Manuscript Title:

Safety Monitoring of Bivalent COVID-19 mRNA Vaccines Among Recipients 6 months and Older in the United States

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Importance

Active monitoring of health outcomes after COVID-19 vaccination provides early detection of rare outcomes post-licensure.

Objective

To evaluate health outcomes following bivalent COVID-19 Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273.222) vaccination among individuals 6 months and older in the United States.

Design

Monthly monitoring of health outcomes from August 2022 to July 2023 in four administrative claims databases. Descriptive analyses monitored vaccine uptake, outcome counts and coadministration of bivalent COVID-19 and influenza vaccines. Sequential analyses tested for elevated risk of each outcome in a prespecified post-vaccination risk interval, or a period of hypothesized elevation based on clinical guidance, compared to a historical baseline.

Participants and Exposures

Persons 6 months and older who received a bivalent COVID-19 BNT162b2 or mRNA-1273.222 vaccine during the study period, with continuous enrollment in a medical insurance plan from the start of an outcome-specific clean interval to the COVID-19 vaccination date. Vaccines were identified using product-specific codes from medical coding systems.

Health Outcomes

Twenty outcomes were monitored in BNT162b2 vaccine recipients 6 months-4 years, and mRNA-1273.222 vaccine recipients 6 months-5 years. Twenty-one outcomes were monitored in BNT162b2 vaccine recipients 5-17 years and mRNA-1273.222 vaccine recipients 6-17 years. Eighteen outcomes were monitored in persons 18 years and older for both mRNA vaccines.

Results

Overall, 13.9 million individuals 6 months and older received a single bivalent COVID-19 mRNA vaccine. The statistical threshold for a signal was met for two outcomes in one database: anaphylaxis following bivalent BNT162b2 and mRNA-1273.222 vaccines in persons 18-64 years and myocarditis/pericarditis following bivalent BNT162b2 vaccines in individuals 18-35 years. There were no signals identified in young children.

Conclusions

Results were consistent with prior observations from published studies on COVID-19 vaccine safety. This study supports the safety profile of bivalent COVID-19 mRNA vaccines and the conclusion that the benefits of vaccination outweigh the risks.

1. Background

The U.S. Food & Drug Administration (FDA) first authorized bivalent formulations of COVID-19 mRNA vaccines in August 2022.[1] These updated vaccines included both the SARS-CoV-2 ancestral strain and omicron BA.4 and BA.5 subvariants and offered added protection against more recently circulating strains of the virus.[1] Vaccines were first authorized in persons 12 years and older for the bivalent COVID-19 Pfizer-BioNTech (BNT162b2) vaccine, and 18 years and older for the bivalent COVID-19 Moderna (mRNA-1273.222) vaccine.[2,3] The authorization for both vaccine brands was expanded in October 2022 to include persons 5 years and older for the bivalent BNT162b2 vaccine and 6 years and older for the mRNA-1273.222 vaccine.[2,3] In December 2022, the authorization for both vaccine brands was further expanded to include populations 6 months and older.[2,3]

There have been approximately 56 million bivalent COVID-19 vaccine doses administered in the U.S. as of May 2023.[4] Of these, 42.0% have been administered to persons 65 years and older, 51.9% to persons aged 18-64 years, 5.9% to persons aged 5-17 years, and <1% to the population aged 6 months- 4 years.[4] Overall, bivalent COVID-19 mRNA vaccines have been administered to about 17.0% of the U.S. population.[4]

FDA has been performing near real-time surveillance to monitor the real-world safety of bivalent COVID-19 vaccines available in the U.S. Near real-time surveillance is a screening method designed to rapidly identify potential safety signals as vaccines are administered. However, results do not establish a causal association due to methodologic limitations. More robust epidemiological studies may be used to evaluate potential safety signals identified from screening methods.

This study presents results from FDA's near real-time safety monitoring of bivalent COVID-19 vaccines using data from three commercial databases representing vaccine recipients aged 6 months to 64 years, and the Centers for Medicare & Medicaid Services (CMS) Medicare database representing vaccine recipients aged 65 years and older.

2. Methods

2.1 Data Sources

This study used administrative commercial health claims data from Carelon Research, CVS Health, and Optum to capture health care data on the population aged 6 months – 64 years old. Medicare Fee-For-Service (FFS) data from the CMS Shared Systems Database was used to capture data on the population aged 65 years and older. These databases contain longitudinal medical and pharmacy claims data that captures patient's demographic information, clinical diagnoses, and vaccine administration information among other health care utilization information. The CMS Medicare enrollment database was used to capture enrollment information for the Medicare population. Where available, local and state-based Immunization Information Systems (IIS) data was linked to commercial claims databases to supplement the capture of patient's COVID-19 vaccination history. Once validated, data from select IIS jurisdictions was included in the analysis. Supplementary Table E1 summarizes individual database-related characteristics including enrollment size and claims delay.

2.2 Study Population and Period

Health plan members aged 6 months and older were included in surveillance if they received a bivalent COVID-19 mRNA vaccine during the vaccine brand- and age-specific authorization periods and were continuously enrolled in their respective health plan for the complete duration of the outcome-specific clean interval. The surveillance period extended from the U.S. authorization date for the bivalent COVID-19 mRNA vaccines (i.e., August 2022 for ages 12 years and older; October 2022 for 5-11 years of age; December 2022 for 6 months to 4 years of age) through mid-2023. Exact surveillance start dates varied by vaccine brand and age group based on vaccine authorization dates (Supplementary Table E2).

2.3 Exposures and Follow-Up

The exposure was defined as the receipt of the bivalent BNT162b2 or mRNA-1273.222 COVID-19 vaccines in any setting during the vaccine brand and age-specific authorization periods. Bivalent COVID-19 mRNA vaccines were identified in claims and IIS data using product and dose-specific codes from the Current Procedural Terminology (CPT)/ Health Care Common Procedure Coding System (HCPCS), National Drug Codes (NDCs), and CVX (vaccine administered) codes.[5] Only individuals' first bivalent vaccine administration was included in surveillance because bivalent COVID-19 vaccines were authorized as a single dose at the start of surveillance.

