.1)

Table 21. Descriptive Analysis of Risk Factors, Clinical Course, and Sequelae of Chart-Confirmed Myocarditis/Pericarditis Cases among Individuals who Received the Pfizer-BioNTech COVID-19 Vaccine

	Individuals with chart-confirmed myocarditis/pericarditis (N=36)

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NR, not reported; NSAID, non-steroidal anti-inflammatory drugs; SD, standard deviation.
‡ Certain counts were not reported to protect patient privacy.
Notes:
[1] Other vaccines included influenza, zoster, TDAP, and tetanus.
[2] Other prior viral infections included upper respiratory infection and rhinovirus.
[3] Evaluated between January 2020 and receipt of the first dose of the Pfizer-BioNTech COVID-19 vaccine.
[4] Comorbid immunocompromising conditions and systemic immune-mediated diseases included recent percutaneous coronary intervention, lung cancer and pneumonia, rheumatoid arthritis, adult-onset Stills Disease, systemic chemotherapy for esophageal cancer, and unspecified comorbidity.
[5] Symptom resolution status for symptoms experienced by <3 individuals were not reported to protect patient privacy.
[6] Other treatments received for myocarditis/pericarditis included pericardial drain, pericardial window, pericardiocentesis, and opium.
[7] Monthly rates of healthcare resource utilization were calculated among individuals with the specific type of encounter and included the encounter occurring on the day of myocarditis/pericarditis event onset.
[8] This number included individual(s) who experienced recurrent pericarditis after the initial event and recovered by the end of follow-up. Individuals with pericarditis who had not recovered by the end of follow-up had chronic pericarditis.

Table 22 describes the baseline risk factors potentially associated with chart-confirmed myocarditis/pericarditis cases. Using multivariate logistic regression, younger compared to older age (ages 12-39 vs. ages ≥65) was associated with higher odds of myocarditis/pericarditis cases (OR [95% CI]: 1.62 [0.52, 5.07]), but the results were not significant (p-value=0.408); this could be due to the limited sample size among individuals under 40 years of age in the VHA system (N=169,686). The only statistically significant risk factor identified to be associated with an increased odds of confirmed myocarditis/pericarditis was a prior history of all-cause hospitalizations at baseline (OR [95% CI]: 5.48 [2.47, 12.17]).

Table 22. Risk Factor Analysis of Chart-Confirmed Myocarditis/Pericarditis Cases Using Multivariate Logistic Regression Model (N=1,652,514)[1]

Baseline risk factors identified using codified data	Estimates	
	OR (95% CI)	P-value
Age (years, ref: ≥65)[2]		
12-39	1.62 (0.52, 5.07)	0.408
40-49	0.87 (0.20, 3.90)	0.859
50-64	0.74 (0.29, 1.88)	0.529
Male Sex	1.40 (0.32, 6.07)	0.656
Race/ethnicity (ref: white non-Hispanic)		
Black	0.52 (0.20, 1.39)	0.195
Other[3]	0.55 (0.19, 1.60)	0.274
VHA service area – US region (ref: non-South)[4]		
South	0.50 (0.24, 1.04)	0.063
Smoking[5]	1.29 (0.61, 2.74)	0.508
BMI (ref: normal weight [18.5–<25] or overweight [25–<30])[6]		
Underweight (<18.5) or unknown	0.47 (0.17, 1.29)	0.141
Obese or severely obese (≥30)	0.80 (0.39, 1.66)	0.555
History of hospitalizations	5.48 (2.47, 12.17)	<0.001*
CCI[7]	1.08 (0.91, 1.28)	0.378
Chronic kidney disease	1.22 (0.51, 2.88)	0.655
Cardiovascular conditions[8]	0.98 (0.44, 2.22)	0.967

Table 22. Risk Factor Analysis of Chart-Confirmed Myocarditis/Pericarditis Cases Using Multivariate Logistic Regression Model (N=1,652,514)[1]

Baseline risk factors identified using codified data	Estimates	
	OR (95% CI)	P-value

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CI, confidence interval; COVID-19, coronavirus disease 2019; ICD-9/10-CM: International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification; OR, odds ratio; US, United States; VHA, Veterans Health Administration.

Notes:

* Denotes p-value <0.01

[1] Individuals with unknown gender were excluded from this analysis. Among all individuals included in this analysis, 36 had confirmed myocarditis/pericarditis.

[2] Age on the date of the first Pfizer-BioNTech COVID-19 vaccination (for Pfizer-BioNTech COVID-19 vaccine recipients).

[3] If multiple categories were noted in the data, individuals were classified as two or more races, with the exception of Hispanic ethnicity. If Hispanic ethnicity was recorded for any individual, they were classified as Hispanic. Individuals with both known and unknown race categories recorded in the data were classified into their known category. Other included Asian, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, individuals with two or more races, and individuals with unknown race categories.

[4] The region information associated with the most recent healthcare encounter prior to index date was used. Midwest included IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; Northeast included CT, ME, MA, NH, NJ, NY, PA, RI, VT; South included AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West included AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; Other included Puerto Rico. The "Non-South" category includes Midwest, Northeast, West, Other and Unknown region.

[5] Smoking status was determined using ICD-9/10-CM diagnosis codes listed in Table 1 of Annex 1. Appendix 9. Smoking status represented current and/or history of smoking as documented in individuals' records during the baseline period.

[6] Most recent BMI record during the baseline period prior to vaccination date was included and was calculated based on individuals' height and weight data as dividing weight in kilograms (kg) by height in meters (m) squared. Individuals with missing BMI or those with BMI <15 or >60 were categorized as "Unknown".

[7] Identified based on ICD-9/10-CM diagnosis codes. For a full list of conditions included in the CCI, and associated ICD-9/10-CM diagnosis codes, see Table 1 of Annex 1. Appendix 9.

[8] Cardiovascular conditions included heart failure, CAD, and cardiomyopathies.

10.4. Other Analyses

Other analyses (including incidence rates of safety events of interest; person-time at risk analysis; analysis of severe COVID-19 disease stratified by SARS-CoV-2 subvariant strains; end-of-surveillance analysis; prioritized safety analysis of myocarditis/pericarditis using 7-day and 42-day risk intervals; and subgroup analyses) are described in Annex 1. Appendix 8.

10.5. Adverse Events/Adverse Reactions

Signal Detection and Signal Evaluation

The signal detection and signal evaluation analyses included in this final report involves data that existed as structured data by the time of database lockdown date or a combination of existing structured data and unstructured data, which were converted to structured form during the implementation of the protocol solely by a computer using natural language processing. In these data sources, individual patient data were not retrieved or validated, and it was not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) could not be met.

Chart Review of Codified Myocarditis/Pericarditis Events

The chart review of codified myocarditis/pericarditis events required human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer was obligated to report AEs with explicit attribution to any Pfizer drug that appeared in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution was not inferred by a temporal relationship between drug administration and an AE, but was based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events of interest on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety were as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appeared in the reviewed information were recorded on the data collection tool (e.g., chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product were reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed was captured in the Event Narrative section of the report form, and constituted all clinical information known regarding these AEs. No follow-up on related AEs was conducted.

All the demographic fields on the NIS AEM Report Form were not necessarily completed, as the form designated, since not all elements were available due to privacy concerns with the use of secondary data sources. While not all demographic fields were completed, at the very least, at least one patient identifier (e.g., sex, age as captured in the narrative field of the form) was reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers were limited to generalities, such as the statement "A 35-year-old female…" or "An elderly male...". Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" were documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

11. DISCUSSION

11.1. Summary and Discussion of Key Results

This final report is based on 30 months of the post-EUA experience of the Pfizer-BioNTech COVID-19 vaccine in the VHA, from 11 December 2020 to 30 June 2023 and included 1,652,514 individuals who received the Pfizer-BioNTech COVID-19 vaccine during this time. The comparator cohort included 4,104,220 individuals who received the seasonal influenza vaccine from the 2014/2015 influenza season to the 2018/2019 influenza season.

Baseline Characteristics

In the Pfizer-BioNTech COVID-19 vaccine sample, 55.0% were aged 65 years or older, 89.8% were males, 59.7% were white non-Hispanic, 22.0% were Black, 7.3% were Hispanic ethnicity, any race, and 1.5% were Asian. The distribution of sex and age was generally comparable between the two samples. The proportion of individuals who were aged 65 years or older in the Pfizer-BioNTech COVID-19 vaccine sample (55.0%) was lower than in the seasonal influenza vaccine sample (60.8%), but both were still consistent with that reported by Luo et al. (2021) in the overall VHA population (59.7%).[67] The standardized differences for white non-Hispanic and Black categories indicated some imbalance for race/ethnicity between the Pfizer-BioNTech COVID-19 vaccine sample and the seasonal influenza vaccine sample, though the remaining race/ethnicity categories were largely similar in the two samples (white non-Hispanic: 59.7% vs. 69.7%, standardized difference 21.0%; Black: 22.0% vs. 15.4%, standardized difference 17.0%; all other race/ethnicity categories: standardized differences <10%). The proportion of individuals with Black race/ethnicity in the Pfizer-BioNTech COVID-19 sample is higher than that in the general US population based on the 2020 Census (22.0% and 12.4%, respectively), so individuals of Black race/ethnicity may be overrepresented in this study.[68]

A higher proportion of individuals with unknown BMI was observed in the Pfizer-BioNTech COVID-19 vaccine sample in the two-year period preceding vaccination compared to the seasonal influenza vaccine sample (unknown BMI: 31.6% vs. 17.4%, standardized difference 33.4%). However, a published systematic review reported that the use of healthcare services decreased by approximately one-third during the COVID-19 pandemic.[69] The reduction in HRU and enhanced use of telehealth in the US during this time could have contributed to this difference as weight and height cannot be measured in telehealth settings.[70] Among the Pfizer-BioNTech COVID-19 vaccine sample, 65.5% of individuals did not receive a seasonal influenza vaccine during the influenza season in which the COVID-19 vaccination occurred.

