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DRUG REACTIONS AND INTERACTIONS

# mRNA COVID-19 vaccines are well tolerated and myopericarditis is a rare adverse event following immunisation

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**Abstract**
mRNA vaccines are considered to be important tools for the management of the COVID-19 pandemic. Although mRNA COVID-19 vaccines are well tolerated in most recipients, post-marketing data have highlighted an association between myocarditis and mRNA vaccines. Post-vaccine myocarditis (PVM) is most commonly reported in male adolescents receiving the second dose of an mRNA vaccine. However, the incidence of PVM is low and the risk of myocarditis should be kept in perspective. Cases of PVM are mostly mild in severity, and may be managed using existing myocarditis guidelines. The pathology of PVM is under investigation, and current data suggest that cross reactivity or hypersensitivity reactions may be involved. Globally, mRNA vaccines are generally recommended for use in children/adolescents, and delaying the administration of the second dose may reduce the risk of PVM.

## Post-marketing data with mRNA COVID-19 vaccines reveals rare adverse events following immunisation

The early availability of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus proved to be a crucial management tool during the novel coronavirus causing coronavirus disease 2019 (COVID-19) pandemic [1]. Although common adverse events following immunisation (AEFIs) were identified in pre-marketing clinical trials for vaccines against the virus (referred to here as COVID-19 vaccines) [2, 3], global post-marketing surveillance and reporting has identified new rare, but serious, AEFIs [4]. For two mRNA vaccines, the Pfizer-BioNTech BNT162b2 (tozinameran, Cominarty®) and the Moderna mRNA-1273 (elasomeran, Spikevax™) vaccines, (hereafter referred to as the BNT162b2 and mRNA-1273 vaccines) [5–7], these AEFIs include myocarditis and pericarditis [1], particularly in male adolescents [2, 3].

Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the tissue surrounding the heart (i.e. the pericardium) [8]; myopericarditis is a catch-all term to include both forms of carditis [1]. Myocarditis was the focus of post-mRNA vaccine studies and more often clinically investigated, with pericarditis occurring less often [7, 9]. This article summarises relevant safety data [2, 3], including real-world data [7, 10, 11] regarding the use of mRNA vaccines, and the possible pathogenesis of post-mRNA vaccine myopericarditis with brief comments on its suggested management, as reviewed by Hajra et al. [1]. The first and second vaccine doses are emphasised in this article, due to the greater availability of data [11, 12]. The data presented in this article are up to date as of 3 Oct 2022.

## Vaccines were well tolerated during clinical trials

Overall, the two approved mRNA vaccines were well tolerated in randomised controlled trials (RCTs) [1], with most AEFIs being mild in severity, and some attributable to the vaccines' intramuscular administration (Table 1) [2, 3]. AEFIs may be slightly more common in teenagers than in older patients [2], and possibly less frequent with the BNT162b2 versus the mRNA-1273 vaccine [1]. Severe events in vaccine recipients enrolled in RCTs were rare and the frequency of these events were similar to those reported in placebo recipients [1].

In recent trials in young children (aged ≤ 4 or 5 years for the BNT162b2 or mRNA-1273 vaccines, respectively), AEFIs were also mostly mild or moderate in severity, and

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**Table 1** Incidence of the most common adverse events following immunisation (incidence ≥ 10%) with COVID-19 vaccines in randomised, controlled trials [14, 15]

| | BNT162b2 primary course | | mRNA-1273 primary course | |
|---|---|---|---|---|
| | Age 12–15 yrs[a] | Age 16–55 yrs | Age 18–64 yrs | Age ≥ 65 yrs |
| **Cutaneous reactions (incidence %)** | | | | |
| IS pain | 91 | 89 | 93 | 88 |
| IS swelling | 9 | 11 | 15 | 13 |
| IS redness | 9 | < 10 | 11 | < 10 |
| **Systemic reactions (incidence %)** | | | | |
| Fatigue | 78 | 70 | 72 | 65 |
| Headache | 76 | 65 | 69 | 53 |
| Muscle pain | 42 | 46 | 65 | 52 |
| Chills | 49 | 42 | 50 | 33 |
| Joint pain | 20 | 28 | 49 | 40 |
| Fever | 24 | 18 | 17 | < 10 |
| Nausea/vomiting | < 8 | < 10 | 26 | 15 |
| Lymphadenopathy/axillary swelling | < 8 | < 10 | 22 | 13 |