Follow-up time included all person-time accrued during the prespecified post-vaccination risk intervals. Risk intervals were defined as a period of hypothesized elevated risk due to vaccination and were established based on guidance from clinicians and literature review. Risk intervals were censored at disenrollment, subsequent COVID-19 vaccination, surveillance end date, or death.

2.4 Health Outcomes

Health outcomes were selected based on literature review, consultation with clinicians, and prior COVID-19 vaccine surveillance activities. Outcomes were monitored separately: an individual with multiple different outcomes was included in surveillance for each outcome, but only the first eligible occurrence of an outcome was included in the analysis. Eligible outcomes were defined as those occurring in the risk interval with no prior occurrence of the respective outcome during the outcome-specific clean interval. The clean interval was a period defined relative to vaccination date used to identify incident outcomes, in which an individual enters the outcome-specific study cohort only if the outcome did not occur during this interval. Table 1 presents the outcomes with clinical care settings, risk intervals, and clean intervals used to identify incident outcomes. It also indicates outcomes that were included in descriptive monitoring and sequential testing, by age group.

While most outcomes underwent sequential testing, outcomes were only descriptively monitored if there were limited historical case counts to estimate background rates, which were required for testing. Among children aged 6 months – 4 years and 6 months – 5 years receiving BNT162b2 and mRNA-1273.222 vaccines respectively, 12 outcomes underwent descriptive monitoring and sequential testing, while eight were only descriptively monitored. For persons 5-17 years and 6-17 years receiving BNT162b2 and mRNA-

1273.222 vaccines respectively, 13 outcomes were both descriptively monitored and sequentially tested, and eight outcomes were only descriptively monitored. Seventeen outcomes were included in descriptive monitoring and sequential testing for adults 18 years and older, while a single outcome was only descriptively monitored (Table 4).

2.5 Statistical Analyses

Descriptive Monitoring

Vaccine uptake and health outcome counts were monitored monthly along with the demographic characteristics of vaccine recipients. The frequency of concomitant bivalent COVID-19 and seasonal influenza vaccination was also monitored. Prevalence of concomitant influenza vaccination was measured on the same-day and within 42 days prior to or following the bivalent COVID-19 mRNA vaccination date. Concomitant influenza vaccination was only descriptively monitored and was not included in inferential testing nor adjusted for in any analyses.

Sequential Testing

The Poisson Maximized Sequential Probability Ratio Test (PMaxSPRT) was used to evaluate the rate of outcomes in specific age groups following vaccination compared to a historical baseline rate.[6] Monthly sequential testing was performed to generate incidence rate ratios (IRRs) of observed outcome rates compared with database-specific historical (expected) rates. Historical rates were adjusted to account for claims processing delay, and where case counts permitted, standardized by age and sex for the population younger than 65 years old, and by age, sex, race, and nursing home residency for the population 65 years and older.[7] We estimated

annual historical rates for a pre-COVID-19 period (2017-2019) and a COVID-19 period between April and December 2020. Selection of the comparator rate was based on the overlap between the 95% confidence intervals for the periods. If rates in the historical period (individual years between 2017 and 2020) did not have overlapping 95% confidence intervals indicating a substantive difference in the rates, we selected the lower or more stable rate as the most conservative approach. This was performed to enhance the sensitivity of the test by increasing the likelihood that potential signals were not missed. Otherwise, the median annual rate was selected. Pre-COVID-19 rates from 2019 were selected for most outcomes; however, rates from the 2020 COVID-19 period were selected if the COVID-19 period rates did not return to pre-COVID-19 levels.

For each outcome, monthly sequential testing was conducted in each database and began when a minimum of three outcomes after bivalent COVID-19 vaccination was observed. Testing was conducted until the earlier of one of the following events occurred: an observed signal, surveillance end, or when the outcome-specific prespecified surveillance length was met, which was defined as the expected number of outcomes within a 6-month period.[5] We used a one-tailed test with a null hypothesis that the observed outcome rate was no greater than the historical comparator beyond a prespecified test margin with an overall alpha of 1%. A strict alpha level was selected to minimize false signals based on the large number of tests performed. Testing margins were determined for each outcome based on input from clinicians to avoid detection of minimal increases in risk that were unlikely to be clinically relevant. A statistical signal occurred if the log likelihood ratio exceeded the critical value, which was a threshold set to determine if the observed result was due to chance.[5] SAS © version 9.4, R version 4.1.2, and R Sequential Package Version 3.3.1 were used for the analysis.

This surveillance activity was performed under the FDA Biologics Effectiveness and Safety (BEST) Initiative and is covered under the scope of the FDA public health surveillance mandate.

3. Results

Descriptive Monitoring

A total of 13.9 million bivalent COVID-19 mRNA vaccine doses were observed, including 5.5 million vaccinations across commercial databases including Carelon Research, CVS Health, and Optum databases, and 8.4 million vaccinations in the Medicare FFS database (Table 2). Figure 1 shows weekly vaccine uptake by vaccine brand and database. Among commercial databases, Carelon had the highest weekly vaccine uptake compared to CVS Health and Optum databases. Figure 2 shows weekly vaccine uptake in commercial and Medicare databases by vaccine brand and age group. For adults 18 years and older, peak vaccination uptake occurred between September and December 2022, with the highest weekly vaccination uptake observed for persons 65 years and older. For children 5-17 years, BNT162b2 vaccine recipients had the highest weekly vaccine uptake between September and December 2022. Minimal weekly vaccine uptake was observed for BNT162b2 and mRNA-1273.222 vaccine users 6 months-4 years and 6 months-5 years respectively, and mRNA-1273.222 vaccine users 6-17 years.

Among vaccine recipients 6 months-64 years in commercial insurance databases, 12% were 6 months-17 years, 24% were 18-35 years, 39% were 36-55 years, and 25% were 56-64 years (Table 2). There was a slightly higher proportion of female recipients (54%) than males, which was consistent for BNT162b2 and mRNA-1273.222 vaccine brands. The majority of vaccine users resided in urban

areas (95%). The prevalence of same-day concomitant bivalent COVID-19 and seasonal influenza vaccination was 40%, increasing to 62% in the 42 days prior to or after the COVID-19 vaccination date. There was a slightly higher proportion of same-day concomitant vaccination among BNT162b2 recipients (41%) than mRNA-1273.222 recipients (39%), increasing to 62% for both vaccine brands in the 42 days before or after bivalent COVID-19 vaccination (Table 2).

