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Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination

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ABSTRACT

Background: Evidence indicates that mRNA COVID-19 vaccination is associated with risk of myocarditis and possibly pericarditis, especially in young males. It is not clear if risk differs between mRNA-1273 versus BNT162b2. We assessed if risk differs using comprehensive health records on a diverse population.
Methods: Members 18–39 years of age at eight integrated healthcare-delivery systems were monitored using data updated weekly and supplemented with medical record review of myocarditis and pericarditis cases. Incidence of myocarditis and pericarditis events that occurred among vaccine recipients 0 to 7 days after either dose 1 or 2 of a messenger RNA (mRNA) vaccine was compared with that of vaccinated concurrent comparators who, on the same calendar day, had received their most recent dose 22 to 42 days earlier. Rate ratios (RRs) were estimated by conditional Poisson regression, adjusted for age, sex, race and ethnicity, health plan, and calendar day. Head-to-head comparison directly assessed risk following mRNA-1273 versus BNT162b2 during 0–7 days post-vaccination.
Results: From December 14, 2020 – January 15, 2022 there were 41 cases after 2,891,498 doses of BNT162b2 and 38 cases after 1,803,267 doses of mRNA-1273. Cases had similar demographic and clinical characteristics. Most were hospitalized for ≤1 day; none required intensive care. During days 0–7 after dose 2 of BNT162b2, the incidence was 14.3 (CI: 6.5–34.9) times higher than the comparison interval, amounting to 22.4 excess cases per million doses; after mRNA-1273 the incidence was 18.8 (CI: 6.7–64.9) times higher than the comparison interval, amounting to 31.2 excess cases per million doses. In head-to-head comparisons 0–7 days after either dose, risk was moderately higher after mRNA-1273 than after BNT162b2 (RR: 1.61, CI 1.02–2.54).
Conclusions: Both vaccines were associated with increased risk of myocarditis and pericarditis in 18–39-year-olds. Risk estimates were modestly higher after mRNA-1273 than after BNT162b2.

1. Introduction

Two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) have been widely used to combat the COVID-19 pandemic [1,2]. By late May 2021, a higher than

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expected number of myocarditis reports following mRNA vaccination were submitted to the United States (US) Vaccine Adverse Event Reporting System (VAERS), particularly among young males after dose 2, suggesting an increased risk for this rare adverse event [3]. These reports coincided with authorization and recommendation of the BNT162b2 vaccine for adolescents aged 12–15 years [4]. The Food and Drug Administration (FDA) added warnings about myocarditis and pericarditis to the BNT162b2 and mRNA-1273 vaccines Emergency Use Authorization fact sheets in June 2021 [5]. Elevated incidence of myocarditis among mRNA COVID-19 vaccine recipients has also been seen in Israel (BNT162b2 only), Canada, and multiple European countries following both BNT162b2 and mRNA-1273 vaccines [6–11]. By fall of 2021 several European countries, Canada, and the United Kingdom made changes to their COVID-19 vaccine recommendations for adolescents and young adults based on internal analyses and media releases which suggested a higher incidence of myocarditis after the mRNA-1273 vaccine compared to the BNT162b2 vaccine [12–17].

As part of ongoing COVID-19 vaccine safety monitoring, the Vaccine Safety Datalink (VSD) reported in interim analyses that the incidence of myocarditis and pericarditis was increased approximately 10-fold among 12–39-year-olds during the 0–7 days after mRNA vaccination, when compared with the 22–42 days post-vaccination [18]. However, whether the risk of myocarditis and pericarditis differs by mRNA vaccine product is not clear. Here we update previously reported comparisons of myocarditis and pericarditis incidence during a risk interval after mRNA vaccination versus a later comparison interval, and present new head-to-head comparisons assessing whether risk differs between the two mRNA vaccines.