*BNT162b2* Pfizer BioNTech BNT162b2 COVID-19 vaccine, *IS* injection site, *mRNA-1273* Moderna mRNA-1273 COVID-19 vaccine

[a]The most common adverse events following immunisation were defined as incidence ≥ 8% in this population

lasted for 1 or 2 days after vaccination [13]. Irritability or crying and drowsiness were reported most often in infants; fatigue was most common in older children [13]. RCTs did not identify myocarditis as an AEFI (Table 1) [2, 3].

## Surveillance identified post-vaccine myocarditis

Post-marketing data, obtained through health care databases [4] and formal reporting systems such as the European Medicines Authority (EMA) EudraVigilance system [16] and the US Mandatory Vaccine Adverse Events Reporting System (VAERS) [11]. The EMA has gathered spontaneous reports of 848,000 AEFIs and 8000 fatalities from 649 million administered doses of the BNT162b2 vaccine (including 55 million doses in people aged < 18 years); 231,000 spontaneous reports of AEFIs and 1100 fatalities were collated from 155 million administered doses of the mRNA-1273 vaccine (including 3.1 million doses in people aged < 18 years). These analyses have revealed less common potential mRNA-vaccine AEFIs, including myocarditis (Table 2) [5]. Some are now included in prescribing information, with others eliminated or under investigation (Table 2) [2, 3, 5].

The risk of myocarditis, mostly affecting young men after receiving the second dose of the BNT162b2 vaccine (the main mRNA vaccine available at the time of the analysis), was also highlighted in an Israeli case-control study using data from December 2020 to May 2021 in people aged ≥ 16 years [4]. In most countries, initial vaccine rollouts focussed on older patients, which may have delayed the recognition of post-vaccine myocarditis (PVM) [11].

## Male adolescents are most susceptible to myocarditis

Several studies [6, 7, 9–11] provide more insights and confirm that male adolescent recipients of mRNA COVID-19 vaccines are most likely to experience PVM, particularly after the second dose of the mRNA-1273 vaccine (Tables 3, 4 and 5) [7, 10, 11]. These include a systematic review of 238 patients with PVM aged > 12 years [6], a review of VAERS data (Table 4) [11] and case control analyses from European health records (Tables 3 and 5) [7, 10].

Mixed mRNA vaccine doses (BNT162b2 then mRNA-1273) administered in a subset of patients (615,000 of 23 million patients) during a Nordic study markedly increased the adjusted incidence rate ratios (IRRs) in post-vaccine vs unvaccinated periods for myocarditis and excess events in males [7]. Adjusted IRRs for all men, and males aged 16–24 years and 25–39 years were 17, 36 and 23, respectively [7], translating to 10.3, 27.5 and 11.3 excess events per 100,000 people, respectively [7].

Fewer data are available for pericarditis, and its incidence may be harder to determine [6]. The Nordic study suggested a higher incidence of pericarditis, generally consistent with trends observed for myocarditis, during post-vaccination periods versus unvaccinated periods after two BNT162b2 and mRNA-1273 doses [7].

