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Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines (Comirnaty [Pfizer-BioNTech] and Spikevax [Moderna]) administered to 12–17-year-olds in Victoria, Australia

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ABSTRACT

Importance:

COVID-19 mRNA vaccine associated myocarditis has previously been described; however specific features in the paediatric / adolescent population are currently not well understood.

Objective

To describe myocarditis adverse events following immunization (AEFI) following any COVID-19 mRNA vaccines in the paediatric and adolescent population in Victoria, Australia.

Design

Statewide, population-based study.

Setting

Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the vaccine-safety service for Victoria, Australia.

Participants

All SAEFVIC reports of myocarditis and myopericarditis in 12–17-year-old COVID-19 mRNA vaccinees submitted between 22 February and 31 December 2021, as well as accompanying diagnostic investigation results where available, were assessed using Brighton Collaboration criteria for diagnostic certainty.

Exposures

Any mRNA COVID-19 vaccine

Main Outcomes/Measure

Confirmed myocarditis as per Brighton Collaboration criteria (levels 1-3)

Results

Rigorous clinical review demonstrated definite (Brighton level 1) or probable (level 2) diagnoses in 68 cases, with one case possible (level 3). The 69 reports of confirmed myocarditis equated to a rate of 8.5 per 100,000 doses in this age group. Cases were predominantly male (n=58, 84.1%) and post dose 2 (n=56, 81.2%). Rates peaked in the 16–17-year-old age group and were higher in males than females (14.1 v 2.8 per 100,000, p=<0.001).

Troponin levels differed between sexes, with males recording substantially higher levels.

Conclusion

Accurate evaluation and confirmation of episodes of COVID-19 mRNA vaccine associated myocarditis enabled understanding of clinical phenotypes in the paediatric and adolescent age group. Any potential vaccination and safety surveillance policies needs to consider age and gender differences.

What is already known on this topic

- Previous case studies suggest that there is an association between COVID-19 mRNA vaccines and increased rates of myocarditis
- Recommendations on use of COVID-19 mRNA vaccines in different age groups vary globally and may not take into account their different risk profiles.

What this study adds

- Incidence of myocarditis post COVID-19 mRNA vaccines are higher after the second dose and appears to differ by age and gender, with younger males being at a higher risk.
- Males with myocarditis have higher median troponin levels compared to females. Ongoing symptoms at one month post diagnosis were recorded in the majority of females, whereas the majority of males reported no ongoing symptoms at the same time point.

How this study might affect research, practice or policy

- Potential policy and safety surveillance adjustments may need to take into account age and gender differentials in myocarditis when reviewing COVID-19 vaccine rollout to the paediatric population

INTRODUCTION

Australia has utilized two mRNA vaccines as part of its COVID-19 vaccine strategy in 12-17 year-olds, namely Comirnaty BNT162b2 (BNT) COVID-19 (Pfizer-BioNTech) and Spikevax mRNA-1273 (Moderna).(1) Comirnaty was initially provisionally licensed by the Australian regulator, the Therapeutic Goods Administration (TGA) for those aged 16 years and older, and administered from 25 January 2021 in adults 18+ years. Spikevax received provisional TGA approval for administration in individuals from 18 years from 9 August 2021. Following the availability of age specific clinical trial data, further approvals were added for the 12–15-year-old group for Comirnaty (22nd July 2021) and 12–17-year-old for Spikevax (4th September 2021).

Of particular interest in the young adult population is post-vaccination myocarditis and pericarditis causally associated with COVID-19 mRNA vaccines. These adverse events of special interest (AESI) were first flagged in Israel, which implemented Comirnaty at a population level as soon as it was available (20th December 2020)(2). In a linked electronic health record observational case control study design from Israel's largest health care insurer, Barda *et al* described an elevated risk of myocarditis following Comirnaty (risk ratio [RR], 3.24; 95% confidence interval [CI], 1.55 to 12.44) , while noting a substantially higher risk following COVID-19 disease (RR 18.28; 95% CI, 3.95 to 25.12).(3)

Subsequent post-licensure observational military and report-based case studies confirmed the highest risk group for post mRNA COVID-19 vaccine myocarditis is young males (<24 years old) following the 2nd vaccine dose (4, 5). Both the spontaneous (passive) Vaccine Adverse Event Reporting System and active Vaccine Safety Datalink surveillance systems in the US have confirmed a myocarditis signal safety (6), along with similar findings in Canada, the UK and various Nordic countries (7).

Due to this AESI signal, the risk, clinical manifestations and follow-up of myocarditis and pericarditis following mRNA COVID-19 in younger populations has been of particular interest. Some regions (e.g., Hong Kong) are only administering a single dose of mRNA vaccine in adolescents aged 12-17 years and notably, there is limited use of Spikevax in this age group internationally. Spikevax is not currently FDA licensed for 12-17 year-olds in the United States, whilst Canada and several European countries have issued preferential recommendations for Comirnaty over Spikevax for young adults (8). This study describes clinical presentation and evaluation of myocarditis AESI following mRNA COVID-19 vaccination in 12–17-year-old adolescents in Victoria, Australia.

METHODS

Victoria is a south-eastern Australian state with a population of approximately 6.6 million (9). AEFI are spontaneously reported by patients, caregivers or health-care providers to SAEFVIC, the state-wide vaccine safety service(10). SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services that has been operating since 2007.

Identified reports of myocarditis and myopericarditis in 12–17-year-old vaccinees submitted to SAEFVIC between 22 February and 31 December 2021 were assessed. Myocarditis and myopericarditis reports (henceforth summarized as myocarditis) were systematically followed up and diagnostic test results (where available) obtained to confirm the diagnoses.

These included electrocardiogram (ECG), cardiac biomarkers, echocardiogram and cardiac magnetic resonance imaging (MRI) scans. All troponin levels obtained were high sensitivity troponin assays, with troponin levels reported as fold increase from the upper limit of normal to facilitate comparison between different assays. Each case was categorized by at least two independent experts utilizing the Brighton Collaboration definition with graded levels of certainty.(11) All reports were forwarded to the national regulator, the Therapeutic Goods Administration (TGA), who report weekly on spontaneous AEFI reports at a national level (12, 13).

Statistical analysis

Data were analysed using Microsoft PowerBI (version 2.91.701.0) with 90% Poisson confidence intervals calculated for rates. Vaccine doses administered and population estimates were obtained from the Australian Immunisation Registry (AIR) (14). Age groups were defined by the vaccine roll-out in Victoria, whereby 16–17-year-olds were eligible for vaccination prior to 12–15-year-olds.

RESULTS

As of 31 December 2021, 488,570 12–17-year-old Victorians had received 807,490 mRNA doses (722,849 Comirnaty and 84,641 Spikevax). This equated to approximately 84.3% first dose and 81.1% of this age cohort fully vaccinated.

At this timepoint, there were 69 reports of confirmed myocarditis (43 myocarditis, 26 myopericarditis) as per Brighton Collaboration criteria level 1-3. 68 cases satisfied Brighton

Collaboration level 1 (definite) or 2 (probable) criteria, with one case level 3 (possible). This equates to a rate of 8.5 per 100,000 doses (90% CI: 5.5, 8.7) in this age group (Table 1).

Cases were predominantly in males (n=58, 84.1%) and post dose 2 (n=56, 81.2%). Presentation was temporally related to Comirnaty in 58 (84.1%) and to Spikevax in 11 (15.9%) cases respectively. Higher rates were observed in the 16–17-year-old age group, and in males compared to females ($p<0.001$) (Table 1).

One patient had evidence of historical COVID-19 infection, with a positive COVID-19 respiratory PCR three weeks prior to receiving first dose Comirnaty vaccination – with subsequent myocarditis two days later.

Onset of symptoms ranged from 0 to 49 days after vaccination, with a median of 2 days (IQR 1-3 days), in males from 0 to 34 days (median 2 days) and in females 1 to 49 days (median 3 days). Forty-seven cases (68.1%) required hospital admission with a median length of stay of two nights. No cases required ICU admission and no deaths were recorded. All admissions were discharged to home. Follow up at one month was completed for 62 cases (Table 2). Symptoms had resolved in 40.3% of those who participated in follow-up, while 50.0% remained on exercise restrictions.

ECG abnormalities were observed in 46 (66.7%) cases. An echocardiogram was performed in 66 cases and was abnormal in 8 (12.1%). A cardiac MRI was performed in 30 cases with abnormalities documented in the majority of these (27 cases, 90.0%).

