Risk of myocarditis after two doses of COVID-19 mRNA vaccines in the US, 2020-2022: a self-controlled case series study

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Abstract

Background: Myocarditis is considered as a potential safety concern after COVID-19 mRNA vaccination; however, limited studies have quantified its risk in the United States population. We aimed to evaluate the risk of myocarditis after BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccination.

Methods: We performed a self-controlled case series analysis of myocarditis reports to the US Vaccine Adverse Event Reporting System (VAERS) that occurred after the COVID-19 mRNA vaccinations from December 24, 2020 to January 28, 2022. We reported the relative incidence (RI) of myocarditis for various periods after COVID-19 mRNA vaccinations as well as the ratio of the RI after the second dose to the RI after the first dose.

Results: 1091 VAERS presumptive myocarditis reports after COVID-19 mRNA vaccinations (median age, 23 years; IQR, 17-36 years; 718 individuals [65.8%] < 30 years; 831 men [76.2%]) were identified. The median time to myocarditis onset was 3 days (IQR, 1-6 days). 824 (75.5%) reports were serious, with 11 (1%) death. We found an increased risk during the 1- to 3-day period after the second dose for both vaccines. The RI was 5.38 (95% CI, 2.20-13.26) for the Pfizer-BioNTech vaccine and 6.12 (95% CI, 2.04-18.97) for the Moderna vaccine. No significant increase was found in other risk periods. This observation was verified by dividing the RI after the second dose by the RI after the first dose. For the Pfizer-BioNTech vaccine, the RI for the period 1 through 3 days after the second dose was 6.33 (95% CI, 3.18-12.61) times as high as that for the same period after the first dose; for the Moderna vaccine, the ratio of RIs was 4.24 (95% CI, 1.94-9.25) for the same risk period. No significant RI differences in other risk periods were identified. A similar increased risk was also detected in people aged below 30 or in males.

Conclusions: We found an increased risk of myocarditis for period 1 through 3 days after the second dose of COVID-19 mRNA vaccines, especially in male and young adults. Our findings should be interpreted with the limitations of VAERS with considerations with the benefits of receiving COVID-19 mRNA vaccination.

1. Background

The coronavirus disease 19 (COVID-19) pandemic has motivated the development of vaccines at an exceptional speed. Many COVID-19 vaccines, such as BNT162b2 (Pfizer-BioNTech) vaccine and mRNA-1273 (Moderna) vaccine, are authorized in many countries. Their efficacy is supported by rich evidence from clinical trials and real-world effectiveness studies.[1 2] None of these trials reported severe safety concerns, and only a low incidence rate of severe adverse events (AEs) was observed.

However, randomized clinical trials may have insufficient power to detect the signal of many rare AEs. These signals are only observable after vaccinating sufficient people. Furthermore, scientists have limited experience with the novel mRNA platforms.[3] Therefore, there is an urgent need to measure the COVID-19 mRNA vaccines' risk of AEs.

Currently, there is emerging evidence on the potential association between myocarditis and COVID-19 vaccination.[4–8] However, this conclusion remains elucidated as a recent study showed that this association is insignificant.[9] On the other hand, some existing studies have limited sample diversity or were performed in the early phase of the vaccination campaigns. Today, as the COVID-19 vaccination process has expanded across the US population, there is an urgent need to examine the risk of myocarditis after COVID-19 mRNA vaccination.

Based on evidence from VAERS, we aim to (1) provide a more recent estimate of the risk of myocarditis after Pfizer-BioNTech or Moderna vaccination by refining the signal from the Vaccine Adverse Event Reporting System (VAERS) and (2) study whether the emerging reports from VAERS imply an association between COVID-19 mRNA vaccination and myocarditis. Our study demonstrated the VAERS's ability to detect the signal of rare AEs and could be a cornerstone of a following pharmacoepidemiologic study.

