U.S. FOOD & DRUG ADMINISTRATION

Update on Original COVID-19 Vaccine and COVID-19 Vaccine, Bivalent Safety

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Outline

- **CBER Active Surveillance Program (BEST Initiative)**
- Bivalent COVID-19 mRNA Vaccines Safety Surveillance
- Conclusion

BEST Initiative Data Sources

Data Source*	Database Type	No. Patients Covered (Millions)	Time Period Covered
CMS- Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
MarketScan Commercial (IBM)	Claims	65	2016 - present
Blue Health Intelligence	Claims	93	2016 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	31	2017 - present
HealthCore	Claims	70	2010 - present
CVS Health	Claims	41	2018 - present
OneFlorida Clinical Research Consortium - Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium - EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims - EHR	Linked EHR Claims	25	2007 – 2020

*Data lag varies based on data source, ranges from a few days to a few months.

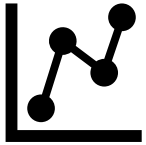
Rapid Cycle Analysis (RCA) Data Sources

Claims Data Source	Age (years)	Population Enrolled (million)
CMS Medicare	65+	36
DP 1	0-4 5-17 18-64	1.2 3.1 14.8
DP 2	0-4 5-17 18-64	1.0 2.6 11.6
DP 3	0-4 5-17 18-64	1.4 3.7 17.1

Immunization Information Systems (IIS)

- Confidential, population-based, computerized databases that record immunization doses administered by participating providers to persons in U.S. public health jurisdictions
- Supplements claims-based COVID-19 vaccine administration data
- Undercapture of COVID-19 vaccines in claims databases due to vaccines administered without insurance reimbursement

Phases of Vaccine Active Surveillance



Descriptive Monitoring provides descriptive statistics of vaccine doses and selected adverse events.

Signal Detection performs sequential testing, while vaccine doses accumulate, to identify potential safety risks early; does not prove causal relationship.

Signal Evaluation uses more robust study designs to evaluate potential safety signals.

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COVID-19 Bivalent mRNA Vaccines Rapid Cycle Analyses

Administered Doses By Age Group

Age Groups (years)	BNT162b2 (# vaccinations)	mRNA-1273 (# vaccinations)	Total (# vaccinations)
5/6-17[1]	196,992	13,016	210,008
18-35[1]	442,870	211,694	654,564
36-64[1]	1,248,430	654,220	1,902,650
65+[2]	4,265,244	3,042,074	7,307,318

1. Data cuts: CVS data through 10/2022, HealthCore data through 11/2022, Optum data through 12/2022
2. Data cuts: CMS data through 12/2022

COVID-19 Bivalent mRNA Vaccines Safety Monitoring

- **FDA Study Design:** Rapid Cycle Analysis (RCA) near real-time surveillance
  - No causal association established
- **Population:** 6 month-4/5 years, 5/6-17 years, 18-64 years*, ≥65 years
- **Exposure:** mRNA-1273.222 and BNT162b2 COVID-19 vaccines
  - Bivalent booster: original SARS-CoV-2 virus and Omicron variants BA.4 and BA.5.
- **Statistical Method**: MaxSPRT
- **Comparator:** Historical rates

*For the myocarditis/pericarditis outcome, the study population was additionally split into 18-35 and 36-64 year age groups.

FDA Adverse Events Monitored

Adverse Events Monitored in Adult and Pediatric Populations	
Acute Myocardial Infarction	Hemorrhagic Stroke
Anaphylaxis	Immune Thrombocytopenia
Appendicitis	Multisystem Inflammatory Syndrome
Bell's Palsy	Myocarditis/Pericarditis (Myo-/Pericarditis)*
Common Site Thrombosis with Thrombocytopenia	Narcolepsy
Disseminated Intravascular Coagulation	Non-hemorrhagic Stroke
Deep Vein Thrombosis	Pulmonary Embolism
Encephalitis/Encephalomyelitis	Transverse Myelitis
Guillain-Barre Syndrome	Unusual Site Thrombosis (Broad) with Thrombocytopenia

Adverse Events Monitored in Pediatric Populations Only
Seizure/Febrile Seizure
Kawasaki Disease
Multisystem Inflammatory Syndrome in children (MIS-C)

*This includes 4 myo-/pericarditis outcome definitions varying care settings (all settings vs. IP/OP-ED) and risk windows (1-7 vs. 1-21 days)
These AEs have not been associated with COVID-19 vaccines based on available pre-licensure evidence.

