Rapid Cycle Analysis to Monitor the Safety of COVID-19 Vaccines in Near Real-Time within the Vaccine Safety Datalink: Myocarditis and Anaphylaxis

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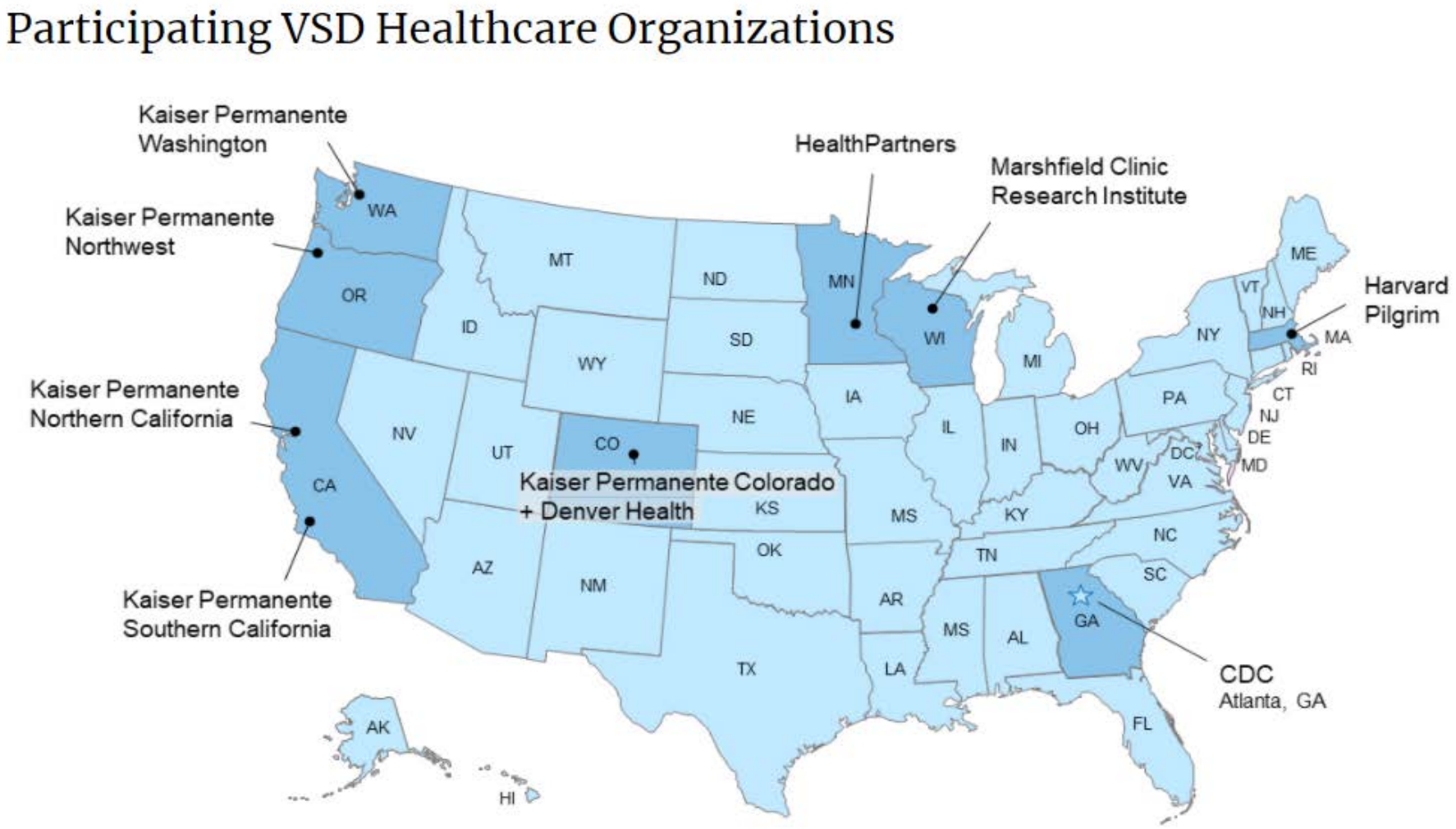
The Vaccine Safety Datalink (VSD)



- Established in 1990
- Collaborative project between CDC and 9 integrated healthcare organizations

VSD Rapid Cycle Analysis (RCA)

Aims:

1. To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

2. To describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity.

Surveillance began in December 2020.

