Great Lakes Health: Mini Grand Rounds: COVID Associated Pediatric Cardiovascular Complications - Part 2 of 2

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Current State of Erie County COVID Infection

Erie County 7-day Rolling Average on 6/9/21 for Children and Adults:

- Reduced % Positivity: 0.52% (on 5/17/21 was 1.7%%)
- Reduced # new positives/day/100,000: 2.6 (on 5/17/21 was 11)
- At about the NYS average, Erie County is better than last summer
- Rochester is worse
- Erie County Point Prevalence is 0.4-1.8/1000 or24 new positives/day.
- Oishei Children's Hospital has averaged 2-4 hospitalized positive patients, some in the PICU.
- Increasing delta variant: 17% nationally and 22% NYS (Not real time)

Yu KO. COVID Counts Update. June 10, 2021.

CDC COVID-NET Surveillance Data: Worrisome Spike in Younger Teen's COVID Hospitalizations: Data Through April Add Urgency to Calls for Adolescent Vaccination

- Younger teens are not as likely to have severe COVID as adults.
- Their hospitalization rates spiked early this year. A large proportion (1/3) required intensive care. 5% required mechanical ventilation.
- Currently, there are rising COVID adolescent (12-17 yo) hospitalization rates/100,000:

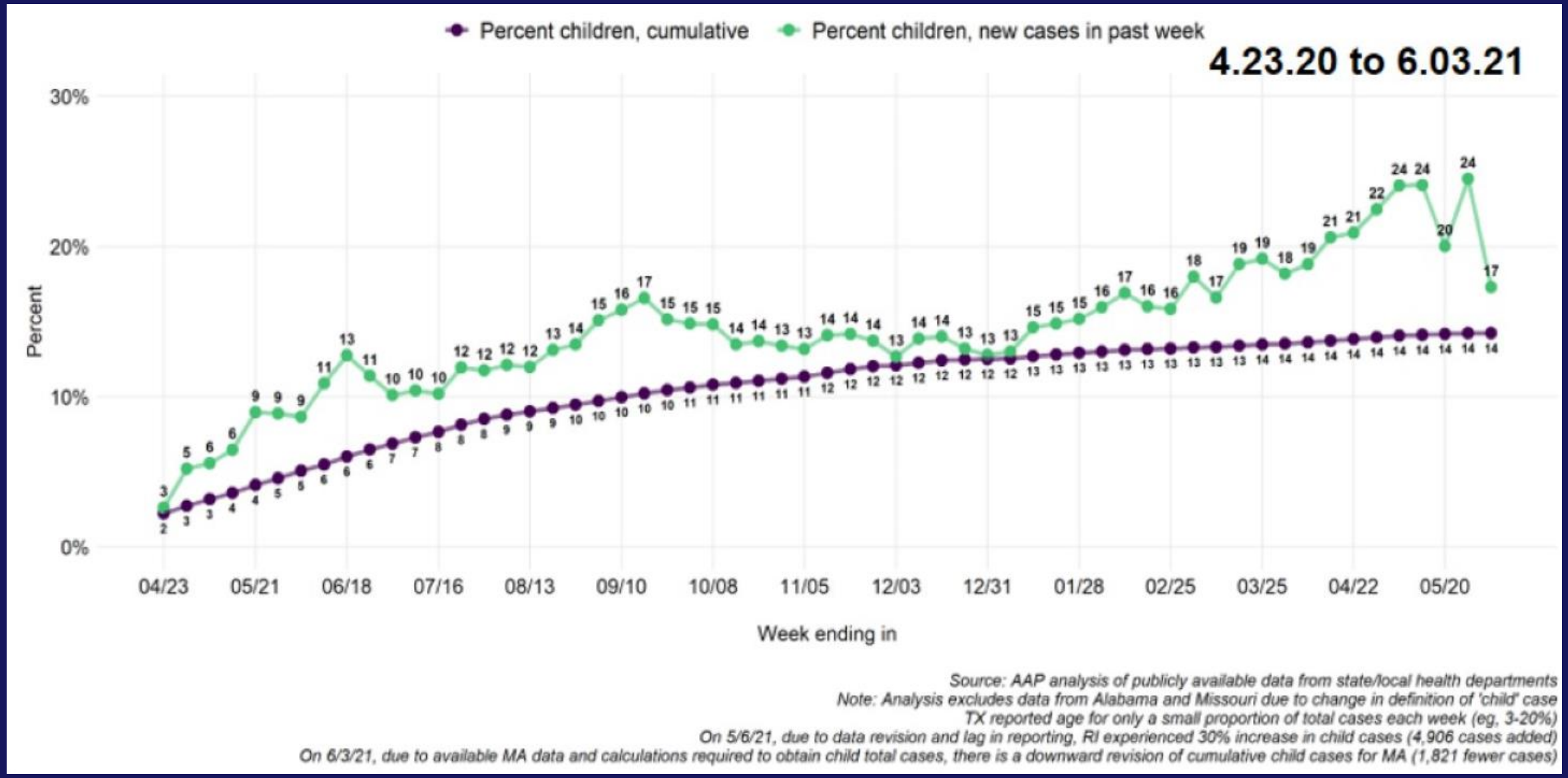
  1/2021: 2.1

  3/2021: 0.6

  4/2021: 1.3
- Reflection of new, more contagious variants. The B. 117 variant is most prevalent. But the delta (B.1.617.2) is concerning and increasing.
- May also reflect: 1. return to school/indoor activities, 2. changes in physical distancing, 3. less mask-wearing, and 4. reduction of other preventive behaviors.
- Reinforces adolescents getting vaccinated and practicing prevention.
- Not just a disease of adults who have stabilized during this time period with vaccines.

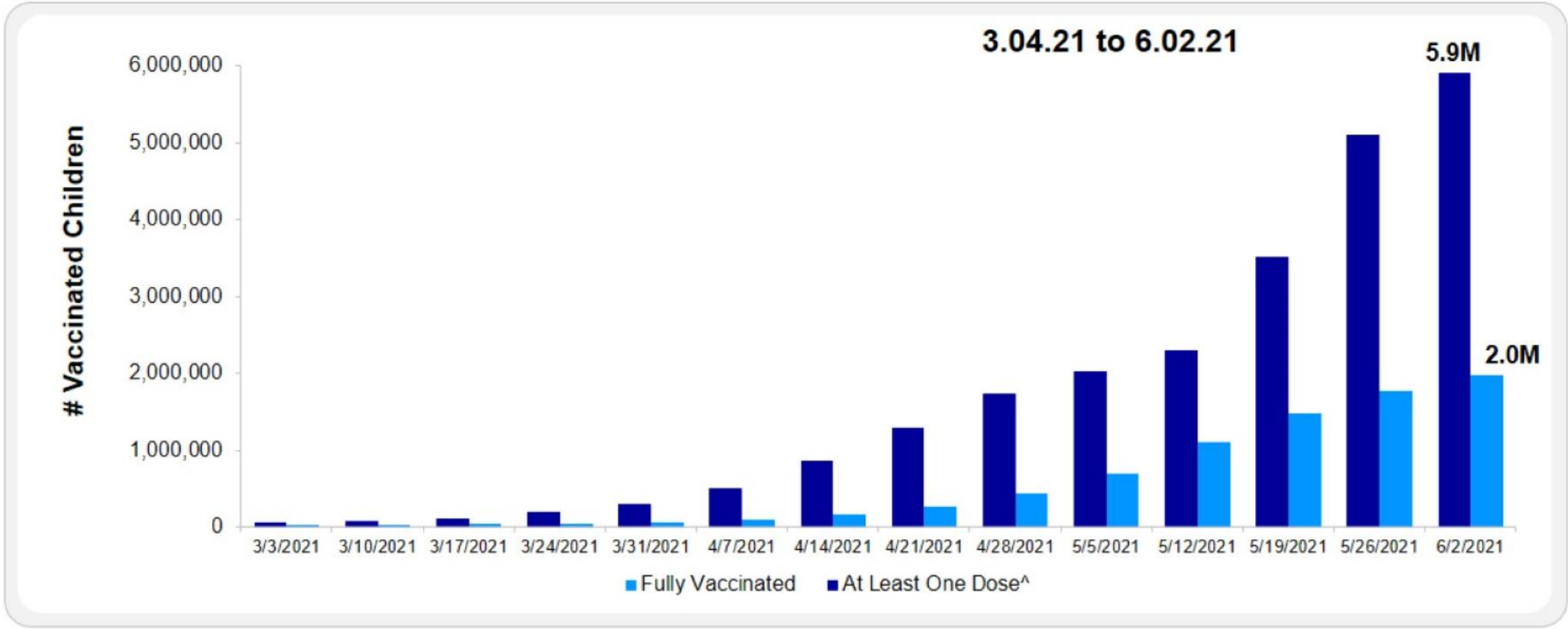
Havers FP et al. CDC Morbid Mortal Weekly Reports. June 4, 2021.