There was a clear differential in troponin levels between sexes, with males exhibiting higher and more variable increases in troponin and a median fold rise of 138 times above normal levels (Figure 1).

DISCUSSION

This study describes 69 cases of myocarditis reported following COVID-10 mRNA vaccination in the adolescent age group. This equates to a rate of 8.5 cases per 100,000 doses (90% CI 6.9, 10.4).

This analysis describes one of the largest series of adolescents with myocarditis post-COVID-19 mRNA vaccination to date. Rigorous clinical review of all cases demonstrated definite or probable diagnoses in all but one case. This approach allows a more accurate evaluation of clinical features and comparison with other presentations of non-COVID-19 mRNA vaccine myocarditis or chest pain in this age group.

There were clear clinical phenotypic differences between sexes. Males tended to present with symptoms in a tight window up to 7 days post dose 2 vaccine and with a significantly elevated peak troponin level. Just under half had no residual symptoms 4 weeks after initial onset. In contrast, females had a much lower median peak troponin level, with similar rates post dose 1 and 2. Symptoms were still almost all female cases 4 weeks after onset. These differences may support a potential impact of testosterone as a risk factor for stronger cardiac inflammation in myocarditis, but with a potentially beneficial impact on duration of symptoms. (15)

Our data indicates a higher rate of cases between the age of 16-17 and a tapering in rate for the 12-15 age group. Further analysis is needed and ongoing to compare rates of myocarditis between Comirnaty and Spikevax when sufficient doses are administered, although there is currently no discernible difference in case severity or clinical presentation.

These observations suggest that any potential policy and safety surveillance adjustments may need to take into account these age and gender differentials. For example, it has implications for younger age groups, including those between 5-11 years, where a reduced dose (10 mcg) Comirnaty vaccine was FDA approved and ACIP recommended in early November 2021. (16) No COVID-19 vaccine clinical trials to date have been sufficiently powered to detect an AESI such as myocarditis. However, with more than 7 million doses administered in this age group at time of writing, real-world phase IV data will help inform the important risk-benefit discussion regarding COVID-19 vaccines in younger children, who from background rates of myocarditis (all causes) would be expected to have fewer cases than adolescents.

Limitations

This study is based on clinical data compiled by SAEFVIC as part of vaccine safety surveillance. A passive vaccine safety surveillance system may underreport potential cases of myocarditis. Nonetheless, the accuracy of patient data was maintained by ensuring that available patient clinical information were reviewed by at least two independent medical specialists to verify reported myocarditis cases and reduce misdiagnosis.

Conclusion

Rates of myocarditis in the adolescent population differ by dose and sex in the 12- to 17-year-old. With the vaccine rollout in younger children and adolescents in mind, these clinical phenotypic differences, particularly between sexes, need to be considered for future COVID vaccine recommendations.

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Footnotes

Contributors: DC, NC, JB conceived and designed the study. HC and ER performed statistical analyses and data management. All authors were involved in drafting, editing and reviewing the article. All corresponding authors meet the authorship criteria. DC is the study's guarantor.

Funding: This study was unfunded and was part of a routine clinical surveillance program.

Competing interests: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: Follow-up of cases was undertaken as part of public health AEFI management. SAEFVIC data is part of a clinical quality registry that forms part of Victoria's vaccine safety surveillance program.

Data sharing: Aggregated de-identified and summarized data is publicly available at https://mvec.mcri.edu.au/vaccinesafety/

Patient Involvement: Patients were not involved in the report and conduct of this research, as data was collected as part of public health AEFI management and was not a specific research trial.

Transparency Declaration: The lead author, Dr Daryl Cheng, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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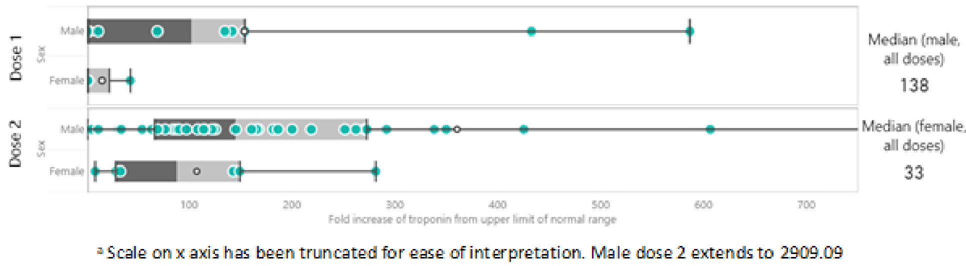
Table 1: Count and rate of cases by sex, age group, dose number, and Brighton Collaboration level

		Male		Female		Total	
		Count	**Rate per 100,000 doses (90%CI)**	**Count**	**Rate per 100,000 doses (90%CI)**	**Count**	**Rate per 100,000 doses (90%CI)**
Total		***58***	***14.1 (11.2, 17.6)***	***11***	***2.8 (1.6, 4.6)***	***69***	***8.5 (6.9, 10.4)***
Age group (years)	12-15	31	11.5 (8.3, 15.5)	6	2.3 (1.0, 4.5)	37	6.9 (5.2, 9.1)
	16-17	27	19.4 (13.7, 26.7)	5	3.7 (1.5, 7.8)	32	11.6 (8.5, 15.6)
Dose	1	10	4.8 (2.6, 8.1)	4	2.0 (0.7, 4.5)	14	3.4 (2.1, 5.3)
	2	49	24.4 (19.0, 31.0)	7	3.6 (1.7, 6.7)	56	14.2 (11.2, 17.7)
Brighton Collaboration level	1	23	5.6 (3.8, 7.9)	3	0.8 (0.2, 2.0)	26	3.2 (2.3, 4.5)
	2	34	8.3 (6.1, 11.0)	8	2.0 (1.0, 3.6)	42	5.2 (4.0, 6.7)
	3	1	0.2 (0.01, 1.2)	0	NA	1	0.1 (0.01, 0.6)

Table 2: One-month follow up outcomes, by sex (n=62)

	Male (n=53)	**Female (n=9)**	**Total (n=62)**
	Count, %	Count, %	Count, %
Symptoms resolved	24, 45.3%	1, 11.1%	25, 40.3%
On exercise restrictions	26, 49.1%	5, 55.6%	31, 50.0%



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ABSTRACT

Importance:

COVID-19 mRNA vaccine associated myocarditis has previously been described; however specific features in the adolescent population are currently not well understood.

Objective

To describe myocarditis adverse events following immunization (AEFI) reported following any COVID-19 mRNA vaccines in the paediatric and adolescent population in Victoria, Australia.

Design

Statewide, population-based study.

Setting

Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the vaccine-safety service for Victoria, Australia.

Participants

All SAEFVIC reports of myocarditis and myopericarditis in 12–17-year-old COVID-19 mRNA vaccinees submitted between 22 February 2021 and 22 February 2022, as well as accompanying diagnostic investigation results where available, were assessed using Brighton Collaboration criteria for diagnostic certainty.

Exposures

Any mRNA COVID-19 vaccine

Main Outcomes/Measure

Confirmed myocarditis as per Brighton Collaboration criteria (levels 1-2)

Results

Rigorous clinical review demonstrated definite (Brighton level 1) or probable (level 2) diagnoses in 75 cases. Confirmed myocarditis reporting rates were 8.3 per 100,000 doses in this age group. Cases were predominantly male (n=62, 82.7%) and post dose 2 (n=61, 81.3%). Rates peaked in the 16–17-year-old age group and were higher in males than females (17.7 v 3.9 per 100,000, p=<0.001).

Troponin levels differed between sexes, with males recording substantially higher levels.

Conclusion

Accurate evaluation and confirmation of episodes of COVID-19 mRNA vaccine associated myocarditis enabled understanding of clinical phenotypes in the adolescent age group. Any potential immunisation safety policies need to take into account age and gender differences.

What is already known on this topic

- Previous studies support an association between COVID-19 mRNA vaccine receipt and increased rates of myocarditis in the following 2 weeks
- Recommendations on use of COVID-19 mRNA vaccines in different age groups vary globally and may not take into account their different risk profiles.