VSD COVID-19 Vaccine RCA Outcomes

#	Outcomes	Settings	Risk Window (days)	Chart Review	Monitoring Only	Exclude if COVID-19 in the Prior X Days
1	Acute disseminated encephalomyelitis	E, I	1-21, 1-42	Yes		
2	Acute myocardial infarction – **First Ever**	E, I	1-21, 1-42			30 days
3	Acute respiratory distress syndrome	E, I	0-84		Yes	42 days
4	Anaphylaxis – **First in 7 days**	E, I	0-1	Yes	Yes	
5	Appendicitis	E, I	1-21, 1-42			
6	Bell's palsy – **First Ever**	E, I, O	1-21, 1-42			30 days
7	Cerebral venous sinus thrombosis	E, I	1-21, 1-42	Yes		30 days
8	Disseminated intravascular coagulation	E, I	1-21, 1-42			42 days
9	Encephalitis / myelitis / encephalomyelitis	E, I	1-21, 1-42			30 days
10	Guillain-Barré syndrome	E, I	1-21, 1-42	Yes		
11	Immune thrombocytopenia	E, I, O	1-21, 1-42			30 days
12	Kawasaki disease	E, I	1-21, 1-42			
13	Multisystem inflammatory syndrome in children/adults (MIS-C/MIS-A)	E, I	0-84		Yes	
14	Myocarditis / pericarditis – **First in 60 Days**	E, I	1-21, 1-42	Yes (subgroup)		30 days
15	Narcolepsy / cataplexy	E, I, O	0-84		Yes	
16	Pulmonary embolism – **First Ever**	E, I	1-21, 1-42			30 days
17	Seizures	E, I	1-21, 1-42			30 days
18	Stroke, hemorrhagic	E, I	1-21, 1-42			30 days
19	Stroke, ischemic	E, I	1-21, 1-42			30 days
20	Thrombosis with thrombocytopenia syndrome – **First Ever**	E, I	1-21, 1-42	Yes		30 days
21	Thrombotic thrombocytopenic purpura	E, I	1-21, 1-42			30 days
22	Transverse myelitis	E, I	1-21, 1-42	Yes		
23	Venous thromboembolism – **First Ever**	E, I, O	1-21, 1-42			30 days

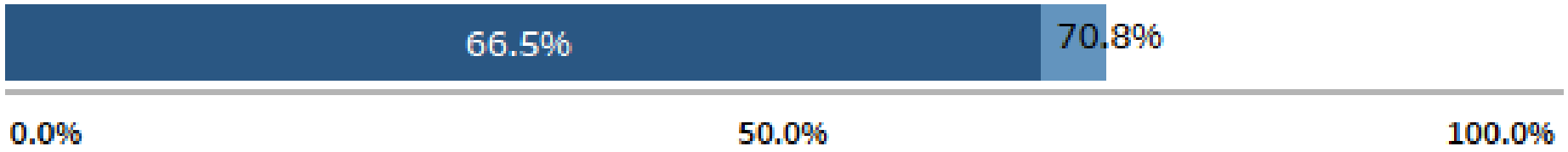
Abbreviations: E=ED, I=Inpatient, O=Outpatient

COVID-19 Vaccine Uptake (Data through 8/21/21)

