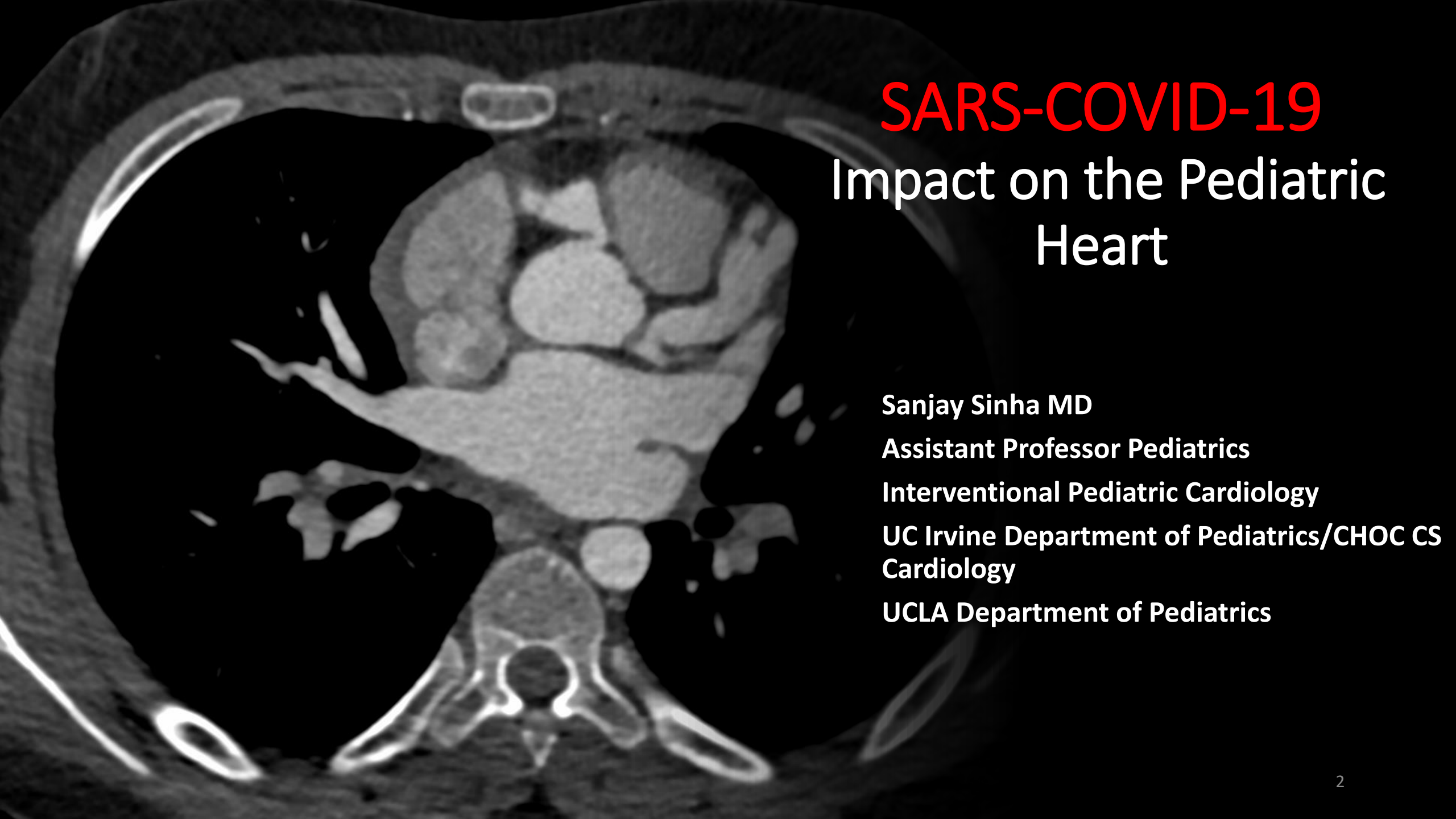




Business Development Virtual
Pediatric Lecture Series
SARS-COVID-19
Impact on the Pediatric Heart

July 28, 2021, 12:30 – 1:30 PM (PST)





SARS-COVID-19

Impact on the Pediatric Heart

Sanjay Sinha MD

Assistant Professor Pediatrics

Interventional Pediatric Cardiology

**UC Irvine Department of Pediatrics/CHOC CS
Cardiology**

UCLA Department of Pediatrics



Disclosures

-No Relevant Disclosures

Goals

- Review the impact of COVID 19 in the context of pediatric mortality/morbidity
- Viral affect on the pediatric heart
- To describe MIS-C and present the most up to date data
- To discuss data on vaccine related cardiac side effects



Last Updated at (M/D/YYYY)
7/21/2021, 8:21 PM

Cases

191,951,455

Deaths

4,126,444

Vaccine Doses Administered

3,713,257,041

Cases and Deaths by Country/Region/Sovereignty

34,226,776 | **609,861**
US

31,216,337 | **418,480**
India

19,473,954 | **545,604**
Brazil

5,973,912 | **111,737**
France

5,955,089 | **148,229**
Russia

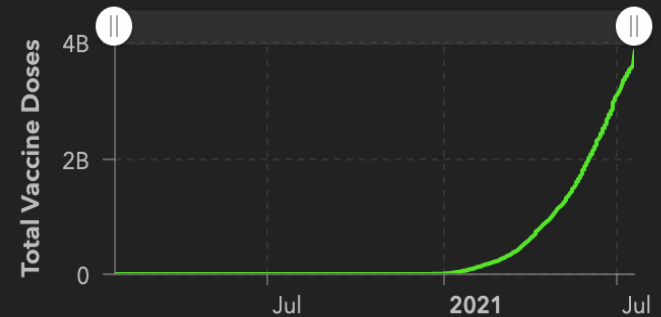
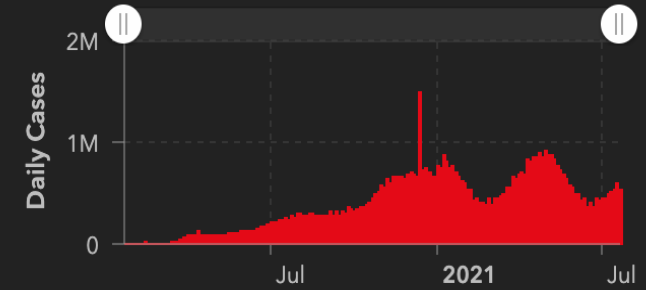
5,586,716 | **129,182**



Esri, FAO, NOAA

Powered by Esri

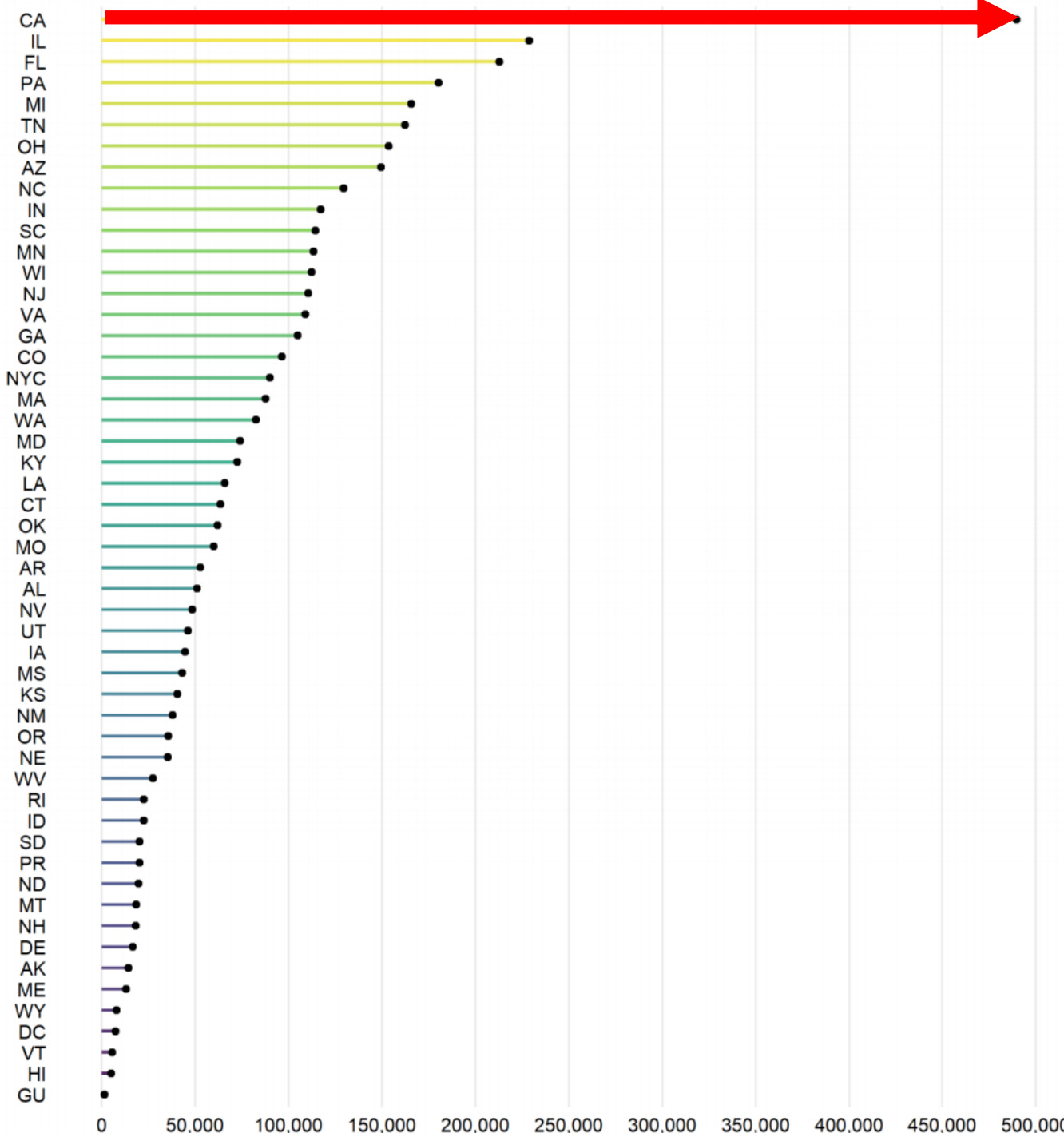
Cumulative Cases



Admin0

Fig 2. Cumulative Number of Child COVID-19 Cases: 7/15/21

- 4,087,916 total child COVID-19 cases (cumulative)
- Sixteen states reported 100,000+ child cases
- Four states reported fewer than 10,000 child cases