2. Methods

2.1. Population

The VSD monitors vaccine safety as part of a collaboration between the Centers for Disease Control and Prevention (CDC) and 8 data-contributing integrated healthcare organizations that have comprehensive electronic medical records on approximately 12 million insured people in the United States [19]. The VSD's ability to capture vaccine records from Immunization Information Systems and non-traditional settings was previously published [20]. VSD sites did not systematically recommend BNT162b2 or mRNA 1273 differentially for people with underlying health conditions. The current study included persons aged 18–39 years who were members of integrated healthcare organizations within the VSD and vaccinated with either mRNA vaccine. The study population was limited to 18–39-year-olds because these ages have been associated with an increased risk for myocarditis and pericarditis following vaccination and both BNT162b2 and mRNA-1273 vaccines are authorized or approved in this age group [21,22].

VSD has been conducting weekly COVID-19 vaccine safety monitoring since vaccination began in December 2020. Interim results based on data through June 26, 2021 were previously published [18]. This report includes data on primary series mRNA vaccinations through January 15, 2022. Booster doses are not included in these analyses.

2.2. Outcome: Myocarditis and pericarditis

We identified potential cases of myocarditis and pericarditis evaluated in emergency department (ED) and inpatient settings in the 1–98 days after dose 1 or dose 2 of mRNA COVID-19 vaccine, using ICD-10 codes (B33.22, B33.23, I30.*, I31.9, I40.*, and I51.4) as previously described [18]. Cases with COVID-19 identified by molecular assay or diagnostic code in the 30 days before diagnosis were excluded.

2.3. Medical record review

All identified potential cases underwent medical record review which verified the diagnosis, assessed timing of symptom onset (which resulted in some onsets shifting to day 0, post-vaccination), and collected clinical details about the event. Clinician adjudication (MEO, TTB) verified that cases met the CDC case definition of confirmed or probable myocarditis, pericarditis, or myopericarditis (cases meeting definition for both myocarditis and pericarditis) and didn't have clear alternative etiology. Cases not meeting CDC case definitions for myocarditis or pericarditis were excluded [21]. Analyses included cases of myocarditis, myopericarditis and pericarditis.

2.4. Statistical analysis

2.4.1. Risk versus comparison interval after mRNA vaccines

As part of ongoing weekly safety surveillance, we used conditional Poisson regression to compare the number of observed versus expected myocarditis and pericarditis cases in the risk interval (0–7 days) after vaccination [18]. Based on our prior work, medical record-verified cases clustered 0–7 day post-vaccination [18]. The number of outcomes expected during the risk interval was derived from vaccinated comparators who were concurrently (on the same calendar days) in a comparison interval (days 22–42) after vaccination. As previously described [18], we used vaccinated concurrent comparators during a 22–42 days post vaccination comparison interval to minimize potential bias that could arise in comparisons between vaccinated and unvaccinated individuals. On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval. Analyses were conditioned on strata defined by calendar date, age group, sex, race/ethnicity, and VSD site. Separate analyses compared the risk versus comparison intervals after each dose of each product, and a combined analysis compared the risk versus comparison intervals after either dose of either product. To estimate excess risk per million doses administered, the risk interval crude incidence rate was divided by the adjusted rate ratio (RR) estimate, and the result was subtracted from the risk interval crude incidence rate.

We examined temporal clustering of the onset of myocarditis and pericarditis by day after vaccination using Kulldorff's scan statistic [23].

2.4.2. Head-to-head comparisons of mRNA-1273 versus BNT162b2 mRNA vaccines

Head-to-head comparisons of mRNA-1273 versus BNT162b2 vaccines were conducted in strata comprised of similar individuals in a post-vaccination risk interval on the same calendar day at the same VSD site. Thus, each stratum was anchored to a single calendar day and included individuals of the same age group, sex, and race/ethnicity who, on that day, were inside the 0–7 day risk interval. Poisson regression was used to estimate the RR for myocarditis and pericarditis in mRNA-1273 vaccinees versus BNT162b2 vaccinees, conditional on the strata. Regressions contained no adjustment for additional covariates beyond age, sex, race/ethnicity, VSD site, and calendar day. We used exact statistics to test the null hypothesis that the RR was 1.0. Separate analyses were also conducted in subgroups defined by sex and specific diagnosis (including or excluding pericarditis). Excess cases per million doses were estimated by dividing the mRNA-1273 crude incidence rate by the

adjusted RR estimate and subtracting the result from the mRNA-1273 incidence rate.

