

Global overview of vaccine related myocarditis

EMA virtual workshop on myocarditis post COVID-19 vaccination
16/01/2023

Professor Kristine Macartney
Director
NCIRS Australia

WHO GACVS Member

Acknowledgements: Dr Rita Helfand, Dr Ketaki Sharma, Dr Anny Yuanfei Huang, Ms Amanda van Eldik, Ms Alexis Pillsbury

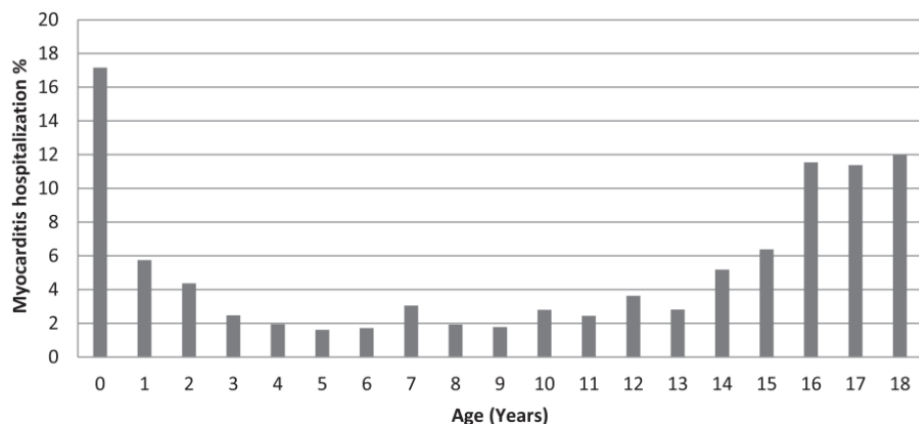


Background: myocarditis¹⁻⁶

Table sourced from: AESI Case Definition Companion Guide for Myocarditis and Pericarditis – SPEAC / Brighton Collaboration

- Highest incidence in late adolescence and early adulthood
- Most cases in males (approx 82%)
- Causes:
 - Infectious
 - Viral most common
 - Non-infectious
 - Includes drugs and vaccines
 - Concurrent autoimmune / metabolic disorders
 - Neoplastic / paraneoplastic
 - Idiopathic

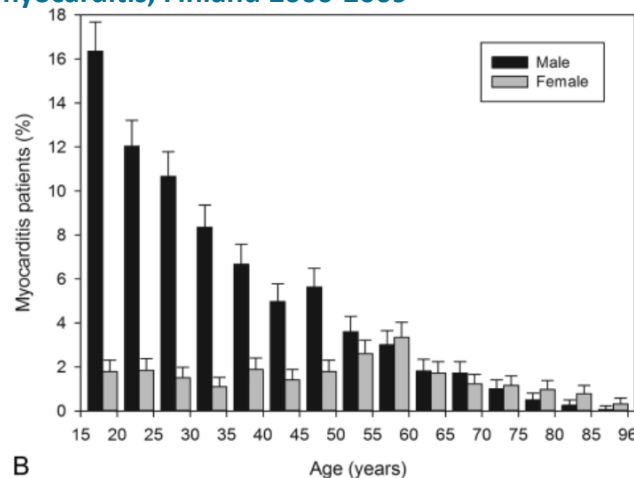
Proportions of children at each age hospitalised for myocarditis, US 2007-2016



Background incidence rates:

- Difficult to determine – probably under-estimated:
 - Many cases are mild and resolve without diagnosis
 - Diagnostic tests not available in all settings
- Variations across studies

Proportion of adults in each age group hospitalised for myocarditis, Finland 2000-2009



Source	Population	Incidence rate per 100,000 person years
Global burden of disease study 2013	All ages	22.0 (20.5 - 23.6)
Denmark 2010	All ages	3.66 (3.19-4.20)
UK 2017	All ages	2.86 (2.34-3.47)
USA hospital data 2007 - 2016	10-14	0.50 (0.46-0.53)
	15-18	1.50 (1.42-1.58)
	All ages	0.80 (0.76-0.84)
	All ages: males only	1.00 (0.96-1.04)
	All ages: females only	0.60 (0.54-0.66)
	All ages: White	0.60 (0.56-0.64)
	All ages: Black	0.90 (0.82-0.98)
	All ages: Hispanic	0.60 (0.54-0.66)
	All ages: Asian / Pacific Islander / Native American	0.60 (0.56-0.69)

Council of International Organizations of Medical Sciences frequency classification

Very rare (<1/10 000)	Rare (<1/1000 to ≥1/10 000)	Uncommon (<1/100 to ≥1/1000)	Common (<1/10 to ≥1/100)	Very common (≥1/10)
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Key to colour-coding used in this presentation:

Background: pericarditis^{1-4,7,8}



- Most common inflammatory heart disorder
- More common in males, and at a younger age (from [review](#) conducted by SPEAC / Brighton Collaboration):
 - Age-adjusted likelihood ratio (M:F) = 1.85 (1.65 to 2.06)
 - Mean age of onset in males 45.9 (SD ±18.3 years)
 - Mean age of onset in females 56.2 (SD ±17.3 years)
 - Sex differential not seen in cases ≥66 years of age
- Causes:
 - Infectious
 - Mostly viral, but TB more common in some parts of the world
 - Non-infectious
 - Includes drugs and vaccines
 - Trauma: including iatrogenic trauma from cardiac procedures
 - Concurrent autoimmune / metabolic disorders
 - Neoplastic
 - Idiopathic
- Cohort [study](#) in Northern Italy (all ages): 15% had concurrent myocarditis

Background rates:

- Few sources report pericarditis rates in isolation
- Rates more commonly given as those of myocarditis and pericarditis together
- Pericarditis only:
 - [Hospitalisation data](#) from Finland 2000-2009 in individuals ≥16 years: **3.32** per 100,000 person-years (95% CI 3.14 - 3.50)
 - Males: 4.52 (4.22 - 4.83)
 - Females: 2.11 (1.91 - 2.32)
- Myocarditis and pericarditis combined:
 - [Network cohort study](#): data from 8 high income countries 2017-2019 (table below)

