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MAJOR ARTICLE

Analysis of Myocarditis Among 252 Million mRNA-1273 Recipients Worldwide

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Background. Growing evidence indicates a causal relationship between SARS-CoV-2 infection and myocarditis. Post-authorization safety data have also identified myocarditis as a rare safety event following mRNA COVID-19 vaccination, particularly among adolescent and young-adult males after dose 2. We further evaluated the potential risk by querying the Moderna global safety database for myocarditis/myopericarditis reports among mRNA-1273 recipients worldwide.

Methods. Myocarditis/myopericarditis reports from 18 December 2020 to 15 February 2022 were reviewed and classified. The reported rate after any known mRNA-1273 dose was calculated according to age and sex, then compared with a population-based incidence rate to calculate observed-to-expected rate ratios (RRs).

Results. During the study period, 3017 myocarditis/myopericarditis cases among 252 million mRNA-1273 recipients who received at least 1 dose were reported to the Moderna global safety database. The overall reporting rate was 9.23 per 100 000 person-years, which was similar to the expected reference rate (9.0 cases per 100 000 person-years; RR [95% confidence interval (CI)], 1.03 [.97–1.08]). When stratified by sex and age, observed rates were highest for males aged <40 years, particularly those 18–24 years (53.76 per 100 000 person-years), which was higher than expected (RR [95% CI], 3.10 [2.68–3.58]). When considering only cases occurring within 7 days of a known dose, the observed rate was highest for males aged 18–24 years after dose 2 (4.23 per 100 000 doses administered).

Conclusions. Myocarditis/myopericarditis rates were not higher than expected for the overall population of mRNA-1273 recipients but were higher than expected in males aged 18–24 years, with most cases occurring 7 days after dose 2.

Keywords. myocarditis; COVID-19; SARS-CoV-2; vaccination; pharmacovigilance

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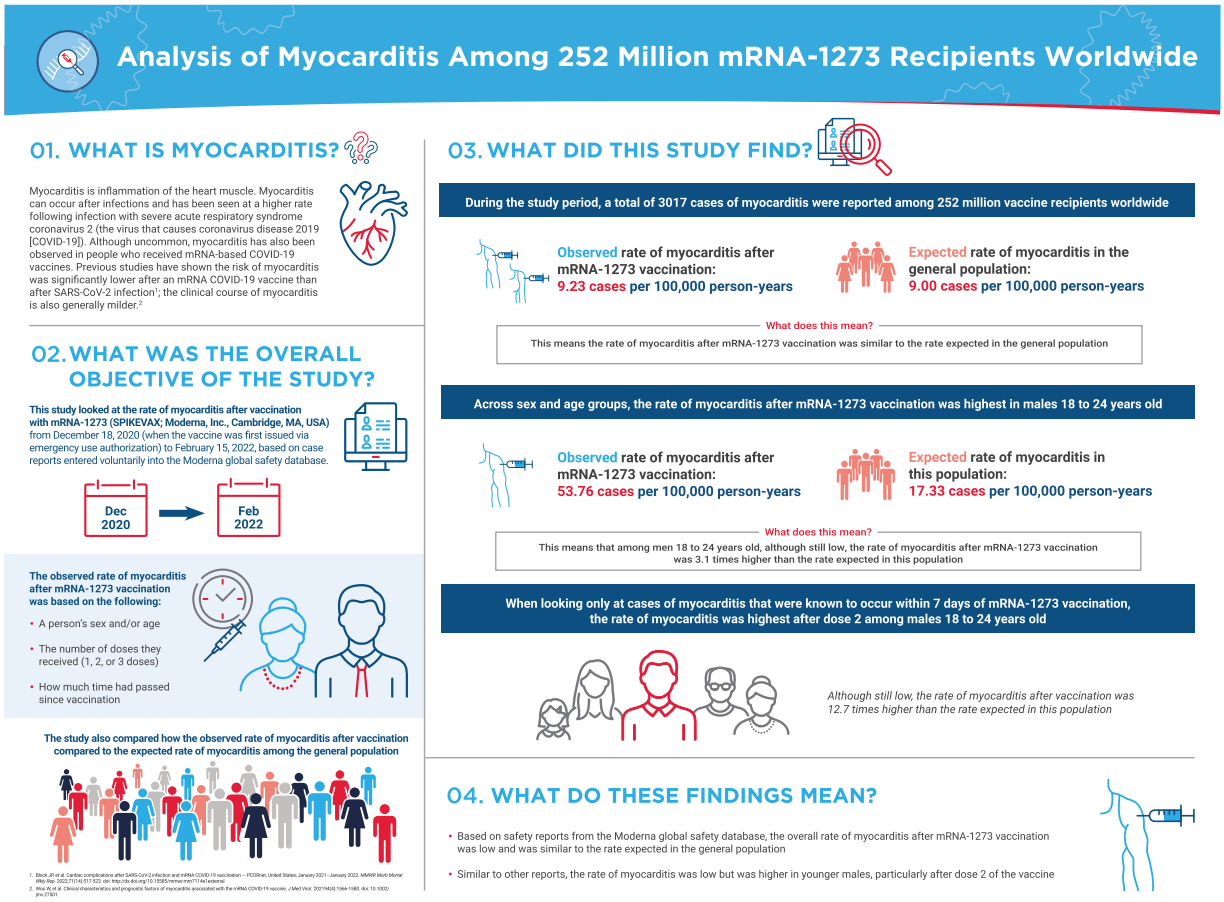
Graphical Abstract