This activity was approved by the Institutional Review Boards of all participating organizations with a waiver of informed consent and was conducted consistent with appliable federal law and CDC policy (45C.F.R. part 46.102(l)(2), 21C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

We used SAS version 9.4 (SAS Institute) for all analyses.

3. Results

From December 14, 2020, through January 15, 2022, a total of 2,891,498 doses of the BNT162b2 vaccine (1,479,596 dose 1 and 1,411,902 dose 2) and 1,803,267 doses of the mRNA-1273 vaccine (923,711 dose 1 and 879, 556 dose 2) were administered to VSD members aged 18–39 years. During the 0–7 days following vaccination, 95 potential cases of myocarditis and pericarditis were identified, and medical record review and adjudication verified 79 (83%): 41 after BNT162b2 (14.2 cases per million doses) and 38 after mRNA-1273 (21.1 cases per million doses). Incidence per million first doses was 4.7 for BNT162b2 and 9.7 for mRNA-1273; incidence per million second doses was 24.1 for BNT162b2 and 33.0 for mRNA-1273 (Table 2). 96% of cases following dose 2 received their 2nd dose +/- 1 day of the recommended day (day 21 for BNT162b2, day 28 for mRNA-1273) or later. Most cases (65%) were adjudicated as myopericarditis (27 post-BNT162b2, 24 post-mRNA-1273), with more cases of myocarditis following BNT162b2 (12 post-BNT162b2, 6 post-mRNA-1273) and more cases of pericarditis following mRNA-1273 (2 post-BNT162b2, 8 post-mRNA-1273).

Median patient age was 22 years (IQR 19–27 years) for cases after BNT162b2 and 23.5 years (IQR 21–31 years) after mRNA-1273. Regardless of vaccine, most cases occurred in males (88% post BNT162b2, 84% post-mRNA-1273) and after dose 2 (83% post-BNT162b2, 76% post-mRNA-1273), with median symptom onset ranging from 1 to 2 days after vaccination. (Table 1). The presence of chest pain, shortness of breath, palpitations, abnormal troponin levels, and abnormal electrocardiogram reports were also similar between products. Most patients were admitted to the hospital (85% post-BNT162b2, 79% post-mRNA-1273), with a median length of stay of 1 day, none were admitted to the intensive care unit, none died, and all were discharged home.

Regardless of product, individuals with pericarditis tended to be older (median age 31.5 years) than those with myocarditis (21.5 years) and myopericarditis (23.0 years) (Supplemental Table 1). For both products, clinical presentation was similar regardless of diagnosis, except for elevated troponins in cases of myocarditis and myopericarditis. Cardiac MRIs, although rarely obtained and only in cases of myocarditis and myopericarditis, were mostly abnormal. Nearly all individuals with myocarditis and myopericarditis were admitted to the hospital (89% and 90%), while those with pericarditis were usually seen in the ED (70%).

Table 1
Demographics and clinical characteristics of verified myocarditis and pericarditis cases in the 0–7 days after any dose of mRNA vaccine by product among individuals aged 18–39 years, December 14, 2020–January 15, 2022.