**Table 2** European Medicines Agency safety data and less common mRNA COVID-19 vaccine AEFIs as at July 2022 [2, 3, 5]

| AEFI status (incidence) | AEFIs |
|---|---|
| **Pfizer BioNTech BNT162b2 COVID-19 vaccine (people aged ≥ 12 yrs)** [2, 5] | |
| Uncommon (< 1%) | Hypersensitivity, decreased appetite, insomnia, lethargy, hyperhidrosis, injection site pruritus, pain in extremity, asthenia, malaise |
| Rare (≤ 0.1%) | Acute peripheral facial paralysis |
| Very rare (< 0.01%) | Myocarditis and pericarditis especially ≤ 7 d after the second dose in males aged ≤ 40 yrs, particularly those aged 12–17 yrs |
| Uncertain incidence | Anaphylaxis, paraesthesia and hypoaesthesia, erythema multiforme, facial swelling and extensive swelling of vaccinated limb, histiocytic necrotising lymphadenitis [5] |
| Now eliminated | Amenorrhoea: no causal relationship indicated by evidence [5] |
| Being investigated | Heavy menstrual bleeding, vulval ulceration [5] |
| **Moderna mRNA-1273 COVID-29 vaccine (people aged ≥ 6 yrs)** [3, 5] | |
| Uncommon (< 1%) | Dizziness, abdominal pain (in children), injection site pruritus |
| Rare (≤ 0.1%) | Acute facial paralysis, paraesthesia and hypoaesthesia, facial swelling |
| Very rare (< 0.01%) | Myocarditis and pericarditis especially ≤ 7 d after the second dose in males aged ≤ 40 yrs, particularly those aged 18–24 yrs |
| Uncertain incidence | Anaphylaxis, hypersensitivity, erythema multiforme, capillary leak syndrome flares; extensive swelling of the vaccinated limb will be added [5] |
| Now eliminated | Amenorrhoea: no causal relationship indicated by evidence [5] |
| Being investigated | Heavy menstrual bleeding [5] |

*AEFI(s)* adverse event(s) following immunisation, *pts* patients

**Table 3** Increased risk of post-mRNA vaccine myocarditis in a meta-analysis of four cohort studies of hospitalised patients in Denmark, Finland, Norway and Sweden from December 2020 to October 2021[a] [7]

| | Myocarditis IRR with BNT162b2 vs unvaccinated people (95% CI) | | Myocarditis IRR with mRNA-1273 vs unvaccinated people (95% CI) | |
|---|---|---|---|---|
| Pt population | First dose [1.1 million pts] | Second dose [13.3 million pts] | First dose [0.4 million pts] | Second dose [2.0 million pts] |
| Male pts aged ≥ 12 yrs | 1.40 (1.09–1.80) | 2.04 (1.61–2.58) | 1.45 (0.84–2.52) | 8.55 (6.40–11.41) |
| Male pts aged 16–24 yrs | 2.16 (1.40–3.33) | 5.31 (3.68–7.68) | 2.90 (1.05–7.97) | 13.83 (8.08–23.68) |
| Male pts aged 25–39 yrs | 1.62 (0.94–2.80) | 1.75 (1.03–2.99) | 1.27 (0.40–3.99) | 12.96 (8.23–20.42) |
| Female pts aged ≥ 12 yrs | 1.46 (1.01–2.11) | 1.25 (0.77–2.05) | 1.45 (0.35–5.97) | 2.73 (1.27–5.87) |
| Female pts aged 16–24 yrs | 1.98 (0.56–7.01) | 2.86 (1.10–7.48) | No cases | No cases |
| Female pts aged 25–39 yrs | ≤ 5 cases | ≤ 5 cases | No cases | ≤ 5 cases |
| All pts | 1.38 (1.12–1.69) | 1.75 (1.43–2.14) | 1.16 (0.69–1.93) | 6.57 (4.64–9.28) |

The defined vaccine-to-symptom interval was 28 d. Diagnoses of myocarditis at discharge were obtained from linked health registers.

*BNT162b2* Pfizer BioNTech BNT162b2 COVID-19 vaccine, *IRR* adjusted incidence rate ratio in post-vaccine vs unvaccinated periods, *mRNA-1273* Moderna mRNA-1273 COVID-19 vaccine, *pt(s)* patient(s)

[a]The analysis included 23 million people aged ≥ 12 yrs living in Nordic countries

Conversely, a smaller Hong Kong study in 120 patients with carditis found almost no increase in post-mRNA-vaccine pericarditis [odds ratio (OR) 1.06 vs 9.29 for myocarditis] [9]. A study in France in women aged ≥ 30 years, however, reported almost identical numbers of myocarditis and pericarditis cases (1612 and 1613 cases, respectively, from 46 million doses of mRNA vaccines), and pericarditis ORs of 13–20 [10].

