

Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and “Head-to-Head” Product Comparisons

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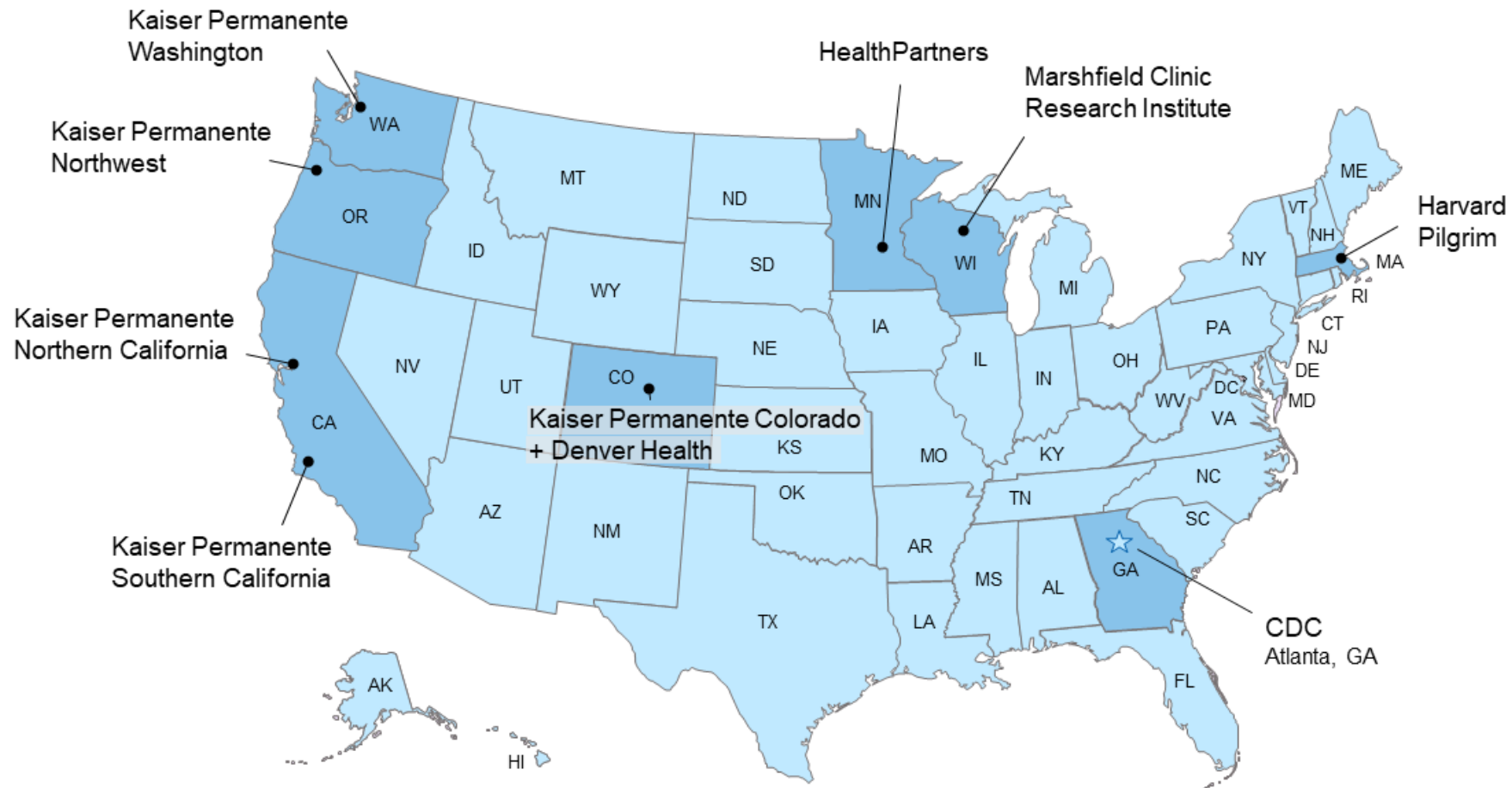
**Kaiser Permanente Vaccine Study Center
Kaiser Permanente Northern California**



Overview

- Brief review of the rapid cycle analyses monitoring COVID-19 vaccine safety conducted by the Vaccine Safety Datalink
- Myocarditis and pericarditis during days 0-7 after mRNA vaccination:
 - Risk after each vaccine compared with risk among comparators who were 22-42 days after vaccination
 - Direct head-to-head comparisons of the Moderna vaccine versus the Pfizer vaccine during days 0-7 after vaccination

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 (<40 years)		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