In the Medicare FFS population 65 years and older, 88% of vaccine recipients were aged 65-84 years with a higher proportion of females (57%) than males. This was relatively consistent across BNT162b2 and mRNA-1273.222 vaccine users (Table 2). The majority of COVID-19 vaccine users resided in urban areas (82%), with a slightly higher proportion of BNT162b2 vaccine users residing in urban areas (85%) compared to mRNA-1273.222 users (79%). Only a small portion of vaccine users resided in the nursing home (2%). The prevalence of same-day concomitant bivalent COVID-19 and seasonal influenza vaccination was 33%, increasing to 72% in the 42 days before or after bivalent COVID-19 vaccination. There was a higher rate of same-day concomitant vaccination with influenza vaccines among BNT162b2 vaccine users (35%) compared to mRNA-1273.222 users (30%), increasing to 73% and 70% respectively in the 42 days prior to or following COVID-19 vaccination.

Sequential Testing

Sequential testing was performed for outcomes with estimable background rates. Of 17 outcomes monitored with sequential testing in adults aged 18-64 years, anaphylaxis and myocarditis/pericarditis met the statistical threshold for a signal in one of three databases (Table 3). An anaphylaxis signal was detected following bivalent BNT162b2 and mRNA-1273.222 vaccination among

participants aged 18-64 years in the Carelon Research database, based on <11 events[1] for each vaccine brand. Similarly, a myocarditis/pericarditis signal was observed among bivalent BNT162b2 vaccine recipients aged 18-35 years in the Carelon Research database, based on <11 events[1]. No statistical signals were observed in CVS Health, Optum, or Medicare FFS databases.

The incidence rate of anaphylaxis following bivalent BNT162b2 and mRNA-1273.222 vaccination was 74.5 and 109.4 cases per 100,000 person-years respectively, among those 18-64 years in the Carelon database. The incidence rate of myocarditis/pericarditis following bivalent BNT162b2 vaccination was 131.4 cases per 100,000 person-years for persons 18-35 years in the Carelon database.

Among the population aged 6 months-4 years and 6 months-5 years receiving the bivalent COVID-19 BNT162b2 and mRNA-1273.222 vaccines, respectively, sequential testing was not initiated for any of the 12 outcomes for which testing was planned, as the minimum number of cases needed to start testing (i.e., 3 cases) was not observed. Similarly, for the population aged 5-17 years, of 13 outcomes included in testing, testing was only initiated for appendicitis, seizures/convulsions, and Bell's Palsy following BNT162b2 vaccination across commercial databases due to limited case counts for the other outcomes. Testing was not initiated for any outcomes among mRNA-1273.222 vaccine recipients aged 5-17 years due to limited case counts. The majority of outcomes did not initiate testing in persons 6 months-17 years due to limited case counts. Of outcomes that initiated testing in this age group, no statistical signals were detected for either vaccine brand (Table 3).

In the Medicare population aged 65 years and older, sequential testing was initiated for all 17 outcomes for both BNT162b2 and mRNA-1273.222 vaccinations, and no statistical signals were detected (Table 3).

[1] Cell counts < 11 have been suppressed in the manuscript text and tables.

4. Discussion

This study monitored the safety of bivalent COVID-19 mRNA vaccines administered to 13.9 million persons 6 months and older in the U.S. by evaluating the risk of several outcomes following vaccination. Two outcomes met the statistical threshold for a signal in one of three commercial databases: anaphylaxis following bivalent BNT162b2 and mRNA-1273.222 vaccination in recipients aged 18-64 years and myocarditis/pericarditis following BNT162b2 vaccination in recipients aged 18-35 years.

These findings are largely consistent with existing safety assessments of COVID-19 mRNA vaccines. An elevated risk of myocarditis/pericarditis and anaphylaxis was identified following monovalent mRNA vaccines.[8-12] Risk of myocarditis/pericarditis was specifically identified in males aged 12-39 years of age in other studies.[8,10,12] While an increased anaphylaxis risk has been reported,[9,11,13] more recent studies have suggested a comparable risk to that of other vaccines.[14] Surveillance for the bivalent COVID-19 mRNA vaccines by the Vaccine Adverse Event Reporting System (VAERS) has similarly shown cases of myocarditis/pericarditis and allergic/anaphylactic events among the population aged 12 years and older.[15] A prior near-real time surveillance study identified a statistical signal for seizures/convulsions following monovalent BNT162b2 and mRNA-1273 vaccination in children 2-4/5 years.[16] Our study identified zero cases of seizures/convulsions in this age group following bivalent vaccination, and no outcomes met the statistical threshold for signal in the young age group.

Our study population had a high prevalence of same-day concomitant administration of bivalent COVID-19 mRNA and influenza vaccines. Clinical trials that have assessed the safety and reactogenicity of concomitant administration of these vaccines have not found any safety concerns or reduced immune response related to the concomitant use of these vaccines.[17-19] While we had a high

prevalence of concomitant vaccination, our study did not perform testing stratified by concomitant influenza vaccination status; thus, we are unable to draw any conclusions about the safety of concomitant vaccination.

This study had several strengths. The study included a large sample size of geographically diverse participants from all age groups authorized to receive bivalent BNT162b2 or mRNA-1273.222 vaccines from both commercially and publicly insured populations across the U.S. The study also evaluated several outcomes as vaccines were administered. The near-real time surveillance method allowed for vaccine safety to be monitored shortly after bivalent COVID-19 mRNA vaccine authorizations. Outcomes were similarly able to be monitored for an extensive period varying from three to eleven months depending on database, vaccine brand and age group.