Incidence rate per 100 000 person years (95% prediction interval)								
Outcomes by sex	1-5 years	6-17 years	18-34 years	35-54 years	55-64 years	65-74 years	75-84 years	≥85 years
Myocarditis or pericarditis								
Female	6 (1 to 25)	7 (2 to 21)	16 (8 to 32)	22 (9 to 53)	31 (13 to 72)	35 (12 to 97)	39 (11 to 138)	34 (8 to 143)
Male	7 (1 to 32)	11 (5 to 24)	37 (16 to 88)	37 (16 to 87)	45 (20 to 102)	49 (17 to 139)	54 (15 to 193)	41 (9 to 193)
Council of International Organizations of Medical Sciences frequency classification								
Very rare (<1/10 000)	Rare (<1/1000 to ≥1/10 000)		Uncommon (<1/100 to ≥1/1000)		Common (<1/10 to ≥1/100)		Very common (≥1/10)	

Background: non-COVID-19 vaccines and myo/pericarditis^{4,9-11}



Clearest association with smallpox vaccines

- Other non-smallpox, non-COVID-19 vaccines: case reports / small case series available only; no clear attributable risk
- Biological mechanism unclear

Smallpox vaccines (**1st/2nd generation replication-competent**):

- First recognised association with myo/pericarditis in the 1950s
- Literature for years 1950-1970 with inconsistent case definitions, 1st gen vaccines used:
 - **Europe:** 2 adult deaths (5 other possible adult deaths), 2 paediatric deaths; **Finland:** 1 in 10,000 myocarditis cases in military recruits; **Australia:** 11 non-fatal and 1 fatal myopericarditis cases; **USA:** Only 2 non-fatal and 2 fatal myocarditis cases
- US 2002-2003: >450,000 military personnel given Dryvax (1st gen):
 - 118 cases of myopericarditis per 1 million doses
 - CDC created myocarditis and pericarditis case definitions
- Overall rates for 2nd generation smallpox vaccines (specifically ACAM2000):
 - SAGE rapid review: 269 cases of myocarditis in 1,743,620 vaccinees – 15.4 cases per 100,000 doses

Background: Smallpox vaccines and myo/pericarditis¹²⁻¹⁴



Smallpox vaccines (1st/2nd generation – continued): [Engler et al \(2015\)](#)

Prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination:

- Cohort study: US military 2004-2010 – members receiving occupational smallpox or trivalent influenza vaccines
 - Different smallpox vaccines used: Dryvax (62%); ACAM2000 (38%)
- Clinical assessment, ECG, troponin T: pre-vaccination, D5 post-vaccination, D30
- Conclusion: Unique association between vaccinia immunisation and myocarditis/pericarditis

Smallpox vaccines (3rd generation non-replicating):

- [Clinical trials](#):
 - 22 trials with >7,800 participants
 - 1 case of possible pericarditis: attributed to Coxsackie virus
- 2022 outbreak to date:
 - More than 1 million doses of MVA-BN administered in the US alone
- [CDC analysis](#):
 - 1 case of myocarditis after dose 1 (= 1.53 per 1 million doses)
 - 1 case of myocarditis after dose 2 (= 2.99 per 1 million doses)
 - lower than background rate of 21.6 cases per million in 30-day period

Table 7. Prospective Cases of New Onset Myocarditis/Pericarditis or cTnT Elevation Following Immunization with Either Smallpox or Trivalent Influenza Vaccine.

Post-Vaccine Event	SPX n = 1081	Healthy 2002* N = 1,390,352	TIV n = 189	Relative Risk (95% CI)
Clinical				
Myocarditis/Pericarditis [‡]	5	30	(0)	
Per 100,000 Incidence Rate	463	2.2	(0)	214 [§]
95% CI	150–1079	1.9–2.3	0–1950	(65, 558)
Possible Subclinical				
Myocarditis	31		0	
Per 100,000 Incidence Rate	2868		0	
95% CI	1948–4070		0–1950	(P = 0.016)

Myocarditis case definitions^{3,4,15}

CDC

CDC and Brighton Collaboration

- Mainly used
 - But some studies use ESC (European Society of Cardiology) diagnostic guidelines
- Main similarities:
 - Incorporate several types of evidence criteria: clinical signs/symptoms, ECG, blood tests, imaging and histopathology
 - 3 levels of evidence corresponding ~ to confirmed / probable / possible
 - Possible / probable levels require the exclusion of other potential diagnoses
 - Positive histopathological findings regarded as diagnostic / gold standard
 - Cannot be classified at any level based on signs/symptoms alone