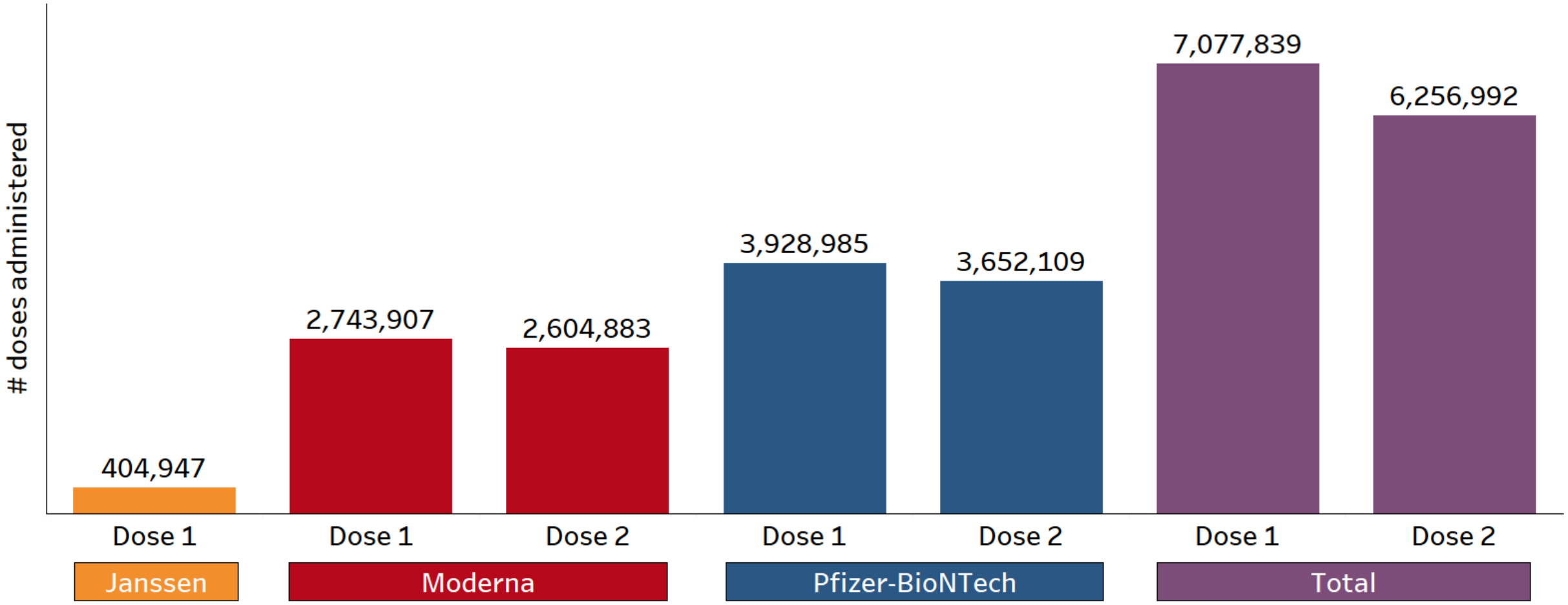
VSD COVID-19 Vaccine Totals

Total Doses Administered	Total Doses Admin per 100K	# People Received At Least One Dose	# People Fully Vaccinated
13,334,831	139,318	7,077,839	6,661,939

To date, 66.5% of the age eligible VSD population is fully vaccinated and 70.8% received at least one dose



VSD COVID-19 Vaccine Totals



Primary Analyses
(Data through 8/21/2021)

