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

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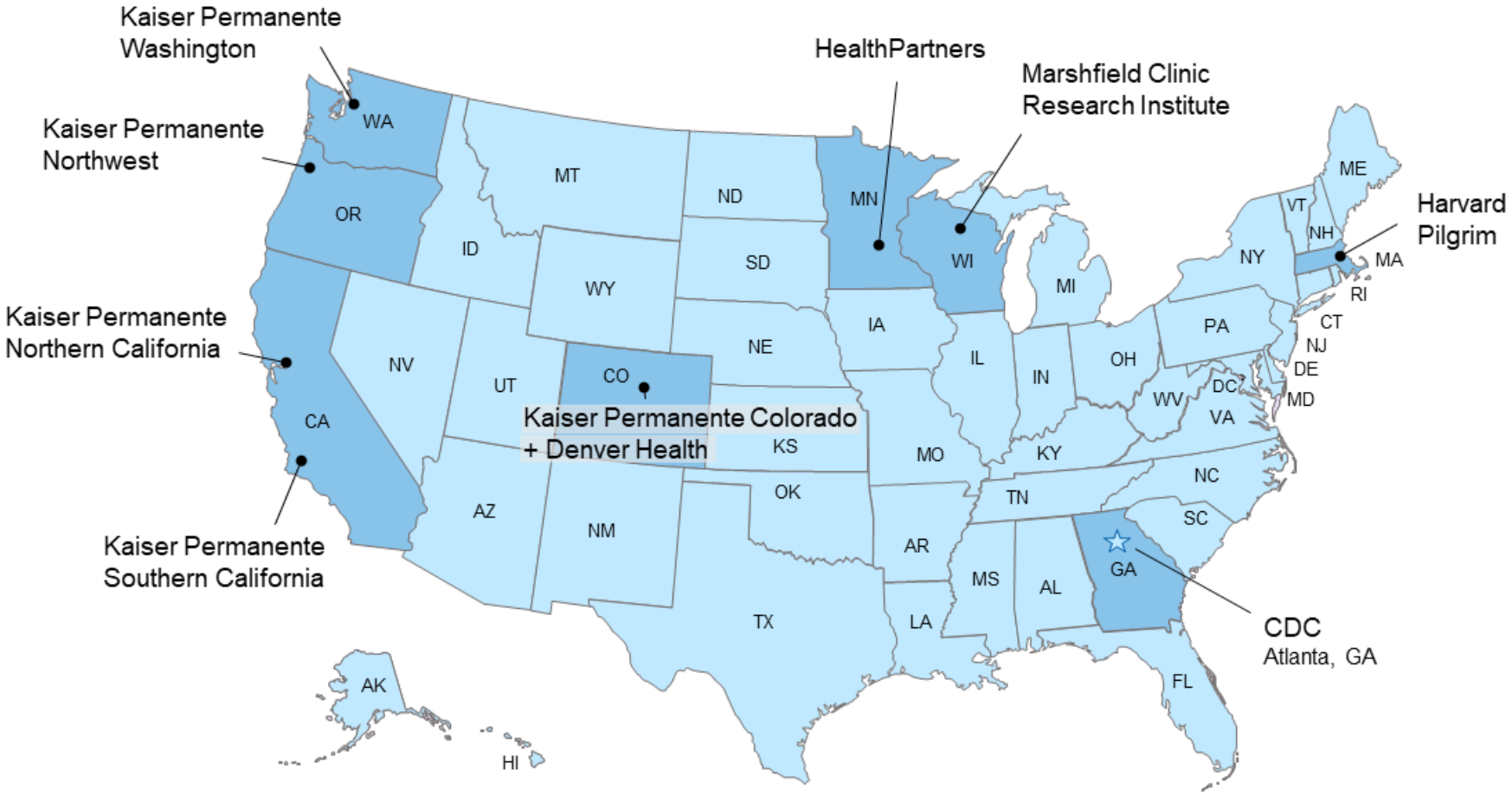
The Vaccine Safety Datalink (VSD)



- 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

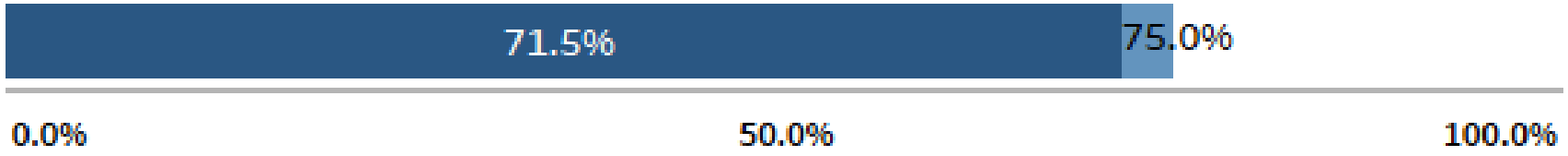
Abbreviations: E=ED, I=Inpatient, O=Outpatient

COVID-19 Vaccine Uptake & Primary Analyses (Data Through 10/09/2021)