	BNT162b2 N = 41	mRNA-1273 N = 38
Age at symptom onset, median (IQR)	22 years (19–27 years)	23.5 years (21–31 years)
18–19 years	12 (29%)	5 (13%)
20–24 years	15 (37%)	16 (42%)
25–29 years	7 (17%)	5 (13%)
30–34 years	4 (10%)	6 (16%)
35–39 years	3 (7%)	6 (16%)
Male sex	36 (88%)	32 (84%)
Race/Ethnicity		
White, non-Hispanic	16 (39%)	18 (47%)
Black, non-Hispanic	1 (2%)	0 (0%)
Asian	4 (10%)	7 (18%)
Hispanic	16 (39%)	9 (24%)
Multiple/Other	2 (5%)	1 (3%)
Unknown	2 (5%)	3 (8%)
History of COVID-19 infection[1]	7 (17%)	5 (13%)
History of myocarditis and/or pericarditis	0 (0%)	4 (11%)
Outcome after Dose 1	7 (17%)	9 (24%)
Time from vaccination to symptom onset, median (range)	1 day (0–7 days)	2 days (0–7 days)
Adjudication diagnosis		
Myocarditis	12 (29%)	6 (16%)
Myopericarditis	27 (66%)	24 (63%)
Pericarditis	2 (5%)	8 (21%)
Signs/Symptoms		
Chest pain/pressure/discomfort	41 (100%)	38 (100%)
Dyspnea/shortness of breath	18 (44%)	18 (47%)
Palpitations	7 (17%)	6 (16%)
Pericardial rub	0 (0%)	1 (3%)
Other[2]	24 (59%)	24 (63%)
Diagnostic testing		
Troponin level obtained	41 (100%)	38 (100%)
Abnormal[3] troponin level	39 (95%)	29 (76%)
ECG obtained	41 (100%)	38 (100%)
Abnormal ECG	34 (83%)	36 (95%)
Echocardiogram obtained	40 (98%)	34 (89%)
Abnormal echocardiogram	18/40 (45%)	14/34 (41%)
Cardiac MRI obtained	8 (20%)	6 (16%)
Abnormal cardiac MRI	6/8 (75%)	6/6 (100%)
Highest level of care		
Emergency department	6 (15%)	8 (21%)
Admitted to hospital, never in ICU	35 (85%)	30 (79%)
Admitted to ICU	0 (0%)	0 (0%)
Length of hospital stay, median (range)	1 day (0–2 days)	1 day (0–13 days)
Status at time of medical record review		
Discharged to home	41 (100%)	38 (100%)
Follow-up visit[4]	37 (90%)	34 (89%)

Abbreviations: ECG = electrocardiogram, MRI = magnetic resonance imaging, ICU = intensive care unit.

[1] Individuals with COVID-19 diagnosis or positive PCR test in the 30 days prior to myocarditis or pericarditis diagnosis were excluded from the study population. Individuals with COVID diagnosis or positive PCR test > 30 days prior to myocarditis or pericarditis diagnosis were included.

[2] Other symptoms included fever, arm pain, syncope, headache, tachycardia, fatigue, chills, numbness, tingling, and nausea.

[3] Troponin levels were classified as abnormal if outside normal range for the particular assay used.

[4] At least one follow-up visit since discharge was noted in the medical record at the time of review.

3.1. Risk during days 0–7 post-vaccination versus days 22–42 post-vaccination

In updated weekly surveillance using vaccinated concurrent comparators, the incidence of verified myocarditis and pericarditis was elevated during days 0–7 post-vaccination when compared with days 22–42 post-vaccination. After either dose (both doses combined), the adjusted RR for the 0–7 day risk interval was 6.9 (95% confidence interval [CI] 3.6–14.1) after BNT162b2 and 9.2 (95% CI 4.1–22.9) after mRNA-1273 (Table 2). After dose 2 of BNT162b2, the RR comparing risk versus comparison interval was 14.3 (95% CI 6.5–34.9), with 22.4 excess cases per million second doses administered; after dose 2 of mRNA-1273, the RR was 18.8 (95% CI 6.7–64.9) with 31.2 excess cases per million second doses administered (Table 2).

Scan statistics indicated myocarditis and pericarditis cases strongly clustered within a week post-vaccination. The clusters least likely to be due to chance alone were overlapping: days

Table 2
Myocarditis and pericarditis during the 0–7-day risk interval post-vaccination versus the comparison interval 22–42 days post-vaccination, in 18–39-year-olds, by product and dose, December 14, 2020–January 15, 2022.

