Preview

Pfizer & Truveta - Myocarditis Analysis May 2022

Last edited by: Leapley, Andrea on: May 6, 2022

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Use Case 2: Incidence of hospitalization for myocarditis following COVID-19 vaccination

Background:

Adverse events (AEs) following COVID-19 vaccination are of high clinical importance; even adverse events with small incidence may be seen in appreciable numbers given the massive scope of the vaccination effort. There is evidence that suggests patients who received a COVID-19 vaccine are at an increased risk of myocarditis. Furthermore, the Brighton Collaboration has established a case definition for myocarditis, leveraging symptom, lab, and imaging data, among others. The following analysis leverages the Truveta Platform to describe the incidence of myocarditis following COVID-19 vaccine doses, including leveraging the Brighton Collaboration case definition, where possible.

Research Questions:

1. What is the demographic breakdown of patients receiving Pfizer vs Moderna vaccine?
2. What is the incidence of myocarditis within 2 weeks of COVID-19 vaccine administration, broken down by dose 1 vs 2 vs 3 (Pfizer vs Moderna)?
3. Which patients have 'suspected' vs 'probable' myocarditis, as evidenced by elevated cardiac biomarkers?

Disclaimers:

This feasibility and capacity assessment is being voluntarily conducted outside of a regulatory commitment / requirement. This feasibility and capacity assessment does not meet criteria for a PASS. This feasibility and capacity assessment is not intended to make an internal or external statement about the safety, effectiveness, or efficacy of a Pfizer product, regardless of whether statistical inferences (P-value or confidence intervals) or hypothesis testing are conducted.

Methods:

Patients were identified as having a Pfizer or a Moderna COVID-19 vaccine dose using the Truveta Platform. Vaccination events were drawn from immunization records from source healthcare system (HCS) electronic health records. Depending on health system, these immunization records may contain data from state registries or other sources for immunizations (e.g., pharmacies) dependent on the ability of that health system's EMR to ingest and reconcile outside immunizations. CVX codes were used to align vaccinations with the specific manufacturer. Doses of vaccination (dose 1, 2, and 3) were defined by bucketing all vaccination events within a particular time interval to account for duplications of records. Buckets for first, second and third doses were defined such that all vaccine events falling within the buckets would be 'lumped' as a single event. The buckets were as follows

1st dose [0, 16 days], 2nd dose [17, 107 days], 3rd dose [108, 10000 days]

Bucketing was mainly used given duplicate immunization records in a patient's chart with mildly disparate dates. Only patients who received a single manufacturer vaccine across multiple doses were considered. Patients with discordant vaccinations were removed from the analysis.

Myocarditis events were defined as encounters with a billing or encounter diagnosis consistent with an ICD10-CM or SNOMED CT code for myocarditis which fell within 2 weeks of receiving dose 1, 2, or 3 of the Pfizer COVID-19 vaccine. These myocarditis events were separated into 'suspected' and 'probable' in alignment with the Brighton Collaboration case definitions where possible. Suspected myocarditis encounters were defined as an encounter which had either normal cardiac biomarkers (normal troponin I, troponin T, and CKMB during encounter) or absent cardiac marker measurement (meaning the clinician did not order the test, a proxy for low clinical suspicion). Normal values for laboratory results were defined by troponin I <= 0.04 ng/mL and troponin T <= 0.01 ng/mL. CKMB labs had heterogeneity in assays and upper limit of normal thresholds therefore were defined by laboratory provided upper thresholds. Probable myocarditis encounters were defined as those encounters where at least one marker was elevated during that encounter. Incidence rates of myocarditis were measured for each vaccine dose with denominator signifying the total number of patients receiving that dose and numerator signifying the total number of patients meeting the above criteria for an encounter for myocarditis following that dose.

Results:

Demographics

The study population for this analysis, outlined below, was pulled on April 27, 2022. Given population size required for this analysis, patients over the age of 80 and those with unknown gender were excluded from this analysis. High rates of unknown race and ethnicity are a result of de-identification and path forward on resolution is underway.