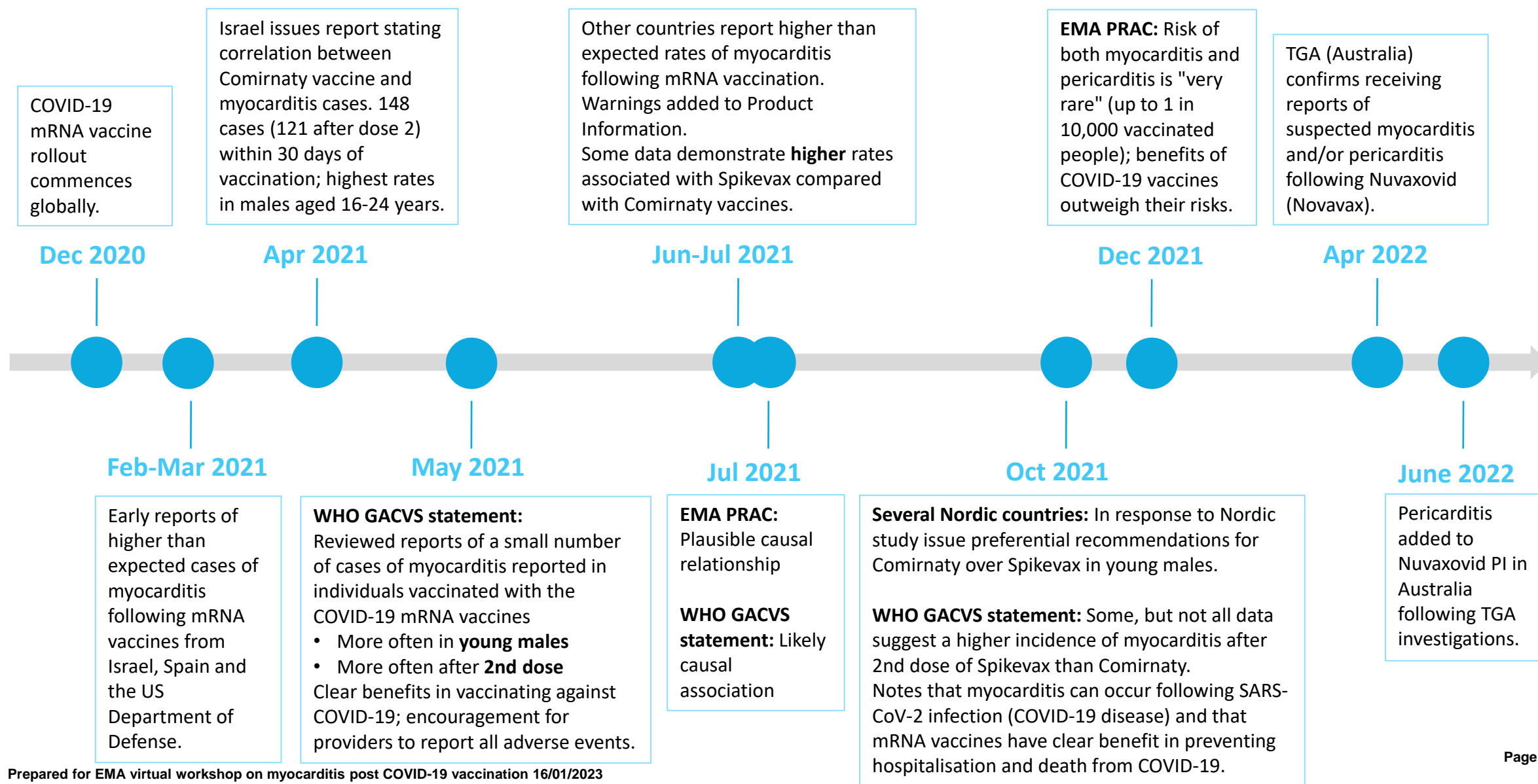
Brighton Collaboration

Diagnostic Criteria	Myocarditis	Pericarditis	Level of Certainty ¹ (for specific details of requirements see algorithm in appendix 5)
Endomyocardial biopsy	✓	✓	<ul style="list-style-type: none"> • Meets level 1 if myocardial/pericardial inflammation (by biopsy or autopsy sample).
Cardiac MRI (cMRI)	✓		<ul style="list-style-type: none"> • Meets level 1 if also elevated Troponin(s) • Supports* level 2 in absence of elevated Troponin(s)
Echocardiography	✓	✓	Myocarditis: <ul style="list-style-type: none"> • Meets level 1 if also elevated Troponin(s) • Supports* level 2 in absence of elevated Troponin(s) Pericarditis: <ul style="list-style-type: none"> • Supports* level 1 and 2 if abnormal pericardial fluid collection demonstrated
ECG	✓	✓	Both entities: <ul style="list-style-type: none"> • Supports* level 2: if ≥1 characteristic finding that is new or normalizes on recovery • Supports* level 3: ≥1 non-specific abnormality that is new or normalizes on recovery
Elevated myocardial biomarker	✓		<ul style="list-style-type: none"> • Supports* level 1: elevated Troponin I or T • Supports* level 2: elevated Troponin I or T or CK myocardial band
Elevated inflammation biomarker	✓		<ul style="list-style-type: none"> • Supports* level 3: ≥1 of elevated ESR, D-dimer, CRP or high-sensitivity CRP
Chest MRI/CT		✓	<ul style="list-style-type: none"> • Supports* level 2: if abnormal pericardial fluid collection demonstrated
Chest X-ray		✓	<ul style="list-style-type: none"> • Supports* level 3: if enlarged heart seen

TABLE 1. Case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis

Condition	Definition	
Acute myocarditis	Probable case	Confirmed case
	Presence of ≥1 new or worsening of the following clinical symptoms: <ul style="list-style-type: none"> • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: <ul style="list-style-type: none"> • irritability • vomiting • poor feeding • tachypnea • lethargy 	Presence of ≥1 new or worsening of the following clinical symptoms: <ul style="list-style-type: none"> • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: <ul style="list-style-type: none"> • irritability • vomiting • poor feeding • tachypnea • lethargy
	AND	AND
	≥1 new finding of <ul style="list-style-type: none"> • troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis⁵ • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis⁴ 	≥1 new finding of <ul style="list-style-type: none"> • Histopathologic confirmation of myocarditis[†] • cMRI findings consistent with myocarditis⁴ in the presence of troponin level above upper limit of normal (any type of troponin)
	AND	AND
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: <ul style="list-style-type: none"> • acute chest pain^{††} • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI 	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Emerging safety signal: myocarditis / pericarditis after COVID-19 vaccines¹⁶⁻²⁰



Rates and attributable risk of myocarditis and pericarditis following COVID-19 vaccination²¹⁻³¹