2. Methods

2.1 Data Source

The VAERS database, organized by the Centers for Disease Control and Prevention, is a well-known pharmacovigilance system that receives and analyzes spontaneous (passive) AE reports from vaccinated persons, medical providers, and vaccine manufacturers. As a spontaneous reporting system (SRS), VAERS is powerful in detecting the early signal of any vaccine-related AEs in post-vaccination surveillance.[10] This study used the deidentified spontaneous reports related to COVID-19 vaccination in VAERS from December 15, 2020 to January 28, 2022.[11] This study is based on publicly available data; no institutional review is needed.

2.2 Study Design and Populations

We used a modified Self-controlled Case Series (SCCS) method to analyze the spontaneous reports of AEs after the COVID-19 vaccination. The original SCCS method is a case-only method that compares the risk of developing events of interest in each risk period with the risk of events from the reference period. Each case is served as his or her control; thus, only case series are involved, and time-invariant confounders are automatically controlled. Although the standard SCCS method is not applicable in analyzing spontaneous reporting data, a modified version of the SCCS method was proposed to address this problem.[12 13] This approach was well utilized in investigating the risk of intussusception after RV1 (Rotarix, GlaxoSmithKline Biologicals) or pentavalent RV5 (RotaTeq, Sanofi-Pasteur MSD) vaccination.[12–14] The technical detail of this modified SCCS model was demonstrated elsewhere.[13]

Two approaches were made in this study. The first approach compared the risk of developing myocarditis in each risk period to risk in the reference period for each dose, and the second approach compared the risk after the first and second doses. Our observation period was from vaccination date (day 0) to the end of the recommended dose interval (i.e., twenty-one days after Pfizer-BioNTech vaccination and twenty-eight days after Moderna vaccination). The observation period is designed to prevent any overlap

between risk periods after each vaccine dose. The risks were estimated for the periods 0 day, 1 through 3 days, and 4 through 14 days after vaccination; day 15 through the end of the recommended dose interval constituted the reference period. Figure 1 illustrates our SCCS study design.

2.3 Exposure

We included all cases in the VAERS who received the first or second dose of Pfizer-BioNTech or Moderna vaccine from December 14, 2020 (the date when vaccinations against COVID-19 in the US began) to January 28, 2022. During our study period, persons aged 18 or older are approved to receive the Moderna vaccination, and persons aged 12 or older are approved to use the Pfizer-BioNTech vaccine. Although the US Food and Drug Administration authorized emergency use of the Pfizer-BioNTech vaccine on October 29, 2021 for persons aged 5 through 11 years old, these reports are excluded as only 9 cases were reported till the study period ends.

2.4 Study Outcome

The report identification process involves two steps. In the first step, we extracted myocarditis reports from VAERS according to Medical Dictionary for Regulatory Activities preferred terms specified by Oster et al.[4] Reports containing any of these terms were identified as potential myocarditis cases. We extracted sex, date of vaccination, date of developing the AE, the time lag between the most recent dose and AE onset, and age at the vaccination time for each case. We only included reports with vaccination preceding the onset of myocarditis. Reports with missing or unknown vaccine manufacturer, vaccine dose series, and date of vaccination were removed. Duplicated reports were combined.

Clinicians were involved in the second step. The clinical review process was based on the protocol proposed by Oster et al.[4] Acute myocardial infarction or only pericarditis cases were excluded. Cases were retained as probable or confirmed acute myocarditis if they satisfied the following requirements: the presence of at least one new or worsening of specified clinical symptoms (e.g., chest pain, chest discomfort, palpitations, dyspnea, syncope, cardiac shock, or sudden death) plus any combination of abnormal finding (e.g., troponin level exceeds the upper limit of normal, abnormal electrocardiogram or rhythm consistent with myocarditis, abnormal cardiac function or wall motion abnormalities on echocardiogram, Magnetic resonance imaging findings consistent with myocarditis or histopathologic confirmation of myocarditis), or a physician’s diagnosis or impression of acute myocarditis. Reports with clinicians’ statements that the patient did not have myocarditis were removed. Finally, we did not conduct medical assessments using the Brighton Collaboration criteria because of the limited medical record information.