Myocarditis and Pericarditis: Electronic Case Identification using ICD-10 Codes

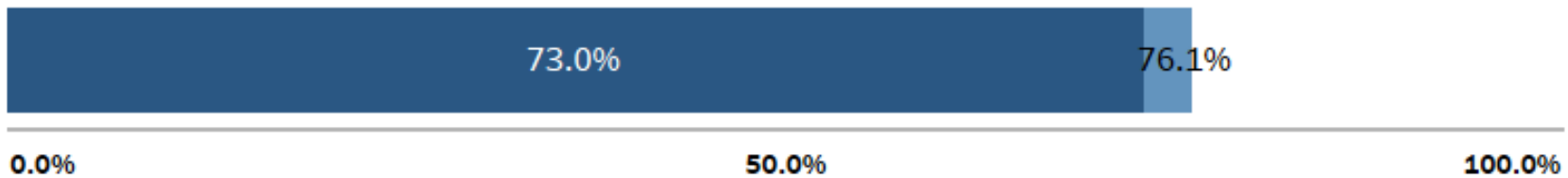
Initial Code List (based on consultation with cardiologist)	Revised Code List (based on VSD feedback)
<ul style="list-style-type: none">• B33.22 Viral myocarditis• B33.23 Viral pericarditis• I30.* Acute pericarditis• I40.* Acute myocarditis	<ul style="list-style-type: none">• B33.22 Viral myocarditis• B33.23 Viral pericarditis• I30.* Acute pericarditis• I40.* Acute myocarditis• I51.4 Myocarditis, unspecified• I31.9 Disease of the pericardium, unspecified

**COVID-19 Vaccine Uptake
& Primary Analyses
(Data Through 1/15/2022)**

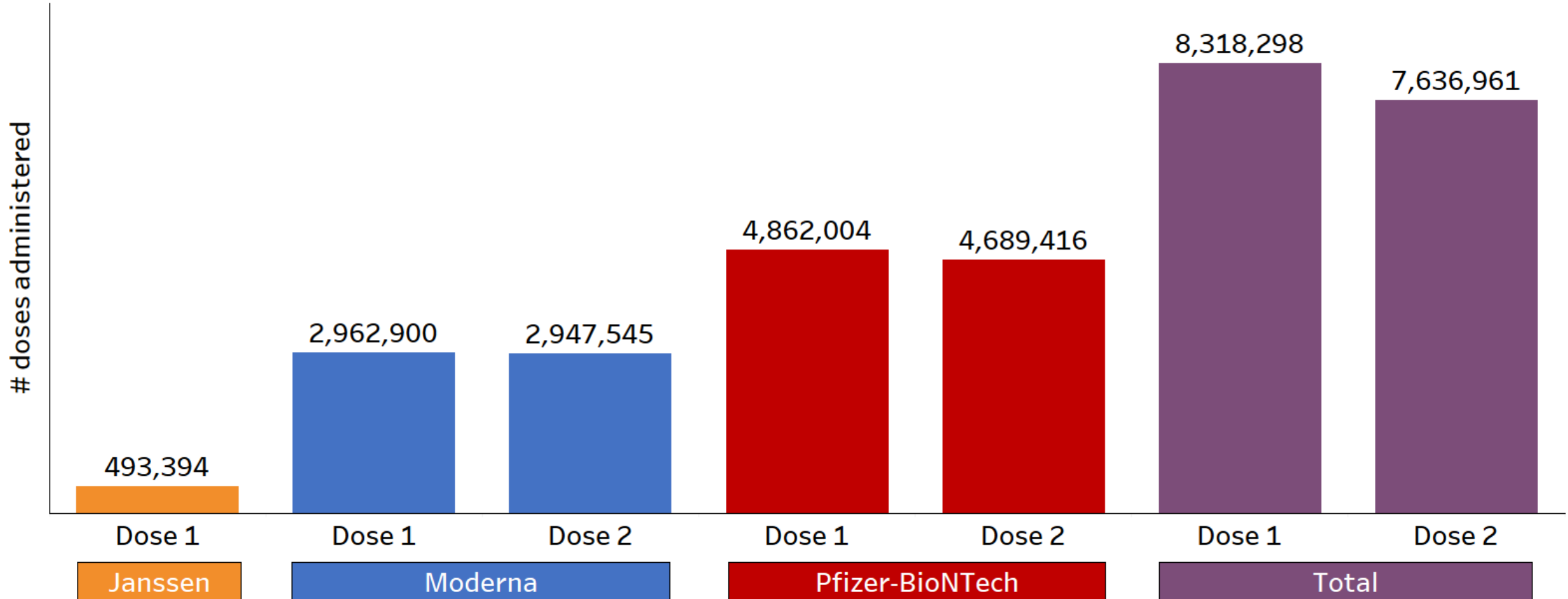
VSD COVID-19 Vaccine Totals



To date, **73.0%** of the age eligible VSD population is fully vaccinated and **76.1%** received at least one dose