Myocarditis

- Vaccine attributable risk demonstrated following mRNA COVID-19 vaccines (BNT162b2, mRNA-1273)
- Limited evidence suggests possible risk after protein adjuvanted (NVX-CoV2373)
- Potential signal for viral vector (ChAdOx1) - requiring further investigation
- Highest risk in males aged under 30 years, within 1-5 days post dose (median 2 days)
- Rates/attributable risk highest following second primary dose of mRNA vaccine and in adolescent/young adult males
 - Also appears higher post boosters and dose 1 in young males
 - Males: reported post vaccination myocarditis rates (*not* absolute attributable risk) ranges from 25 to 300 per million doses
 - Risk elevation also reported in older age groups and in females

Pericarditis

- Less clarity on the pattern and population at risk for pericarditis but evidence suggests:
 - More common post dose 2 and for mRNA-1273 compared to BNT162b2
 - Majority of cases occur in those aged 18 to 24 years, but there are no gender-based differences.
- Early data suggests there could be increased rates of pericarditis following NVX-CoV2373

Reported rates of myocarditis following mRNA COVID-19 vaccines in high-risk age groups: data derived from 6 published studies and additional surveillance reports from 11 countries²¹⁻³²

By dose number, cases per million doses administered – colour-coding by highest reported frequency

(Table published by ATAGI, Australia September 2022:)



Vaccine Brand	Dose 1	Dose 2	Dose 3 / subsequent
Males aged 12 to 17 years			
BNT162b2 (Comirnaty)	7	71 to 136	11 to 61
mRNA-1273 (Spikevax)	Not Available	237	Not Available
Females aged 12 to 17 years			
BNT162b2 (Comirnaty)	1	2 to 28	0 to 0.7
mRNA-1273 (Spikevax)	0	0 to 28	Not Available
Males aged 18 to 29 years			
BNT162b2 (Comirnaty)	1 to 26	25 to 94	4.1 to 30
mRNA-1273 (Spikevax)	10 to 57	56 to 300	8.7 to 21
Females aged 18 to 29 years			
BNT162b2 (Comirnaty)	0 to 8	4 to 27	0.6 to 2.2
mRNA-1273 (Spikevax)	0 to 1	7 to 69	0.6 to 2.2
Females and males aged 18 to 29 years			
ChAdOx1	10	16	Not available

Challenges in assessment of vaccine attributable risk for myocarditis/pericarditis



- Variations in populations, vaccine exposures
- Variations in study methodologies
- Variation in surveillance systems
- Case ascertainment varies widely
 - differing healthcare seeking behavior, investigations, classification at HC encounter
- Challenges in applying case definitions
- Variable background rates eg of rates of myocarditis and pericarditis
 - prior to pandemic and during pandemic in non risk windows
- Myocarditis risk from other infectious causes, eg SARS-CoV-2 infection
 - Limited data
 - Post SARS-CoV-2 infection associated myocarditis rates reported to be 30-32 excess cases per million (for all age cohorts – no reported rates for population at risk of vaccine-associated myocarditis)

Nuvaxovid (Novavax) / Covovax (Serum Institute India)^{20,33}



- Spike-protein adjuvanted COVID-19 vaccine
- Ninth COVID-19 vaccine given WHO EUA – December 2021
 - Approval by EMA, India Drug Controller (as Covaxoid SII), TGA Australia – similar time and others subsequent; initially as primary series and 18 years +, subsequently 12 years + and as booster
 - Limited global utilisation due to timing of release
 - Limited ability to assess/investigate risk for myocarditis/pericarditis
- Signal for pericarditis from reporting in Australia, Europe
 - Eg in Australia
 - Investigations from May 2022 suggested signal for risk of pericarditis ~ reported rate 13/100,000 doses administered, most common in males 18-49 years.
 - Rate of pericarditis following Nuvaxovid currently higher than for Comirnaty and Spikevax but findings less certain due to low numbers of Nuvaxovid given (228,000 doses to end November) .
 - TGA has not identified a unique Australian safety signal for Nuvaxovid and myocarditis but is closely monitoring both national and international data.
 - EMA, FDA, others also had case reports of pericarditis/myocarditis post Nuvaxovid

Outcomes after COVID-19 vaccine-related myocarditis³⁴⁻⁴⁵



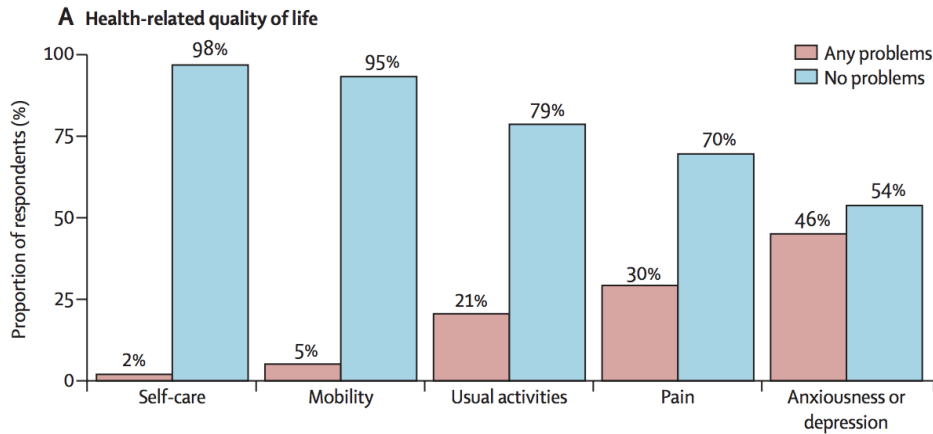
- Cases are usually mild and short-lived
- Most reported had hospitalization but length of stay is short and with minimal intervention
- Medium term follow-up (3-6 months):
 - US CDC data at 3 months (next slide)
 - Cardiac MRI follow-up studies suggest some with scarring but clinical consequences uncertain
- Some deaths reported as following vaccine-associated myocarditis
 - Note challenges in individual causality assessment, especially in context of limited investigation of alternate causes
- No long-term follow-up (≥6 months) data published yet
 - Both [Pfizer](#) and [Moderna](#) have registered clinical trial studies on potential long-term (up to 5 years) sequelae of myocarditis after vaccination

