Research

Observed versus expected rates of myocarditis after SARS-CoV-2 vaccination: a population-based cohort study

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Cite as: *CMAJ* 2022 November 21;194:E1529-36. doi: 10.1503/cmaj.220676

Abstract

Background: Postmarketing evaluations have linked myocarditis to SARS-CoV-2 mRNA vaccines. We sought to estimate the incidence of myocarditis after mRNA vaccination against SARS-CoV-2, and to compare the incidence with expected rates based on historical background rates in British Columbia.

Methods: We conducted an observational study using population health administrative data from the BC COVID-19 Cohort from Dec. 15, 2020, to Mar. 10, 2022. The primary exposure was any dose of an mRNA vaccine against SARS-CoV-2. The primary outcome was incidence of hospital admission or emergency department visit for myocarditis or myopericarditis within 7 and 21 days postvaccination, calculated as myocarditis rates per 100 000 mRNA vaccine doses, expected rates of myocarditis cases and observed-to-expected ratios. We stratified analyses by age, sex, vaccine type and dose number.

Results: We observed 99 incident cases of myocarditis within 7 days (0.97 cases per 100 000 vaccine doses; observed v. expected ratio 14.81, 95% confidence interval [CI] 10.83–16.55) and 141 cases within 21 days (1.37 cases per 100 000 vaccine doses; observed v. expected ratio 7.03, 95% CI 5.92–8.29) postvaccination. Cases of myocarditis per 100 000 vaccine doses were higher for people aged 12–17 years (2.64, 95% CI 1.54–4.22) and 18–29 years (2.63, 95% CI 1.94–3.50) than for older age groups, for males compared with females (1.64, 95% CI 1.30–2.04 v. 0.35, 95% CI 0.21–0.55), for those receiving a second dose compared with a third dose (1.90, 95% CI 1.50–2.39 v. 0.76, 95% CI 0.45–1.30) and for those who received the mRNA-1273 (Moderna) vaccine compared with the BNT162b2 (Pfizer-BioNTech) vaccine (1.44, 95% CI 1.06–1.91 v. 0.74, 95% CI 0.56–0.98). The highest observed-to-expected ratio was seen after the second dose among males aged 18–29 years who received the mRNA-1273 vaccine (148.32, 95% CI 95.03–220.69).

Interpretation: Although absolute rates of myocarditis were low, vaccine type, age and sex are important factors to consider when strategizing vaccine administration to reduce the risk of postvaccination myocarditis. Our findings support the preferential use of the BNT162b2 vaccine over the mRNA-1273 vaccine for people aged 18–29 years.

As of September 2022, more than 32 million people in Canada, including around 4.5 million in British Columbia, have received a vaccine to prevent SARS-CoV-2 infection.[1] With any novel vaccine, safety and effectiveness are important to public health and may determine the success of achieving the targeted immunization coverage. According to a recent systematic review, the overall rate of SARS-CoV-2 vaccination acceptance ranges from 53.6% to 84.4% in the United States.[2] One of the key reasons for vaccine hesitancy is the fear of adverse effects.[3,4]

As large populations are vaccinated, certain uncommon events may be observed that were not detected during the premarketing clinical trials, whether or not these events are related to the vaccine. The same is the case with SARS-CoV-2 vaccination. The prelicensure study data did not suggest any risk of postvaccination myocarditis. However, postmarketing studies have suggested an association between mRNA SARS-CoV-2 vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]) and myocarditis, among other adverse events after immunization, which has raised concern regarding the safety of mRNA vaccines, specifically among younger populations.[5–7] Most evidence comes from case reports and case series. Earlier data have suggested higher rates of myocarditis among young adults after the mRNA-1273 compared with the BNT162b2 vaccine. Limited data are available on the rate of myocarditis after the third dose, which is relevant as further boosters are planned. Given the important economic and health consequences of COVID-19, it is vital to further evaluate the likelihood of this signal.

One of the pharmacoepidemiologic methods that refine a previously detected signal is an observed-to-expected analysis, which compares the number of cases observed or reported to a calculated number of cases expected under the null hypothesis of no association between the intervention and the disease.[8] Thus, the primary objective of this study was to determine the incidence of patients who visited the emergency department or were admitted to the hospital with myocarditis after mRNA SARS-CoV-2 vaccination, and to compare these observed results to expected numbers based on historical rates before the rollout of SARS-CoV-2 vaccination.

Methods

Study design

We conducted an observational study using population health administrative data from the BC COVID-19 Cohort from Dec. 15, 2020, to Mar. 10, 2022. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[9]

Data source

We used data from the BC COVID-19 Cohort, a surveillance platform that integrates COVID-19 data (e.g., laboratory tests, surveillance case data, hospital and intensive care unit [ICU] admissions, SARS-CoV-2 vaccinations) and administrative data sets dating back to 2008 (e.g., emergency department visits, hospital admissions, physician billings, pharmaceutical dispensations, laboratory tests, chronic diseases, deaths) (Appendix 1, Supplementary Table S1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.220676/tab-related-content). The COVID-19 data are updated daily in this dynamic cohort; most of the administrative data sets are updated weekly or monthly.[10]

Study population

We included individuals (age ≥ 12 yr) with a record of an mRNA SARS-CoV-2 vaccination in the BC Provincial Immunization Registry between Dec. 15, 2020, and Mar. 10, 2022. We excluded individuals with a history of myocarditis or myopericarditis (depending on the outcome assessed) within 1 year before a dose of SARS-CoV-2 vaccine.