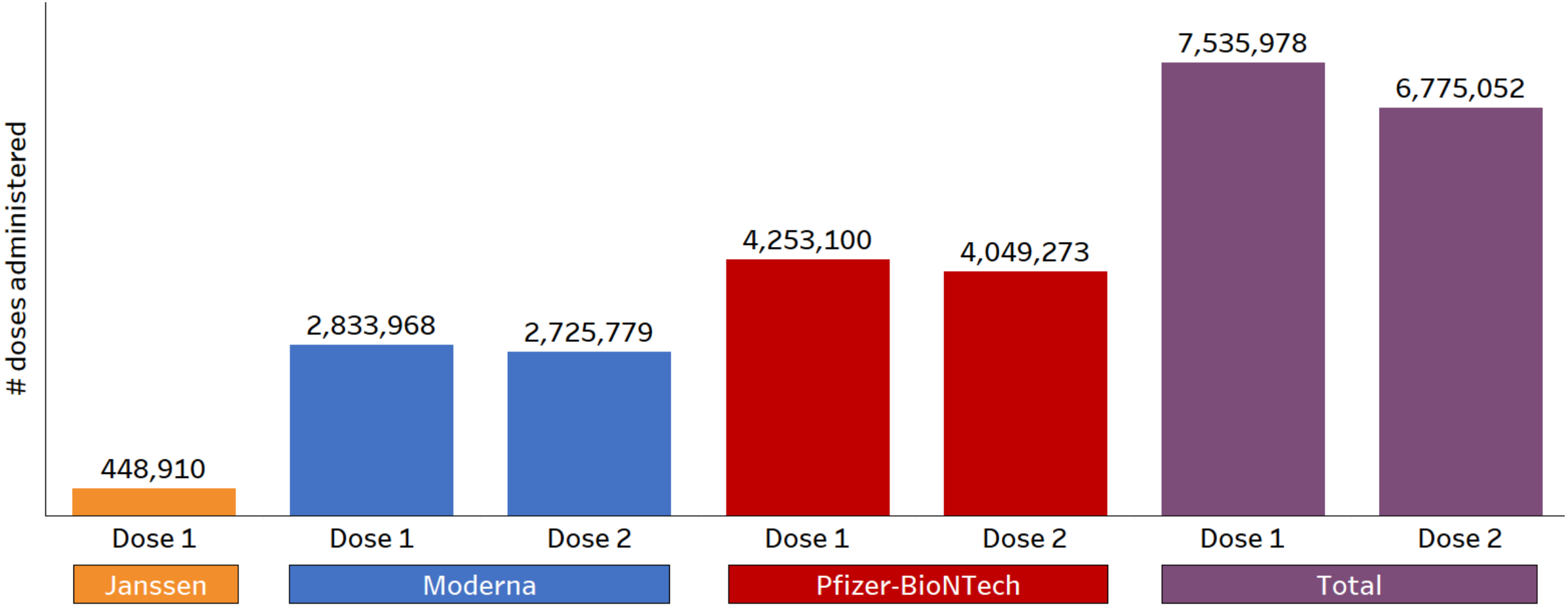
VSD COVID-19 Vaccine Totals

Total Doses Administered	Total Doses Admin per 100K	# People Received At Least One Dose	# People Fully Vaccinated
14,214,955	148,020	7,492,340	7,166,936

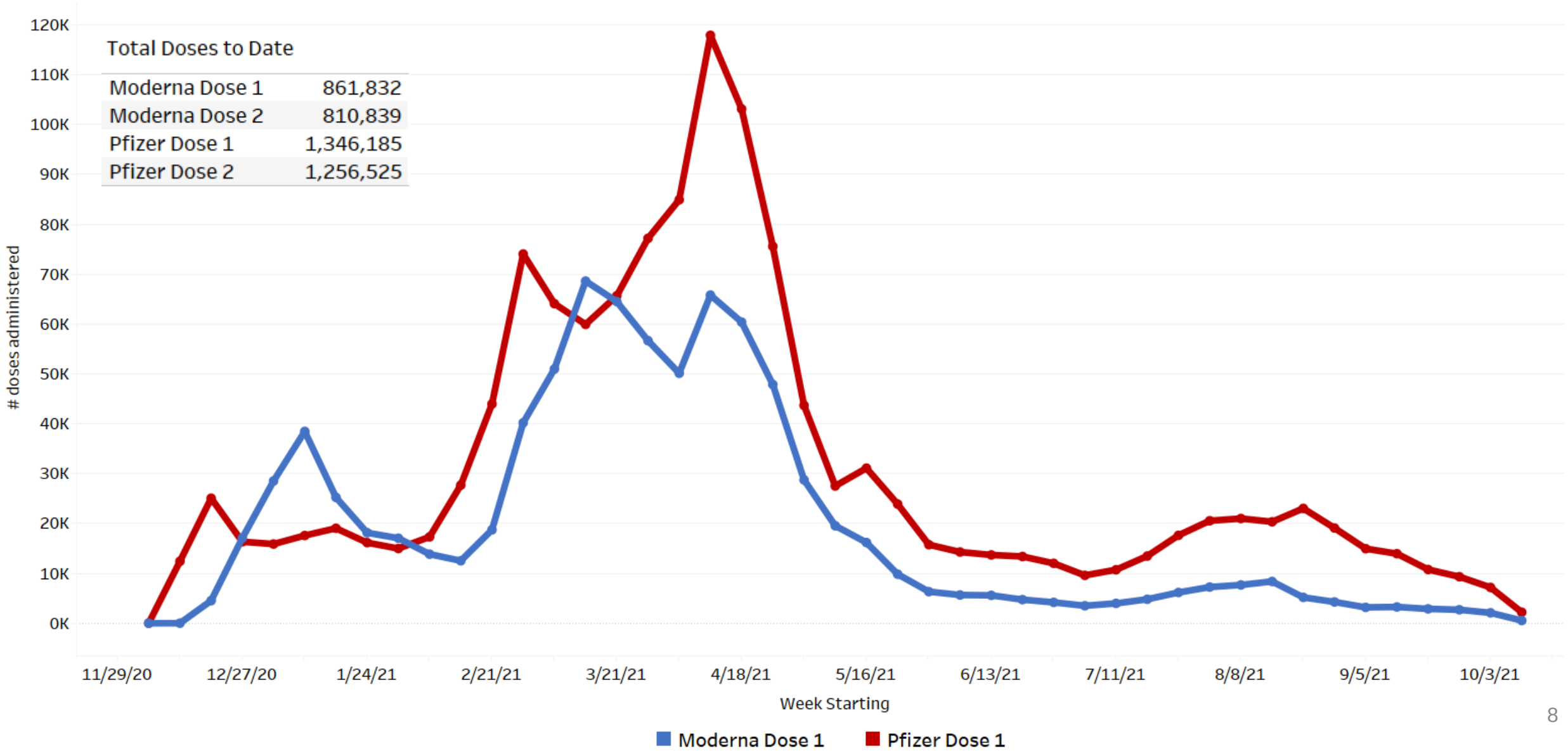
To date, 71.5% of the age eligible VSD population is fully vaccinated and 75.0% received at least one dose



