International Journal of Infectious Diseases 131 (2023) 75–78

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

A population-based assessment of myocarditis after messenger RNA COVID-19 booster vaccination among adult recipients

Zaeema Naveed[1,2], Julia Li[1,2], Monika Naus[1,2], Héctor Alexander Velásquez García[1,2], James Wilton[1], Naveed Z. Janjua[1,2,3,*], on behalf of the Canadian Immunization Research Network Provincial Collaborative Network investigators

[1] *British Columbia Centre for Disease Control, Vancouver, Canada*
[2] *School of Population and Public Health, University of British Columbia, Vancouver, Canada*
[3] *Centre for Health Outcomes and Evaluation, St Paul's Hospital, Vancouver, Canada*

ARTICLE INFO

Article history:
Received 19 December 2022
Revised 1 March 2023
Accepted 14 March 2023

Keywords:
SARS-CoV-2
mRNA vaccination
Myocarditis
Booster dose

ABSTRACT

Objectives: We aimed to estimate the rate of myocarditis after the messenger RNA (mRNA) COVID-19 booster vaccination by vaccine type, age, and sex.
Methods: We used data from the British Columbia COVID-19 Cohort, a population-based cohort surveillance platform. The exposure was a booster dose of an mRNA vaccine. The outcome was diagnosis of myocarditis during hospitalization or an emergency department visit within 7-21 days of booster vaccination.
Results: The overall rate of myocarditis was lower for the booster dose (6.41, 95% confidence interval [CI]: 3.50-10.75) than the second dose (17.97, 95% CI: 13.78-23.04); (Rate ratio$_{\text{booster vs dose-2}}$ = 0.34, 95% CI: 0.17-0.61). This difference was more apparent for the mRNA-1273 vaccine type. After the second dose, the myocarditis rate in males was significantly lower for BNT162b2 than mRNA-1273 overall and among those aged 18-39 years. In contrast, after the booster dose, no significant differences between myocarditis and vaccine type was observed overall or within the specific age groups among males or females.
Conclusion: Myocarditis after mRNA COVID-19 vaccines is a rare event. A lower absolute risk of myocarditis was observed after a booster dose of mRNA vaccine than the primary series second dose.

Introduction

Studies have found messenger RNA (mRNA) COVID-19 vaccines to be associated with myocarditis, particularly among younger men, after a second dose of mRNA-1273 [1,2]. However, limited population-based research has been conducted to assess the safety of booster doses. Particularly, a direct safety comparison between the two mRNA COVID-19 vaccines is understudied. We estimated the rate of myocarditis after a booster dose of mRNA vaccine by vaccine type, age, and sex, followed by a comparison between the mRNA vaccine types.

Methods

We used data from the British Columbia COVID-19 Cohort (BCC19C). The BCC19C integrates provincial COVID-19 data sets (laboratory testing, case surveillance, provincial immunization registry, hospitalizations) with administrative health and registry data holdings for the British Columbia population (medical visits, hospital admissions, emergency department visits, chronic conditions, dispensations, mortality, among others) (Supplemental Table-S1). Our study included individuals aged ≥18 years who received an mRNA booster vaccination (BNT162b2 or mRNA-1273) between December 15, 2020 and July 10, 2022. Individuals with a history of myocarditis within 1 year before the vaccine dose, residents of long-term care facilities, and those whose vaccine dose was administered outside of British Columbia were excluded from the analyses. The outcome of interest was the diagnosis of myocarditis (International Classification of Diseases Tenth Revision codes I40.1,

* Corresponding author: Tel: +1 604–707–2514.
E-mail address: Naveed.Janjua@bccdc.ca (N.Z. Janjua).

https://doi.org/10.1016/j.ijid.2023.03.027

Table 1
Myocarditis events post second and booster doses, rates per million doses, and RR (BNT162b2/MRNA-1273) by vaccine product, age, and sex during a 7-day risk window in British Columbia.

OVERALL

	Dose 2			Dose 3			Rate ratio$_{\text{booster vs dose 2}}$ (95% CI)
	Cases	Doses	Rate	Cases	Doses	Rate	
	62	3,459,609	17.92 (13.74-22.97)	14	2,299,909	6.08 (3.32-10.21)	0.34 (0.17-0.61)

BOTH MALES & FEMALES

Dose 2							Dose 3						
BNT162b2			mRNA-1273			RR (95% CI)	BNT162b2			mRNA-1273			RR (95% CI)
Cases	doses	Rate	Cases	doses	Rate		Cases	doses	Rate	Cases	doses	Rate	
26	2,448,522	10.62 (6.94 - 15.56)	36	1,011,087	35.60 (24.94 - 49.29)	0.30 (0.17 - 0.51)	6	1,057,096	5.67 (2.08-12.35)	8	1,242,813	6.43 (2.77-12.68)	0.88 (0.31-2.54)