Table 1 summarizes the demographic and clinical characteristics of the probable or confirmed myocarditis cases. The date difference between vaccination and onset of myocarditis cases was noted. The statistical analysis was only performed on reports with known date differences. Furthermore, we excluded reports with time to onset of myocarditis exceeding the recommended dose interval.

Table 1
Demographics of myocarditis reports after COVID-19 mRNA vaccination, as of January 28, 2022

	Myocarditis (N = 1091)			
	Moderna (%)		Pfizer-BioNTech (%)	
Characteristics	After dose 1	After dose 2	After dose 1	After dose 2
Reported sex				
No.	129	238	142	582
Male	75 (58.1)	185 (77.7)	94 (66.2)	477 (82)
Female	52 (40.3)	51 (21.4)	47 (33.1)	103 (17.7)
Unknown	2 (1.6)	2 (0.8)	1 (0.7)	2 (0.3)
Age, y				
Median (IQR)	36.5 (25.75-50)	27 (22–39)	24 (16–38)	19 (15.5–28.5)
12–17	0 (0)	0 (0)	49 (34.5)	252 (43.3)
18–24	28 (21.7)	94 (39.5)	26 (18.3)	141 (24.2)
25–29	14 (10.9)	40 (16.8)	10 (7.0)	45 (7.7)
30–34	15 (11.6)	28 (11.8)	15 (10.6)	30 (5.2)
35–39	15 (11.6)	16 (6.7)	6 (4.2)	30 (5.2)
40–44	11 (8.5)	14 (10.9)	6 (4.2)	22 (3.8)
≥ 45	41 (31.8)	45 (18.9)	29 (20.4)	55 (9.5)
Unknown	5 (3.9)	1 (0.4)	1 (0.7)	7 (1.2)
Time to myocarditis onset, d				
Median (IQR)	5 (1–21)	3 (1–4)	4 (1–12)	2 (1–3)
≤ 28 d after Moderna vaccination	104 (80.6)	211 (88.7)	NA	NA
≤ 21 d after Pfizer-BioNTech vaccination	NA	NA	129 (90.8)	522 (89.7)
Unknown	5 (3.9)	3 (1.3)	3 (2.1)	7 (1.2)
Seriousness [a]				
Hospitalized	81 (62.8)	176 (73.9)	95 (66.9)	472 (81.1)
Life-threatening condition	24 (18.6)	44 (18.5)	22 (15.5)	99 (17)

	Myocarditis (N = 1091)			
Permanent disability	5 (3.9)	9 (3.8)	3 (2.1)	17 (2.9)
Died	2 (1.6)	3 (1.3)	4 (2.8)	2 (0.3)
Unknown	44 (34.1)	54 (22.7)	42 (29.6)	101 (17.4)
Recovered				
Yes	38 (29.5)	77 (32.4)	33 (23.2)	205 (35.2)
No	49 (38.0)	76 (31.9)	73 (51.4)	214 (36.8)
Unknown	42 (32.6)	85 (35.7)	36 (25.4)	163 (28)

[a] These conditions are determined by reporter's statement and are not mutually exclusive.

2.5 Statistical Analysis

The relative incidences (RIs) and 95% CI of myocarditis were calculated using a modified version of the SCCS method, which is designed to account for the underreporting and time-varying reporting since vaccination.[12 13] The RIs are the incidence rate of myocarditis in the risk period relative to the reference period after each dose. The RIs are estimated via two approaches. The first parametric approach reports the RIs after each dose by explicitly modeling the reporting process via an exponentially decreasing reporting probability. An RI greater than 1 represents an increased risk in the risk period compared with the reference period after each dose. The second non-parametric approach compares the ratio of the RIs after the second dose to the RI after the first dose. If the ratio of RIs is greater than 1 for a certain risk period, then the RI in that risk period after the second dose has increased compared with the RI in the same risk period after the first dose.

Our observation period is from day 0 (vaccination day) to the end of recommended dose interval. The risk periods are 0, 1–3, 4–14 days after each dose of vaccination, and the remaining period is the reference period. Day 0 was defined as a separate risk period to avoid reporting bias. Even though we get a significant result, we will generally not consider it a potential safety signal.