Exposure

The primary exposure was any dose of an mRNA vaccine, either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna), received between Dec. 15, 2020, and Mar. 10, 2022, in BC.

Outcome

The primary outcome was hospital admission or emergency department visit for myocarditis and the secondary outcome was myopericarditis. Based on the literature review, we used the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10) codes I40.1 (isolated myocarditis), I40.8 (other acute myocarditis), I40.9 (acute myocarditis, unspecified) and I51.4 (myocarditis unspecified) to identify the observed number of myocarditis cases between Dec. 15, 2020, and Mar. 31, 2022 (see Appendix 1 for additional information).[11–13] For myopericarditis, we used additional ICD-10 codes, namely I30.0 (acute nonspecific idiopathic pericarditis), I30.8 (other forms of acute pericarditis) and I30.9 (acute pericarditis, unspecified). We employed a 7-day and a 21-day postvaccination observation window (i.e., symptom onset from the day of vaccination through day 7 or day 21 after vaccination).

Study period

We calculated background (expected) rates using data on hospital admissions and emergency department visits from 2015 to 2020. As these rates increased over time, we used the rates from 2019 for the observed-to-expected analyses. We identified postvaccination cases from the administration of the first mRNA SARS-CoV-2 vaccine in BC on Dec. 15, 2020, through Mar. 10, 2022.

Statistical analysis

As the risk period (i.e., postvaccine observation window) was shorter than the average time window between the 3 scheduled vaccine doses, the risk period after each dose did not overlap. Thus, we considered each dose to have independently contributed to a fixed time at risk. We calculated rates of myocarditis per 100 000 mRNA vaccines by sex, age, vaccine type and dose number. We calculated the 95% confidence intervals (CIs) for rates using the exact method. We calculated the expected number of cases as the accumulated person-time in days (i.e., number of doses administered multiplied by 7 for a 7-day risk window, or by 21 for a 21-day risk period), multiplied by the background rate per 100 000 person-days. We used the 2019 BC population aged 12 years and older to calculate the expected number of cases. We stratified calculations of background rates and expected number of cases by age and sex to identify if an excess risk existed specific to a particular stratum. Furthermore, as statistical uncertainty is often driven by the observed number of cases, we estimated 95% Poisson exact CIs for observed numbers. We expressed the comparison between the observed and expected number of cases as the ratio of the observed over expected cases. Lastly, we derived the 95% CIs for the observed-to-expected ratios by dividing the exact CIs for the number of observed cases by the expected number of cases.[14] If the lower limit of the 95% CI of the observed-to-expected ratio was greater than 1, we considered the observed value as significantly higher than expected.

Ethics approval

This study was reviewed and approved by the Behavioural Research Ethics Board at the University of British Columbia (approval no. H20-02097).

Results

A total of 10 255 385 doses of mRNA vaccines, including 6 989 921 doses of BNT162b2 (Pfizer-BioNTech) and 3 265 464 doses of mRNA-1273 (Moderna), were administered during the study period. Among these, 3 994 380 were first doses, 3 884 987 were second doses and 2 376 018 were third doses. The BC population aged 12 years and older, used to calculate the expected number of cases, was 4 815 085.

We identified 99 incident cases of myocarditis within 7 days, compared with 7 expected cases, and 141 cases within 21 days postvaccination, compared with 20 expected cases. Most cases were among males and after the second dose (Table 1). Among individuals with myocarditis, on average, the males were younger than females (28 v. 45 yr among cases within 7 d; 31 v. 49 yr among cases within 21 d).

The overall rate of myocarditis was 0.97 per 100 000 mRNA vaccine doses (95% CI 0.78–1.17) using a 7-day risk window, compared with the expected rate of 0.13 per 100 000 population (95% CI 0.06–0.28) (Table 2). The overall rate using a 21-day risk window was 1.37 per 100 000 mRNA vaccine doses (95% CI 1.16–1.62), compared with an expected rate of 0.39 per 100 000 population (95% CI 0.26–0.63) (Table 3). Using a 7-day risk window, we observed higher rates of myocarditis among males than among females (1.64, 95% CI 1.30–2.04 v. 0.35, 95% CI 0.21–0.55) (Table 2). Myocarditis rates were highest among people aged 12–17 years (2.64, 95% CI 1.54–4.22) and those aged 18–29 years (2.63, 95% CI 1.94–3.50), and lowest among those aged 70–79 years (0.24, 95% CI 0.05–0.71). We observed these differences with both vaccine types, but higher rates of myocarditis were observed with the mRNA-1273 vaccine than the BNT162b2 vaccine (1.44, 95% CI 1.06–1.91 v. 0.74, 95% CI 0.56–0.98). The greatest difference in myocarditis rates between the mRNA-1273 and BNT162b2 vaccines was observed after the second dose in males aged 18–29 years (22.1, 95% CI 14.1–32.8 v. 5.1, 95% CI 2.7–8.7) (Table 4). Overall myocarditis rates were lower after the third dose than after the second dose (0.76, 95% CI 0.45–1.20 v. 1.90, 95% CI 1.50–2.39) (Table 2). Among those aged 12–17 years, who only received BNT162b2 vaccines, myocarditis rates after the second and third doses were similar (males: 6.7, 95% CI 3.1–12.8 v. 7.0, 95% CI 1.4–20.5; females: 1.5, 95% CI 0.2–5.5 v. 0, 95% CI 0–8.2) (Table 4). We observed a similar pattern of results using a 21-day risk window (Table 3 and Table 4).