Outcomes after COVID-19 vaccine-related myocarditis: US CDC study^{46,47}

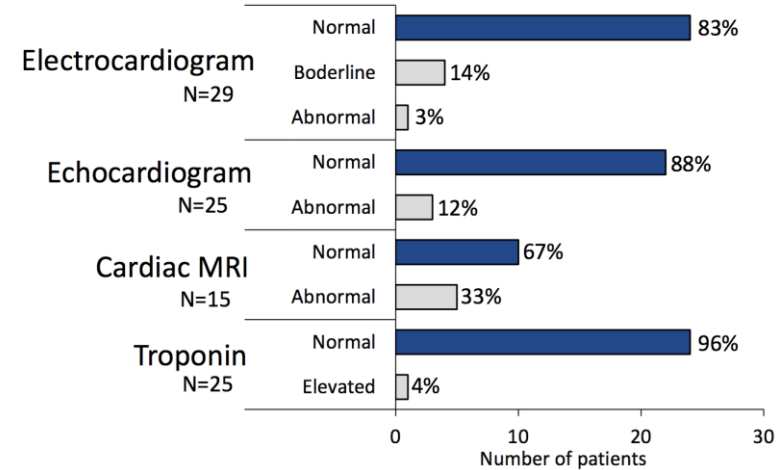


Included: age 12-29 years (median = 17 years), onset of myocarditis >90 days prior to survey (median = 143);

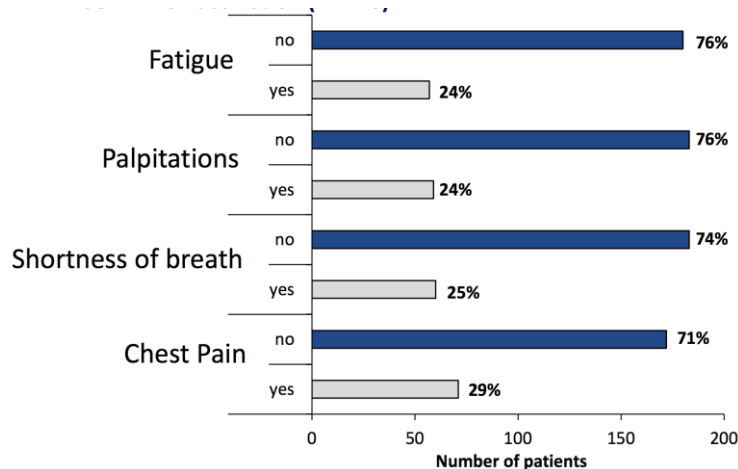
Figures B-D courtesy of Dr Matthew Oster, US CDC, Presentation to US ACIP



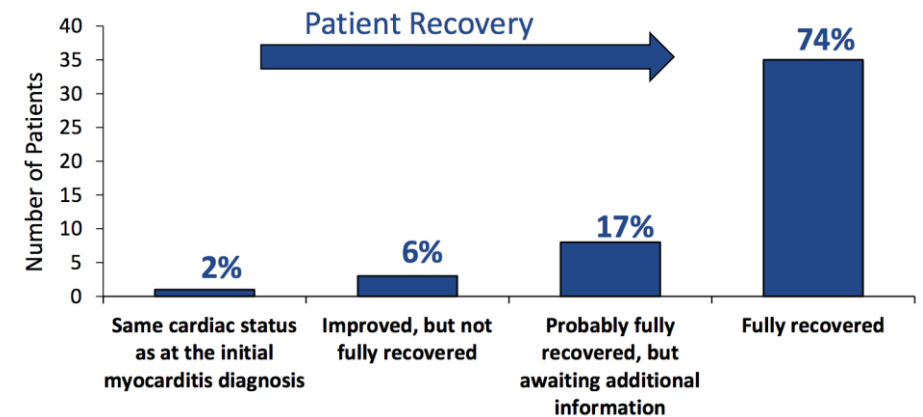
C. Results of 3-month follow-up cardiac testing in patients with myocarditis after COVID-19 vaccination



B. Patient self-report of symptoms within prior 2 weeks at 3-month follow-up of myocarditis after COVID-19 vaccination (N=248)



D. Cardiologist / healthcare provider assessment of recovery from myocarditis after COVID-19 vaccination by 3 months (n=47)

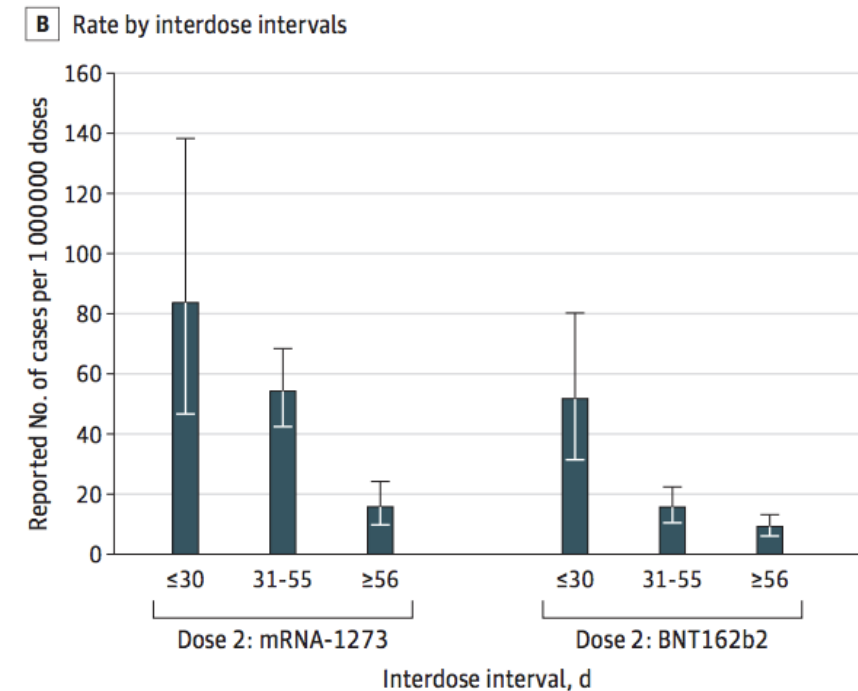


Global policy changes for myocarditis and pericarditis^{21,48-53}



1. 8-week dose interval change

- Study from Canada suggested extended interval of 8 weeks (compared with 3-4 weeks) between mRNA doses 1 and 2 associated with reduced risk of myocarditis and pericarditis
 - Some countries changed recommendations to 8 week primary dose interval
 - Some countries also recommend this interval for non-mRNA vaccines such as Nuvaxovid