Graphical summary describing the main outcomes of a surveillance study assessing the rates of myocarditis among 252 million mRNA-1273 recipients worldwide. Reports of myocarditis were obtained from the Moderna global safety database between December 18, 2020 and February 15, 2022. Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

As the coronavirus disease 2019 (COVID-19) pandemic continues to pose serious challenges to global health, vaccination in combination with behavioral strategies remains our best approach for controlling the virus. Multiple vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, have been developed; most prominent were 2 first-in-class vaccines utilizing messenger RNA (mRNA) technology (mRNA-1273 [SPIKEVAX; Moderna, Inc., Cambridge, MA] and BNT162b2 [COMIRNATY; Biontech, Mainz, Germany, and Pfizer, Inc., New York, NY]). These vaccines were evaluated in numerous clinical studies, including phase 3 studies that randomized approximately 15 000 individuals aged 18 years and older and 22 000 individuals aged 16 years and older to receive mRNA-1273 or BNT162b2, respectively, wherein the vaccines showed no serious safety concerns and were more than 94% effective against symptomatic infection [1, 2].

In December 2020, both mRNA-1273 and BNT162b2 received Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) for adults aged 18 years and older and 16 years and older, respectively [3, 4]. Interim recommendations for these age groups were made in December 2020 by the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) [3, 4]. Globally, both vaccines have since been approved for use in numerous countries, and public health agencies have issued vaccination recommendations for use in adult and adolescent populations.

After authorization, pharmacovigilance surveillance serves as a key source for identifying any rare vaccine-related adverse events not detected in phase 3 studies due to limited sample size. For mRNA COVID-19 vaccines in particular, the importance of these data is heightened because there was no prior post-authorization experience for vaccines

developed using the mRNA platform. Since initiation of mRNA COVID-19 vaccination campaigns, a growing body of evidence has largely confirmed safety findings from clinical studies [5]; however, reports emerging within 4 to 5 months of EUA also identified cases of vaccinated individuals presenting with myocarditis (with or without pericarditis), most notably in young males after dose 2 [6–9]. Myocarditis was not identified as a safety concern in phase 3 studies of mRNA-1273 or BNT162b2, including those in adolescents [1, 2, 10, 11].

Initial findings from Israeli and US military studies [6, 7] prompted researchers, vaccine manufacturers, and public health agencies, including the CDC, to further investigate a potential association between myocarditis and mRNA COVID-19 vaccination [12–16]. Here, we reviewed the cumulative risk of myocarditis/myopericarditis among global mRNA-1273 recipients since 18 December 2020, using the Moderna global safety database as the primary data source.

METHODS

Data Source and Case Definitions

Worldwide reports of potential myocarditis and myopericarditis entered into the Moderna global safety database from 18 December 2020 (date of first international EUA issuance) to 15 February 2022 were reviewed (see Supplementary Methods for database description). This study was based on data collected in the Moderna global safety database, mostly from adverse event reports submitted voluntarily, as part of routine ongoing post-authorization safety surveillance efforts by Moderna, Inc., as required by regulatory authorities (and including reports submitted to regulatory authorities [eg, FDA]); accordingly, a central institutional review board (IRB; Advarra) confirmed that this study met criteria for an exemption from IRB oversight under 45 CFR 46.104(d)(4).

The Moderna global safety database was queried for valid case reports of myocarditis and myopericarditis using the Medical Dictionary for Regulatory Activities (MedDRA v24.0) preferred terms (Supplementary Table 1). A systematic approach based on available references was used to characterize suspected reports of myocarditis following mRNA vaccination and to assess causality. Specifically, the Brighton Collaboration case definition for myocarditis was used to categorize individual cases into 1 of 5 established categories (level 1, definitive case; level 2, probable case; level 3, possible case; level 4, reported events with insufficient evidence; level 5, not a case of myocarditis/pericarditis) based on clinical findings and diagnostic evidence [17]. The World Health Organization (WHO)–Uppsala Monitoring Centre standardized case causality assessment tool [18] was then used to assess the likelihood that a case was attributable to the vaccine. This instrument grades cases into 1 of 6 categories (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable).