**Table 4** Increased risk of post-mRNA vaccine myocarditis in a database analysis of mostly (96.4%) hospitalised patients in the USA from December 2020 to August 2021 [11]

| | Expected background myocarditis cases per million doses (95% CI) | Myocarditis cases per million doses with BNT162b2 (95% CI) | | Myocarditis cases per million doses with mRNA-1273 (95% CI) | |
|---|---|---|---|---|---|
| | | First dose [95.5 million doses] | Second dose [114.2 million doses] | First dose [66.2 million doses] | Second dose [78.2 million doses] |
| **Male adolescents or men** | | | | | |
| Aged 12–15 yrs | 0.53 (0.40–0.70) | 7.06 (4.88–10.23) | 70.73 (61.68–81.11) | Not approved during this analysis | |
| Aged 16–17 yrs | 1.34 (1.05–1.72) | 7.26 (4.45–11.86) | 105.86 (91.65–122.27) | Not approved during this analysis | |
| Aged 18–24 yrs | 1.76 (1.58–1.98) | 3.82 (2.40–6.06) | 52.43 (45.56–60.33) | 10.73 (7.50–15.34) | 56.31 (47.08–67.34) |
| Aged 25–29 yrs | 1.45 (1.21–1.74) | 1.74 (0.78–3.87) | 17.28 (13.02–22.93) | 4.88 (2.70–8.80) | 24.18 (17.93–32.61) |
| Aged 30–39 yrs | 0.63 (0.54–0.73) | 0.54 (0.20–1.44) | 7.10 (5.26–9.57) | 3.00 (1.81–4.97) | 7.93 (5.61–11.21) |
| **Female adolescents or women** | | | | | |
| Aged 12–15 yrs | 0.17 (0.11–0.29) | 0.49 (0.12–1.98) | 6.35 (4.05–9.96) | Not approved during this analysis | |
| Aged 16–17 yrs | 0.42 (0.27–0.66) | 0.84 (0.21–3.37) | 10.98 (7.16–16.84) | Not approved during this analysis | |
| Aged 18–24 yrs | 0.38 (0.30–0.49) | 0.18 (0.03–1.31) | 4.12 (2.60–6.54) | 0.96 (0.31–2.96) | 6.87 (4.27–11.05) |
| Aged 25–29 yrs | 0.48 (0.35–0.65) | 0.26 (0.04–1.84) | 2.23 (1.07–4.69) | 0.41 (0.06–2.94) | 8.22 (5.03–13.41) |
| Aged 30–39 yrs | 0.47 (0.39–0.57) | 0.72 (0.32–1.60) | 1.02 (0.49–2.14) | 0.74 (0.28–1.98) | 0.68 (0.22–2.10) |

The defined vaccine-to-symptom interval was 7 d. The analysis included cases meeting the definition by the CDC for myocarditis, reported via VAERS

*BNT162b2* Pfizer BioNTech BNT162b2 COVID-19 vaccine, *IRR* adjusted incidence rate ratio in post-vaccine vs unvaccinated periods, *mRNA-1273* Moderna mRNA-1273 COVID-19 vaccine

**Table 5** Excess myocarditis cases in younger people after receiving the second dose of an mRNA vaccine in European database analyses [2, 3, 7, 10]

| Population analysed (vaccine-symptom interval) | Population subgroup | Excess cases per million doses[a] | |
|---|---|---|---|
| | | BNT162b2 | mRNA-1273 |
| 23.1 million people, 81% vaccinated by study end, in 4 Nordic countries; December 2020 to October 2021 (28d) [7] | All men | 6.7 | 49.7 |
| | Men aged 16–24 yrs | 55.5 | 183.9 |
| | Men aged 25–39 yrs | 5.9 | 80.1 |
| | All women | 0.9 | 4.8 |
| | Women aged 16–24 yrs | 5.7 | No data |
| 50 million vaccinated people, equal to 88% of population aged ≥ 12 y, vs controls in France; April to October 2021 (7 d) [10] | Male adolescents aged 12–17 yrs | 19 | Not yet approved |
| | Men 18–24 aged yrs | 47 | 170 |
| | Women 18–24 aged yrs | 6 | 53 |
| European Medicines Agency (7 d)[b] [2, 3] | Men 12–29 aged yrs | 27 | 132 |
| European Medicines Agency (28 d)[b] [2, 3] | Men 16–24 aged yrs | 56 | 188 |

*BNT162b2* Pfizer BioNTech BNT162b2 COVID-19 vaccine, *mRNA-1273* Moderna mRNA-1273 COVID-19 vaccine