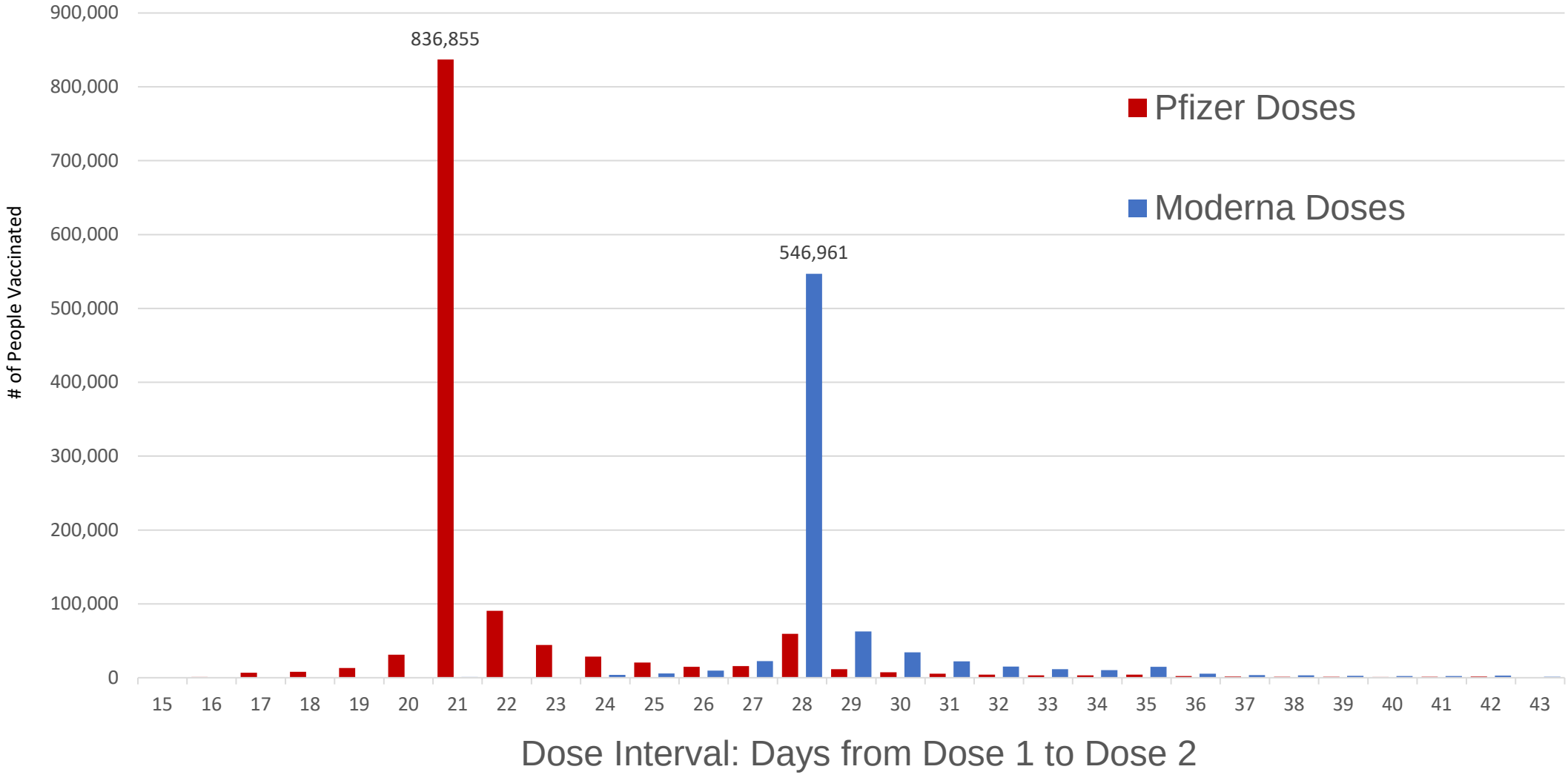
VSD COVID-19 Vaccine Totals



First Dose Totals by Week for the 18-39 Year-Old Age Group



Days Between Dose 1 & Dose 2 for mRNA Vaccines Administered in the VSD among 18-39 Year-Olds



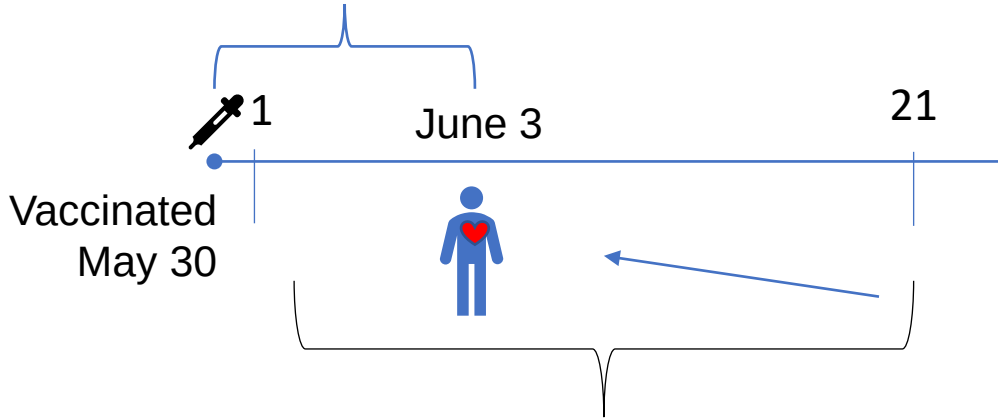
Analytic Strategy

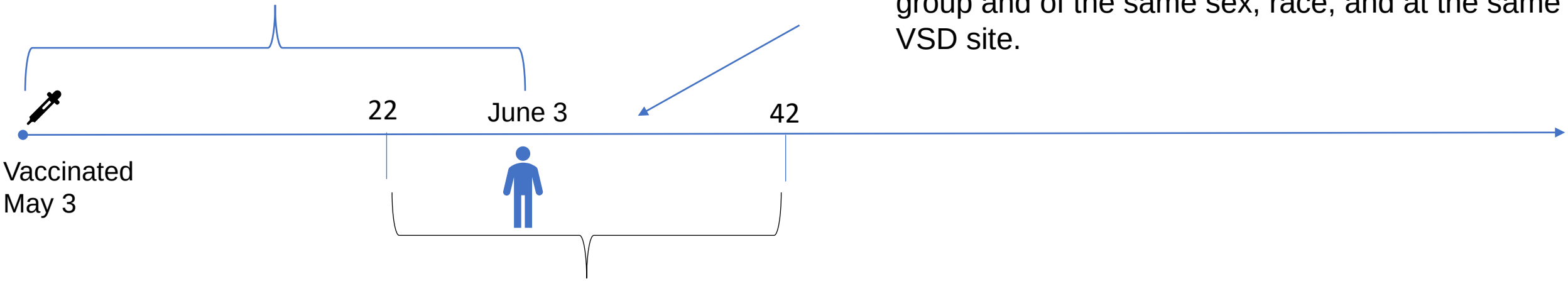
- For the primary analysis, the number of outcomes observed in the risk interval (1-21 days) after COVID-19 vaccination were compared to the number expected.

- 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.

Myocarditis/Pericarditis 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
Myocarditis / pericarditis	138	1.72	<.001	yes

[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.

Subgroup Analysis of Confirmed Myocarditis/Pericarditis after mRNA Vaccines among 12-39 Year-Olds (Data Through 10/09/2021)