What this study adds

- Incidence of myocarditis post COVID-19 mRNA vaccines are higher after the second dose and appears to differ by age and gender, with adolescent and young adult males being at a higher risk.
- The clinical phenotype of myocarditis differs between genders in adolescents, with females recording lower median troponin levels but longer lasting clinical symptoms

How this study might affect research, practice or policy

- Potential policy and safety surveillance adjustments may need to take into account age and gender differentials in myocarditis when reviewing the COVID-19 primary (2-dose) vaccine rollout to the paediatric population

INTRODUCTION

Australia has utilized two mRNA vaccines as part of its COVID-19 vaccine strategy in 12-17 year-olds, namely Comirnaty® BNT162b2 COVID-19 (Pfizer-BioNTech) and Spikevax® mRNA-1273 (Moderna). (1) Comirnaty was initially provisionally licensed by the Australian regulator, the Therapeutic Goods Administration (TGA) for those aged 16 years and older, and administered from 25 January 2021 in adults 18+ years. Spikevax received provisional TGA approval for administration in individuals from 18 years from 9 August 2021. Following the availability of age specific clinical trial data, further approvals were added for the 12–15-year-old group for Comirnaty (22nd July 2021) and 12–17-year-old for Spikevax (4th September 2021).

Of particular interest in the young adult population is post-vaccination myocarditis and pericarditis causally associated with COVID-19 mRNA vaccines. These adverse events of special interest (AESI) were first flagged in Israel, which implemented Comirnaty at a population level as soon as it was available (20th December 2020). (2) In a linked electronic health record observational case control study design from Israel's largest health care insurer, Barda *et al* described an elevated risk of myocarditis following Comirnaty (risk ratio [RR], 3.24; 95% confidence interval [CI], 1.55, 12.44) , while noting a substantially higher risk following COVID-19 disease (RR 18.28; 95% CI, 3.95, 25.12). (3)

Subsequent post-licensure observational military and report-based case studies confirmed the highest risk group for post mRNA COVID-19 vaccine myocarditis is young males (<24 years old) following the 2nd vaccine dose. (4-6) Both the spontaneous Vaccine Adverse Event Reporting System and active Vaccine Safety Datalink surveillance systems in the US have confirmed a myocarditis signal safety (7), along with similar findings in Canada, the UK and various Nordic countries. (6)

Due to this AESI signal, the risk, clinical manifestations and follow-up of myocarditis and pericarditis following mRNA COVID-19 in younger populations has been of particular interest. Some regions (e.g., Hong Kong) are only administering a single dose of mRNA vaccine in adolescents aged 12-17 years and notably, there is limited use of Spikevax in this age group internationally. Spikevax is not currently licensed by the US Food and Drug Administration (FDA) for 12-17 year-olds, whilst Canada and several European countries have issued preferential recommendations for Comirnaty over Spikevax for young adults. (8) This study describes clinical presentation and evaluation of myocarditis AESI following mRNA COVID-19 vaccination in 12–17-year-old adolescents in Victoria, Australia.

METHODS

Victoria is a south-eastern Australian state with a population of approximately 6.6 million. (9) AEFI are spontaneously reported by patients, caregivers or health-care providers to SAEFVIC, the state-wide vaccine safety service. (10) SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services that has been operating since 2007.

Identified reports of myocarditis and myopericarditis in 12–17-year-old vaccinees submitted to SAEFVIC between 22 February 2021 and 22 February 2022 were assessed. The majority of these were practitioner reported. Myocarditis and myopericarditis reports (henceforth summarized as myocarditis) were systematically followed up and diagnostic test results (where available) obtained to confirm the diagnoses, including potential alternative causes such as viral, autoimmune or medication related myocarditis. Data gathered included symptoms such as chest pain, shortness of breath, dizziness and fatigue, as well as investigations undertaken by treating clinicians, including electrocardiogram (ECG), cardiac biomarkers, echocardiogram and cardiac magnetic resonance imaging (MRI) scans. All troponin levels obtained were high sensitivity troponin assays, with troponin levels reported as fold increase from the upper limit of normal to facilitate comparison between different assays.

Each case was categorized by at least two independent experts utilizing the Brighton Collaboration definition with graded levels of certainty. (11) All reports were forwarded to the Australian national regulator, the Therapeutic Goods Administration (TGA), who report weekly on spontaneous AEFI reports at a national level. (12, 13)

Cases where vaccination was the most likely cause of their diagnosis were followed up after 1 month to answer a series of questions about ongoing symptoms and clinical management. Cases were declared lost to follow up after 3 calls.

Statistical analysis

Data were analysed using Microsoft PowerBI (version 2.91.701.0) with 90% Poisson confidence intervals calculated for rates. Vaccine doses administered and population estimates were obtained from the Australian Immunisation Registry (AIR). (14) Age groups were defined by the vaccine roll-out in Victoria, whereby 16–17-year-olds were eligible for vaccination prior to 12–15-year-olds.

RESULTS

As of 22 February 2022, 454,974 12–17-year-old Victorians had received 871,689 mRNA doses (782,964 Comirnaty and 88,725 Spikevax). This equated to approximately 97.9% first dose and 93.7% 2nd dose coverage of this age cohort.

At this timepoint, there were 75 reports of confirmed myocarditis (45 myocarditis, 31 myopericarditis) as per Brighton Collaboration level 1 (definite) or 2 (probable) criteria. This equates to a rate of 8.3 per 100,000 doses (90% CI: 6.8, 10.1) in this age group (Table 1).

Cases were predominantly in males (n=62, 82.7%) and post dose 2 (n=61, 81.3%). Presentation was temporally related to Comirnaty in 63 (84.0%) and to Spikevax in 12 (16.0%) cases respectively. Higher rates were observed in the 16–17-year-old age group, and in males compared to females ($p<0.001$) (Table 1).

Of the 75 cases in the study period, 5 of them were found to have a cause for myocarditis that was considered more likely by treating clinicians than COVID-19 vaccination. One patient had evidence of historical COVID-19 infection, with a positive COVID-19 respiratory PCR three weeks prior to receiving first dose Comirnaty vaccination – with subsequent myocarditis two days later.

For the 70 cases related to COVID-10 mRNA vaccination, onset of symptoms ranged from 0 to 49 days after vaccination, with a median of 2 days (IQR 1-3 days), in males from 0 to 34 days (median 2 days) and in females 1 to 49 days (median 2 days). Fifty-one cases (68.0%) required hospital admission with a median length of stay of two nights. No cases required ICU admission and no deaths were recorded. All admissions were discharged to home.

ECG abnormalities were observed in 51 (68.0%) cases. An echocardiogram was performed in 70 cases and was abnormal in 8 (11.4%). An initial diagnostic cardiac MRI was performed in 35 cases with abnormalities documented in the majority of these (31 cases, 88.6%).

There was a clear differential in troponin levels between sexes, with males exhibiting higher and more variable increases in troponin and a median fold rise of 144 times above normal levels (Figure 1).

Follow up at one month was completed for 64 of the 70 cases where COVID-19 vaccination was the most likely cause of their diagnosis (Table 2). The remaining 6 cases were lost to follow-up and excluded from analysis. Symptoms had resolved in 50.0% while 64.1% remained on exercise restrictions.

DISCUSSION

We describe 75 cases of myocarditis reported following COVID-10 mRNA vaccination in the adolescent age group. This equates to a rate of 8.3 cases per 100,000 doses (90% CI: 6.8, 10.1). This rate is similar to other international studies in Israel, the UK and the USA. (13)

This analysis describes one of the largest series of adolescents with myocarditis post-COVID-19 mRNA vaccination to date. Rigorous clinical review of all cases demonstrated definite or probable diagnoses (as per Brighton criteria). This approach allows a more accurate evaluation of clinical features and comparison with other presentations of non-COVID-19 mRNA vaccine myocarditis or chest pain in this age group.

Findings were similar to other international cohorts of adolescents. Dionne *et al* described similar symptom prevalence in a cohort of myocarditis patients <19 years. (15) There was also similar cardiac MRI abnormalities noted in similar cohorts. (16) In contrast to our findings, the cohort from Truong *et al* had a high number of patients (18.7%) requiring ICU admission, although only 2 required inotropic support. (17) It is likely that the difference in ICU admission criteria, rather than true clinical severity accounts for this discrepancy.

Unique to this study is the clear clinical phenotypic differences identified between sexes. Males tended to present with symptoms in a tight window up to 7 days post dose 2 vaccine and with a significantly elevated peak troponin level. Just under half had no residual symptoms 4 weeks after initial onset. In contrast, females had a much lower median peak troponin level, with similar rates post dose 1 and 2. Symptoms were still experienced in the majority of female cases 4 weeks after onset. These differences may support a potential impact of testosterone as a risk factor for stronger cardiac inflammation in myocarditis, but with a potentially beneficial impact on duration of symptoms. (18)

Our data indicates a higher rate of cases between the age of 16-17 years and a tapering in rate for the 12-15 year old age group. Further analysis is needed and ongoing to compare rates of myocarditis between Comirnaty and Spikevax when sufficient doses are administered, although there is currently no discernible difference in case severity or clinical presentation.