[a]Extrapolated from cases per 10,000 or 100,000 doses

[b]Study details not reported

## Myocarditis and/or pericarditis may be more common with mRNA-1273

In an analysis of electronic insurance records from 12 million patients aged 18–39 years in the USA, the adjusted IRR for myocarditis and pericarditis during the risk period (0–7 days post-vaccination) versus the comparison period (22–42 days post-vaccination) was 13.63 (95% CI 7.39–26.55; $p < 0.001$) for both mRNA vaccines across both genders [17]. Additionally, a head-to-head analysis of the mRNA-1273 versus the BNT162b2 vaccines in the same dataset did not demonstrate a difference in the risk for myocarditis, myopericarditis, and pericarditis after the second dose [adjusted IRR 1.48 (95% CI 0.88–2.50)]. However, a significant ($p = 0.041$) increase in the risk for myocarditis, myopericarditis, and pericarditis was observed in patients receiving either the first or the

second dose of the mRNA-1273 vaccine than the BNT162b2 vaccine [adjusted IRR 1.61 (95% CI 1.02–2.54)] [17].

The mRNA-1273 vaccine was also associated with a greater risk of myocarditis or pericarditis compared with the BNT162b2 vaccine in a cohort study in Canada [18]. Based on almost 20 million doses of mRNA vaccines administered between December 2020 and September 2021, the adjusted rate ratio was significantly ($p \leq 0.006$) higher with the mRNA-1273 than the BNT162b2 vaccine in women aged 18–24 years [9.6 (95% CI 1.9–48.8)], men aged 18–24 years [6.6 (95% CI 3.3–13.2)] and men aged 25–39 years [5.1 (95% CI 2.3–11.5)] [18].

### Excess cases highlighted in recent analyses

Table 5 details excess PVM event calculations from Nordic and French studies [10], and limited data from the EMA are consistent with these studies [7, 10]. The Nordic study reported 4–7 excess PVM events per 100,000 vaccinated people after the second dose of BNT162b2 and 9–28 after mRNA-1273 [7]. In men aged 18–24 years in France, results translated to one estimated PVM case per 21,000 second doses of the BNT1262b vaccine versus 5,900 second doses of mRNA-1273 vaccine [10]; comparable numbers in women were 159,000 BNT162b2 and 18,600 mRNA-1273 recipients [10].

### More data are needed in youngest and oldest patients

Scant data regarding PVM in younger patients are available reflecting later vaccine approvals, especially for mRNA-1273 [7], and older patients may have been excluded from some studies [10, 11]. In Nordic countries, fewer than 200,000 children aged 12–15 years were vaccinated in 2021; for male children in that group receiving either mRNA vaccine, myopericarditis IRRs were 4.77 (95% CI 1.85–12.26) and 13.86 (95% CI 5.78–33.22) after the first and second dose, respectively [7]. Surveillance data from Australia, which includes non-hospitalised patients, indicates 130 cases per million doses after the second dose of the BNT162b2 vaccine in male children/adolescents aged 12–17 years and reports a likely case of PVM in a 6-year-old [8]. In Canada, the crude rates of myocarditis or pericarditis per million doses of the BNT162b2 vaccine in patients aged 12–17 years were 9.7 (95% CI 1.2–35.1) in females and 97.3 (95% CI 60.3–148.8) in males after receiving their second dose [18]. A Hong Kong case-control study found a PVM OR of 13.79 (95% CI 2.86–110.38) with BNT162b2 in a small subgroup of 14 adolescents [9].

More recently, the EMA has concluded the risk of myocarditis and pericarditis with the BNT162b2 and mRNA-1273 vaccines is lower in children aged 5–11 years than in adolescents aged 12–17 years, based on safety data reported from the USA [5].

With regards to older patients, in a global review [6], 27 women with PVM were older than men (mean 41 vs 26 years), with a longer interval between vaccine and PVM (mean 6.5 vs 3.7 days) [6].