Vaccine Utilization Patterns

Among the estimated 7.4 million individuals with at least one healthcare encounter during the 11 December 2020 to 30 June 2023 assessment period, the Pfizer-BioNTech COVID-19 vaccination rate (at least one dose) was 31.3%. The Pfizer-BioNTech COVID-19 monovalent vaccine two-dose, three dose/booster dose, and four dose/booster dose completion rate in this study was 96.2%, 52.5%, and 16.7%, respectively, and the majority of individuals in the VHA system received the Pfizer-BioNTech COVID-19 monovalent vaccine in an outpatient setting (>55%). A total of 365,972 (22.2%) individuals received a bivalent dose of the Pfizer-BioNTech COVID-19 vaccine. Among the US population, the CDC reported that the proportion of individuals who completed their primary series with the Pfizer-BioNTech COVID-19 monovalent vaccine was 40.0%, 51.0% of whom received a third monovalent dose/booster dose of the Pfizer-BioNTech COVID-19 vaccine after completing the primary series, and 21.5% of whom received a fourth monovalent dose/booster dose of the Pfizer-BioNTech COVID-19 vaccine up until 11 May 2023.[71] The proportion of the US population that received a bivalent dose of the Pfizer-BioNTech COVID-19 vaccine was 11.1%.[71]

Among 1,960,228 individuals with their first record of Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023 and two years of continuous enrollment in VHA healthcare benefits, 5.5% received a dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of two Pfizer-BioNTech vaccine doses (i.e., heterologous booster).

Signal Detection

Using the SCRI design, a potential signal was detected for severe COVID-19 disease using binomial MaxSPRT. Using the active comparator design, cerebrovascular non-hemorrhagic stroke, other acute demyelinating disease, AMI, anaphylaxis, arrhythmia, CAD, myocarditis, chilblain-like lesions, PE, ON, heart failure and cardiogenic shock, acute kidney injury, stress cardiomyopathy, and DVT had potential signals detected. Although a signal was not detected for GBS, microangiopathy, and hemorrhagic disease, these safety events proceeded to signal evaluation out of an abundance of caution. In total, based on the signal detection analyses, 18 of 48 safety events of interest warranted further investigation and were advanced to the signal evaluation phase.

This study had more safety events of interest with signals detected following the fourth monovalent dose/booster dose than the third monovalent dose/booster dose or the two primary doses of the Pfizer-BioNTech COVID-19 vaccine, although no detected signals remained after signal evaluation. In another study using electronic health records, more non-severe safety events following the third dose/booster dose than the first two doses of the primary series were observed, but the risk of severe safety events was similar between the third dose/booster dose and the primary series.[72] This study observed more safety events of interest with signals detected following the fourth monovalent dose/booster dose likely due to the higher proportion of older and immunocompromised individuals in the VHA population compared to the other studies. As older and immunocompromised individuals may not have a strong immune response to COVID-19 vaccination until they receive their booster doses, safety events of interest may be observed more often following the third dose/booster dose and fourth dose/booster dose of the Pfizer-BioNTech COVID-19 vaccine in this population.[73] Note, this study did not conduct a formal comparative trend analysis across doses or describe the demographic and clinical characteristics of individuals at each Pfizer-BioNTech COVID-19 vaccine dose, which may have impacted this descriptive trend if characteristics differed by vaccine dose.

This study observed a similar number and type of safety events of interest with signals detected following the monovalent dose 4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine. Based on this qualitative assessment, the monovalent and bivalent doses seemed to have comparable safety profiles. This is consistent with the literature as the CDC reported similar safety findings between the monovalent and bivalent vaccines among individuals age 12 years and older based on US v-safe and Vaccination Adverse Event Reporting System (VAERS) data.[74] This was further supported by CDC VSD analyses through March 2023 that found none of their 18 safety events of interest met the signaling criteria in the 21-day risk interval after the Pfizer-BioNTech COVID-19 bivalent booster vaccine among individuals ages 5-64 years old.[75] In the CDC VSD study, ischemic stroke was the only safety event with a signal detected following the Pfizer-BioNTech COVID-19 bivalent booster vaccine among individuals age 65 and older, while in this study, cerebrovascular non-hemorrhagic stroke did not have a signal detected after either the bivalent or monovalent doses. The divergent results may be due to methodological differences whereby the CDC VSD study used a concurrent comparator design varied study populations and observed high rates of simultaneous high-dose or adjuvanted flu vaccination with COVID-19 vaccination.[76] In addition, the safety of the Pfizer-BioNTech COVID-19 bivalent booster dose was examined in a nationwide cohort study in Denmark, and no association was observed between the bivalent booster dose and 27 different adverse events, including ischemic cardiac event.[77]

In the available literature, mainly descriptive or case studies of chilblain-like lesions, stress cardiomyopathy, microangiopathy, and heart failure and cardiogenic shock have been reported.[78-84] The current study more robustly examined the potential risk of chilblain-like lesions, stress cardiomyopathy, microangiopathy, as well as heart failure and cardiogenic shock after Pfizer-BioNTech COVID-19 vaccination. One registry study describing the morphology of chilblain-like lesions after Pfizer-BioNTech COVID-19 vaccination hypothesized that the chilblain-like lesions occurred due to an individual's immune response

to the COVID-19 virus trigged by the vaccine, as chilblain-like lesions have been observed in reaction to COVID-19 infection.[85] There is also limited literature examining CAD following Pfizer-BioNTech COVID-19 vaccination as more emphasis is placed on individuals with pre-existing CAD as a high-risk group for developing severe COVID-19.[5] In a SCCS study of individuals from Hong Kong with established cardiovascular disease, the primary series of the Pfizer-BioNTech COVID-19 vaccine was not associated with an increased risk of major adverse cardiovascular events.[86]

In addition, the currently available literature for each specific safety event of interest with signals detected in this study varied greatly. Some safety events of interest have mainly been examined in relation to COVID-19 vaccines from multiple manufacturers combined. First, in this study, only 0.12% of 1,637,996 individuals who received at least one dose of the Pfizer-BioNTech COVID-19 vaccine had severe COVID-19 disease following vaccination, which is consistent with another study using VHA data that found 0.09% individuals were hospitalized with COVID-19 pneumonia or died after receiving primary series vaccination and booster dose of the Pfizer-BioNTech, Moderna, or Johnson & Johnson COVID-19 vaccines.[87] Second, a SCCS study investigating hospital admissions from neurological complications in the 28 days following the first dose of COVID-19 vaccinations found no association between the Pfizer-BioNTech COVID-19 vaccine and acute central nervous system demyelinating diseases.[88] Furthermore, a safety study examining both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines among US nursing home residents did not detect a signal for demyelinating diseases in general, though this may be due to insufficient power with a smaller study population (<10,000 vaccine recipients) and because COVID-19 vaccines from different manufacturers were examined in combination.[89] Third, while cases of ON have been reported following COVID-19 vaccines,[90] one study using the WHO pharmacovigilance database and disproportionality analysis did not detect a safety signal for ON following mRNA-based COVID-19 vaccines. These results may differ from this study due to the different methodology and examination of mRNA COVID-19 vaccines together.[91] Fourth, thromboembolic events such as DVT have been mainly observed following viral-vector based vaccines (e.g., Oxford-AstraZeneca, Johnson & Johnson) at higher rates than expected and compared to mRNA vaccines, which led some European countries to suspend use of viral-vector vaccines.[92-94]

AMI, arrhythmia, anaphylaxis, cerebrovascular non-hemorrhagic stroke, hemorrhagic disease, acute kidney injury, PE, and GBS following Pfizer-BioNTech COVID-19 vaccine have been studied more frequently. In a near real-time surveillance study using Medicare healthcare claims, the FDA's BEST Initiative reported a potential signal for PE and AMI among individuals aged 65 years or older who received the Pfizer-BioNTech COVID-19 vaccine in July 2021.[95] The FDA emphasized that these initial findings did not determine causality between the Pfizer-BioNTech COVID-19 vaccine and AMI, and could be due to characteristics of the Medicare population being older, high-risk, and with significant comorbidities.[95] In addition, in the VSD final analyses using data through May 2022, a signal was detected for AMI and venous thromboembolism in the 21-day risk interval following the second monovalent dose of the Pfizer-BioNTech COVID-19 vaccine based on a comparison to concurrent vaccinated comparators.[75] This is similar to a WHO database study that linked AMI to COVID-19 vaccines among individuals aged 75 years or older and concluded that

further research is required to establish causality as the prevalence of AMI in the elderly population may impact the study's findings.[96] These results are consistent with this study, in which the signal that was detected for AMI may also be explained by the fact that the VHA population mainly consists of older veterans with a high comorbidity burden. In a SCCS study using national data from 30 million vaccinated individuals 16 years or older in England, no association was found between myocardial infarctions and the Pfizer-BioNTech COVID-19 vaccine.[97] Furthermore, two SCCS studies conducted in France also found no association between the primary series of the Pfizer-BioNTech COVID-19 vaccine and AMI.[98,99]

Similarly, several real-world case studies of arrhythmia have been reported following Pfizer-BioNTech COVID-19 vaccination, but in a study using England's immunization database and SCCS design, there was no increased risk of arrhythmia after Pfizer-BioNTech COVID-19 vaccination.[100,101] These results may differ from this study's due to England's vaccinated population being younger and healthier than the VHA population. Similarly, an association between the Pfizer-BioNTech COVID-19 vaccine and arrhythmia was not found in a nationwide safety surveillance study of more than 2.4 million individuals in Israel, where the population is also younger and healthier.[102]

Several real-world studies have observed anaphylaxis to be rare, but occurring more commonly after Pfizer-BioNTech COVID-19 vaccination than influenza vaccination.[103-105] This study found similar results; a higher rate of anaphylaxis was observed in the risk interval after the Pfizer-BioNTech COVID-19 vaccine than after seasonal influenza vaccinations (incidence rate per 100,000 person-years [95% CI]: 42.3 [22.8, 78.6] and 9.0 [3.8, 21.6], respectively). In the FDA's BEST Initiative rapid safety surveillance study using three large commercial insurance databases, a signal was detected for anaphylaxis following the Pfizer-BioNTech COVID-19 vaccine, consistent with this study.[106] Nevertheless, the incidence of anaphylaxis following Pfizer-BioNTech COVID-19 vaccination is generally low,[107] with one surveillance study using electronic health records from the multistate Mayo Clinic Enterprise reporting that out of approximately 38,000 individuals who received three doses of the Pfizer-BioNTech COVID-19 vaccine, only two experienced anaphylaxis.[72]

A limited number of studies have examined the risk of cerebrovascular non-hemorrhagic stroke or hemorrhagic disease following the Pfizer-BioNTech COVID-19 vaccine, although the AstraZeneca COVID-19 vaccine has been potentially associated with cerebrovascular non-hemorrhagic stroke.[108-112] Real-world SCCS analyses were conducted among vaccinated adults in England to examine neurological complications following COVID-19 vaccines and found an increased risk of ischemic and hemorrhagic strokes after the first dose of the Pfizer-BioNTech vaccine.[88,97] These results may be due to the SCCS design including the time period prior to the Pfizer-BioNTech COVID-19 vaccination date into the analyses, which could bias the results if the occurrence of the safety event of interest impacted the probability of vaccine exposure (e.g., individuals with ischemic stroke may be less likely to subsequently receive the Pfizer-BioNTech COVID-19 vaccine and therefore would be excluded from the analysis; this could lead to a false association between the Pfizer-BioNTech COVID-19 vaccine and ischemic stroke). Indeed, in sensitivity analyses

restricted to the period after Pfizer-BioNTech COVID-19 vaccination, the Pfizer-BioNTech COVID-19 vaccine was no longer associated with an increased risk of ischemic or hemorrhagic strokes. These sensitivity analyses are consistent with this study's SCCS analyses and results in the signal evaluation phase (described below).