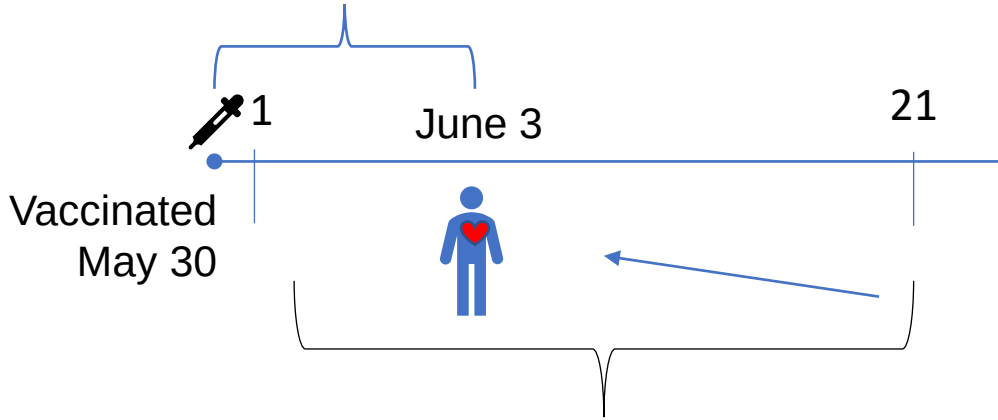
Analytic Strategy

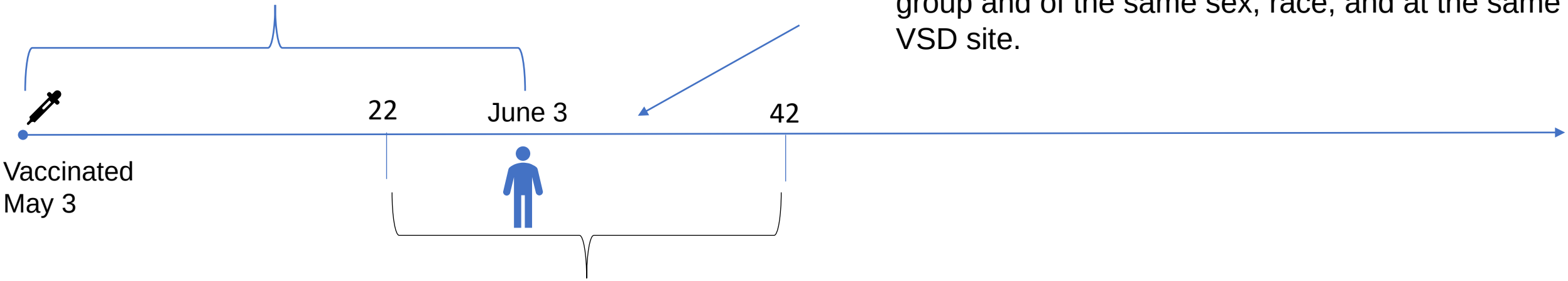
- For the primary analysis, the number of outcomes observed in the risk interval (1-21 days) after COVID-19 vaccination were compared to the number expected.

- The expected was derived from “vaccinated concurrent comparators” who were in a comparison interval (days 22-42) after COVID-19 vaccination.

- On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval.
  - Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, as well as calendar date.

Vaccinee with Myocarditis in Risk Interval and a Concurrent Comparator





On each calendar day that an outcome occurred in a vaccinee (e.g., June 3), we compared vaccinees in their risk interval (day 1-21) with similar vaccinees in their comparison interval (day 22-42).

By similar, we mean they were in the same age group and of the same sex, race, and at the same VSD site.

Outcome Events in 21-Day Risk Interval after Either Dose of Any mRNA Vaccine

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

			Sequential Test[1]	
Outcome Event	Events in Risk Interval	Adjusted Rate Ratio[2]	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute disseminated encephalomyelitis	1	NE	0.794	no
Acute myocardial infarction	655	1.03	0.328	no
Appendicitis	890	0.85	0.998	no
Bell's palsy	583	1.00	0.527	no
Cerebral venous sinus thrombosis	8	1.66	0.373	no
Disseminated intravascular coagulation	32	0.72	0.903	no
Encephalitis / myelitis / encephalomyelitis	20	1.76	0.188	no
Guillain-Barré syndrome	12	0.63	0.887	no
Immune thrombocytopenia	49	0.91	0.693	no
Kawasaki disease	0	0.00	0.252	no
Myocarditis / pericarditis	**115**	**1.57**	**0.010**	**no**
Pulmonary embolism	541	0.99	0.582	no
Seizures	312	0.95	0.706	no
Stroke, hemorrhagic	255	0.98	0.593	no
Stroke, ischemic	1152	1.01	0.458	no
Transverse myelitis	1	1.61	0.620	no
Thrombotic thrombocytopenic purpura	7	2.26	0.216	no
Thrombosis with thrombocytopenia syndrome	83	0.91	0.723	no
Venous thromboembolism	668	1.20	0.006	no

NE= not estimable

[1]**Sequential test** requires 1-sided p < 0.0048 (Fisher) for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.

[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. Comparison interval is 22–42 days after either dose.

Myocarditis/pericarditis Chart Review Summary 12–39-Year-Olds after mRNA Vaccines (Data through 8/21/2021)

Myocarditis/pericarditis Following an mRNA Vaccine: Chart Review Summary

- Chart review completed for cases through **August 21, 2021** for 100/102 cases (2 pending)
  - ✓12–39 year-olds
  - ✓Cases identified during post-vaccination days 1-98
- Initial chart review followed with adjudication by an infectious disease clinician and/or a cardiologist.
  - ✓confirm incident following vaccination
  - ✓confirmed based on CDC definitions
  - ✓evaluate level of certainty for myocarditis

✓**Adjudication confirmed 78/100 (78%) post-vaccination myocarditis/pericarditis**

- ✓ **56 confirmed cases among 12–39-year-olds, with onset 0-21 days after dose 1 or 2**

Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of Either mRNA Vaccine: Descriptive Characteristics by Age Group