The global number of mRNA-1273 recipients who received at least 1 dose was estimated based on information retrieved on 16 February 2021, through the CDC [19], the European CDC [20], Public Health Agency of Canada [21], the Swiss Federal Office of Public Health [22], and Our World in Data [23]. For countries not publishing estimates of mRNA-1273 use, doses administered were estimated as 50% of doses distributed. US distributions by age, sex, and doses received supported estimation of stratum-specific vaccine recipient counts. Because mRNA-1273 has not been authorized for use in US adolescents (aged 12–17 years), the total assumed accrued exposure in adolescents aged younger than 18 years was limited to 3% of the total. As these demographic distributions were not available by dose, the same distribution was applied to each dose series to estimate age-specific rates in each dose group.

Statistical Analysis

Myocarditis/myopericarditis cases among mRNA-1273 recipients were characterized by age, sex, time to onset after vaccination, and dose number using descriptive statistics. To calculate the reporting rate, data were stratified and analyzed by age group per available demographic distributions of vaccine recipients published by the US CDC [19] (aged $<$12, 12–17, 18–24, 25–39, 40–49, 50–64, 65–74, and $\geq$75 years), sex, as well as sex and age group. The reporting rate observed at any time after mRNA-1273 was calculated as the number of reported cases per 100 000 person-years according to age group and sex. Person-years of follow-up were estimated by assigning a 21-day risk window following each estimated dose administered, noting that all cases were included regardless of their time to onset to produce a more conservative estimate. This observed reporting rate was compared with an expected rate from a population-based data estimate derived from individuals without a diagnosis of COVID-19 between March 2020 and January 2021 from the US Premier Healthcare Database [24]. Because age by sex-stratified estimates of the reference rate were not available in the source material, estimates were obtained by multiplying the age-specific rate estimate by the ratio of the sex-specific, stratum-specific rate to the overall rate. The observed reporting rate was divided by the expected rate and presented alongside associated 95% confidence intervals (CIs) calculated as follows: $e^{(\log(IRR) \pm 1.96*SE(\log(IRR)))}$.

RESULTS

Myocarditis and Myopericarditis Cases

From 18 December 2020 to 15 February 2022, an estimated 568 668 391 doses of mRNA-1273 were administered globally to 252 million recipients who received at least 1 dose based on information received from health officials worldwide; during this period, a total of 477 932 individual case reports (containing 1 819 802 adverse events, of which 324 734 were considered