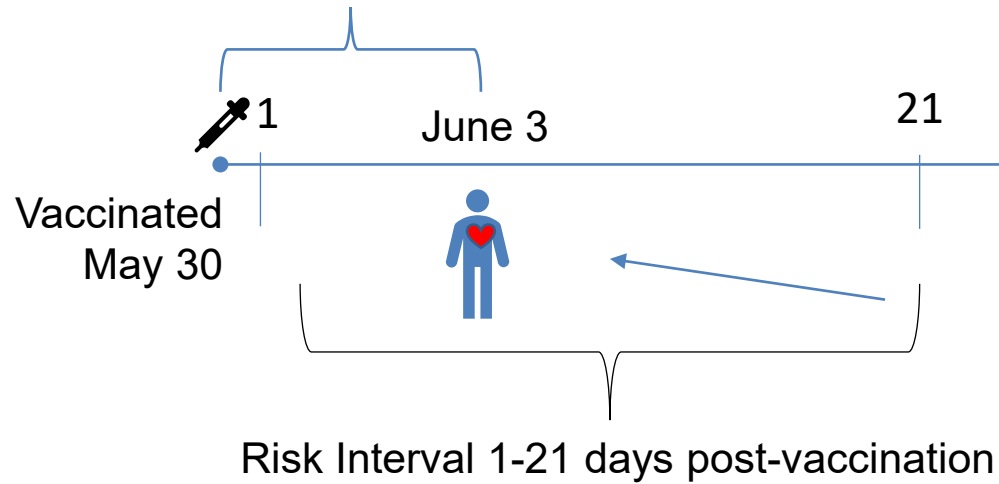
VSD COVID-19 Vaccine Totals



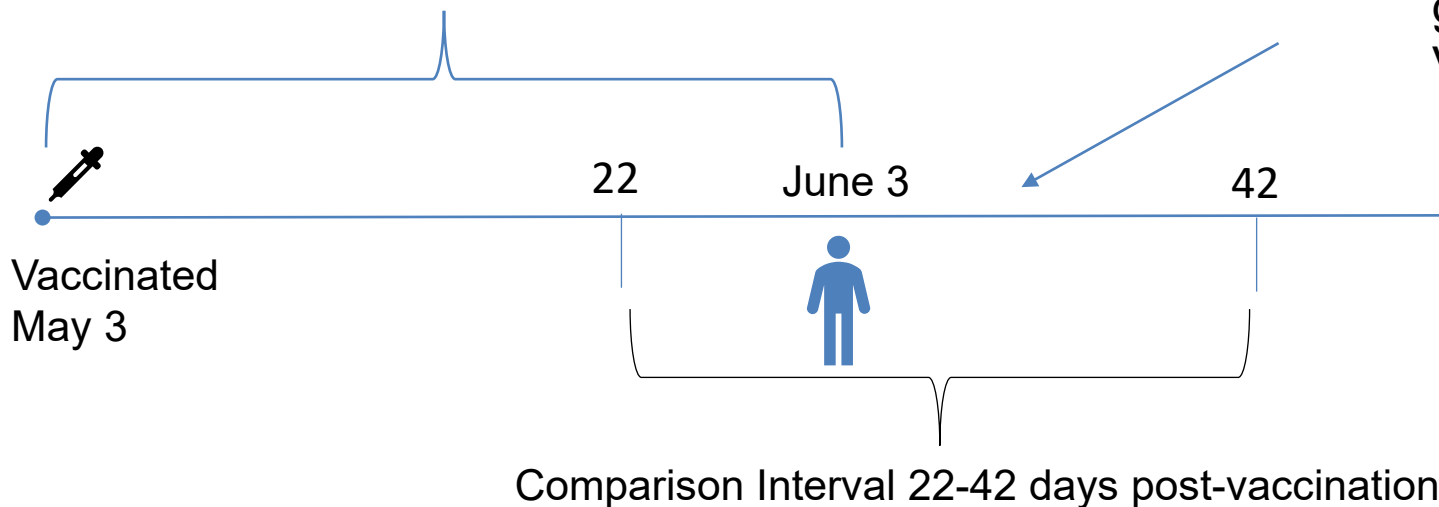
Analytic Strategy

- 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

Vaccinees with Myocarditis in the Risk Interval and a Concurrent Comparator



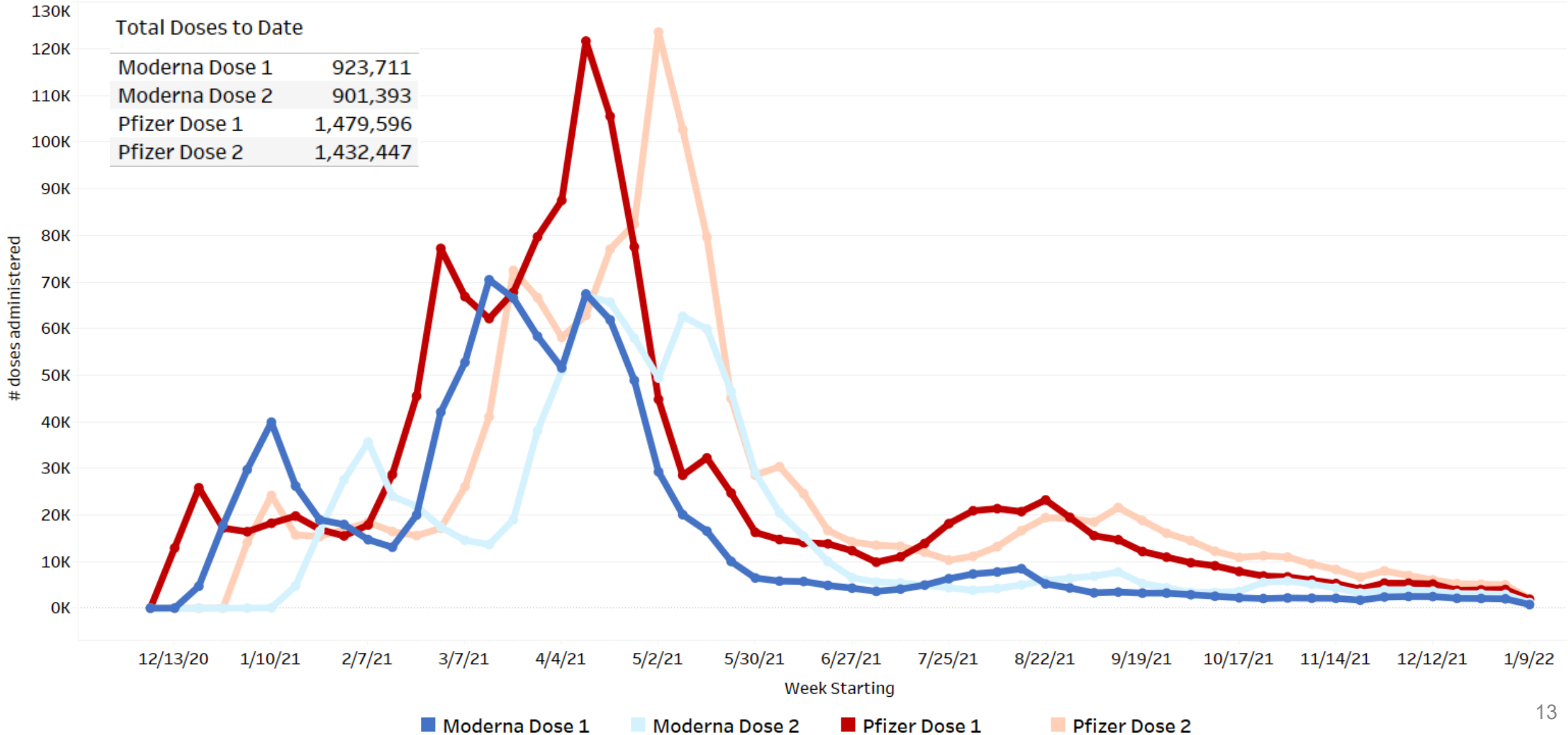