The overall observed-to-expected ratio of myocarditis rates was 14.81 (95% CI 10.83–16.55) using a 7-day risk window (Table 2) and 7.03 (95% CI 5.92–8.29) using a 21-day risk window (Table 3). Observed rates of myocarditis were significantly higher than expected rates in all subgroups by age (except the 70–79 yr age group), sex, dose and vaccine type (Table 2). We observed the highest observed-to-expected ratios among younger age groups and males, for both vaccine types. Using a 7-day risk window, the observed-to-expected ratios were higher for the mRNA-1273 vaccine than the BNT162b2 vaccine among males aged 18–29 years (71.44, 95% CI 46.67–104.68 v. 16.98, 95% CI 9.89–27.19) and males aged 30–39 years (20.55, 95% CI 8.87–40.50 v. 3.94, 95% CI 0.81–11.51), particularly after the second dose (18–29 yr: 148.32, 95% CI 95.03–220.69 v. 34.05, 95% CI 18.13–58.23; 30–39 yr, 50.77, 95% CI 20.41–104.6 v. 3.35, 95% CI 0.08–18.68) (Table 5). After the third dose, we also observed significantly increased observed-to-expected ratios with the BNT162b2 vaccine for males aged 12–17 years (139.80, 95% CI 28.83–408.55) and those aged 18–29 years (20.02, 95% CI 4.13–58.50), and numerically similar (but not statistically significant) results with the mRNA-1273 vaccine for males aged 18–29 years (26.58, 95% 0.67–148.11). Observed-to-expected ratios among females were generally lower than among males but showed a similar pattern across age and dose groups (Appendix 1, Table S2). We found

Table 1: Descriptive statistics among patients with myocarditis within 7 or 21 days after SARS-CoV-2 vaccination

	No. of patients with myocarditis within 7 days*		No. of patients with myocarditis within 21 days*	
Variable	Male *n* = 80	Female *n* = 19	Male *n* = 105	Female *n* = 36
Age, yr				
Range	12–82	15–80	12–87	15–88
Mean ± SD	28 ± 16	45 ± 21	31 ± 17	49 ± 22
Median (IQR)	22 (18–31)	46 (25–62)	24 (19–38)	53 (31–68)
Vaccine type				
Pfizer				
Dose 1	5	0	15	5
Dose 2	29	8	34	14
Dose 3	8	2	12	4
Moderna				
Dose 1	2	0	5	1
Dose 2	32	5	33	7
Dose 3	4	4	6	5

Note: IQR = interquartile range, Moderna = mRNA-1273 (Moderna), Pfizer = BNT162b2 (Pfizer-BioNTech), SD = standard deviation.
*Unless indicated otherwise.

Table 2: Expected and observed rates of myocarditis with observed-to-expected ratios within a 7-day risk window after SARS-CoV-2 vaccination

	Observed*			Expected†			
Variable	No. of cases	No. of vaccine doses	Rate per 100 000 (95% CI)	No. of cases	Population	Rate per 100 000 (95% CI)	OE ratio (95% CI)
Overall	99	10 255 385	0.97 (0.78–1.17)	6.7	5 090 955	0.13 (0.06–0.28)	14.81 (10.83–16.55)
Sex							
Male	80	4 891 011	1.64 (1.30–2.04)	2.4	2 571 779	0.09 (0.02–0.34)	33.74 (26.76–42.00)
Female	19	5 364 374	0.35 (0.21–0.55)	4.4	2 519 176	0.18 (0.06–0.46)	4.31 (2.59–6.73)
Age, yr							
12–17	17	644 705	2.64 (1.54–4.22)	0.2	300 573	0.08 (0.01–1.85)	68.88 (40.12–110.28)
18–29	47	1 784 950	2.63 (1.94–3.50)	1.8	822 028	0.22 (0.03–0.88)	26.25 (19.29–34.90)
30–39	14	1 624 133	0.86 (0.47–1.45)	1.5	721 055	0.21 (0.03–1.00)	9.26 (5.06–15.54)
40–49	4	1 340 746	0.30 (0.08–0.76)	0.9	647 731	0.13 (0.00–0.86)	4.58 (1.25–11.73)
50–59	5	1 420 691	0.35 (0.11–0.82)	0.8	725 412	0.10 (0.00–0.77)	6.66 (2.16–15.53)
60–69	6	1 552 275	0.39 (0.14–0.84)	0.8	660 685	0.12 (0.00–0.84)	7.83 (2.87–17.05)
70–79	3	1 228 162	0.24 (0.05–0.71)	1.1	413 888	0.26 (0.06–1.75)	2.77 (0.57–8.11)
≥ 80	3	659 723	0.45 (0.09–1.33)	0.3	229 260	0.14 (0.01–2.43)	9.06 (1.87–26.48)
Vaccine							
Pfizer	52	6 989 921	0.74 (0.56–0.98)	4.6	5 090 955	0.09 (0.03–0.23)	11.42 (8.53–14.97)
Moderna	47	3 265 464	1.44 (1.06–1.91)	2.1	5 090 955	0.04 (0.00–0.14)	22.09 (16.23–29.37)
Dose							
Dose 1	7	3 994 380	0.18 (0.07–0.36)	2.6	5 090 955	0.05 (0.01–0.17)	2.69 (1.08–5.54)
Dose 2	74	3 884 987	1.90 (1.50–2.39)	2.5	5 090 955	0.05 (0.01–0.17)	29.23 (22.95–36.69)
Dose 3	18	2 376 018	0.76 (0.45–1.20)	1.5	5 090 955	0.03 (0.00–0.14)	11.62 (6.89–18.37)