Signals Detected

Adverse Event (AE)	Medicare Population[1] (Ages 65+)	Adult Population[2] (Ages 18-64)	Pediatric Population[2] (Ages 5-17/6-17)
Acute Myocardial Infarction	No	No	Descriptive Only
Anaphylaxis	No	No	No
Appendicitis	No	No	No
Disseminated Intravascular Coagulation	No	No	No
Deep Vein Thrombosis	No	No	No
Bell's Palsy	No	No	No
Encephalomyelitis/Encephalitis	No	No	No
Guillain-Barré Syndrome	No	No	Descriptive Only
Hemorrhagic Stroke	No	No	Descriptive Only
Myocarditis/Pericarditis	No	**BNT162b2 Bivalent (18-35)**	No
Common Site Thrombosis with Thrombocytopenia	No	No	No
Uncommon Site Thrombosis with Thrombocytopenia Syndrome	No	No	Descriptive Only
Narcolepsy	No	No	No
Non-Hemorrhagic Stroke	No	No	No
Pulmonary Embolism	No	No	No
Transverse Myelitis	No	No	Descriptive Only
Immune Thrombocytopenia	No	No	No
Febrile Seizures	N/A	N/A	Descriptive Only
Seizures/Convulsions	N/A	N/A	No
Kawasaki disease	N/A	N/A	Descriptive Only
Multisystem Inflammatory Syndrome	Descriptive Only	Descriptive Only	Descriptive Only

1. Data cuts: CMS 12/2022
2. Data cuts: CVS Health data through 10/2022; HealthCore data through 11/2022, Optum data through 12/2022

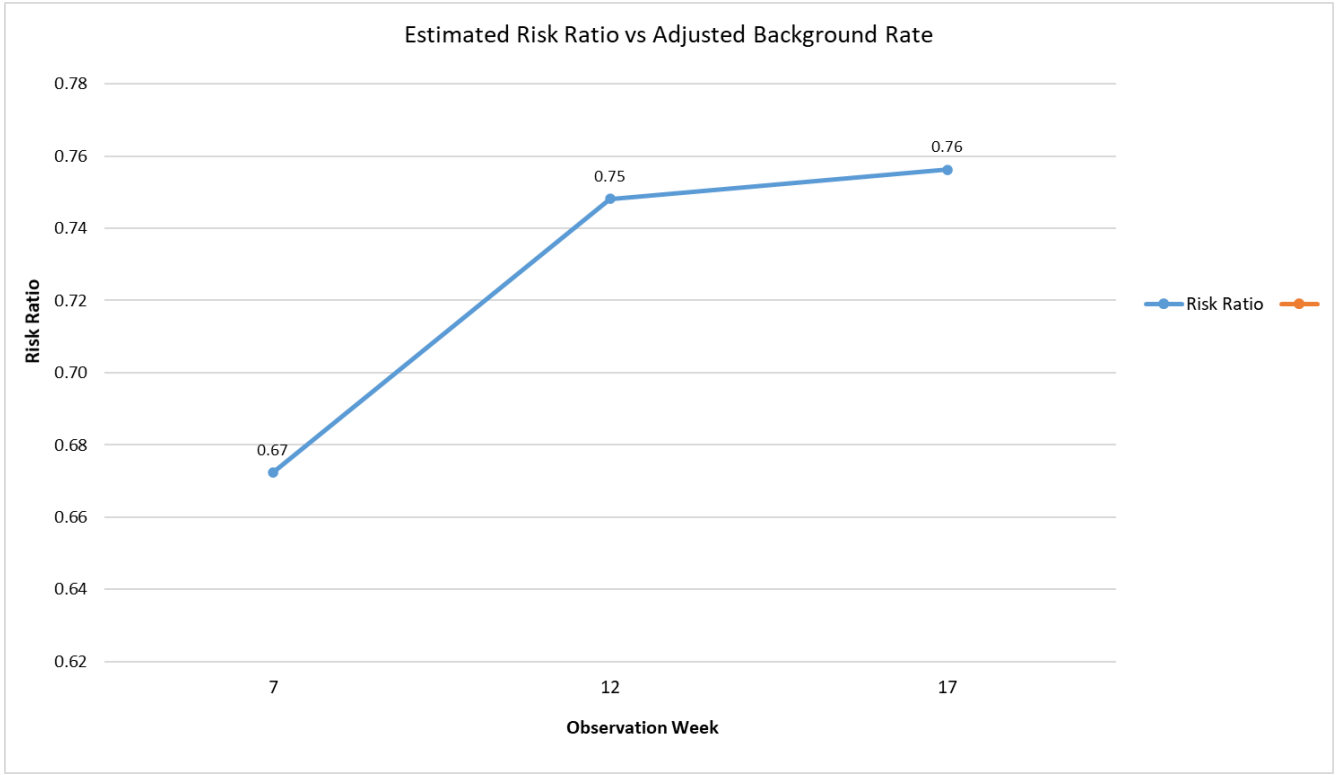
AEs and the associated vaccine brand with a safety signal are noted.

