

Supplemental Online Content

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eTable 1. Diagnostic codes used to identify outcomes and adjust onset date.

eTable 2. Exclusionary diagnostic codes.

eFigure 1. Illustration of primary analyses using vaccinated concurrent comparators and supplemental analyses using unvaccinated concurrent comparators.

eTable 3. Summary of Signals during 21-day Risk Interval, from separate Dose 1, Dose 2 and Vaccine Product Analyses.

eFigure 2. Clustering of medical record confirmed myocarditis/pericarditis cases by days since most recent dose of any mRNA vaccine among individuals 12-39 years of age.

eTable 4. Medical record review of 34 confirmed myocarditis/pericarditis cases 0-21 days after mRNA vaccines within individuals aged 12-39 years, December 14, 2021 - June 19, 2021.

eTable 5. Confirmed myocarditis/pericarditis following mRNA vaccines compared with vaccinated comparators among individuals aged 12 – 39 years by vaccine type and dose, December 14, 2020-June 19, 2021.

eTable 6. Unvaccinated concurrent comparator analyses, December 14, 2020-June 26, 2021.

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnostic codes used to identify outcomes and adjust onset date.

Outcomes for Comparative Analyses	ICD-10 code(s)	Planned Medical Record Review	Codes for Lookback to Adjust Onset Date (All Settings)
Acute disseminated encephalomyelitis	G04.00, G04.02	Y	n/a
Acute myocardial infarction	I21.*	N	n/a
Appendicitis	K35.*, K36, K37, K38.8	N	n/a
Bell's palsy	G51.0	N	n/a
Cerebral venous sinus thrombosis	G08, I63.6, I67.6	Y	n/a
Convulsions / seizures	R56.0*, R56.9	N	n/a
Disseminated intravascular coagulation	D65	N	n/a
Encephalitis / myelitis / encephalomyelitis / (not acute disseminated encephalomyelitis or transverse myelitis)	G04.30, G04.32, G04.39, G04.8*, G04.9*, G05.*, G37.4	N	n/a
Guillain-Barré syndrome	G61.0	Y	n/a
Immune thrombocytopenia	D69.3	N	<u>If in 1 year prior to case:</u> low platelet count <100 K/uL
Kawasaki disease	M30.3	N	n/a
Myocarditis / pericarditis	B33.22, B33.23, I30.*, I40.*	Y (subgroup only)	n/a
Pulmonary embolism	I26.*	N	n/a
Stroke, hemorrhagic	I60.*, I61.*, I62.*	N	<u>If in 1 day prior to case:</u> G81.9*, H53.13*, H53.9, I63.9, R29.810, R40.4, R41.82, R42.*, R47.*, R51.*, R53.1
Stroke, ischemic	G45.8, G45.9, I63.*	N	<u>If in 1 day prior to case:</u> G81.9*, H53.13*, H53.9, R29.810, R40.4, R41.82, R42.*, R47.*, R51.*, R53.1, Z92.82
Thrombosis with thrombocytopenia ¹	G08, I63.6, I67.6, I74.0*, I74.1*, I74.3, I74.5, I74.8, I74.9, I81, I82.0, I82.890, K55.0*, N28.0	Y	n/a
Thrombotic thrombocytopenic purpura	M31.1	N	n/a
Transverse myelitis	G37.3	Y	n/a
Venous thromboembolism	I26.*, I82.210, I82.220, I82.290, I82.3, I82.4*, I82.60*, I82.62*, I82.A1*	N	<u>If in 14 days prior to case:</u> M79.65*, M79.66*, R22.4*

Outcomes for Comparative Analyses	ICD-10 code(s)	Planned Medical Record Review	Codes for Lookback to Adjust Onset Date (All Settings)
	I82.B1*, I82.C1*, I82.890, I82.90		
Outcomes for descriptive monitoring only	ICD-10 code(s)	Planned Medical Record Review	Monitoring Period
Acute respiratory distress syndrome	J80	N	0-84 days
Anaphylaxis	T78.2*, T80.52*, T88.6*	Y	0-1 days
Multisystem inflammatory syndrome in children / Multisystem inflammatory syndrome in adults	M35.8 + U07.1, or M35.81	N	0-84 days
Narcolepsy / cataplexy	G47.41*	N	0-84 days

*Cases required to have one of the listed ICD-10 codes and a platelet count of <150,000 for inclusion.

eTable 2. Exclusionary diagnostic codes.