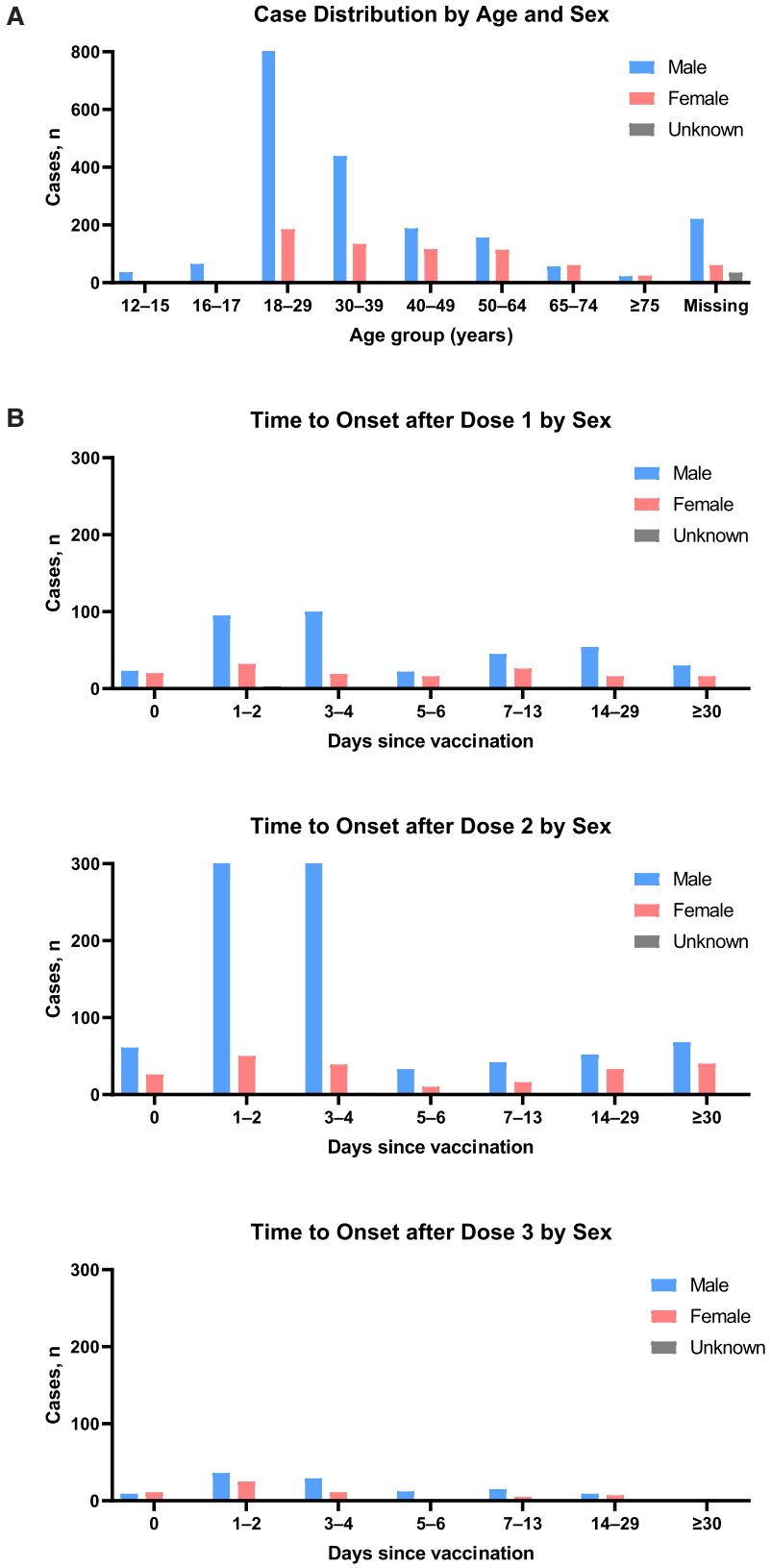


Figure 1. Distribution and time to onset of myocarditis and myopericarditis cases after mRNA-1273. (*A*) Distribution of the 3017 reported myocarditis and myopericarditis cases among mRNA-1273 recipients according to age and sex. A total of 317 cases were missing age and/or sex information. (*B*) Timing of the 518 reported cases of myocarditis and myopericarditis after dose 1, 1201 reported cases of myocarditis and myopericarditis after dose 2, and 175 reported cases of myocarditis and myopericarditis after dose 3. A total of 1123 cases were missing dose number information.

Table 1. Time to Onset of Myocarditis and Myopericarditis Cases by mRNA-1273 Dose Number

	Myocarditis/Myopericarditis Cases, n (%)			
Time to Onset, Days	Dose 1	Dose 2	Dose 3	Any Dose
<7	330 (63.7)	949 (79.0)	136 (77.7)	1415 (74.7)
7–29	141 (27.2)	144 (12.0)	36 (20.6)	321 (17.0)
≥30	46 (8.9)	108 (9.0)	3 (1.71)	157 (8.3)
Unknown	1 (.2)	…	…	1 (0.1)
Total[a]	518	1201	175	1894

[a]A total of 1124 cases contained insufficient information to determine dose or time to onset after mRNA-1273.

serious) were entered into the Moderna global safety database. Note that a single case can contain more than 1 reported event.

Of these 477 932 reported individual cases, a total of 3017 were cases of myocarditis/myopericarditis (0.6% of reported cases). Of the 3017 reported cases, 2180 (72.3%) were reported by a medically qualified healthcare professional involved in the patient's care and 2943 (97.5%) were considered serious. Among the 2414 (80.0%) cases with an outcome described at the time of reporting, 1457 (60.4%) were recovered or recovering, 913 (37.8%) were not recovered, and 44 (1.8%) were fatal (detailed in the Supplementary Results). There were 36 cases with COVID-19 reported at the time of myocarditis; however, no polymerase chain reaction or antibody data were provided.