These observations suggest that any potential immunisation policy and vaccine safety surveillance adjustments may need to take into account these age and gender differentials. For example, it has implications for younger age groups, including those between 5-11 years, where a reduced dose (10 mcg) Comirnaty vaccine was FDA approved and Advisory Committee on Immunization Practices (ACIP) recommended in early November 2021. (19)

No COVID-19 vaccine clinical trials to date have been sufficiently powered to detect an AESI such as myocarditis. However, with millions of doses administered worldwide in this age group at time of writing, real-world phase IV data will help inform the important risk-benefit discussion regarding COVID-19 vaccines in younger children, who from background rates of myocarditis (all causes) would be expected to have fewer cases than adolescents.

LIMITATIONS

This study is based on clinical data compiled by SAEFVIC as part of vaccine safety surveillance. A passive vaccine safety surveillance system may underreport potential cases of myocarditis. Furthermore, there was lack of clinical data on some cases (eg. investigations not performed), making evaluation and diagnosis more challenging. Whilst patient reported symptoms were included as part of the evaluation, Brighton diagnostic criteria was used as a benchmark to reduce recall bias. The accuracy of diagnosis was also maintained by ensuring that available patient clinical information were reviewed by at least two independent medical specialists to verify reported myocarditis cases and reduce misdiagnosis.

CONCLUSION

Rates of myocarditis in the adolescent population differ by dose and sex in the 12 to 17 year-old age-group. With the vaccine rollout in younger children and adolescents in mind, these clinical phenotypic differences, should be considered for future COVID vaccine recommendations, including ‘booster’ doses.

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Footnotes

Contributors: DC, NC, JB conceived and designed the study. HC, ER and HM performed statistical analyses and data management. All authors were involved in drafting, editing and reviewing the article. All corresponding authors meet the authorship criteria. DC is the study's guarantor.

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Data sharing: Aggregated de-identified and summarized data is publicly available at https://mvec.mcri.edu.au/vaccinesafety/

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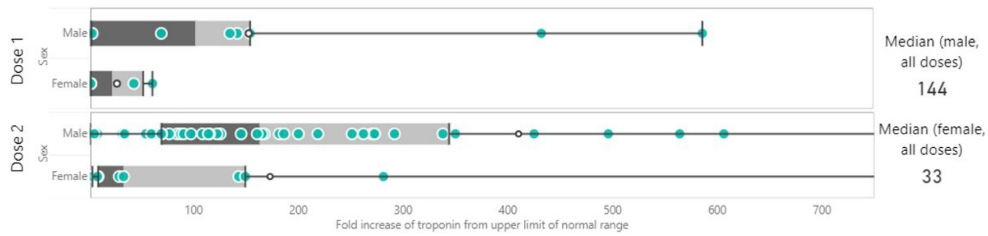
Table 1: Count and rate of cases by sex, age group, dose number, and Brighton Collaboration level

		Male		Female		Total	
		Count	**Rate per 100,000 doses (90%CI)**	**Count**	**Rate per 100,000 doses (90%CI)**	**Count**	**Rate per 100,000 doses (90%CI)**
Total		***62***	***13.6 (10.9, 16.8)***	***13***	***2.9 (1.7, 4.7)***	***75***	***8.3 (6.8, 10.1)***
Age group (years)	12-15	34	11.4 (8.4, 15.2)	7	2.4 (1.1, 4.6)	41	7.0 (5.3, 9.1)
	16-17	28	17.7 (12.6, 24.2)	6	3.9 (1.7, 7.6)	34	10.8 (8.0, 14.4)
Dose	1	10	4.4 (2.4, 7.5)	4	1.8 (0.6, 4.2)	14	3.2 (1.9, 4.9)
	2	52	24.2 (19.0, 30.5)	9	4.3 (2.3, 7.5)	61	14.4 (11.5, 17.8)
Brighton Collaboration level	1	27	5.9 (4.2, 8.2)	3	0.7 (0.2, 1.8)	30	3.3 (2.4, 4.5)
	2	35	7.7 (5.7, 10.2)	10	2.3 (1.2, 3.8)	45	5.0 (3.8, 6.4)

	Male (n=56)	Female (n=8)	Total (n=64)	Chi-square statistic (p-value)
	Count, %	Count, %	Count, %	
Symptoms resolved	31, 55.4%	1, 12.5%	32, 50.0%	5.14 (p=0.02)
On exercise restrictions	35, 62.5%	6, 75.0%	41, 64.1%	0.48 (p=0.49)

Table 2: One-month follow up outcomes, by sex (n=64)



[a] Scale on x axis has been truncated for ease of interpretation. Male dose extends to 2909.09

327x93mm (96 x 96 DPI)

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Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines administered to 12–17 year-olds in Victoria, Australia

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ABSTRACT

Importance:

COVID-19 mRNA vaccine associated myocarditis has previously been described; however specific features in the adolescent population are currently not well understood.

Objective

To describe myocarditis adverse events following immunization (AEFI) reported following any COVID-19 mRNA vaccines in the adolescent population in Victoria, Australia.

Design

Statewide, population-based study.

Setting

Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the vaccine-safety service for Victoria, Australia.

Participants

All SAEFVIC reports of myocarditis and myopericarditis in 12–17-year-old COVID-19 mRNA vaccinees submitted between 22 February and 22 February 2021, as well as accompanying diagnostic investigation results where available, were assessed using Brighton Collaboration criteria for diagnostic certainty.

Exposures

Any mRNA COVID-19 vaccine

Main Outcomes/Measure

Confirmed myocarditis as per Brighton Collaboration criteria (levels 1-3)

Results

Clinical review demonstrated definitive (Brighton level 1) or probable (level 2) diagnoses in 75 cases. Confirmed myocarditis reporting rates were 8.3 per 100,000 doses in this age group. Cases were predominantly male (n=62, 82.7%) and post dose 2 (n=61, 81.3%). Rates peaked in the 16–17year-old age group and were higher in males than females (17.7 v 3.9 per 100,000, p=<0.001).

Troponin levels differed between sexes, with males recording higher levels (p=0.222).

Conclusion

Accurate evaluation and confirmation of episodes of COVID-19 mRNA vaccine associated myocarditis enabled understanding of clinical phenotypes in the adolescent age group. Any potential vaccination and safety surveillance policies needs to consider age and gender differences.

What is already known on this topic

- Previous case studies suggest that there is an association between COVID-19 mRNA vaccines and increased rates of myocarditis, most commonly in the following 2 weeks
- Recommendations on use of COVID-19 mRNA vaccines in different age groups vary globally and may not take into account their different risk profiles.

What this study adds

- Incidence of myocarditis post COVID-19 mRNA vaccines are higher after the second dose and appears to differ by age and gender, with adolescent and young adult males being at a higher risk.
- The clinical phenotype of myocarditis differs between genders in adolescents, with females recording lower median troponin levels but longer lasting clinical symptoms

How this study might affect research, practice or policy

- Potential policy and safety surveillance adjustments may need to take into account age and gender differentials in myocarditis when reviewing COVID-19 primary (2-dose) vaccine rollout to the adolescent population

INTRODUCTION

Australia has utilized two mRNA vaccines as part of its COVID-19 vaccine strategy in 12-17 year-olds, namely Comirnaty® BNT162b2 COVID-19 (Pfizer-BioNTech) and Spikevax® mRNA-1273 (Moderna).(1) Comirnaty was initially provisionally licensed by the Australian regulator, the Therapeutic Goods Administration (TGA) for those aged 16 years and older, and administered from 25 January 2021 in adults 18+ years. Spikevax received provisional TGA approval for administration in individuals from 18 years from 9 August 2021. Following the availability of age specific clinical trial data, further approvals were added for the 12–15-year-old group for Comirnaty (22nd July 2021) and 12–17-year-old for Spikevax (4th September 2021).