Percent of COVID-19 Cases that Were Children: Cumulative and for New Cases in Past Week



Source: AAP analysis of publicly available data from state/local health departments
Note: Analysis excludes data from Alabama and Missouri due to change in definition of 'child' case
TX reported age for only a small proportion of total cases each week (eg, 3-20%)
On 5/6/21, due to data revision and lag in reporting, RI experienced 30% increase in child cases (4,906 cases added)
On 6/3/21, due to available MA data and calculations required to obtain child total cases, there is a downward revision of cumulative child cases for MA (1,821 fewer cases)

Cumulative Weekly Number of US COVID-19 Vaccine Recipients Under Age 18



^ Count includes those having received only 1 of 2 doses and those fully-vaccinated.
Source: AAP analysis of data series reported by the CDC titled "Demographic Trends of People Receiving COVID-19 Vaccinations in the United States"

Viral Co-infection Risks for Pediatric Patients

- **CDC** National Respiratory and Enteric Virus Surveillance System (NREVSS): **Respiratory Syncytial Virus (RSV)** cases up since March across the Southern US.
- Unusual time of year-usually peaks during cold and flu season (Fall/Winter) but did not happen.
- Due to reduced circulation of RSV during Winter 2020-21, older infants and toddlers might now be at increased risk of severe RSV-associated illness since they have not had typical levels of exposure to RSV during the past 15 months.
- The leading cause of infant bronchiolitis and pneumonia morbidity and mortality.
- Very high risk: Babies and toddlers and **children with underlying congenital heart disease and heart failure**. Also, young kids, and older adults with chronic medical conditions.
- Co-infection of RSV with COVID particularly concerning.
- Consider RSV (rRT-PCR) testing in high-risk populations with acute respiratory symptoms.

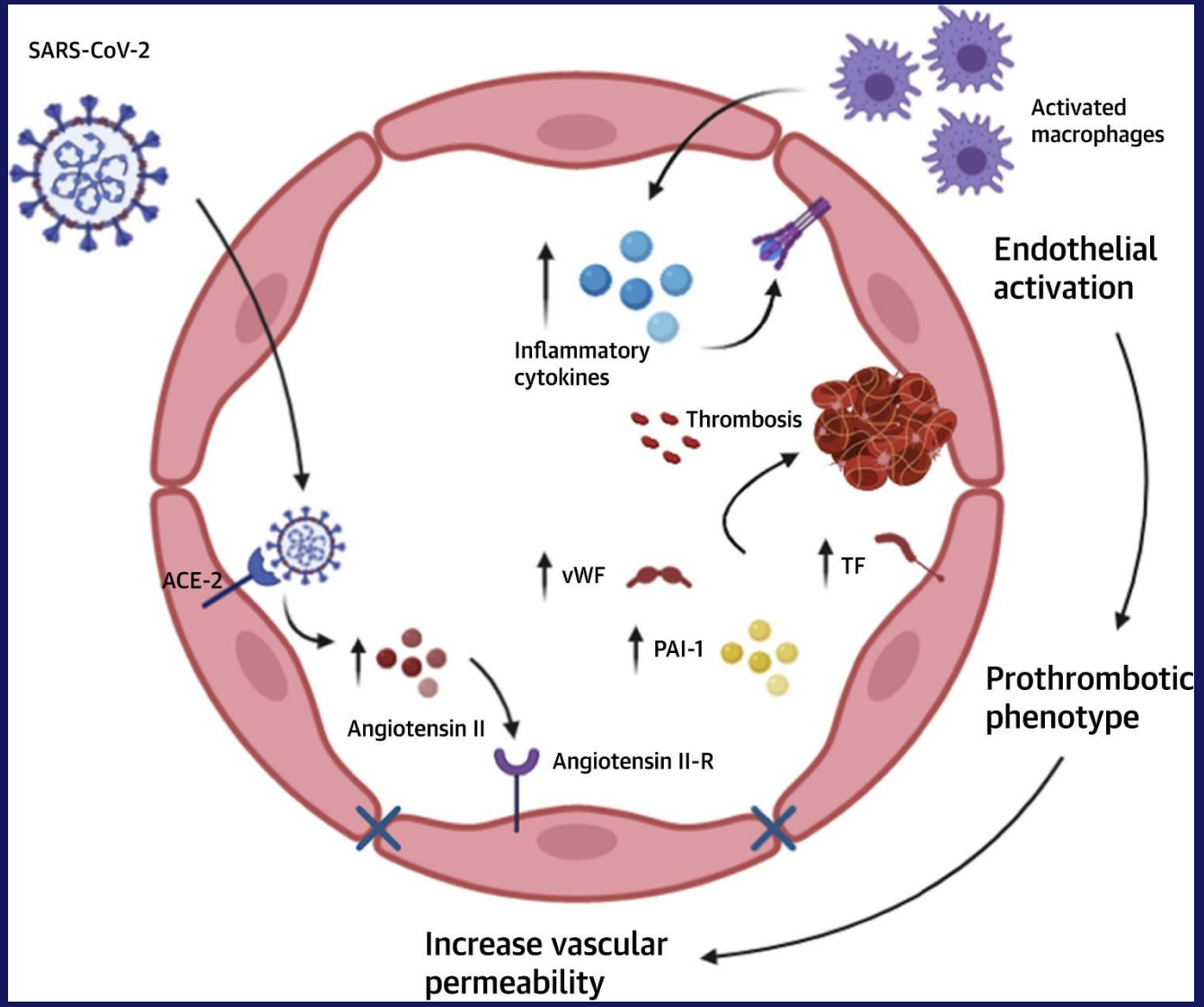
CDC Heath Advisory Network Warning. June 10, 2021.