Outcome for comparative analyses	Exclusions for Prevalence - with lookback period for exclusion	Exclusions – other known causes (in all settings) - with lookback period for exclusion (not including same day unless noted in column to the right)	Exclusions – same day, other known causes (in all settings)
Acute disseminated encephalomyelitis	n/a	n/a	n/a
Acute myocardial infarction	<u>If occurs EVER prior to case:</u> I22.*, I23.*, I25.2	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 7 days prior to case:</u> Physical trauma code ² <u>If EVER prior to case:</u> I25.1	Same exclusions as column to the left
Appendicitis	n/a	n/a	n/a
Bell's palsy	n/a	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 14 days prior to case:</u> A69.2*, A92.5, B00.*, B02.* <u>If EVER prior to case:</u> D86.*	Same exclusions as column to the left
Cerebral venous sinus thrombosis	n/a	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>Exclude if incident case occurs any time during pregnancy or within 6 weeks after pregnancy ends:</u> <u>O22.5*, O87.3</u>	<u>If same day as incident case:</u> <u>S02.*, S06.*, S09.*, S15.*</u> , <u>Physical trauma code²</u>
Convulsions / seizures	<u>If occurs EVER prior to case:</u> F44.5, G40.A*, G40.B*, G40.0*, G40.1*, G40.2*, G40.3*, G40.4*, G40.5*, G40.8*, G40.9*	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 1 year prior to case:</u> G03.1 S06.3*, S06.9*, Z86.61 <u>If EVER prior to case:</u> I69.*, Z86.73, <u>If in last 3 days prior to case:</u> I60.*, I61.*, I62.*, I63.* <u>If in last 7 days prior to case:</u> A17.0, A17.82, A27.81, A32.1*, A39.0, A39.81, A41.9, A69.21, A85.*, A86, A87.* A88.0, A88.8, A89, A92.31, A92.5, B00.*, B01.0, B01.11, B02.*, B05.*, B06.*, B10.81, B26.*, B45.1, B58.2, B96.0, G00.*, G01, G02, G03.0, G03.8, G04.3*, G04.81, G04.90, G05.3, G92, G93.41, G95.1*, G95.89, J09.*, J10.*, J11.*, R65.20, R65.21	<u>If same day as case:</u> S06.0X9A, S06.3*, S06.9*
Disseminated intravascular coagulation	n/a	<u>If in last 42 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 14 days prior to case:</u> Physical trauma code ² C92.4*, K85.*, O45.02*, O46.02*, O67.0, S06.*, T30-T32	Same exclusions as column to the left

Outcome for comparative analyses	Exclusions for Prevalence - with lookback period for exclusion	Exclusions – other known causes (in all settings) - with lookback period for exclusion (not including same day unless noted in column to the right)	Exclusions – same day, other known causes (in all settings)
Encephalitis / myelitis / encephalomyelitis / encephalopathy (not acute disseminated encephalomyelitis or transverse myelitis)	<u>If occurs EVER prior to case:</u> G03.1, Z86.61	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 7 days prior to case:</u> A17.0, A17.82, A27.81, A32.1*, A39.0, A39.81, A41.9, A69.21, A85.*, A86, A87.*, A88.0, A88.8, A89, A92.31, A92.5, B00.*, B01.0, B01.1*, B02.*, B05.*, B06.*, B10.81, B26.*, B45.1, B58.2, B96.0, G00.*, G01, G02, G03.0, G03.8, G04.31, G95.1*, G95.89, J09.*, J10.*, J11.*, R65.20, R65.21	Same exclusions as column to the left
Guillain-Barré syndrome	<u>If occurs EVER prior to case:</u> G65.0	n/a	n/a
Immune thrombocytopenia	n/a	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If EVER prior to case:</u> B20, C00-C96, D18.0*, D59.0-D59.2, D59.3, D61.*, D65, D69.0, D80-D89, K70-K77, M32.*, Z51.11	n/a
Kawasaki disease	n/a	n/a	n/a
Myocarditis / pericarditis	n/a	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test	Same exclusions as column to the left
Pulmonary embolism	<u>If occurs EVER prior to case:</u> I27.82, Z86.71*	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 14 days prior to case:</u> Physical trauma code ² , O88.0*, O88.1*, T79.1*	Same exclusions as column to the left minus COVID-19
Stroke, hemorrhagic	<u>If occurs EVER prior to case:</u> I69.*, Z86.73	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 1 day prior to case:</u> S06.*	<u>If same day as case:</u> S06.*, Physical trauma code ²
Stroke, ischemic	<u>If occurs EVER prior to case:</u> I69.*, Z86.73	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 1 day prior to case:</u> S15.*, I74.* <u>If in last 28 days prior to case:</u> I21.* <u>If EVER prior to case:</u> I48.*, D57.*, D68.5*	<u>If same day as case:</u> S15.*, I74.*, Physical trauma code ²
Thrombosis with thrombocytopenia syndrome	n/a	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test	n/a
Thrombotic thrombocytopenia purpura	n/a	<u>If in last 30 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 1 year prior to case:</u> B20, C00-C96, Z51.11, Z94.84	n/a