Of particular interest in the young adult population is post-vaccination myocarditis and pericarditis causally associated with COVID-19 mRNA vaccines. These adverse events of special interest (AESI) were first flagged in Israel, which implemented Comirnaty at a population level as soon as it was available (20th December 2020)(2). In a linked electronic health record observational case control study design from Israel's largest health care insurer, Barda *et al* described an elevated risk of myocarditis following Comirnaty (risk ratio [RR], 3.24; 95% confidence interval [CI], 1.55 to 12.44) , while noting a substantially higher risk following COVID-19 disease (RR 18.28; 95% CI, 3.95 to 25.12).(3)

Subsequent post-licensure observational military and report-based case studies confirmed the highest risk group for post mRNA COVID-19 vaccine myocarditis is young males (<24 years old) following the 2nd vaccine dose (4-6). Both the spontaneous Vaccine Adverse Event Reporting System and active Vaccine Safety Datalink surveillance systems in the US have confirmed a myocarditis signal safety (7), along with similar findings in Canada, the UK and various Nordic countries (6).

Due to this AESI signal, the risk, clinical manifestations and follow-up of myocarditis and pericarditis following mRNA COVID-19 in younger populations has been of particular interest. Some regions (e.g., Hong Kong) are only administering a single dose of mRNA vaccine in adolescents aged 12-17 years and notably, there is limited use of Spikevax in this age group internationally. Spikevax is not currently licensed by the US Food and Drug Administration (FDA) for 12-17 year-olds, whilst Canada and several European countries have issued preferential recommendations for Comirnaty over Spikevax for young adults. (8) This study describes clinical presentation and evaluation of myocarditis AESI following mRNA COVID-19 vaccination in 12–17-year-old adolescents in Victoria, Australia.

METHODS

Victoria is a south-eastern Australian state with a population of approximately 6.6 million. (9) AEFI are spontaneously reported by patients, caregivers or health-care providers to SAEFVIC, the state-wide vaccine safety service. (10) SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services and has been operating since 2007.

Identified reports of myocarditis and myopericarditis in 12–17-year-old vaccinees submitted to SAEFVIC between 22 February and 22 February 2022 were assessed. The majority of these were practitioner reported. Myocarditis and myopericarditis reports (henceforth summarized as myocarditis) were systematically followed up and diagnostic test results (where available) obtained to confirm the diagnoses, including potential alternative causes such as viral, autoimmune or medication related myocarditis. Data gathered included a list of symptoms such as chest pain, shortness of breath, dizziness and fatigue (Table 1), as well as investigations undertaken by treating clinicians, including electrocardiogram (ECG), cardiac biomarkers, echocardiogram and cardiac magnetic resonance imaging (MRI) scans. All troponin levels obtained were high sensitivity troponin assays, with troponin levels reported as fold increase from the upper limit of normal to facilitate comparison between different assays.

Once data were available, each case was categorized by at least two independent experts utilizing the Brighton Collaboration definition with graded levels of certainty (Table 1). (11) All reports were forwarded to the national regulator, the Therapeutic Goods Administration (TGA), who report weekly on spontaneous AEFI reports at a national level. (12, 13)

Cases where vaccination was the most likely cause of their diagnosis were followed up after one month to answer a series of questions about ongoing symptoms and clinical management. Cases were declared lost to follow up after three unsuccessful attempts to contact.

Statistical analysis

Data were analysed using Microsoft PowerBI (version 2.91.701.0) with 90% Poisson confidence intervals calculated for rates. Vaccine doses administered and population estimates were obtained from the Australian Immunisation Registry (AIR). (14) Age groups were defined by the vaccine roll-out in Victoria, whereby 16–17-year-olds were eligible for vaccination prior to 12–15-year-olds. Mood's median test was used to compare median fold increase in troponin levels.

RESULTS

As of 22 February 2022, 454,974 12–17-year-old Victorians had received 871,689 mRNA doses (782,964 Comirnaty and 88,725 Spikevax). This equated to approximately 97.9% first dose and 93.7% 2nd dose coverage of this age cohort.

At this timepoint, there were 75 reports of confirmed myocarditis (44 myocarditis, 31 myopericarditis) as per Brighton Collaboration level 1 (definitive) or 2 (probable) criteria. This equates to a rate of 8.3 per 100,000 doses (90% CI: 6.8, 10.1) in this age group (Table 1).

Cases were predominantly in males (n=62, 82.7%) and post dose 2 (n=61, 81.3%). Presentation was temporally related to Comirnaty in 63 (84.10) and to Spikevax in 12 (16.0%) cases respectively. Higher rates were observed in the 16–17-year-old age group, and in males compared to females (p<0.001) (Table 2).

Of the 75 cases in the study period, 5 of them were considered by the treating clinician to have an alternative cause for myocarditis more likely than COVID-19 vaccination. One of these cases had evidence of historical COVID-19 infection, with a positive COVID-19 respiratory PCR three weeks prior to receiving first dose Comirnaty vaccination – with subsequent onset of myocarditis two days later.

For the 70 cases related to COVID-19 mRNA vaccination, onset of symptoms ranged from 0 to 49 days after vaccination, with a median of 2 days (IQR 1-3 days), in males from 0 to 34 days (median 2 days) and in females 1 to 49 days (median 2 days). Fifty-one cases (68.0%) required hospital admission with a median length of stay of two nights. No cases required ICU admission and no deaths were recorded. All admissions were discharged to home.

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There was a differential in troponin levels between sexes, with males exhibiting higher and more variable increases in troponin and a median fold rise of 144 times above normal levels compared to females at 33 times above normal (p=0.222) (Figure 1).

Follow up at one month was completed for 64 of the 70 cases where COVID-19 vaccination was the most likely cause of their diagnosis (Table 3). The remaining 6 cases were lost to follow-up and excluded from analysis. Symptoms had resolved in 50.0% of those who participated in follow-up, while 64.1% remained on exercise restrictions.

DISCUSSION

We describe 75 cases of myocarditis reported following COVID-19 mRNA vaccination in the adolescent age group. Our rate of cases was similar to other international studies in Israel, the UK and the USA. (13)

This analysis describes one of the largest series of adolescents with myocarditis post-COVID-19 mRNA vaccination to date. Rigorous clinical review demonstrated Brighton criteria defined 'definitive' or 'probable' diagnoses for all cases. By utilising this international standardised approach to evaluating this AESI, it allows a more accurate evaluation of clinical features and comparison with other presentations of non-COVID-19 mRNA vaccine myocarditis or chest pain in this age group.

Clinical findings were similar to other international cohorts of adolescents. Dionne *et al* described similar symptom prevalence in a cohort of myocarditis patients <19 years. (15) There was also similar cardiac MRI abnormalities noted in similar cohorts. (16) In contrast to our findings, the cohort from Truong *et al* had a high number of patients (18.7%) requiring ICU admission, although only 2 required inotropic support. (17) It is likely that the difference in ICU admission criteria, rather than true clinical severity accounts for this discrepancy.

Unique to this study is the clear clinical phenotypic differences identified between sexes. Males tended to present with symptoms and a significantly elevated peak troponin level. Just under half had no residual symptoms 4 weeks after initial onset. In contrast, females had a much lower median peak troponin level, with similar rates post dose 1 and 2. Symptoms were still experienced by a majority of females 4 weeks after onset. These differences may support a potential impact of testosterone as a risk factor for stronger cardiac inflammation in myocarditis, but with a potentially beneficial impact on duration of symptoms. (18)

Our data indicates a higher rate of cases between the age of 16-17 years and a tapering in rate for the 12-15 year-old age group. Further analysis is needed and ongoing to compare rates of myocarditis between Comirnaty and Spikevax when sufficient doses are administered, although there is currently no discernible difference in case severity or clinical presentation.

These observations suggest that any potential immunisation policy and vaccine safety surveillance adjustments may need to take into account these age and gender differentials. For example, it has implications for younger age groups, including those between 5-11 years, where a reduced dose (10 mcg) Comirnaty vaccine was FDA approved and Advisory Committee on Immunization Practices (ACIP) recommended in early November 2021. (19)

No COVID-19 vaccine clinical trials to date have been sufficiently powered to detect an AESI such as myocarditis. However, with millions of doses administered worldwide in this age group at time of writing, real-world phase IV data will help inform the important risk-benefit discussion regarding COVID-19 vaccines in younger children, who from background rates of myocarditis (all causes) would be expected to have fewer cases than adolescents.

LIMITATIONS

This study is based on clinical data compiled by SAEFVIC as part of vaccine safety surveillance. A passive vaccine safety surveillance system may underreport potential cases of myocarditis. Furthermore, there was lack of clinical data on some cases (eg. investigations not performed), making evaluation and diagnosis more challenging. While patient-reported symptoms were included as part of the evaluation, Brighton diagnostic criteria were used as a benchmark to reduce recall bias. The accuracy of diagnosis was also maintained by ensuring that available patient clinical information were reviewed by at least two independent medical specialists to verify reported myocarditis cases and reduce misclassification.