Note: CI = confidence interval, Moderna = mRNA-1273 (Moderna), OE = observed-to-expected, Pfizer = BNT162b2 (Pfizer-BioNTech).
*Myocarditis cases recorded within 7 days postvaccination between Dec. 15, 2020, and Mar. 31, 2022.
†The background rates from 2019 were used to calculate the expected numbers.

similar results using a 21-day risk period. The detailed number of doses, observed cases and expected cases for the substratified groups are reported in Appendix 1, Table S9 and Table S10.

We identified 179 incident cases of myopericarditis within 7 days and 308 cases within 21 days postvaccination (Appendix 1, Table S3). The rate of myopericarditis in the study cohort was 1.75 (95% CI 1.50–2.02) per 100 000 mRNA vaccine doses for the 7-day risk window, with an observed-to-expected ratio of 5.18 (95% CI 4.45–5.99), and 3.00 (95% CI 2.68–3.36) per 100 000 doses for the 21-day risk window, with an observed-to-expected ratio of 2.97 (95% CI 2.65–3.32). By sex, vaccine type and dose number, the rates per 100 000 doses and the observed-to-expected ratios were higher among males, among mRNA-1273 recipients and after the second dose of the mRNA vaccine. By age category, we observed the highest rate per 100 000 doses among those aged 18–29 years, whereas the highest observed-to-expected ratio was among those aged 12–17 years (Appendix 1, Table S4, Table S5). Further stratified analyses for myopericarditis showed identical patterns to the results of the myocarditis analyses (Appendix 1, Table S6, Table S7, Appendix S8).

Interpretation

In this population-based cohort study, observed rates of hospital admissions or emergency department visits for myocarditis after mRNA vaccination for SARS-CoV-2 were higher than expected based on historical background rates, particularly after the second dose, among those who received the mRNA-1273 (Moderna) vaccine, among males and among younger patients (18–29 yr). The highest rates of myocarditis were seen after the second vaccine dose among males aged 18–29 years. In this subgroup, rates were about fourfold higher with the mRNA-1273 vaccine than the BNT162b2 (Pfizer-BioNTech) vaccine. We also found that myocarditis rates were lower after the third vaccine dose than after the second dose. Ultimately, our results show the overall safety of the mRNA vaccine. The overall rates of myocarditis per 100 000 doses were still very low for both vaccine products.

Our findings are consistent with the literature. An evaluation conducted in a large Israeli health care system among patients who had received at least 1 dose of the BNT162b2 vaccine reported that male patients aged 16–29 years had the highest incidence of myocarditis within 42 days postvaccination.[15] Similar

Table 3: Expected and observed rates of myocarditis with observed-to-expected ratios within a 21-day risk window after SARS-CoV-2 vaccination