	General Population		Pfizer		Moderna	
	40,578,757		3,522,40'		2,038,340	
Gender	N	N	N	N	N	N
Female	21,944,348	54.1%	2,066,191	58.7%	1,200,838	58.9%
Male	18,634,409	45.9%	1,456,210	41.3%	837,502	41.1%
Age	N	%	N	%	N	%
0-1	241,577	0.6%	1,044	0.0%	6	0.0%
2-4	604,860	1.5%	170	0.0%	69	0.0%
5-11	2,644,082	6.5%	112,653	3.2%	192	0.0%
12-15	1,450,246	3.6%	197,917	5.6%	24	0.0%
16-17	785,881	1.9%	117,497	3.3%	705	0.0%
18-29	5,963,839	14.7%	476,882	13.5%	242,041	11.9%
30-39	6,297,039	15.5%	504,882	14.3%	276,4'9	13.6%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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Demographics

The study population for this analysis, outlined below, was pulled on April 27, 2022. Given population size required for this analysis, patients over the age of 80 and those with unknown gender were excluded from this analysis. High rates of unknown race and ethnicity are a result of de-identification and path forward on resolution is underway.

	General Population		Pfizer		Moderna	
	40,578,757		3,522,480		2,098,340	
Gender	N	%	N	%	N	%
Female	23,944,148	54.1%	2,066,193	58.3%	1,200,838	58.9%
Male	18,634,479	45.9%	1,458,210	41.3%	837,502	41.1%
Age	N	%	N	%	N	%
0-1	241,577	0.6%	1,044	0.0%	9	0.0%
2-4	604,860	1.5%	1,761	0.0%	69	0.0%
5-11	2,644,082	6.5%	112,653	3.2%	1,962	0.0%
12-15	1,420,246	3.6%	197,917	5.6%	24	0.0%
16-17	785,881	1.9%	117,457	3.3%	705	0.0%
18-29	5,961,839	14.7%	476,987	3.7%	747,041	35.9%
30-39	6,297,039	15.5%	504,882	4.3%	279,478	13.6%
40-49	5,877,736	14.4%	513,967	4.6%	301,739	14.8%
50-59	5,861,789	14.4%	588,203	6.7%	386,476	19.0%
60-64	3,687,648	7.8%	318,660	9.0%	220,979	11.2%
65-69	3,008,684	7.4%	315,748	8.8%	264,548	13.0%
70-79	4725,096	11.6%	379,734	10.8%	337,061	16.5%
Race	N	%	N	%	N	%
American Indian or Alaska Native	141,892	0.3%	17,760	0.5%	13,968	0.7%
Asian	1,240,717	3.1%	252,943	7.2%	134,521	6.6%
Black or African American	3,802,130	9.4%	324,486	9.2%	121,263	6.3%
Native Hawaiian or Other Pacific Islander	87,116	0.2%	14,056	0.4%	7,844	0.4%
White	19,896,945	49.9%	2,238,879	63.6%	1,273,138	67.7%
NA	15,449,647	38.1%	674,314	19.1%	347,623	18.5%
Ethnicity	N	%	N	%	N	%
Hispanic or Latino	3,889,601	9.6%	446,553	12.7%	242,769	13.0%
Not Hispanic or Latino	25,379,875	62.5%	2,719,860	77.2%	1,606,699	78.8%
NA	11,307,281	27.9%	355,948	17%	188,872	9.0%

Incidence of Myocarditis Within Two Weeks of COVID Vaccine Dose

Incidence of myocarditis was examined by dose and by vaccine. This analysis was unadjusted and descriptive in nature; statistical significance was not assessed.

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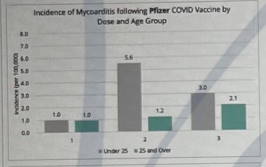
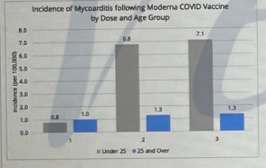
Incidence of Myocarditis Within Two Weeks of COVID Vaccine by Age Group, Dose, & Manufacturer

Incidence of myocarditis was broken down by patient age <25 and >=25. Age was determined at the time of vaccination event. This analysis was unadjusted and descriptive in nature; statistical significance was not assessed.





Incidence of Suspected vs. Probable Mycarditis by Dose and Manufacturer

Incidence of myocarditis was broken down by suspected vs. probable, as evidenced by elevated cardiac biomarkers. This analysis was unadjusted and descriptive in nature; statistical significance was not assessed.