Using data from the US VAERS, a signal was detected for acute kidney injury following the Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines, particularly among elderly individuals.[113] However, as VAERS is based on voluntary reporting that may bias the results, the study's authors stated that causality between COVID-19 vaccinations and acute kidney injury could not be determined and further investigation was necessary. This is consistent with this study whereby among the older VHA population, a signal was detected for acute kidney injury following the Pfizer-BioNTech COVID-19 vaccine. However, as described below, the signal did not persist following signal evaluation analyses.

Several real-world safety surveillance studies in different countries (i.e., US, Israel, France) did not detect any signals or find an increased risk of PE following Pfizer-BioNTech COVID-19 vaccination.[98,99,102,103] Differences between this study's population and methodology and those country-wide surveillance studies may help explain why this study detected a signal for PE. Specifically, a substantial proportion of the Pfizer-BioNTech COVID-19 vaccine sample from the VHA population had baseline risk factors for PE, including older age (age 65 years and older: 55.0%), cardiovascular conditions (14.9%), COPD/interstitial lung disease (11.3%), hypertension (55.7%), and obesity (32.0%). A weekly safety surveillance study using CMS data among elderly person aged 65 years and older identified a statistical signal for PE, consistent with this study.[114]

GBS has been reported to occur, though rarely, after COVID-19 vaccination from Pfizer-BioNTech and a variety of other COVID-19 vaccine manufacturers.[88,115] Based on data from the US VAERS, higher odds of GBS was observed after the Pfizer-BioNTech COVID-19 vaccine compared to the prevalence of GBS in the general population, though the frequency of GBS events was lower among individuals who received the Pfizer-BioNTech COVID-19 vaccine (0.5 per million doses) and the Moderna vaccine (0.7 per million doses) than the Janssen vaccine (3.7 per million doses).[107,116] A higher risk of GBS was observed in older individuals and males compared to females, which may explain why this study detected a signal for GBS following Pfizer-BioNTech COVID-19 vaccination with the VHA population consisting of mainly older men, while other studies did not detect a signal for GBS.[75,89,103,117]

A signal was detected for myocarditis as a separate safety event, which differs from the results from the prioritized safety analysis of myocarditis/pericarditis. Myocarditis is discussed in greater detail below for the prioritized analysis for myocarditis/pericarditis.

While this study detected potential signals for several safety events of interest, none of which remained after further evaluation as described below, Klein et al. (2021) did not detect any potential signals for the 23 safety events of interest reported (including ischemic stroke [which is similar to cerebrovascular non-hemorrhagic stroke in this study], myocarditis, hemorrhagic stroke, AMI, GBS and PE) using US VSD data.[103] In the final VSD analyses

using data through May 2022, signals were detected for AMI, myocarditis/pericarditis, and venous thromboembolism following the Pfizer-BioNTech COVID-19 vaccine.[75] In the FDA's BEST Initiative rapid surveillance study examining 17 safety events of interest using three large commercial insurance databases, only myocarditis/pericarditis and anaphylaxis had signals detected following the Pfizer-BioNTech COVID-19 vaccine.[106] Potential signals may have been detected for cerebrovascular non-hemorrhagic stroke, hemorrhagic disease, GBS, PE, and other safety events of interest in this study and not in other studies due to differences in the populations examined, as the risk of safety events is likely to vary by demographic characteristics (e.g., age, sex, etc.) in addition to methodological differences between studies. Specifically, the FDA's BEST Initiative rapid surveillance study only included individuals ages 12-64 years old, while this study's population included mainly elderly individuals with 55.0% of the Pfizer-BioNTech COVID-19 samples age 65 or older.[106] The Klein et al. (2021) and the final VSD analyses compared the incidence of safety events during the 21-day risk interval after Pfizer-BioNTech COVID-19 vaccination to the corresponding incidence during the comparison interval in concurrent vaccinated comparators who, as of the same calendar day, had received their most recent Pfizer-BioNTech COVID-19 vaccination 22 to 42 days earlier.[75,103] In this study, the rate of safety events in a 42-day risk interval after the Pfizer-BioNTech COVID-19 vaccine was primarily compared to the background rate of the same safety event occurring after seasonal influenza vaccine among the historical seasonal influenza vaccine sample, and therefore the choice of risk interval and comparator may impact the differences between these studies. Additionally, Klein et al. (2021) and the final VSD analyses adjusted the incidence of safety events for age, sex, race/ethnicity, and site, whereas this study made no adjustments for signal detection.[75,103] Therefore, this study's signal detection analyses may be impacted by seasonality and differences between the Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine samples.

Signal Evaluation

Arrhythmia, CAD, heart failure and cardiogenic shock, DVT, and PE were the only safety events of interest with signals that persisted in the SCRI design using binomial MaxSPRT analysis; therefore, they proceeded to the next signal evaluation analysis (i.e., multivariate Poisson regression). However, out of an abundance of caution, the remaining 13 safety events of interest with potential signals detected also proceeded to the multivariate Poisson regression analysis due to the small number of events observed for some safety events of interest leading to low power in the binomial MaxSPRT analysis.

Multivariate Poisson regression analyses were performed to compare the incidence rate of cerebrovascular non-hemorrhagic stroke, other acute demyelinating disease, GBS, anaphylaxis, AMI, arrhythmia, CAD, myocarditis, stress cardiomyopathy, microangiopathy, chilblain-like lesions, hemorrhagic disease, PE, ON, heart failure and cardiogenic shock, DVT, and acute kidney injury between individuals who received the Pfizer-BioNTech COVID-19 vaccine and historical seasonal influenza comparators. Severe COVID-19 disease could not be examined through the multivariate Poisson regression analyses as the historical seasonal influenza comparator sample was evaluated prior to the COVID-19 pandemic and would not have COVID-19 diagnosis codes. After controlling for key covariates,

chilblain-like lesions had adjusted IRR [95% CI] of 5.36 [3.38, 8.51] with p-value <0.01, and thus met the pre-defined safety signal definition of IRR >3 and p <0.01. Myocarditis, stress cardiomyopathy, and anaphylaxis had adjusted IRRs [95% CI] (p-value) of 2.22 [1.59, 3.10] (<0.01), 2.89 [1.71, 4.87] (<0.01), and 4.54 [1.29, 16.01] (0.019), respectively, so none met the pre-defined safety signal definition. The multivariate Poisson regression models did not converge when examining microangiopathy and hemorrhagic disease due to the small number of events. Since small p-values for many of the safety events of interest examined in this analysis are expected given the large number of individuals being examined (>5 million individuals total), it was pre-specified that detected signals would only remain if safety events of interest had IRR >3 and p-value <0.01. Based on these criteria, only chilblain-like lesions had a signal that remained from the multivariate Poisson regression analysis, however, microangiopathy, hemorrhagic stroke, and severe COVID-19 disease were also proceeded to the next step of signal evaluation for further analyses given multivariate Poisson regression could not be conducted for these events.

Conditional Poisson regression was conducted to compare the incidence of microangiopathy, chilblain-like lesions, hemorrhagic disease, and severe COVID-19 disease during the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine to the incidence of the same safety event of interest during the post-vaccination control time period using the SCCS design. Microangiopathy and severe COVID-19 disease both had RI<1. Chilblain-like lesions and hemorrhagic disease had RI>1 (RI [95% CI] (p-value): 1.49 [0.86, 2.59] (0.06) and 1.22 [0.54, 2.76] (0.63), respectively). Therefore, no signals remained based on the conditional Poisson regression with SCCS design as no safety events of interest with signals detected had RI >3 and p-value <0.01. As no safety events of interest had a signal that remained following four steps of signal evaluation analyses, no further signal evaluation analyses or signal verification through chart review were conducted. These results are consistent with those from other safety surveillance studies.[95,102,103]

Prioritized Safety Analysis of Myocarditis/Pericarditis

All individuals in the Pfizer-BioNTech COVID-19 vaccine sample (N=1,652,514) were included in this separate analysis of myocarditis/pericarditis. There was a total of 130,904 males aged 12-39 years old (population of special interest based on CDC as myocarditis/pericarditis is most common in this group). Within the 21-day risk interval after any dose of the Pfizer-BioNTech COVID-19 vaccine, there were a total of 52 myocarditis/pericarditis events in the codified data, and males had a slightly higher incidence rate than females, with the 95% CIs overlapping between the two groups (incidence rate per million doses [95% CI]: 11.4 [8.6, 15.1] vs. 6.5 [2.1, 20.1]).

In the aggregated monovalent doses 1-4 and bivalent dose 1 analyses, individuals 12-39 years old had a higher incidence rate of codified myocarditis/pericarditis events (i.e., based on diagnosis codes) than older age groups in the 21-day risk interval with overlapping 95% CIs. Among individuals 12-39 years old, the incidence rate in the aggregated risk interval after monovalent doses 1-4 and bivalent dose 1 was higher for males than females with overlapping 95% CIs (incidence rate per million doses [95% CI]: 20.4 [9.2, 45.4] vs. 11.3