On each calendar day that an outcome occurred in a vaccinee (e.g., June 3), we compared vaccinees in their risk interval (day 1-21) with similar vaccinees in their comparison interval (day 22-42)



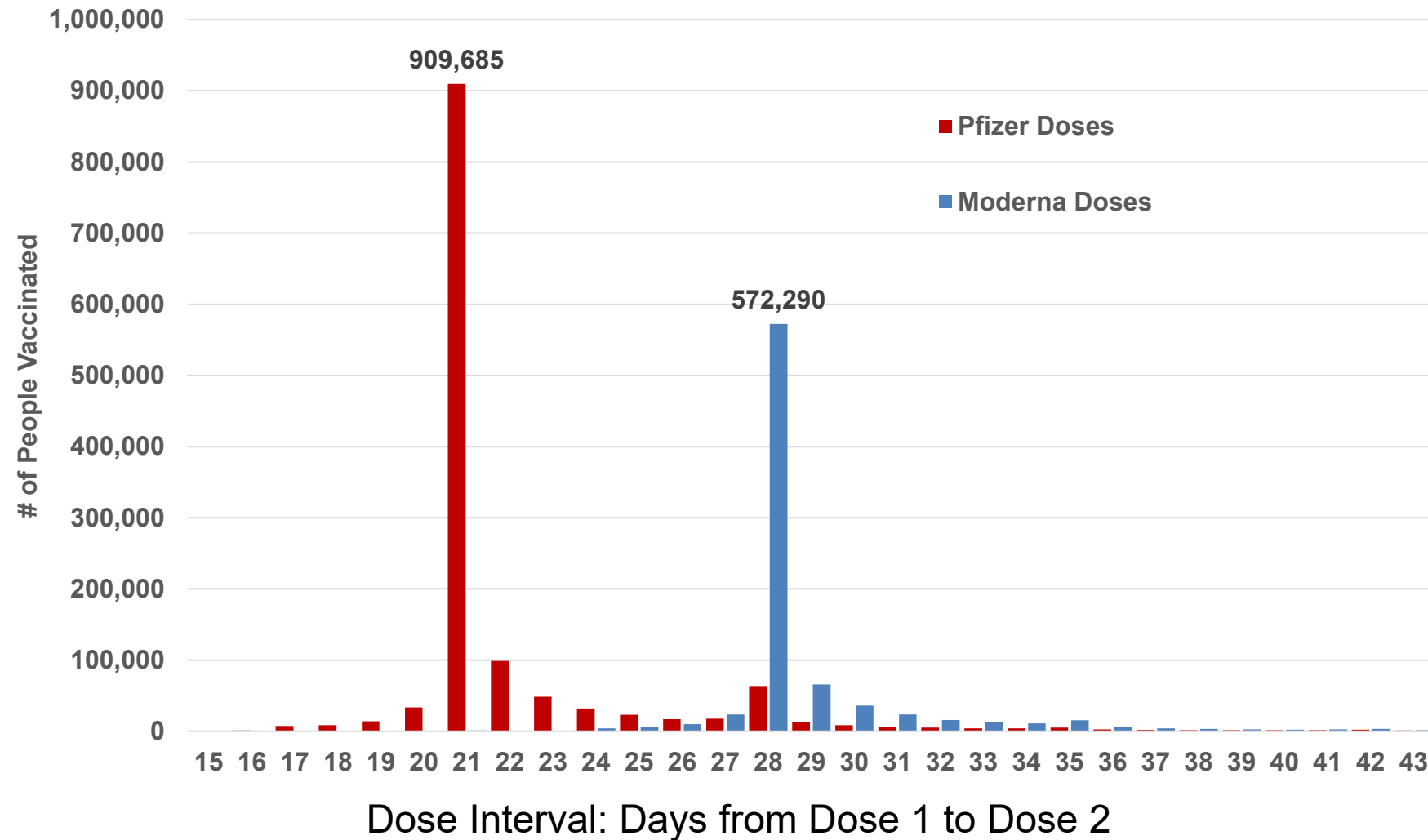
By similar, we mean they were in the same age group and of the same sex, race, and at the same VSD site