The near-real time surveillance method applied in this study is a crude signal detection method used for rapid safety screening. This method uses a comparator (i.e., aggregate historical rates) with limited adjustment for confounding factors. This method, similarly, requires the specification of multiple parameters that, if misspecified, could affect the presence or absence of detected signals such as risk interval timing and length, and the testing margin used to identify meaningful elevations in risk. Additionally, we did not adjust for multiple testing of outcomes which may have increased the likelihood of observing a false positive safety signal when risk is not truly elevated. Therefore, this method does not establish a causal association between the vaccines and outcomes. Furthermore, although we observed substantial uptake of bivalent COVID-19 mRNA vaccines, this was reduced relative to administration of monovalent COVID-19 mRNA vaccine doses. This could have decreased our power to detect statistical signals, particularly for rare outcomes, and may explain some differences in signals detected or not detected across databases. Our study was

also limited by the use of administrative claims data, collected for billing purposes, but used for safety surveillance activities. Our medical record review has shown that certain outcomes are detected in claims data more accurately than others.[20,21] Since we did not conduct medical record review nor adjust for outcome misclassification for outcomes evaluated in this study, the presence and extent of outcome misclassification is unknown and could apply to at least some of the outcomes included in surveillance. This can bias signal detection in either direction.

The surveillance of bivalent COVID-19 mRNA vaccines supports the safety of these vaccines and is consistent with findings from surveillance results of monovalent COVID-19 mRNA vaccines. This study contributes to regulatory decision-making for COVID-19 vaccines and public health and supports the conclusion that the benefits of vaccination outweigh the risks.

All authors attest they meet the ICMJE criteria for authorship.

Conflicts of Interest Statement

Co-authors from U.S. Food and Drug Administration and Acumen LLC declared no conflicts of interests. The following authors reported a conflict of interest: Kandace L. Amend, [1] John D. Seeger, [1] Jennifer Song,[1] Robin Clifford, [1] Cheryl N. McMahill-Walraven,[2] Djeneba Audrey Djibo,[2] Jonathan P. DeShazo,[2] Eugenio Abente,[2] Daniel C. Bleacher,[3] Alex Secora,[4] Nandini Selvam.[4]

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386 **Table 1. Health outcome definitions (settings, clean intervals, risk intervals), and analysis types**

Outcome	Age Group (years)	Care Setting	Clean Interval (days)*	Risk Interval (days)	Descriptive Analysis	Sequential Testing
Acute myocardial infarction	6 mos.-4/6 mos.-5	IP	365	1-28[22,23]	Yes	No
	5-17/6-17				Yes	No
	18-64				Yes	Yes
	65+				Yes	Yes
Anaphylaxis	6 mos.-4/6 mos.-5.	IP, OP-ED	30	0-1[24,25]	Yes	Yes
	5-17/6-17.				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Appendicitis	6 mos.-4/6 mos.-5	IP, OP-ED	365	1-42[26,27]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Bell's palsy	6 mos.-4 /6 mos.-5	IP, OP/PB	183	1-42[28,29]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Common site thrombosis with thrombocytopenia	6 mos.-4/6 mos.-5	[Definition below]**	365	1-28[30]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Deep vein thrombosis	6 mos.-4/6 mos.-5	IP, OP/PB	365	1-28[31-33]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+.				Yes	Yes
Disseminated intravascular coagulation	6 mos.-4/6 mos.-5	IP, OP-ED	365	1-28[34]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes

Encephalitis/ encephalomyelitis	6 mos.-4/6 mos.-5	IP	183	1-42[35]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Febrile seizures	6 mos.-4/6 mos.-5	IP, OP-ED	42	0-7[36]	Yes	No
	5-17/6-17				Yes	No
Guillain-Barré syndrome	6 mos.-4/6 mos.-5	IP- primary position only	365	1-42[37,38]	Yes	Yes
	5-17/6-17				Yes	No
	18-64				Yes	Yes
	65+				Yes	Yes
Hemorrhagic stroke	6 mos.-4/6 mos.-5	IP	365	1-28[22,23]	Yes	Yes
	5-17/6-17				Yes	No
	18-64				Yes	Yes
	65+				Yes	Yes
Immune thrombocytopenia	6 mos.-4/6 mos.-5	IP (primary diagnosis only)	365	1-42[39,40]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Kawasaki disease	6 mos.-4/6 mos.-5	IP, OP/PB	365	1-28[41,42]	Yes	No
	5-17/6-17				Yes	No
Multisystem inflammatory syndrome	6 mos.-4/6 mos.-5	IP, OP-ED	365	1-42[43]	Yes	No
	5-17/6-17				Yes	No
	18-64				Yes	No
	65+.				Yes	No
Myocarditis/ pericarditis	6 mos.-4/6 mos.-5.	IP, OP/PB IP, OP-ED	365	1-7[10,44] 1-21[45]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-35				Yes	Yes
	18-64				Yes	Yes
	36-64				Yes	Yes
	65+				Yes	Yes
Narcolepsy	6 mos.-4/6 mos.-5	IP, OP/PB	365	1-42[46-48]	Yes	No

	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Non-hemorrhagic stroke	6 mos.-4/6 mos.-5	IP	365	1-28[22,23]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Pulmonary embolism	6 mos.-4/6 mos.-5	IP	365	1-28[31-33]	Yes	Yes
	5-17/6-17				Yes	Yes
	18-64				Yes	Yes
	65+				Yes	Yes
Seizures/ convulsions	6 mos.-1	IP, OP-ED	42	0-7[36]	Yes	Yes
	2-4 /2-5				Yes	Yes
	5-17/6-17				Yes	Yes
Transverse myelitis	6 mos.-4/6 mos.-5	IP, OP-ED	365	1-42[49]	Yes	No
	5-17/6-17				Yes	No
	18-64				Yes	Yes
	65+				Yes	Yes
Unusual site thrombosis with thrombocytopenia	6 mos.-4/6 mos.-5	[Definition below]**	365	1-28[50]	Yes	No
	5-17/6-17				Yes	No
	18-64				Yes	Yes
	65+				Yes	Yes

Definitions: Clean interval is defined as an interval used to define incident outcomes where an individual enters the study cohort only if the outcome did not occur during that interval. Risk interval is defined as an interval during which occurrence of the outcome will be included in the analysis.