## Keep myocarditis risks in perspective

While the excess rates of PVM, especially in young men, can seem substantial, PVM is very rare in most age groups [7]. Over almost a year, in four Nordic countries, there were 1077 cases of myocarditis from any cause in 23.1 million people (incidence 0.005%), more than two-thirds of which (731 cases) were in unvaccinated people [7]. In the UK, the IRR for myocarditis occurring within 28 days in people aged < 40 years following the second dose of BNT162b2 or mRNA-1273 vaccine was 3.40 (95% CI 1.91–6.04) and 20.71 (95% CI 4.02–106.68), respectively [19]. In contrast, the IRR for myocarditis occurring within 28 days of a positive SARS-CoV-2 test was 4.06 (95% CI 2.21–7.45) [19].

Myocarditis has been noted following receipt of other vaccines in a recent meta-analysis [12]. The analysis covered 291 million mRNA vaccine doses, 52 million doses of other COVID-19 vaccines and 10 million vaccinations in total for other diseases. Calculated rates of PVM per million doses, typically defined as occurring within 7–14 days, were [12]:

- 22.6 with COVID-19 mRNA vaccines;
- 7.9 with non-mRNA COVID-19 vaccines;
- 56.0 with any non-COVID vaccine (including many smallpox studies, see below); and
- 132.1 with smallpox vaccine doses, although this figure may reflect a young male bias, as most studies were undertaken in US military personnel.

### Balance bias against consistent myocarditis data

Rare cases of PVM after mRNA COVID-19 vaccines are consistently reported [6, 7, 9–11] but bias, which is characteristic of retrospective studies, may affect results [20]. Compared to RCTs, active surveillance studies lack a rigorous control group, limiting their ability to establish causation [1].

Public awareness of potential PVM has probably increased reporting rates for both total events and milder cases [8], although this is not the case in France [10]. The

Australian Therapeutic Goods Administration (TGA) lists chest pain among the most commonly reported post-COVID vaccine AEFIs, especially in younger men [8]. However, of the approximately 1400 PVM and 2800 pericarditis reactions notified after 44 million BNT126b2 doses (with similar trends with mRNA-1273), ICU care was needed in 17 people for PVM and 6 people for pericarditis [8].

Despite potential biases, the validity of PVM findings in large retrospective and observational studies is supported by similar findings between studies [1, 20]. In particular, the consistent vaccine-to-symptom time course is noteworthy [1, 20].

## The pathogenesis of post-vaccine myocarditis is perplexing

Various theories exist for the pathogenesis of PVM associated with mRNA vaccines [1, 5, 8]. The pathogenesis may differ between patients and with age [21] or gender, and may reflect genetic or population-based factors that cause different background rates of myocarditis [7].

Previous myocarditis was not a risk factor for PVM in a US Health Management Organisation analysis of 2.8 million racially diverse mRNA vaccine recipients [22]. None of the 567 patients with a history of myocarditis were hospitalised after either mRNA vaccine dose [22]. However, at least one case of PVM in a BNT162b2 recipient with a history of myocarditis has been reported [23] and a French study found previous myocarditis to be a significant risk factor for subsequent myocarditis (OR of 160, with a similar OR of 250 for past and subsequent endocarditis) [10].

Vaccines aside, young males are the group most susceptible to myocarditis [11, 24]. Non-vaccine cases usually result from viral infection and 25% of cases are severe [24]. Autoimmune responses, hypersensitivity reactions, medications or toxins are other precipitants [9, 24]; including exposure to drugs, such as amphetamines [25]. Similar, but so far elusive, processes may underlie PVM [1, 6], such as exaggerated immune reactions [1], cross-reactivity between SARS-CoV-2 spike antibodies and other proteins, and hormonal effects [1, 21].

mRNA vaccines facilitate the encoding of the viral spike glycoprotein to induce an immune response, which subsequently works against viruses expressing this protein [6, 21]. The induction of IgG antibodies against the viral spike protein prevents the virus from entering host cells via interactions with the angiotensin-converting enzyme (ACE)-2 receptor [21]. Despite nucleoside modifications of the vaccine mRNA, it may be detected as an antigen by the immune system, which activates inflammatory and immunological responses [21]. This does not, however, explain why the heart in particular is affected [21]. It is possible that interaction with host ACE-2 receptors enhances cardiac sensitivity or inflammatory responses [6].