[1.6, 80.1]). In the risk interval after monovalent dose 1 and dose 2 among individuals 12-39 years old, males had an incidence rate per million doses [95% CI] of 23.0 [7.4, 71.2] and 24.8 [8.0, 76.9], respectively, and no females had any myocarditis/pericarditis events. In the risk interval after monovalent dose 3 among individuals 12-39 years old, the incidence rate per million doses [95% CI] for females was 94.8 [13.4, 673.3], and no myocarditis/pericarditis events were observed in males. In the risk interval after monovalent dose 4 and bivalent dose 1, no females or males had any myocarditis/pericarditis events.
The rate of codified myocarditis/pericarditis events during the 21-day risk interval after the Pfizer-BioNTech COVID-19 vaccine was not significantly greater than the rate in the comparison interval across any dose (adjusted rate ratio [95% CI] for aggregated monovalent doses 1-4 and bivalent dose 1: 0.96 [0.65, 1.40]), monovalent dose 1 (1.33 [0.61, 2.91]), monovalent dose 2 (1.24 [0.56, 2.75], monovalent dose 3 (0.73 [0.35, 1.49])), monovalent dose 4 (0.62 [0.18, 2.17]), or bivalent dose 1 (2.51 [0.48, 13.21]). Similar results were observed when examining the rate of myocarditis/pericarditis events during the 7-day and 42-day risk interval after the Pfizer-BioNTech COVID-19 vaccine. While the adjusted rate ratio [95% CI] of myocarditis/pericarditis events in the 42-day risk interval after the Pfizer-BioNTech COVID-19 vaccine compared to the comparison interval for aggregated monovalent doses 1-4 and bivalent dose 1 was 1.47 [1.07, 2.01] with p-value <0.05, these results did not meet the pre-defined safety signal definition of RR >3 and p <0.01. Overall, based on this analysis of the codified data, no signal was detected for myocarditis/pericarditis. However, the sample size for young men 12-39 years of age may be too small to meaningfully detect rare myocarditis/pericarditis events.
Of the 52 codified myocarditis/pericarditis events that occurred in the 21-day risk interval (the primary risk interval of interest as defined by the VSD) after any dose of the Pfizer-BioNTech COVID-19 vaccine, 36 cases were confirmed through chart review. Of these, 34 (94.4%) individuals had chart-confirmed pericarditis, 6 (16.7%) had chart-confirmed myocarditis, and 4 individuals had both chart-confirmed myocarditis and pericarditis. Among individuals with at least one dose, males had a higher incidence rate than females, with the 95% CIs overlapping between the two groups (incidence rate per million doses [95% CI]: 7.9 [5.7, 11.1] vs. 4.3 [1.1, 17.3]). Among individuals 12-39 years old, the incidence rate in the aggregated risk interval after monovalent doses 1-4 and bivalent doses 1 was lower for males than females with overlapping 95% CIs (incidence rate per million doses [95% CI]: 11.3 [1.6, 80.1] vs. 10.2 [3.3, 31.6]). In the risk interval after monovalent dose 1 and dose 2, 12-39 year old males had an incidence rate per million doses [95% CI] of 15.3 [3.8, 61.2] and 8.3 [1.2, 58.7], respectively, and no females had any confirmed myocarditis/pericarditis cases. In the risk interval after monovalent dose 3, the 12-39 year old females had an incidence rate per million doses [95% CI]: 94.8 [13.4, 673.3], and no males had any confirmed myocarditis/pericarditis cases. In the risk interval after monovalent dose 4 and bivalent dose 1, no 12-39 years old males or females had any confirmed myocarditis/pericarditis cases.

With regard to etiologies/risk factors evaluated in the 365 days prior to the occurrence of chart-confirmed myocarditis/pericarditis, 7 (19.4%) individuals had other vaccines (including influenza, zoster, TDAP, and tetanus), 6 (16.7%) individuals had other prior viral infections (including SARS-CoV-2 viral infection, upper respiratory infection and rhinovirus), and 7 (19.4%) individuals had comorbid immunocompromising conditions and systemic

immune-mediated disease. During the myocarditis/pericarditis episode, individuals experienced chest pain (91.7%) and shortness of breath (44.4%), though the majority had symptom resolution. All 5 individuals with myocarditis and 32 (94.1%) individuals with pericarditis had recovered by the end of follow-up, at an average of 6.0 months later. History of hospitalization was the only baseline risk factor significantly associated with myocarditis/pericarditis risk (OR 95% CI: 5.48 [2.47, 12.17]. Detection bias may play a role because of more vigilant clinical workups and more complete documentation in health records of sicker individuals.

Results observed in this study were generally consistent with the preliminary findings regarding myocarditis/pericarditis following COVID-19 vaccination first published by ACIP on 23 June 2021.[60] In both studies, among individuals 12-39 years old and in the 21-day risk interval after Pfizer-BioNTech COVID-19 vaccine, males had a higher incidence rate per million doses of codified myocarditis/pericarditis than females with overlapping 95% CIs. However, this study's incidence rate of codified myocarditis/pericarditis was consistently higher than ACIP's preliminary findings for both sexes, regardless of dose (incidence rate per million doses [95% CI] for males: 20.4 [9.2, 45.4] in this study vs. 11.1 [5.5, 19.8] in ACIP; for females: 11.3 [1.6, 80.1] in this study vs. 0.8 [0.0, 4.7] in ACIP). In addition, while ACIP's preliminary findings showed much higher incidence rates of codified myocarditis/pericarditis after monovalent dose 2 compared to dose 1 in males (23.0 [11.0, 42.3] for monovalent dose 2 vs. 1.8 [0.0, 10.0] for monovalent dose 1), this study's incidence rates of codified myocarditis/pericarditis were similar after both doses in males (24.8 [8.0, 76.9] for monovalent dose 2 vs. 23.0 [7.4, 71.2] for monovalent dose 1), and there was no codified myocarditis/pericarditis events after monovalent doses 3-4 or bivalent dose 1, suggesting that there is no dose-response effect observed in the current study during the 21-day risk interval.

In more recent results published by ACIP using VSD data through August 2022 that examined verified myocarditis/pericarditis cases among males 18-29 years old in the 7-day risk interval after the Pfizer-BioNTech COVID-19 vaccine, the incidence rates per million doses for monovalent dose 1, dose 2, and dose 3 were 11.5, 81.4, and 41.9, respectively.[118,119] This trend in incidence rates of myocarditis/pericarditis cases being higher following dose 2 than dose 3 or dose 1 occurred in females and other age groups as well, implying that there may not be a dose-response effect. These results differ from the current study in that among males 12-39 years old, the incidence rates of codified myocarditis/pericarditis events in the 7-day risk interval after the Pfizer-BioNTech COVID-19 vaccine was 7.7 events per million doses for monovalent dose 1, and there were no events for monovalent dose 2 or dose 3. In addition, while the rate of codified myocarditis/pericarditis events during the 7-day or 21-day risk interval after the Pfizer-BioNTech COVID-19 vaccine was not significantly greater than the rate in the comparison interval across any dose among individuals of any age with at least one dose of the Pfizer-BioNTech COVID-19 vaccine in this study, the rate of verified myocarditis/pericarditis cases in the 0-7 day risk interval among male individuals 18-39 years old in ACIP's recent results were significantly greater than the rate in the comparison interval after dose 2 (adjusted RR [95% CI]: 13.98 [6.01, 36.14]) and dose 3 (adjusted RR [95% CI]: 13.72 [2.86, 104.20]) of the Pfizer-BioNTech COVID-19 vaccine.[118,120] These differences in

results may be due to this study having a small sample size of young men of 12-39 years of age to meaningfully detect rare myocarditis/pericarditis events.

The CIs for incidence rates of chart-confirmed myocarditis/pericarditis cases after each dose of the Pfizer-BioNTech COVID-19 vaccine among individuals 12-39 years old in this study overlapped with those reported in ACIP's preliminary findings (incidence rate per million doses [95% CI] for monovalent dose 1: 11.8 [3.0, 47.2] in this study vs. 2.6 [0.5, 7.7] in ACIP; for monovalent dose 2: 6.4 [0.9, 45.3] in this study vs. 8.0 [3.2, 16.5] in ACIP).[60] More recent ACIP results through March 2023 observed a chart-confirmed myocarditis/pericarditis incidence rate per million doses [95% CI] of 16.6 [0.4, 92.3] following the Pfizer-BioNTech COVID-19 bivalent booster dose, while for this study, no chart-confirmed myocarditis/pericarditis cases were observed for young males after bivalent dose 1.[75] The wide CIs observed for chart-confirmed cases are due to the small number of events in this study.

The incidence rate observed in this study for myocarditis/pericarditis was also higher than the rate of 8.2 myocarditis/pericarditis events per million doses among active military members as reported by Montgomery et al. (2021).[121] These differences may be due to individuals in the VHA having more comorbidities (e.g., diabetes, cancer) associated with increased risk of myocarditis/pericarditis than active duty military members.[122] In addition, among individuals 12-39 years old, this study's higher incidence rates of chart-confirmed myocarditis/pericarditis cases than ACIP's may be due to individuals in this study being older. Specifically, this study does not have any individuals 12-17 years old, so the mean age among the stratum of individuals 12-39 years old in this study is expected to be higher than the mean age of the stratum of individuals 12-39 years old in ACIP's study. In addition, when examining the incidence rate per million doses [95% CI] for codified myocarditis/pericarditis events in the 21-day risk interval for males of any age, this study observed similar rates between monovalent dose 1 (10.1 [6.1, 16.8] and monovalent dose 2 (9.8 [5.8, 16.5]), and higher rates for monovalent dose 3 (15.2 [8.7, 26.8]), monovalent dose 4 (11.8 [3.8, 36.6]), and bivalent dose 1 (15.1 [6.3, 36.3]), which seems to be driven by codified myocarditis/pericarditis cases among males age 50 or older. This suggests that the codified myocarditis/pericarditis events may be caused less due to an immunogenic or inflammatory response to vaccination, but more due to cardiac predisposing factors in the older VA population.

Myocarditis/pericarditis is a rare event, so there may be variability in results across studies and may impact the reliability of the incidence rate estimate in the VA population given the small number of male individuals 12-39 years old. Based on codified myocarditis/pericarditis events in the aggregated 21-day risk interval after any dose of the Pfizer-BioNTech COVID-19 vaccine compared to events in concurrent vaccinated comparators on the same calendar day, no signals were detected for myocarditis/pericarditis in this study. For individuals with chart-confirmed myocarditis/pericarditis cases after the Pfizer-BioNTech COVID-19 vaccine in this study, the vast majority fully recovered, consistent with other studies, and suggesting no permanent or long-term health impact.[103,123]

Other Analyses

Among the subgroup of the Pfizer BioNTech COVID-19 sample with dual Medicare coverage, the completion rates for monovalent doses 2, 3, 4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine were 97.6%, 60.3%, 22.2%, and 25.1% respectively, which are higher than the full study population's completion rates. This may be due to the fact that some individuals received Pfizer-BioNTech COVID-19 vaccinations outside of VHA facilities (e.g., retail pharmacies) and thus were not captured within the CDW, but were captured within Medicare claims given the billing for vaccinations by external entities. In addition, this subgroup included a higher proportion of elderly individuals with comorbidities who are more likely to have received additional doses of the Pfizer-BioNTech COVID-19 vaccine than the full study population.