Acronyms: IP – inpatient; OP-ED - outpatient emergency department; OP/PB outpatient & professional

* References for the clean interval could not be located in the literature and are based on clinician input

** Common site thrombosis with thrombocytopenia and unusual site thrombosis with thrombocytopenia are combined outcomes consisting of a thrombotic event (made up of other events such as acute myocardial infarction, deep vein thrombosis etc.,) and a thrombocytopenia event (defined in the IP, OP/PB setting). The overall setting definition for each outcome depends on individual setting definitions for each of these components

Table 2. Characteristics of the population vaccinated with bivalent COVID-19 mRNA vaccines aged 6 months-64 years in CVS Health, Carelon Research, and Optum Databases; aged ≥ 65+ years in Medicare Database

Patient Characteristics	Any Bivalent COVID-19 mRNA Vaccine				BNT162b2 Bivalent				mRNA-1273.222			
	Commercial Databases		Medicare		Commercial Databases		Medicare		Commercial Databases		Medicare	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	**5,498,556**	**100**	**8,380,283**	**100**	**3,769,301**	**100**	**4,869,360**	**100**	**1,729,255**	**100**	**3,510,923**	**100**
Age at Vaccine Administration (years)												
6 mos.-4	33,051	0.6	--	--	33,051	0.9	--	--	--	--	--	--
5-11	234,201	4.3	--	--	234,201	6.2	--	--	--	--	--	--
6 mos.-5	23,864	0.4	--	--	--	--	--	--	23,864	1.4	--	--
6-11	21,719	0.4	--	--	--	--	--	--	21,719	1.3	--	--
12-17	329,297	6.0	--	--	301,069	8.0	--	--	28,228	1.6	--	--
18-25	454,374	8.3	--	--	319,187	8.5	--	--	135,187	7.8	--	--
26-35	872,613	15.9	--	--	579,921	15.4	--	--	292,692	16.9	--	--
36-45	1,026,398	18.7	--	--	684,872	18.2	--	--	341,526	19.7	--	--
46-55	1,128,330	20.5	--	--	748,022	19.8	--	--	380,308	22.0	--	--
56-64	1,374,709	25.0	--	--	868,978	23.1	--	--	505,731	29.2	--	--
65-74	--	--	4,414,887	52.7	--	--	2,544,098	52.2	--	--	1,870,789	53.3
75-84	--	--	2,937,151	35.0	--	--	1,699,813	34.9	--	--	1,237,338	35.2
85+	--	--	1,028,245	12.3	--	--	625,449	12.8	--	--	402,796	11.5
Missing/ Unknown	0	0.0	0	0.00	0	0.0	0	0.0	0	0.0	0	0.0
Sex												
Female	2,973,454	54.1	4,760,468	56.8	2,039,091	54.1	2,784,173	57.2	934,363	54.0	1,976,295	56.3
Male	2,522,429	45.9	3,619,815	43.2	1,728,476	45.9	2,085,187	42.8	793,953	45.9	1,534,628	43.7
Missing/ Unknown	2,673	0.0	0	0.0	1,734	0.0	0	0.0	939	0.1	0	0.0
Urban/Rural												

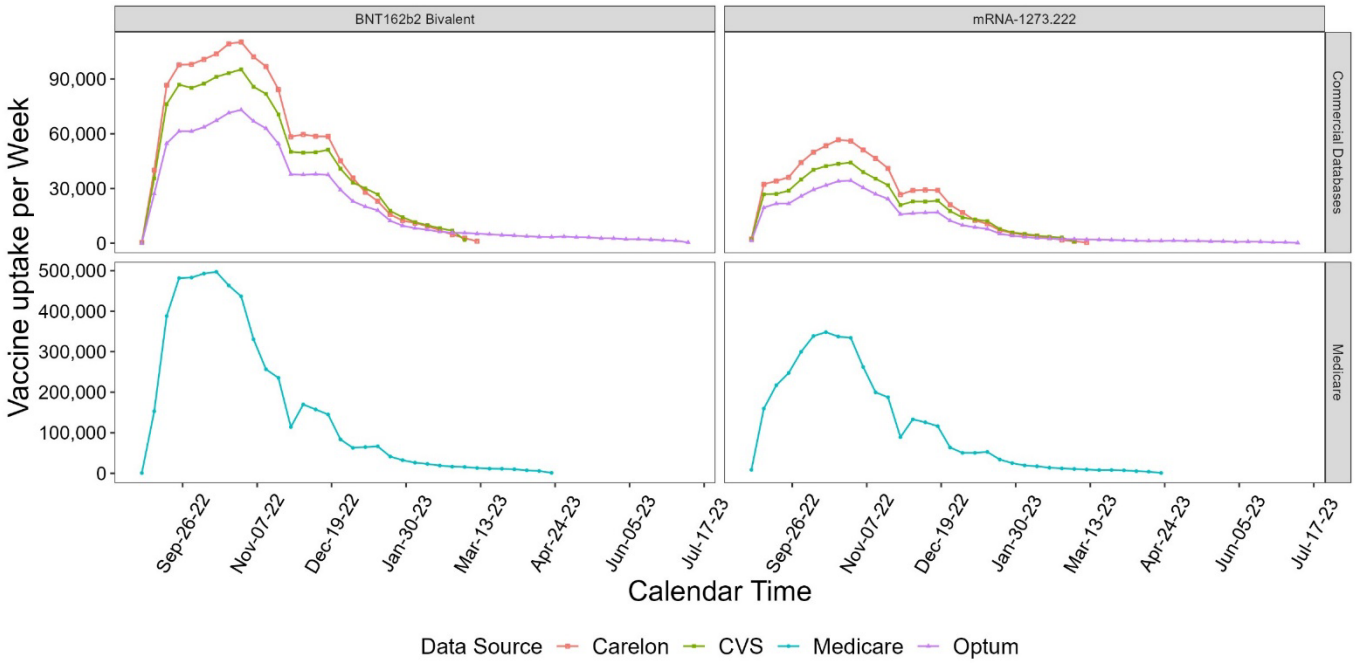
Rural	270,566	4.9	1,437,843	17.2	155,304	4.1	706,057	14.5	115,262	6.7	731,786	20.8
Urban	5,224,680	95.0	6,906,602	82.4	3,611,592	95.8	4,143,587	85.1	1,613,088	93.3	2,763,015	78.7
Missing/ Unknown	3,310	0.1	35,838	0.4	2,405	0.1	19,716	0.4	905	0.1	16,122	0.5
Nursing Home Residency												
Nursing Home	--	--	162,676	1.9	--	--	114,823	2.4	--	--	47,853	1.4
Non-Nursing Home	--	--	8,217,607	98.1	--	--	4,754,537	97.6	--	--	3,463,070	98.6
HHS Region**												
Region 1	415,184	7.6	636,543	7.6	260,059	6.9	375,493	7.7	155,125	9.0	261,050	7.4
Region 2	717,615	13.1	772,359	9.2	497,768	13.2	445,935	9.2	219,847	12.7	326,424	9.3
Region 3	663,777	12.1	1,041,119	12.4	456,144	12.1	605,595	12.4	207,633	12.0	435,524	12.4
Region 4	700,716	12.7	1,436,145	17.1	484,902	12.9	780,141	16.0	215,814	12.5	656,004	18.7
Region 5	840,248	15.3	1,510,948	18.0	594,476	15.8	933,502	19.2	245,772	14.2	577,446	16.4
Region 6	335,791	6.1	712,875	8.5	222,060	5.9	376,103	7.7	113,731	6.6	336,772	9.6
Region 7	196,416	3.6	486,163	5.8	143,920	3.8	309,893	6.4	52,496	3.0	176,270	5.0
Region 8	243,198	4.4	308,916	3.7	178,681	4.7	209,853	4.3	64,517	3.7	99,063	2.8
Region 9	1,162,526	21.1	1,076,085	12.8	763,870	20.3	586,787	12.1	398,656	23.1	489,298	13.9
Region 10	220,579	4.0	391,565	4.7	165,541	4.4	241,908	5.0	55,038	3.2	149,657	4.3
Missing/ Unknown	2,506	0.0	7,565	0.1	1,880	0.0	4,150	0.1	626	0.0	3,415	0.1
Concomitant Vaccination Status												
Influenza (Same Day)	2,223,077	40.4	2,764,112	33.0	1,545,503	41.0	1,720,039	35.3	677,574	39.2	1,044,073	29.7
Influenza (+/- 42 days)*	3,391,431	61.7	6,005,972	71.7	2,325,523	61.7	3,539,611	72.7	1,065,908	61.6	2,466,361	70.2