2. Preferential recommendations: BNT162b2 (Comirnaty) over mRNA-1273 (Spikevax)

- Most evidence suggests risk of myocarditis greater following mRNA-1273 compared to BNT162b2
- Policy changes varied globally:
 - Some countries discontinued use of mRNA-1273 for certain age groups (e.g. Norway)
 - Some countries made age-based preferential recommendations (e.g. Canada)
 - Some countries no specific preference but communicate brand risk differential (e.g. Australia, USA)

Examples of changes to recommendations for mRNA vaccines⁴⁸⁻⁵³



Country (NITAG)	Age group	Primary dose interval extended		Preferential recommendation to mitigate myocarditis*	
		Y/N	Details	Y/N	Details
Australia (ATAGI)	All	Y	8 week interval for Comirnaty, Spikevax and Nuvaxovid	N	No brand preference but advise on risk differential between brands
Canada (NACI)	12-17 years	Y	8 week interval for Comirnaty	Y	Comirnaty preferred over Spikevax in people aged 12-17
Finland	≥12 years	Y	6-12 weeks	Y	Use of Spikevax suspended in males aged 12-30 years
Norway	12-15 years	Y	12 weeks (for those with underlying conditions eligible for 2 doses)	Y	Use of Spikevax suspended for people ≤18 years
	16-17 years	Y	12 weeks	Y	Use of Spikevax suspended for people ≤18 years
	18-<30 years	N	21 days (no change)	Y	Suggestion that this group should consider Comirnaty over Spikevax
Sweden	≥12 years	N	3-7 weeks (no change)	Y	Use of Spikevax suspended for people ≤30 years
UK (JCVI)	12-15 years	Y	12 weeks	Y	Comirnaty preferred over Spikevax in people aged 12-17 years
US (ACIP)	12-39 years	N**	3 or 4 – 8 weeks; males in this age group advised to consider 8-week interval (no change to existing interval)	N	No brand preference

*There may be preferential recommendations for other purposes - this is not included in this table.

