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Short communication

Acute myocarditis following a third dose of COVID-19 mRNA vaccination in adults

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ABSTRACT

Introduction: Myocarditis has been reported following the second dose of COVID-19 mRNA vaccination. Whether administration of additional doses of COVID-19 vaccines further increases the risk of myocarditis is unknown.
Methods: We included individuals who received one to three doses of BNT162b2 or mRNA-1273 mRNA vaccine between 12/14/2020 and 2/18/2022. Myocarditis within 21 days of vaccine administration was identified using electronic medical records. Incidence rate ratios were calculated by comparing the observed incidence with the expected incidence from the same population during a 365-day baseline period.
Results: Of 3,076,660 KPSC members who received at least one dose of COVID-19 mRNA vaccines, 2,916,739 (94.5%) received at least two doses, and 1,146,254 (47.0%) received three doses. The incidence rate ratio for myocarditis was 0.86 (95% CI 0.31–1.93) for the first dose, 4.22 (95% CI 2.63–6.53) for the second dose, and 2.61 (1.13–5.29) for the third dose. Most myocarditis cases following the second and third dose occurred within seven days of vaccination.
Conclusion: Myocarditis was a rare event observed after the second or third dose of vaccination. Most cases presented within seven days of vaccination. The incidence of myocarditis following the third dose was not significantly higher than that observed after the second dose.

1. Introduction

The COVID-19 mRNA vaccines are effective in reducing COVID-19-related severe disease and death [1]. Waning vaccine effectiveness has prompted the recommendation to administer additional (booster) doses. Third-dose vaccination is associated with improved protection [2]. Recent studies suggest some individuals benefit from receiving a fourth dose [3]. With additional doses of COVID-19 mRNA vaccines being recommended, it is essential to monitor its safety. Myocarditis has been reported following COVID-19 mRNA vaccination [4–7]. Studies showed the rates of myocarditis to be highest after the second dose. Whether administration of a third vaccination dose further increases the risk of myocarditis is not known.

This study aimed to evaluate whether a third dose of COVID-19 mRNA vaccine was associated with an increased risk of myocarditis.

2. Methods

We included Kaiser Permanente Southern California (KPSC) members aged ≥18 years who received one to three doses of the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) mRNA vaccine between 12/14/2020 and 2/18/2022. KPSC is an integrated healthcare delivery system with more than 4 million members in the United States. Members enroll through the Kaiser Foundation Health Plan for comprehensive insurance including prescription coverage. Comprehensive medical information of KPSC members is prospectively captured electronically. This includes demographics, administrative, pharmacy, laboratory, and healthcare utilization data from both ambulatory and inpatient encounters. The present study was approved by the KPSC Institutional Review Board. A waiver of informed consent was obtained due to the study's observational nature.

We used *International Classification of Diseases (ICD), 10th Revision* codes to identify individuals hospitalized for myocarditis within 21 days

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Table 1
Baseline characteristics.

	First dose (n = 3,076,660)	Second dose (n = 2,916,739)	Third dose (n = 1,446,254)
Age group, year			
18–39	1,171,382 (38.1)	1,093,029 (37.5)	372,622 (25.8)
40–64	1,270,414 (41.3)	1,205,345 (41.3)	626,221 (43.3)
65–80	523,502 (17.0)	510,168 (17.5)	372,504 (25.7)
>80	111,362 (3.6)	108,197 (3.7)	74,907 (5.2)
Gender			
Male	1,426,331 (46.4)	1,343,771 (46.1)	641,073 (44.3)
Female	1,649,909 (53.6)	1,572,593 (53.9)	805,050 (55.7)
Other	420 (0.01)	375 (0.01)	131 (0.01)
Race / Ethnicity			
White	912,348 (29.7)	869,085 (29.8)	491,720 (34.0)
Black	218,051 (7.1)	205,877 (7.1)	101,882 (7.0)
Hispanic	1,194,059 (38.8)	1,132,149 (38.8)	496,420 (34.3)
Asian	409,385 (13.3)	393,616 (13.5)	239,961 (16.6)
Other	342,817 (11.1)	316,012 (10.8)	116,271 (8.0)
Medical comorbidities			
Hypertension	515,015 (16.7)	497,828 (17.1)	333,763 (23.1)
Diabetes	257,715 (8.4)	248,946 (8.5)	166,900 (11.5)
Obesity	296,401 (9.6)	282,867 (9.7)	159,558 (11.0)
Heart failure	54,571 (1.8)	52,363 (1.8)	34,091 (2.4)
Renal failure	137,146 (4.5)	133,079 (4.6)	94,009 (6.5)
Liver disease	75,429 (2.5)	72,004 (2.5)	44,219 (3.1)
Pulmonary disease	215,606 (7.0)	206,790 (7.1)	126,793 (8.8)
Hypothyroidism	143,614 (4.7)	138,642 (4.8)	91,232 (6.3)

of vaccine administration. All cases were independently reviewed and adjudicated by two cardiologists. The following criteria were used to confirm myocarditis: 1) symptoms consistent with myocarditis, 2) elevated troponin I level above the upper limit of normal, 3) electrocardiogram findings consistent with myocarditis, new wall motion abnormalities on cardiac imaging, or cardiac magnetic resonance imaging findings consistent with myocarditis, and 4) presentation not attributed to other causes.