A delayed hypersensitivity mechanism is supported by the short vaccine-to-symptom interval and by known previous COVID-19 infection in some patients who developed PVM after the first dose [1]. Hypersensitivity reactions to a vaccine component (e.g. polyethylene glycol) are also possible [6].

Molecular mimicry, effectively creating autoantibodies following vaccination, may occur if there is a genetic predisposition to hyperimmunity [21]. This possibility is supported by the myocardial damage often seen with COVID-19 infections [1] and by demonstrated cross-reactivity of SARS-CoV-2 spike glycoprotein antibodies with α-myosin and similar peptide protein sequences [6].

Hormonal influences may affect immune responses [21]. Testosterone is associated with a more aggressive T-helper type 1 response, reflecting its inhibition of some anti-inflammatory cells; whereas oestrogen inhibits pro-inflammatory T-cells thereby having the opposite effect [21].

Experiments in mice suggest that accidental intravenous administration of mRNA vaccines in contrast to intended intramuscular administration may precipitate acute myoperidarditis [26]. A practical approach to minimising this risk is to check for blood aspiration prior to injection to avoid intravenous administration [26].

## Post-vaccine myocarditis is manageable in the majority of cases

Most cases of PVM are mild in severity [6], with hospitalised patients discharged after 4–5 days [7]. However, cardiogenic shock may occur [6] and PVM is fatal in 5–6% of older people in particular [7]. Patients aged 20 years or more spent approximately 6 days in hospital, versus 3 days in younger patients and 14 days for all women (mean age 41 years), in a systematic review [6]. In other studies, no myocarditis-related deaths were reported [17, 18] and the median duration of hospitalisation was 1 day [17]. Long-term PVM outcomes are unknown and data are awaited with interest.

While PVM may present differently from a typical presentation of myocarditis, recommended investigations are similar (Table 6) [24] and the exclusion of myocarditis due to other causes is important [13]. Chest pain is present in 90% of patients with PVM (vs ≤ 42% of other patients

**Table 6** Post-mRNA COVID-19 vaccine myocarditis treatment, as reviewed by Ilonz and Guglin [6] and Oster et al [11]

| | Details | PVM treatment experience [6] in context of AHA paediatric myocarditis recommendations [24] |
|---|---|---|
| **Investigations** | | |
| Laboratory tests | Troponin and BNP, +/− inflammatory markers | ↑ troponin in almost all young pts with PVM [6] |
| | | ↑ BNP and N-terminal pro-BNP [6] |
| | | Troponin and BNP not sensitive or specific for myocarditis, but are useful indicators of its severity and BNP of the degree of HF [24] |
| Imaging | ECG | Undertake in all pts; ST-segment and T-wave changes in 72–80% of pts with PVM [6, 11] |
| | Echocardiogram | Undertake if practicable; normal systolic function in 69% of pts with PVM (LVEF ≥ 55%), severe dysfunction (LVEF < 35%) in 7% of pts |
| | | Pericardial effusion (usually small) in 19% of pts [6] |
| | | Disproportionately severe LV dysfunction and cardiac wall thickening suggest more typical paediatric myocarditis [24] |
| | Cardiac MRI | Gold standard myocarditis diagnostic tool [24]; abnormal in ≥ 72% of pts with PVM [6, 11] |
| | | Late gadolinium enhancement and myocardial oedema in 96% and 69% of pts with PVM [6] |
| | | May avoid the need for invasive biopsies [24] as it can histologically characterise myocarditis and quantify ventricular volumes, EF and mass |
| **In-hospital management** | | |
| Immediate triage; identify very sick and/or older pts | | Transfer pts with cardiogenic shock (5% of PVM pts [6]) +/− tachyarrhythmias to a facility able to provide MCS [24]; watch older pts with PVM, who may be sicker [7, 11] |
| | | Monitor all pts for atrial or ventricular arrhythmias, which are associated with a poor prognosis [24] |
| Potential treatments | Anti-inflammatory agents | Most pts with PVM received only anti-inflammatory agents, particularly nonsteroidal anti-inflammatory drugs; colchicine or corticosteroids were also administered [6, 11] |
| | | Corticosteroid data are conflicting; immunosuppression may be helpful during the autoimmune phase in adults with myocarditis without viral infection [24] |
| | Pts with low cardiac output syndrome | Treat with positive inotropes, such as milrinone [24] |
| | | Noradrenaline and dopamine are usually not needed in milder cases; they have vasopressor activity and antiarrhythmic properties [24] |
| | Other therapy | 15% (criteria unspecified) of pts with PVM received therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta blockers [6] |
| | | < 10% of pts received anticoagulants, antiarrhythmics, oxygen, diuretics or vasoactive agents |
| | | 12% of pts with PVM aged ≤ 30 yrs received intravenous immunoglobulins |
| | | Common use of immunotherapy for acutely decompensated pts is not supported by evidence [24] |
| **Post-discharge management** | | |
| Cardiology follow-up | | For pts discharged on cardiac medication, follow AHA recommendations [24] |
| | | Follow-up with electromyography and/or echocardiograms; and if ventricular fraction or inflammatory markers are abnormal, perform cardiac MRI [24] |
| Exercise and activity | | Myocarditis, even if systolic function normal, associated with sudden death, notably post-exercise; advise pts to avoid competitive sport if active inflammation is present [24] |
| | | After 3–6 mo, perform Holter monitoring and exercise stress testing in athletes prior to returning to competition [24] |