MALES

	Dose 2							Dose 3						
	BNT162b2			mRNA-1273			RR (95% CI)	BNT162b2			mRNA-1273			RR (95% CI)
	Cases	doses	Rate	Cases	doses	Rate		Cases	doses	Rate	Cases	doses	Rate	
Total	20	1,154,571	17.32 (10.58-26.75)	31	510,179	60.76 (41.28-86.25)	0.28 (0.16-0.50)	4	479,933	8.33 (2.27-21.34)	4	571,928	6.99 (1.90-17.91)	1.19 (0.29-4.76)
Age (Years)														
18-29	13	243,946	53.29 (28.37-91.13)	23	102,223	224.99 (143.63-337.61)	0.23 (0.12-0.47)	2	107,083	18.67 (2.26-67.46)	1	25,599	39.06 (0.98-217.65)	0.47 (0.04-5.27)
30-39	1	208,513	4.79 (0.12-26.72)	7	96,288	72.69 (29.23-149.78)	0.06 (0.01-0.53)	1	65,867	15.18 (0.38-84.58)	1	86,618	11.54 (0.29-64.32)	1.31 (0.08-21.02)
40-49	1	165,804	6.03 (0.15-33.60)	1	73,795	13.55 (0.34-75.50)	0.44 (0.03-7.12)	1	57,518	17.38 (0.44-96.86)	0	80,768	0.00 (0.00-45.67)	NA
≥50	5	536,308	9.32 (3.03-21.75)	0	237,873	0.00 (0.00-15.51)	NA	0	249,465	0.00 (0.00-14.78)	2	378,943	5.27 (0.63-19.06)	NA

FEMALES

	Dose 2							Dose 3						
	BNT162b2			mRNA-1273			RR (95% CI)	BNT162b2			mRNA-1273			RR (95% CI)
	Cases	doses	Rate	Cases	doses	Rate		Cases	doses	Rate	Cases	doses	Rate	
Total	6	1,293,951	4.64 (1.70-10.09)	5	500,908	9.98 (3.24-23.29)	0.46 (0.14-1.52)	2	577,163	3.46 (0.42-12.52)	4	670,885	5.96 (1.62-15.26)	0.58 (0.11-3.17)
Age (Years)														
18-29	3	249,099	12.04 (2.48-35.19)	1	92,710	10.78 (0.27-60.09)	1.12 (0.12-10.73)	0	128,948	0.00 (0.00-28.61)	0	37,979	0.00 (0.00-97.13)	NA
30-39	0	224,816	0.00 (0.00-16.41)	2	88,631	22.56 (2.73-81.51)	NA	0	78,845	0.00 (0.00-46.78)	1	101,484	9.85 (0.25-54.90)	NA
4-49	1	191,335	5.22 (0.13-29.12)	0	71,191	0.00 (0.00-51.81)	NA	0	73,372	0.00 (0.00-50.27)	0	95,822	0.00 (0.00-8.49)	NA
≥50	2	628,701	3.18 (0.38-11.49)	2	248,376	8.06 (0.97-29.09)	0.39 (0.06-2.80)	2	295,998	6.75 (0.82-24.41)	3	435,600	6.88 (1.42-20.12)	0.98 (0.16-5.87)

CI, confidence interval; mRNA, messenger RNA; RR, rate ratio.

I40.8, I40.9, and I51.4) during a hospitalization or emergency department visit within 7 and 21 days of receiving a booster dose (first monovalent booster) of an mRNA vaccine.

The rates of myocarditis per million doses (within 7 and 21 days after vaccine administration) were calculated by vaccine type, sex, and age group. Rate ratios (RRs) with exact 95% confidence intervals (95% CIs) were used to compare the two types of mRNA vaccines. Separate analyses were conducted after the primary series (first and second dose) and the booster dose and for 7- and 21-day risk windows.

Results

A total of 2,299,909 booster doses of an mRNA vaccine, including 1,057,096 BNT162b2 and 1,242,813 mRNA-1273 doses, were administered over the study period. A total of 14 cases of myocarditis were observed after the booster doses, 62 after the second doses, and four after the first doses (Table 1, Supplemental Table-S2). The overall rate of myocarditis per million doses in the 7-day window after the vaccination was lower for the booster dose (6.08, 95% CI: 3.32-10.21) than the second dose (17.92, 95% CI: 13.74-22.07), with a rate ratio$_{\text{booster vs dose-2}}$ of 0.34 (95% CI: 0.17-0.61) and a risk difference$_{\text{booster vs dose-2}}$ of −11.84 (95% CI: −17.31 to −6.35) per million doses. This lower rate for booster versus the second dose was particularly apparent for mRNA-1273 (6.43, 95% CI: 2.77-12.68 vs 35.60, 95% CI: 24.94-49.29) (Table 1).