CONCLUSION

Rates of myocarditis in the adolescent population differ by dose and sex in the 12 to 17year-old age group. With the vaccine rollout in younger children and adolescents in mind, these clinical phenotypic differences should be considered for future COVID vaccine recommendations including 'booster' doses.

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Footnotes

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Transparency Declaration: The lead author, Dr Daryl Cheng, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figure 1: Peak troponin differential between male and females

Table 1: Brighton Collaboration Criteria for Myocarditis

Level 1 – "Definitive" Case	Level 2 – "Probable Case"	Level 3 – "Possible Case"
Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation OR ≥ 1 new finding of • Troponin T or I level above upper limit of normal AND ≥ 1 new Cardiac MRI (cMRI) findings consistent with • Oedema on T2 weighted study, typically patchy in nature • Late gadolinium enhancement on T1 weighted study with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one non-	Clinical symptoms and exclusion as per Level 3 case AND Elevated myocardial biomarkers ≥ 1 new finding of • Troponin T level above upper limit of normal • Troponin I level above upper limit of normal • CK Myocardial band OR Echocardiogram (ECHO) abnormalities ≥ 1 new finding of • focal or diffuse left or right ventricular function abnormalities (eg. decreased ejection fraction) • Segmental wall motion abnormalities	Presence of ≥ 1 new or worsening of the following clinical symptoms: • chest pain/pressure • dyspnoea /shortness of breath/pain breathing • diaphoresis • palpitations • Sudden Death OR Presence of ≥ 2 new or worsening of the following clinical symptoms: • Fatigue • Abdominal Pain • Syncope • Oedema • Cough AND

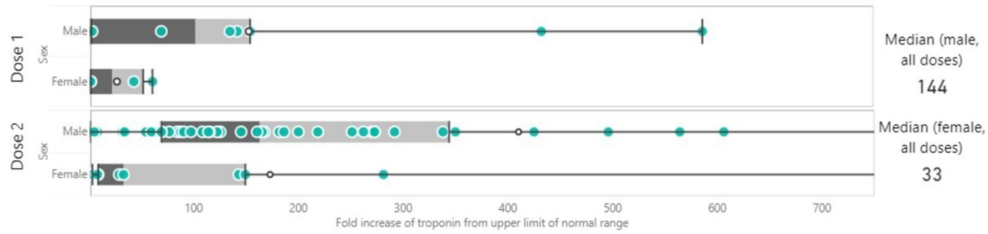
ischemic regional distribution with recovery (myocyte injury). **OR** Echocardiogram (ECHO) abnormalities biomarkers ≥ 1 new finding of as per level 2 case	• Global systolic or diastolic function depression/abnormality • Ventricular dilation • Wall thickness change • Intracavitary thrombi **OR** Electrocardiogram (ECG) abnormalities ≥ 1 new finding of • Paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages) • AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block) • Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy	≥ 1 new supported finding of inflammation Elevated CRP/ESR or D-Dimer **AND** Presence of ≥ 1 new abnormal electrocardiogram (ECG) such as: • ST-segment or T-wave abnormalities (elevation or inversion) • PACs and PVCs **AND** • no other identifiable cause of the symptoms and findings

Table 2: Count and rate of cases by sex, age group, dose number, and Brighton Collaboration level

		Male		Female		Total	
		Count	Rate per 100,000 doses (90% CI)	Count	Rate per 100,000 doses (90% CI)	Count	Rate per 100,000 doses (90% CI)
Total		***62***	***13.6 (10.9, 16.8)***	***13***	***2.9 (1.7, 4.7)***	***75***	***8.3 (6.8, 10.1)***
Age group (years)	12-15	34	11.4 (8.4, 15.2)	7	2.4 (1.1, 4.6)	41	7.0 (5.3, 9.1)
	16-17	28	17.7 (12.6, 24.2)	6	3.9 (1.7, 7.6)	34	10.8 (8.0, 14.4)
Dose	1	10	4.4 (2.4, 7.5)	4	1.8 (0.6, 4.2)	14	3.2 (1.9, 4.9)
	2	52	24.2 (19.0, 30.5)	9	4.3 (2.3, 7.5)	61	14.4 (11.5, 17.8)
Brighton Collaboration level	Definitive	27	5.9 (4.2, 8.2)	3	0.7 (0.2, 1.8)	30	3.3 (2.4, 4.5)
	Probable	35	7.7 (5.7, 10.2)	10	2.3 (1.2, 3.8)	45	5.0 (3.8, 6.4)

Table 3: One-month follow up outcomes, by sex (n=64)

	Male (n=56)	Female (n=8)	Total (n=64)	Chi-square statistic (p-value)
	Count, %	Count, %	Count, %	
Symptoms resolved	31, 55.4%	1, 12.5%	32, 50.0%	5.14 (p=0.02)
On exercise restrictions	35, 62.5%	6, 75.0%	41, 64.1%	0.48 (p=0.49)



[a] Scale on x axis has been truncated for ease of interpretation. Male dose extends to 2909.09

327x93mm (96 x 96 DPI)

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Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines administered to 12–17-year-olds in Victoria, Australia

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Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines administered to 12–17 year-olds in Victoria, Australia

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ABSTRACT

Importance:

COVID-19 mRNA vaccine associated myocarditis has previously been described; however specific features in the adolescent population are currently not well understood.

Objective

To describe myocarditis adverse events following immunization (AEFI) reported following any COVID-19 mRNA vaccines in the adolescent population in Victoria, Australia.

Design

Statewide, population-based study.

Setting

Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the vaccine-safety service for Victoria, Australia.

Participants

All SAEFVIC reports of myocarditis and myopericarditis in 12–17-year-old COVID-19 mRNA vaccinees submitted between 22 February 2021 and 22 February 2022, as well as accompanying diagnostic investigation results where available, were assessed using Brighton Collaboration criteria for diagnostic certainty.

Exposures

Any mRNA COVID-19 vaccine

Main Outcomes/Measure

Confirmed myocarditis as per Brighton Collaboration criteria (levels 1-3)

Results

Clinical review demonstrated definitive (Brighton level 1) or probable (level 2) diagnoses in 75 cases. Confirmed myocarditis reporting rates were 8.3 per 100,000 doses in this age group. Cases were predominantly male (n=62, 82.7%) and post dose 2 (n=61, 81.3%). Rates peaked in the 16–17year-old age group and were higher in males than females (17.7 v 3.9 per 100,000, p=<0.001).

The most common presenting symptoms were chest pain, dyspnoea and palpitations. A large majority of cases who had a cardiac MRI had abnormalities (n=33, 91.7%). Females were more likely to have ongoing clinical symptoms at 1 month follow-up (p=0.02).

Conclusion

Accurate evaluation and confirmation of episodes of COVID-19 mRNA vaccine associated myocarditis enabled understanding of clinical phenotypes in the adolescent age group. Any potential vaccination and safety surveillance policies needs to consider age and gender differences.

What is already known on this topic

- Previous case studies suggest that there is an association between COVID-19 mRNA vaccines and increased rates of myocarditis, most commonly in the following 2 weeks
- Recommendations on use of COVID-19 mRNA vaccines in different age groups vary globally and may not take into account their different risk profiles.

What this study adds

- Incidence of myocarditis post COVID-19 mRNA vaccines are higher after the second dose and appears to differ by age and gender, with adolescent and young adult males being at a higher risk.
- Females were more likely to have ongoing clinical symptoms at one month followup compared to males

How this study might affect research, practice or policy

- Potential policy and safety surveillance adjustments may need to take into account age and gender differentials in myocarditis when reviewing COVID-19 primary (2-dose) vaccine rollout to the adolescent population

INTRODUCTION

Australia has utilized two mRNA vaccines as part of its COVID-19 vaccine strategy in 12-17 year-olds, namely Comirnaty® BNT162b2 COVID-19 (Pfizer-BioNTech) and Spikevax® mRNA-1273 (Moderna). (1) Comirnaty was initially provisionally licensed by the Australian regulator, the Therapeutic Goods Administration (TGA) for those aged 16 years and older, and administered from 25 January 2021 in adults 18+ years. Spikevax received provisional TGA approval for administration in individuals from 18 years from 9 August 2021. Following the availability of age specific clinical trial data, further approvals were added for the 12–15-year-old group for Comirnaty (22nd July 2021) and 12–17-year-old for Spikevax (4th September 2021).