*AHA* American Heart Association, *BNP* B-type natriuretic peptide, *ECG* electrocardiogram, *EF* ejection fraction, *GI* gastrointestinal, *HF* heart failure, *LV* left ventricular, *MCS* mechanical circulatory support, *MRI* magnetic resonance imaging, *pts* patients, ↑ increase(d)

with myocarditis), with fatigue, breathlessness or dyspnoea observed in up to one-third of patients (vs ≤ 70% in typical myocarditis) [1, 6]. Younger children may display non-specific symptoms, such as irritability, lethargy and vomiting or poor feeding [13].

## Follow guidelines for the management of myocarditis

Recommendations for the management of PVM are varied [27]. The UK takes a similar approach to the AHA (Table 6)

[24] for inpatients, but has a relaxed approach to outpatient management [27]. Expert guidelines may also offer helpful guidance [24, 28].

## mRNA vaccines are generally recommended for use in children

Experts are united in recommending vaccines [5, 13, 21], and generally recommend the use of mRNA vaccines in children:

- Norway, Sweden and France no longer restrict access to the mRNA-1273 vaccine to patients aged ≥ 30 years [29–31]; however, Denmark has placed restrictions on the vaccination of children and adolescents aged ≤ 18 years as they are unlikely to become severely ill [32].
- The US has extended authorisation for both mRNA vaccines to everyone aged ≥ 6 months [33] and the CDC recommends vaccination in all indicated populations, including people who have myocarditis or pericarditis unrelated to vaccination [13]. However, they do not recommend the subsequent dose of any COVID-19 vaccine in people who develop PVM [13].

Patients who develop PVM may receive additional doses of vaccines in some countries [8, 27]. In the UK, the BNT162b2 vaccine may be offered to patients who develop PVM, provided they no longer have active myocarditis symptoms [27]. The Australian Technical Advisory Group advises patients with PVM to defer further doses [8]. Given that PVM usually occurs after the second dose, most questions may arise around booster doses, and at present data are insufficient to characterise PVM risk with boosters [5].

The second dose of mRNA vaccines may be delayed to reduce the risk of PVM in high-risk populations [13, 34]. The time between the first and second doses of mRNA vaccines may be increased to 8 weeks for children aged 5–11 years in the UK [34] and in males aged 12–39 years in the US [13].

## Take home messages

- In the majority of patients, mRNA COVID-19 vaccines are well tolerated; most reactions are mild to moderate in severity
- PVM following mRNA COVID-19 vaccines is a rare, but consistently reported AEFI; it is most common in male adolescents after their second mRNA vaccine dose
- PVM is usually mild and most patients do not require intensive cardiac care, AHA myocarditis guidelines may be useful for the management of PVM
- The pathogenesis of PVM is unclear, but cross reactivity or hypersensitivity reactions may be implicated
- mRNA vaccines are generally recommended for use in children, and the second dose may be delayed to decrease the risk of PVM

## Declarations

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