**Subgroup Analyses of Verified
Myocarditis and Pericarditis
after mRNA Vaccines
among 18–39-Year-Olds
(Data Through 1/15/2022)**

Doses Administered for 18–39-Year-Olds by Week



Days Between Dose 1 & Dose 2 Among 18–39-Year-Olds



Myocarditis and Pericarditis after an mRNA Vaccine: Chart Review Summary

- Chart review completed for 297 cases through **January 15, 2022** for cases (19 pending, all under 18 years of age)
 - 5–39-year-olds
 - Cases identified any time post-vaccination
- Initial chart review followed with adjudication by an infectious disease clinician and/or a cardiologist
 - Confirm incident following vaccination
 - Meet CDC case definition (myocarditis, pericarditis, or myopericarditis)
 - Evaluate level of certainty for myocarditis
- **Adjudication verified 213/297 (71%) myocarditis and pericarditis cases**
 - 79 verified cases among 18–39-year-olds with onset in the 0-7 day risk interval; 16 after dose 1 and 63 after dose 2

Verified Myocarditis and 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/Million Doses)	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
Either mRNA vaccine	Both Doses	79 (16.8)	20	7.55	4.52 – 13.04	<.001	14.6
	Dose 1	16 (6.7)	20	3.29	1.52 – 7.07	0.003	4.6
	Dose 2	63 (27.5)	13	13.63	7.39 – 26.55	<.001	25.5
Pfizer	Both Doses	41 (14.2)	13	6.94	3.57 – 14.13	<.001	12.1
	Dose 1	7 (4.7)	13	3.02	1.03 – 8.33	0.044	3.2
	Dose 2	34 (24.1)	8	14.34	6.45 – 34.85	<.001	22.4
Moderna	Both Doses	38 (21.1)	7	9.18	4.12 – 22.89	<.001	18.8
	Dose 1	9 (9.7)	7	3.46	1.12 – 11.07	0.031	6.9
	Dose 2	29 (33.0)	4	18.75	6.73 – 64.94	<.001	31.2

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

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

Verified Myocarditis and pericarditis 0-7 Days after Any Dose of mRNA Vaccine: Level of Care and Status by Age Group/Product