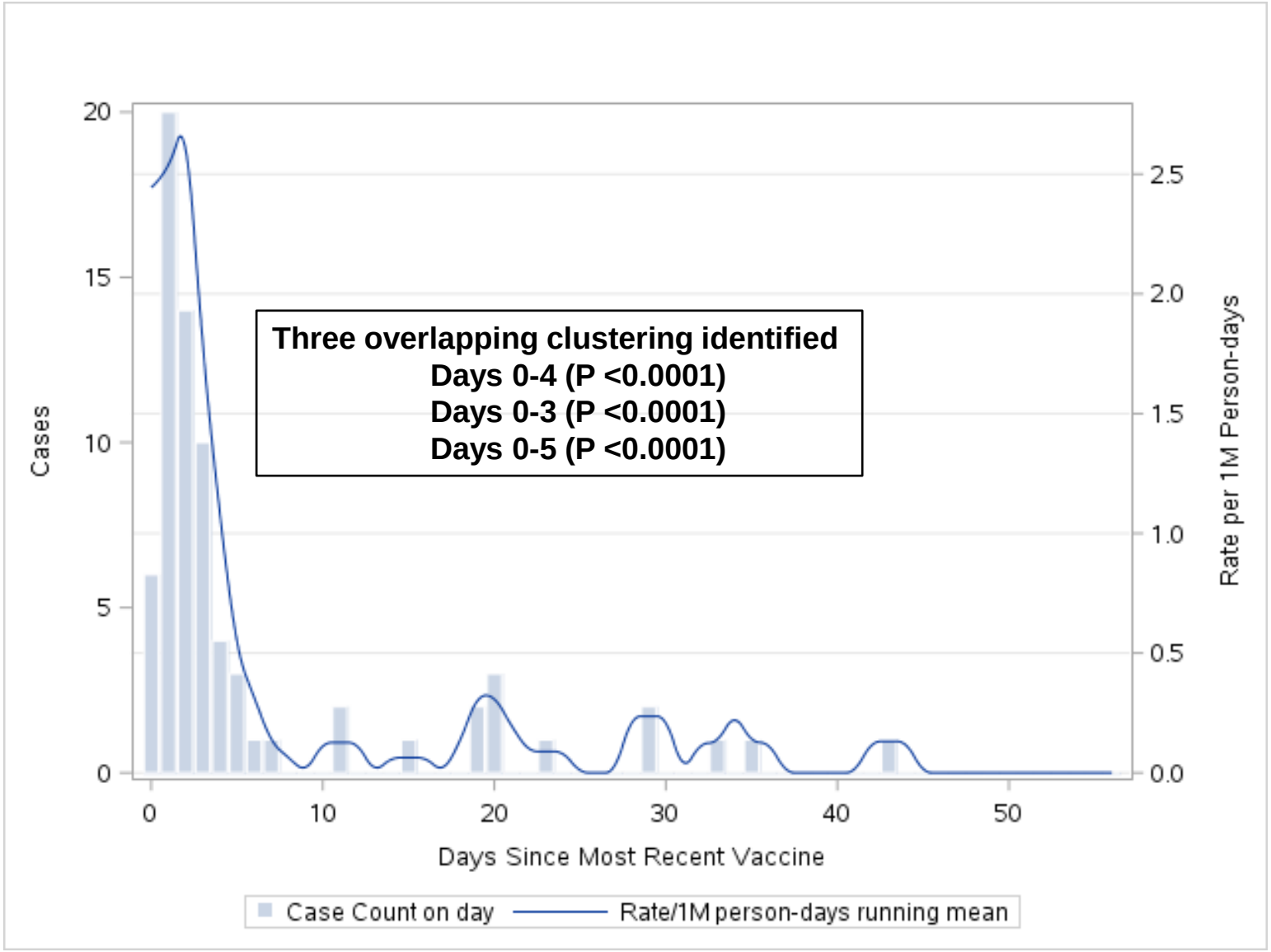
Myocarditis/Pericarditis Following an mRNA Vaccine: Chart Review Summary

- Chart review completed for cases through **October 09, 2021** for 132/135 cases (3 pending)
  - ✓12–39-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 confirmed 103/132 (78%) myocarditis/pericarditis cases**

- ✓ 74 confirmed cases among 12-39-year-olds, with onset 0-21 days after dose 1 (15) or 2 (59)
- ✓ 44 confirmed cases among 18-39-year-olds, with onset 0-21 days after dose 1 (13) or 2 (31)
- ✓ 39 confirmed cases among 18-39-year-olds, with onset 0-7 days after dose 1 (10) or 2 (29)

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



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

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

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	66	6	21.73	9.53 - 57.34	<0.001	11.8
	Dose 1	10	6	10.18	3.01 - 36.36	<0.001	3.3
	Dose 2	52	5	31.28	12.83 - 91.40	<0.001	21.1
Pfizer Ages 12-39	Both Doses	44	5	19.31	7.66 - 57.79	<0.001	11.5
	Dose 1	5	5	8.65	2.01 - 36.99	0.005	2.3
	Dose 2	35	4	30.27	11.01 - 104.40	<0.001	21.5
Moderna Ages 18-39	Both Doses	22	1	37.51	6.69 - 803.00	<0.001	12.8
	Dose 1	5	1	10.47	1.38 - 258.35	0.020	5.2
	Dose 2	17	0	very high[3]	11.75 -∞	<0.001	21.0

[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.
[3]The focus should be on the lower bound of the confidence interval.