The observed incidence of myocarditis following vaccination after each dose was compared with the expected incidence using data obtained from the same population during a 365-day baseline period, two years before the vaccination date. Incidence rate ratios (IRR) and 95% confidence intervals (CIs) were calculated. A 2-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using STATA/MP 17 (Stata-Corp, College Station, TX).

2.1. Findings

Of 3,076,660 KPSC members who received at least one dose of COVID-19 mRNA vaccines, 2,916,739 (94.5%) received at least two doses, and 1,146,254 (47.0%) received three doses. Table 1 shows the baseline characteristics. Median age was 47 years (IQR 32, 62), 53.6% were women, 29.7% White, 7.1% Black, 38.8% Hispanic, and 13.3% were Asian. 1,673,672 (54.5%) received at least one dose of BNT162b2, and 1,490,941 (48.5%) received at least one dose of mRNA-1273.

Within 21 days after vaccination, there were 6 cases of myocarditis following the first dose, 26 cases following the second dose, and 9 cases following the third dose (Table 2). The incidence rate ratio for myocarditis was 0.86 (95% CI 0.31–1.93) for the first dose, 4.22 (95% CI 2.63–6.53) for the second dose, and 2.61 (1.13–5.29) for the third dose (Fig. S1). Most myocarditis cases following the second and third dose occurred within seven days of vaccination. The increased incidence was observed primarily among patients younger than 40 years (Supplementary Table S1).

Of the nine cases of myocarditis following the third dose, eight were men, and five were between 18 and 40 years of age. Median follow-up was 224 days (IQR 167, 336). During the follow-up period, one patient died from events unrelated to myocarditis (cancer). All other patients recovered with resolution of symptoms.

Table 2
Incidence rate ratios of myocarditis in vaccinated individuals compared to control groups.

	Myocarditis cases, no.	Follow-up time, person-days	Incidence rate ratio (95% CI)	P value
First dose (n = 3,076,660)				
Day 1–7[a]	2	21,536,620	0.86 (0.10–3.18)	0.92
Day 8–14[b]	2	21,536,620	0.86 (0.10–3.18)	0.92
Day 15–21[c]	2	21,536,620	0.86 (0.10–3.18)	0.92
Day 1–21[d]	6	64,609,860	0.86 (0.31–1.93)	0.76
Baseline comparison interval[e]	121	1,122,980,900	reference	
Second dose (n = 2,916,739)				
Day 1–7[a]	21	20,417,173	10.23 (6.09–16.4)	<0.0001
Day 8–14[b]	3	20,417,173	1.46 (0.30–4.39)	0.5
Day 15–21[c]	2	20,417,173	0.97 (0.11–3.61)	0.95
Day 1–21[d]	26	61,251,519	4.22 (2.63–6.53)	<0.0001
Baseline comparison interval[e]	107	1,064,609,735	reference	
Third dose (n = 1,446,254)				
Day 1–7[a]	7	10,123,778	6.08 (2.34–13.3)	0.0003
Day 8–14[b]	2	10,123,778	1.74 (0.21–6.56)	0.44
Day 15–21[c]	0	10,123,778	0	0.32
Day 1–21[d]	9	30,371,334	2.61 (1.13–5.29)	0.01
Baseline comparison interval[e]	60	527,882,710	reference	

[a] Risk interval: day 1 to day 7 after vaccination.
[b] Risk interval: day 8 to day 14 after vaccination.
[c] Risk interval: day 15 to day 21 after vaccination.
[d] Risk interval: day 1 to day 21 after vaccination.
[e] Risk interval: 2 years prior to vaccination date until 1 year prior to vaccination date (i.e., a 365-day risk interval).

3. Discussion

In this population-based cohort study of 3,076,660 individuals who received one, two, or three doses of COVID-19 mRNA vaccines, myocarditis was a rare event observed after the second or third dose of vaccination. Most cases presented within seven days of vaccination. The incidence of myocarditis following the third dose did not appear to be significantly higher than that observed after the second dose.

This vaccinated cohort is unique in its racial and ethnic diversity and in receiving care at community hospitals with treatment reflective of real-world practice. Several study limitations should be acknowledged. First, only myocarditis cases that required hospitalization were included, and patients who did not seek care could not be captured. Second, myocarditis was managed at the discretion of the treating clinicians; there was a lack of uniform testing, and myocardial biopsy was not performed. Third, the follow-up period was short, and potential long-term risks of vaccination could have been missed. Fourth, despite drawing from more than 3 million vaccinated individuals, the number of

myocarditis cases was still small, limiting the precision of the point estimates. Fifth, myocarditis cases were identified using ICD codes, so cases not diagnosed as myocarditis by the primary clinician would have been missed. Finally, no causal relationship between COVID-19 mRNA vaccination and post-vaccination myocarditis can be established, given the observational nature of this study.

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CRediT authorship contribution statement

Anthony Simone: Conceptualization, Data curation, Writing – original draft. **John Herald:** Conceptualization, Data curation, Writing – review & editing. **Aiyu Chen:** Data curation, Investigation, Methodology, Formal analysis, Validation. **Rohith Nayak:** Conceptualization, Investigation, Writing – review & editing. **Yuh-Jer Albert Shen:** Conceptualization, Data curation, Writing – review & editing. **Ming-Sum Lee:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.07.031.

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