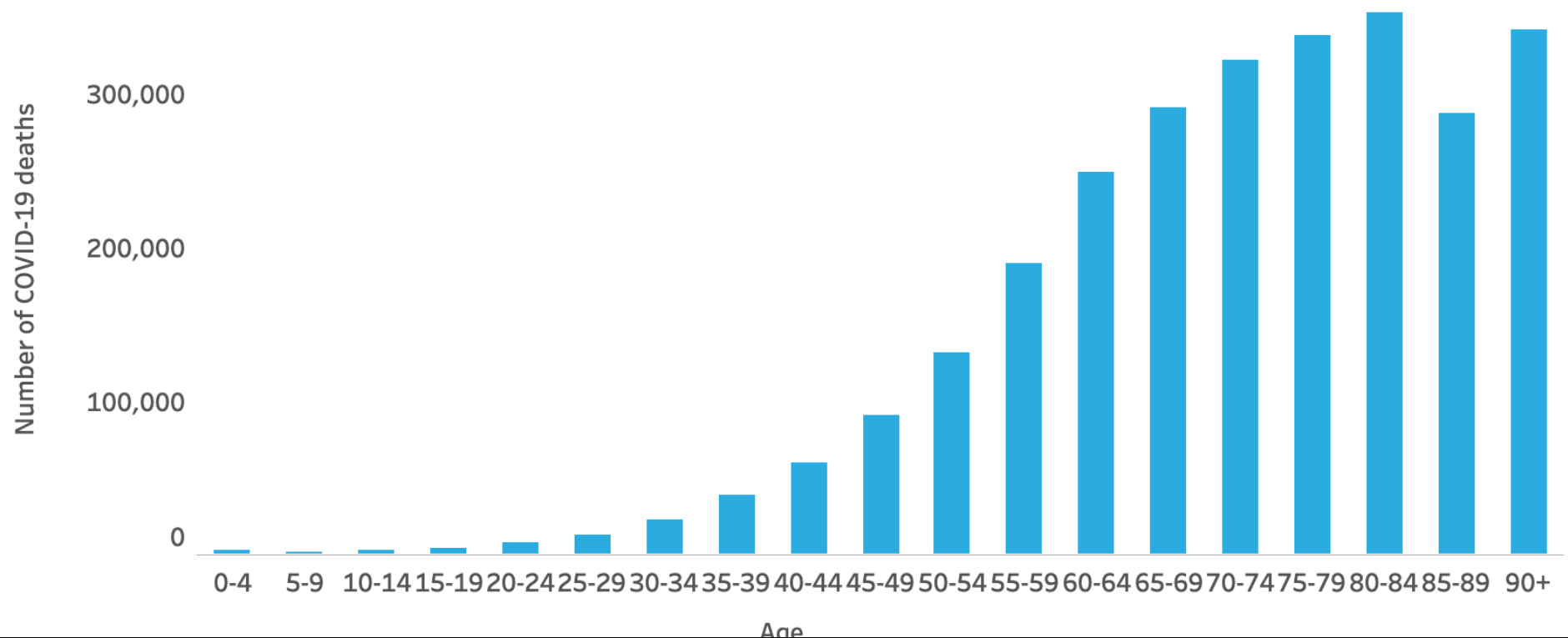


See detail in Appendix: Data from 48 states, NYC, DC, PR, and GU (TX excluded from figure)
 All data reported by state/local health departments are preliminary and subject to change
 Analysis by American Academy of Pediatrics and Children's Hospital Association
 As of 6/30/21, NE COVID-19 dashboard is no longer available; NE cumulative cases through 6/24/21

Over 8,700 children and adolescents died from COVID-19, which is 0.3 per cent of the 2.7 million COVID-19 deaths in 78 countries



COVID-19 deaths by 5-year age groups



Hospitalizations (23 states and NYC reported)*

- Children were 1.3%-3.6% of total reported hospitalizations, and between 0.1%-1.9% of all child COVID-19 cases resulted in hospitalization

Mortality (43 states, NYC, PR and GU reported)*

- Children were 0.00%-0.26% of all COVID-19 deaths, and 8 states reported zero child deaths
- In states reporting, 0.00%-0.03% of all child COVID-19 cases resulted in death

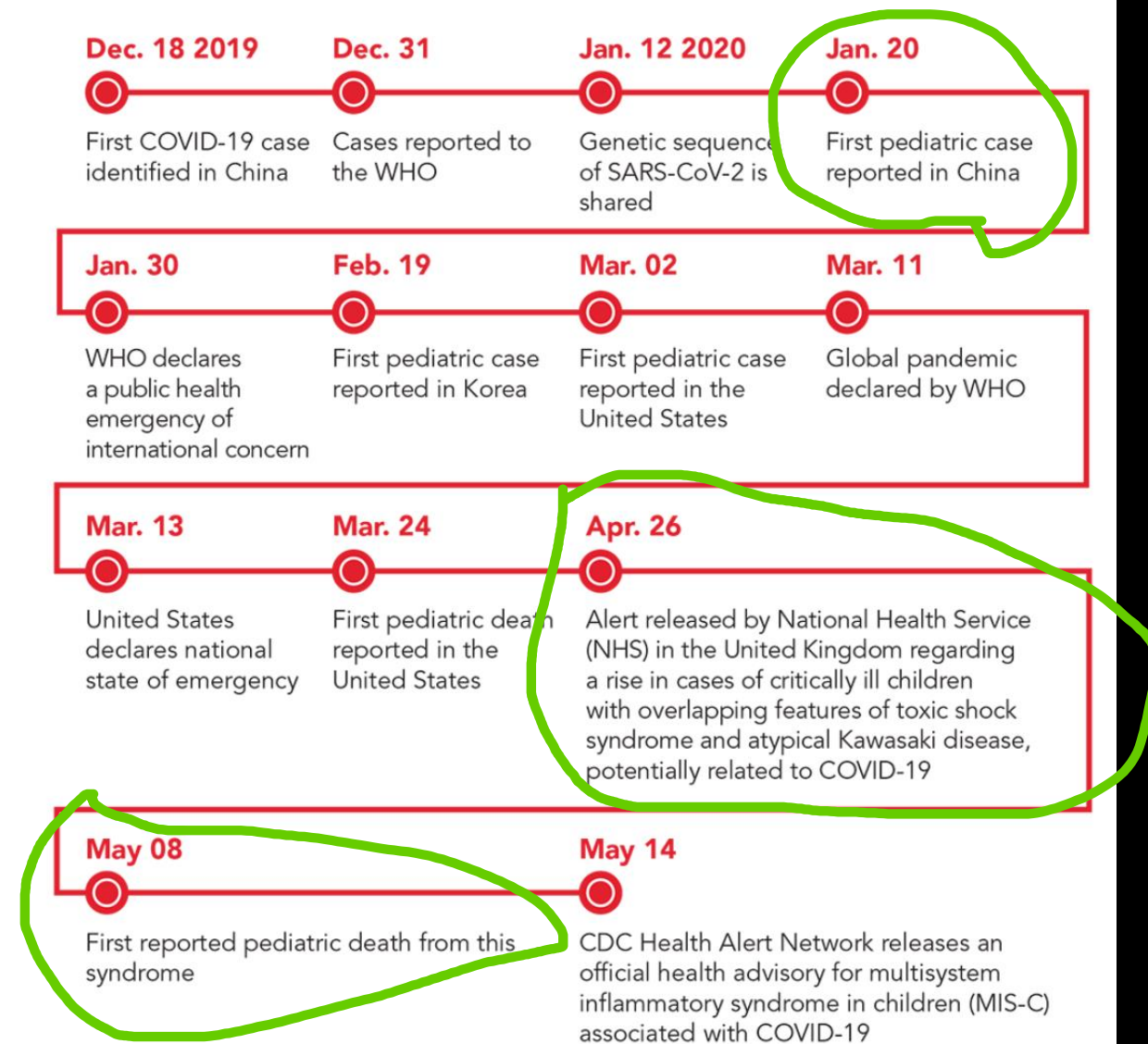
Pediatric Global effect

- Infected estimated:
+4 million
- Dead estimated: 10k
- Loss of primary caregiver:
1,134,000
- Loss of primary or secondary caregiver:
1,562,000
- Orphaned:
1,042,000

• Hillis, S., Unwin, H., Chen, Y., Cluver, L., Sherr, L., Goldman, P., ... & Flaxman, S. (2021). Under the radar: global minimum estimates for COVID-19-associated orphanhood and deaths among caregivers.