Outcome for comparative analyses	Exclusions for Prevalence - with lookback period for exclusion	Exclusions – other known causes (in all settings) - with lookback period for exclusion (not including same day unless noted in column to the right)	Exclusions – same day, other known causes (in all settings)
		<u>If anytime during pregnancy or within 6 weeks after pregnancy ends: Search pregnancy database OR O99.1*</u>	
Transverse myelitis	n/a	n/a	n/a
Venous thromboembolism	<u>If occurs EVER prior to case:</u> I27.82, I82.211, I82.221, I82.291, I82.5*, I82.7*, I82.A2, I82.B2*, I82.C2*, I82.891, I82.91, Z86.71*	<u>If in last 60 days prior to case:</u> Physical trauma code ² , C00-C96, M67.9*, M80.* , M84.3*, M99.* , O08.2, O22.3*, O22.5*, O87.1, O88.2*, S00-T88, Z08, Z09, Z51.5, Z51.89, Z30.011, Z79.890 <u>If in last 14 days prior to case:</u> Pneumonia code ³ , I50.* , O88.0*, O88.1*, T79.1* <u>If EVER prior to case:</u> D68.5*, D68.6*	Same exclusions as column to the left minus COVID-19
Outcomes for descriptive monitoring only	Exclusions for Prevalence - with lookback period for exclusion	Exclusions – other known causes (in all settings) - with lookback period for exclusion (not including same day unless noted in column to the right)	Exclusions – same day, other known causes (in all settings)
Acute respiratory distress syndrome	n/a	<u>If in last 42 days prior to case:</u> First COVID-19 diagnosis code or COVID-19 positive lab test <u>If in last 14 days prior to case:</u> Sepsis code ¹ Physical trauma code ² J09.* , J10.* , J11.* , J68.* , J69.0, J70.5, J70.8, J70.9, K85.* , T75.1*	Same exclusions as column to the left
Anaphylaxis	n/a	n/a	n/a
Multisystem inflammatory syndrome in children / Multisystem inflammatory syndrome in adults	n/a	n/a	n/a
Narcolepsy and cataplexy	n/a	n/a	n/a

¹ Sepsis codes: A02.1, A20.7, A22.7, A26.7, A32.7, A39.1, A39.2, A39.3, A39.4, A39.89, A39.9, A40.* , A41.* , A42.7, A54.86, B00.7, B37.7, O85, O86.04, R65.2*, R78.81, T81.44*