The safety surveillance results for this subgroup were generally consistent with those from the full study population, with the exception of chilblain-like lesions which had a signal remain following the signal evaluation analysis of the conditional Poisson regression with an SCCS design. This study's results may have been driven by a number of factors, including individuals in this subgroup with dual Medicare coverage having more conditions (e.g., COVID-19 infection, blood or connective tissue diseases) that may increase their risk of chilblain-like lesions.[124] In addition, individuals with dual Medicare coverage may have more health-seeking behavior, leading to chilblain-like lesions being reported more often, hence why a signal remained for chilblain-like lesions in this subgroup but not in the full study population. This is supported by the literature that describes increased incidence of chilblain-like lesions during the COVID-19 pandemic that may be attributed to increased care-seeking behavior by individuals during the pandemic or behavioral changes during lockdown down measures.[125] Though the next step in signal evaluation analyses (i.e., comparison to contemporary unvaccinated controls) could not be conducted due to unexpected data constraints, the association was further explored to determine if it could, in fact, be due to confounding. The literature describes potential associations between COVID-19 infection and chilblain-like lesions.[126,127] Therefore, patients with chilblain-like lesions who also had COVID-19 diagnosis prior to or during the risk interval or control time period were excluded from the SCCS analysis (as COVID-19 infection itself could result in chilblain-like lesions), and the signal no longer remained (RI = 2.76; 95% CI = [1.37, 5.57]; p-value <0.01) as it did not meet the pre-specified criteria whereby signals only remained if the RI >3 and p-value <0.01.

Furthermore, as noted in the FDA BEST safety surveillance study among Medicare beneficiaries which observed statistically significant associations between AMI, PE and Bell's Palsy following mRNA COVID-19 vaccines, the signal for chilblain-like lesions in this study may have been an artifact of conducting multiple analyses and designs with a large sample size which could increase the chance of detecting statistically significant results that are not actually clinically meaningful.[128] Chilblain-like lesions in particular may not be clinically important as they are typically not severe, and chilblain-like lesions following COVID-19 vaccination have been reported to be typically mild and self-resolving in a few weeks.[128,129] This might explain why both the VSD and FDA BEST safety surveillance studies may not have included chilblain-like lesions in their list of safety event of interest to

monitor.[75,106] Therefore, these results should also not discourage individuals from receiving COVID-19 vaccines.

As all other analyses (e.g., subgroup of individuals who received a bivalent COVID-19 booster from any manufacturer following the Pfizer-BioNTech COVID-19 primary series) were overall similar to the full study population results, they are described in further detail in Annex 1. Appendix 8.

11.2. Limitations

While the VHA CDW provides a range of important advantages, including its comprehensive structure, large number of variables, and electronic accessibility, there may be gaps in the data since individuals may receive healthcare services outside of VHA facilities that are not recorded in the CDW. For example, veterans with secondary insurance (e.g., TRICARE through Department of Defense, Medicare for those aged 65 years of age or older, or Medicaid for those with low socioeconomic status) may receive health care services outside of VHA facilities. One study on VHA enrollees in seven states found that of all individuals admitted to VHA hospitals in 2007, one-fifth also had a non-VHA hospitalization during that year.[47] Another study reported that about 53% of veterans 65 years of age or older who were dually eligible for VHA and Medicare services in 2003-2004 used both.[130] As such, if individuals received the Pfizer-BioNTech COVID-19 vaccine outside of a VHA facility and the outside vaccination records were not forwarded back to the VA EHR system , this information would not be captured in the data. Similarly, individuals might have also received past seasonal influenza vaccinations outside of the VHA system, and thus could be misclassified as not having received the vaccine in the current descriptive analysis. Therefore, data on vaccination status and other health information may be incomplete. However, since the VA has a designated vaccine record database whereas most EHR systems do not, the VHA CDW is still considered as one of more complete and comprehensive data sources for vaccine studies.

To address this limitation, subgroup analyses were conducted for individuals with dual coverage in the VHA and Medicare for this final report. The CDW data were supplemented and linked with Medicare administrative claims data at the individual level to ensure a more comprehensive evaluation of the care an individual receives. Fewer safety events of interest with potential signals were detected in the Medicare subgroup, likely due to a number of reasons, including this subgroup having a smaller sample size, and therefore less power, and reduced information bias impacting both arms differentially. The safety surveillance results for this subgroup were generally consistent with those from the full study population, with the exception of chilblain-like lesions that had a signal remain. However, the signal no longer remained during the signal evaluation phase after further analyses of EHR patterns by excluding patients with a COVID-19 diagnosis from the SCCS analysis, indicating that COVID-19 infection may be a plausible competing risk factor that explains the previously observed signal. This is supported by the literature which indicates that COVID-19 is a risk factor for chilblain-like lesions.[124] Furthermore, the signal may have originally remained in this subgroup for a number of reasons, including individuals in this subgroup being older and sicker than the full study population, such that they are more likely to seek care or be monitored more closely by healthcare practitioners, causing mild conditions such as

chilblain-like lesions to be reported more often. Indeed, for all other safety events of interest examined, which were typically more severe conditions, the results were similar between the Medicare subgroup and the full study population where no signals remained. Therefore, for safety events of interest of greater severity, data may be missing at random from the CDW for the elderly, and therefore would not bias this study's conclusions for older age groups.

The reduction in HRU during the COVID-19 pandemic may also impact the detection of safety events of interest and comorbidities identified in the outpatient setting. As none of the safety events of interest examined in this study were identified in the outpatient setting only, the likelihood of underestimating outcomes in the Pfizer-BioNTech COVID-19 sample is more limited. In addition, the VHA database is comprehensive as it includes EHR from several healthcare settings (e.g., IP, ER, OP, etc.), so this study can better detect safety events of interest (including those that are milder and potentially diagnosed in outpatient settings) and capture comorbidity information. However, prevalence of some underlying comorbidities identified in the outpatient setting during the baseline period may still be underestimated in the Pfizer-BioNTech COVID-19 sample.

As with any large EMR database, occasional data entry errors may result in misclassification of exposures, outcomes, or covariates for some individuals. In addition, for safety events of identified using structured data, it is not known whether individuals actually had the safety event of interest (as shown in the prioritized safety analysis of myocarditis/pericarditis where only 36 of 52 (69.2%) codified events were confirmed cases through chart review) or if there was a coding error or if the diagnosis was entered as a comorbidity or as a reason for clinical workups as opposed to a confirmed diagnosis; thus, outcome misclassification likely exists but affects study samples non-differentially. Moreover, information on the etiological relationship of diagnoses with the vaccine is not available in the codified EMR data; therefore, the true numbers of vaccine-induced adverse events are likely substantially lower than reported. Furthermore, intensive quality checks and pattern analyses were performed in the signal evaluation phase for safety events of interest for which a potential signal is detected in the signal detection phase.

The active comparator study design required the selection of a historical comparator sample to calculate the expected rates for each of the safety events of interest. Similar to prior studies that conducted post-vaccination safety surveillance, this study used seasonal influenza recipients as historical active comparators.[24,25] The current study relied on individuals who received the seasonal influenza vaccine in the five prior seasons in the VHA system to calculate the expected rates for each of the safety events of interest. While seasonal influenza vaccine recipients were deemed to be an appropriate comparison group due to similarities in preventative healthcare behaviors and the large number of vaccine recipients each year, differences in secular trends, coding practices or diagnostic techniques could lead to potential bias.[25] To address this, a multivariate Poisson regression analysis was conducted as part of signal evaluation to account for potential baseline differences between the Pfizer-BioNTech COVID-19 and seasonal influenza vaccine recipients. Stratified analyses were also used to address confounding and possible heterogeneity in the risk of adverse events across specific populations of interest in the final study report.

11.3. Interpretation

This final report presents the sample selection, baseline characteristics, and vaccine utilization patterns among individuals who received the Pfizer-BioNTech COVID-19 vaccine within the VHA system and an active comparator of a historical sample of individuals who received seasonal influenza vaccine before the COVID-19 pandemic, in addition to the safety signal analyses for the Pfizer-BioNTech COVID-19 vaccine.

Most baseline characteristics were well-balanced between the study samples during the baseline period before monovalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine and before each dose of the seasonal influenza vaccine, suggesting that seasonal influenza vaccine from the five prior seasons is an appropriate comparator for the safety surveillance of Pfizer-BioNTech COVID-19 vaccine.

Recipients of the Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023 had a higher prevalence of the shingles vaccine during the two years prior to Pfizer-BioNTech COVID-19 vaccination, as compared to the seasonal influenza comparator sample. Conversely, seasonal influenza vaccine recipients had a higher prevalence of Tdap or Td, pneumococcal conjugate, and pneumococcal polysaccharide vaccines during the two years prior to seasonal influenza vaccination. These differences are likely explained by changes in the immunization guidelines for older individuals over time.[131,132]

The higher proportion of men in this study as compared to the general population was expected as the VHA population is predominantly male (approximately 90%). In this final report, the Pfizer-BioNTech COVID-19 sample was slightly younger than the seasonal influenza vaccine sample (mean age at vaccination: 64.0 vs 65.9, standardized differences 11.9%), which reflects the trend seen in the fourth interim report. In earlier interim reports, the Pfizer-BioNTech COVID-19 sample was older and closer in age to the seasonal influenza vaccine sample (e.g., second interim report from December 2021: mean age at vaccination: 65.2 vs 65.9, standardized differences 4.3%). This is likely due to the Pfizer-BioNTech COVID-19 vaccine and booster doses being available to all individuals at least 18 years old enrolled in the VHA after 19 November 2021, whereas older and immunocompromised populations had been prioritized in early phases of the COVID-19 vaccine and booster dose rollout.

In this final report, a large proportion of individuals received a third monovalent dose/booster dose of the Pfizer-BioNTech COVID-19 vaccine (52.5%) with a gap of around 7-8 months (median [IQR] time in days: 237.0 [213.0, 264.0]) between the second monovalent and third monovalent dose/booster dose. Furthermore, 16.7% of individuals received a fourth monovalent dose/booster dose of the Pfizer-BioNTech COVID-19 with a gap of 6-7 months (median [IQR] time in days: 203.0 [181.0, 236.0]) between the third monovalent and fourth monovalent doses/booster doses. Among 365,972 (22.2%) individuals that received the bivalent dose of the Pfizer-BioNTech COVID-19 vaccine, the time between the last monovalent dose and first bivalent dose was around 10.0 months (median [IQR] time in days: 301.0 [175.0, 384.0]). In addition, a substantial number of individuals received COVID-19 vaccines from both Pfizer-BioNTech and another manufacturer (307,714 individuals) who were excluded from subsequent safety surveillance analyses in this final

report. This number was partly driven by 116,949 individuals with heterologous boosters (i.e., dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of two Pfizer-BioNTech vaccine doses), which is expected as individuals could have received heterologous boosters starting from 20 October 2021.[133,134]

Cerebrovascular non-hemorrhagic stroke, other acute demyelinating disease, AMI, anaphylaxis, arrhythmia, CAD, myocarditis, chilblain-like lesions, PE, ON, heart failure and cardiogenic shock, acute kidney injury, stress cardiomyopathy, DVT and severe COVID-19 disease were detected as potential signals from safety signal analyses, and GBS, microangiopathy, and hemorrhagic disease were identified as warranting further evaluation (i.e., these were proceeded to safety signal evaluation analyses). There was variation in the signal detection results between this study and other published studies, with another safety surveillance study detecting no signals for 23 safety events of interest.[103] These differences may be confounded by the underlying study population differences. This study included VHA enrollees, who are typically older and have poorer health status than the general US population.[37] Other studies also confirmed safety events of interest through chart review while this study relied on diagnosis codes to identify safety events of interest in the VHA database, which could have led to the misclassification of safety events of interest.[103,104] The detection of severe COVID-19 as a signal in this study was based on the ICD-10-CM COVID-19 diagnosis code (U07.1), which may be used for billing or ordering laboratory tests rather than as a confirmed diagnosis of COVID-19 disease.[135,136] In addition, this study's signal detection main methodology of comparing safety events of interest in the risk interval after the Pfizer-BioNTech COVID-19 vaccine to the background rate of the safety events of interest among the seasonal influenza vaccine sample from 2014/2015 to 2018/2019 may have led the signal detection analyses impacted by seasonality and differences between the two study samples.