COVID-19 Timeline

Figure 1. Timeline of the Impact of the COVID-19 Pandemic on Pediatric Patients^{8,9}



Abbreviations: CDC, United States Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Walker DM, Tolentino VR. COVID-19: The impact on pediatric emergency care. *Pediatr Emerg Med Pract.* 2020 Jun 5;17(Suppl 6-1):1-27. PMID: 32496723.

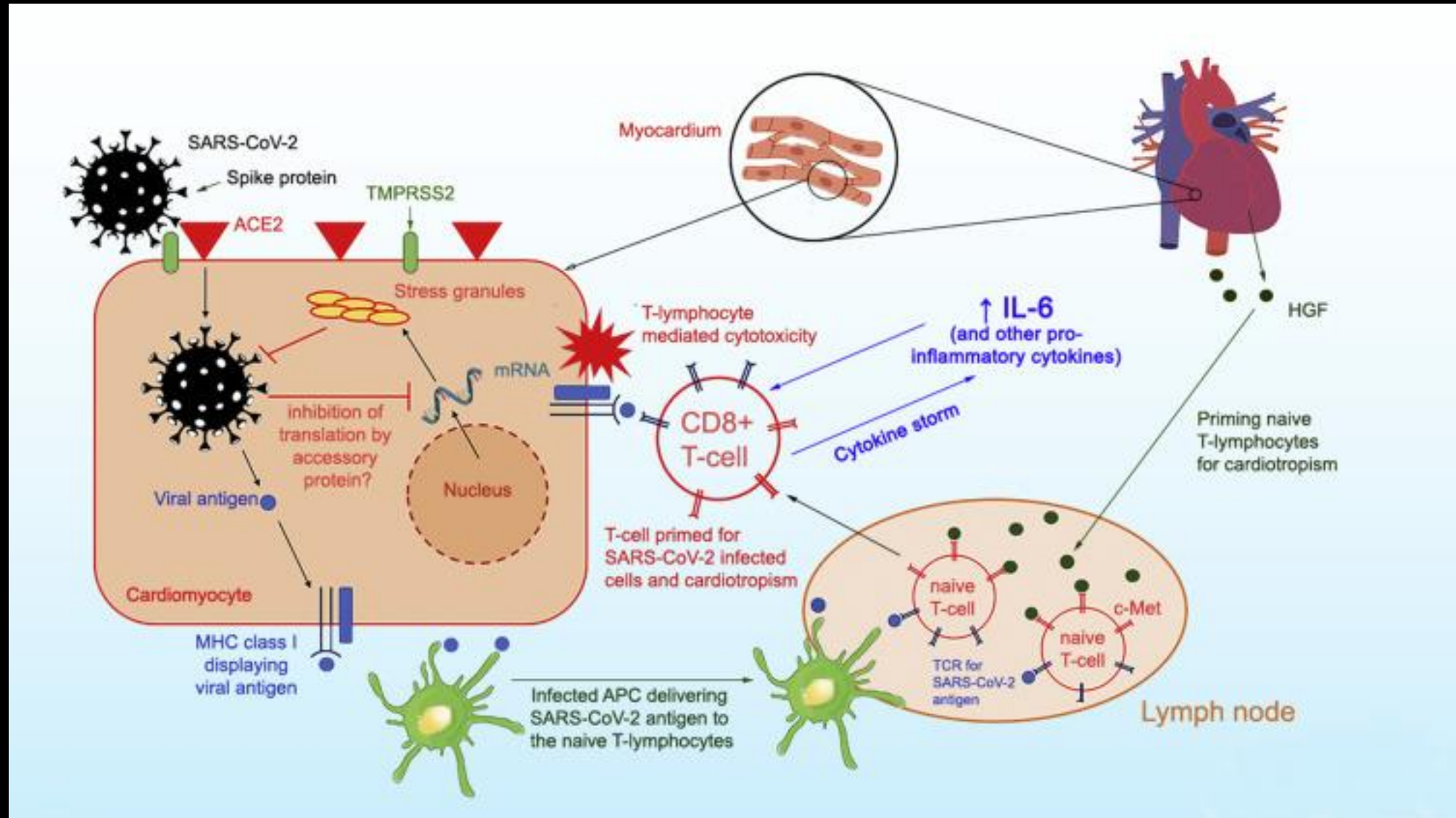
Clinical characteristics	Children (n=20), n (%)	Adult (n=964), n (%)	P
Gender			
Male	9 (45)	752 (78.01)	0.00048
Female	11 (55)	212 (21.99)	
History of contact	6 (30)	86 (8.92)	0.00138
Asymptomatic	5 (25)	00	
Symptomatic	15 (75)	964 (100)	0.00001
Symptoms			
Fever	11 (55)	716 (74.27)	0.00001
Cough	12 (60)	672 (69.70)	0.3523
Dyspnea	4 (20)	490 (50.82)	0.00634
COVID-19 severity			
Mild	11 (55)	462 (47.92)	0.5287
Moderate	6 (30)	269 (27.90)	0.8336
Severe	3 (15)	233 (24.17)	0.3421
Treatment			
HCQ	15 (75)	673 (69.81)	0.6173
Azithromycin	9 (45)	673 (69.81)	0.0173
LMWH	5 (25)	642 (66.59)	0.0001
Injection dexona	3 (15)	673 (69.81)	0.0001
Antibiotic	15 (75)	426 (44.1)	0.0107
Remdesivir	0	226 (23.44)	-
Convalescent plasma	1 (5)	59 (6.12)	0.8336
Tocilizumab	0	47 (4.87)	-
Oxygen	5 (25)	520 (53.94)	0.0101
Ward	12 (60)	804 (83.40)	0.00596
ICU	8 (40)	293 (30.39)	0.3575
NIV	5 (25)	119 (12.34)	0.0910
Mechanical ventilation	1 (5)	75 (7.78)	0.6455
Death	4 (20)	249 (25.82)	0.5552

Number in bracket shows percentage. LMWH: Low molecular weight heparin, HCQ: Hydroxychloroquine, ICU: Intensive care unit, NIV: Noninvasive ventilation

- Cardiac Effect mixed
 - No echocardiographic evidence of effect
 - In patients with severe disease, cardiac effects were related to lung disease, pna
 - Athletes recovering from COVID-19 showed some evidence of myocarditis by MRI

Rai, D., et al. (2021). "Differences in clinical and lab characteristics between adults and children hospitalized with COVID-19 infection over a 2-month period at a tertiary COVID care center: A cross-sectional study." *Lung India* 38(4): 402-404.

ADULT LITERATURE



Siripanthong, B., et al. (2020). "Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management." *Heart Rhythm* 17(9): 1463-1471.

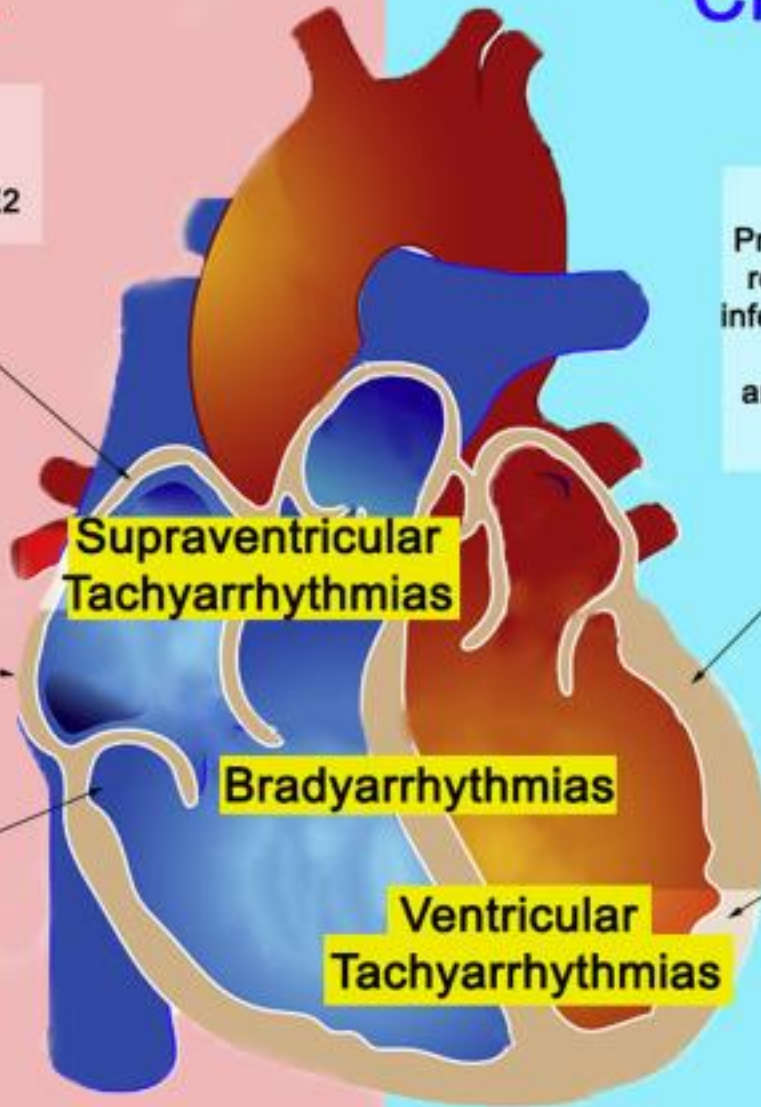
ACUTE

CHRONIC

1. **Cardiomyocyte injury**
SARS-CoV-2 gaining entry into the cardiomyocytes via ACE2

2. **Pericardial inflammation**
Massive pericardial edema/effusion seen in fulminant myocarditis could precipitate arrhythmias