Results in this slide cannot be directly compared between Pfizer and Moderna because of the different age groups who are authorized to receive each vaccine

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	39	6	12.61	5.27 - 34.47	<0.001	8.4
	Dose 1	10	6	9.69	2.90 - 34.22	<0.001	4.1
	Dose 2	29	5	14.33	5.50 - 43.88	<0.001	13.1
Pfizer	Both Doses	17	5	7.98	2.72 - 26.50	<0.001	5.7
	Dose 1	5	5	8.05	1.89 - 33.89	0.006	3.3
	Dose 2	12	4	8.77	2.56 - 35.34	<0.001	8.5
Moderna	Both Doses	22	1	37.42	6.68 - 801.33	<0.001	12.8
	Dose 1	5	1	10.47	1.38 - 258.35	0.020	5.2
	Dose 2	17	0	very high[3]	11.70 - ∞	<0.001	21.0

[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.
[3]The focus should be on the lower bound of the confidence interval.

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			
Risk Interval	**Dose**	**Events in Risk Interval**	**Events in Comparison Interval[1]**	**Adjusted Rate Ratio[2,3]**	**95% Confidence Interval**	**2-Sided P-value**	**Excess Cases in Risk Period per 1 Million Doses**
Days 0-21	**Both Doses**	30	0	**very high**	**5.68 - ∞**	**<0.001**	**29.6**
	Dose 1	2	0	very high	0.31 - ∞	0.198	3.8
	Dose 2	24	0	**very high**	**9.09 - ∞**	**<0.001**	**56.7**
Days 0-7	**Both Doses**	27	0	**very high**	**16.88 - ∞**	**<0.001**	**25.9**
	Dose 1	0	0	NE	NE	NE	NE
	Dose 2	23	0	**very high**	**28.83 - ∞**	**<0.001**	**54.0**

NE= not estimable; indicates that vaccine effect cannot be estimated.
[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.
[3]The focus should be on the lower bound of the confidence interval.

Myocarditis/Pericarditis: Moderna vs Pfizer

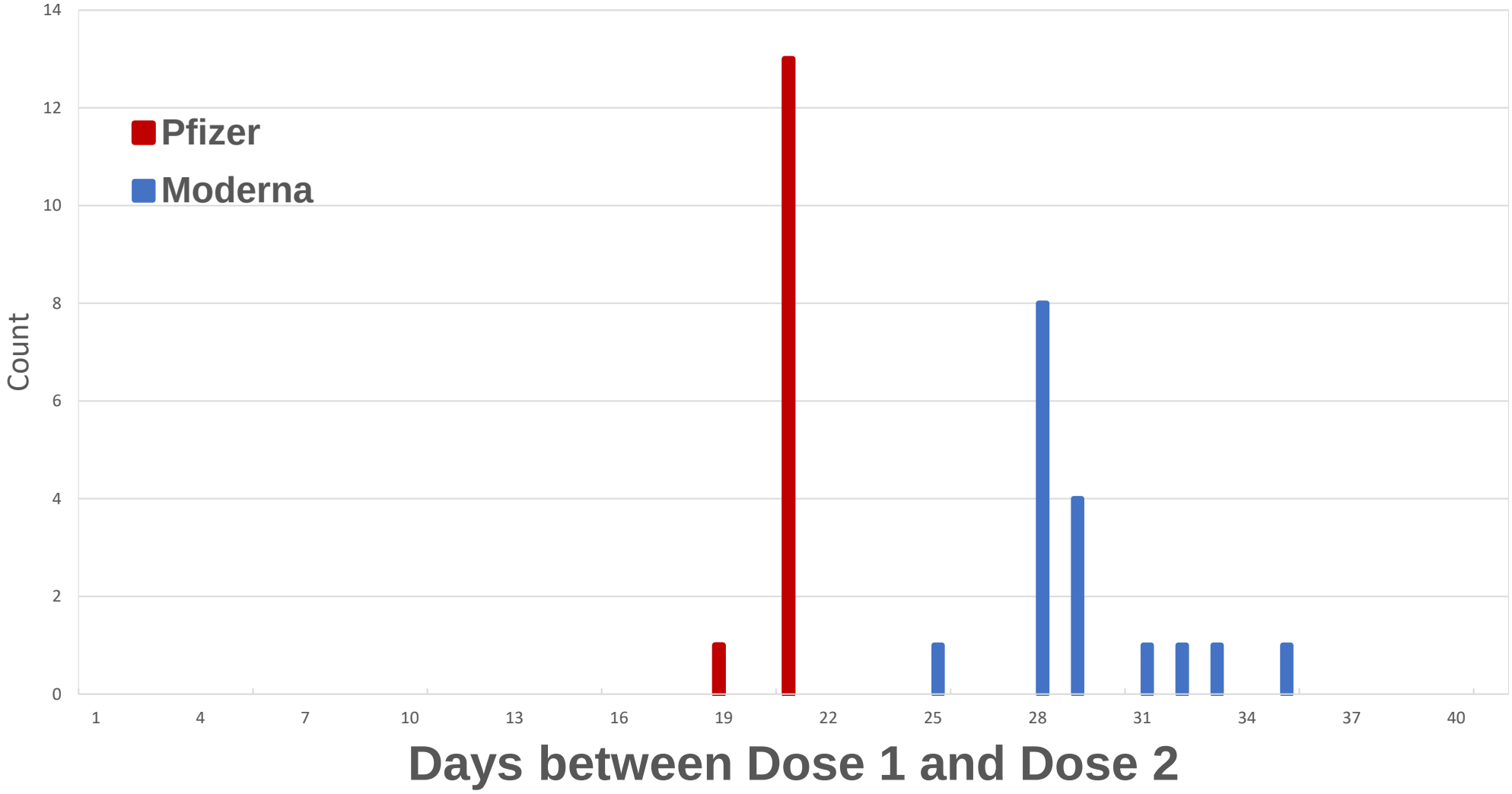
- Analyses with vaccinated concurrent comparators indicate that both Pfizer and Moderna are associated with increased risk of myocarditis/pericarditis in 12–39-year-olds.
  - Pfizer results include 12–39-year-olds while Moderna only includes 18–39-year-olds.