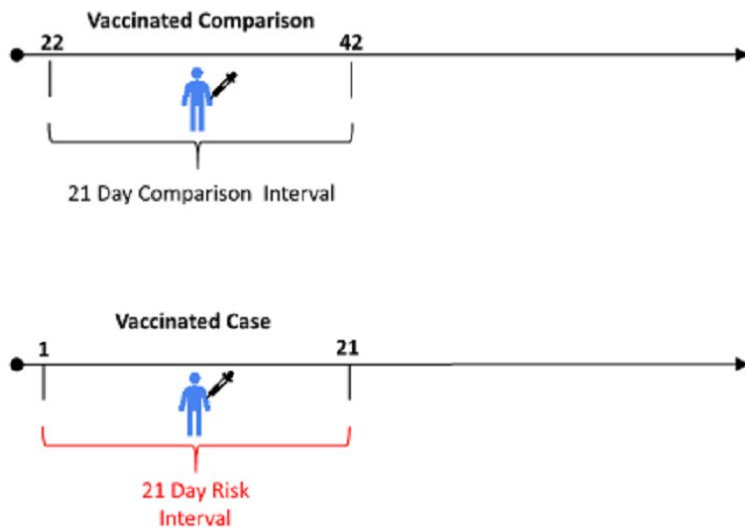
² Physical trauma codes: V00-Y99

³ Pneumonia codes: A22.1, B25.0, A37.01, A37.11, A37.81, A37.91, A48.1, B44.0, B77.81, J12.* , J13, J14, J15.* , J16.* , J17, J18.*

eFigure 1. Illustration of primary analyses using vaccinated concurrent comparators and supplemental analyses using unvaccinated concurrent comparators.

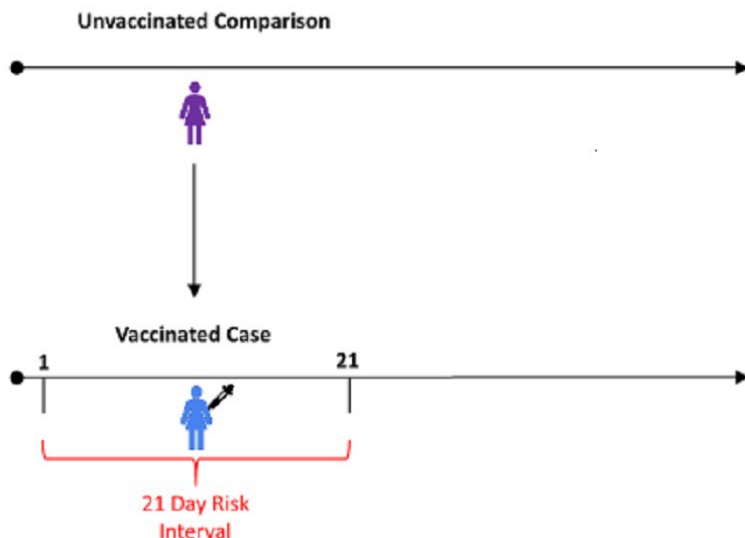
VSD COVID-19 RCA – Vaccinated Comparison

- To have an informative vaccinated case in their risk interval, there must be a vaccinated person in their comparison interval on that same calendar day in the same age, sex, race/ethnicity, site stratum
- There does not have to be a case, just a person who has comparison time from the same stratum



VSD COVID-19 RCA – Unvaccinated Comparison

- To have an informative vaccinated case in their risk interval, there must be an unvaccinated person on that same calendar day in the same age, sex, race/ethnicity, site stratum
- There does not have to be a case, just a person who from the same stratum



Top graph illustrates the primary analyses of the 1-21-day risk interval using vaccinated concurrent comparators. Each week, all the data since the surveillance period began Dec 14, 2020 were analyzed, adjusted for age, sex, race/ethnicity, site and calendar day. Bottom graph illustrates the supplemental analyses using unvaccinated concurrent comparators. Supplemental analyses similarly adjusted for age, sex, race/ethnicity, site and calendar day.

eTable 3. Summary of Signals* during 21-day Risk Interval, from separate Dose 1, Dose 2 and Vaccine Product Analyses.