3. **Microvascular ischemia**
SARS-CoV-2 might damage the pericytes around the cardiac microvasculature, causing ischemia



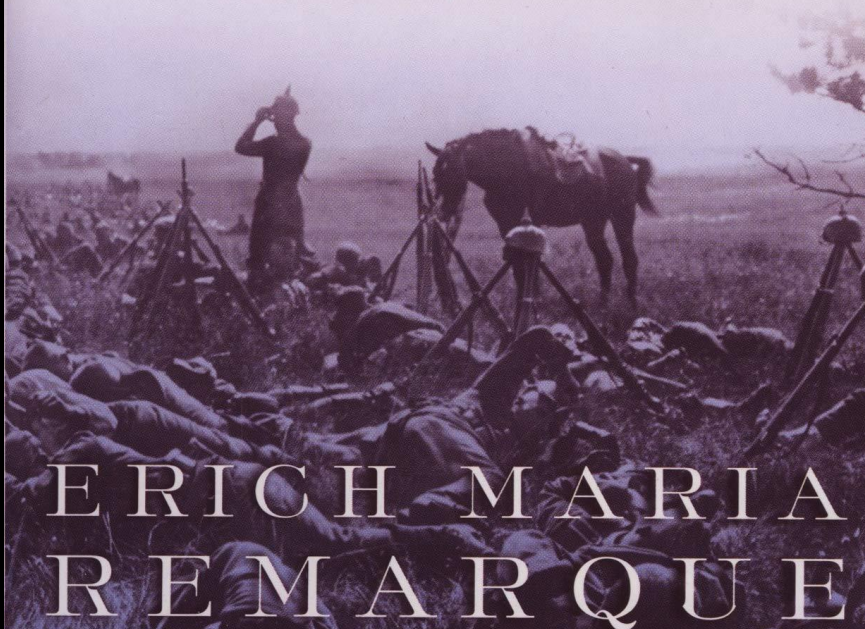
5. **Gap junction dysfunction**
Pro-inflammatory cytokines (e.g. IL-6) released secondary to SARS-CoV-2 infection may displace plakoglobin from the desmosomes. This could be arrhythmogenic especially if there is a genetic predisposition.

4. **Non-ischemic scar**
Post-inflammatory fibrosis or scarring and chronic inflammation causing re-entrant arrhythmias

Meanwhile in
Kids.....

ALL QUIET
ON THE
WESTERN
FRONT

The GREATEST WAR NOVEL of ALL TIME

The illustration depicts a somber war scene. In the foreground, a soldier stands in a trench, looking through binoculars. To his right, a horse stands amidst the debris of the battlefield. The trench is filled with sandbags and other soldiers. The background shows a hazy, desolate landscape under a pale sky.

ERICH MARIA
REMARKUE

Then this on May 6 2020.....

Hyperinflammatory shock in children during COVID-19 pandemic

South Thames Retrieval Service in London, UK, provides paediatric intensive care support and retrieval

to 2 million children in South East England. During a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome,¹ or toxic shock

syndrome (typical number is one or two children per week). This case cluster formed the basis of a national alert.

All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. All children except one were well above the 75th centile

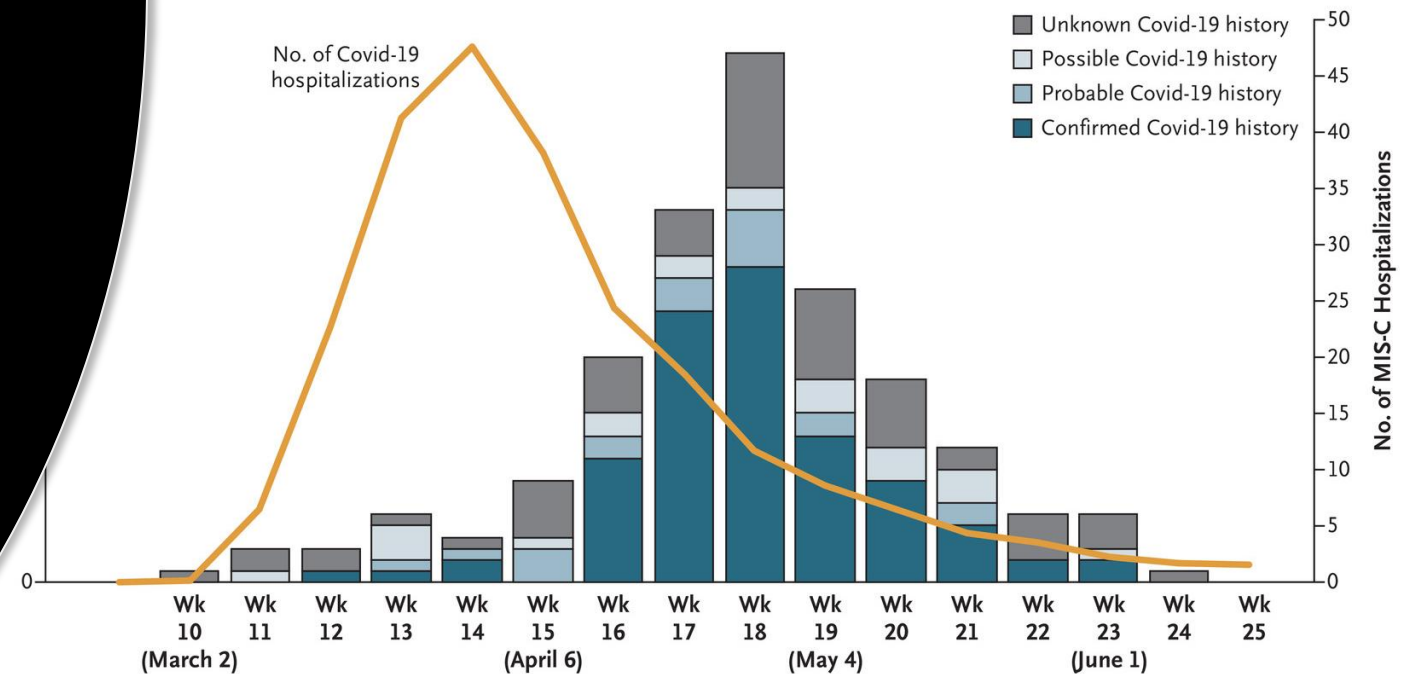


Published Online
May 6, 2020
[https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1)

MIS-C

Multisystem Inflammatory Syndrome in Children

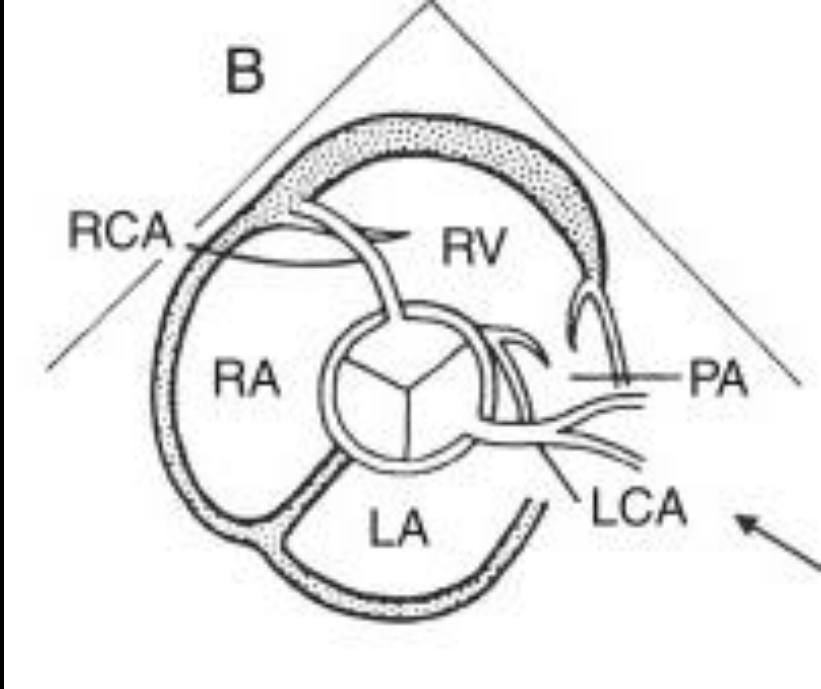
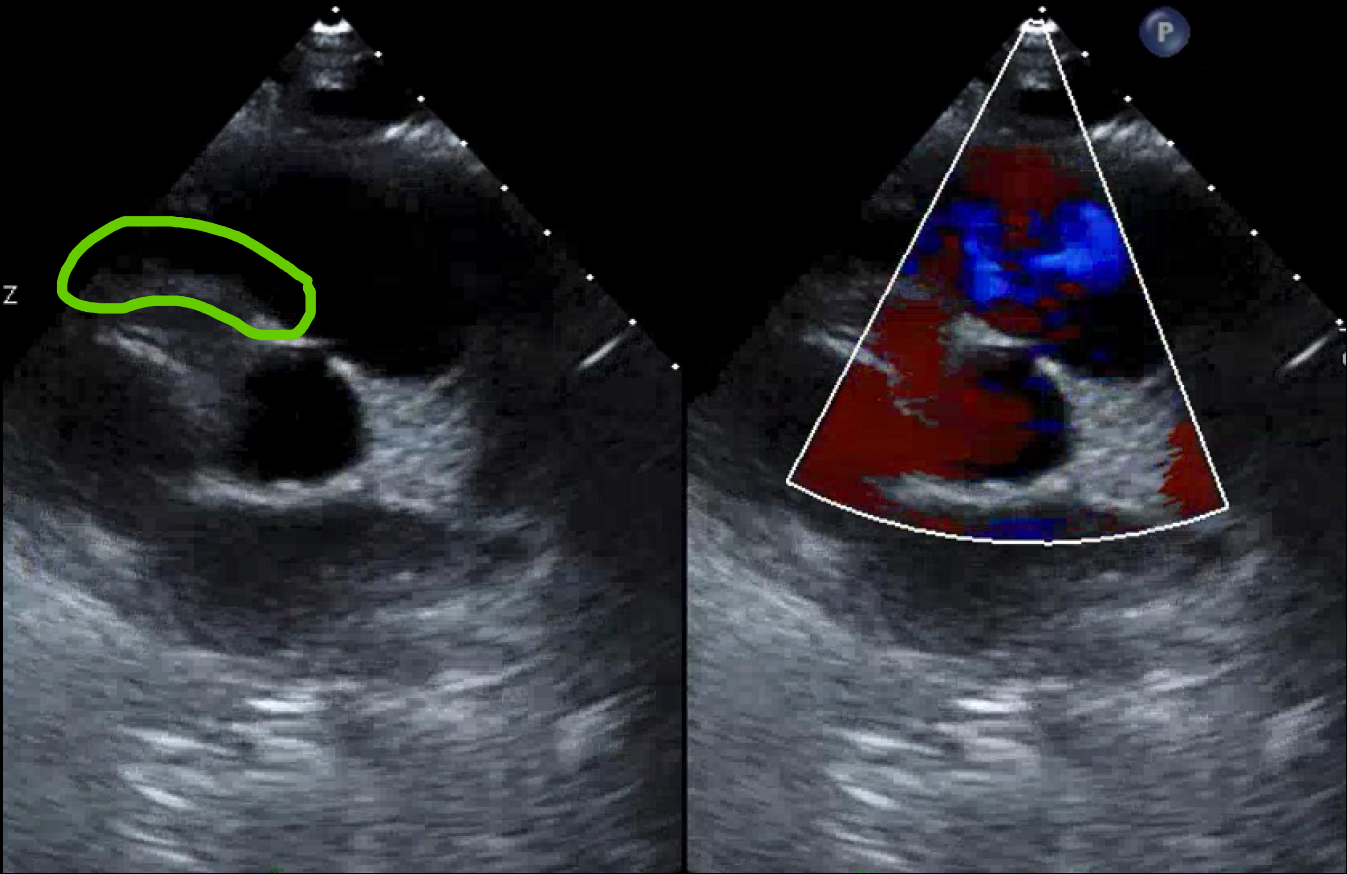
- October 29, 2020
N Engl J Med 2020; 383:1793-1796
DOI: 10.1056/NEJMc2026136