Myocarditis / pericarditis can be associated with COVID-19 in other ways⁴⁷

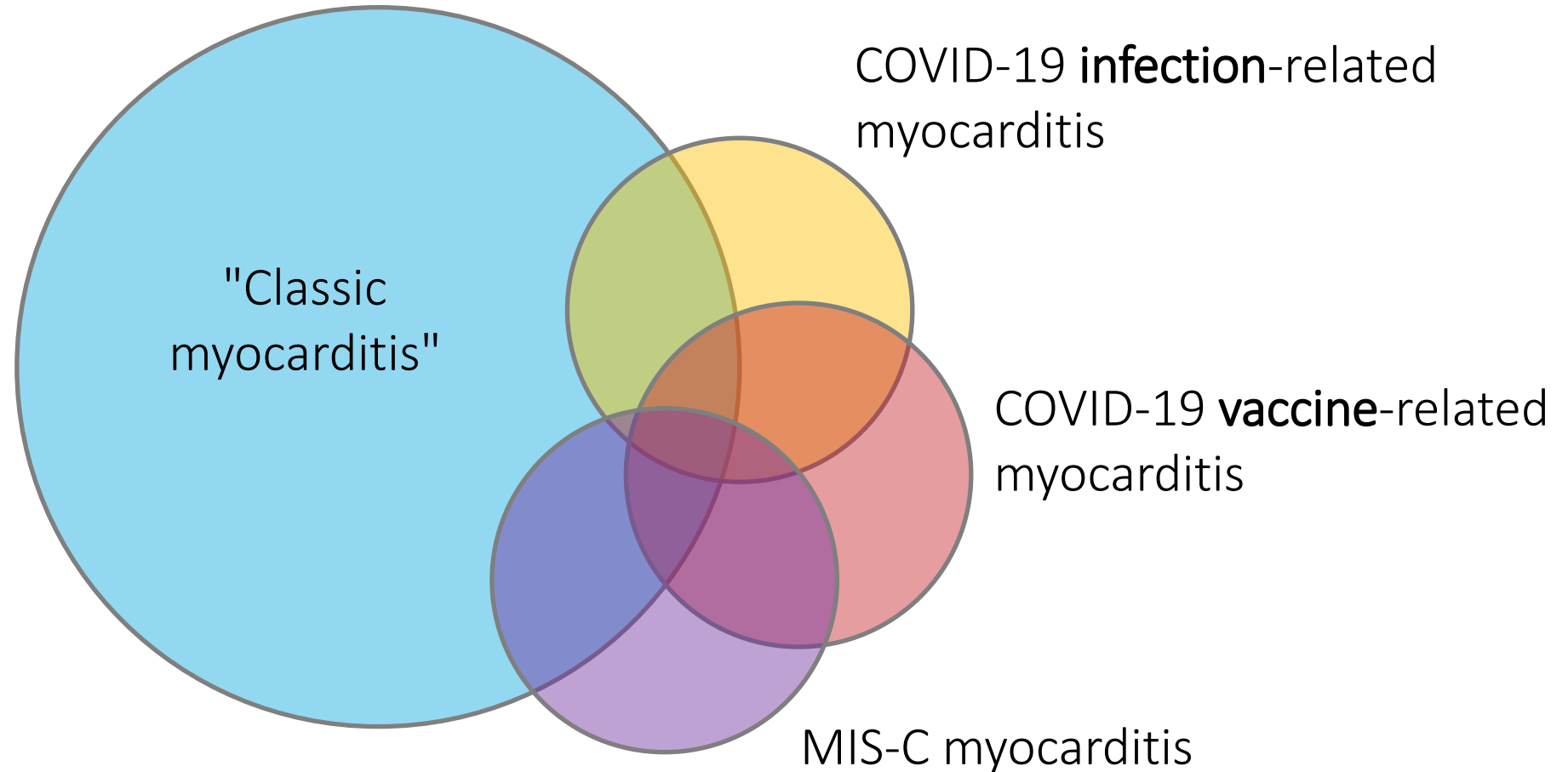


Image credits:
Adapted from original diagram
by Dr Matthew Oster, US CDC

Myocarditis after SARS-CoV-2 infection vs vaccination^{54,55}



- Barda et al (2021), Israel
 - Matched analyses from medical records (Dec 2020 to May 2021)
 - Myocarditis after COVID-19 **vaccination** (BNT162b2) vs unvaccinated: **RR 3.24** (95% CI 1.55 to 12.44)
 - Myocarditis after **infection** vs uninfected: **RR 18.28** (95% CI 3.95 to 25.12)
- Patone et al (2022), UK
 - Self-controlled case series from medical records (Dec 2020 to Aug 2021)
 - Myocarditis after **dose 2** (age <40 years):
 - BNT162b2 RR **3.40** (95% CI 1.91 to 6.04);
 - mRNA-1273 RR **20.71** (95% CI 4.02 to 106.68)
 - Myocarditis after **infection** (age <40 years):
 - RR **4.06** (95% CI 2.21 to 7.45)

Figure 3. Risk Ratios for Adverse Events after Vaccination or SARS-CoV-2 Infection.

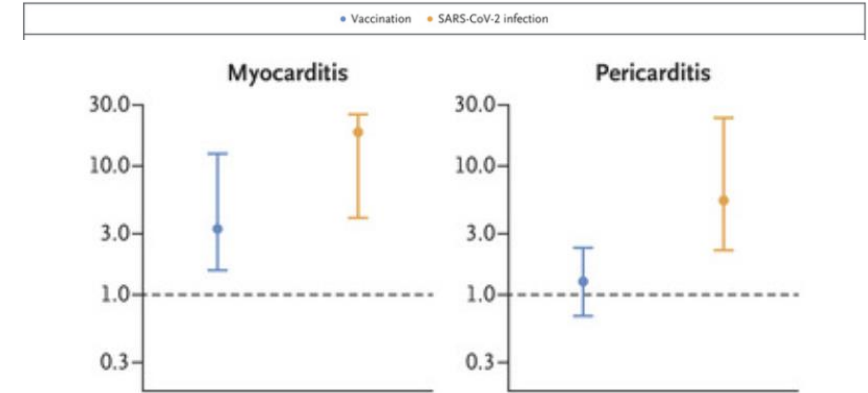
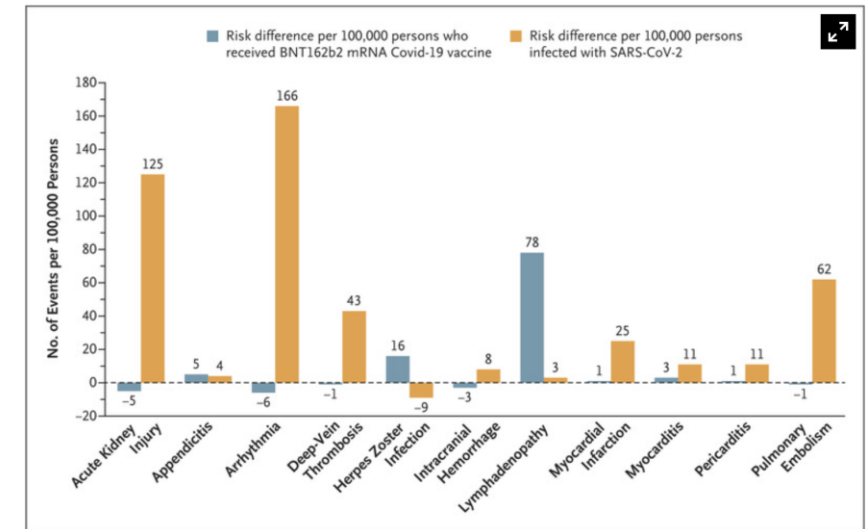


Figure 4. Absolute Excess Risk of Various Adverse Events after Vaccination or SARS-CoV-2 Infection.



Barda: DOI: [10.1056/NEJMoa2110475](https://doi.org/10.1056/NEJMoa2110475)

