Vaccines and Related Biological Products Advisory Committee Meeting

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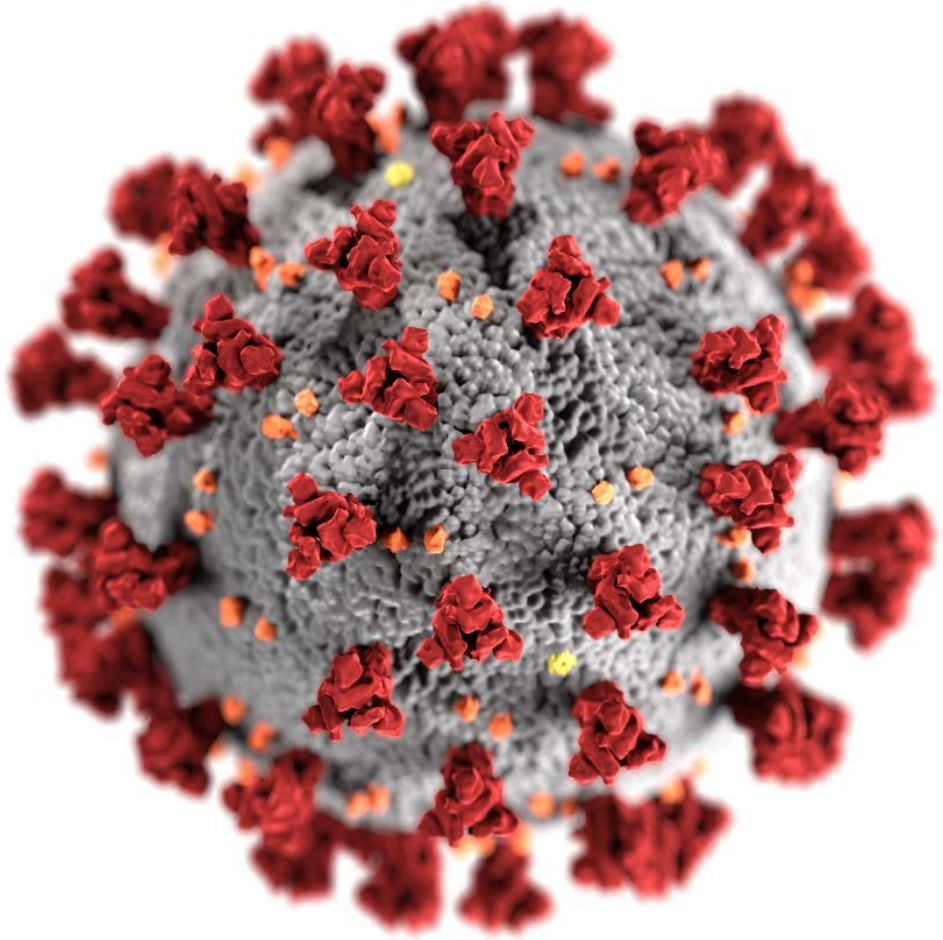
mRNA COVID-19 Vaccine-Associated Myocarditis



Matthew Oster, MD, MPH
CDC COVID-19 Vaccine Task Force

cdc.gov/coronavirus

Disclaimer

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

Outline

- Cases of myocarditis after COVID-19 vaccine
- Comparing types of myocarditis
- 3-6 month outcomes of myocarditis

Vaccine Adverse Event Reporting System (VAERS): Reporting rates (per 1 million doses administered) of myocarditis among males after mRNA COVID-19 vaccines, 7-day risk period (N=797)*

- **169,740,953** doses of mRNA vaccine administered to males (dose 1 and dose 2) *
- Reporting rates exceed background incidence**

Highest % is among males aged 16-17 years: 0.007%

	Pfizer		Moderna	
	(Males)		(Males)	
Ages	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
12-15	**4.2**	**39.9**		
16-17	**5.7**	**69.1**		
18-24	**2.3**	**36.8**	**6.1**	**38.5**
25-29	1.3	**10.8**	**3.4**	**17.2**
30-39	0.5	**5.2**	**2.3**	**6.7**
40-49	0.3	**2.0**	0.2	**2.9**
50-64	0.2	0.3	0.5	0.6
65+	0.2	0.1	0.1	0.3

* As of Oct 6, 2021; 797 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among males; reports verified to meet case definition by provider interview or medical record review

** An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is **0.2 to 1.9 per 1 million person 7-day risk period**

Vaccine Adverse Event Reporting System (VAERS): Reporting rates (per 1 million doses administered) of myocarditis among females after mRNA COVID-19 vaccines, 7-day risk period (N=138)*

- **193,215,313** doses of mRNA vaccine administered to females (dose 1 and dose 2)*
- Reporting rates exceed background incidence**

	Pfizer		Moderna	
	(Females)		(Females)	
Ages	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
12-15	0.4	**3.9**		
16-17	0.0	**7.9**		
18-24	0.2	**2.5**	0.6	**5.3**
25-29	0.2	1.2	0.4	**5.7**
30-39	0.6	0.7	0.5	0.4
40-49	0.1	1.1	0.2	1.4
50-64	0.3	0.5	0.5	0.4
65+	0.1	0.3	0.0	0.3

* As of Oct 6, 2021; 138 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among females; reports verified to meet case definition by provider interview or medical record review

** An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is **0.2 to 1.9 per 1 million person 7-day risk period**

Care and outcomes of preliminary myocarditis cases reported to VAERS after COVID-19 vaccination in persons aged ≤29 years (N=1,640)

(data thru Oct 6, 2021)

1,640 total preliminary reports

- **877** met CDC case definition* of myocarditis
- 637 under review

Of 877 meeting case definition:

- 829 were hospitalized
  - 789 discharged
    - **607/789 (77%) known to have recovered from symptoms at time of report**
  - 19 still hospitalized (5 in ICU)
  - 21 with unknown disposition
- 34 were not hospitalized (seen in emergency room, urgent care, outpatient clinic, not specified)