***N/A** indicates neither descriptive monitoring nor sequential testing is being conducted in the indicated age group for a given AE. **NO** indicates that a safety signal has not been detected. **Descriptive Only** indicates sequential testing is not being conducted in the indicated age group for a given AE.*

Adverse Events that Completed Surveillance Period

Adverse Event (AE)	Ages 65+ years
Acute Myocardial Infarction	BNT162b2, mRNA-1273
Deep Vein Thrombosis	BNT162b2, mRNA-1273
Bell's Palsy	BNT162b2
Common Site Thrombosis with Thrombocytopenia	BNT162b2
Non-Hemorrhagic Stroke	BNT162b2, mRNA-1273
Pulmonary Embolism	BNT162b2

Risk Ratio Non-hemorrhagic Stroke for Pfizer Bivalent Compared to Historical Rates (2019)



We reached the maximum length of surveillance without a signal

Concomitant Influenza Vaccination

- Approximately 4.25 million doses of the Pfizer-BioNTech bivalent vaccine have been administered in the CMS database in individuals 65 years and older
- 38% of the Medicare recipients who received a Pfizer bivalent COVID-19 booster received a seasonal influenza vaccination on the same day
- 78% received a seasonal influenza vaccination within +/- 42 days
- Further work to be done to segment out the different influenza vaccine types administered with the COVID-19 vaccines
- No signal seen at this time for non-hemorrhagic stroke

COVID-19 Bivalent mRNA Vaccines RCA

Summary

- This is a large-scale signal detection study of two COVID-19 mRNA bivalent vaccines conducted in multiple claims databases.
- RCA surveillance detected a signal for myocarditis/pericarditis following BNT162b2 bivalent vaccine doses among 18-35 year olds.
- Among adults 65 years and older, several AEs have completed the surveillance period.
- Signal detection studies do not establish a causal relationship and further evaluation of signals is required in more robust studies.
- Surveillance is ongoing and expanded to < 5 year olds.

Data Suggesting Absence of Safety Risk for the Bivalent Boosters in Age 65y+

1) No excess reports of stroke from VAERS
2) CMS database with about 4.25 million doses shows no increase in stroke
3) VA database run shows no increase in stroke on preliminary query
4) Various countries in Europe as well as Israel indicate no increased risk of stroke in their surveillance systems
5) Pfizer notes no increase in signal in their global safety database or when comparing the monovalent to bivalent vaccines

In any case, a formal epidemiologic study is being initiated by FDA to prepare for potential vaccine coadministration in 2023-2024

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