Outcome	mRNA-1273			BNT162b2			Both mRNA Vaccines		
	<i>Dose 1</i>	<i>Dose 2</i>	<i>Both Doses</i>	<i>Dose 1</i>	<i>Dose 2</i>	<i>Both Doses</i>	<i>Dose 1</i>	<i>Dose 2</i>	<i>Both Doses</i>
Acute disseminated encephalomyelitis	-	-	-	No	-	No	No	-	No
Acute myocardial infarction	No	No	No	No	No	No	No	No	No
Appendicitis	No	No	No	No	No	No	No	No	No
Bell's palsy	No	No	No	No	No	No	No	No	No
Cerebral venous sinus thrombosis	No	No	No	No	No	No	No	No	No
Convulsions / seizures	No	No	No	No	No	No	No	No	No
Disseminated intravascular coagulation	No	No	No	No	No	No	No	No	No
Encephalitis / myelitis / encephalomyelitis	No	No	No	No	No	No	No	No	No
Guillain-Barré syndrome	No	No	No	No	No	No	No	No	No
Immune thrombocytopenia	No	No	No	No	No	No	No	No	No
Kawasaki disease	No	No	No	-	-	-	No	No	No
Myocarditis / pericarditis	No	No	No	No	No	No	No	No	No
Pulmonary embolism	No	No	No	No	No	No	No	No	No
Stroke, hemorrhagic	No	No	No	No	No	No	No	No	No
Stroke, ischemic	No	No	No	No	No	No	No	No	No
Thrombotic thrombocytopenic purpura	No	No	No	No	No	No	No	No	No
Transverse myelitis	No	No	No	No	No	No	No	No	No
Venous thromboembolism	No	No	No	No	No	No	No	No	No

* Yes = statistical signal; No = no statistical signal; - = not estimable

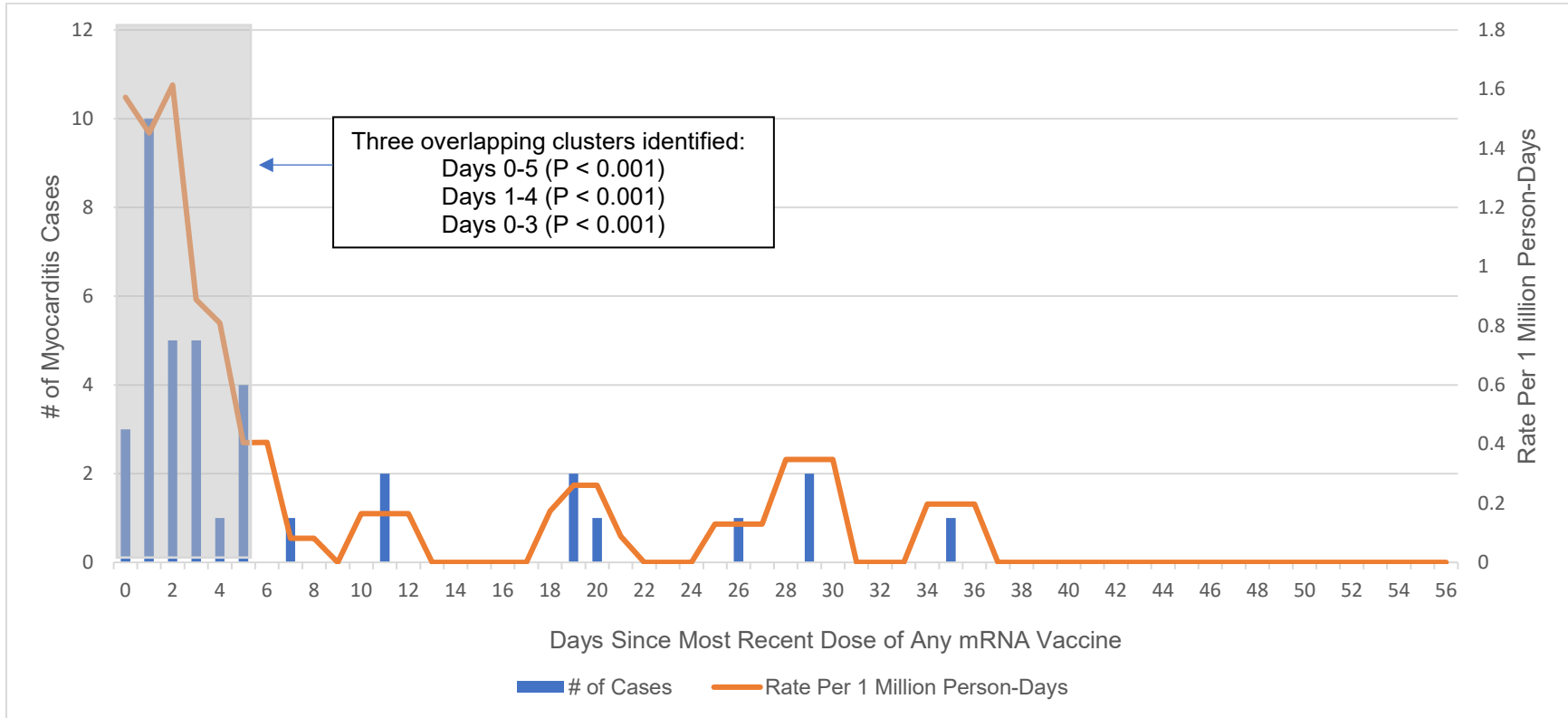
eTable 4. Medical record review of 34 confirmed myocarditis/pericarditis cases 0-21 days after mRNA vaccines among individuals aged 12-39 years, December 14, 2021 - June 19, 2021.