The majority of cases originated from the European Economic Area (EEA; 1218 cases; 40.3%) and the United States (760 cases; 25.2%); 346 cases (11.5%) were from Asia, 154 (5.1%) were from Switzerland, 257 (8.5%) were from the United Kingdom, 265 (8.8%) were from Canada, and less than 1% were from the Middle East (7 cases; 0.2%) and Australia (3 cases; 0.1%). The median age of patients was

Table 2. Observed Versus Expected Rates of Myocarditis and Myopericarditis Among mRNA-1273 Recipients (per 100 000 Person-Years): Moderna Global Safety Database From 18 December 2020 to 15 February 2022

		Observed		Expected		
	Person-Years[a]	Cases, n	Rate[b]	Cases,[c] n	Rate[b]	Rate Ratio (95% CI)
All recipients						
All ages	32 695 513	3017	9.23	2943	9.00	1.03 (.97–1.08)
<12 years	49 043	0	0	2	4.00	NA
12–17 years	931 822	111	11.91	121	13.00	.92 (.71–1.19)
18–24 years	2 942 596	862	29.29	383	13.00	2.25 (2–2.54)
25–39 years	7 193 013	984	13.68	719	10.00	1.37 (1.24–1.51)
40–49 years	4 904 327	306	6.24	490	10.00	.62 (.54–.72)
50–64 years	8 500 833	274	3.22	680	8.00	.4 (.35–.46)
65–74 years	4 904 327	117	2.39	392	8.00	.3 (.24–.37)
≥75 years	3 269 551	46	1.41	229	7.00	.2 (.15–.28)
Male recipients						
All ages	15 563 064	2263	14.54	1868	12.00	1.21 (1.14–1.29)
<12 years	23 345	0	0	1	5.33	NA
12–17 years	443 547	101	22.77	77	17.33	1.31 (.98–1.77)
18–24 years	1 400 676	753	53.76	243	17.33	3.1 (2.68–3.58)
25–39 years	3 423 874	766	22.37	457	13.33	1.68 (1.49–1.88)
40–49 years	2 334 460	188	8.05	311	13.33	.6 (.5–.72)
50–64 years	4 046 397	156	3.86	432	10.67	.36 (.3–.43)
65–74 years	2 334 460	56	2.40	249	10.67	.22 (.17–.3)
≥75 years	1 556 306	22	1.41	145	9.33	.15 (.1–.24)
Female recipients						
All ages	17 132 449	705	4.11	1028	6.00	.69 (.62–.75)
<12 years	25 699	0	0	1	2.67	NA
12–17 years	488 274	10	2.05	42	8.67	.24 (.12–.47)
18–24 years	1 541 920	108	7.00	134	8.67	.81 (.7–1.04)
25–39 years	3 769 139	211	5.60	251	6.67	.84 (.7–1.01)
40–49 years	2 569 867	116	4.51	171	6.67	.68 (.53–.86)
50–64 years	4 454 437	114	2.56	238	5.33	.48 (.38–.4)
65–74 years	2 569 867	61	2.37	137	5.33	.45 (.33–.6)
≥75 years	1 713 245	24	1.40	80	4.67	.3 (.12–.47)

Abbreviations: CI, confidence interval; NA, not applicable.

[a]Rates presented per 100 000 person-years with calculation of person-time based on a 21-day risk window. All reported cases were included regardless of time to onset.

[b]Calculated as the rate of myocarditis and myopericarditis cases per 100 000 person-years.

[c]Numbers of cases were based on data from the US Premier Healthcare Database [24]. Because age by sex-stratified estimates of the reference rate were not available, estimates were obtained by multiplying the age-specific rate estimate by the ratio of the sex-specific, stratum-specific rate to the overall rate.

Table 3. Reported Rates of Myocarditis and Myopericarditis Within 7 Days of mRNA-1273 According to Age and Dose Number (per 100 000 Doses Administered): Moderna Global Safety Database: From 18 December 2020 to 15 February 2022

	Reported Rate of Myocarditis/Myopericarditis Within 7 Days[a]		
	Dose 1	Dose 2	Dose 3
All recipients			
<12 years	0	0	0
12–17 years	.15	.77	0
18–24 years	.47	2.21	.22
25–39 years	.26	.75	.23
40–49 years	.08	.29	.12
50–64 years	.05	.07	.08
65–74 years	.02	.05	.07
≥75 years	.02	.02	.05
Male recipients			
<12 years	0	0	0
12–17 years	.26	1.46	0
18–24 years	.82	4.23	.40
25–39 years	.41	1.40	.33
40–49 years	.12	.43	.13
50–64 years	.04	.10	.09
65–74 years	.03	.05	.08
≥75 years	.02	.01	.04
Female recipients			
<12 years	0	0	0
12–17 years	.05	.13	0
18–24 years	.15	.38	.06
25–39 years	.12	.16	.14
40–49 years	.06	.17	.12
50–64 years	.06	.04	.06
65–74 years	.01	.04	.07
≥75 years	.02	.03	.05

[a]Includes cases with known dose and time to onset. Number of mRNA-1273 recipients by dose recipients extrapolated based on the proportion of vaccine administrations given as the first, second, and third dose in the United States.