Vaccine	Dose	Cases in 0–7 day risk interval (Rate of cases /million person years)	Cases in 22–42-day comparison interval (Rate of cases/million person years)	Adjusted rate ratio[2] (95% confidence interval)	2-Sided P-value	Cases in risk period per million doses	Excess cases in risk period per million doses[4]
Both mRNA	Either Dose[1]	79 (768.2)	20 (125.2)	7.55 (4.52–13.04)	<0.001	16.8	14.6
	Dose 1[1]	16 (303.9)	20 (125.2)	3.29 (1.52–7.07)	0.003	6.7	4.6
	Dose 2	63 (1255.2)	13 (99.4)	13.63 (7.39–26.55)	<0.001	27.5	25.5
BNT162b2	Either Dose[1]	41 (647.2)	13 (143.9)	6.94 (3.57–14.13)	<0.001	14.2	12.1
	Dose 1[1]	7 (216.0)	13 (144.2)	3.02 (1.03–8.33)	0.044	4.7	3.2
	Dose 2	34 (1099.1)	8[3] (111.5)	14.34 (6.45–34.85)	<0.001	24.1	22.4
mRNA-1273	Either Dose[1]	38 (962.4)	7 (100.2)	9.18 (4.12–22.89)	<0.001	21.1	18.8
	Dose 1[1]	9 (444.9)	7 (100.5)	3.46 (1.12–11.07)	0.031	9.7	6.9
	Dose 2	29 (1506.1)	4 (80.0)	18.75 (6.73–64.94)	<0.001	33.0	31.2

[1] Comparison interval is 22–42 days after either dose.
[2] Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.
[3] One case was non-informative in the BNT162b2, Dose 2 comparator interval.
[4] Excess cases are in addition to an estimated background rate of 2 cases/per million doses.

0–5, 0–4, and 0–3 after mRNA-1273 and days 0–3, 0–4, and 0–2 after BNT162b2 ($p < 0.0001$ for each cluster) (Fig. 1).

3.2. Head-to-head comparison of mRNA-1273 versus BNT162b2 during days 0–7 post-vaccination

In direct head-to-head comparisons during the 0–7 days after either dose, incidence of myocarditis and pericarditis was 1.61 times higher after mRNA-1273 than after BNT162b2 (95% CI, 1.02–2.54, $p = 0.041$), amounting to an estimated 8.0 excess cases per million doses of mRNA-1273 compared with BNT162b2. After dose 2, incidence was 1.48 times higher after mRNA-1273 than after BNT162b2 (95% CI 0.88–2.50, $p = 0.141$), amounting to 10.7 excess cases per million second doses of mRNA-1273 compared with BNT162b2 (Table 3). In analyses restricted to males only, incidence after dose 2 was 1.50 (95%CI 0.86–2.61, $p = 0.152$) times higher after mRNA-1273 than after BNT162b2. In analyses restricted to females, incidence after dose 2 was 1.35 (95% CI 0.23–7.15, $p = 0.714$) times higher after mRNA-1273 than after BNT162b2. Analyses that excluded pericarditis yielded similar trends (Table 3).

4. Discussion

Among 18–39-year-olds in the large, diverse VSD population, both BNT162b2 and mRNA-1273 COVID-19 vaccines were associated with a significant increased risk of myocarditis and pericarditis during days 0–7 after vaccination. Notably, each product was associated with an estimated excess of over 20 cases per million second doses. However, during the 0–7 days post-vaccination, the estimated excess cases after mRNA-1273 were higher than after BNT162b2, which indirectly suggests that mRNA-1273 was