	12-17 Year-Olds (Pfizer) (N=22)	18-29 Year-Olds (N=21)	30-39 Years-Olds (N=13)
Male sex	18 (82%)	20 (95%)	9 (69%)
Race/ethnicity			
White	11 (50%)	11 (52%)	4 (31%)
Black	1 (5%)	0 (0%)	0 (0%)
Asian	0 (0%)	3 (14%)	2 (15%)
Hispanic	8 (36%)	5 (24%)	4 (31%)
Multiple/other	1 (5%)	1 (5%)	1 (8%)
Unknown	1 (5%)	1 (5%)	2 (15%)
History of COVID-19 infection	0 (0%)	2 (10%)	1 (8%)
History of myo/pericarditis	1 (5%)	0 (0%)	3 (23%)
Symptom onset post-vaccination, median (range)	2 days (1-20 days)	1 days (0-11 days)	5 days (1-20 days)
Adjudication diagnosis			
Acute myocarditis	11 (50%)	3 (14%)	3 (23%)
Myopericarditis	10 (45%)	16 (76%)	5 (38%)
Acute pericarditis	1 (5%)	2 (10%)	5 (38%)

Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of Either mRNA Vaccine: Symptoms and Diagnostic Testing by Age Group

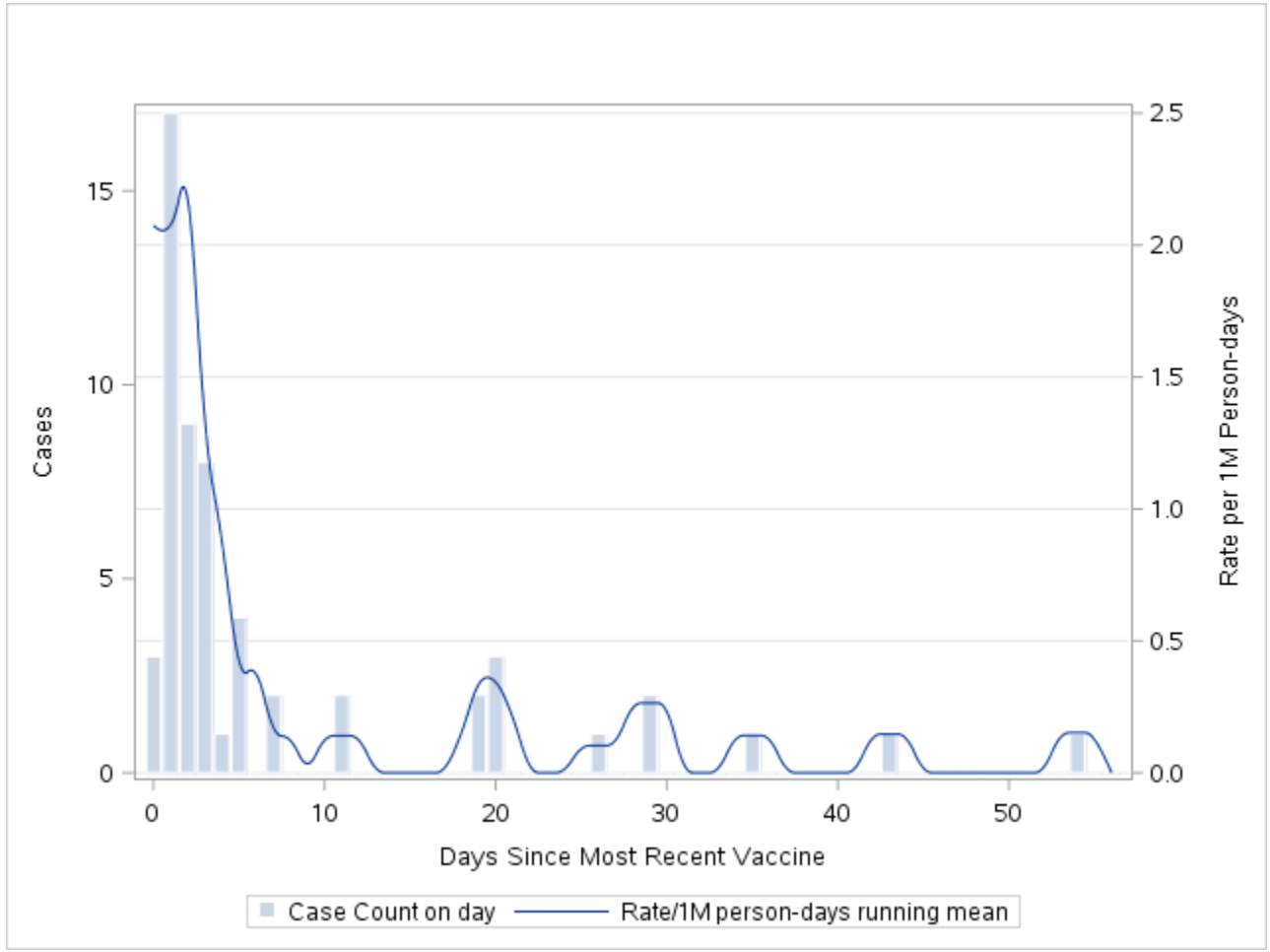
Signs and Symptoms	12-17 Year-Olds (Pfizer) (N=22)	18-29 Year-Olds (N=21)	30-39 Years-Olds (N=13)
Chest pain/pressure/discomfort	22 (100%)	21 (100%)	13 (100%)
Dyspnea/shortness of breath	14 (64%)	7 (33%)	7 (54%)
Palpitations	1 (5%)	5 (24%)	0 (0%)
Pericardial rub on exam	0 (0%)	0 (0%)	1 (8%)
Other (fever, fatigue, chills, headache, numbness, tingling, syncope, nausea, sweating, etc.)	13 (59%)	12 (57%)	8 (62%)
Diagnostic Testing			
Troponin levels obtained	22 (100%)	21 (100%)	13 (100%)
Abnormal troponin level	21 (95%)	19 (90%)	7 (54%)
ECG completed	22 (100%)	21 (100%)	13 (100%)
Abnormal findings	16 (73%)	19 (90%)	12 (92%)
Echocardiogram completed	21 (95%)	20 (95%)	11 (85%)
Abnormal findings	9/21 (43%)	6/20 (30%)	9/11 (82%)
Cardiac MRI completed	4 (19%)	7 (33%)	1 (8%)
Abnormal findings	4/4 (100%)	6/7 (86%)	1/1 (100%)

Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of Either mRNA Vaccine: Level of Care and Discharge Status by Age Group

	12-17 Year-Olds (Pfizer) (N=22)	18-29 Year-Olds (N=21)	30-39 Years-Olds (N=13)
Highest level of care			
Outpatient	0 (0%)	2 (10%)	0 (0%)
Emergency department	3 (14%)	1 (5%)	3 (23%)
Admitted to hospital	12 (55%)	18 (86%)	10 (77%)
Admitted to ICU	7 (32%)	0 (0%)	0 (0%)
Length of stay			
0 days (same day discharge)	2 (9%)	3 (14%)	3 (23%)
1 day	5 (23%)	9 (43%)	7 (54%)
2 days	6 (27%)	7 (33%)	0 (0%)
3 days	4 (18%)	2 (10%)	1 (8%)
4 days	3 (14%)	0 (0%)	0 (0%)
5 days	2 (9%)	0 (0%)	0 (0%)
≥6 days	0 (0%)	0 (0%)	2 (15%)
Discharged to home	22 (100%)	21 (100%)	13 (100%)
Follow-up visit noted at the time of chart review	15 (68%)	20 (95%)	12 (92%)

Subgroup Analysis of Confirmed Myocarditis/pericarditis after mRNA Vaccines among 12-39 Year-Olds (Data Through 8/21/2021)

Day of Onset of Confirmed Myocarditis/pericarditis among 12-39 Year-Olds after Either Dose of an mRNA Vaccine



Confirmed Myocarditis/Pericarditis in the 0-21 Day Risk Interval, among 12–39-year-olds by Product and Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Vaccine	Dose	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Both mRNA	**Both Doses**	**51**	**5**	**5.63**	**2.31 - 16.44**	**<.001**	**8.9**
	Dose 1	**11**	**5**	**3.81**	**1.14 - 14.26**	**0.029**	**3.3**
	Dose 2	**36**	**4**	**8.31**	**3.07 - 28.28**	**<.001**	**15.5**
Pfizer	**Both Doses**	**31**	**5**	**3.62**	**1.39 - 11.11**	**0.007**	**7.2**
	Dose 1	6	5	2.26	0.56 - 9.30	0.251	2.1
	Dose 2	**21**	**4**	**5.74**	**1.98 - 20.52**	**<.001**	**13.6**
Moderna	**Both Doses**	**20**	**0**	**NE**	**3.32 - NE**	**<.001**	**12.7**
	Dose 1	5	0	NE	0.89 - NE	0.065	6.1
	Dose 2	**15**	**0**	**NE**	**3.79 - NE**	**<.001**	**19.8**

NE= not estimable

[1]**Comparison interval** is 22–42 days after either dose.