	Confirmed Myocarditis/Pericarditis N=34 (%)
Age, median (range)	24 years (13 – 39 years)
12-15 years	1 (3)
16-19 years	7 (21)
20-24 years	10 (29)
25-29 years	3 (9)
30-34 years	7 (21)
35-39 years	6 (18)
Male sex	29 (85)
Race/Ethnicity	
Hispanic/Latino	7 (21)
White, Non-Hispanic	17 (50)
Black, Non-Hispanic	0 (0)
Asian, Non-Hispanic	5 (15)
Native Hawaiian/Pacific Islander, Non-Hispanic	0 (0)
American Indian/Alaskan Native, Non-Hispanic	0 (0)
Multiple/Other	2 (6)
Unknown	3 (9)
History of COVID-19 infection	3 (9)
History of myocarditis/pericarditis	3 (9)
Time from vaccination to symptom onset, median (range)	2 days (0 – 20 days)
Signs and symptoms	
Chest pain/pressure/discomfort	34 (100)
Dyspnea/Shortness of breath	15 (44)
Palpitations	4 (12)
Pericardial rub	1 (3)
Other (fever, fatigue, chills, numbness, tingling nausea, etc)	20 (59)
Diagnostic testing	
Troponin level obtained	34 (100)
Abnormal troponin Level	28 (82)
ECG obtained	34 (100)
Abnormal ECG	30 (88)
Echocardiogram obtained	30/34 (88)
Abnormal echocardiogram	15/30 (50)
Cardiac MRI obtained	9/34 (26)
Abnormal cardiac MRI	8/9 (89)
Diagnosis after adjudication	
Acute myocarditis	7 (21)
Acute pericarditis	6 (18)
Myopericarditis	21 (62)
Highest level of care	
Outpatient	1 (3)
Emergency department	5 (14)

	Confirmed Myocarditis/Pericarditis N=34 (%)
Admitted to hospital	26 (76)
Admitted to ICU	2 (6)
Length of hospital stay, median (range)	1 day (0 – 13 days)
Status at time of medical record review	
Discharged to home	34 (100)
Follow-up visit ¹	31 (91)

¹Nearly all follow-up notes indicated resolution of symptoms time of follow-up visit. Of those that had follow-up ECG/echo or lab testing, most had returned to normal or baseline. Most patients were noted to be tapering off some medications (nonsteroidal anti-inflammatory drug, prednisone, etc). Follow-up Notes also indicated use of colchicine maintenance and recommendations for reduced activity for 3-6 months.

eFigure 2. Clustering of medical record confirmed myocarditis/pericarditis cases by days since most recent dose of any mRNA vaccine among individuals 12-39 years of age.



Blue bars denote number of cases of medical-record confirmed myocarditis/pericarditis during days 0-56 after either dose of an mRNA vaccine. Orange line represents the rate of confirmed myocarditis/pericarditis per 1 million person-days. The rate is a moving 3 day mean. Clusters were identified using Kulldorff's scan statistic ¹⁷.

eTable 5. Confirmed myocarditis/pericarditis following mRNA vaccines compared with vaccinated comparators among individuals aged 12 – 39 years by vaccine type and dose, December 14, 2020-June 19, 2021.