- Analyses with vaccinated concurrent comparators indirectly suggest that Moderna is associated with more risk of myocarditis/pericarditis than Pfizer.

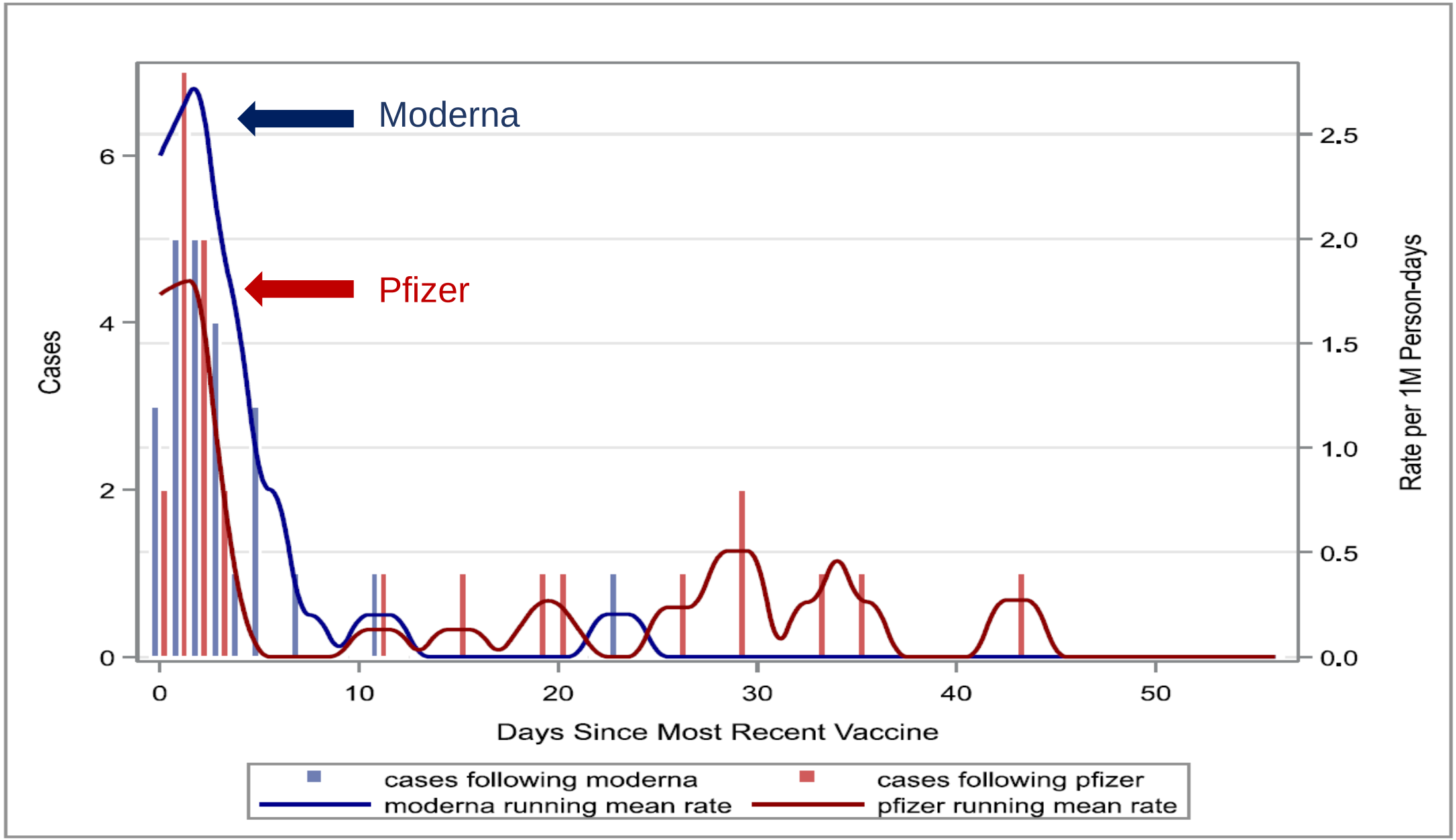
- To directly test whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer, we conducted head-to-head comparisons among 18–39-year-olds.

Confirmed Myocarditis/Pericarditis: Moderna vs Pfizer (Data Through 10/09/2021)

Days between Dose 1 & Dose 2 for the Confirmed Myocarditis/Pericarditis Cases in the 0-21 Day Risk Interval for 18-39 Year Olds



Incidence of Confirmed Myocarditis/Pericarditis in 18-39 Year-Olds: Moderna vs Pfizer



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 or 0-21 post-vaccination)
  - Individuals of the same age group, sex, and race/ethnicity
  - 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 / pericarditis after vaccination does not differ between Moderna and Pfizer.