Of particular interest in the young adult population is post-vaccination myocarditis and pericarditis causally associated with COVID-19 mRNA vaccines. These adverse events of special interest (AESI) were first flagged in Israel, which implemented Comirnaty at a population level as soon as it was available (20th December 2020). (2) In a linked electronic health record observational case control study design from Israel's largest health care insurer, Barda *et al* described an elevated risk of myocarditis following Comirnaty (risk ratio [RR], 3.24; 95% confidence interval [CI], 1.55 to 12.44) , while noting a substantially higher risk following COVID-19 disease (RR 18.28; 95% CI, 3.95 to 25.12). (3)

Subsequent post-licensure observational military and report-based case studies confirmed the highest risk group for post mRNA COVID-19 vaccine myocarditis is young males (<24 years old) following the 2nd vaccine dose. (4-6) Both the spontaneous Vaccine Adverse Event Reporting System and active Vaccine Safety Datalink surveillance systems in the US have confirmed a myocarditis signal safety (7), along with similar findings in Canada, the UK and various Nordic countries. (6)

The case phenotype includes chest pain as the most common symptom, but also includes fever, shortness of breath and other non-specific symptoms such as headache, myalgia and vomiting. Common investigation findings include a raised troponin, abnormal electrocardiogram (ECG) with ST or T wave changes, and late gadolinium enhancement or myocardial oedema seen on cardiac magnetic resonance imaging (MRI). (8-11)

Due to this AESI signal, the risk, clinical manifestations and follow-up of myocarditis and pericarditis following mRNA COVID-19 in younger populations has been of particular interest. Some regions (e.g., Hong Kong) are only administering a single dose of mRNA vaccine in adolescents aged 12-17 years and notably, there is limited use of Spikevax in this age group internationally. Spikevax is not currently licensed by the US Food and Drug Administration (FDA) for 12-17 year-olds, whilst Canada and several European countries have issued preferential recommendations for Comirnaty over Spikevax for young adults. (12) This study describes clinical presentation and evaluation of myocarditis AESI following mRNA COVID-19 vaccination in 12–17-year-old adolescents in Victoria, Australia.

METHODS

Victoria is a south-eastern Australian state with a population of approximately 6.6 million. (13) AEFI are spontaneously reported by patients, caregivers or health-care providers to SAEFVIC, the state-wide vaccine safety service. (14) SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services and has been operating since 2007.

Identified reports of myocarditis and myopericarditis in 12–17-year-old vaccinees submitted to SAEFVIC between 22 February 2021 and 22 February 2022 were assessed. The majority of these were practitioner reported. Myocarditis and myopericarditis reports (henceforth summarized as myocarditis) were systematically followed up and diagnostic test results (where available) obtained to confirm the diagnoses, including potential alternative causes such as viral, autoimmune or medication related myocarditis. Data gathered included a list of symptoms such as chest pain, shortness of breath, dizziness and fatigue (Table 1), as well as investigations undertaken by treating clinicians, including ECG, cardiac biomarkers, echocardiogram and cardiac MRI scans. All troponin levels obtained were high sensitivity troponin assays, with troponin levels reported as fold increase from the upper limit of normal to facilitate comparison between different assays.

Once data were available, each case was categorized by at least two independent experts utilizing the Brighton Collaboration definition with graded levels of certainty (Table 1). (15) All reports were forwarded to the national regulator, the Therapeutic Goods Administration (TGA), who report weekly on spontaneous AEFI reports at a national level. (16, 17)

Cases where vaccination was the most likely cause of their diagnosis were followed up after one month to answer a series of questions about ongoing symptoms and clinical management. Cases were declared lost to follow up after three unsuccessful attempts to contact.

Statistical analysis

Data were analysed using Microsoft PowerBI (version 2.91.701.0) with 90% Poisson confidence intervals calculated for rates. Vaccine doses administered and population estimates were obtained from the Australian Immunisation Registry (AIR). (18) Age groups were defined by the vaccine roll-out in Victoria, whereby 16–17-year-olds were eligible for vaccination prior to 12–15-year-olds. Mood's median test was used to compare median fold increase in troponin levels.

RESULTS

As of 22 February 2022, 454,974 12–17-year-old Victorians had received 871,689 mRNA doses (782,964 Comirnaty and 88,725 Spikevax). This equated to approximately 97.9% first dose and 93.7% 2nd dose coverage of this age cohort.

At this timepoint, there were 75 reports of confirmed myocarditis (44 myocarditis, 31 myopericarditis) as per Brighton Collaboration level 1 (definitive) or 2 (probable) criteria. This equates to a rate of 8.3 per 100,000 doses (90% CI: 6.8, 10.1) in this age group (Table 1).

Cases were predominantly in males (n=62, 82.7%) and post dose 2 (n=61, 81.3%). Presentation was temporally related to Comirnaty in 63 (84.10) and to Spikevax in 12 (16.0%) cases respectively. Higher rates were observed in the 16–17-year-old age group, and in males compared to females ($p<0.001$) (Table 2).

Of the 75 cases in the study period, 5 of them were considered by the treating clinician to have an alternative cause for myocarditis more likely than COVID-19 vaccination. One of these cases had evidence of historical COVID-19 infection, with a positive COVID-19 respiratory PCR three weeks prior to receiving first dose Comirnaty vaccination – with subsequent onset of myocarditis two days later.

For the 70 cases related to COVID-19 mRNA vaccination, onset of symptoms ranged from 0 to 49 days after vaccination, with a median of 2 days (IQR 1-3 days), in males from 0 to 34 days (median 2 days) and in females 1 to 49 days (median 2 days). Fifty-one cases (77.1%) required hospital admission with a median length of stay of two nights. No cases required ICU admission and no deaths were recorded. All admissions were discharged to home.

All cases had chest pain as a presenting symptom. Other common symptoms included dyspnoea (21 cases, 30%), palpitations (14,20%) and diaphoresis. 33 cases (47.1%) had concomitant non-specific symptoms such as dizziness, vomiting and fatigue (Table 3).

ECG abnormalities were observed in 49 (70.0%) cases, with the most common finding being ST-elevation. An echocardiogram was performed in 70 cases and was abnormal in 8 (11.4%). An initial diagnostic cardiac MRI was performed in 36 cases with abnormalities documented in the majority of these (33 cases, 91.7%) (Table 3).

There was a trend for males toward higher and more variable increases in troponin, with a median fold rise of 144 times above normal levels compared to females at 33 times above normal (p=0.222) (Figure 1).

Follow up at one month was completed for 64 of the 70 cases where COVID-19 vaccination was the most likely cause of their diagnosis (Table 4). The remaining 6 cases were lost to follow-up and excluded from analysis. Symptoms remained in 50.0% of those who participated in follow-up, with a higher percentage of females having ongoing symptoms (44.6 vs 87.5%, p=0.02) including chest pain (48.0 vs 71.4%, p=0.01) (Table 4).

DISCUSSION

We describe 75 cases of myocarditis reported following COVID-19 mRNA vaccination in the adolescent age group. Our rate of cases was similar, albeit slightly higher than other international studies in Israel, the UK and the USA. (17)

This rate likely reflects concerted public health messaging and awareness of the AESI, coupled with the combination of active and passive surveillance methodology to ascertain these cases. Whilst this may have led to increased reporting rates, the robust diagnostic criteria requiring laboratory and imaging tests to confirm myocarditis, together with tight COVID-19 related environmental restrictions that significantly reduced the chance of COVID-19 infection related myocarditis, indicate that this is likely to represent an accurate rate.

Clinical findings were also similar to other international cohorts of adolescents. Dionne *et al* described similar symptom prevalence in a cohort of myocarditis patients <19 years. (19) There was also similar cardiac MRI abnormalities noted in similar cohorts. (20) In contrast to our findings, the cohort from Truong *et al* had a high number of patients (18.7%) requiring ICU admission, although only 2 required inotropic support. (8) It is likely that the difference in ICU admission criteria, rather than true clinical severity accounts for this discrepancy.

Unique to this study is the clear clinical phenotypic differences identified between sexes. Males tended to present with symptoms and a significantly elevated peak troponin level. Just under half had no residual symptoms 4 weeks after initial onset. In contrast, females tended to have had a much lower median peak troponin level, with similar rates post dose 1 and 2. Symptoms were still experienced by a majority of females 4 weeks after onset. These differences may support a potential impact of testosterone as a risk factor for stronger cardiac inflammation in myocarditis, but with a potentially beneficial impact on duration of symptoms. (21)

Our data indicates a higher rate of cases between the age of 16-17 years and a tapering in rate for the 12-15 year-old age group. Further analysis is needed and ongoing to compare rates of myocarditis between Comirnaty and Spikevax when sufficient doses are administered, although there is currently no discernible difference in case severity or clinical presentation.