29 years (range, 12–94 years). Cases were most frequently reported among males (1117 cases; 75.0%), with approximately half of all cases involving males aged 18–39 years (1519 cases; 50.3%) (Figure 1).

Of the 3017 reported myocarditis/myopericarditis cases, a total of 1123 cases (37.2%) had missing dose information and 1894 (62.8%) had known dose information. Of those with known dose information, 518 (27.3%) were reported to have occurred after dose 1, 1201 (63.4%) after dose 2, and 175 (9.2%) after dose 3 (Table 1; Figure 1).

Among those with symptom-onset information available, the median time to onset was 3 days.

Observed Versus Expected Myocarditis/Myopericarditis Rates

The 3017 reported cases of myocarditis/myopericarditis corresponded to an overall observed reporting rate of 9.23 per 100 000 person-years when including all cases regardless of time to onset. The observed reporting rate among mRNA-1273 recipients varied substantially by age and sex (Table 2). Reporting rates were 14.54 per 100 000 person-years for males and 4.11 per 100 000 person-years for females. Across age groups, reporting rates were highest for individuals aged 18–24 years (29.29 per 100 000 person-years). When stratified by age and sex, younger males aged less than 40 years had the highest myocarditis/myopericarditis reporting rates, particularly those aged 18–24 years (53.76 per 100 000 person-years); among females, rates were also highest for those aged 18–24 years (7.0 per 100 000 person-years).

Comparing overall observed myocarditis/myopericarditis rates after mRNA-1273 with expected rates (based on background incidence in a US population-based study [24]) resulted in a rate ratio of 1.03 (95% CI, .97–1.08) (Table 2). Across age groups, a higher-than-expected rate was observed for those individuals aged 18–24 years (2.25; 95% CI, 2.00–2.54). When further stratified by sex, a higher-than-expected rate was more pronounced for males aged 18–24 years (3.10; 95% CI, 2.68–3.58); rate ratios were 1.31 (95% CI, .98–1.77) for males aged 12–17 years and 1.68 (95% CI, 1.49–1.88) for males aged 25–39 years. Females aged 18–24 and 25–39 years had rate ratios of .81 (95% CI, .63–1.04) and .84 (95% CI, .70–1.01), respectively. A sensitivity analysis discounting the exposed person-time estimate by 25% was conducted (Supplementary Table 2) and produced rates comparable to those estimated in the initial analysis (Table 2); increases in the rate of myocarditis in adolescent and young males were consistent with the initial analysis.

Myocarditis/Myopericarditis Rates Within 7 Days of mRNA-1273

When analysis was restricted to cases with onset within 7 days of a known dose, the observed rate for all vaccine recipients per 100 000 doses administered was generally higher after dose 2 (Table 3). Overall, the highest rates within 7 days of vaccination were reported after dose 2 in males aged 39 years or younger, particularly those aged 18–24 years (4.23 per 100 000 doses administered). Comparing to expected rates yielded a rate ratio of 12.74 (95% CI, 8.75–18.54) for males aged 18–24 years within 7 days of dose 2 (Table 4). Overall, rates were generally lower after dose 3 compared with dose 2 (Table 4); however, precision was low and these estimates may change as the demographic characteristics of dose 3 vaccine recipients change over time.

DISCUSSION

To further understand the potential association between myocarditis and mRNA-1273 vaccination, we evaluated worldwide myocarditis/myopericarditis rates among mRNA-1273 recipients as cumulatively reported to the Moderna global safety database through 15 February 2022. Since first EUA (18 December 2020), this database has collected spontaneous adverse events following mRNA-1273 administration as

Table 4. Observed Versus Expected Rates of Myocarditis and Myopericarditis Within 7 Days of mRNA-1273 According to Age and Dose Number (per 100 000 Doses Administered): Moderna Global Safety Database From 18 December 2020 to 15 February 2022