[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

Confirmed Myocarditis/Pericarditis in the 0-7 Day Risk Interval, among 12–39-year-olds by Product and Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Vaccine	Dose	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Both mRNA	Both Doses	44	5	15.55	6.07 - 47.22	<.001	8.6
	Dose 1	6	4	6.73	1.43 - 35.12	0.015	2.0
	Dose 2	34	4	23.84	8.49 - 83.64	<.001	15.9
Pfizer	Both Doses	25	4	11.34	3.70 - 42.24	<.001	7.1
	Dose 1	2	4	2.38	0.21 - 20.11	0.454	0.7
	Dose 2	19	3	22.88	6.60 - 106.13	<.001	14.4
Moderna	Both Doses	19	0	NE	9.04 – NE	<.001	12.0
	Dose 1	4	0	NE	2.17 - NE	0.008	4.9
	Dose 2	15	0	NE	9.36 – NE	<.001	19.7

NE= not estimable

[1]**Comparison interval** is 22–42 days after either dose.

[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

Confirmed Myocarditis/Pericarditis in the 0-7 Day Risk Interval, among 18–39-year-olds by Product and Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Vaccine	Dose	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Both mRNA	**Both Doses**	**29**	**5**	**10.4**	**3.9 - 32.54**	**<.001**	**6.7**
	Dose 1	**5**	**4**	**6.34**	**1.27 - 34.08**	**0.024**	**2.1**
	Dose 2	**24**	**4**	**13.8**	**4.73 - 49.64**	**<.001**	**11.9**
Pfizer	**Both Doses**	**10**	**4**	**4.82**	**1.26 - 20.91**	**0.021**	**3.4**
	Dose 1	1	4	1.76	0.05 - 18.77	0.662	0.4
	Dose 2	**9**	**3**	**9.12**	**2.14 - 48.59**	**0.002**	**7.2**
Moderna	**Both Doses**	**19**	**0**	**NE**	**9.04 – NE**	**<.001**	**12.0**
	Dose 1	**4**	**0**	**NE**	**2.17 – NE**	**0.008**	**4.9**
	Dose 2	**15**	**0**	**NE**	**9.36 - NE**	**<.001**	**19.7**

NE= not estimable

[1]**Comparison interval** is 22–42 days after either dose.

[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

Confirmed Myocarditis/Pericarditis, among 12–17-year-olds (Pfizer only) in the 0-7 and 0-21 Day Risk Interval by Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Vaccine	Dose	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Days 0-21	**Both Doses**	**18**	**0**	**NE**	**3.07 - NE**	**<.001**	**20.9**
	Dose 1	3	0	NE	0.39 - NE	0.172	6.6
	Dose 2	**11**	**0**	**NE**	**4.22 – NE**	**<.001**	**37.0**
Days 0-7	**Both Doses**	**15**	**0**	**NE**	**8.19 – NE**	**<.001**	**16.7**
	Dose 1	1	0	NE	0.02 - NE	0.706	2.1
	Dose 2	**10**	**0**	**NE**	**13.53 - NE**	**<.001**	**33.7**

NE= not estimable

[1]**Comparison interval** is 22–42 days after either dose.

[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

Myocarditis/pericarditis Following an mRNA Vaccine: 3-month Follow-up Chart Review

- As of August 27, 2021, chart reviews have been completed for 29/34 cases time-eligible for 3-month follow-up review.

- Of these, 24 had at least 1 follow-up visit at least 7 days since the initial encounter.