	Observed*			Expected†			
	No. of cases	No. of vaccine doses	Rate per 100 000 (95% CI)	No. of cases	Population	Rate per 100 000 (95% CI)	OE ratio (95% CI)
Overall	141	10 255 385	1.37 (1.16–1.62)	20.1	5 090 955	0.39 (0.26–0.63)	7.03 (5.92–8.29)
Sex							
Male	105	4 891 011	2.15 (1.76–2.60)	7.1	2 571 779	0.28 (0.13–0.61)	14.76 (12.07–17.87)
Female	36	5 364 374	0.67 (0.47–0.93)	13.2	2 519 176	0.53 (0.30–0.93)	2.72 (1.91–3.77)
Age, yr							
12–17	19	644 705	2.95 (1.77–4.60)	0.7	300 573	0.25 (0.01–1.85)	25.66 (15.45–40.07)
18–29	53	1 784 950	2.97 (2.22–3.88)	5.4	822 028	0.65 (0.27–1.59)	9.87 (7.39–12.9)
30–39	28	1 624 133	1.72 (1.15–2.49)	4.5	721 055	0.63 (0.23–1.62)	6.17 (4.10–8.92)
40–49	7	1 340 746	0.52 (0.21–1.08)	2.6	647 731	0.40 (0.10–1.35)	2.67 (1.07–5.50)
50–59	11	1 420 691	0.77 (0.39–1.39)	2.3	725 412	0.31 (0.09–1.21)	4.88 (2.44–8.73)
60–69	11	1 552 275	0.71 (0.35–1.27)	2.3	660 685	0.35 (0.09–1.33)	4.79 (2.39–8.56)
70–79	5	1 228 162	0.41 (0.13–0.95)	3.2	413 888	0.78 (0.26–2.47)	1.54 (0.50–3.60)
≥ 80	7	659 723	1.06 (0.43–2.19)	1.0	229 260	0.43 (0.01–2.43)	7.05 (2.83–14.52)
Vaccine							
Pfizer	84	6 989 921	1.20 (0.96–1.49)	13.7	5 090 955	0.27 (0.15–0.46)	6.15 (4.90–7.61)
Moderna	57	3 265 464	1.75 (1.32–2.26)	6.4	5 090 955	0.13 (0.06–0.28)	8.93 (6.76–11.57)
Dose							
Dose 1	26	3 994 380	0.65 (0.43–0.95)	7.8	5 090 955	0.15 (0.07–0.31)	3.33 (2.17–4.88)
Dose 2	88	3 884 987	2.27 (1.82–2.79)	7.6	5 090 955	0.15 (0.07–0.31)	11.59 (9.29–14.27)
Dose 3	27	2 376 018	1.14 (0.75–1.65)	4.6	5 090 955	0.09 (0.03–0.23)	5.81 (3.83–8.46)

Note: CI = confidence interval, Moderna = mRNA-1273 (Moderna), OE = observed-to-expected, Pfizer = BNT162b2 (Pfizer-BioNTech).
*Myocarditis cases recorded within 21 days postvaccination between Dec. 15, 2020, and Mar. 31, 2022.
†The background rates from 2019 were used to calculate the expected numbers.

findings were reported in an analysis done by a collaborative project between the United States Centers for Disease Control and Prevention and 9 integrated health care organizations in the US. It was found that both mRNA vaccines were associated with an increased risk of myocarditis or pericarditis for people aged 18–39 years; this increased risk was also observed for people aged 12–17 years who received the BNT162b2 vaccine. Head-to-head comparisons provided evidence that the risk of myocarditis or pericarditis was higher after receiving the mRNA-1273 vaccine than after the BNT162b2 vaccine.[16] A Danish study also reported similar findings, where the risk of myocarditis was three- to fourfold higher after the mRNA-1273 vaccine, both overall and among people aged 12–39 years.[17] However, in this study, BNT162b2 vaccination was associated with a significantly increased risk among women only.[17] The data on myocarditis rate after receiving a third vaccine dose are limited. In a study from Israel, the myocarditis rate after a third dose of BNT162b2 vaccine was 6.43 (95% CI 0.13–12.73), which is higher than the rate observed in our study. Further data are needed to characterize myocarditis rate and risk after boosters.[18]

With the BNT162b2 vaccine, we noted the highest absolute rates and observed-to-expected ratios of myocarditis among males aged 12–17 years. However, no comparison between mRNA-1273 and BNT162b2 was possible, as mRNA-1273 was not administered to this age group. We do not know of any studies that report this comparison, and other studies either combined age groups (e.g., 16–29 yr, 12–39 yr) or analyzed rates for BNT162b2 only for those aged 12–17 years.[15–17,19] Although our analyses with the existing age group comparators indirectly suggest a higher risk of myocarditis with the mRNA-1273 vaccine than the BNT162b2 vaccine among younger age groups, the 12–17-year age group needs further investigation.

Given the emerging evidence, a potential causal association between SARS-CoV-2 mRNA vaccines and myocarditis may exist. However, risk–benefit assessments have determined that the benefits of using mRNA SARS-CoV-2 vaccines outweigh the risks of myocarditis.[20] According to a US analysis, 11 000 COVID-19 cases, 560 hospital admissions, 138 ICU admissions and 6 deaths from COVID-19 could be prevented per million-second doses of mRNA SARS-CoV-2 vaccine administered to males aged 12–29 years, compared with 39–47 expected cases of myocarditis after SARS-CoV-2 vaccination.[20] We also observed a decreased risk of myocarditis after the third dose. Moreover, most cases of

Table 4: Myocarditis rates following mRNA SARS-CoV-2 vaccination using 7- and 21-day risk windows by vaccine type, sex, and age*