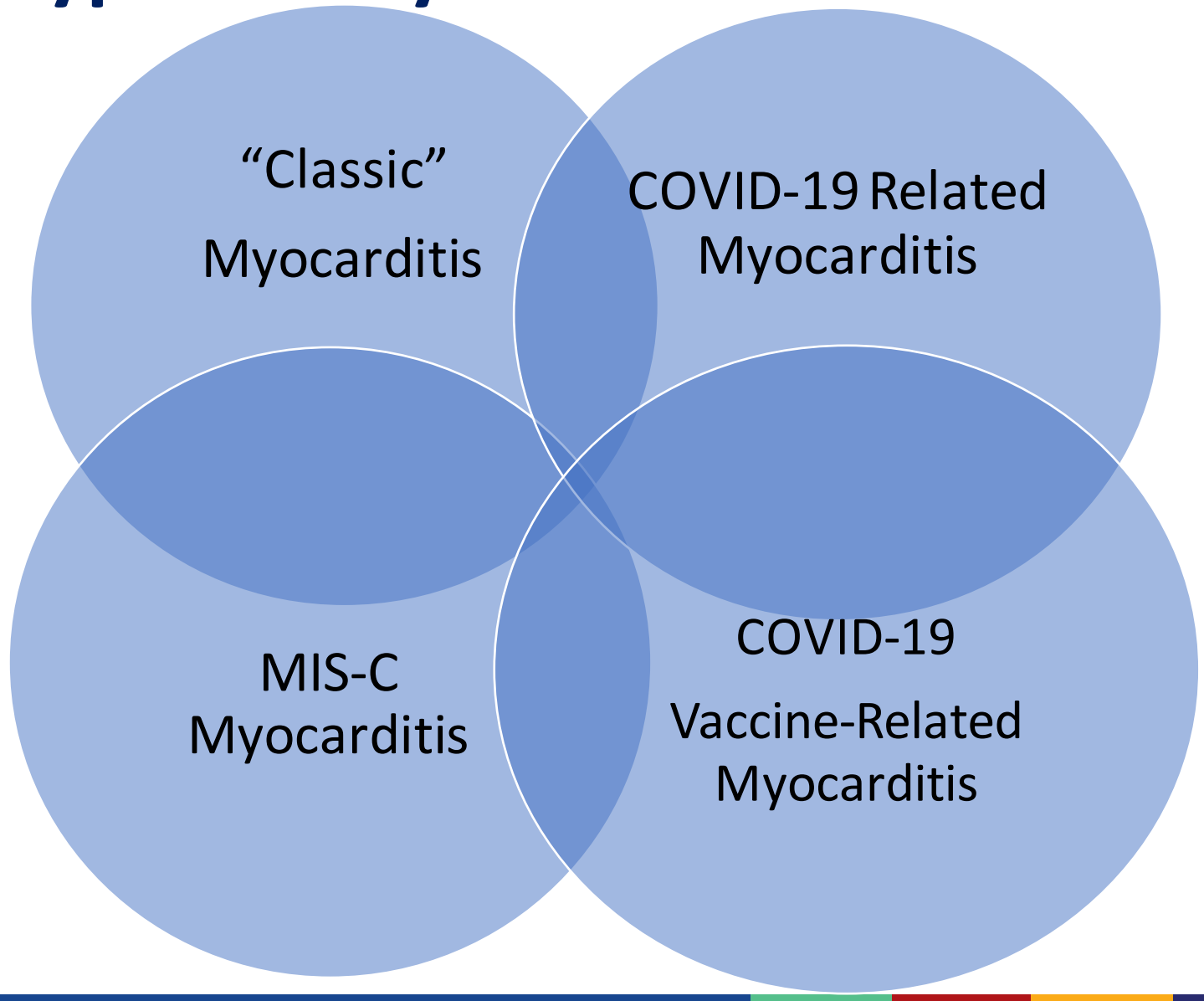
* Definition available from Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982. https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7027e2-H.pdf

Vaccine Safety Datalink Confirmed Myocarditis/Pericarditis, among persons aged 12-17 years (Pfizer-BioNTech only) in the 0-7 and 0-21 Day Risk Interval by Dose Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Risk Interval	**Dose**	**Events in Risk Interval**	**Events in Comparison Interval[1]**	**Adjusted Rate Ratio[2,3]**	**95% Confidence Interval**	**2-Sided P-value**	**Excess Cases in Risk Period per 1 Million Doses**
Days 0-21	**Both Doses**	30	0	**very high**	**5.68 - ∞**	**<0.001**	**29.6**
	Dose 1	2	0	very high	0.31 - ∞	0.198	3.8
	Dose 2	24	0	**very high**	**9.09 - ∞**	**<0.001**	**56.7**
Days 0-7	**Both Doses**	27	0	**very high**	**16.88 - ∞**	**<0.001**	**25.9**
	Dose 1	0	0	NE	NE	NE	NE
	Dose 2	23	0	**very high**	**28.83 - ∞**	**<0.001**	**54.0**

NE= not estimable; indicates that vaccine effect cannot be estimated.
[1]Comparison interval is 22–42 days after either dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.
[3]The focus should be on the lower bound of the confidence interval.

Comparing types of myocarditis



Causes of “classic” myocarditis

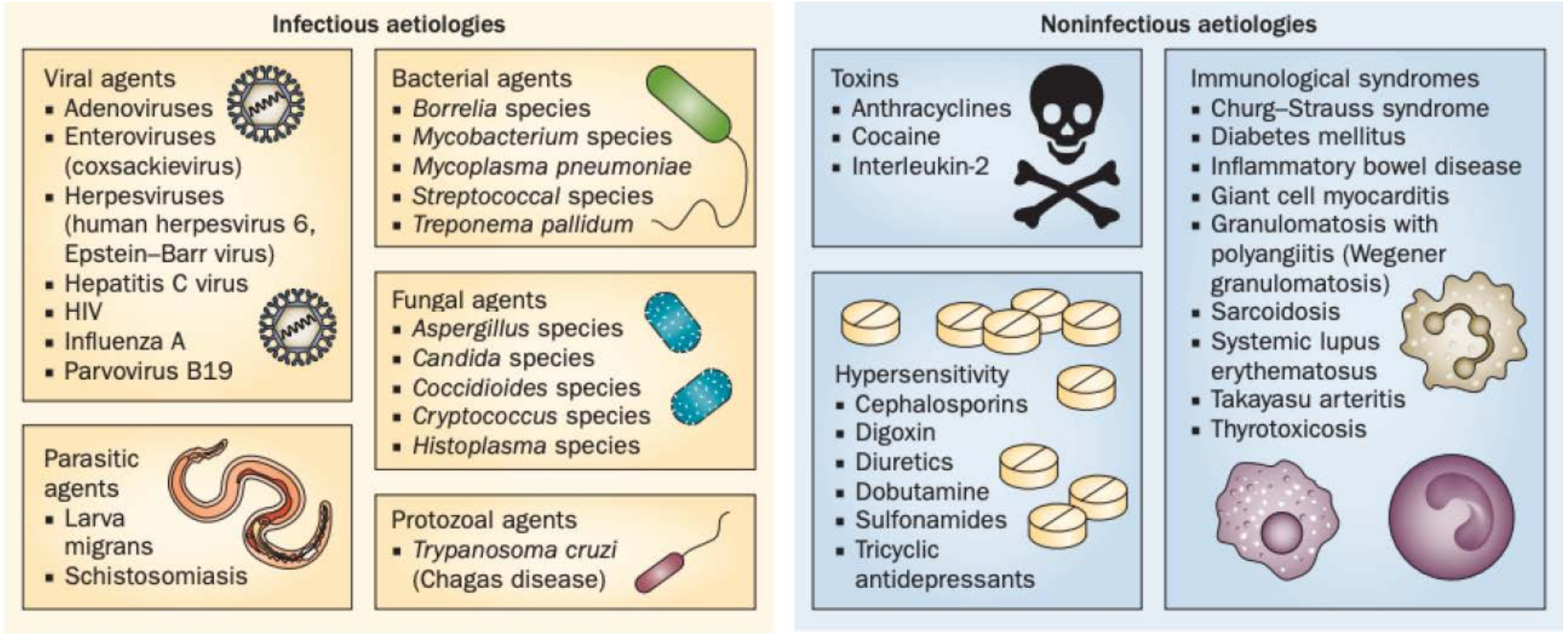
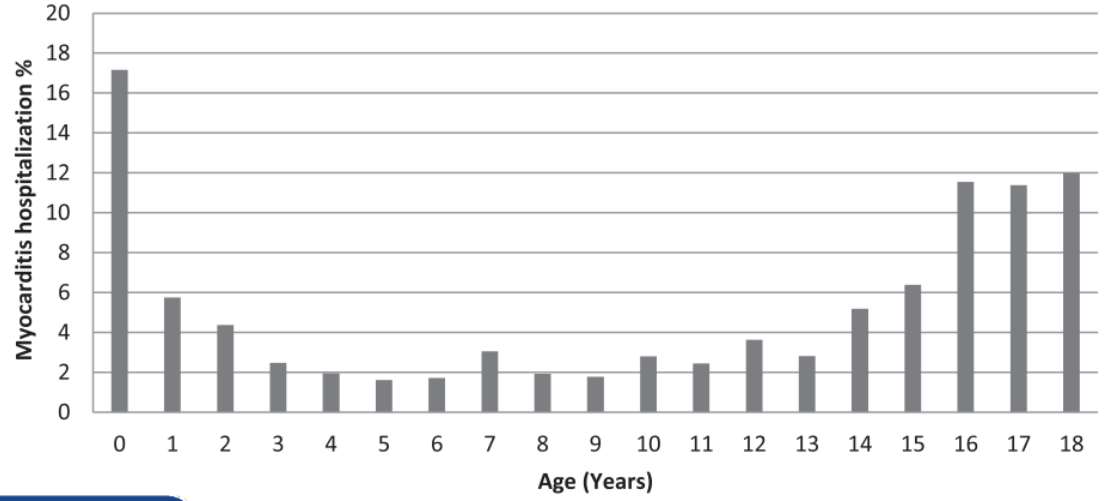