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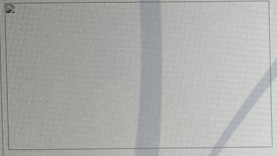

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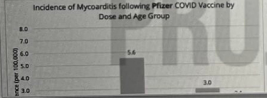

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Incidence of Suspected vs. Probable Myocarditis by Dose and Manufacturer

Incidence of myocarditis was broken down by suspected vs. probable, as evidenced by elevated cardiac biomarkers. This analysis was unadjusted and descriptive in nature; statistical significance was not assessed.

Limitations:

Missingness of Vaccinations: Source data contains vaccination records from sources including: vaccinations taken within the healthcare system, reconciled vaccinations from outside the system (e.g., from state records or local pharmacies), and self-reported vaccinations. Vaccines taken outside the health system generally must be volitionally reconciled and placed into the patient's health record. Thus, patients who were vaccinated outside the health system and did not have a healthcare contact that would result in a vaccination reconciliation would be missing from our data. Therefore, patients identified as being vaccinated would be biased towards those who received vaccinations within the health system.

Vaccine discordance. The analysis was limited to patients who received the same manufacturer. Patients receiving discordant manufacturers (e.g., Pfizer, then Moderna) were excluded.

EKG, echocardiogram, & histopathology data: The Truveta Platform does not currently contain clinical data from EKG, echo, or histopathology procedures, which would be required to fully align patient conditions with the Brighton Collaboration case definitions. This analysis leveraged both diagnostic codes and lab results (Troponin T, Troponin I, and CKMB) but future studies could include echo results to better categorize patients according to the Brighton Collaboration case definition of myocarditis. Of note, elevated cardiac enzymes may be due to causes other than myocarditis, e.g. sepsis, chronic kidney disease, type II NSTEMI, therefore adding additional clinical parameters may improve specificity of the myocarditis definition.

Potential next steps:

Refine myocarditis data definitions. This may include conducting sensitivity analysis on code sets utilized to more accurately identify myocarditis. This may include activating Truveta to ingest and normalize new data types to more closely align with the Brighton Collaboration case definitions.

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			protein, LNP, preservative free, 100 mcg/0.5 mL dose
1204624	CVX	208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose
1216376	CVX	217	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose, tris-sucrose formulation
1216377	CVX	218	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 10 mcg/0.2 mL dose, tris-sucrose formulation
1216378	CVX	219	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 3 mcg/0.2 mL dose, tris-sucrose formulation

Myocarditis Diagnosis Codes:

ConceptId	CodeSystem	ConceptCode	ConceptName
17358	SNOMED CT	18484008	Subacute interstitial myocarditis
21298	SNOMED CT	22653005	Myocarditis due to infectious agent
28688	SNOMED CT	30496006	Dilated cardiomyopathy due to viral myocarditis
44013	SNOMED CT	46701001	Acute myocarditis
47968	SNOMED CT	50920009	Myocarditis
60304	SNOMED CT	64043005	Bacterial myocarditis
68316	SNOMED CT	75527006	Myocarditis due to drug
83951	SNOMED CT	89141000	Viral myocarditis
177362	SNOMED CT	194709000	Acute rheumatic myocarditis
177684	SNOMED CT	195033009	Sarcoid heart muscle disease
459324	SNOMED CT	1240531000000103	Myocarditis due to disease caused by Severe acute respiratory syndrome coronavirus 2
528496	ICD10CM	I40	Acute myocarditis

Cardiac Enzyme Labs

ConceptId	CodeSystem	ConceptCode	ConceptName
777898	LOINC	6597-9	Troponin T.cardiac [Mass/volume] in Venous blood
777899	LOINC	6598-7	Troponin T.cardiac [Mass/volume] in Serum or Plasma
819040	LOINC	48425-3	Troponin T.cardiac [Mass/volume] in Blood
782108	LOINC	10839-9	Troponin I.cardiac [Mass/volume] in Serum or Plasma
787508	LOINC	16255-2	Troponin I.cardiac [Units/volume] in Serum or Plasma
813394	LOINC	42757-5	Troponin I.cardiac [Mass/volume] in Blood
820187	LOINC	49563-0	Troponin I.cardiac [Mass/volume] in Serum or Plasma by Detection limit <= 0.01 ng/mL
859144	LOINC	89579-7	Troponin I.cardiac [Mass/volume] in Serum or Plasma by High sensitivity method
785228	LOINC	13969-1	Creatine kinase.MB [Mass/volume] in Serum or Plasma
820175	LOINC	49551-5	Creatine kinase.MB [Mass/volume] in Blood