More Severe Pediatric COVID Disease and Utility of ECMO for MIS-C

- **CDC:** Over 4 million COVID cases have been diagnosed in children <18 in the US. Severe COIVD illness has remained rare in the population under age 30, but as of June 9, 2021, **over 2,637 COVID deaths have occurred in the under-30 age group, and over 15,000 under age 18 years have been hospitalized in the US alone**.
- **ECMO Useful in MIS-C** for Cardiogenic Shock with Severely Depressed Myocardial Function and Arrhythmias.
- 3/3 Michigan children had complete recovery of myocardial function and no 6-mo morbidity.
- ECMO has been successful in a **2-year-old** with ALL with full recovery.
- ECMO in 100 Consecutive Patients at 20 hospitals: ECMO may facilitate salvage and result in rescue survival of crucially ill patients with COVID. Survivors were younger.
- Prospective studies of ECMO in adults with acute viral COVID refractory respiratory failure are sobering and show survival of <50% in heavily pretreated patients without severe comorbidities at an average age of 52 years.

Shapiro N. Health. June 14, 2021. Fiore K. MedPage Today June 10, 2021
Cohen E. CNN June 13, 2021.
Schneider et al. Perfusion. May 26, 2021.
Ebach et al. Ped Blood Cancer. April 2021.
Jacobs et al. ASAIO J. May 1, 2021.
Lorusso and Mueller. Lancet Respir Med. April 19, 2021.