Figure 1 | Common causes of myocarditis. Viral infection is the most common aetiology, but several other aetiologies of myocarditis have also been implicated.

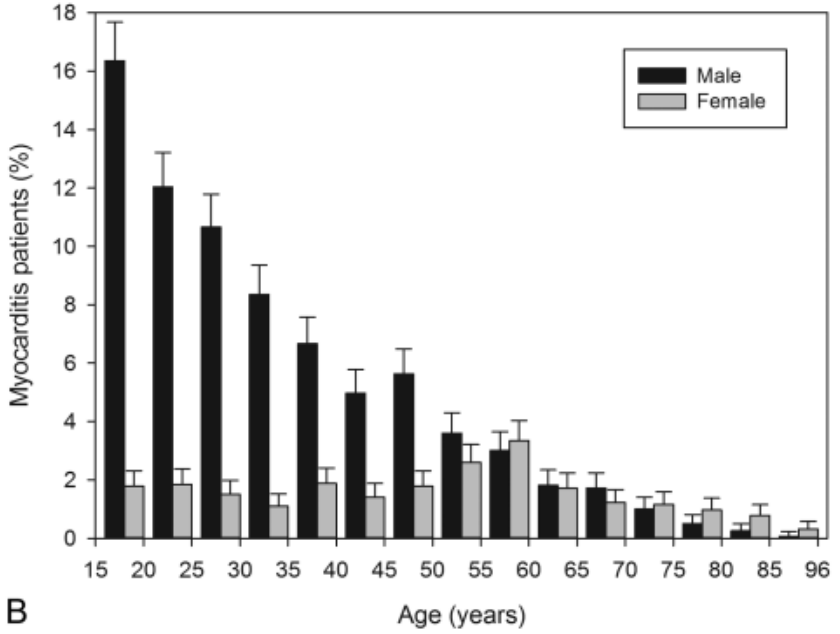
Epidemiology of myocarditis in pre-COVID era

- Children
  - Annual incidence 0.8 per 100,000
    - In persons aged 15-18 years, 1.8 per 100,000 in 2015-2016
  - 66% male
  - Median length of stay 6.1 days



Vasudeva et al. *American J Cardiology.* 2021.

- Adults
  - Gradual decrease in incidence with age
  - 76% male



Kyto et al. *Heart*. 2013.

Outcomes of “Classic” Myocarditis in Children

- Mortality: 4-7% during acute illness
- Heart Transplant: 4-9%

Ghelani et al. *Circ Cardiovasc Qual Outcomes.* 2012
Butts et al. *Pediatric Cardiology.* 2017
Sachdeva et al. *Am J Cardiol.* 2015

MIS-C Myocarditis

JAMA Pediatrics | Original Investigation

Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic

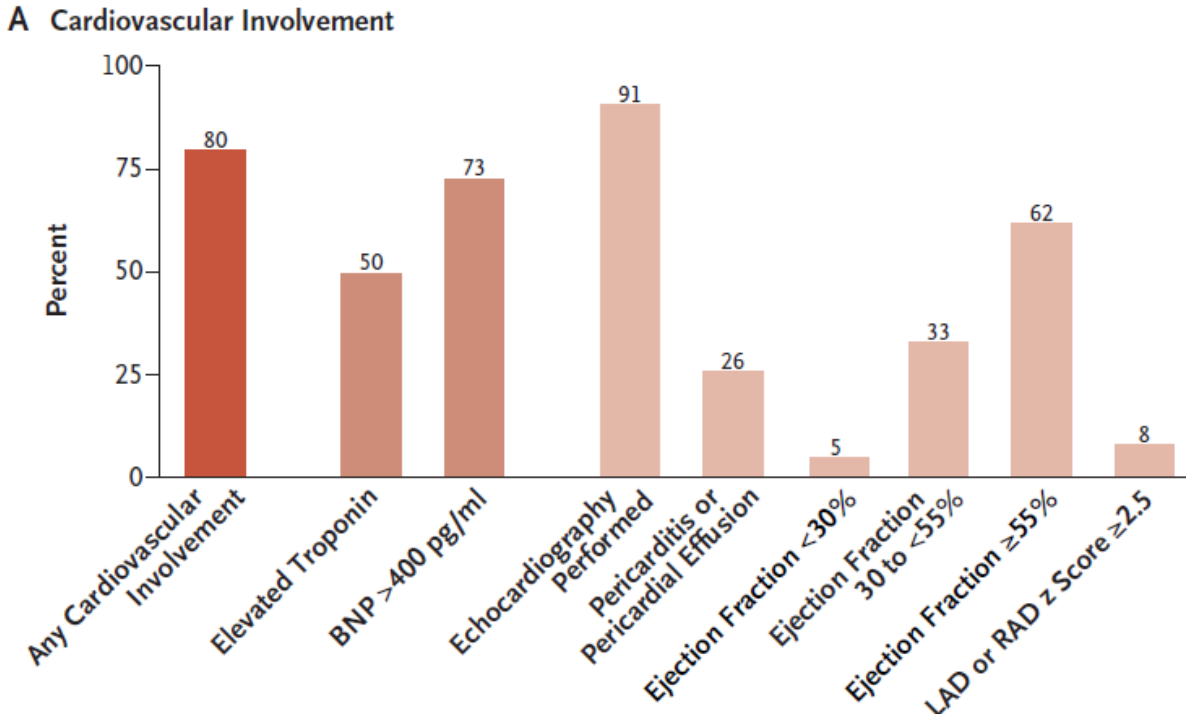
Myocarditis	300 (17.3)