We further conducted subgroup analyses within strata defined by age and sex. SCCS analysis was only performed in males as the sample size for females and unknown groups is insufficient. Cases were also classified into two age groups (> 30 years and < = 30 years). An observed-to-expected (OE) analysis was performed in people aged 12–18 who received Pfizer-BioNTech vaccination, using the publicly available vaccine administration data[15] and published background incidence rate.[8 16 17], for a 28-day risk period. Only reports within this period were involved in the analysis. The OE analysis will raise a safety concern if the observed number of cases in VAERS exceeds the expected number of cases computed from the published background incidence rate.

A sensitivity analysis was performed to ensure the robustness of our results. We assumed 80% of the reports can meet the Brighton Collaboration criteria for AE of interest. All calculations were performed with the R software, version 4.0.3 (www.r-project.org).

3. Results

3.1 Demographic Characteristics and Clinical Properties of the Study Targets

The demographic characteristics of the reports are presented in Table 1. From December 24, 2020 to January 28, 2022, VAERS received 1934 reports of myocarditis after at least one dose of Pfizer-BioNTech or Moderna vaccine. After the two-step data cleaning process, 1091 reports were retained as probable or presumptive myocarditis cases. Of these reports, 367 reports were related to the Moderna vaccine and 724 to the Pfizer-BioNTech vaccine. A male predominance was observed for each dose of both vaccines. For example, males comprised 82% of reports after receiving the second dose of the Pfizer-BioNTech vaccine. The young population was the primary source of the myocarditis reports. For Pfizer-BioNTech vaccine, the median age was 19 (IQR, 15.5–28.5) years old for the second dose and 24 (IQR, 16–38) years old for the first dose. With regard to the Moderna vaccine, the median age was 28 (IQR, 22–41) years old for the second dose of Moderna vaccination and 36.5 (IQR, 25.75-50) years old for the first dose. Most of the reports were made within the first week after the vaccination. Furthermore, over 85% (359/419, 651/724) of reports were made within the recommended dose time interval for each COVID-19 mRNA vaccine.

The median time to onset of myocarditis was 3 days (IQR, 1–6 days). Among the 1091 myocarditis reports, 75.5% (824/1091) of myocarditis reports were serious, 17.3% (189/1091) were reported under life-threatening conditions, 3.3% (36/1091) were permanently disabled, and 1% (11/1091) were dead. Finally, most reports (85.8% for Moderna and 89.9% for Pfizer-BioNTech) encountered myocarditis within the recommended dose time interval; therefore, excluding reports with myocarditis onset time interval longer than recommended dose time interval will not affect the result much.

3.2 RIs from the Self-Controlled Case Series Analysis

A safety concern was found after the second dose of Pfizer-BioNTech or Moderna vaccination. The risk of myocarditis 1–3 days after the second dose of the Pfizer-BioNTech vaccination was increased, with an RI of 5.38 (95% CI, 2.20-13.26) compared to the risk in the reference period (i.e., 15–21 days after vaccination). On the other hand, the RI in the same risk period after the second dose of the Moderna vaccine was increased by 6.12-fold (95% CI, 2.04–18.97) compared to the risk in the reference period (i.e., 15–28 days after vaccination). No significant increase was found in other risk periods for both vaccines. The ratio of RIs between the two doses showed that the risk after the second dose was significantly higher than the risk after the first dose. The RI for the period of 1 through 3 days after the second dose of the Pfizer-BioNTech vaccine was 6.33 (95% CI, 1.94–9.25) times higher for the same risk period after the

first dose and 4.24 (95% CI, 1.94–9.25) for Moderna vaccine (Table 2). We do not find any significant RI difference in other risk periods for Moderna and Pfizer-BioNTech vaccines. Additionally, a sensitivity analysis which assumed that 80% of reports that could meet the Brighton Collaboration Criteria of myocarditis still returned an elevated risk on days 1–3 **(Additional file 1: Table S1)**.