Although the myocarditis rate after the booster dose among males was slightly higher for BNT162b2 (rate = 8.33, 95% CI: 2.27-21.34) than mRNA-1273 (rate = 6.99, 95% CI: 1.90-17.91), the difference was not statistically significant (RR = 1.19, 95% CI: 0.29-4.76). Similarly, no significant differences between vaccine type and myocarditis were observed within the specific age groups for males and females.

In contrast, after the second dose, the myocarditis rate in males was significantly lower for BNT162b2 than mRNA-1273 overall (rate$_{\text{BNT162b2}}$: 17.32, 95% CI: 10.58-26.75; rate$_{\text{mRNA-1273}}$: 60.76, 95% CI: 41.28-86.25; RR: 0.28, 95% CI: 0.16-0.50) and among those aged 18-29 and 30-39 years.

The analyses for the 21-day risk window demonstrated nine additional myocarditis cases, *i.e.*, a total of 23 cases. The overall rate of myocarditis per million booster doses in the 21-day window was 10.00 (95% CI: 6.33-15.01) and significantly lower than the second dose (RR$_{\text{booster vs dose-2}}$ = 0.45 [95% CI: 0.27-0.37]), as observed with the 7-day period. Overall, within the booster dose, the rate of myocarditis was higher for BNT162b2 versus mRNA-1273, but the difference was not statistically significant (Supplemental Table-S3).

Discussion

In this population-based cohort study, we observed a lower absolute risk of myocarditis after a booster dose of mRNA vaccines than the primary series second dose (risk difference = −11.84 [95% CI: −17.31 to −6.35]). Although the risk of myocarditis is higher for mRNA-1273 versus BNT162b2 after a second dose (particularly among younger males), no statistically significant difference in rates was observed between these two vaccines after the booster dose.

Few population-based studies have assessed the safety of the booster dose. An assessment of myocarditis after the BNT162b2 booster dose among Israeli military population aged 18-24 years reported a rate of 6.43 (95% CI: 0.13-12.73) per 100,000 doses [3]. Another study conducted in Israel, limited to the safety evaluation of BNT162b2 vaccine, reported an overall rate of 1.42 myocarditis cases per 100,000 third doses among male recipients. Although they observed a higher post-booster rate of myocarditis than our study; consistent with our findings, the risk was lower than the second dose (risk difference = −2.72, 95% CI: −3.67 to −1.73). Furthermore, their higher post-booster dose rate may be due to the longer postvaccination follow-up period than ours (30 days vs 7 days) [4]. An evaluation of Kaiser Permanente Southern California members compared the observed to expected myocarditis incidence, identifying a lower observed to expected RR after the booster than the second dose [5].

Consistent with our results, a US-based study using the Vaccine Adverse Event Reporting System (VAERS) data found the reporting rate of myocarditis/pericarditis for the booster dose to be significantly lower than the second dose (1.44 vs 5.34 events per million doses). In addition, in a disproportionality analysis, this study found the reporting odds ratios of myocarditis/pericarditis for the booster dose to be lower than the second dose. Furthermore, within the booster vaccination, they observed a slightly higher reporting rate of myocarditis/pericarditis after BNT162b2 (1.47, 95% CI: 1.16-1.83) than mRNA-1273 (1.40, 95% CI: 1.06-1.81) [6]. Corroborating our findings, a study by Goddard et al., using a combined incidence of myocarditis or pericarditis as the outcome, reported higher rate after the mRNA-1273 (64.0, 95% CI: 25.7-131.9) versus the BNT162b2 (41.9, 95% CI: 16.9-86.4) booster vaccinations among males aged 18-29 years but a lower rate after the mRNA-1273 (6.7, 95% CI: 0.2-37.3) versus the BNT162b2 (15.2, 95% CI: 3.1-44.4) booster vaccinations among males aged 30-39 years [7]. Finally, another study using VAERS data found a higher reporting rate of myocarditis among men aged 18-24 years after the mRNA-1273 COVID-19 vaccine booster (8.7 per million doses) than BNT162b2 booster (4.1 per million doses) [8]. None of the studies discussed above conducted a quantitative comparative analysis.

A contrasting finding was reported by Patone et al., who conducted a self-controlled case series study in England. They observed an overall higher (although not statistically significant) rate of myocarditis 28 days after the booster doses of BNT162b2 than the second dose. However, further stratification showed women and the age group ≥40 years to be driving cases after the booster dose [9]. This study used a broader set of myocarditis International Classification of Diseases Tenth Revision codes and included myocarditis cases with known etiology.