Belay et al. 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents



Feldstein et al. 2020

COVID-19 Myocarditis

Morbidity and Mortality Weekly Report

Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021

TABLE. Frequency of and risk for myocarditis among patients with and without COVID-19 and adjusted* myocarditis risk differences and risk ratios comparing patients with and without COVID-19 — Premier Healthcare Database Special COVID-19 Release, United States, March 2020–January 2021

Characteristic	No. of patients with COVID-19	No. of patients without COVID-19	No. of patients with myocarditis	Myocarditis among patients with COVID-19		Myocarditis among patients without COVID-19		Adjusted myocarditis risk difference (95% CI)	Adjusted myocarditis risk ratio (95% CI)
				No. (% of patients with myocarditis)	Risk, %	No. (% of patients with myocarditis)	Risk, %		
Overall	**1,452,773**	**34,552,521**	**5,069**	**2,116 (41.7)**	**0.146**	**2,953 (58.3)**	**0.009**	**0.126 (0.112–0.140)**	**15.7 (14.1–17.2)**
Sex									
Male	680,722	14,339,356	3,008	1,274 (42.4)	0.187	1,734 (57.6)	0.012	0.165 (0.146–0.183)	13.8 (12.3–15.3)
Female	772,051	20,213,165	2,061	842 (40.9)	0.109	1,219 (59.1)	0.006	0.100 (0.087–0.113)	17.8 (15.6–20.0)
Age group, yrs									
<16	64,898	3,670,762	218	86 (39.4)	0.133	132 (60.6)	0.004	0.122 (0.065–0.179)	36.8 (25.0–48.6)
16–24	123,865	3,067,575	511	121 (23.7)	0.098	390 (76.3)	0.013	0.088 (0.061–0.115)	7.4 (5.5–9.2)
25–39	268,549	6,246,568	862	208 (24.1)	0.077	654 (75.9)	0.010	0.067 (0.052–0.081)	6.7 (5.5–8.0)
40–49	198,561	4,147,909	620	213 (34.4)	0.107	407 (65.6)	0.010	0.093 (0.078–0.109)	10.0 (8.1–11.9)
50–64	356,697	7,965,264	1,226	553 (45.1)	0.155	673 (54.9)	0.008	0.137 (0.121–0.154)	17.0 (14.7–19.3)
65–74	214,331	5,318,474	801	398 (49.7)	0.186	403 (50.3)	0.008	0.160 (0.135–0.184)	23.0 (19.4–26.7)
≥75	225,872	4,135,969	831	537 (64.6)	0.238	294 (35.4)	0.007	0.208 (0.179–0.237)	31.6 (25.9–37.2)

Boehmer et al. 2021

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Boehmer et al. 2021

COVID-19 Myocarditis

Pediatric inpatient admissions

	Myocarditis Diagnosed (%)	Myocarditis NOT Diagnosed (%)
COVID-19 (without MIS-C)	78 (0.02%)	356,721 (99.98%)
MIS-C	203 (8.10%)	2303 (91.90%)

	Myocarditis Diagnosed (%)	Myocarditis NOT Diagnosed (%)
COVID-19 (without MIS-C)	20 (0.08%)	24,144 (99.92%)
MIS-C	172 (9.04%)	1730 (90.96%)