Table 2
Ratio of relative incidences and relative incidence of myocarditis after two doses of COVID-19 vaccination a

		No. of Events		RI after dose 1 (95% CI)	RI after dose 2 (95% CI)	Ratio of RIs (95% CI)[b]
		After dose 1	After dose 2			
mRNA-1273 vaccine						
	No. of days after vaccination, d					
	0[c]	15	16	1.39 (0.38–5.07)	1.68 (0.46–6.18)	1.21 (0.45, 3.25)
	1–3	38	142	1.44 (0.47–4.55)	6.12 (2.04–18.97)	4.24 (1.94, 9.25)
	4–14	34	38	0.70 (0.30–1.70)	0.89 (0.37–2.18)	1.27 (0.55, 2.92)
	15–28	13	12	1 [Reference]	1 [Reference]	1 [Reference]
BNT162b2 vaccine						
	No. of days after vaccination, d					
	0[c]	15	48	0.59 (0.19–1.81)	1.56 (0.56–4.32)	2.62 (1.12, 6.13)
	1–3	50	387	0.85 (0.33–2.22)	5.38 (2.20-13.26)	6.33 (3.18, 12.61)
	4–14	46	65	0.49 (0.23–1.02)	0.56 (0.28–1.13)	1.16 (0.56, 2.4)
	15–21	18	16	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: CI, confidence interval; RI, relative incidence

[a] Of the 1091 myocarditis reports, our analysis excluded (i) reports whose time to symptom onset are unknown or exceed the recommended dose interval (28 days for mRNA-1273 vaccine and 21 days for BNT162b2 vaccine) to ensure reports were related to a single dose, (ii) reports with unknown dose series, (iii) reports with unknown age, younger than 12 years or 18 years when receiving the BNT162b2 vaccine or mRNA-1273 vaccine respectively, and (iv) duplicated reports. The final analysis included 953 reports.

[b] The ratios are estimated by dividing the relative incidences after dose 2 by the relative incidences after dose 1.

	No. of Events		RI after dose 1 (95% CI)	RI after dose 2 (95% CI)	Ratio of RIs (95% CI)[b]
	After dose 1	After dose 2			
[c] Zero refers to the day of vaccination.					

A significantly increased risk was observed for the period 1 through 3 days after the second dose of both COVID-19 mRNA vaccines in males (Table 3). After the second dose, the myocarditis risk for males was 9.01-fold higher (95% CI, 2.30-37.35) in the 1–3 days after Moderna vaccination and 4.33-fold higher (95% CI, 1.56–12.09) in the 1–3 days after Pfizer-BioNTech vaccination. No significant increased risk was detected after the first dose. Such observation can be verified by comparing males' myocarditis risk between doses. The RI of developing myocarditis on days 1–3 after the second dose of Moderna vaccine was increased 8.85 (95% CI, 3.39, 23.12) times compared with the same period after the first dose; for males vaccinated by Pfizer-BioNTech, this ratio of RIs turns to 5.82 (95% CI, 2.62–12.93). We did not observe any significant RI differences in other risk periods.

Table 3
Ratio of relative incidences and relative incidence of myocarditis after two doses of COVID-19 vaccination, stratified by reported gender a

		Events		RI after dose 1 (95% CI)	RI after dose 2 (95% CI)	Ratio of RIs (95% CI)[b]
		After dose 1	After dose 2			
Female						
mRNA-1273 vaccine						
	No. of days after vaccination, d					
	0[c]	10	4	Sample size is not enough		
	1–3	12	23			
	4–14	18	8			
	15–28	2	5			
BNT162b2 vaccine						
	No. of days after vaccination, d					
	0[c]	6	9	Sample size is not enough		
	1–3	15	55			
	4–14	16	17			
	15–21	6	2			
Male						
mRNA-1273 vaccine						
	No. of days after vaccination, d					
	0[c]	4	12	0.39 (0.07–2.14)	2.22 (0.46–11.15)	5.62 (1.36, 23.27)
	1–3	25	118	1.02 (0.27-4.00)	9.01 (2.30-37.35)	8.85 (3.39, 23.12)