Risk window	Vaccine	Age group, yr	Rate per 100 000 doses (95% CI)					
			Male			Female		
			Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
7 days	Pfizer	12–17	2.13 (0.44–6.24)	6.73 (3.08–12.78)	7.01 (1.45–20.49)	0.00 (0.00–2.69)	1.53 (0.19–5.53)	0.00 (0.00–8.20)
		18–29	0.36 (0.01–2.03)	5.06 (2.70–8.66)	2.98 (0.61–8.70)	0.00 (0.00–1.30)	1.13 (0.23–3.30)	0.00 (0.00–2.96)
		30–39	0.43 (0.01–2.40)	0.46 (0.01–2.57)	1.63 (0.04–9.08)	0.00 (0.00–1.49)	0.00 (0.00–1.58)	0.00 (0.00–5.04)
		40–49	0.00 (0.00–2.01)	0.59 (0.01–3.27)	1.86 (0.05–10.35)	0.00 (0.00–1.76)	0.51 (0.01–2.84)	0.00 (0.00–5.37)
		50–59	0.00 (0.00–1.99)	1.20 (0.14–4.32)	0.00 (0.00–6.02)	0.00 (0.00–1.71)	0.51 (0.01–2.82)	0.00 (0.00–4.84)
		60–69	0.00 (0.00–1.86)	0.58 (0.01–3.24)	0.00 (0.00–4.91)	0.00 (0.00–1.61)	0.50 (0.01–2.78)	2.23 (0.27–8.07)
		70–79	0.00 (0.00–2.27)	0.00 (0.00–2.49)	0.00 (0.00–4.95)	0.00 (0.00–2.05)	0.00 (0.00–2.23)	0.00 (0.00–4.43)
		≥ 80	0.00 (0.00–4.81)	2.78 (0.34–10.03)	0.00 (0.00–10.31)	0.00 (0.00–3.62)	0.00 (0.00–3.84)	0.00 (0.00–8.15)
	Moderna	12–17	NA	NA	NA	NA	NA	NA
		18–29	0.90 (0.02–5.04)	22.05 (14.13–32.81)	3.95 (0.10–22.02)	0.00 (0.00–3.81)	1.00 (0.03–5.58)	0.00 (0.00–9.59)
		30–39	0.00 (0.00–3.82)	6.99 (2.81–14.40)	1.16 (0.03–6.48)	0.00 (0.00–4.31)	2.18 (0.26–7.87)	1.00 (0.03–5.54)
		40–49	0.00 (0.00–5.21)	1.32 (0.03–7.33)	0.00 (0.00–4.63)	0.00 (0.00–5.67)	0.00 (0.00–5.07)	0.00 (0.00–3.91)
		50–59	1.41 (0.04–7.85)	0.00 (0.00–4.50)	0.00 (0.00–3.77)	0.00 (0.00–5.34)	1.22 (0.03–6.79)	0.00 (0.00–3.19)
		60–69	0.00 (0.00–5.51)	0.00 (0.00–4.21)	0.00 (0.00–2.91)	0.00 (0.00–5.34)	0.00 (0.00–4.02)	1.38 (0.17–4.97)
		70–79	0.00 (0.00–9.13)	0.00 (0.00–6.93)	1.83 (0.22–6.62)	0.00 (0.00–9.06)	1.85 (0.05–10.3)	0.00 (0.00–3.15)
		≥ 80	0.00 (0.00–18.31)	0.00 (0.00–14.87)	0.00 (0.00–6.85)	0.00 (0.00–13.47)	0.00 (0.00–11.23)	1.37 (0.03–7.64)
21 days	Pfizer	12–17	2.85 (0.78–7.29)	6.73 (3.08–12.78)	9.35 (2.55–23.93)	0.00 (0.00–2.69)	1.53 (0.19–5.53)	0.00 (0.00–8.20)
		18–29	0.73 (0.09–2.63)	5.84 (3.27–9.63)	2.98 (0.61–8.70)	0.35 (0.01–1.97)	1.13 (0.23–3.30)	0.00 (0.00–2.96)
		30–39	2.59 (0.95–5.63)	1.38 (0.29–4.05)	3.26 (0.39–11.77)	0.81 (0.10–2.92)	0.43 (0.01–2.39)	0.00 (0.00–5.04)
		40–49	0.54 (0.01–3.03)	1.17 (0.14–4.23)	1.86 (0.05–10.35)	0.00 (0.00–1.76)	0.51 (0.01–2.84)	1.46 (0.04–8.12)
		50–59	1.08 (0.13–3.90)	1.20 (0.14–4.32)	1.63 (0.04–9.09)	0.00 (0.00–1.71)	1.52 (0.31–4.44)	0.00 (0.00–4.84)
		60–69	0.00 (0.00–1.86)	0.58 (0.01–3.24)	1.33 (0.03–7.41)	0.44 (0.01–2.44)	1.00 (0.12–3.60)	2.23 (0.27–8.07)
		70–79	0.00 (0.00–2.27)	0.00 (0.00–2.49)	0.00 (0.00–4.95)	0.00 (0.00–2.05)	0.61 (0.02–3.37)	0.00 (0.00–4.43)
		≥ 80	0.00 (0.00–4.81)	2.78 (0.34–10.03)	0.00 (0.00–10.31)	0.98 (0.02–5.47)	1.04 (0.03–5.80)	2.21 (0.06–12.32)
	Moderna	12–17	NA	NA	NA	NA	NA	NA
		18–29	0.90 (0.02–5.04)	22.97 (14.87–33.91)	3.95 (0.10–22.02)	0.00 (0.00–3.81)	2.00 (0.24–7.23)	0.00 (0.00–9.59)
		30–39	2.07 (0.25–7.48)	6.99 (2.81–14.40)	1.16 (0.03–6.48)	0.00 (0.00–4.31)	3.27 (0.67–9.55)	1.00 (0.03–5.54)
		40–49	0.00 (0.00–5.21)	1.32 (0.03–7.33)	0.00 (0.00–4.63)	0.00 (0.00–5.67)	0.00 (0.00–5.07)	0.00 (0.00–3.91)
		50–59	2.82 (0.34–10.17)	0.00 (0.00–4.50)	0.00 (0.00–3.77)	0.00 (0.00–5.34)	1.22 (0.03–6.79)	0.00 (0.00–3.19)
		60–69	0.00 (0.00–5.51)	0.00 (0.00–4.21)	0.79 (0.02–4.40)	0.00 (0.00–5.34)	0.00 (0.00–4.02)	2.06 (0.43–6.03)
		70–79	0.00 (0.00–9.13)	0.00 (0.00–6.93)	1.83 (0.22–6.62)	2.45 (0.06–13.68)	1.85 (0.05–10.3)	0.00 (0.00–3.15)
		≥ 80	0.00 (0.00–18.31)	0.00 (0.00–14.87)	1.86 (0.05–10.34)	0.00 (0.00–13.47)	0.00 (0.00–11.23)	1.37 (0.03–7.64)