https://www.epic.com/software#Cosmos

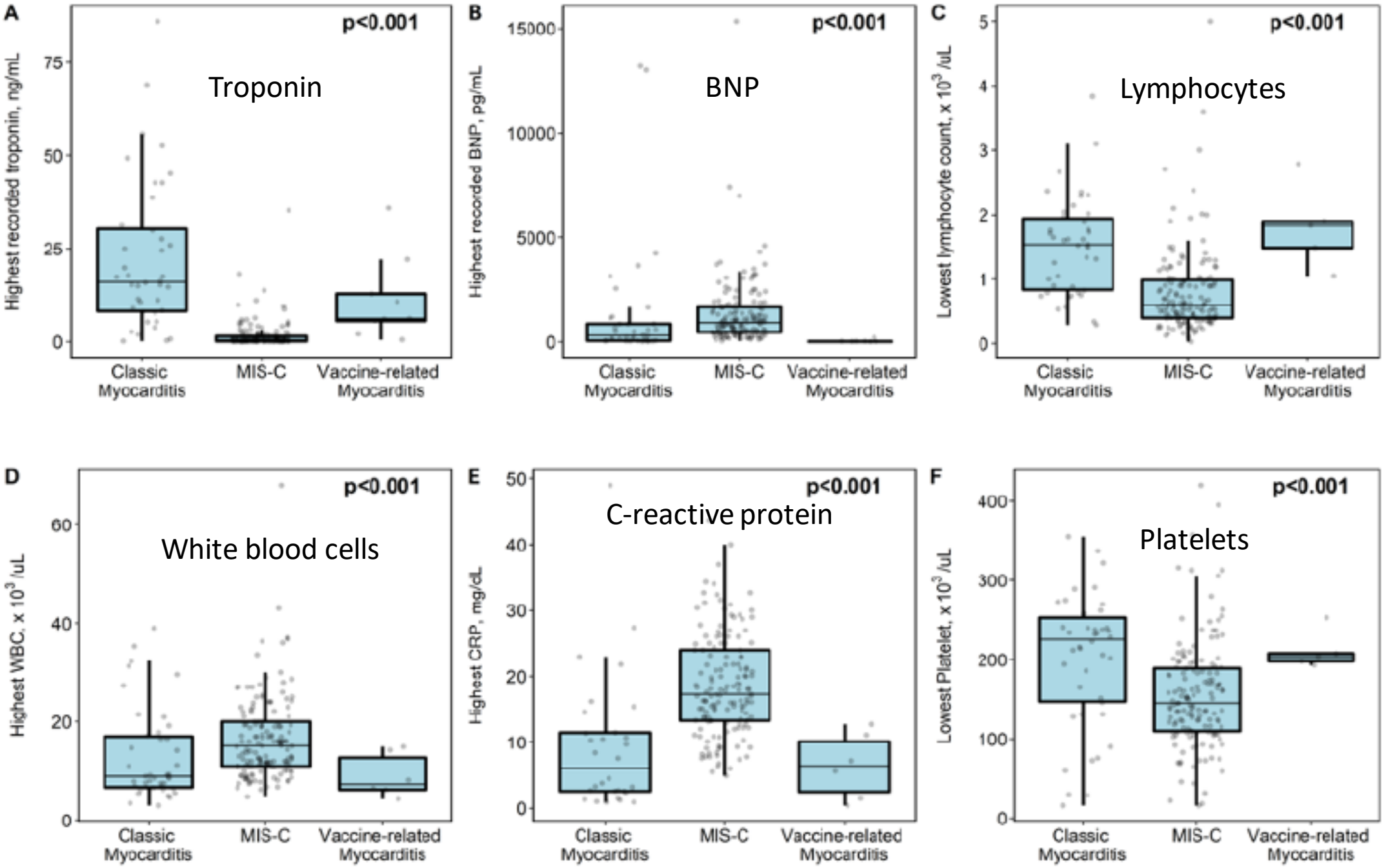
https://www.childrenshospitals.org/phis

Comparing Types of Myocarditis

Comparison of MIS-C Related Myocarditis, Classic Viral Myocarditis, and COVID-19 Vaccine related Myocarditis in Children

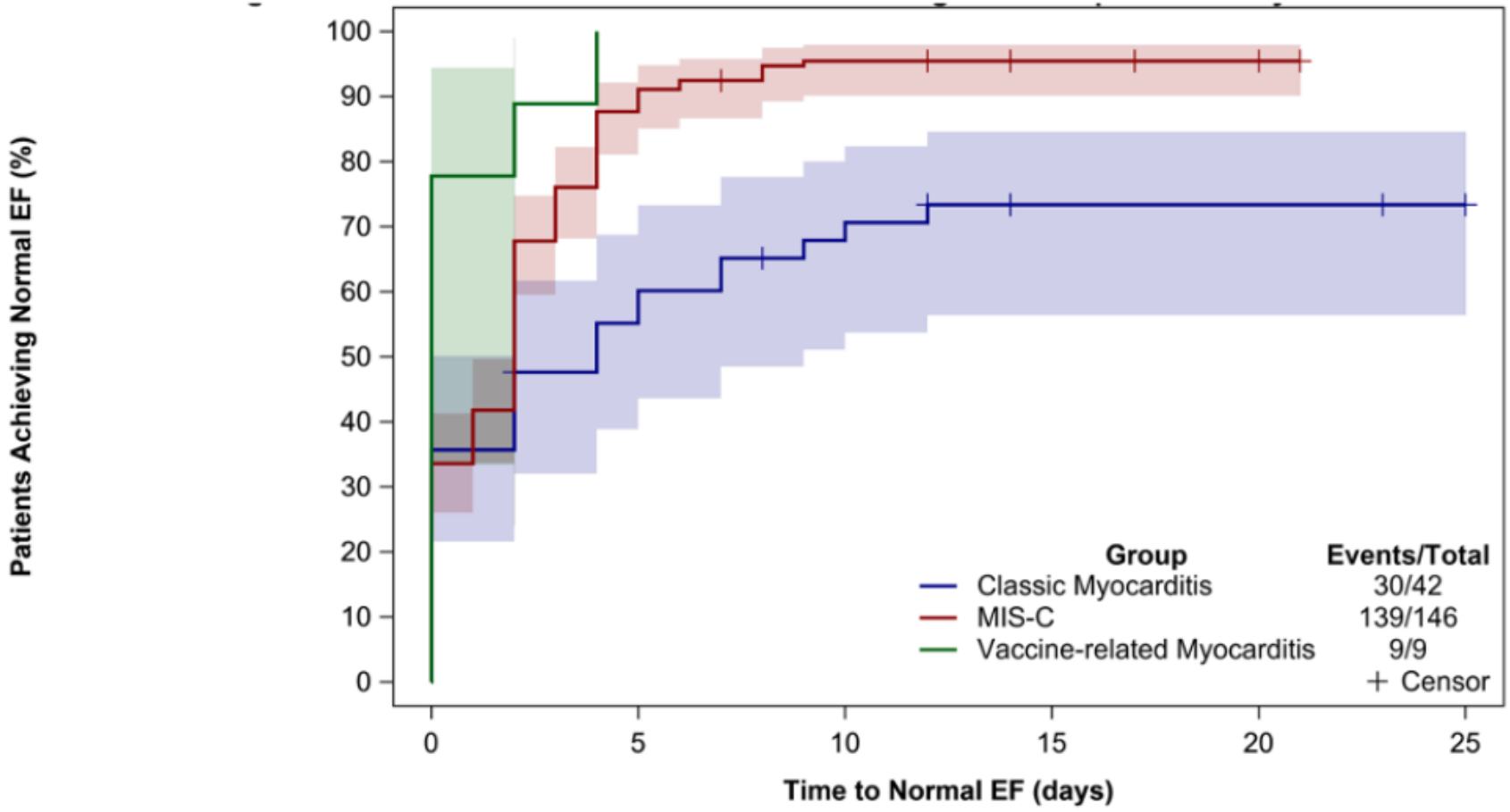
medRxiv

Patel et al. 2021



Patel et al. 2021

Comparing Types of Myocarditis: Time to Normal Ejection Fraction (EF) by Echocardiogram



Patel et al. 2021

3-6 month outcomes

- Risk of sudden death pre-COVID
  - 5-10% of sudden death in adolescents and young adults attributable to myocarditis (typically not previously diagnosed)
- 2015 Guidelines from American Heart Association and American College of Cardiology

1. Before returning to competitive sports, athletes who initially present with an acute clinical syndrome consistent with myocarditis should undergo a resting echocardiogram, 24-hour Holter monitoring, and an exercise ECG no less than 3 to 6 months after the initial illness *(Class I; Level of Evidence C)*.
2. It is reasonable that athletes resume training and competition if all of the following criteria are met *(Class IIa; Level of Evidence C)*:
   a. Ventricular systolic function has returned to the normal range.
   b. Serum markers of myocardial injury, inflammation, and heart failure have normalized.
   c. Clinically relevant arrhythmias such as frequent or complex repetitive forms of ventricular or supraventricular ectopic activity are absent on Holter monitor and graded exercise ECGs.

   At present, it is unresolved whether resolution of myocarditis-related LGE should be required to permit return to competitive sports.
3. Athletes with probable or definite myocarditis should not participate in competitive sports while active inflammation is present. This recommendation is independent of age, gender, and LV function *(Class III; Level of Evidence C)*.

Maron et al. *JACC.* 2015
Burns et al. *J Peds X.* 2020.