*Relative to bivalent COVID-19 mRNA vaccination date to align with broadest adverse event-specific risk interval

**Health and Human Services (HHS) regions are designated by the U.S. HHS Department to serve state and local organizations. Information on individual U.S. states and territories included in each region is linked.

Data cuts: CVS Health (2/28), Carelon (3/4), Optum (7/8), Medicare (4/22)

Figure 1. Pattern of vaccination trends in vaccine administrations of bivalent COVID-19 mRNA vaccines, August 2022 - April 2023 by vaccine brand and database



409 **Figure 2. Pattern of bivalent COVID-19 mRNA vaccines uptake August 2022- July 2023 by age group and database**

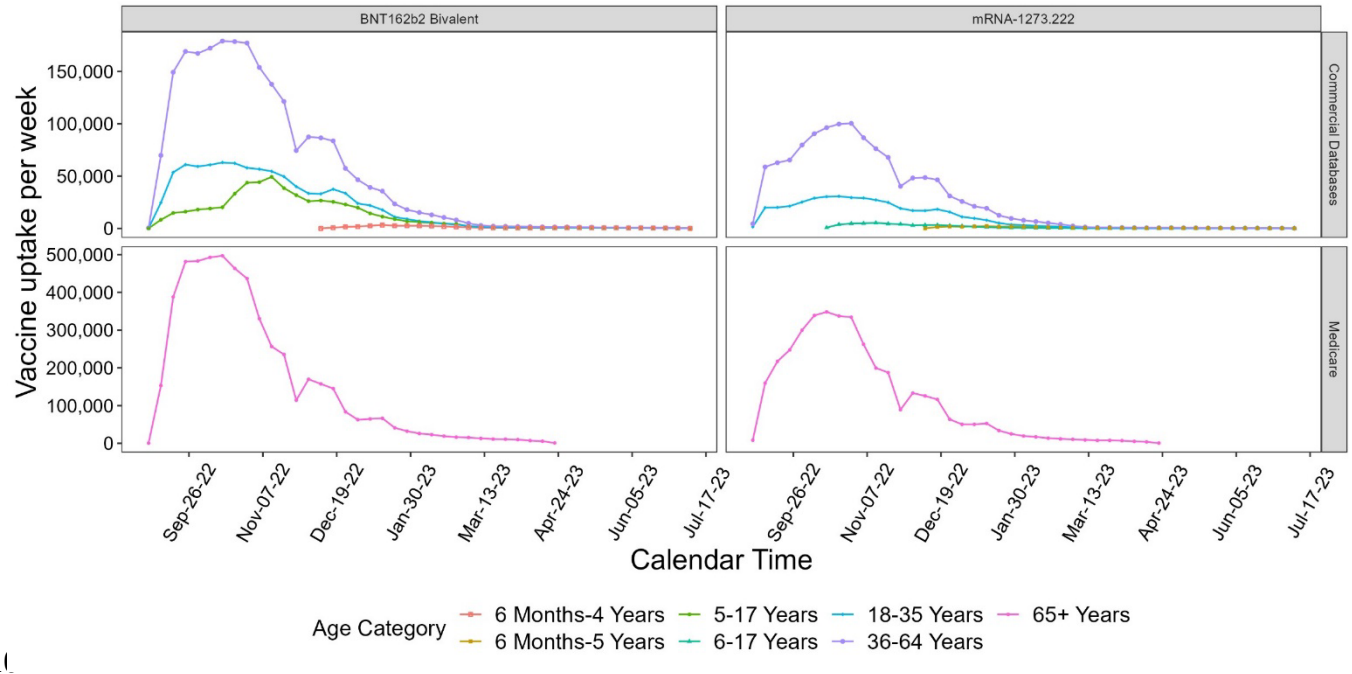


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Table 3. Sequential testing results in population vaccinated with bivalent COVID-19 mRNA vaccines