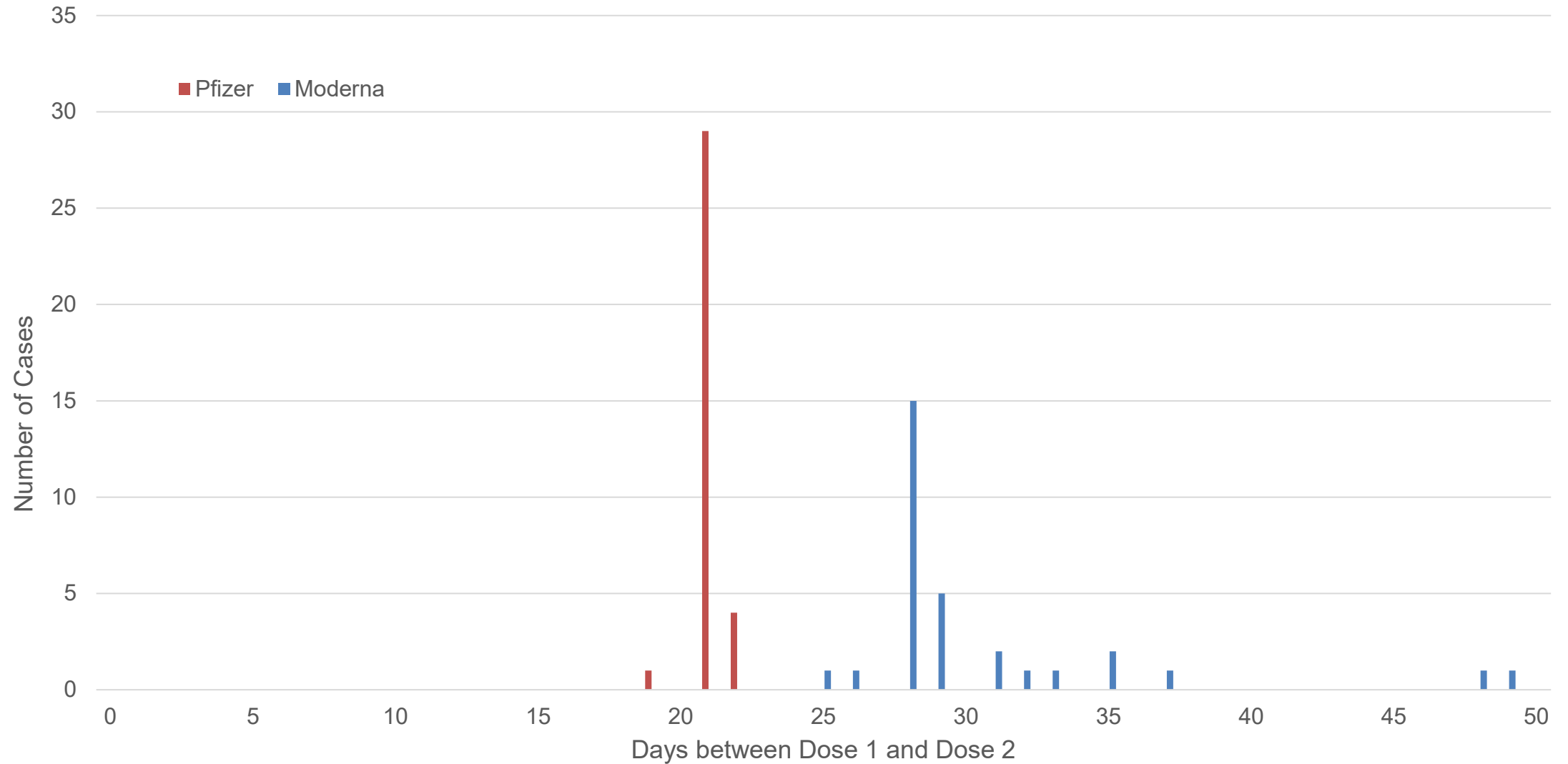
Level of Care and Status	18–39-Year-Olds (Pfizer) N=41	18–39-Year-Olds (Moderna) N=38
Highest level of care		
Outpatient	1 (2%)	1 (3%)
Emergency department	5 (12%)	7 (18%)
Admitted to hospital	35 (85%)	30 (79%)
Admitted to ICU	0 (0%)	0 (0%)
Length of hospital stay, median (range)	1 day (0–2 days)	1 day (0–13 days)
0 days (same day discharge)	8 (20%)	7 (18%)
1 day	18 (44%)	19 (50%)
2 days	15 (37%)	9 (25%)
3 days	0 (0%)	2 (5%)
4 days	0 (0%)	0 (0%)
5 days	0 (0%)	0 (0%)
6+ days	0 (0%)	1 (3%)
Discharged to home	41 (100%)	38 (100%)
At least one follow-up visit noted at the time of chart review	37 (90%)	34 (90%)

Is There a Difference in Risk of Myocarditis and Pericarditis between mRNA Vaccines?