Vaccine Type	Risk Interval	Dose	Events in Risk Interval	Events in Comparison Interval ¹	Adjusted Rate Ratio (95% Confidence Interval) ²	2-sided P-value
BNT162b2	0-21	Both doses	14	4	1.45 (0.43-5.79)	0.59
		Dose 1 ³	4	4	2.01 (0.37-10.89)	0.41
		Dose 2	9	4	1.61 (0.45-6.66)	0.49
	0-7	Both doses	10	3	3.16 (0.66-19.29)	0.16
		Dose1 ³	1	3	2.17 (0.06-29.95)	0.60
		Dose 2	8	3	4.58 (1.00-26.89)	0.05
mRNA-1273	0-21	Both doses	20	0	NE (3.24-NE)	<0.001
		Dose 1	5	0	NE (0.78-NE)	0.09
		Dose 2	15	0	NE (3.84-NE)	<0.001
	0-7	Both doses	19	0	NE (8.79-NE)	<0.001
		Dose 1	4	0	NE (1.93-NE)	0.01
		Dose 2	15	0	NE (9.34-NE)	<0.001

¹ Comparison interval for all analyses was 22-42 days after vaccination.

² Overall estimate from Poisson regression stratified by site, 5-year age group, sex, race/ethnicity, and calendar date.

³ One case in both risk intervals of days 0-21 and 0-7 after Dose 2 did not contribute to these Dose 2 analyses.

**eTable 6. Unvaccinated concurrent comparator analyses, December 14, 2020-
June 26, 2021.**

Outcome Event	Informative Events ³		Adjusted Rate Ratio ⁴	Weekly Analysis ^{1,2}	
	Events in Risk Interval	Events in Unvaccinated		95% Confidence Interval	2-Sided P-Value
Kawasaki disease	0	12	0.00	0.00 - 2.81	0.23
Disseminated intravascular coagulation	30	173	0.61	0.39 - 0.93	0.02
Thrombosis with thrombocytopenia syndrome	74	334	0.67	0.50 - 0.88	0.004
Guillain-Barré syndrome	16	98	0.73	0.39 - 1.29	0.29
Stroke, hemorrhagic	241	947	0.74	0.63 - 0.86	<0.001
Pulmonary embolism	504	2103	0.75	0.67 - 0.83	<0.001
Thrombotic thrombocytopenic purpura	6	43	0.81	0.30 - 1.95	0.69
Acute myocardial infarction	618	2216	0.82	0.74 - 0.91	<0.001
Convulsion / seizures	285	1712	0.86	0.74 - 0.98	0.03
Stroke, ischemic	1065	3529	0.91	0.84 - 0.99	0.02
Immune thrombocytopenia	48	191	0.92	0.63 - 1.31	0.64
Appendicitis	779	4289	1.06	0.97 - 1.15	0.21
Bell's palsy	543	2379	1.06	0.95 - 1.17	0.31
Venous thromboembolism	629	2191	1.08	0.97 - 1.19	0.15
Cerebral venous sinus thrombosis	18	53	1.10	0.58 - 2.03	0.75
Encephalitis / myelitis / encephalomyelitis	17	59	1.11	0.57 - 2.11	0.75
Myocarditis / pericarditis	87	293	1.39	1.05 - 1.82	0.02
Transverse myelitis	10	23	1.79	0.75 - 4.12	0.19
Acute disseminated encephalomyelitis	5	7	2.65	0.61 - 10.92	0.19

¹Weekly analyses include all data to date, but confidence intervals and P-values do not account for the multiple chances for a false positive signal during surveillance.

²Per protocol, sequential analyses for a signal are only conducted with vaccinated comparators and no sequential testing is conducted using unvaccinated comparator analyses. Rather, these analyses are done routinely to supplement our sequential analyses. These analyses are particularly useful early in surveillance before sufficient vaccinated concurrent comparators is available.

³Events in each stratum were only informative on a day when there was at least one person in the risk interval, at least one unvaccinated person, and at least one outcome among either the vaccinated or unvaccinated. Therefore, the number of risk interval events in this table may not be the same as the number of risk interval events in vaccinated concurrent comparator analyses (Table 3).

⁴Overall estimate from Poisson regression stratified by site, 5-year age group, sex, race/ethnicity, and calendar date.