Endothelia Activation, Inflammation and Thrombosis in COVID-19



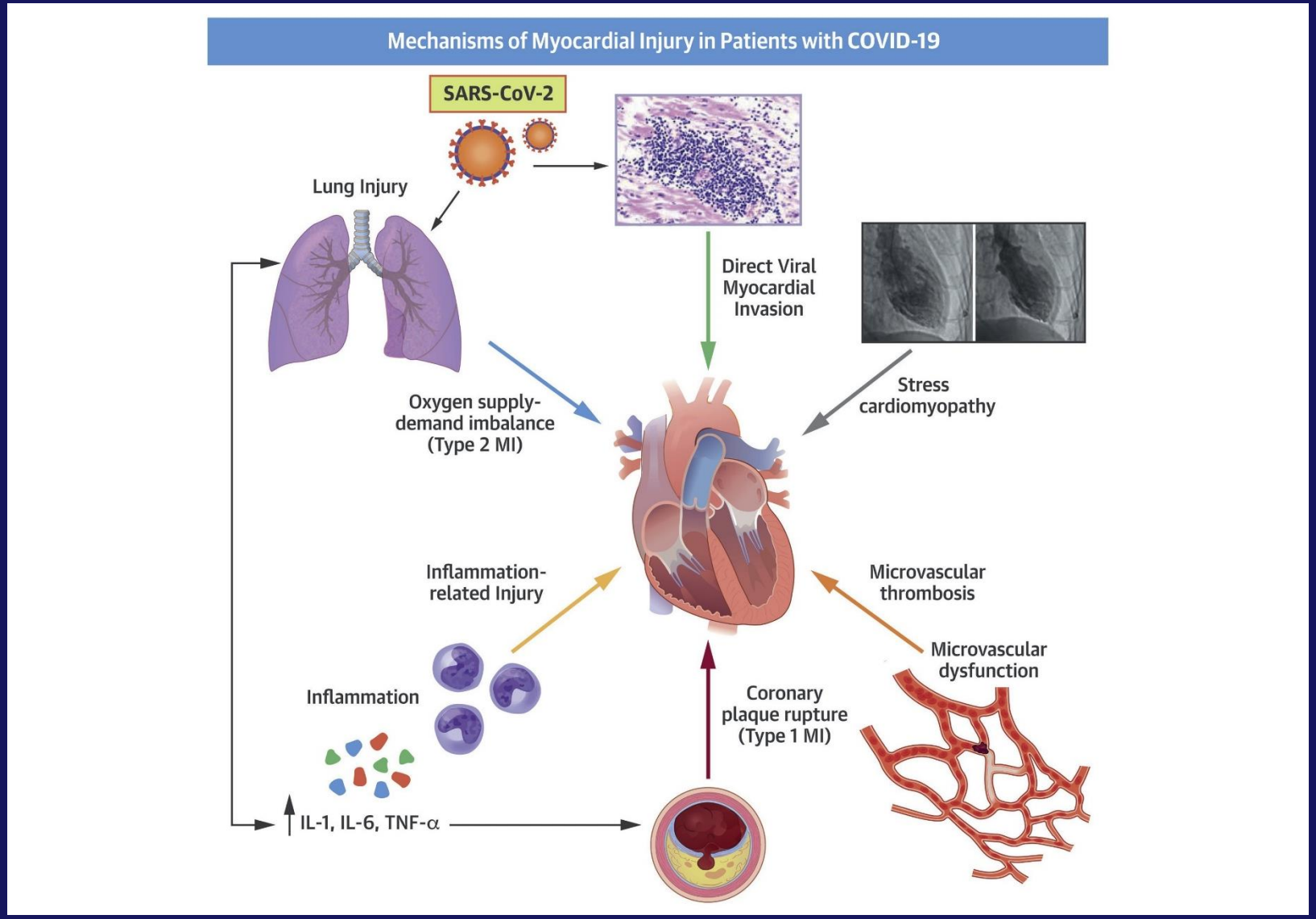
Giustino G et al. JACC. October 2020.

Thrombosis-related Disease in Children/Adolescents/Young Adults

- **Vaccine-induced Thrombotic Thrombocytopenia** (VITT with acute thrombosis and thrombocytopenia) and COVID Vaccines has **not been reported in children**.
- Extremely rare (3.6 per million after Astra Zeneca and 0.9 per million after J&J/Jansen).
- At risk window: 5-42 days post vaccination.
- Unusual affected sites like cerebral veins or splanchnic veins.
- Initial work-up CT or MRI venogram and CBC with platelet count. D-dimer.
- ST-elevation **myocardial infarction (STEMI)** due to acute coronary thrombosis **at presentation in pediatric COVID-19** without MIS-C but with LV dysfunction.
- Clot Prevention Outside the ICU in COVID patients with extended therapeutic-level prophylactic anticoagulation with rivaroxaban (Xarelto) with elevated D-dimer levels was not beneficial and carried more bleeding risk.