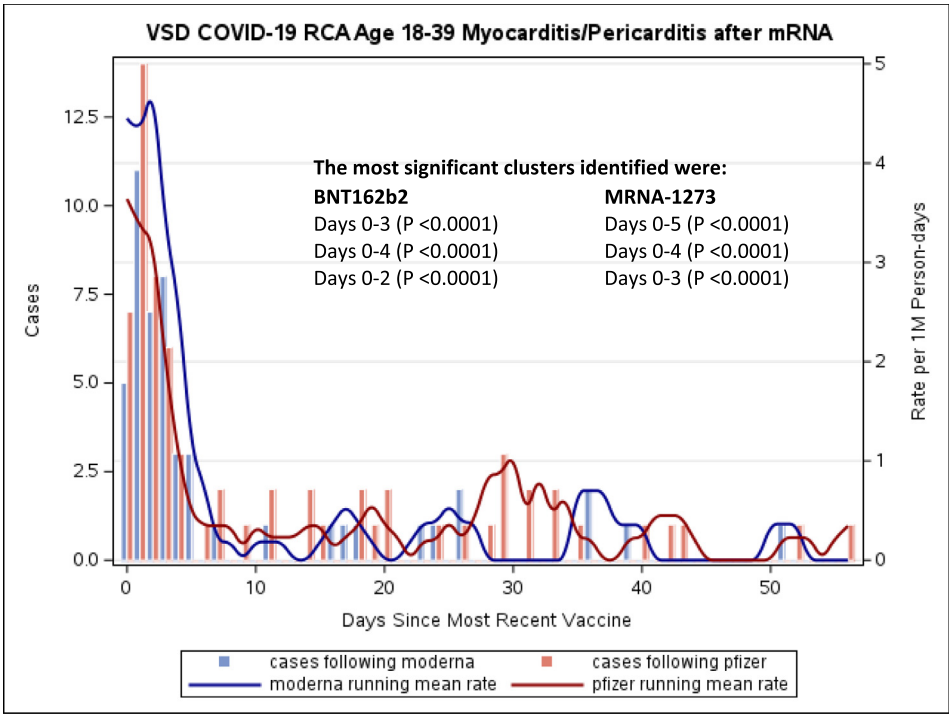

Fig. 1. Temporal clustering of verified myocarditis and pericarditis cases by product and day of symptom onset post-vaccination* *Scan parameters include days 0 to 56 and all possible windows of length 1 to 28 days.

Table 3
Head-to-head comparison of the mRNA-1273 versus BNT162b2 vaccines regarding myocarditis and pericarditis during days 0–7 post-vaccination in 18–39- year-olds, December 14, 2020–January 15, 2022.

Dose	Sex	Myocarditis, myopericarditis, and pericarditis			Myocarditis and myopericarditis (pericarditis excluded)		
		Adjusted rate ratio[1] (95% CI)	2-sided p-value	Excess cases in risk period per 1 M doses of mRNA-1273 vs BNT162b2 [2]	Adjusted rate ratio[1] (95% CI)	2-sided p-value	Excess cases in risk period per 1 M doses of mRNA-1273 vs BNT162b2 [2]
Either Dose	All	1.61 (1.02–2.54)	0.041	8.0	1.35 (0.82–2.19)	0.237	4.3
	Male	1.52 (0.93–2.48)	0.097	13.4	1.32 (0.78–2.22)	0.288	8.1
	Female	2.34 (0.65–8.71)	0.188	3.5	1.57 (0.27–8.12)	0.585	1.1
Dose 2	All	1.48 (0.88–2.50)	0.141	10.7	1.24 (0.70–2.14)	0.454	5.2
	Male	1.50 (0.86–2.61)	0.152	21.9	1.31 (0.73–2.31)	0.361	13.6
	Female	1.35 (0.23–7.15)	0.714	1.6	0.53 (0.02–5.81)	0.658	−1.8

Abbreviation: CI = confidence interval.
[1] Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the mRNA-1273 rate divided by the BNT162b2 rate.
[2] Excess cases is an estimate of the mRNA-1273 rate minus the BNT162b2 rate. Excess cases per million doses were estimated by dividing the mRNA-1273 incidence rate by the rate ratio estimate and subtracting the result from the mRNA-1273 rate.

associated with a greater risk of myocarditis and pericarditis than BNT162b2. Direct head-to-head comparisons including both sexes found that rates of myocarditis and pericarditis after either dose of mRNA-1273 were modestly higher than for BNT162b2 during the 0–7 days post-vaccination. Incidence was also higher after mRNA-1273 than after BNT162b2 in separate head-to-head comparisons restricted to males, dose 2, and myocarditis excluding pericarditis, but the subgroup-specific elevated rate ratios were not statistically significant, possibly due to limited power to detect rate ratios below 2.0. Overall, these results indicate that both mRNA vaccines were associated with markedly elevated risk of myocarditis and pericarditis in 18–39-year-olds and that the risk during the 7 days after vaccination was modestly greater after mRNA-1273 than after BNT162b2.