Pre-COVID Myocarditis Outcomes

Contents lists available at ScienceDirect

Cardiovascular Pathology

journal homepage: www.elsevier.com/locate/carpath

Review

Diagnosis, treatment and predictors of prognosis of myocarditis. A narrative review ☆,☆☆

Picarillo et al. 2021

Variables	Good outcome	Poor outcome
Clinical presentation	• Chest pain [2] • Class NYHA I-II [82]	• Heart Failure at the onset [81] • Class NYHA III-IV [82] • Sustained Ventricular Arrhythmias [51,83] • Acute Kidney Injury [84] • High SOFA [85], APACHE IV [85] and SAPS II [85] admission scores [86]
Electrocardiogram	• Absence of abnormalities [2] • ST elevation with a pericarditis pattern [91]	• Widened QRS and Q waves [56] • Wide QRS-T angle (≥100°) [91] • QTc interval prolongation [10]
Biomarkers	Troponin • Early rise and fast decline [41]	Troponin • Recurrently or persistently abnormal levels [41] BNP • Elevated levels (>4245 pg/mL) [89] • Low levels associated to elevated troponin levels [90]
Echocardiography	• Preserved LV ejection fraction at the onset [2,94] • Normal wall motion [2] • Early improvement or normalization of LV ejection [94,95]	• Increased LV end diastolic diameter [94,95] • Reduced LV ejection fraction (<50%) at the onset [2,9,94] • Persistently reduced LV ejection fraction [94,95] • Left atrium enlargement [94,96] • Worse LV strain and strain rate [98] • Right ventricle dysfunction [1]
Cardiac Magnetic Resonance	• Absence of LGE [81,101] • Decreased LGE over time [81] • LGE in the inferolateral wall [101] • Baseline LV ejection fraction preserved (≥50%) [102]	• Presence of LGE [81] • Persistent LGE over time [81] • Mid-wall LGE in the (antero-) septal segments [101]
Endomyocardial biopsy and immunohistological features		• Invading immune cells and expression of HLA-DR-alpha molecules [82] • Presence of viral genome in patients not treated with anti-viral drugs [103] • Giant-cell myocarditis [41]

Picarillo et al. 2021

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Picarillo et al. 2021

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LGE=Late gadolinium enhancement

Picarillo et al. 2021

Pre-COVID Myocarditis Outcomes

CARDIOVASCULAR MEDICINE

Long term follow up of children with myocarditis treated by immunosuppression and of children with dilated cardiomyopathy

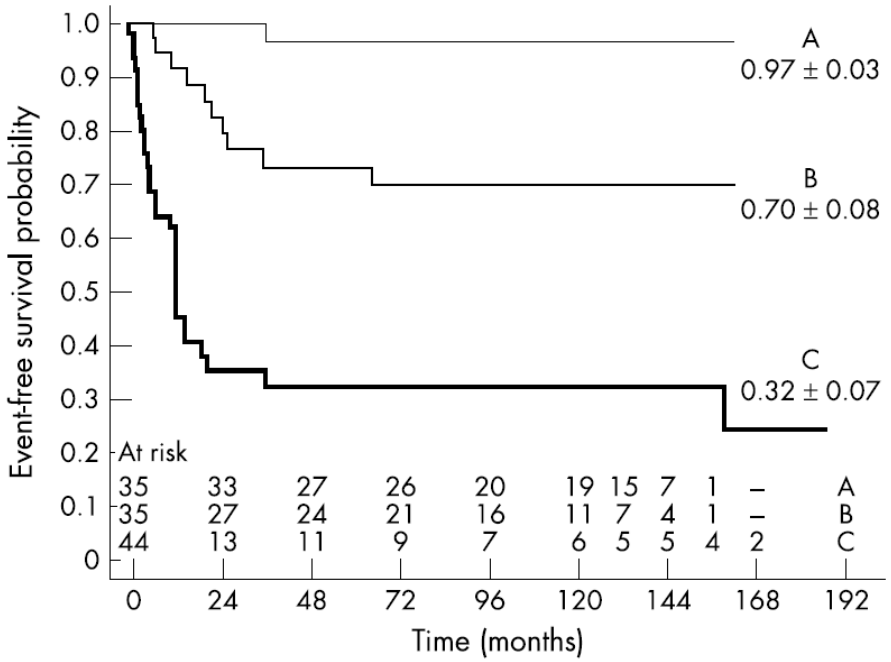


Figure 1 Plot of event-free survival probability for children with acute myocarditis (group A), borderline myocarditis (group B), and non-inflammatory dilated cardiomyopathy (group C). For groups B and C the adverse events (transplant or death) are concentrated almost entirely in the first two years after the initial diagnosis.