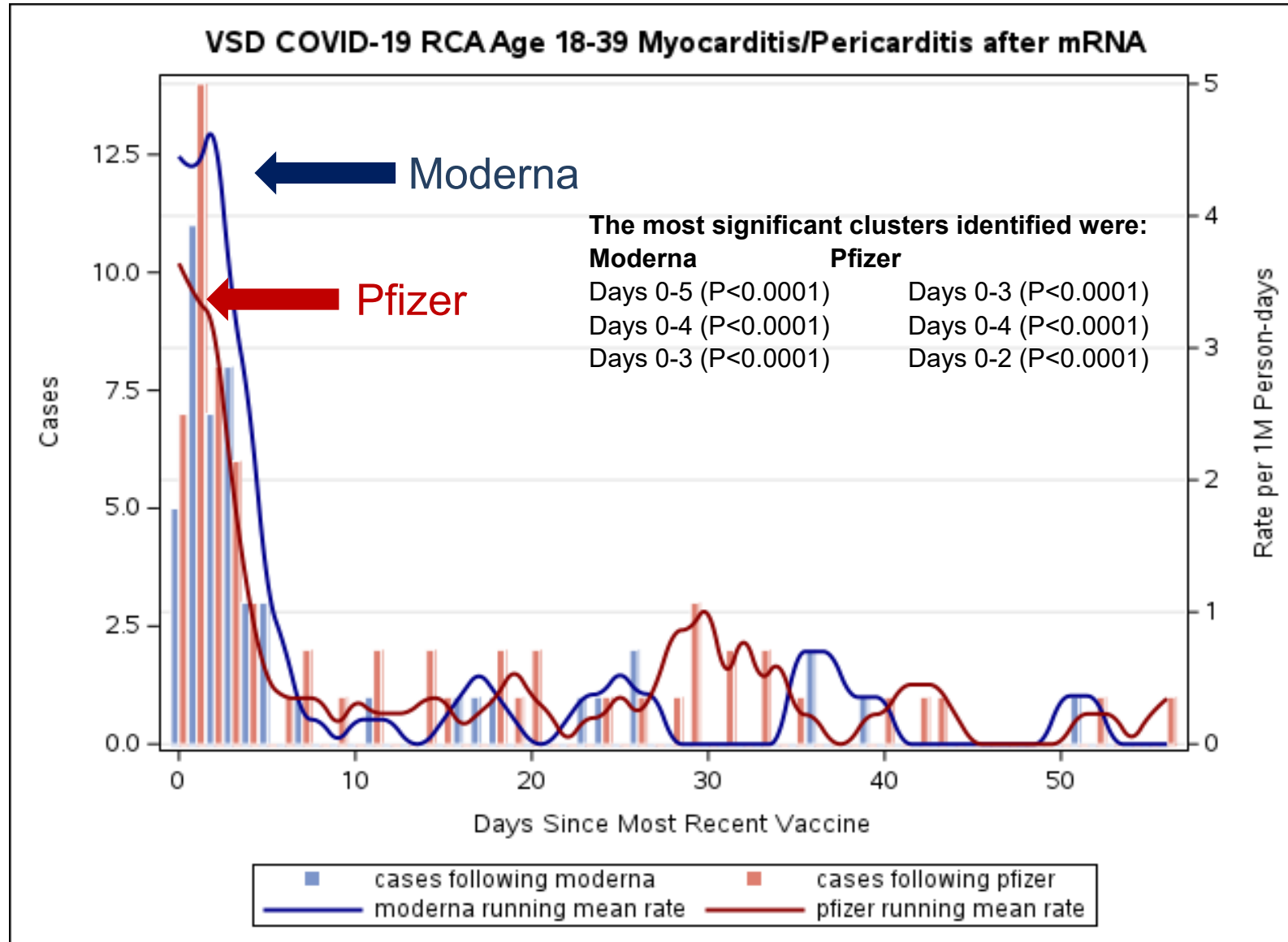
- Analyses with vaccinated concurrent comparators indicate that both Pfizer and Moderna are associated with increased risk of myocarditis/pericarditis in 18–39-year-olds
- Analyses with vaccinated concurrent comparators indirectly suggest that Moderna may be associated with more risk of myocarditis/pericarditis than Pfizer
- To directly test whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer, we conducted head-to-head comparisons among 18–39-year-olds

**Verified Myocarditis and Pericarditis
in 18–39-Year-Olds: Moderna vs Pfizer
(Data Through 1/15/2022)**

Days between Dose 1 & Dose 2 for the Verified Myocarditis and Pericarditis Cases in the 0-7 Day Risk Interval for 18–39-Year-Olds



Symptom Onset of Verified Myocarditis and Pericarditis among 18–39-Year-Olds by Vaccine Product

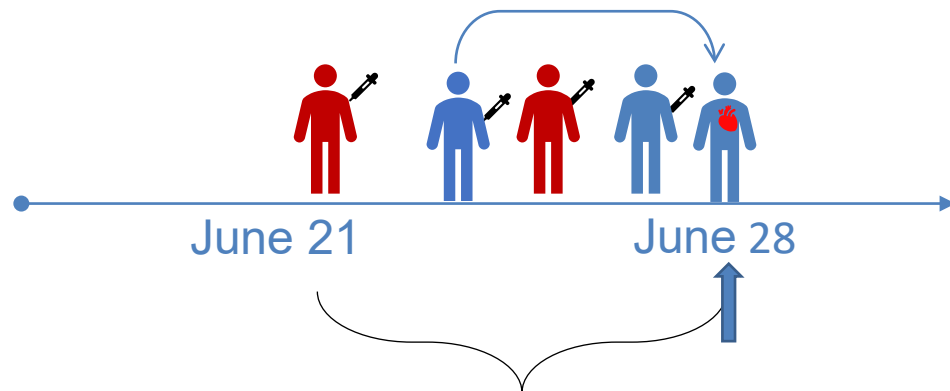


Moderna vs Pfizer “Head-to-Head” Comparison

- **Moderna** and **Pfizer** vaccinees were directly compared during the risk interval within groups
- The groups are comprised of:
 - Individuals inside the risk interval (days 0-7 post-vaccination)
 - Individuals of the same age group, sex, and race/ethnicity and from the same VSD site
 - On a calendar day when an mRNA vaccinee had myocarditis/pericarditis
- We estimated rate ratios with 95% confidence intervals (rate post-Moderna / rate post-Pfizer)
- We tested the null hypothesis that the rate of myocarditis and pericarditis after vaccination does not differ between Moderna and Pfizer