Outcome	Age Group of Interest (years)	BNT162b2 Bivalent						mRNA 1273.222					
		Commercial Databases			Medicare			Commercial Databases			Medicare		
		No. Cases	Person-Years	Signal[+]	No. Cases	Person-Years	Signal[+]	No. Cases	Person-Years	Signal[+]	No. Cases	Person-Years	Signal[+]
Acute myocardial infarction	18-64	173	183,346	No	--	--	--	111	95,413	No	--	--	--
	65+	--	--	--	1,391	185,695	No	--	--	--	847	124,521	No
Anaphylaxis	6 mos.-4 /6 mos.-5	0	169	NA	--	--	--	0	123	NA	--	--	--
	5-17/6-17	0	2,879	NA	--	--	--	0	269	NA	--	--	--
	18-64	<11	17,190	Yes*	--	--	--	<11	8,895	Yes*	--	--	--
	65+	--	--	--	<11	26,573	No	--	--	--	<11	19,167	No
Appendicitis	6 mos.-4 /6 mos.-5	0	1,650	NA	--	--	--	<11	1,432	NA	--	--	--
	5-17/6-17	57	46,901	No	--	--	--	<11	4,350	NA	--	--	--
	18-64	270	271,731	No	--	--	--	153	141,412	No	--	--	--
	65+	--	--	--	378	520,510	No	--	--	--	286	377,255	No
Bell's palsy	6 mos.-4 /6 mos.-5	0	2,591	NA	--	--	--	<11	1,964	NA	--	--	--
	5-17/6-17	19	54,336	No	--	--	--	<11	5,041	NA	--	--	--
	18-64	313	319,957	No	--	--	--	147	166,052	No	--	--	--
	65+	--	--	--	853	434,115	No	--	--	--	793	389,836	No
Common site thrombosis with thrombocytopenia	6 mos.-4 /6 mos.-5 **	0	603	NA	--	--	--	0	568	NA	--	--	--
	5-17/6-17	<11	32,218	NA	--	--	--	0	3,000	NA	--	--	--
	18-64	38	185,056	No	--	--	--	17	96,260	No	--	--	--
	65+	--	--	--	680	281,427	No	--	--	--	597	248,391	No

Deep vein thrombosis	6 mos.-4 /6 mos.-5	0	1,308	NA	--	--	--	0	1,113	NA	--	--	--
	5-17/6-17	<11	32,229	NA	--	--	--	0	2,998	NA	--	--	--
	18-64	403	184,442	No	--	--	--	203	95,926	No	--	--	--
	65+	--	--	--	1,641	207,772	No	--	--	--	1,055	141,714	No
Disseminated intravascular coagulation	6 mos.-4 /6 mos.-5	0	1,112	NA	--	--	--	0	966	NA	--	--	--
	5-17/6-17	<11	31,587	NA	--	--	--	0	2,934	NA	--	--	--
	18-64	<11	182,927	No	--	--	--	<11	95,193	No	--	--	--
	65+	--	--	--	72	348,559	No	--	--	--	47	252,617	No
Encephalitis/ encephalomyelitis	6 mos.-4 /6 mos.-5	0	1,984	NA	--	--	--	0	1,535	NA	--	--	--
	5-17/6-17	0	52,101	NA	--	--	--	0	4,806	NA	--	--	--
	18-64	<11	311,472	NA	--	--	--	<11	161,738	NA	--	--	--
	65+	--	--	--	52	537,826	No	--	--	--	37	388,869	No
Guillain-Barré syndrome	6 mos.-4 /6 mos.-5	0	1,579	NA	--	--	--	0	1,377	NA	--	--	--
	18-64	<11	270,776	No	--	--	--	<11	140,894	NA	--	--	--
	65+	--	--	--	21	518,627	No	--	--	--	11	375,854	No
Hemorrhagic stroke	6 mos.-4 /6 mos.-5	<11	1,222	NA	--	--	--	0	1,049	NA	--	--	--
	18-64	30	184,170	No	--	--	--	15	95,832	No	--	--	--
	65+	--	--	--	555	348,265	No	--	--	--	356	252,438	No
Immune thrombocytopenia	6 mos.-4 /6 mos.-5 ***	0	320	NA	--	--	--	0	323	NA	--	--	--
	5-17/6-17	0	47,461	NA	--	--	--	0	4,411	NA	--	--	--
	18-64	<11	273,946	No	--	--	--	<11	142,520	No	--	--	--

	65+	--	--	--	42	521,851	No	--	--	--	23	378,240	No
Myocarditis/Pericarditis (1-7 day risk window, all settings)	6 mos.-4/6 mos.-5	0	381	NA	--	--	--	0	319	NA	--	--	--
	5-17/6-17	<11	8,295	NA	--	--	--	0	773	NA	--	--	--
	18-35	<11	11,832	Yes	--	--	--	<11	5,618	NA	--	--	--
	18-64	26	47,204	No	--	--	--	13	24,550	No	--	--	--
	36-64	17	35,371	No	--	--	--	<11	18,932	No	--	--	--
	65+	--	--	--	72	87,542	No	--	--	--	51	63,449	No
Myocarditis/Pericarditis (1-21 day risk window, all settings)	6 mos.-4/6 mos.-5	0	1,077	NA	--	--	--	0	905	NA	--	--	--
	5-17/6-17	<11	24,533	NA	--	--	--	0	2,283	NA	--	--	--
	18-35	19	35,061	No	--	--	--	<11	16,641	No	--	--	--
	18-64	61	140,157	No	--	--	--	30	72,891	No	--	--	--
	36-64	42	105,096	No	--	--	--	23	56,250	No	--	--	--
	65+	--	--	--	253	261,992	No	--	--	--	149	189,899	No
Myocarditis/Pericarditis (1-7 day risk window, IP/OP-ED)	6 mos.-4/6 mos.-5	0	357	NA	--	--	--	0	300	NA	--	--	--
	5-17/6-17	<11	8,220	NA	--	--	--	0	767	NA	--	--	--
	18-35	<11	11,773	NA	--	--	--	<11	5,591	NA	--	--	--
	18-64	<11	47,003	No	--	--	--	<11	24,450	NA	--	--	--
	36-64	<11	35,230	NA	--	--	--	<11	18,859	NA	--	--	--
	65+	--	--	--	27	87,613	No	--	--	--	16	63,497	No
Myocarditis/Pericarditis (1-21 day risk window,	6 mos.-4/6 mos.-5	0	993	NA	--	--	--	0	841	NA	--	--	--
	5-17/6-17	<11	24,277	NA	--	--	--	0	2,258	NA	--	--	--