“You could feel it going through your veins and it was almost like someone injected you with straight-up fire,”

*14 year old on his
experience with MISC-C*

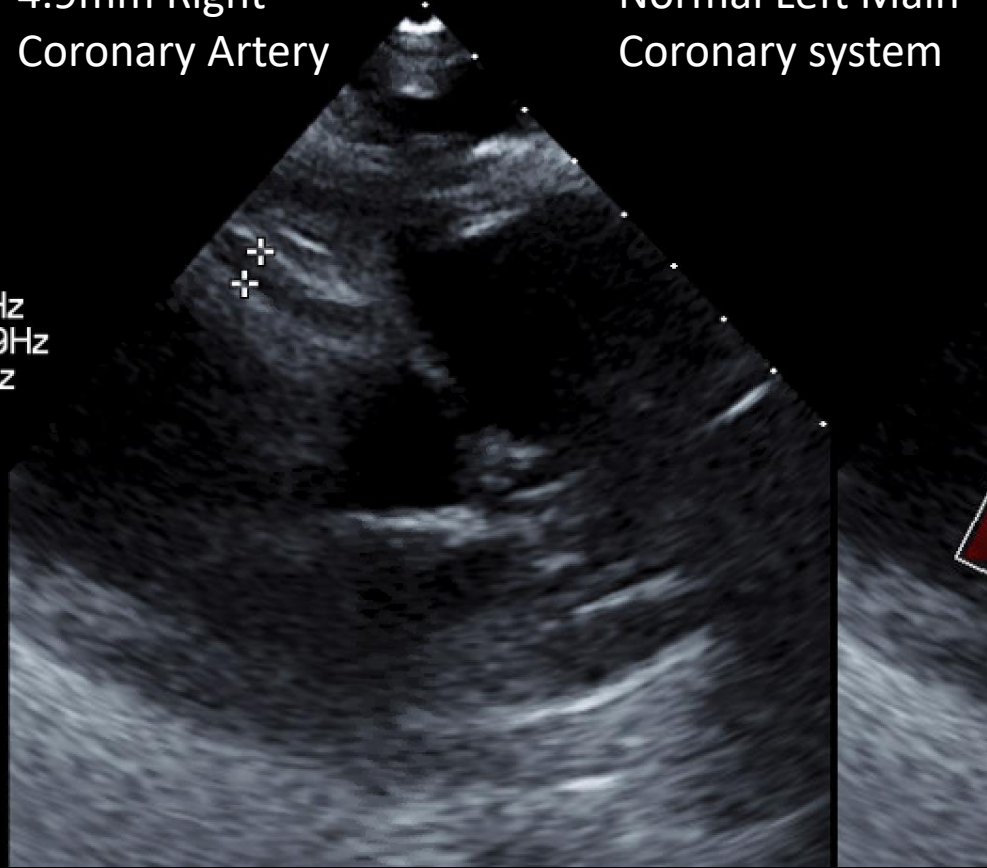
April 8th 2020



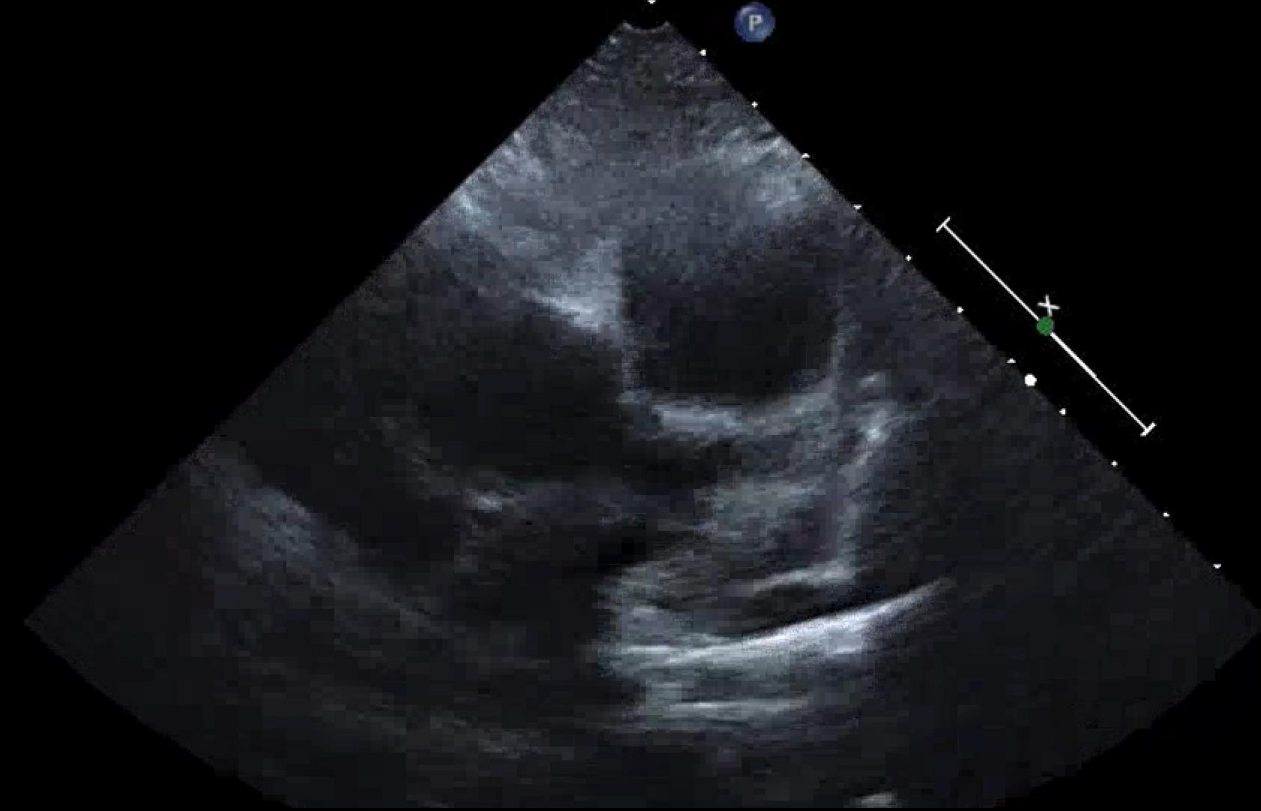
4.9mm Right
Coronary Artery

Normal Left Main
Coronary system

1z
3Hz
z



4/8/2020

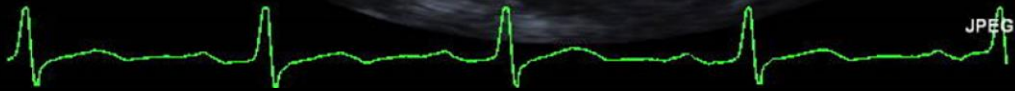
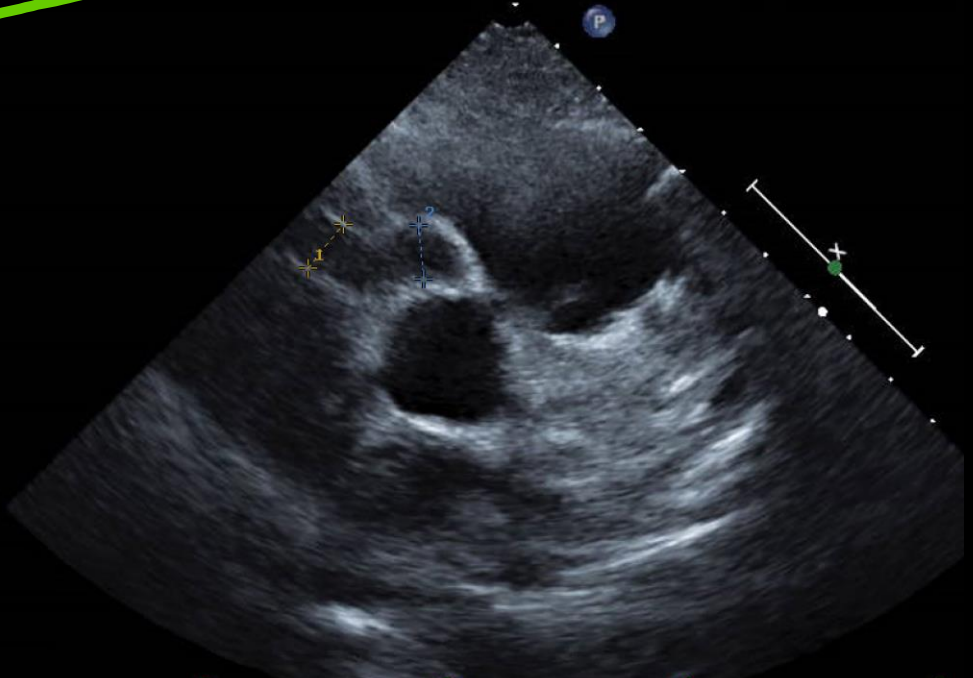


4/26/2020

1 Distance = 0.96 cm
2 Distance = 0.90 cm

S8-3/CHOC

2D
79%
C 46
P Low
HGen

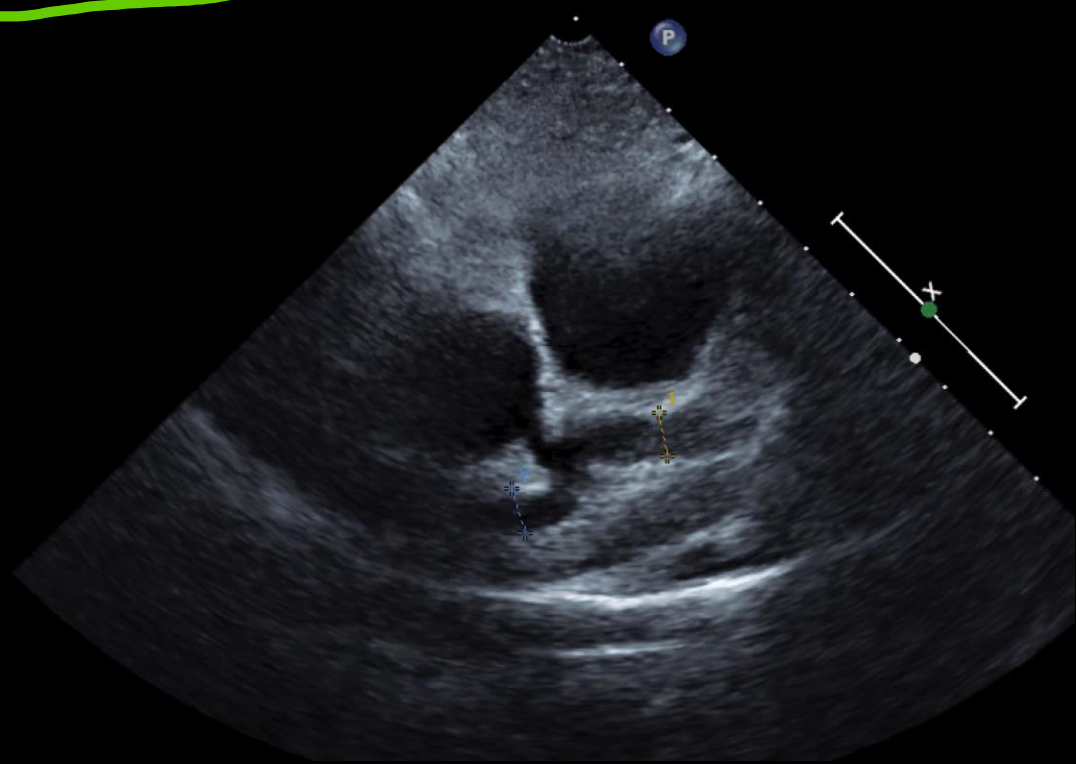


1 Distance = 0.67 cm
2 Distance = 0.71 cm

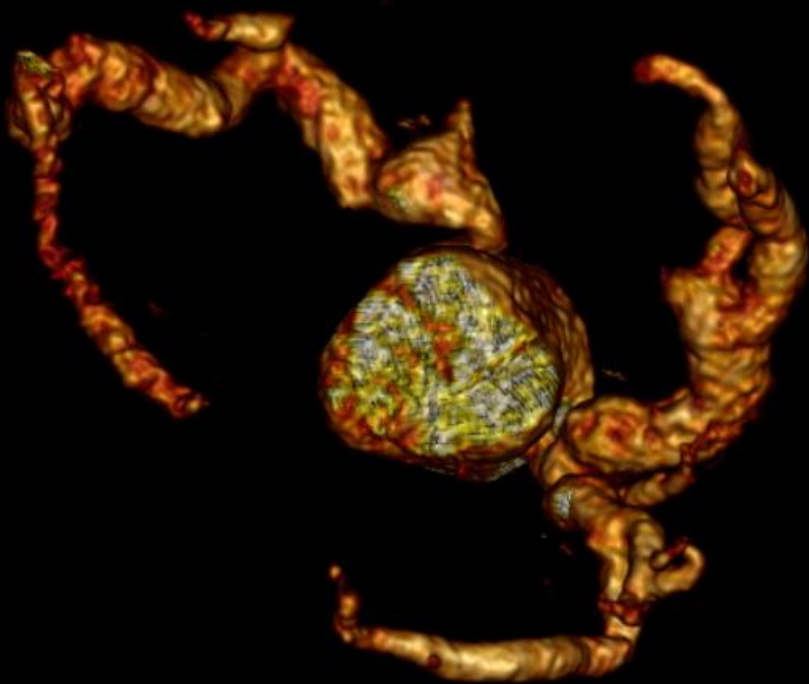
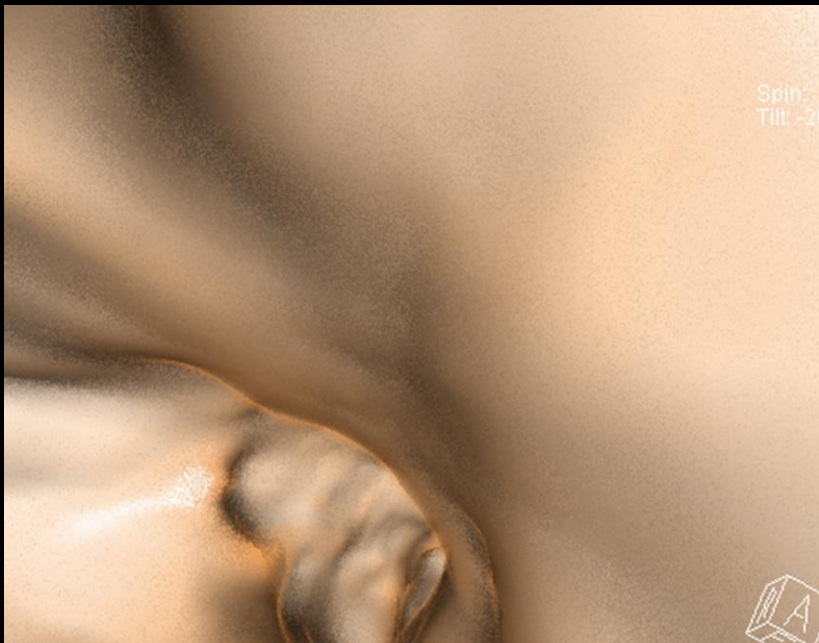
CHOC 2

S8-3/CHOC

2D
77%
C 46
P Low
HGen



Coronary Artery Dilatation and Aneurysm



AI



Cardiac Impact

- Decreased left ventricular ejection fraction
- Pericarditis, myocarditis
- Coronary artery dilation and aneurysm formation
- Heart block

- Royal College of Paediatrics and Child Health Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Imaging and ECG

- Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- CXR – patchy symmetrical infiltrates, pleural effusion
- Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast

Clinical and laboratory features:

Clinical

All:

- Persistent fever >38.5°C

Most:

- Oxygen requirement
- Hypotension

Some:

- Abdominal pain
- Confusion
- Conjunctivitis
- Cough
- Diarrhoea
- Headache
- Lymphadenopathy
- Mucus membrane changes
- Neck swelling
- Rash
- Resp symptoms
- Sore throat
- Swollen hands and feet
- Syncope
- Vomiting

Laboratory

All:

- Abnormal Fibrinogen
- Absence of potential causative organisms (other than SARS-CoV-2)
- High CRP
- High D-Dimers
- High ferritin
- Hypoalbuminaemia
- Lymphopenia
- Neutrophilia in most – normal neutrophils in some

Some:

- Acute kidney injury
- Anaemia
- Coagulopathy
- High IL-10 (if available)*
- High IL-6 (if available)*
- Neutrophilia
- Proteinuria
- Raised CK
- Raised LDH
- Raised triglycerides
- Raised troponin
- Thrombocytopenia
- Transaminitis

Circulation

Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children

Tarek Alsaied, Adriana H. Tremoulet, Jane C. Burns, Arwa Saidi, Audrey Dionne, Sean M. Lang, Jane W. Newburger, Sarah de Ferranti, Kevin G. Friedman ✉

Originally published 9 Nov 2020 | <https://doi.org/10.1161/CIRCULATIONAHA.120.049836> | Circulation. 2021;143:78–88

Key Points

- Occurs 2-4 weeks after SARS-CoV-2 Infection
- Dysregulated Immune response to infection
- Most Common Presenting Sx
 - GI pain
 - Fever

CARDIAC EFFECT

- Decreased left ventricular ejection fraction
- Pericarditis, myocarditis
- Coronary artery dilation and aneurysm formation
- Heart block

ANTI-INFLAMMATORY/IMMUN MOD TREATMENT

RECOVERY IN 1-2 WEEKS

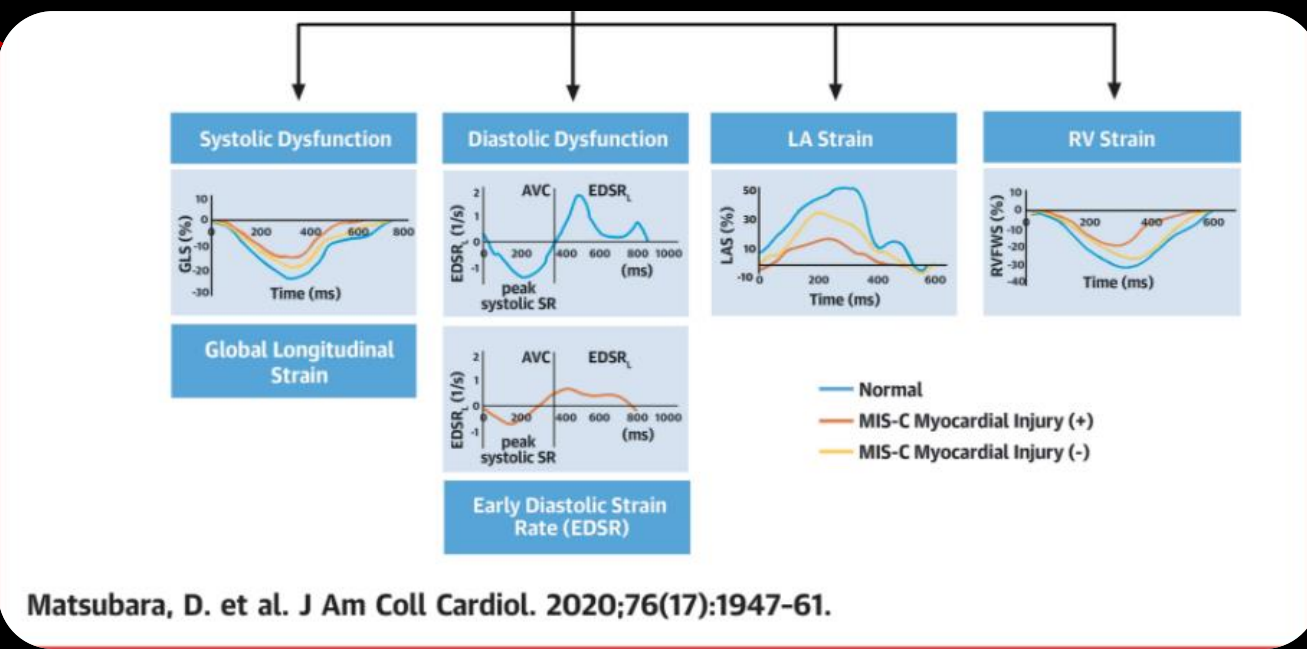
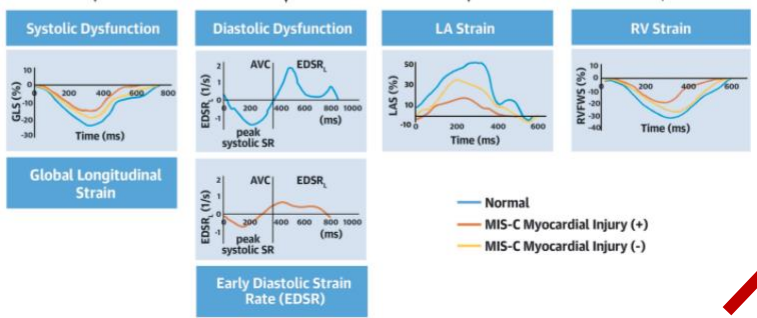
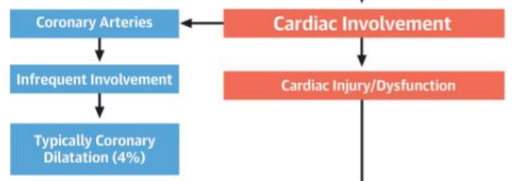
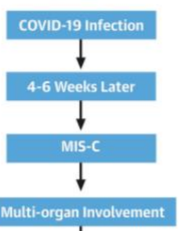
LONG TERM CV EFFECTS ARE UNKNOWN

“KAWASAKI LIKE ILLNESS”

Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States

Original Investigation

Daisuke Matsubara, Hunter L. Kauffman, Yan Wang, Renzo Calderon-Anyosa, Sumekala Nadaraj, Matthew D. Elias, Travus J. White, Deborah L. Torowicz, Putri Yubbu, Therese M. Giglia, Alexa N. Hogarty, Joseph W. Rossano, Michael D. Quartermain, and Anirban Banerjee



Matsubara, D. et al. J Am Coll Cardiol. 2020;76(17):1947-61.

Matsubara, D. et al. J Am Coll Cardiol. 2020;76(17):1947-61.

Patient diagnosed with
multisystem inflammatory syndrome

- All patients received
- Steroids
 - IVIG 2 g/kg
 - Enoxaparin prophylaxis or low-dose aspirin
 - GI prophylaxis

Mild Presentation

No need for vasoactives
Minimal or no respiratory support

- Treated with methylprednisolone 2 mg/kg per day
- 2- to 3-week steroid taper

Moderate Presentation

VIS $\leq 10^b$
Mild organ injury

- Treated with methylprednisolone pulse 10 mg/kg per day followed by 2 mg/kg per day
- Consider anakinra if steroid refractory
- 6- to 8-week steroid taper

Severe Presentation

VIS >10
Noninvasive or invasive ventilator support
Moderate or severe organ injury
Moderate or severe ventricular dysfunction

- Treated with methylprednisolone 20 to 30 mg/kg per day for 1 to 3 days followed by 2 mg/kg per day
- Anakinra 10 mg/kg per dose q6h if steroid refractory
- 6- to 8-week steroid taper

Aspirin 81 mg daily
Steroid taper

Patient diagnosed with MIS-C syndrome discharged

First follow-up
2 weeks postdischarge

Second follow-up
6 weeks postdischarge

Third follow-up
6 months postdischarge

Fourth follow-up
1 year postdischarge

- Multidisciplinary team assessment
- Echocardiogram^a
- ECG
- Laboratory work: CBC count, liver function, inflammatory cardiac markers, T-cell panel

- Multidisciplinary team assessment
- Echocardiogram
- ECG
- Laboratory work: CBC count, liver function, inflammatory cardiac markers, T-cell panel

- Multidisciplinary team assessment
- Echocardiogram
- ECG
- Cardiac MRI^b
- Laboratory work: if not previously normalized

- Multidisciplinary team assessment
- Echocardiogram
- ECG

But then!



mRNA VACCINE RELATED MYOCARDITIS

Circulation

Myocarditis with COVID-19 mRNA Vaccines

Biykem Bozkurt , Ishan Kamat, and Peter J. Hotez

Originally published 20 Jul 2021 |

<https://doi.org/10.1161/CIRCULATIONAHA.121.056135> | Circulation. ;0

KEY POINTS

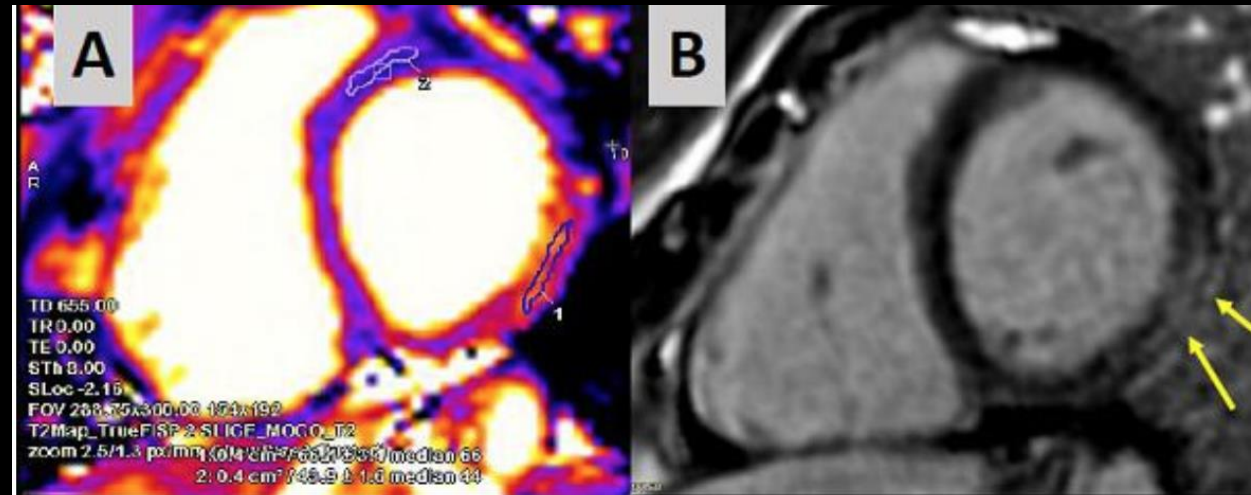
- 12.6 CASES/MILLION DOSES OF 2ND SHOT
- 12-39 YEAR OLDS
- ADOLESCENT MALE PREDOMINANT
- PRESENTATION
 - CHEST PAIN 2-3 DAYS AFTER 2ND DOSE (86%)
 - Elevated Cardiac Enzymes (64%)
 - CRP/ESR elevated, but decreased with Cardiac Enzymes
 - ST ELEVATIONS IN MULTIPLE LEADS
 - Abnormal Echo in 40%
 - MRI EVIDENCE OF MYOCARDITIS
 - NO EVIDENCE OF CONCOMITANT INFECTION

mRNA VACCINE RELATED MYOCARDITIS

- Approximately 300 Million doses given through June 11 2021
- 1,226 case reported through VAERs
- 67% after 2nd dose
- 79% Males
- Majority younger than 30y/o (median age 24)