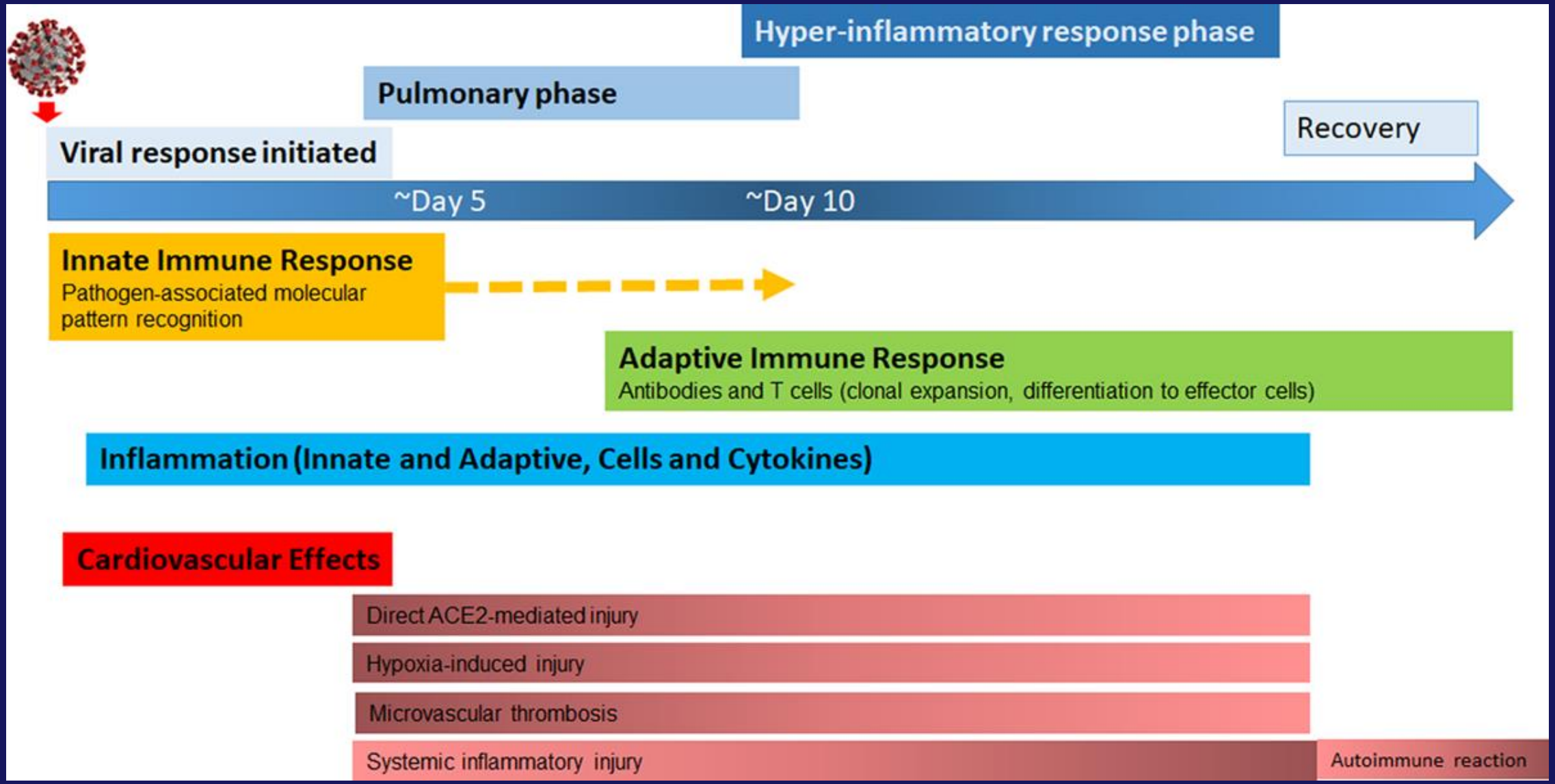
Barnes et al. JACC. April 21, 2021. ACC Cardiology, June 8, 2021
Hersson et al. Pediatrics May 2021.
Lopes et al. JACC. May 19, 2021.

Overview of the Mechanisms of Myocardial Injury in Patients with Coronavirus Disease 2019