		Events		RI after dose 1 (95% CI)	RI after dose 2 (95% CI)	Ratio of RIs (95% CI)[b]
		After dose 1	After dose 2			
	4–14	16	29	0.36 (0.12–1.04)	1.23 (0.41–3.86)	3.4 (1.19, 9.74)
	15–28	11	7	1 [Reference]	1 [Reference]	1 [Reference]
BNT162b2 vaccine						
	No. of days after vaccination, d					
	0[c]	9	39	0.45 (0.12–1.72)	1.17 (0.37–3.75)	2.6 (0.94, 7.2)
	1–3	34	330	0.74 (0.24–2.33)	4.33 (1.56–12.09)	5.82 (2.62, 12.93)
	4–14	30	48	0.43 (0.18–1.06)	0.42 (0.19–0.91)	0.96 (0.41, 2.24)
	15–21	12	14	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: CI, confidence interval; RI, relative incidence

[a] Seven cases that reported unknown or missing sex are excluded.

[b] The ratios are estimated by dividing the relative incidences after dose 2 by the relative incidences after dose 1.

[c] Zero refers to the day of vaccination

While we did not find any safety signal in people older than 30, an elevated risk after the second dose was identified for people aged below 30 (Table 4). Specifically, for young people vaccinated with Moderna, we found an elevated risk of myocarditis 1–3 days after the second dose, with an RI of 12.44 (95% CI, 2.22–75.95). The same safety signal was observed for Pfizer-BioNTech vaccinated young people in which the RI is 5.81 (95% CI, 1.95–17.61). These observations were supported by comparing the RI after dose 2 to the RI after dose 1. The RI for days 1–3 after the Moderna vaccine's second dose was 6.59 (95% CI, 8.97–22.01) times as high as the same period after the first dose. For people vaccinated by Pfizer-BioNTech vaccine, the RI for days 1–3 after the second also increased 9.55 (95% CI, 3.89–23.43) times compared with the same period after the first dose.

Table 4
Ratio of relative incidences and relative incidence of myocarditis after two doses of COVID-19 vaccination, stratified by age a

		Events		RI after dose 1 (95% CI)	RI after dose 2 (95% CI)	Ratio of RIs (95% CI)[b]
		After dose 1	After dose 2			
Age < 30						
mRNA-1273 vaccine						
	No. of days after vaccination, d					
	0[c]	2	9	0.55 (0.05–5.37)	2.90 (0.40-22.37)	5.25 (0.80-34.43)
	1–3	17	96	1.89 (0.33–11.72)	12.44 (2.22–75.95)	6.59 (1.97–22.01)
	4–14	9	16	0.51 (0.12–2.16)	1.06 (0.27–4.43)	2.07 (0.53–8.10)
	15–28	5	4	1 [Reference]	1 [Reference]	1 [Reference]
BNT162b2 vaccine						
	No. of days after vaccination, d					
	0[c]	6	26	0.26 (0.06–1.09)	1.04 (0.30–3.67)	3.97 (1.19–13.28)
	1–3	31	323	0.61 (0.19–1.96)	5.81 (1.95–17.61)	9.55 (3.89–23.43)
	4–14	29	51	0.40 (0.16–1.02)	0.65 (0.28–1.57)	1.61 (0.63–4.11)
	15–21	11	8	1 [Reference]	1 [Reference]	1 [Reference]
Age > = 30						
mRNA-1273 vaccine						
	No. of days after vaccination, d					

		Events		RI after dose 1 (95% CI)	RI after dose 2 (95% CI)	Ratio of RIs (95% CI)[b]
		After dose 1	After dose 2			
	0[c]	12	7	1.68 (0.33–8.84)	1.09 (0.19–6.15)	0.65 (0.18–2.37)
	1–3	19	46	1.10 (0.25–4.99)	2.96 (0.70-13.18)	2.69 (0.94–7.67)
	4–14	24	21	0.78 (0.26–2.46)	0.76 (0.24–2.47)	0.97 (0.33–2.85)
	15–28	8	8	1 [Reference]	1 [Reference]	1 [Reference]
BNT162b2 vaccine						
	No. of days after vaccination, d					
	0[c]	9	20	2.33 (0.33–16.5)	4.03 (0.63–25.98)	1.73 (0.49–6.11)
	1–3	19	61	1.91 (0.34–10.91)	4.76 (0.92–25.08)	2.50 (0.82–7.61)
	4–14	17	14	0.77 (0.22–2.75)	0.49 (0.14–1.68)	0.64 (0.19–2.16)
	15–21	7	8	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: CI, confidence interval; RI, relative incidence

[a] Ten cases that reported unknown or missing age are excluded.