Acute Myocarditis

Borderline Myocarditis

Non-inflammatory dilated cardiomyopathy

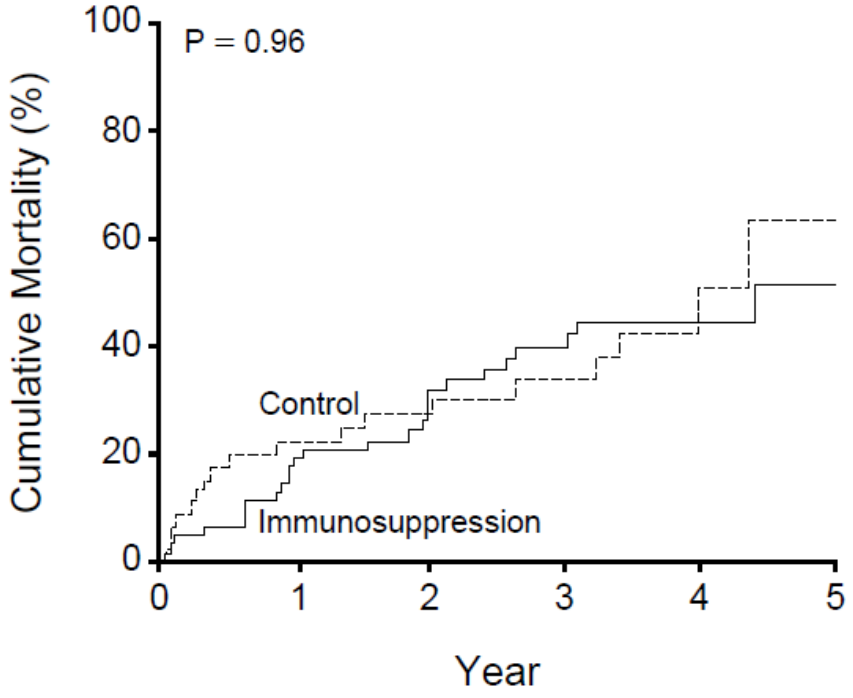
Giulia Gagliardi et al. Heart 2004

Pre-COVID Myocarditis Outcomes

The New England Journal of Medicine

Volume 333 AUGUST 3, 1995 Number 5

A CLINICAL TRIAL OF IMMUNOSUPPRESSIVE THERAPY FOR MYOCARDITIS



Adults mean age 42 years

N=111 total

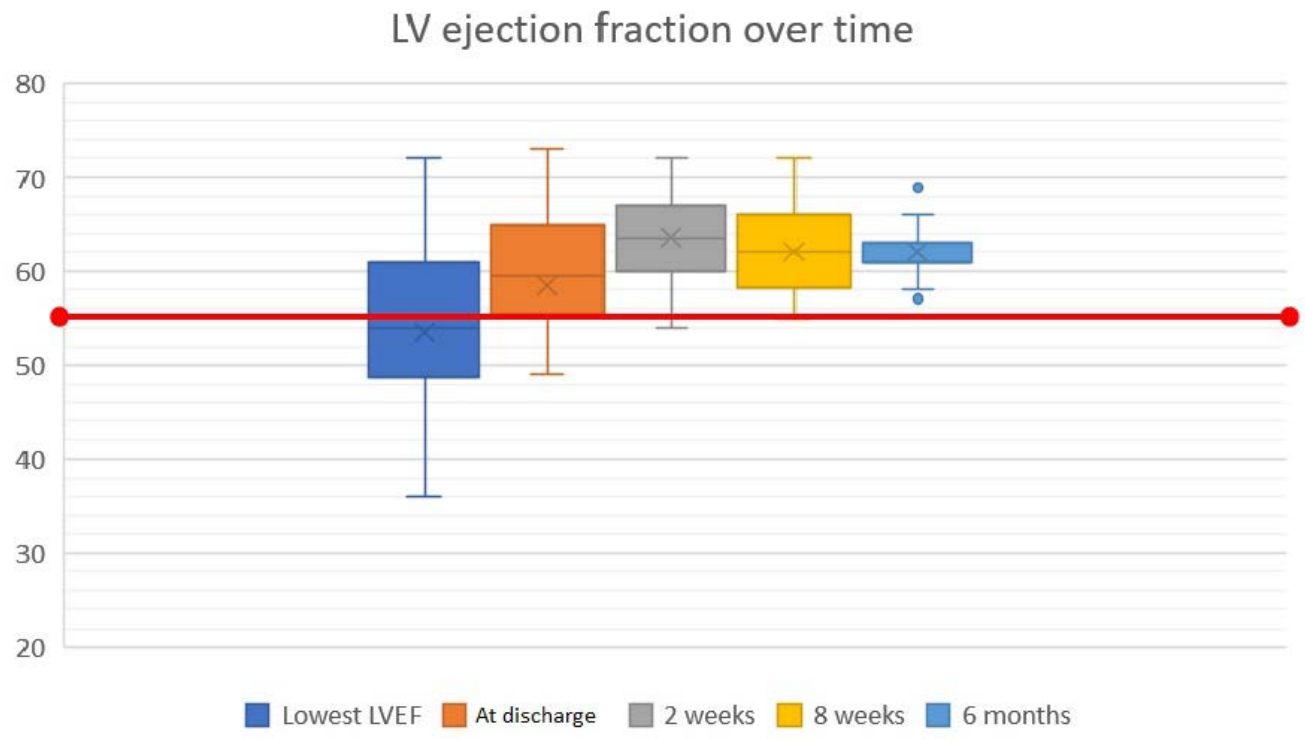
Mason et al. 1995

3-6 Month Outcomes

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Six Month Follow-up of Patients With Multisystem Inflammatory Syndrome in Children



Normal ejection fraction

50 children
Median age 8.5 years

Capone et al. 2021

3-6 Month Outcomes

Cardiac Magnetic Resonance Follow-Up of Children After Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 With Initial Cardiac Involvement

Marta Bartoszek, MD,[1] Łukasz A. Małek, MD, PhD,[2*] Marzena Barczuk-Falęcka, MD, PhD,[1] and Michał Brzewski, MD, PhD[1]

Background: Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) is an inflammatory disease occurring in a small minority of children a few weeks after acute infection. Cardiac manifestations are common, but little is known about the potentially persistent heart changes after PIMS-TS.
Purpose: To analyze the frequency and type of myocardial complications of PIMS-TS with initial cardiac involvement assessed with cardiac magnetic resonance imaging (MRI), including parametric imaging, performed 3 months after hospitalization.
Study Type: Retrospective.
Population: Nineteen consecutive children (median age 10 years, interquartile range (IQR) 10–15 years, 74% male).
Field Strength/Sequence: Balanced steady state free precession (bSSFP, cine imaging), modified Look-Locker (T1 mapping), T2-prepared bSSFP (T2-mapping), dark-blood T2-weighted turbo spin echo with fat suppression and phase sensitive inversion recovery (late gadolinium enhancement (LGE)) sequences at 1.5 T.
Assessment: Patients were scanned after a median of 99 days (IQR 89–104 days) from the diagnosis. MR data were reviewed by three independent observers, with 13, 2, and 5 years' experience in cardiac MRI. Pre- and post-contrast T1, T2, extra-cellular volume, and T2 signal intensity (T2 SI) ratio were calculated. Diagnosis of acute myocarditis was based on modified Lake Louise criteria. Cardiac MRI parameters were compared, where possible, to previously published pediatric normal values.
Statistical Tests: Interclass correlation coefficient and Bland–Altman repeatability analysis. A *P*-value <0.05 was considered statistically significant.
Results: Despite cardiac involvement including decreased left ventricular ejection fraction (LVEF) (median LVEF = 47%, IQR 43%–53%) and increased troponin I (median 101 ng/mL, IQR 50–661 ng/mL) during hospitalization, there were no persistent cardiac changes observed in cardiac MR at follow-up. All patients had normal size and function of the left ventricle and normal precontrast T1 and T2 relaxation times. There were no signs of LGE. Persistent, mild pericardial effusion (8–9 mm) was found in three (16%) patients.
Data Conclusion: There were no persistent changes on cardiac MRI in a group of children approximately 3 months post hospitalization due to PIMS-TS with cardiac involvement. This supports the hypothesis that cardiac involvement during PIMS-TS is a form of transient inflammatory response rather than direct and potentially persistent injury from the virus.
Level of Evidence: 4
Technical Efficacy: Stage 3

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3-6 Month Outcomes

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3-6 Month Outcomes

COVID-19 Vaccination-Associated Myocarditis in Adolescents

- 54 patients
  - Mean age 15.6 years, 92% male
  - Follow up mean 35 days since vaccination
  - 7 (13%) with persistent symptoms
  - Echocardiogram: All normal
  - ECG: 80% normal
  - Troponin: 24/27 normal, 3/27 borderline
  - MRI: Follow-up obtained in 2 (at 66 and 71 days)
    - Improvement in myocardial edema
    - Persistence of Late Gadolinium Enhancement (improved in 1 patient)

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Vaccine Safety Datalink Preliminary Data Confirmed myocarditis/pericarditis 0-21 days after any dose of an mRNA Vaccine: 3-month Follow-up Chart Review

- As of October 9, 2021, chart reviews have been completed for 47 cases that were time-eligible for 3-month follow-up review

- Of these, 37 had at least 1 follow-up visit at least 7 days since the initial encounter

- These **37** cases were reviewed to obtain information regarding
  - ✓ symptoms and diagnostic evaluation at most recent follow-up visit
  - ✓ any additional doses of COVID-19 vaccine since initial encounter
  - ✓ recovery status for
    - ongoing symptoms
    - medication
    - exercise restrictions