There could be three potential explanations for our finding of a lower rate of myocarditis after a booster dose. First, there is a decreased amount of antigen in booster mRNA-1273 dose (50 μg) compared with the primary series (100 μg). Secondly, a longer interval between administration of second and booster dose compared with that of first and second dose because it has been observed that a longer dose-interval confers a lower risk of myocarditis [10]. Lastly, reduced predisposition, *i.e.*, the number of individuals at risk of myocarditis may have declined, because those at a higher risk may have already developed myocarditis after the second dose and did not receive a booster dose. However, it is difficult to disentangle which factors are contributing to the decrease in rate. The major strength of this study is the use of comprehensive population-based datasets. An overall limitation is the impact of the rare outcome on statistical power; thus, the interpretation of the subgroup analysis results needs caution.

Conclusion

Myocarditis after mRNA COVID-19 vaccines is a rare event. We observed a lower absolute risk of myocarditis after a booster dose than the second dose. In contrast to the second dose, no vaccine-specific differences with myocarditis were observed within the age and sex groups for the booster dose.

Declarations of competing interest

NZJ participated in advisory boards and has spoken for AbbVie and Gilead, not related to current work. The other authors have no competing interests to declare.

Funding

The BCC19C was established and is maintained through operational support from Data Analytics, Reporting and Evaluation, and British Columbia Centre for Disease Control at the Provincial Health Services Authority. This work was supported by the Canadian Immunization Research Network through a grant from the Public Health Agency of Canada and the Canadian Institutes of Health Research (CNF 151944). This project was also supported by funding from the Public Health Agency of Canada through the Vaccine Surveillance Reference Group and the COVID-19 Immunity Task Force.

Ethical approval

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines and was reviewed and approved by the Behavioral Research Ethics Board at the University of British Columbia (approval # H20-02097).

Acknowledgments

The authors acknowledge the assistance of the Provincial Health Services Authority, British Columbia Ministry of Health, and Regional Health Authority staff involved in the data access, procurement, and management. The authors gratefully acknowledge the residents of British Columbia whose data are integrated in the British Columbia COVID-19 Cohort.

Author contributions

ZN, JL, MN, HAV, JW, and NZJ participated in the conceptualization and designing of the study. Data management and data analyses were performed by JL and ZN. ZN, JL, MN, HAV, JW, and NZJ participated in the interpretation of the findings. The initial draft manuscript was written by ZN. All authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Disclaimer

All inferences, opinions, and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.03.027.

References

[1] Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. *JAMA Cardiol* 2022;**7**:600–12. doi:10.1001/jamacardio.2022.0583.

[2] Wong HL, Hu M, Zhou CK, Lloyd PC, Amend KL, Beachler DC, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. *Lancet* 2022;**399**:2191–9. doi:10.1016/S0140-6736(22)00791-7.

[3] Friedensohn L, Levin D, Fadlon-Derai M, Gershovitz L, Fink N, Glassberg E, et al. Myocarditis following a third BNT162b2 vaccination dose in military recruits in Israel. *JAMA* 2022;**327**:1611–12. doi:10.1001/jama.2022.4425.

[4] Mevorach D, Anis E, Cedar N, Hasin T, Bromberg M, Goldberg L, et al. Myocarditis after BNT162b2 COVID-19 third booster vaccine in Israel. *Circulation* 2022;**146**:802–4. doi:10.1161/CIRCULATIONAHA.122.060961.

[5] Simone A, Herald J, Chen A, Nayak R, Shen YA, Lee MS. Acute myocarditis following a third dose of COVID-19 mRNA vaccination in adults. *Int J Cardiol* 2022;**365**:41–3. doi:10.1016/j.ijcard.2022.07.031.

[6] Chen C, Fu F, Ding L, Fang J, Xiao J. Booster dose of COVID-19 mRNA vaccine does not increase risks of myocarditis and pericarditis compared with primary vaccination: new insights from the vaccine adverse event reporting system. *Front Immunol* 2022;**13**:938322. doi:10.3389/fimmu.2022.938322.

[7] Goddard K, Hanson KE, Lewis N, Weintraub E, Fireman B, Klein NP. Incidence of myocarditis/pericarditis following mRNA COVID-19 vaccination among children and younger adults in the United States. *Ann Intern Med* 2022;**175**:1169–771. doi:10.7326/M22-2274.

[8] Hause AM, Baggs J, Marquez P, Myers TR, Su JR, Blanc PG, et al. Safety monitoring of COVID-19 vaccine booster doses among adults - United States, September 22, 2021–February 6, 2022. *MMWR Morb Mortal Wkly Rep* 2022;**71**:249–54. doi:10.15585/mmwr.mm7107e1.

[9] Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex. *Circulation* 2022;**146**:743–54. doi:10.1161/CIRCULATIONAHA.122.059970.

[10] Pillay J, Gaudet L, Wingert A, Bialy L, Mackie AS, Paterson DI, et al. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following Covid-19 vaccination: living evidence syntheses and review. *BMJ* 2022;**378**:e069445. doi:10.1136/bmj-2021-069445.