[b] The ratios are estimated by dividing the relative incidences after dose 2 by the relative incidences after dose 1.

[c] Zero refers to the day of vaccination

Finally, an SCCS and an OE analysis were performed in people aged 12–18 and received the Pfizer-BioNTech vaccine because of the considerable amounts of report in this subgroup. The SCCS analysis showed that the risk was about 5.49-fold (95% CI, 1.16–27.82) higher during days 1–3 as compared to days 15–21; furthermore, the ratio of RIs for days 1–3 after the second dose to the RIs for days 1–3 after the first dose was 10.96 (3.09–38.88) **(Additional file 1: Table S2)**. The OE analysis also raised a safety concern. During our study period, 13,990,719 people aged 12 to 18 completed the dose series of the

Pfizer-BioNTech vaccine.[15] While the calculated expected number of cases ranged from 76.89 to 134.57, the observed number of cases was 283, which was substantially higher than expected.

4. Discussion

This observational study found a significant increase in myocarditis risk 1–3 days after the second dose of both Moderna and Pfizer-BioNTech vaccines. On the other hand, we did not any other significant increased risk in other risk periods. These findings suggested a safety concern regarding myocarditis for both Moderna and Pfizer-BioNTech vaccines. Furthermore, the age subgroup analysis showed that the safety concern mainly arises from the increased risk in the young population with age below 30. The same safety concern was detected when the analysis was stratified by gender, in which males showed an increased risk of myocarditis after the second dose of both COVID-19 mRNA vaccines.

Our analysis utilized a novel SCCS model to refine signals from a nationwide pharmacovigilance database, with proper validation of the inherent reporting bias in the dataset, i.e., underreporting. As discussed by Oster et al.,[4] although VAERS suffers from both overreporting and underreporting, the high confirmation rate of myocarditis implies that underreporting is more likely. On the other hand, the time proximity between AE onset and vaccine exposure affects the reporting probability. However, the lack of reports on day 0 after the second dose of the mRNA vaccine suggests that the clustering on days 1–3 cannot be fully explained by reporting bias.[18]

The observed significant increased myocarditis risk after the second dose, along with the male preponderance, and young population domination match the findings in multiple studies in US and Israel.[4–7] Notably, Oster et al[4] conducted a descriptive study of the myocarditis reports in VAERS as of September 30, 2020 and observed a significant difference between the observed reporting rate and expected myocarditis rate during the first week after COVID-19 mRNA vaccination. While they did not provide an estimate for the risk of myocarditis, our analysis complemented their work.

Several other strengths of our study are worth noticing. First, our analysis benefits from the VAERS's national scope, considerable sample size and diversity, and sensitivity to the rare AEs. Besides, despite that many studies have raised safety concerns regarding myocarditis, few of them have quantified the RIs in different periods after each dose, let alone the ratio of RIs between two doses of vaccination. Finally, because our analysis is entirely based on a well-known publicly available dataset, it enjoys complete transparency. It thus may circumvent some doubtless regarding the safety of current mRNA vaccines.

4.1 Limitations

Our analysis is subject to several limitations. First, although a safety concern related to myocarditis is raised, our analysis should be considered as an attempt to refine the signal from SRS. The definitive estimate of the risk should come from a more rigorous pharmacoepidemiology study. Furthermore, given

the risk of COVID-19, we believe the benefits of receiving the COVID-19 mRNA vaccines still outweighs the risk of developing AEs.