IP/OP-ED)	18-35	<11	34,823	No	--	--	--	<11	16,538	NA	--	--	--
	18-64	13	139,362	No	--	--	--	<11	72,503	No	--	--	--
	36-64	<11	104,539	No	--	--	--	<11	55,964	No	--	--	--
	65+	--	--	--	75	262,202	No	--	--	--	42	190,042	No
Narcolepsy	5-17/6-17	<11	47,933	NA	--	--	--	<11	4,454	NA	--	--	--
	18-64	140	275,418	No	--	--	--	67	143,284	No	--	--	--
	65+	--	--	--	181	521,422	No	--	--	--	149	377,965	No
Non-hemorrhagic stroke	6 mos.-4 /6 mos.-5	0	1,177	NA	--	--	--	0	1,012	NA	--	--	--
	5-17/6-17	<11	31,792	NA	--	--	--	0	2,953	NA	--	--	--
	18-64	70	183,450	No	--	--	--	37	95,472	No	--	--	--
	65+	--	--	--	871	186,210	No	--	--	--	900	198,968	No
Pulmonary embolism	5-17/6-17	0	32,099	NA	--	--	--	0	2,987	NA	--	--	--
	18-64	57	184,601	No	--	--	--	29	96,041	No	--	--	--
	65+	--	--	--	767	290,496	No	--	--	--	630	249,022	No
Seizures/Convulsions	6 mos.-1	<11	274	NA	--	--	--	<11	160	NA	--	--	--
	2-4/2-5	0	373	NA	--	--	--	0	311	NA	--	--	--
	5-17/6-17	17	11,374	No	--	--	--	<11	1,061	NA	--	--	--
Transverse myelitis	18-64	<11	272,051	No	--	--	--	0	141,575	NA	--	--	--
	65+	--	--	--	11	519,838	No	--	--	--	<11	376,755	No
Unusual site thrombosis with thrombocytopenia	18-64	<11	183,537	NA	--	--	--	<11	95,512	NA	--	--	--
	65+	--	--	--	42	347,927	No	--	--	--	13	252,150	No

Counts less than 11 have been masked/suppressed

NA indicates that for the outcome and age group no testing was initiated due to case counts < 3.

"--" indicates that the outcome and age group combination did not apply to a given database(s).
Acronyms: IP - inpatient, OP-ED - outpatient emergency department, OP/PB outpatient & professional
† Indicates whether or not a statistical signal was observed in the database(s) for the outcome and age group.
*Signal observed in Carelon database, only
**Sequential testing not conducted in Optum database
***Sequential testing conducted in Carelon database, only

Table 4. Frequency of vaccine doses and outcomes among outcomes only descriptively monitored

Outcome	Age Group of Interest (years)	BNT162b2 Bivalent				mRNA 1273.222			
		Commercial Databases		Medicare		Commercial Databases		Medicare	
		No. Cases	No. Doses	No. Cases	No. Doses	No. Cases	No. Doses	No. Cases	No. Doses
Acute myocardial infarction	6 mos.-4 / 6 mos.-5	0	20,857	--	--	0	17,361	--	--
	5-17/6-17	0	436,784	--	--	0	40,746	--	--
Common site thrombosis with thrombocytopenia	6 mos.-4 / 6 mos.-5 *	0	9,764	--	--	0	7,551	--	--
Febrile seizures	6 mos.-4 / 6 mos.-5	<11	31,571	--	--	<11	22,990	--	--
	5-17/6-17	<11	525,424	--	--	<11	49,056	--	--
Guillain-Barré syndrome	5-17/6-17	0	436,785	--	--	0	40,746	--	--
Hemorrhagic stroke	5-17/6-17	<11	436,775	--	--	0	40,746	--	--
Immune thrombocytopenia	6 mos.-4 / 6 mos.-5 **	0	15,111	--	--	0	12,432	--	--
Kawasaki disease	6 mos.-4 / 6 mos.-5	0	20,837	--	--	0	17,348	--	--
	5-17/6-17	<11	436,688	--	--	<11	40,736	--	--
Multisystem inflammatory syndrome	6 mos.-4 / 6 mos.-5	0	20,856	--	--	0	17,359	--	--
	5-17/6-17	0	436,772	--	--	0	40,745	--	--
	18-64	0	2,478,389	--	--	0	1,288,891	--	--
	65+	--	--	<11	4,574,507	--	--	0	3,315,135
Narcolepsy	6 mos.-4 / 6 mos.-5	0	20,856	--	--	0	17,361	--	--
Pulmonary embolism	6 mos.-4 / 6 mos.-5	0	20,857	--	--	0	17,361	--	--
Transverse myelitis	6 mos.-4 / 6 mos.-5	0	20,856	--	--	0	17,361	--	--
	5-17/6-17	<11	436,784	--	--	0	40,746	--	--
Unusual site thrombosis with thrombocytopenia	6 mos.-4 / 6 mos.-5	0	20,857	--	--	0	17,361	--	--
	5-17/6-17	0	436,784	--	--	0	40,746	--	--

Counts less than 11 have been masked/suppressed.
"--" indicates that the outcome and age group combination did not apply to a given database(s).
*Contain counts from Optum, only
**Contain counts from CVS Health and Optum, only
Data cuts: CVS Health (2/28), Carelon (3/4), Optum (7/8), Medicare (4/22)