Vaccine Safety Datalink Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of mRNA Vaccine by Age Group/Product: 3 month follow-up review of Cases with at least 1 follow-up visit since initial episode

	12-17 Year-Olds (Pfizer) N=10*	18-39 Year-Olds (Pfizer) N=12	18-39 Years-Olds (Moderna) N=15
Time from symptom onset to most recent follow-up visit (median, range)	75 days (13 – 111 days)	72 days (16 – 179 days)	47 days (9 – 150 days)
Follow-up visit at least 3 months since initial encounter	3 (30%)	5 (42%)	6 (40%)
Additional vaccine doses since initial review	0	0	1 (Janssen)
No new or worsening symptoms noted	5 (50%)	9 (75%)	12 (80%)
Any new or worsening symptom	5 (50%)	3 (25%)	3 (20%)
Chest pain/pressure/discomfort	3	2	3
Shortness of breath/pain with breathing	2	1	1
Palpitations	3	0	1
Fatigue	1	1	1
Elevated heart rate	0	1	1
Other (orthostatic hypotension, dizziness, etc.)	2	1	0
Troponin levels obtained	9 (90%)	6 (50%)	7 (47%)
Abnormal troponin level	2	3	4
ECG completed	7 (70%)	8 (67%)	6 (40%)
Abnormal findings	3	3	5
Echocardiogram completed	8 (80%)	3 (25%)	6 (40%)
Abnormal findings	1	0	2
Cardiac MRI completed	1 (10%)	0	0
Abnormal findings	0	NA	NA

* 4 of these cases had been in the ICU at their initial encounter.

Vaccine Safety Datalink Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of mRNA Vaccine by Age Group/Product: 3 month follow-up review of Cases with at least 1 follow-up visit since initial episode

3-month chart review status	12-17 Year-Olds (Pfizer) N=10	18-39 Year-Olds (Pfizer) N=12	18-39 Year-Olds (Moderna) N=15
Current Status (not mutually exclusive)			
Recovered, no medication, exercise restriction or symptoms	3 (30%)	6 (50%)	8 (53%)
Still symptomatic	4 (40%)	5 (42%)	2 (13%)
Still on medication (primarily NSAIDS, Colchicine)	0 (0%)	3 (25%)	6 (40%)
Still on exercise/physical activity restrictions	5 (50%)	2 (17%)	0 (0%)

3-6 Month Outcomes

Investigating Long-Term Effects of Myocarditis

How CDC Is Investigating Myocarditis Health Effects after COVID-19 Vaccination

Updated Aug. 20, 2021 Languages Print

What You Need to Know

- CDC is conducting surveys of patients (or their parents or guardians) and healthcare providers to gather information about myocarditis after mRNA COVID-19 vaccination.
- CDC is contacting people who meet the case definition for myocarditis following mRNA COVID-19 vaccination.

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

CDC enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports

- Purpose: Assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination
- Methods: A two-component survey conducted at least 90 days after the onset of myocarditis symptoms
  - Patient survey: Ascertains functional status, clinical symptoms, quality of life, and need for medication or other medical treatment
  - Healthcare provider (e.g., cardiologist): Gather data on cardiac health and functional status
- Status: Data collection phase

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

CDC enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports

- As of August 2021, VAERS had received 826 reports of myocarditis or myopericarditis after COVID-19 vaccination that met case definition
- To date, around 680 patients have reached 90 days post-myocarditis diagnosis
  - Of these, 282 (41%) have received at least one phone call
    - Of the 282 patients who have received a call, 168 (60%) completed the survey and 67 (24%) were unreachable or declined to participate
      - Of the 168 patients surveyed, 132 (79%) provided cardiologist or healthcare provider contact information
        - Of the 132 cardiologist or healthcare providers, 26 have completed the survey
        - Remaining 106 in the process of being contacted

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

Summary

- Myocarditis is a rare but important adverse event following COVID-19 vaccination
- Not all myocarditis is the same
- Early follow-up results of COVID-19 vaccine-associated myocarditis sparse
  - Ongoing follow-up in progress

Thank you!

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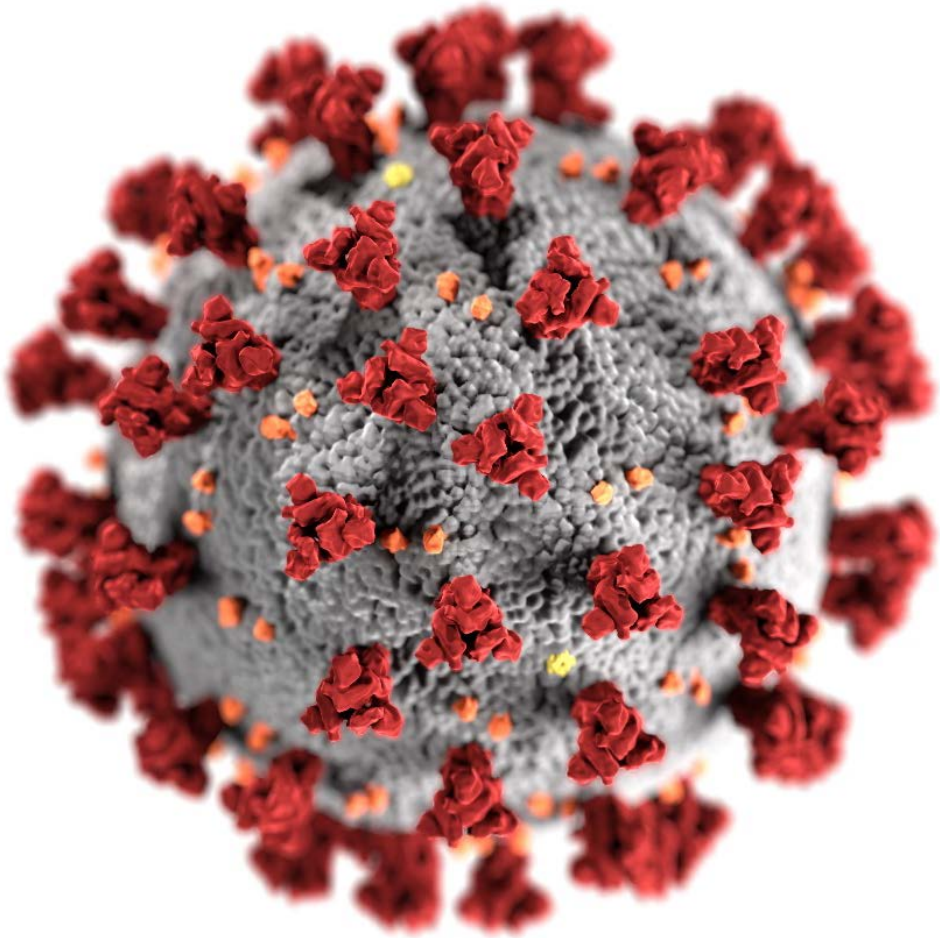
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov



The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.