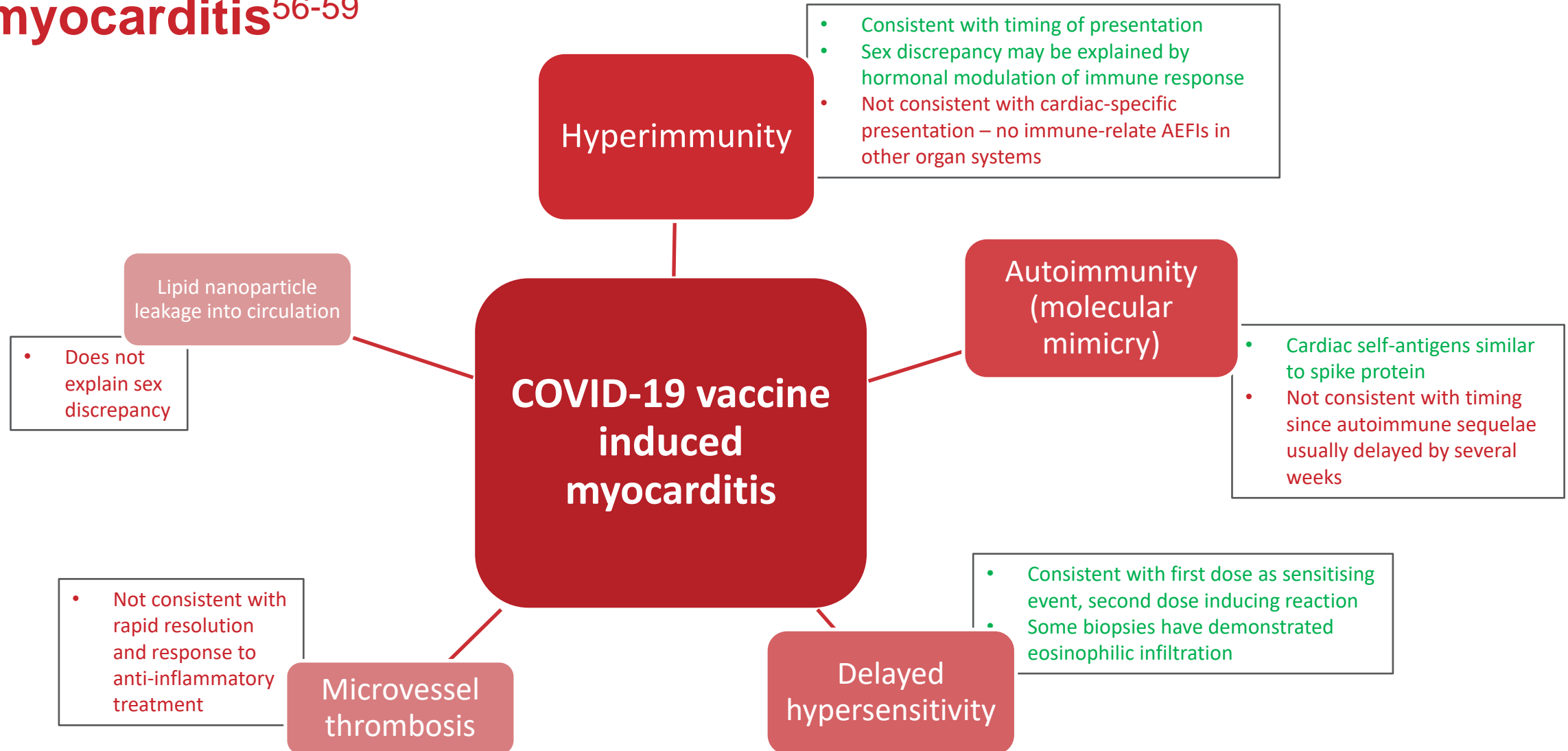
Patone: <https://doi.org/10.1038/s41591-021-01630-0>



The mechanism of vaccine-induced myopericarditis: challenges in understanding⁵⁶⁻⁵⁹

- Vast majority of cases are mild and do not require significant investigation (i.e. biopsy/cMRI)
- Case reports/series of non-invasive investigations and biopsy findings show varying pathological patterns
- Some vaccine-proximate cases may have other aetiology (sampling error)
- Not known if same mechanism of SARS-CoV-2 infection-induced myo/pericarditis

Some proposed mechanisms of COVID-19 vaccine-induced myocarditis⁵⁶⁻⁵⁹



WHO GACVS statements¹⁶⁻¹⁸



The image shows three overlapping screenshots of the WHO Global Advisory Committee on Vaccine Safety (GACVS) website. The top screenshot is the May 2021 statement, the middle is the July 2021 statement, and the bottom is the October 2021 statement. Each screenshot displays the WHO logo, navigation tabs (Health Topics, Countries, Newsroom, Emergencies), and the title of the statement. The May statement is titled 'COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviews cases of mild myocarditis reported with COVID-19 mRNA vaccines'. The July statement is titled 'COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS): updated guidance regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines'. The October statement is titled 'COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS): updated statement regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines'.

GACVS Statement May 2021

GACVS
Statement
July 2021

GACVS
Statement
October
2021

Australian (ATAGI)
Guidance – features
Nuvaxovid information³²

The image shows the cover of the Australian Government's COVID-19 Vaccination Guidance on Myocarditis and Pericarditis after COVID-19 vaccines. The cover features the Australian Government logo at the top, followed by the 'COVID-19 VACCINATION' logo. The title 'Guidance on Myocarditis and Pericarditis after COVID-19 vaccines' is prominently displayed. Below the title, it states that the guidance is endorsed by the Australian Technical Advisory Group on Immunisation (ATAGI) and the Cardiac Society of Australia and New Zealand (CSANZ). It also mentions that ATAGI and CSANZ acknowledge the contributions of the Royal Australian College of General Practitioners (RACGP), the Australian College of Rural and Remote Medicine (ACRRM), the Australasian College for Emergency Medicine (ACEM), and the Paediatric Research in Emergency Departments International Collaborative (PREDICT) in the development of this guideline. The date 'Updated 9 November 2022' is at the bottom.

GACVS Statements: (May) <https://www.who.int/news/item/26-05-2021-gacvs-myocarditis-reported-with-covid-19-mrna-vaccines>;
(July) <https://www.who.int/news/item/09-07-2021-gacvs-guidance-myocarditis-pericarditis-covid-19-mrna-vaccines>; (October) <https://www.who.int/news/item/27-10-2021-gacvs-statement-myo>
ATAGI Guidance: <https://www.health.gov.au/sites/default/files/documents/2022/11/covid-19-vaccination-guidance-on-myocarditis-and-pericarditis-after-covid-19-vaccines.pdf>

Prepared for EMA virtual workshop on myocarditis post COVID-19 vaccination 16/01/2023

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