Second, data from SRS, including VAERS, is often recorded imprecisely or incompletely. Besides, we have discarded cases with myocarditis onset interval exceeds each vaccines' minimum doses interval. Though unlikely, these errors may introduce extra bias in our estimation.[13] Furthermore, our analysis used a relatively strong exponential decreasing reporting probability assumption to tackle the underreporting problem, which may not be that valid in the real setting. However, an extensive simulation and a real data analysis showed that the functional form of the reporting probability would not affect the result much. [13]

Third, the cases used in our study have not undergone medical record review regarding the Brighton Collaboration Criteria. Our case selection was based on the limited information in the original reports and the clinician's impression, which caused a burden on the verification of some myocarditis reports. For example, some reports mentioned chest pain or cardiac enzymes increasing may be related to pericarditis or acute myocardial infarction. We attempted to solve this problem via sensitivity analysis, assuming that only a certain proportion of cases can ultimately be determined as myocarditis cases.

5. Conclusions

Based on US VAERS data, this study has found a significantly increased risk after days 1–3 of the second dose of Moderna or Pfizer-BioNTech vaccination. However, our findings should be interpreted with limitations in mind. Our analysis should not be a stumbling block to the vaccination process; instead, it shows that VAERS is indeed capable of discovering some AEs that randomized clinical trials cannot detect.

Abbreviations

COVID-19: Coronavirus disease 2019; Pfizer-BioNTech vaccine: BNT162-b2 vaccine; Moderna vaccine: mRNA-1273 vaccine; AE: adverse event; VAERS: Vaccine Adverse Event Reporting System; SRS: spontaneous reporting system; SCCS: Self-controlled Case Series; 95% CI: 95% confidence intervals; RI: relative incidence; OE analysis: observed-to-expected analysis; IQR: interquartile range

Declarations

Availability of data and materials

The datasets analyzed during the current study are available in the US Vaccine Adverse Events Reporting System repository, https://vaers.hhs.gov/data/datasets.html

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Not applicable.

Authors' contributions

Zhang had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Zhang designed and supervised the study. Lai, Lu and Lim collected and interpreted the data. Lai analysed the data. Lai drafted the first manuscript with input from all others. Zhang and Wang revised the manuscript. All authors approved the final manuscript as submitted.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interest:

None declared.

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Figures

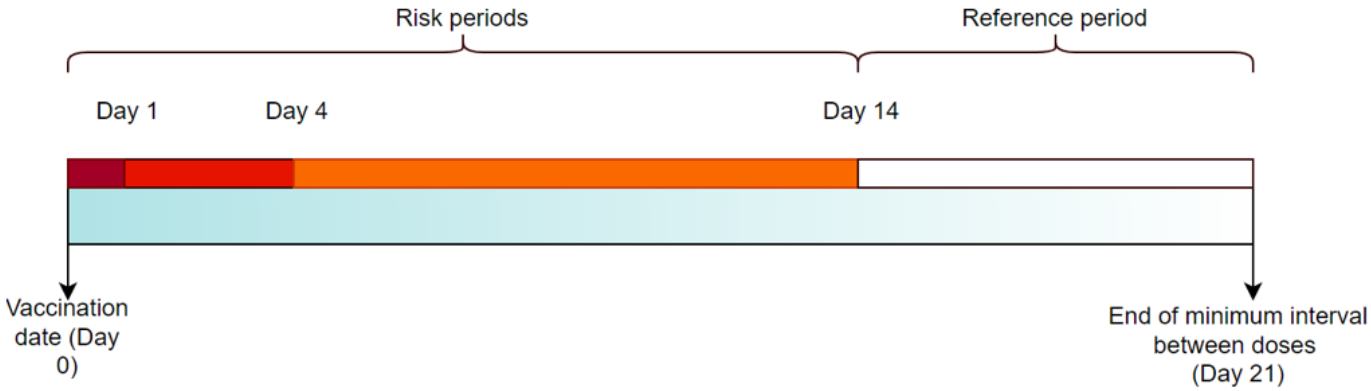

Figure 1

Overview of the Self-controlled Case Series Designs, Using the Pfizer-BioNTech Vaccine (Recommended Dose Time Interval is 21 days) as an Example

Supplementary Files

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