Note: CI = confidence interval, Moderna = mRNA-1273 (Moderna), NA = not applicable, OE = observed-to-expected, Pfizer = BNT162b2 (Pfizer-BioNTech).
*Observed rates of myocarditis were calculated per 100 000 vaccine doses. Expected rates of myocarditis were expressed per 100 000 population.

myocarditis after SARS-CoV-2 vaccination have been found to be mild, with short durations of hospital admission and quick resolution.[5,15,21,22] Lastly, Patone and colleagues found an extra 10 (95% CI 7–11) myocarditis events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273 vaccine, compared with an extra 40 (95% CI 38–41) myocarditis events per 1 million patients in the 28 days after testing positive for SARS-CoV-2.[23]

A major strength of this study includes our comprehensive, population-based capture of vaccination, hospital admission and emergency department data, as well as data on myocarditis after third doses. As the background rates were calculated from the same data sources in the prevaccination period as that of the observed rates in the postvaccination period, the populations are likely to have very similar demographic characteristics.

Limitations

As the outcome definition was based on diagnostic codes with no further validation or chart reviews, misclassification may

Table 5: Ratio of observed-to-expected rates of myocarditis among males following mRNA SARS-CoV-2 vaccination*

Risk window	Vaccine	Age group, yr	OE ratio (95% CI)			
			All doses	Dose 1	Dose 2	Dose 3
7 days	Pfizer	12–17	95.59 (53.5–157.66)	42.56 (8.78–124.38)	134.29 (61.41–254.93)	139.80 (28.83–408.55)
		18–29	16.98 (9.89–27.19)	2.45 (0.06–13.66)	34.05 (18.13–58.23)	20.02 (4.13–58.50)
		30–39	3.94 (0.81–11.51)	3.13 (0.08–17.45)	3.35 (0.08–18.68)	11.84 (0.30–65.95)
		40–49	5.80 (0.70–20.94)	0.00 (0.00–27.54)	8.05 (0.20–44.85)	25.51 (0.65–142.11)
		50–59	6.85 (0.83–24.74)	0.00 (0.00–33.4)	20.05 (2.43–72.45)	0.00 (0.00–100.90)
		60–69	4.01 (0.10–22.32)	0.00 (0.00–38.59)	12.10 (0.31–67.40)	0.00 (0.00–102.01)
		70–79	0.00 (0.00–11.15)	0.00 (0.00–29.43)	0.00 (0.00–32.29)	0.00 (0.00–64.13)
		≥ 80	10.45 (1.26–37.73)	0.00 (0.00–61.02)	35.25 (4.27–127.32)	0.00 (0.00–130.95)
	Moderna	12–17	NA	NA	NA	NA
		18–29	71.44 (46.67–104.68)	6.08 (0.15–33.87)	148.32 (95.03–220.69)	26.58 (0.67–148.11)
		30–39	20.55 (8.87–40.50)	0.00 (0.00–27.75)	50.77 (20.41–104.6)	8.45 (0.21–47.06)
		40–49	6.07 (0.15–33.80)	0.00 (0.00–71.62)	18.08 (0.46–100.73)	0.00 (0.00–63.56)
		50–59	6.69 (0.17–37.26)	23.61 (0.60–131.53)	0.00 (0.00–75.52)	0.00 (0.00–63.26)
		60–69	0.00 (0.00–27.28)	0.00 (0.00–114.68)	0.00 (0.00–87.46)	0.00 (0.00–60.58)
		70–79	12.78 (1.55–46.17)	0.00 (0.00–118.33)	0.00 (0.00–89.82)	23.74 (2.88–85.77)
		≥ 80	0.00 (0.00–47.39)	0.00 (0.00–232.48)	0.00 (0.00–188.82)	0.00 (0.00–86.93)
21 days	Pfizer	12–17	36.11 (21.04–57.82)	18.92 (5.15–48.43)	44.76 (20.47–84.98)	62.13 (16.93–159.08)
		18–29	6.66 (4.07–10.28)	1.63 (0.20–5.91)	13.10 (7.33–21.60)	6.67 (1.38–19.50)
		30–39	4.81 (2.40–8.62)	6.26 (2.30–13.63)	3.35 (0.69–9.80)	7.89 (0.96–28.50)
		40–49	3.86 (1.05–9.89)	2.49 (0.06–13.87)	5.37 (0.65–19.38)	8.50 (0.22–47.37)
		50–59	5.71 (1.85–13.32)	6.04 (0.73–21.8)	6.68 (0.81–24.15)	9.12 (0.23–50.80)
		60–69	2.67 (0.32–9.65)	0.00 (0.00–12.86)	4.03 (0.10–22.47)	9.22 (0.23–51.36)
		70–79	0.00 (0.00–3.72)	0.00 (0.00–9.81)	0.00 (0.00–10.76)	0.00 (0.00–21.38)
		≥ 80	3.48 (0.42–12.58)	0.00 (0.00–20.34)	11.75 (1.42–42.44)	0.00 (0.00–43.65)
	Moderna	12–17	NA	NA	NA	NA
		18–29	24.73 (16.30–35.98)	2.03 (0.05–11.29)	51.50 (33.33–76.03)	8.86 (0.22–49.37)
		30–39	8.56 (4.11–15.75)	5.01 (0.61–18.11)	16.92 (6.80–34.87)	2.82 (0.07–15.69)
		40–49	2.02 (0.05–11.27)	0.00 (0.00–23.87)	6.03 (0.15–33.58)	0.00 (0.00–21.19)
		50–59	4.46 (0.54–16.11)	15.74 (1.91–56.85)	0.00 (0.00–25.17)	0.00 (0.00–21.09)
		60–69	2.46 (0.06–13.73)	0.00 (0.00–38.23)	0.00 (0.00–29.15)	5.47 (0.14–30.50)
		70–79	4.26 (0.52–15.39)	0.00 (0.00–39.44)	0.00 (0.00–29.94)	7.91 (0.96–28.59)
		≥ 80	4.28 (0.11–23.86)	0.00 (0.00–77.49)	0.00 (0.00–62.94)	7.86 (0.20–43.77)