- These **24** cases were reviewed to obtain information regarding
  - ✓symptoms and diagnostic evaluation at most recent follow-up visit
  - ✓recovery status for
    - ongoing symptoms
    - medication
    - exercise restrictions

Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of Either mRNA Vaccine by Age Group: Cases with at least 1 follow-up visit since initial episode

	12-17 Year-Olds (N=3)*	18-29 Year-Olds (N=11)	30-39 Years-Olds (N=10)
Time from symptom onset to most recent follow-up visit (median, range)	53 days (13-57 days)	31 days (11-99 days)	86 days (10-152 days)
Follow-up visit at least 3 months since initial encounter	0 (0%)	3 (27%)	5 (50%)
No new or worsening symptoms noted	2 (67%)	8 (73%)	8 (80%)
Any new or worsening symptom	1 (33%)	3 (27%)	2 (20%)
Chest pain/pressure/discomfort	1	2	2
Shortness of breath/pain with breathing	1	1	1
Palpitations	1	1	0
Fatigue	1	1	1
Elevated heart rate	1	1	1
Other (orthostatic hypotension, dizziness, etc.)	1	0	0
Troponin levels obtained	3 (100%)	5 (45%)	4 (40%)
Abnormal troponin level	0	2	2
ECG completed	2 (67%)	7 (64%)	2 (20%)
Abnormal findings	0	4	2
Echocardiogram completed	2 (67%)	3 (27%)	3 (30%)
Abnormal findings	1	1	0
Cardiac MRI completed	1 (33%)	0	0
Abnormal findings	0	N/A	N/A

* The 3 cases had all been in the ICU at their initial encounter.

Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of Either mRNA Vaccine by Age Group: Current Status at Most Follow-up Recent Visit

	12-17 Year-Olds (N=3)	18-29 Year-Olds (N=11)	30-39 Years-Olds (N=10)
Current Status (not mutually exclusive)			
Recovered, no medication, exercise restriction or symptoms	0	8 (73%)	1 (10%)
Still symptomatic	1 (33%)	1 (9%)	4 (50%)
Still on medication (primarily NSAIDS, Colchicine)	0	2 (18%)	3 (30%)
Still on exercise/physical activity restrictions	3 (100%)	2 (18%)	0

Anaphylaxis Chart Review Summary (Data Through 7/31/2021)

Anaphylaxis Chart Review Summary

*Full review not completed until 30 days after the event

- Chart review completed for 213/216 cases through July 31, 2021*
- 66/213 (31%) cases confirmed as post-vaccination anaphylaxis with day 0-1 ED visit

	Pfizer (N=37)	Moderna (N=26)	Janssen (N=3)
Age in years, median (range)	42 (15-74)	40 (18-76)	43 (30-65)
Female sex	36 (97%)	23 (88%)	3 (100%)
Minutes to symptom onset, median (range)	10 (0-300)	10 (2-39)	--
Symptom onset within 15 minutes	25 (68%)	18 (69%)	1 (33%)
Symptom onset within 30 minutes	32 (86%)	23 (88%)	2 (67%)
Prior history of allergies	29 (78%)	20 (77%)	1 (33%)
Prior history of anaphylaxis	20 (54%)	6 (23%)	1 (33%)
Dose 1	31 (84%)	21 (81%)	N/A
Brighton Collaboration case definition level			
1	15 (41%)	6 (23%)	0 (0%)
2	22 (59%)	19 (73%)	3 (100%)
3	0 (0%)	1 (4%)	0 (0%)
Cases (95% CI) per million doses	5.0 (3.5-6.9)	4.9 (3.2-7.2)	7.6 (1.6-22.3)
Cases (95% CI) per million doses in females	9.0 (6.3-12.5)	8.0 (5.0-11.9)	16.3 (3.4-47.6)
Cases (95% CI) per million first doses	8.1 (5.5-11.5)	7.7 (4.8-11.8)	--
Cases (95% CI) per million first doses in females	14.6 (9.8-20.8)	12.2 (7.2-19.2)	--

Summary

- In the VSD, rate of anaphylaxis after mRNA vaccines is ~ 5 cases / million doses.
- No signals for myocarditis/pericarditis or for any other outcome in the 21 days after both mRNA doses in the overall VSD population, including all ages ≥12 years.
- In the subgroup aged 12–39 years, the rate ratio for myocarditis/pericarditis was elevated after both Pfizer and Moderna during days 0-21 after vaccination, and especially during days 0-7.
- In subgroup analyses, both mRNA vaccines were associated with myocarditis/pericarditis in persons aged 12-39 years.

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