	Rate Ratio (95% CI)[a]		
	Dose 1	Dose 2	Dose 3
All recipients			
All ages	.80 (.7–.93)	2.71 (2.4–3.06)	.73 (.59–.91)
<12 years	NA	NA	NA
12–17 years	.61 (.29–1.3)	3.07 (1.7–5.54)	NA
18–24 years	1.89 (1.37–2.61)	8.88 (6.55–12.04)	.89 (.5–1.58)
25–39 years	1.38 (1.08–1.77)	3.93 (3.11–4.97)	1.21 (.82–1.78)
40–49 years	.44 (.29–.67)	1.52 (1.09–2.11)	.63 (.36–1.11)
50–64 years	.34 (.23–.50)	.45 (.31–.66)	.50 (.30–.84)
65–74 years	.12 (.06–.26)	.30 (.16–.54)	.47 (.24–.94)
≥75 years	.15 (.06–.38)	.14 (.05–.41)	.34 (.12–.93)
Male recipients			
All ages	.92 (.78–1.09)	3.67 (3.17–4.26)	.74 (.56–.97)
<12 years	NA	NA	NA
12–17 years	.79 (.33–1.9)	4.41 (2.16–8.99)	NA
18–24 years	2.48 (1.68–3.65)	12.74 (8.75–18.54)	1.21 (.62–2.37)
25–39 years	1.61 (1.19–2.19)	5.49 (4.12–7.31)	1.29 (.80–2.09)
40–49 years	.46 (.27–.76)	1.67 (1.12–2.51)	.50 (.23–1.06)
50–64 years	.20 (.11–.37)	.50 (.31–.80)	.43 (.22–.85)
65–74 years	.14 (.05–.35)	.27 (.12–.58)	.37 (.15–.95)
≥75 years	.14 (.04–.47)	.06 (.01–.43)	.21 (.05–.98)
Female recipients			
All ages	.61 (.47–.79)	1.05 (.82–1.34)	.74 (.51–1.07)
<12 years	NA	NA	NA
12–17 years	.32 (.07–1.57)	.78 (.21–2.89)	NA
18–24 years	.91 (.48–1.72)	2.29 (1.28–4.11)	.35 (.09–1.3)
25–39 years	.97 (.61–1.53)	1.28 (.80–2.06)	1.11 (.57–2.17)
40–49 years	.43 (.21–.88)	1.30 (.74–2.31)	.91 (.38–2.13)
50–64 years	.57 (.33–.99)	.38 (.19–.77)	.59 (.26–1.34)
65–74 years	.10 (.02–.42)	.36 (.14–.92)	.68 (.24–1.91)
≥75 years	.17 (.04–.76)	.31 (.08–1.13)	.58 (.14–2.42)

Abbreviations: CI, confidence interval; NA, not applicable.

[a]Expected rates were based on data from US Premier Healthcare Database [24]. Because age by sex-stratified estimates of the reference rate were not available, estimates were obtained by multiplying the age-specific rate estimate by the ratio of the sex-specific, stratum-specific rate to the overall rate.

reported from multiple data sources. In this analysis, the majority of reports were received from regulatory authorities, primarily originating from the United States and the EEA. Overall, the rate of myocarditis/myopericarditis among mRNA-1273 recipients was low (3017 cases; 9.23 per 100 000 person-years); however, as with reports in the literature [6, 12, 13, 15, 16, 25], higher rates than expected were observed for younger males aged 39 years or younger, particularly after dose 2. Males aged 18–24 years had the highest rate after vaccination (53.76 per 100 000 person-years), 3.1-fold higher than the expected rate.

Although myocarditis after vaccination is generally considered a rare safety event, infrequent cases have been previously reported [26]. In addition to reports after mRNA COVID-19 vaccination [6, 12, 13, 15, 16, 27], myocarditis has also been observed following smallpox vaccination using the standard live viral (vaccinia) vaccine. In 1 study, a rate of 7.8 per 100 000 smallpox vaccine recipients was reported over a 30-day window, a 3.6-fold higher rate than expected [28].

Before the COVID-19 pandemic, it was recognized that there are numerous infectious and noninfectious causes of myocarditis, and that viral infection represented the most common cause [29]. Since the emergence of SARS-CoV-2, growing evidence also indicates a causal relationship between SARS-CoV-2 infection and myocarditis, with an analysis from the CDC estimating that the risk of myocarditis among hospitalized persons was 15.7 times higher for patients with than those without COVID-19 [24]. Further, the risk of developing myocarditis from SARS-CoV-2 infection was higher for males than females and highest for children (aged <16 years) and older adults (aged ≥50 years) [24]. The prominent role that SARS-CoV-2 infection plays in myocarditis for young males was also highlighted in a separate analysis, which estimated the rate of myocarditis from primary infection as 450 per million among males aged 12–17 years, a rate approximately 6 times higher than that observed after mRNA COVID-19 vaccination [30].