Note: CI = confidence interval, Moderna = mRNA-1273 (Moderna), NA = not applicable, OE = observed-to-expected, Pfizer = BNT162b2 (Pfizer-BioNTech).
*Observed rates of myocarditis were calculated per 100 000 vaccine doses. Expected rates of myocarditis were expressed per 100 000 population.

have been present. However, a crosscheck using data from the Provincial Laboratory Information Solution found that 98% (138 of 141) of myocarditis cases that we had identified were subjected to at least 1 type of troponin test within 30 days after the relevant vaccination dose. Of these 138, the resulting values for 13 people were within the normal range, and the troponin levels were higher than normal for the remaining 125 people. As we relied on data from hospital admissions and emergency department visits, we may have missed less severe myocarditis or myopericarditis events that were diagnosed in outpatient settings. Observed-to-expected analyses cannot determine the causality between an adverse outcome and the administered vaccine. However, they can help quantify the unexpectedness of observing a given number of cases. As noted above, these results show the overall low risk of myocarditis with the mRNA vaccine, given that the number of events is small. The confidence intervals for subgroup analyses are wide and, thus, caution is required when interpreting these results.

Conclusion

In this study, we found higher observed rates of myocarditis after receipt of mRNA vaccines than expected, but absolute rates were low. We observed a higher rate of myocarditis among males aged 18–29 years after receipt of the second dose of mRNA-1273 (Moderna) vaccine compared with those who received BNT162b2 (Pfizer-BioNTech) , though the rate was lower after the third dose. Comparisons of observed with expected rates also confirmed these findings, with the highest observed-to-expected ratios among males 18–29 years of age after the second dose of the mRNA-1273 vaccine. Although observed rates of myocarditis were higher than expected, the benefits of vaccination against SARS-CoV-2 in reducing the severity of COVID-19, hospital admission and deaths far outweigh the risk of developing myocarditis. We observed lower rates of myocarditis after a third vaccine dose, including among people aged 18–29 years who were among those with the highest rates of myocarditis. Thus, continued vaccination of this group, along with monitoring of adverse events, including myocarditis, should remain the preferred strategy.

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Competing interests: Naveed Zafar Janjua reports honoraria from AbbVie and Gilead, as well as participation on advisory boards with AbbVie, outside the submitted work. He also reports roles as coprincipal investigator and member of the steering committee with the Canadian Hepatitis C Network. No other competing interests were declared.

This article has been peer reviewed.

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Contributors: All authors participated in the conceptualization and designing of the study. Zaeema Naveed, Julia Li and Michelle Spencer managed data and performed data analyses. All authors participated in the interpretation of the findings. Zaeema Naveed drafted the manuscript. All authors revised it 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.

Funding: This work was supported by the Canadian Immunization Research Network (CIRN) 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. None of the funders had any role in the analyses and the development of this manuscript.

Data sharing: The study is based on data contained in various provincial registries and databases. Access to data could be requested through the British Columbia Centre for Disease Control Institutional Data Access for researchers who meet the criteria for access to confidential data. Requests for the data may be sent to datarequest@bccdc.ca.

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

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).

Accepted: Oct. 13, 2022

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