MECHANISM OF ACTION

- SPIKE PROTEIN MOLECULAR MIMICRY
- Trigger dysregulated immune pathways in some individuals
- Unknown why male predominance



Case that fulfills the updated Lake Louise CMR criteria for acute myocarditis in a teenage patient presenting with chest pain, abnormal ECG, and elevated troponin 48 hours after the second dose of Pfizer/BioNTech vaccine. Panel A: regional myocardial edema involving the basal inferolateral segment shown on elevation of T2 mapping (region of interest #1 is > 55 ms). Panel B: late-gadolinium enhancement imaging of nonischemic myocardial injury (yellow arrows) involving the same segments. (Photo Credit: João Cavalcante)

Case Series

Table 2. Case Reports and Case Series of Myocarditis after COVID-19 Vaccination

Case series	Case Report
-------------	-------------

Table 2. Case Reports and Case Series of Myocarditis after COVID-19 Vaccination

Case series							Case Report							Summary
Author	Marshall M et al. ⁷	Rosner DM et al. ⁸	Larson K et al. ¹⁰	Abu M et al. ⁹	Kim H et al. ¹⁸	Montgomery J et al. ¹⁷	Author	Ammirati E et al. ¹¹	Bautista Garcia J et al. ¹²	McLean L et al (US) ¹³	D'Angelo T et al. ¹⁴	Albert E et al. ¹⁵	Muthukumar A et al. ¹⁶	
Cases, n	7	7	8	6	4	23	Case, n	1	1	1	1	1	1	61 patients
Case source	Hospitalized patients different centers in US	Hospitalized patients in 2 US centers	Hospitalized patients in Italy and US	Hospitalized patients in Israel	Hospitalized patients in 1 US center	Case series from US Military Health System	Case source	Hospitalized patient in Italy	Hospitalized patient in Spain	Hospitalized patient in US	Hospitalized patient in Italy	Hospitalized patient in US	Hospitalized patient in US	All hospitalized

Vaccine Related Myocarditis Data

Table 1. Expected / Observed Number, Crude Reporting Rates in Vaccine Adverse Event Reporting System (VAERS) and ICD-10 Coding Rates of Myocarditis/Pericarditis following mRNA COVID-19 Vaccination

Expected versus Observed Number of Myocarditis/Pericarditis Cases in 7-day Risk Window Following Dose 2 of mRNA Covid-19 Vaccination *						
Age groups	Females			Males		
	Doses administered	Expected*†	Observed*	Doses administered	Expected*†	Observed*
12-17 years	2,189,726	0-2	19	2,039,871	0-4	128
18-24 years	5,237,262	1-6	23	4,337,287	1-8	219
25-29 years	4,151,975	0-5	7	3,625,574	1-7	59
30-39 years	9,356,296	2-18	11	8,311,301	2-16	61
40-49 years	9,927,773	2-19	18	8,577,766	2-16	34
50-64 years	18,696,450	4-36	18	16,255,927	3-31	18
65+ years	21,708,975	4-42	10	18,041,547	3-35	11
Crude Reporting Rates of Myocarditis/Pericarditis Cases per Million Doses following mRNA COVID-19 Vaccination‡						
Age groups	Female rates per million doses			Male rates per million doses		
	All doses	Dose 1	Dose 2	All doses	Dose 1	Dose 2
12-17 years	4.2	1.1	9.1	32.4	9.8	66.7
18-24 years	3.6	1.5	5.5	30.7	8.7	56.3
25-29 years	2.0	0.8	2.6	12.2	4.5	20.4
30-39 years	1.8	1.4	1.8	6.9	2.0	10.0
40-49 years	2.0	0.9	2.8	3.5	1.0	5.1
50-64 years	1.6	1.0	1.8	1.9	1.0	2.3
65+ years	1.1	0.6	1.2	1.2	0.7	1.4
Myocarditis/Pericarditis Rates based on ICD-10 Codes §						
Age group	Female cases	Female rates per million doses (95 % CI)		Male cases	Male rates per million doses (95 % CI)	
12-39 years						
Any mRNA both doses	6	3.2 (1.2-6.9)		26	16.9 (11.0-24.8)	

Risk Benefit- Vaccine Counseling

- Share the Facts
- Be updated on the facts
- NEJM
- CIRCULATION
- CDC
- Recognize politically charged environment
- Realize that we are all fathers/brothers/sisters who are afraid.

Risk Benefit

4/30/2020, 10:06 AM
WL: 306 WW: 191

SR



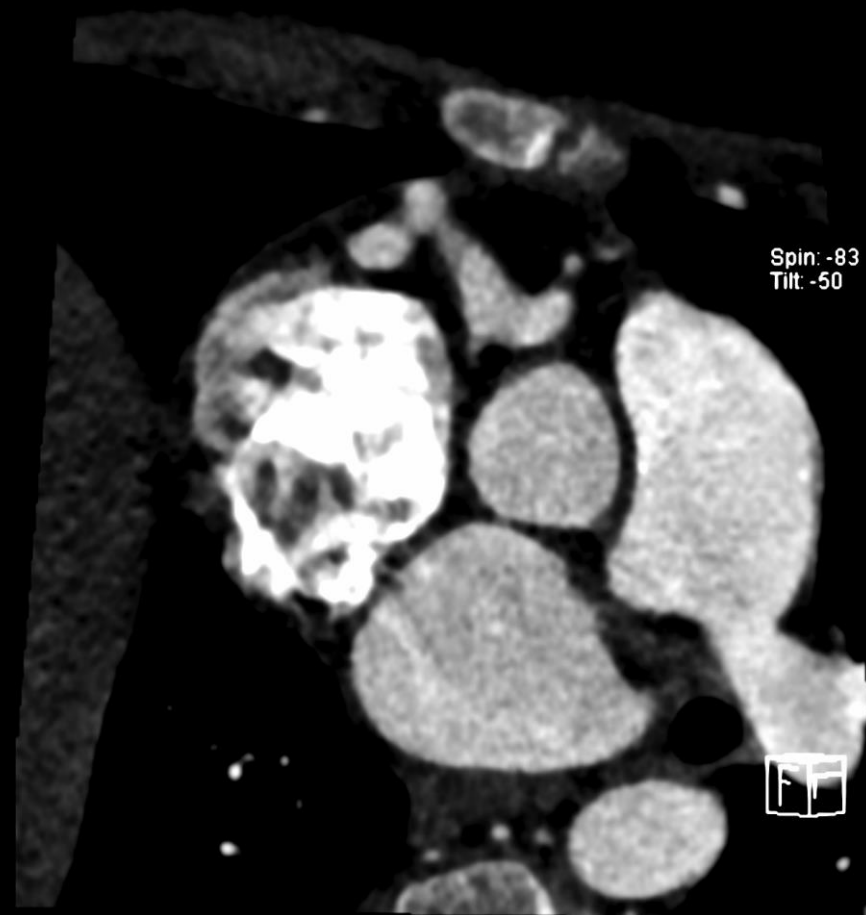
RAI



LPS

IL

S-I: 22.8
L-R: 27.1
Roll: -16.8



Spin: -83
Tilt: -50



Thank you for your
time!



Additional Bibliography

- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020 May 23;395(10237):1607-1608. doi: 10.1016/S0140-6736(20)31094-1. Epub 2020 May 7. PMID: 32386565; PMCID: PMC7204765.
- Farooqi KM, Chan A, Weller RJ, Mi J, Jiang P, Abrahams E, Ferris A, Krishnan US, Pasumarti N, Suh S, Shah AM, DiLorenzo MP, Zachariah P, Milner JD, Rosenzweig EB, Gorelik M, Anderson BR; Columbia University Interdisciplinary MIS-C Follow-up Program and the CUIMC Pediatric/Adult Congenital Heart Research Collaborative. Longitudinal Outcomes for Multisystem Inflammatory Syndrome in Children. *Pediatrics*. 2021 Jul 15:e2021051155. doi: 10.1542/peds.2021-051155. Epub ahead of print. PMID: 34266903.
- Farooqi, K. M., et al. (2021). "Longitudinal Outcomes for Multisystem Inflammatory Syndrome in Children." *Pediatrics*: e2021051155.
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PRACTICE INFORMATION

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