Notably, a population-based cohort study of approximately 2.4 million patients aged 18 years and older observed 15 cases of confirmed myocarditis after any dose of an mRNA COVID-19 vaccine (2 cases after dose 1; 13 cases after dose 2), for an incidence of 0.08 per 100 000 first doses and 0.58 per 100 000 second doses; acute myocarditis was described as a rare event [13]. All reported cases occurred in younger males (median age, 25 years) who were hospitalized and had symptoms resolve with conservative management. The US FDA previously presented an assessment of myocarditis/pericarditis rates using the FDA Biologics and Effectiveness Safety (BEST) active surveillance system, which consists of 4 health claims data sources with a total of 76.5 to 89.5 million annual enrollees [31]. Within the first 7 days of administration of any mRNA COVID-19 vaccine dose (eg, mRNA-1273 or BNT162b2), the incidence rate of myocarditis/pericarditis per 1 million person-days was generally low for all age groups; rates were highest for males aged 18–25 years after dose 2. At the 21 October 2021 CDC ACIP meeting, the COVID-19 Vaccine Safety Technical Work Group summarized the available data to date on myocarditis rates after mRNA COVID-19 vaccination from multiple worldwide safety monitoring systems [32]; the data indicated that myocarditis was associated with both mRNA-1273 and BNT162b2 among adolescents and young adults, more frequently among males. The COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety also reviewed available evidence from multiple countries and noted that, while some data suggest increased myocarditis incidence in young males after dose 2 of mRNA-based vaccines, the overall risk is low [8].

Several large US surveillance systems have shown comparable risk of myocarditis between mRNA-1273 and BNT162b2 (eg, Vaccine Adverse Event Reporting System, FDA BEST System, and Department of Veterans Affairs active surveillance Rapid Cycle Analysis for COVID-19 vaccines) [32, 33]. However, a recent analysis from the Vaccine Safety Datalink estimated an excess 5.2 myocarditis/myopericarditis cases per million doses of mRNA-1273 versus BNT162b2 among 18- to 39-year-olds (adjusted rate ratio [95% CI], 1.24 [.70–2.14]; 2-sided $P = .454$), although no major clinical differences in cases between vaccines were observed [33].

Most important, it is critical to put these rare and generally mild events in the context of the number of myocarditis cases prevented by COVID-19 vaccination. Numerous studies have demonstrated the robust effectiveness of mRNA-1273 in real-life practice [33–36]. Further, a report by members of the CDC COVID-19 Response Team and colleagues, summarized at the ACIP meeting on 23 June 2021, estimated that, over a 120-day period, 45 to 56 myocarditis cases per million dose 2 vaccinations were predicted to occur in males aged 18 to 24 years, whereas mRNA COVID-19 vaccination would simultaneously prevent 12 000 COVID-19 cases, 530 hospitalizations, 127 intensive care unit admissions, and 3 deaths [14].

Recently, the US FDA approved mRNA-1273 as a COVID-19 vaccine in adults aged 18 years old and older. Considering evidence to date regarding the increased risk of myocarditis among mRNA-1273 vaccine recipients aged 18–29 years, especially young-adult males, several public health authorities, including the CDC, consider that the risk of vaccine-related myocarditis can be reduced by increasing the dosing interval between dose 1 and 2 of the primary series. The CDC ACIP now recommends a 4- to 8-week interval between the first and second doses of mRNA-1273 and indicates that an 8-week interval may be optimal for young-adult males [37].

Based upon extensive review of this and other available evidence, the authors concluded that the benefit of mRNA COVID-19 vaccination clearly outweighed the risk of myocarditis in all recommended age groups, including younger male adolescents at heightened risk for myocarditis after vaccination [14]. Notably, in contrast to viral myocarditis [29], reported myocarditis and myopericarditis cases after vaccination are generally mild, self-limiting, and resolve using conservative treatment [8, 12–14, 16, 25, 38].

The current analysis utilized information submitted to the Moderna global safety database, which continuously receives safety reports from a large, geographically diverse population, enabling detection and assessment of rare safety events on an ongoing and up-to-date basis. A key limitation of this analysis is that the submitted information is primarily derived from passive, spontaneous adverse event reporting, which lacks a denominator (to clearly define the number of mRNA-1273 recipients) and often provides limited details on clinical features and outcomes of reported cases. As such, chart reviews and follow-ups on case resolutions were precluded.

In conclusion, our findings demonstrate that myocarditis/myopericarditis in mRNA-1273 recipients is a rare event; previous reports suggest these cases are likely generally mild and self-limiting [12–14, 16, 38]. As noted in a recent update based on data presented to the ACIP, the benefits of mRNA COVID-19 vaccination (ie, prevention of COVID-19, hospitalization, intensive care unit admissions, and death) clearly outweigh the potential harm of vaccine-related myocarditis [14]. In safely and effectively preventing COVID-19 and its complications (including myocarditis, a natural complication of SARS-CoV-2 infection), mRNA COVID-19 vaccines thus remain essential for controlling COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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