Importantly, signal detection analyses are hypothesis-generating and only indicate that further investigation is needed. Therefore, signal evaluation analyses were conducted for safety events of interest where potential signals were detected. Specifically, binomial MaxSPRT with SCRI design, multivariate Poisson regression models (which controlled for differences between the study samples where applicable), and conditional Poisson regression were used. Overall, no safety events of interest had a signal that remained following signal evaluation, so no safety events of interest proceeded to signal verification through chart review. Other signal evaluation analyses (i.e., comparison with contemporary unvaccinated controls, assessment of temporal clusters), seasonality-adjusted cases-centered method, and end-of-season analyses were not conducted because no signals remained after signal evaluation.

Based on a qualitative assessment where similar signal detection results were observed for monovalent dose 4 and bivalent dose 1 of the Pfizer-BioNTech COVID-19 vaccine, the monovalent and bivalent doses were considered to have comparable safety profiles. This is consistent with the CDC's findings of similar safety results between the monovalent and bivalent vaccines among individuals age 12 years and older.[74]

For the prioritized safety analysis of myocarditis/pericarditis, while the incidence rates of myocarditis/pericarditis were higher for males than females and for individuals 12-39 years old than individuals in older age groups with overlapping 95% CIs, the adjusted analyses comparing events in the risk interval vs. comparison interval among Pfizer-BioNTech COVID-19 vaccine recipients detected no signals for myocarditis/pericarditis following the CDC's methodology as pre-specified in the protocol. Although no signal was found between myocarditis/pericarditis and the Pfizer-BioNTech COVID-19 vaccine, the small sample size of young men in the VHA population provided limited statistical power to detect the rare events like myocarditis/pericarditis.[60,103] For individuals with chart-confirmed myocarditis/pericarditis cases after the Pfizer-BioNTech COVID-19 vaccine in this study, the majority fully recovered, consistent with other studies.[103,123] Incidence rate estimates for myocarditis/pericarditis and all other safety events of interest following the Pfizer-BioNTech COVID-19 vaccine that were reported in this final report are more stable than those described in previous reports with the accumulation of more data over time, leading to greater sample size and power.

Among the subgroup of individuals enrolled in the VHA with dual Medicare coverage, the safety surveillance results were generally consistent. Though chilblain-like lesions had a signal remain in SCCS analyses, this signal did not remain after conducting further signal evaluation to rule out other possible explanations whereby patients with COVID-19 diagnosis prior to or during the risk interval or control time period were excluded. Since COVID-19 infection is a risk factor for chilblain-like lesions, this may explain the occurrence of this safety event of interest more than the role of the COVID-19 vaccine.

11.4. Generalizability

The VHA population included in this final report is largely male and elderly with underlying medical conditions. Therefore, this population may not be generalizable to younger men or to women and children in the US, especially as children are not included in this study's sample. These findings may also not be generalizable beyond individuals similar to those enrolled in the VHA, who were eligible to receive the initial distribution of the Pfizer-BioNTech COVID-19 vaccine.[28] Further, the results of this study are specific to the Pfizer-BioNTech COVID-19 vaccine and are not generalizable to COVID-19 vaccines from a manufacturer other than Pfizer-BioNTech.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

Among the 1,652,514 eligible VHA enrollees who received at least one dose of the Pfizer-BioNTech COVID-19 vaccine from 11 December 2020 to 30 June 2023, 96.2% were administered two monovalent doses. Most individuals in the VHA received the monovalent Pfizer-BioNTech COVID-19 vaccine in the outpatient setting (>55%). The majority of individuals who received two monovalent doses of the vaccine received the second monovalent dose precisely 21 days following the first dose (64.9%). Approximately half of individuals received three doses of the Pfizer-BioNTech COVID-19 vaccine (N=868,181; 52.5%); 16.7% (N=275,601) subsequently received the fourth dose/booster dose, and 22.2%

(N=365,972) received a bivalent dose. Among individuals with at least one dose of the Pfizer-BioNTech COVID-19 vaccine and two years of continuous enrollment in VHA, a minority (N=307,714; 15.7%) received mixed doses of COVID-19 vaccines (i.e., receiving the Pfizer-BioNTech COVID-19 vaccine and a different manufacturer's COVID-19 vaccine).

The Pfizer-BioNTech COVID-19 and seasonal influenza vaccine recipients within the VHA system were comparable based on both baseline demographic and clinical characteristics, supporting the use of seasonal influenza vaccine recipients from the five prior seasons as an appropriate active comparator group for the safety surveillance of Pfizer-BioNTech COVID-19 vaccine.

While further investigation was warranted for cerebrovascular non-hemorrhagic stroke, other acute demyelinating disease, GBS, anaphylaxis, AMI, arrhythmia, CAD, myocarditis, stress cardiomyopathy, microangiopathy, chilblain-like lesions, hemorrhagic disease, PE, ON, heart failure and cardiogenic shock, acute kidney injury, DVT, and severe COVID-19 disease after signal detection analyses, no safety events of interest had a signal that remained following signal evaluation based on multivariate Poisson regression and conditional Poisson regression with SCCS design. The monovalent and bivalent doses of the Pfizer-BioNTech COVID-19 vaccine had similar safety profiles as similar signal detection results were observed. In addition, no increased rate of myocarditis/pericarditis events after the Pfizer-BioNTech COVID-19 vaccine was found in comparative analyses using codified data, meaning that a signal was not detected for myocarditis/pericarditis. After myocarditis/pericarditis case confirmation through medical chart review, results remained consistent with those based on codified data, and the majority of individuals with chart-confirmed myocarditis/pericarditis after the Pfizer-BioNTech COVID-19 vaccine fully recovered. Among the subgroup of individuals enrolled in the VHA with dual Medicare coverage, the safety surveillance results were consistent with those from the full study population. Though chilblain-like lesions had a signal remain in SCCS analyses, this signal did not remain after conducting further signal evaluation to rule out other possible explanations whereby patients with COVID-19 diagnosis prior to or during the risk interval or control time period were excluded. Since COVID-19 infection is a risk factor for chilblain-like lesions, this may explain the occurrence of this safety event of interest more than the role of the COVID-19 vaccine.

Overall, no examined safety events of interest were found to be associated with the Pfizer-BioNTech COVID-19 vaccine based on the analyses conducted in this final report.

14. REFERENCES

1. World Health Organization (WHO). (2020). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed on: 11 Nov 2020.
2. Johns Hopkins University and Medicine. Coronavirus Resource Center. Available from: https://coronavirus.jhu.edu/map.html. Accessed on: 13 Oct 2022.
3. Centers for Disease Control and Prevention (CDC). About variants of the virus that causes COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html. Accessed on: 21 Apr 2021.
4. Schoeni RF, Wiemers EE, Seltzer JA, et al. Association between risk factors for complications from COVID-19, perceived chances of infection and complications, and protective behavior in the US. JAMA Netw Open. 2021;4(3):e213984.
5. Centers for Disease Control and Prevention (CDC). People with certain medical conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed on: 02 May 2022.
6. Challen R, Brooks-Pollock E, Read JM, et al. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: Matched cohort study. BMJ. 2021;372:n579.
7. Davies NG, Jarvis CI, Edmunds WJ, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B. 1.1. 7. Nature. 2021;593:270-74.
8. Kirby T. New variant of SARS-CoV-2 in UK causes surge of COVID-19. Lancet Respir Med. 2021;9(2):e20-1.
9. U.S. Food and Drug Administration (FDA). Pfizer-BioNTech COVID-19 vaccine Biologics License Application (BLA) Approval (issued 23 Aug 2021). Available from: https://www.fda.gov/media/151710/download. Accessed on: 19 Oct 2021.
10. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med. 2020;383(25):2439-50.
11. Clinicaltrials.gov. Identifier NCT04368728: Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals. Available from: https://clinicaltrials.gov/ct2/show/NCT04368728. Accessed on: 23 Apr 2021.
12. U.S. Food and Drug Administration (FDA). Vaccines and related biological products advisory committee meeting (10 Dec 2020): FDA briefing document Pfizer-BioNTech COVID-19 vaccine. Available from: https://www.fda.gov/media/144245/download. Accessed on: 23 Apr 2021.
13. U.S. Food and Drug Administration (FDA). Pfizer COVID-19 vaccine EUA Letter of Authorization (reissued 25 Feb 2021). Available from: https://www.fda.gov/media/144412/download. Accessed on: 23 Apr 2021.
14. U.S. Food and Drug Administration (FDA). Comirnaty and Pfizer-BioNTech COVID-19 vaccine. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine. Accessed on: 21 Nov 2021.
15. U.S. Food and Drug Administration (FDA). Vaccine information fact sheet for recipients and caregivers about the Pfizer-BioNTech COVID-19 vaccine to prevent

Coronavirus disease 2019 (COVID-19) for use in individuals 5 through 11 years of age. 2021. Available from: https://www.fda.gov/media/153717/download.
16. U.S. Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA authorizes second booster dose of two COVID-19 vaccines for older and immunocompromised individuals. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-second-booster-dose-two-covid-19-vaccines-older-and. Accessed on: 30 Mar 2022.
17. Pfizer-BioNTech. Comirnaty® (COVID-19 vaccine, mRNA) is FDA approved for 16 years and older. Available from: https://www.comirnaty.com/. Accessed on: 21 Nov 2021.
18. U.S. Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA expands eligibility for COVID-19 vaccine boosters. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-covid-19-vaccine-boosters Accessed on: 02 Dec 2021.
19. Centers for Disease Control and Prevention (CDC). (2022). CDC recommends Pfizer booster at 5 months, additional primary dose for certain immunocompromised children. Available from: https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html. Accessed on: 27 Apr 2022.
20. U.S. Food and Drug Administration (FDA). (2022). Coronavirus (COVID-19) update: FDA authorizes Moderna, Pfizer-BioNTech bivalent COVID-19 vaccines for use as a booster dose. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use. Accessed on: 17 Oct 2022.
21. Law B. Safety Platform for Emergency vACcines (SPEAC) SO2-D2.1.2 Priority list of COVID-19 adverse events of special interest: Quarterly update (23 Dec 2020). Available from: https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf. Accessed on: 23 Apr 2021.
22. Shimabukuro T. National Center for Immunization & Respiratory Disease: Enhanced safety monitoring for COVID-19 vaccines in early phase vaccination. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-09/COVID-03-Shimabukuro.pdf. Accessed on: 01 Feb 2021.
23. U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) Office of Biostatistics and Epidemiology. COVID-19 vaccine safety surveillance: Active monitoring master protocol. 2021. Available from: https://www.bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-Protocol-2021.pdf.
24. Yih WK, Lee GM, Lieu TA, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. Am J Epidemiol. 2012;175(11):1120-8.
25. Lee GM, Greene SK, Weintraub ES, et al. H1N1 and seasonal influenza vaccine safety in the Vaccine Safety Datalink Project. Am J Prev Med. 2011;41(2):121-8.
26. Fireman B, Lee J, Lewis N, et al. Influenza vaccination and mortality: Differentiating vaccine effects from bias. Am J Epidemiol. 2009;170(5):650-6.

27. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA. 2005;294(17):2188-94.
28. U.S. Department of Veteran Affairs. COVID-19 vaccines at VA. Available from: https://www.va.gov/health-care/covid-19-vaccine/. Accessed on: 23 Apr 2021.
29. U.S. Department of Veteran Affairs National Center for Health Promotion and Disease Prevention. Influenza (flu). Available from: https://www.prevention.va.gov/flu/. Accessed on: 23 Apr 2021.
30. Patel M, Chen J, Kim S, et al. Analysis of MarketScan data for immunosuppressive conditions and hospitalizations for acute respiratory illness, United States. Emerg Infect Dis. 2020;26(8):1720-30.
31. U.S. Department of Veteran Affairs. VA priority groups. Available from: https://www.va.gov/health-care/eligibility/priority-groups/. Accessed on: 23 Apr 2021.
32. Liu CH, Yeh YC, Huang WT, et al. Assessment of pre-specified adverse events following varicella vaccine: A population-based self-controlled risk interval study. Vaccine. 2020;38(11):2495-502.
33. Manjunath R, Paradis PE, Parise H, et al. Burden of uncontrolled epilepsy in patients requiring an emergency room visit or hospitalization. Neurology. 2012;79(18):1908-16.
34. Baker MA, Baer B, Kulldorff M, et al. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: A self-controlled risk interval and cohort study with null results. PLoS Med. 2019;16(7):e1002844.
35. U.S. Department of Veteran Affairs; Veterans Health Administration. Providing health care for veterans. Available from: https://www.va.gov/health/. Accessed on: 23 Apr 2021.
36. Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr. 2006;4:2.
37. Agha Z, Lofgren RP, VanRuiswyk JV, et al. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. Arch Intern Med. 2000;160(21):3252-7.
38. U.S. Department of Veteran Affairs. (2021). Veterans Health Administration (VHA) Coronavirus Disease 2019 (COVID-19) Response Report - Annex B Available from: https://www.va.gov/health/docs/VHA-COVID-19-Response-2021-Annex-B.pdf.
39. Baxter R, Eaton A, Hansen J, et al. Safety of quadrivalent live attenuated influenza vaccine in subjects aged 2-49years. Vaccine. 2017;35(9):1254-58.
40. Johns Hopkins Vasculitis Center. Types of vasculitis. Available from: https://www.hopkinsvasculitis.org/types-vasculitis/#:~:text=%E2%80%9CAngiitis%E2%80%9D%20and%20%E2%80%9CArteritis%E2%80%9D,lit'%20i%20deez%E2%80%9D. Accessed on: 19 Jan 2021.
41. OptumInsight Inc. Guide to clinical validation, documentation and coding: Acute kidney injury. 2013. Available from: https://www.optum360coding.com/upload/pdf/ECDCG14/CDCG14_v2.pdf.
42. U.S. Department of Health and Human Services. (2017). Common Terminology Criteria for Adverse Events (CTCAE). Available from:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_QuickReference_5x7.pdf. Accessed on: 17 Jan 2021.
43. Forns J, Cainzos-Achirica M, Hellfritzsch M, et al. Validity of ICD-9 and ICD-10 codes used to identify acute liver injury: A study in three European data sources. Pharmacoepidemiol Drug Saf. 2019;28(7):965-75.
44. American Medical Association (AMA). Appendix Q: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccines. Available from: https://www.ama-assn.org/system/files/2020-11/covid-19-immunizations-appendix-q-table.pdf. Accessed on: 12 Jan 2021.
45. Menendez ME, Neuhaus V, van Dijk CN, et al. The Elixhauser comorbidity method outperforms the Charlson index in predicting inpatient death after orthopaedic surgery. Clin Orthop Relat Res. 2014;472(9):2878-86.
46. Centers for Disease Control and Prevention (CDC). (2019). QuickStats: Average Daily Number of Deaths, by Month — United States, 2017. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed on: 23 Apr 2021.
47. West AN, Charlton ME, Vaughan-Sarrazin M. Dual use of VA and non-VA hospitals by Veterans with multiple hospitalizations. BMC Health Serv Res. 2015;15:431.
48. Kulldorff M, Davis RL, Kolczak† M, et al. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Seq Anal. 2011;30(1):58-78.
49. When are risks real? Clinical Nutrition Insight. Vol 332007:6.
50. Flury BK, Riedwyl H. Standard distance in univariate and multivariate analysis. Am Stat. 1986;40(3):249-51.
51. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat B: Simul Comput. 2009;38(6):1228-34.
52. Ahmed A, Perry GJ, Fleg JL, et al. Outcomes in ambulatory chronic systolic and diastolic heart failure: A propensity score analysis. Am Heart J. 2006;152(5):956-66.
53. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed.;https://doi.org/10.4324/9780203771587. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
54. Yang D-S, Dalton JE, editors. A unified approach to measuring the effect size between two groups using SAS. SAS Global Forum 2012; Statistics and Data Analysis; 2012.
55. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods. 2010;15(3):234-49.
56. Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. J Clin Epidemiol. 2013;66(8 Suppl):S84-S90 e1.
57. Greene SK, Kulldorff M, Yin R, et al. Near real-time vaccine safety surveillance with partially accrued data. Pharmacoepidemiol Drug Saf. 2011;20(6):583-90.
58. Li L, Kulldorff M. A conditional maximized sequential probability ratio test for pharmacovigilance. Stat Med. 2010;29(2):284-95.
59. U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) Office of Biostatistics and Epidemiology. Draft master protocol:

Assessment of risk of safety outcomes following COVID-19 vaccination. 23 March 2021. Available from: https://www.bestinitiative.org/wp-content/uploads/2021/04/COVID-19-Vaccine-Safety-Inferential-Draft-Master-Protocol.pdf.

60. Shimabukuro T. Center for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP): COVID-19 vaccine safety updates. 2021. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf.
61. Klein N, Donahue J, Weintraub E. Center for Disease Control (CDC): Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. 2021. Available from: https://www.cdc.gov/vaccinesafety/pdf/VSD-1342-COVID19-RCA-Protocol_FinalV1.1_508.pdf.
62. Brighton Collaboration. Myocarditis/Pericarditis case definition. 2021. Available from: https://brightoncollaboration.us/myocarditis-case-definition-update/.
63. Centers for Disease Control and Prevention (CDC). (2022). SARS-CoV-2 Variant Classifications and Definitions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html.
64. International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2008;17(2):200-8.
65. International Epidemiological Association (IEA). Good Epidemiological Practice (GEP), IEA Guidelines for Proper Conduct of Epidemiological Research. 2007. Available from: https://ieaweb.org/IEAWeb/Content/IEA_Publications.aspx.
66. U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). (2013). Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic. Accessed on: 19 Jan 2021.
67. Luo J, Jeyapalina S, Stoddard GJ, et al. Coronavirus disease 2019 in veterans receiving care at veterans health administration facilities. Ann Epidemiol. 2021;55:10-14.
68. U.S. Census Bureau. (2021). 2020 Census illuminates racial and ethnic composition of the country. Available from: https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html#:~:text=Black%20or%20African%20American%20Population,-The%20Black%20or&text=In%202020%2C%20the%20Black%20or,million%20and%2012.6%25%20in%202010. Accessed on: 27 Apr 2022.
69. Moynihan R, Sanders S, Michaleff ZA, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: A systematic review. BMJ Open. 2021;11(3):e045343.
70. Lieneck C, Garvey J, Collins C, et al. Rapid telehealth implementation during the COVID-19 global pandemic: A rapid review. Healthcare (Basel). 2020;8(4).

71. Centers for Disease Control and Prevention (CDC). (2022). COVID-19 vaccinations in the United States Available from: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-onedose-pop-5yr. Accessed on: 27 Apr 2022.
72. Niesen MJM, Pawlowski C, O'Horo JC, et al. Surveillance of safety of 3 doses of COVID-19 mRNA vaccination using electronic health records. JAMA Netw Open. 2022;5(4):e227038.
73. Centers for Disease Control and Prevention (CDC). (2022). COVID-19 vaccines for moderately or severely immunocompromised people. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html#:~:text=PRIMARY%20SERIES%20COVID%2D19%20VACCINE,-Pfizer%2DBioNTech&text=%E2%80%A0-,People%20ages%2012%20years%20and%20older%20who%20are%20moderately%20or,BioNTech%20COVID%2D19%20vaccine%20booster. Accessed on: 02 May 2022.
74. Hause AM, Marquez P, Zhang B, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among persons aged≥ 12 years—United States, August 31 – October 23, 2022. Morbidity and Mortality Weekly Report. 2022;71(44):1401.
75. Klein N. COVID-19 Vaccine Safety Surveillance: Summary from VSD RCA. 2023. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-12/07-COVID-Klein-508.pdf.
76. Shimabukuro T. Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP): COVID-19 mRNA bivalent booster vaccine safety. 2023. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-02-Shimabukuro-508.pdf.
77. Andersson NW, Thiesson EM, Hansen JV, et al. Safety of BA. 4-5 or BA. 1 bivalent mRNA booster vaccines: nationwide cohort study. bmj. 2023;382.
78. Lesort C, Kanitakis J, Donzier L, et al. Chilblain-like lesions after BNT162b2 mRNA COVID-19 vaccine: A case report suggesting that 'COVID toes' are due to the immune reaction to SARS-CoV-2. J Eur Acad Dermatol Venereol. 2021;35(10):e630-e32.
79. Cameli N, Silvestri M, Mariano M, et al. Pernio-like skin lesions after the second dose of Pfizer-BioNTech COVID-19 vaccine. J Eur Acad Dermatol Venereol. 2021;35(11):e725-e27.
80. Ahmed SK, Mohamed MG, Essa RA, et al. Global reports of takotsubo (stress) cardiomyopathy following COVID-19 vaccination: First systematic review and meta-analysis. medRxiv. 2022;10.1101/2022.04.16.22273937:2022.04.16.22273937.
81. De Fabritiis M, Angelini ML, Fabbrizio B, et al. Renal thrombotic microangiopathy in concurrent COVID-19 vaccination and infection. Pathogens. 2021;10(8).
82. Ho JS, Sia CH, Ngiam JN, et al. A review of COVID-19 vaccination and the reported cardiac manifestations. Singapore Med J. 2021;10.11622/smedj.2021210.
83. Araki T, Morimoto R, Ito R, et al. a case of systemic capillary leak syndrome with severe cardiac dysfunction after mRNA vaccination for COVID-19. CJC Open. 2022;4(7):656-59.