Moderna vs Pfizer "Head-to-Head" Comparison

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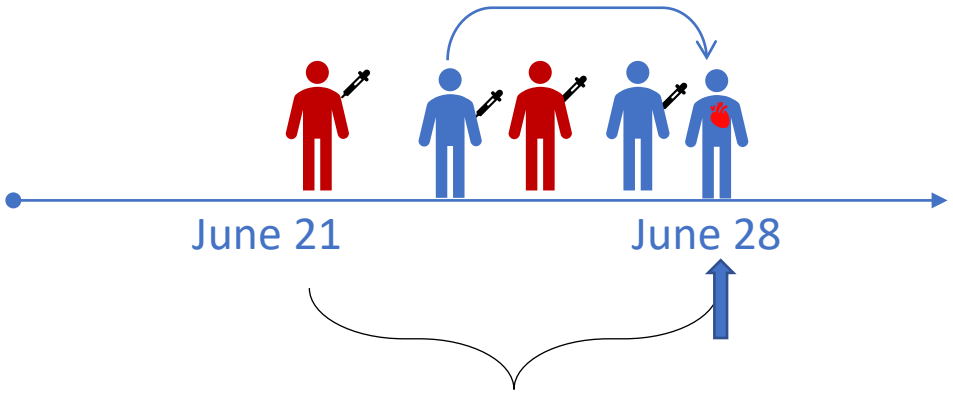
- The groups are comprised of:
  - Individuals inside the risk interval (days 0-7 or 0-21 post-vaccination)
  - Individuals of the same age group, sex, and race/ethnicity
  - From the same VSD site
  - On a calendar day when an mRNA vaccinee had myocarditis / pericarditis
- We estimated rate ratios with 95% confidence intervals (rate post-Moderna / rate post-Pfizer).
- We tested the null hypothesis that the rate of myocarditis / pericarditis after vaccination does not differ between Moderna and Pfizer.



- 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/Pericarditis in 18-39 Year Olds: Moderna vs Pfizer

	Risk Interval days	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]
Both Doses	0-7	22	16	**2.56**	**1.32 - 5.03**	**0.005**	**8.0**
	0-21	23	20	**2.05**	**1.11 - 3.83**	**0.023**	**7.1**
Dose 1	0-7	5	4	2.63	0.62 - 11.83	0.186	3.6
	0-21	6	6	1.76	0.51 - 6.07	0.365	3.0
Dose 2	0-7	17	12	**2.72**	**1.25 - 6.05**	**0.012**	**13.3**
	0-21	17	14	**2.19**	**1.05 - 4.65**	**0.037**	**11.5**

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

Myocarditis/Myopericarditis (Pericarditis Excluded) in 18-39 Year Olds: Moderna vs Pfizer

	Risk Interval days	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]
Both Doses	0-7	17	15	**2.24**	**1.09 - 4.63**	**0.028**	**5.6**
	0-21	18	17	1.96	0.99 - 3.91	0.054	5.3
Dose 1	0-7	3	3	2.69	0.43 - 16.94	0.276	2.2
	0-21	4	5	1.45	0.32 - 6.15	0.605	1.4
Dose 2	0-7	14	12	**2.28**	**1.00 - 5.22**	**0.049**	**9.7**
	0-21	14	12	2.19	0.98 - 4.97	0.057	9.4

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

Summary of Myocarditis/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	Both Sex	**2.72**	**1.25 - 6.05**	**0.012**	**13.3**
	Male	**2.26**	**1.00 - 5.19**	**0.051**	**21.5**
No	Both Sex	**2.28**	**1.00 - 5.22**	**0.049**	**9.7**
	Male	2.14	0.93 - 4.98	0.074	19.1

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

Summary of Vaccinated Concurrent Comparators RCA Analyses

- The VSD formally signaled for myocarditis/pericarditis 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.
  - Pfizer results include 12–39-year-olds while Moderna only includes 18–39-year-olds.

- In subgroup analyses, both mRNA vaccines were associated with myocarditis/pericarditis in persons aged 12-39 years.

Summary of Head-to-Head Comparison of Moderna vs Pfizer

- Among 18–39-year-olds, rates of myocarditis/pericarditis after Moderna were significantly higher than after Pfizer during both the 0-21 and 0-7 day risk intervals.
  - Results were consistent when analyses excluded pericarditis.

- Comparing Moderna vs Pfizer during the 0-7 days after dose 2, we estimated 13.3 excess cases of myocarditis/pericarditis per million doses.

- Among 18–39-year-olds, there were no clear clinical differences among myocarditis/pericarditis cases between Moderna and Pfizer recipients.
  - Most had hospital length of stay 0-1 day.
  - None were admitted to the ICU.

- Both mRNA vaccines were associated with increased risk of myocarditis/pericarditis for ages 18-39 years, as was Pfizer for ages 12-17 years. Head-to-head comparisons provide evidence that the risk of myocarditis/pericarditis was higher after Moderna than after Pfizer.

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