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Potential next steps:

Refine myocarditis data definitions . This may include conducting sensitivity analysis on code sets utilized to more accurately identify myocarditis . This may include activating Truveta to ingest and normalize new data types to more closely align with the Brighton Collaboration case definitions.

Conduct statistical analysis. This may include calculating p-values between groups as well as controlling for confounding.

Broaden study population. This may include adding patients with discordant vaccines (e.g., Pfizer, then Moderna) or patients over the age of 80.

Appendix – Data Definitions:

Demographics

Demographic Category	ConceptId	ConceptName
Ethnicity	1065359	Hispanic or Latino
Ethnicity	1065401	Not Hispanic or Latino
Gender	1065400	Female
Gender	1065406	Male
Race	1066866	American Indian or Alaska Native
Race	1067338	Native Hawaiian or Other Pacific Islander
Race	1067319	Black or African American
Race	1067294	Asian
Race	1067364	White

COVID Immunization:

ConceptId	CodeSystem	ConceptCode	ConceptName
1204623	CVX	207	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose
1204624	CVX	208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose
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1216378	CVX	219	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 3 mcg/0.2 mL dose, tris-sucrose formulation

Myocarditis Diagnosis Codes:

AER Number(PBRER Detailed Analysis)	Dose Number	Dose Number (Concat)	Dose Description	Therapy Start Date - Entered	Onset Date - Entered	PT Decode (Event)
202101182009	NO DATA	DOSE NUMBER UNKNOWN, SINGLE				Chest discomfort
202101182009	NO DATA	DOSE NUMBER UNKNOWN, SINGLE				Dyspnoea
202101182009	NO DATA	DOSE NUMBER UNKNOWN, SINGLE				Myocarditis
202101182009	NO DATA	DOSE NUMBER UNKNOWN, SINGLE				Pulmonary embolism
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021		Arthralgia
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021		Loss of personal independence in daily activities
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021		Malaise
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021		Myocarditis
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021	23-AUG-2021	Inappropriate schedule of product administration
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021	25-AUG-2021	Dizziness
202101217106	2	2	DOSE 2, SINGLE	23-AUG-2021	25-AUG-2021	Headache
202101331957	1	1	DOSE 1, SINGLE			Myocardial infarction
202101331957	1	1	DOSE 1, SINGLE			Myocarditis
202101331957	1	1	DOSE 1, SINGLE			Tachycardia
202101629469	1	1	DOSE 1, SINGLE	19-DEC-2020		Chest pain
202101629469	1	1	DOSE 1, SINGLE	19-DEC-2020		Dyspnoea
202101629469	1	1	DOSE 1, SINGLE	19-DEC-2020		Myocarditis
202101629469	1	1	DOSE 1, SINGLE	19-DEC-2020		Palpitations
202101629469	1	1	DOSE 1, SINGLE	19-DEC-2020		Pericarditis
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021		Myocarditis
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021		Pericarditis
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021	19-NOV-2021	Maternal exposure during pregnancy
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021	20-NOV-2021	Chest pain
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021	---NOV-2021	Dyspnoea
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021	---NOV-2021	Fatigue
202101629525	2	2	DOSE 2, SINGLE	19-NOV-2021	---NOV-2021	Palpitations
202101632280	2	2	DOSE 2, 0.3 ML	SINGLE 06-MAY-2021	09-MAY-2021	Ventricular extrasystoles
202101632280	2	2	DOSE 2, 0.3 ML	SINGLE 06-MAY-2021	26-JAN-2022	Myopericarditis
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Dyspnoea
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Left ventricular dysfunction
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Myocardial infarction
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Myocarditis
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Palpitations
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Pericarditis
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Tachycardia
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Urinary incontinence
202101697508	3	3	DOSE 3 (BOOSTER),	SINGLE 25-OCT-2021		Bundle branch block left