84. Jean-Marie EM, Tabbalat A, Raymond C, et al. Cardiogenic shock temporally associated with COVID-19 vaccination after prior COVID-19 infection: A case report. Am Heart J Plus. 2022;13:100113.
85. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. J Am Acad Dermatol. 2021;85(1):46-55.
86. Ye X, Ma T, Blais JE, et al. Association between BNT162b2 or CoronaVac COVID-19 vaccines and major adverse cardiovascular events among individuals with cardiovascular disease. Cardiovascular Research. 2022;118(10):2329-38.
87. Kelly JD, Leonard S, Hoggatt KJ, et al. Incidence of severe COVID-19 illness following vaccination and booster with BNT162b2, mRNA-1273, and Ad26. COV2. S vaccines. Jama. 2022;328(14):1427-37.
88. Patone M, Handunnetthi L, Saatci D, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021;27(12):2144-53.
89. Bardenheier BH, Gravenstein S, Blackman C, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents. Vaccine. 2021;39(29):3844-51.
90. Elnahry AG, Al-Nawaflh MY, Gamal Eldin AA, et al. COVID-19 vaccine-associated optic neuropathy: a systematic review of 45 patients. Vaccines. 2022;10(10):1758.
91. Kim J-E, Park J, Song T-J. A disproportionality analysis for the association of central nervous system demyelinating diseases with COVID-19 vaccination using the World Health Organization pharmacovigilance database. Multiple Sclerosis Journal. 2022:13524585221109397.
92. Bernardi FF, Mascolo A, Sarno M, et al. Thromboembolic Events after COVID-19 Vaccination: An Italian Retrospective Real-World Safety Study. Vaccines. 2023;11(10):1575.
93. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. British Medical Journal Publishing Group; 2021.
94. Andrews NJ, Stowe J, Ramsay ME, et al. Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2 COVID-19 vaccines: a national cohort study in England. The Lancet Regional Health–Europe. 2022;13.
95. U.S. Food and Drug Administration (FDA). (2021). Initial results of near real-time safety monitoring of COVID-19 vaccines in persons aged 65 years and older. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/initial-results-near-real-time-safety-monitoring-covid-19-vaccines-persons-aged-65-years-and-older. Accessed on: 27 Oct 2021.
96. Jeet Kaur R, Dutta S, Charan J, et al. Cardiovascular adverse events reported from COVID-19 vaccines: A study based on WHO database. Int J Gen Med. 2021;14:3909-27.
97. Hippisley-Cox J, Patone M, Mei XW, et al. Risk of thrombocytopenia and thromboembolism after COVID-19 vaccination and SARS-CoV-2 positive testing: Self-controlled case series study. BMJ. 2021;374:n1931.
98. Botton J, Jabagi MJ, Bertrand M, et al. Risk for myocardial infarction, stroke, and pulmonary embolism following COVID-19 vaccines in adults younger than 75 years in France. Ann Intern Med. 2022;175(9):1250-57.

99. Jabagi MJ, Botton J, Bertrand M, et al. Myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA COVID-19 vaccine in people aged 75 years or older. JAMA. 2022;327(1):80-82.
100. Shiravi AA, Ardekani A, Sheikhbahaei E, et al. Cardiovascular complications of SARS-CoV-2 vaccines: An overview. Cardiol Ther. 2022;11(1):13-21.
101. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2022;28(2):410-22.
102. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. N Engl J Med. 2021;385(12):1078-90.
103. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021;326(14):1390-99.
104. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol. 2016;137(3):868-78.
105. Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US-December 14, 2020-January 18, 2021. JAMA. 2021;325(11):1101-02.
106. Lloyd PC, Hu M, Wong H-L, et al. Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years. Vaccine. 2022;40(45):6481-88.
107. Singh A, Khillan R, Mishra Y, et al. The safety profile of COVID-19 vaccinations in the United States. Am J Infect Control. 2022;50(1):15-19.
108. De Michele M, Iacobucci M, Chistolini A, et al. Malignant cerebral infarction after ChAdOx1 nCov-19 vaccination: A catastrophic variant of vaccine-induced immune thrombotic thrombocytopenia. Nat Commun. 2021;12(1):4663.
109. See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
110. BMJ. First reported cases of clots in large arteries causing stroke following covid-19 vaccination. Available from: https://www.bmj.com/company/newsroom/first-reported-cases-of-clots-in-large-arteries-causing-stroke-following-covid-19-vaccination/. Accessed on: 27 Oct 2021.
111. Andrews NJ, Stowe J, Ramsay ME, et al. Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2 COVID-19 vaccines: A national cohort study in England. Lancet Reg Health Eur. 2022;13:100260.
112. Nicholson M, Goubran H, Chan N, et al. No apparent association between mRNA COVID-19 vaccination and venous thromboembolism. Blood Rev. 2022;10.1016/j.blre.2022.100970:100970.
113. Luo H, Li X, Ren Q, et al. Acute kidney injury after COVID-19 vaccines: A real-world study. Ren Fail. 2022;44(1):958-65.
114. Wong H-L, Tworkoski E, Zhou CK, et al. Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older. Vaccine. 2023;41(2):532-39.
115. Aliasin MM, Yazdanpanah N, Rezaei N. Neurological and neuropsychological adverse effects of SARS-CoV-2 vaccines - where do we stand? Rev Neurosci. 2022;10.1515/revneuro-2022-0006.

116. Gallo K, Goede A, Mura C, et al. A comparative analysis of COVID-19 vaccines based on over 580,000 cases from the Vaccination Adverse Event Reporting System. Vaccines (Basel). 2022;10(3).
117. Hanson KE, Goddard K, Lewis N, et al. Incidence of Guillain-Barre Syndrome after COVID-19 vaccination in the Vaccine Safety Datalink. JAMA Netw Open. 2022;5(4):e228879.
118. Shimabukuro T. Center for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP): Myocarditis following mRNA COVID-19 vaccination. 2022. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-07-19/03-COVID-Shimabukuro-508.pdf.
119. Goddard K, Hanson KE, Lewis N, et al. Incidence of myocarditis/pericarditis following mRNA COVID-19 vaccination among children and younger adults in the United States. Annals of internal medicine. 2022;175(11):1169-771.
120. Centers for Disease Control and Prevention (CDC). Myocarditis analyses in the Vaccine Safety Datalink: Rapid cycle analyses and "head-to-head" product comparisons. 2022. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/10-COVID-Klein-508.pdf.
121. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US Military. JAMA Cardiol. 2021;6(10):1202-06.
122. National Heart Lung and Blood Institute. Heart inflammation. Available from: https://www.nhlbi.nih.gov/health-topics/heart-inflammation. Accessed on: 27 Oct 2021.
123. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021;144(6):471-84.
124. Kapnia AK, Ziaka S, Ioannou LG, et al. Population characteristics, symptoms, and risk factors of idiopathic chilblains: A systematic review, meta-analysis, and meta-regression. Biology. 2022;11(11):1651.
125. McCleskey PE, Zimmerman B, Lieberman A, et al. Epidemiologic analysis of chilblains cohorts before and during the COVID-19 pandemic. JAMA dermatology. 2021;157(8):947-53.
126. Starkey SY, Mar K, Kashetsky N, et al. Chilblain-like lesions coinciding with the SARS-CoV-2 pandemic. Clinics in Dermatology. 2023;41(1):223-29.
127. Shaikh TG, Waseem S, Ahmed SH, et al. SARS-CoV-2 Vaccination and Chilblain-like Lesions: What Do We Know so Far? Dermatology Practical & Conceptual. 2022;12(4).
128. Shoaibi A, Lloyd PC, Wong H-L, et al. Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the US. Vaccine. 2023.
129. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. Journal of the American Academy of Dermatology. 2021;85(1):46-55.

130. Petersen LA, Byrne MM, Daw CN, et al. Relationship between clinical conditions and use of Veterans Affairs health care among Medicare-enrolled veterans. Health Serv Res. 2010;45(3):762-91.
131. Centers for Disease Control and Prevention (CDC). (2012). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adults aged 65 years and older — Advisory Committee on Immunization Practices (ACIP) Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6125a4.htm. Accessed on: 15 Apr 2021.
132. American Association of Retired Persons (AARP). (2019). Recommendation for pneumonia vaccine revised. Available from: https://www.aarp.org/health/conditions-treatments/info-2019/pneumonia-vaccine-recommendation.html. Accessed on: 15 Apr 2021.
133. Centers for Disease Control and Prevention (CDC). (2022). COVID-19 vaccine boosters. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html. Accessed on: 02 May 2022.
134. U.S. Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA takes additional actions on the use of a booster dose for COVID-19 vaccines. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-additional-actions-use-booster-dose-covid-19-vaccines. Accessed on: 27 Apr 2022.
135. Lynch KE, Viernes B, Gatsby E, et al. Positive predictive value of COVID-19 ICD-10 Diagnosis Codes across calendar time and clinical setting. Clin Epidemiol. 2021;13:1011-18.
136. Bhatt AS, McElrath EE, Claggett BL, et al. Accuracy of ICD-10 Diagnostic Codes to identify COVID-19 among hospitalized patients. J Gen Intern Med. 2021;36(8):2532-35.

Document Approval Record

Document Name:	C4591012_FINAL REPORT_08DEC2023
Document Title:	C4591012

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	13-Dec-2023 15:41:33	Manager Approval
De Bernardi, Barbara	14-Dec-2023 13:37:08	EUQPPV Approval