Consistent with the current study, international passive and active surveillance systems in Europe, Canada, and Nordic countries have reported risk of myocarditis in adolescents and young adults varying from 1.7 to 7.3 times higher after mRNA-1273 than after BNT162b2 [15,24,25]. A report in France matched 1612 myocarditis cases to 16,120 controls without myocarditis and found the risk of myocarditis was higher after mRNA-1273 (OR:30, 95% CI: 21–43) than after BNT162b2 (OR:8.1, 95% CI: 6.7–9.9) vaccines for myocarditis [26]. One recent study from Canada found in a head-to-head comparison that risk of myocarditis/ and pericarditis was 3.87 times higher after mRNA-1273 than after BNT162b2 among 18–39 year olds [27], while another from Canada reported that risk of myocarditis/pericarditis was 6.6 times higher after mRNA-1273 dose 2 than after BNT162b2 dose 2 among males 18–24 years old, and 5.1 times higher among males 25–39 years old [28]. Differences in study population characteristics, statistical methods used, and variation in length of time between vaccine doses may have led to differences between studies in how much risk after mRNA-1273 exceeded risk after BNT162b2. In contrast, data from the FDA's Biologics Effectiveness and Safety (BEST) Surveillance System, which includes data from 4 different insurance organizations and a pharmacy, did not find consistent evidence of increased risk after mRNA-1273 when compared with BNT162b2 in males aged 18–25 years [29]. However, confidence intervals were wide, and results were heterogenous across the different data sources, with some showing evidence of increased risk after mRNA-1273 [29].

Our updated findings that both mRNA vaccines were associated with increased risk of myocarditis within the week after vaccination compared with a comparison period 3–6 weeks post-vaccination is consistent with our prior report which estimated a RR of 9.83 (95% CI, 3.35–35.77) for myocarditis and pericarditis during the 0–7 days post-vaccination when compared with the 22–42 days post-vaccination [18]. We also reported previously that mRNA vaccines were associated with an elevated RR (10.4, 95%CI 3.54–37.76) after dose 2 of both BNT162b2 and mRNA-1273 vaccines. Although our results cannot be compared directly to previous studies, a recent study based on passive surveillance in the US, reported that the risk of myocarditis after receiving mRNA-based COVID-19 vaccines was highest after the second vaccination dose in adolescent males and young men with slightly higher reporting rates observed for mRNA-1273 compared to BNT162b2 vaccine in most age groups [22]. Surveillance systems in other countries and regions have also reported similar findings [11,15,30–34]. Unlike studies which were limited to BNT162b2 vaccines, this study included two vaccine products which allowed both an estimation of risk by product and direct head-to-head comparison between products.

Medical record review found that verified myocarditis and pericarditis cases appeared to have similar presentation, clinical course, and recovery regardless of vaccine product, suggesting that clinical severity may not differ between the two products. Similar to other reports, we found that most cases were mild and symptomatically resolved after a short hospital stay [35–38].

This study had important strengths. Analyses were based on a large and diverse population and vaccination data was captured directly from electronic health records and linkage with state immunization registries. All myocarditis and pericarditis cases in the analyses presented were verified by medical record review and adjudicated by clinical specialists with expertise in infectious disease and cardiology. This enabled us to include only verified incident cases and accurately determine symptom onset date relative to vaccination. All analyses (both vaccinated concurrent and head-to head) adjusted carefully for calendar time and demographic factors. In both the vaccinated concurrent and head-to head analyses, vaccinees were compared with each other, rather than with unvaccinated or with historical comparators; thus, comparators were similar in demographic characteristics to the cases and therefore less likely to differ in ways that could lead to bias. In contrast to previous studies, which were limited to indirectly comparing the risk of myocarditis and pericarditis between BNT162b2 and mRNA-1273, this study conducted both indirect and direct head-to-head comparisons of the two vaccines.