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- A 28-year-old male had myocarditis on 6/28
- He was vaccinated 6/23 and therefore in the 0-7 day in risk interval
- Comparators include everyone who, on 6/28, was in the 0–7 day post vaccination risk interval after either mRNA vaccine (i.e., they were vaccinated 6/21 – 6/28)

Myocarditis and Pericarditis in 18–39-Year-Olds in the 0-7 Day Risk Interval: Moderna vs Pfizer

	Sex	Moderna (N)	Pfizer (N)	Adjusted Rate Ratio ¹	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1M Doses of Moderna vs Pfizer ²
Either Dose	All	38	41	1.61	1.02 – 2.54	0.041	8.0
	Male	32	36	1.52	0.93 – 2.48	0.097	13.4
	Female	6	5	2.34	0.65 – 8.71	0.188	3.5
Dose 1	All	9	7	2.27	0.80 – 6.65	0.122	5.5
	Male	6	6	1.65	0.49 – 5.57	0.414	5.6
	Female	3	1	6.79	0.65 – 197.90	0.116	5.1
Dose 2	All	29	34	1.48	0.88 – 2.50	0.141	10.7
	Male	26	30	1.50	0.86 – 2.61	0.152	21.9
	Female	3	4	1.35	0.23 – 7.15	0.714	1.6

¹Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna rate divided by Pfizer rate.

²Excess cases is an estimate of the Moderna rate minus the Pfizer rate. Excess cases per million doses were estimated by dividing the Moderna incidence rate by the rate ratio estimate and subtracting the result from the Moderna rate.

Myocarditis/Myopericarditis, **Pericarditis Excluded**, in 18–39-Year-Olds in the 0-7 Day Risk Interval: **Moderna vs Pfizer**

	Sex	Moderna (N)	Pfizer (N)	Adjusted Rate Ratio ¹	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1M Doses of Moderna vs Pfizer ²
Either Dose	All	30	39	1.35	0.82 – 2.19	0.237	4.3
	Male	27	35	1.32	0.78 – 2.22	0.288	8.1
	Female	3	4	1.57	0.27- 8.12	0.585	1.1
Dose 1	All	6	6	1.84	0.54 – 6.30	0.320	3.0
	Male	4	5	1.43	0.33 – 5.86	0.612	2.9
	Female	2	1	4.28	0.28 – 151.15	0.311	3.0
Dose 2	All	24	33	1.24	0.70 – 2.14	0.454	5.2
	Male	23	30	1.31	0.73 – 2.31	0.361	13.6
	Female	1	3	0.53	0.02 – 5.81	0.658	-1.8

¹Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna rate divided by Pfizer rate.

²Excess cases is an estimate of the Moderna rate minus the Pfizer rate. Excess cases per million doses were estimated by dividing the Moderna incidence rate by the rate ratio estimate and subtracting the result from the Moderna rate.

Summary of Myocarditis and Pericarditis Analyses Days 0-7 after Dose 2 among 18–39-Year-Olds: **Moderna vs Pfizer**

Includes Pericarditis	Sex	Adjusted Rate Ratio ¹	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1M Doses of Moderna vs Pfizer ²
Yes	All	1.48	0.88 – 2.50	0.141	10.7
	Male	1.50	0.86 – 2.61	0.152	21.9
No	All	1.24	0.70 – 2.14	0.454	5.2
	Male	1.31	0.73 – 2.31	0.361	13.6

¹Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna rate divided by Pfizer rate.

²Excess cases is an estimate of the Moderna rate minus the Pfizer rate. Excess cases per million doses were estimated by dividing the Moderna incidence rate by the rate ratio estimate and subtracting the result from the Moderna rate.

Summary

- Among 18–39-year-olds, both mRNA vaccines were associated with increased risk of myocarditis and pericarditis in the 0-7 days post-vaccination, particularly after dose 2
 - We estimated 22.4 excess cases per million second doses after Pfizer and 31.2 excess cases per million second doses after Moderna
- Among 18–39-year-olds, there were no noticeable clinical differences between cases after Moderna and those after Pfizer
 - Most had hospital length of stay of 0-1 days
 - None were admitted to the ICU
- Direct head-to-head comparisons provide evidence that the risk of myocarditis and pericarditis may be higher after Moderna than after Pfizer
 - Comparing Moderna vs Pfizer, we estimated that Moderna was associated with an additional 10.7 cases of myocarditis and pericarditis per million second doses
- Both mRNA vaccines were associated with increased risk of myocarditis and pericarditis for individuals aged 18-39 years

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- **VSD Sites:**
 - HealthPartners Institute, Minneapolis, Minnesota
 - Kaiser Permanente Colorado, Denver, Colorado
 - Kaiser Permanente Northwest, Portland, Oregon
 - Kaiser Permanente Southern California, Los Angeles, California
 - Kaiser Permanente Washington, Seattle, Washington
 - Denver Health, Denver, Colorado