These observations suggest that any potential immunisation policy and vaccine safety surveillance adjustments may need to take into account these age and gender differentials. For example, it has implications for younger age groups, including those between 5-11 years, where a reduced dose (10 mcg) Comirnaty vaccine was FDA approved and Advisory Committee on Immunization Practices (ACIP) recommended in early November 2021. (22)

No COVID-19 vaccine clinical trials to date have been sufficiently powered to detect an AESI such as myocarditis. However, with millions of doses administered worldwide in this age group at time of writing, real-world phase IV data will help inform the important risk-benefit discussion regarding COVID-19 vaccines in younger children, who from background rates of myocarditis (all causes) would be expected to have fewer cases than adolescents.

LIMITATIONS

This study is based on clinical data compiled by SAEFVIC as part of vaccine safety surveillance. A passive vaccine safety surveillance system may underreport potential cases of myocarditis. Furthermore, there was lack of clinical data on some cases (eg. investigations not performed), making full description of clinical phenotype, evaluation and diagnosis more challenging. While patient-reported symptoms were included as part of the evaluation, Brighton diagnostic criteria were used as a benchmark to reduce recall bias. The accuracy of diagnosis was also maintained by ensuring that available patient clinical information were reviewed by at least two independent medical specialists to verify reported myocarditis cases and reduce misclassification.

CONCLUSION

Rates of myocarditis in the adolescent population differ by dose and sex in the 12 to 17year-old age group. With the vaccine rollout in younger children and adolescents in mind, these clinical phenotypic differences should be considered for future COVID vaccine recommendations including 'booster' doses.

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Footnotes

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Figure 1: Peak troponin differential between male and females

Table 1: Brighton Collaboration Criteria for Myocarditis

Level 1 – "Definitive" Case	**Level 2 – "Probable Case"**	**Level 3 – "Possible Case"**
Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation OR ≥ 1 new finding of • Troponin T or I level above upper limit of normal AND ≥ 1 new Cardiac MRI (cMRI) findings consistent with • Oedema on T2 weighted study, typically patchy in nature • Late gadolinium enhancement on T1 weighted study with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one non-	Clinical symptoms and exclusion as per Level 3 case AND Elevated myocardial biomarkers ≥ 1 new finding of • Troponin T level above upper limit of normal • Troponin I level above upper limit of normal • CK Myocardial band OR Echocardiogram (ECHO) abnormalities ≥ 1 new finding of • focal or diffuse left or right ventricular function abnormalities (eg. decreased ejection fraction) • Segmental wall motion abnormalities	Presence of ≥ 1 new or worsening of the following clinical symptoms: • chest pain/pressure • dyspnoea /shortness of breath/pain breathing • diaphoresis • palpitations • Sudden Death OR Presence of ≥ 2 new or worsening of the following clinical symptoms: • Fatigue • Abdominal Pain • Syncope • Oedema • Cough AND

ischemic regional distribution with recovery (myocyte injury). OR Echocardiogram (ECHO) abnormalities biomarkers ≥ 1 new finding of as per level 2 case	• Global systolic or diastolic function depression/abnormality • Ventricular dilation • Wall thickness change • Intracavitary thrombi OR Electrocardiogram (ECG) abnormalities ≥ 1 new finding of • Paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages) • AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block) • Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy	≥ 1 new supported finding of inflammation Elevated CRP/ESR or D-Dimer AND Presence of ≥ 1 new abnormal electrocardiogram (ECG) such as: • ST-segment or T-wave abnormalities (elevation or inversion) • PACs and PVCs AND • no other identifiable cause of the symptoms and findings

Table 2: Count and rate of cases by sex, age group, dose number, and Brighton Collaboration level

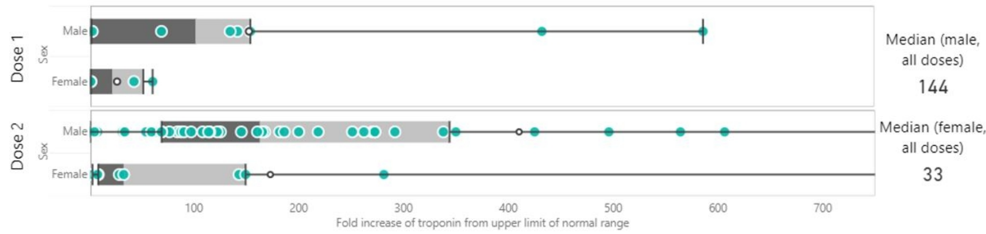
		Male		Female		Total	
		Count	**Rate per 100,000 doses (90% CI)**	**Count**	**Rate per 100,000 doses (90% CI)**	**Count**	**Rate per 100,000 doses (90% CI)**
Total		***62***	***13.6 (10.9, 16.8)***	***13***	***2.9 (1.7, 4.7)***	***75***	***8.3 (6.8, 10.1)***
Age group (years)	12-15	34	11.4 (8.4, 15.2)	7	2.4 (1.1, 4.6)	41	7.0 (5.3, 9.1)
	16-17	28	17.7 (12.6, 24.2)	6	3.9 (1.7, 7.6)	34	10.8 (8.0, 14.4)
Dose	1	10	4.4 (2.4, 7.5)	4	1.8 (0.6, 4.2)	14	3.2 (1.9, 4.9)
	2	52	24.2 (19.0, 30.5)	9	4.3 (2.3, 7.5)	61	14.4 (11.5, 17.8)
Brighton Collaboration level	Definitive	27	5.9 (4.2, 8.2)	3	0.7 (0.2, 1.8)	30	3.3 (2.4, 4.5)
	Probable	35	7.7 (5.7, 10.2)	10	2.3 (1.2, 3.8)	45	5.0 (3.8, 6.4)

Table 3 - Symptoms, Laboratory, ECG, and Imaging Data	
Symptoms (N=70), n (%)	**Count**
Chest Pain	70 (100%)
Palpitations	14 (20.0%)
Dyspnoea	21 (30.0%)
Diaphoresis	6 (8.6%)
Non-specific symptoms (dizziness, vomiting, fatigue)	33 (47.1%)
Laboratory Test	**Value**
Troponin (N=70), median fold increase	138.3 (IQR 56.9-315.0)
Testing/Imaging	**Count**
ECG (N=70), n (%)	
Abnormal	49 (70.0%)
Normal	21 (30.0%)
Abnormal ECG findings or arrhythmias (n=49)	
ST- or T-wave changes/elevation	28 (57.1%)
ST segment depression in AVR	9 (18.4%)
PR depression without reciprocal ST depression	7 (14.3%)
AV Node conduction delay	3 (6.1%)
T wave inversion	3 (6.1%)
Other	9 (18.4%)
Echocardiogram (N=68)	
Normal function	62 (91.2%)
Abnormal function	8 (8.8%)
Systolic dysfunction	5 (62.5%)
Wall motion abnormalities	2 (25.0%)
LV strain	1 (12.5%)
Cardiac MRI (N=36)	
Abnormal findings, n (%)	33 (91.7%)
Late gadolinium enhancement	32 (97.0%)
Myocardial oedema	20 (60.6%)
Other abnormality on T2 imaging	9 (27.3%)
Pericardial effusion or inflammation	5 (15.2%)
Fibrosis	2 (2.4%)

Table 4: One-month follow up outcomes, by sex (n=64)

	Male (n=56)	Female (n=8)	Total (n=64)	Chi-square statistic (p-value)
	Count, %	Count, %	Count, %	
Ongoing symptoms	25, 44.6%	7, 87.5%	32, 50.0%	5.14 (p=0.02)
Chest pain	12, 48.0%	5, 71.4%	17, 53.1%	6.05 (p=0.01)

Fatigue	11, 44.0%	4, 57.1%	15, 46.9%	3.60 (p=0.58)
Palpitations	6, 24.0%	3, 42.8%	9, 28.1%	4.16 (p=0.41)
Dyspnoea	6, 24.0%	3, 42.8%	9, 28.1%	4.16 (p=0.41)



[a] Scale on x axis has been truncated for ease of interpretation. Male dose extends to 2909.09

327x93mm (96 x 96 DPI)