This study had at least 5 limitations. First, case identification was limited to those who received ED or inpatient care with a diagnosis code specific to acute myocarditis or pericarditis. Thus, potential cases were not identified if they were seen only in the outpatient setting or if they were seen in an ED or hospital but received only a less-specific diagnosis code such as chest pain (R07.9) and therefore were not included in our analyses. Second, although this study included data on over 4.5 million doses of mRNA vaccines, there were only 79 verified cases of myocarditis and pericarditis events during the 0–7 days post-vaccination and confidence intervals were wide around the RR estimates for some

analyses. Third, due to increased awareness of potential myocarditis after mRNA vaccines in the public and among healthcare providers, there may have been some detection or diagnosis bias. However, any such bias would be unlikely to differ between the two mRNA vaccines on a given calendar day in a specific geographic area. Fourth, we cannot rule out the possibility that individual choice of vaccine product was related to unmeasured risk factors for myocarditis, when vaccine product choice was possible. Fifth, as only one product (BNT162b2) was authorized for use in the 12–17-year age group, head-to-head comparisons in this age range were not possible.

This study found that among 18–39-year-olds, both mRNA COVID-19 vaccines were associated with a substantial increased risk of myocarditis and pericarditis, with the highest risk in 0–7 days after dose 2. Most myocarditis and pericarditis cases after vaccination with either product were mild and symptomatically resolved after a short hospital stay. Head-to-head comparisons of the two mRNA vaccines suggest that risk of myocarditis and pericarditis is modestly higher following vaccination with mRNA-1273 than following BNT162b2. Continued monitoring of this outcome is warranted, especially after booster doses.

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CRediT authorship contribution statement

Kristin Goddard: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Visualization, Writing. **Ned Lewis:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing. **Bruce Fireman:** Conceptualization, Formal analysis, Investigation, Methodology, Writing. **Eric Weintraub:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing. **Tom Shimabukuro:** Conceptualization, Supervision, Writing. **Ousseny Zerbo:** Conceptualization, Funding acquisition, Writing. **Thomas G. Boyce:** Investigation. **Matthew E. Osterc:** Investigation. **Kayla E. Hanson:** Funding acquisition, Investigation, Project administration, Resources, Writing. **James G. Donahue:** Funding acquisition, Methodology, Writing. **Allison Nalewaye:** Data curation, Supervision, Writing. **Jennifer C.Nelson:** Data curation, Supervision, Writing. **Bruno Lewin:** Data curation, Supervision, Writing. **Jason M. Glanz:** Supervision, Writing. **Joshua T.B. Williams:** Data curation, Supervision, Writing. **Elyse O. Kharbanda:** Data curation, Supervision, Writing. **W. Katherine Yih:** Writing. **Nicola P. Klein:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Visualization, Writing.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nicola Klein reports financial support was provided by Centers for Disease Control and Prevention. Nicola Klein reports a relationship with Pfizer Inc that includes: funding grants. Nicola Klein reports a relationship with Merck & Co Inc that includes: funding grants. Nicola Klein reports a relationship with GlaxoSmithKline USA that includes: funding grants. Nicola Klein reports a relationship with Sanofi Pasteur Inc that includes: funding grants. Allison Naleway reports a relationship with Pfizer Inc that includes: funding grants. Allison Naleway reports a relationship with VIR Biotechnology Inc that includes: funding grants. W. Katherine Yih reports a relationship with Pfizer Inc that includes: funding grants. James Donahue reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants.

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The study sponsor, CDC, participated as a co-investigator and contributed to protocol development; conduct of the study; interpretation of the data; review and revision of the manuscript; approval of the manuscript through official CDC scientific clearance processes; and the decision to submit the manuscript for publication. CDC authors must receive approval through the CDC scientific clearance process to submit an article for publication. Final decision to submit rests with the first author. The study sponsor does not have the right to direct the submission to a particular journal.

Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC.

Disclosures

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.07.007.

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