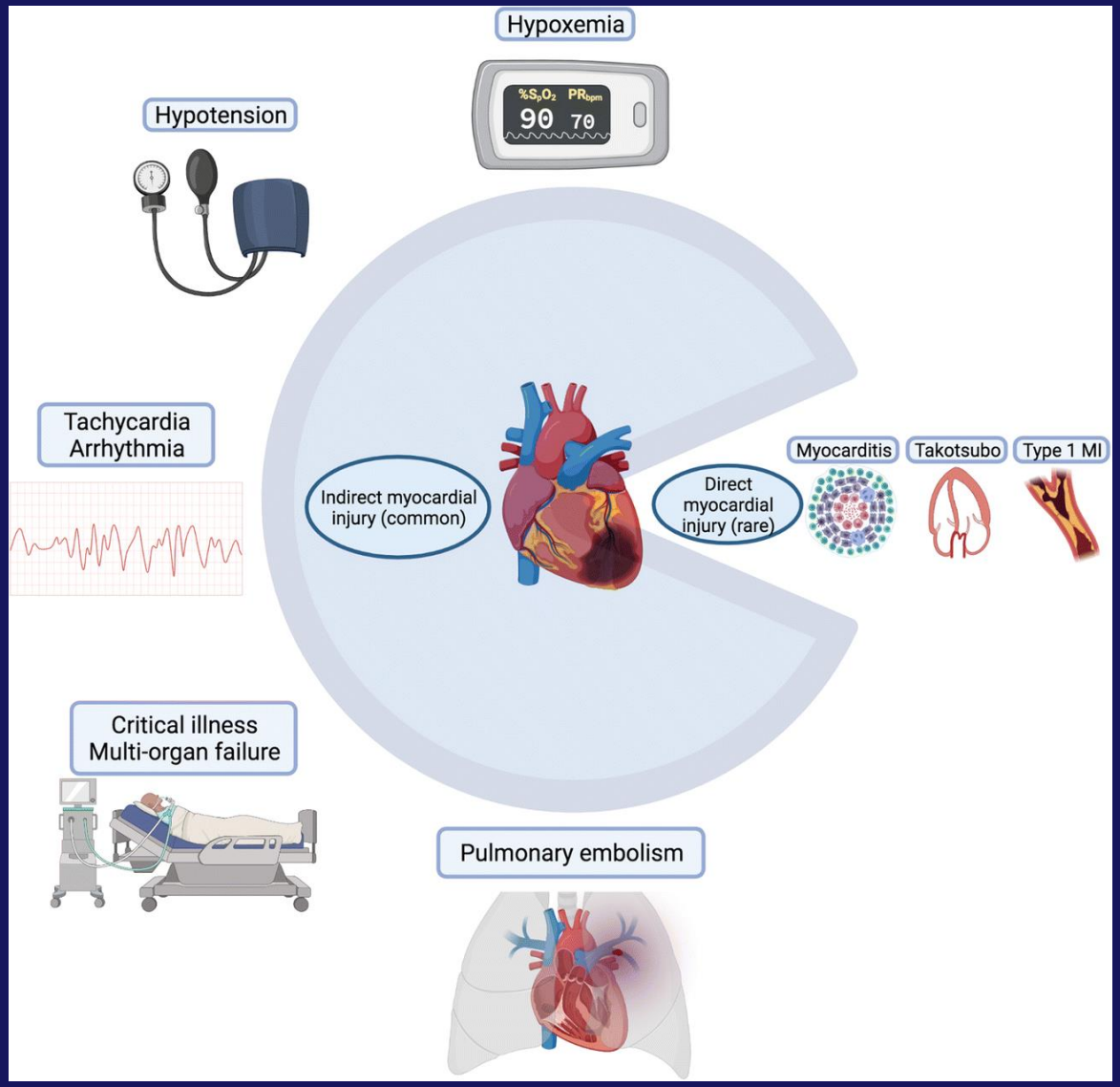
Giustino G et al. JACC. October 2020.

Approximate Time Course of Immune Response and Cardiovascular Effects



Chung M et al. Circ Research. April 15, 2021.

Symbolic Pie Chart Illustrating Common Causes of Indirect Myocardial Injury and More Rare Causes of Direct Myocardial Injury in COVID-19 Infection



Chilazi M et al. Coronary Heart Disease. May 13, 2021.

Arrhythmias and Cardiac Arrests: 13% of Pediatric Hospitalized Patients with COVID have Arrhythmias

- **COVID Prolongs the QT Interval Independent of Other Factors.** At Columbia-NYC.
- 2 and 5 days after admission the **QTc was >500 msec in 25%** of COVID+ patients compared with 10% of critically ill patients without COVID (P=.002).
- Increased QTc was **associated with elevated serum troponin** levels and is a predictor of myocyte viral damage.
- COVID **affects ion channels** leading to cardiac channelopathies, QT prolongation, and **arrhythmias** such as Torsade de pointes, polymorphic ventricular tachycardia, and ventricular fibrillation
- Meta-analysis of 12,713 COVID patients showed **QTc prolongation, ST-segment deviation, and other arrhythmias and were associated with a worse prognosis**.
- **A COVID-19-Positive Infant Presenting with Sudden Cardiac Arrest.**

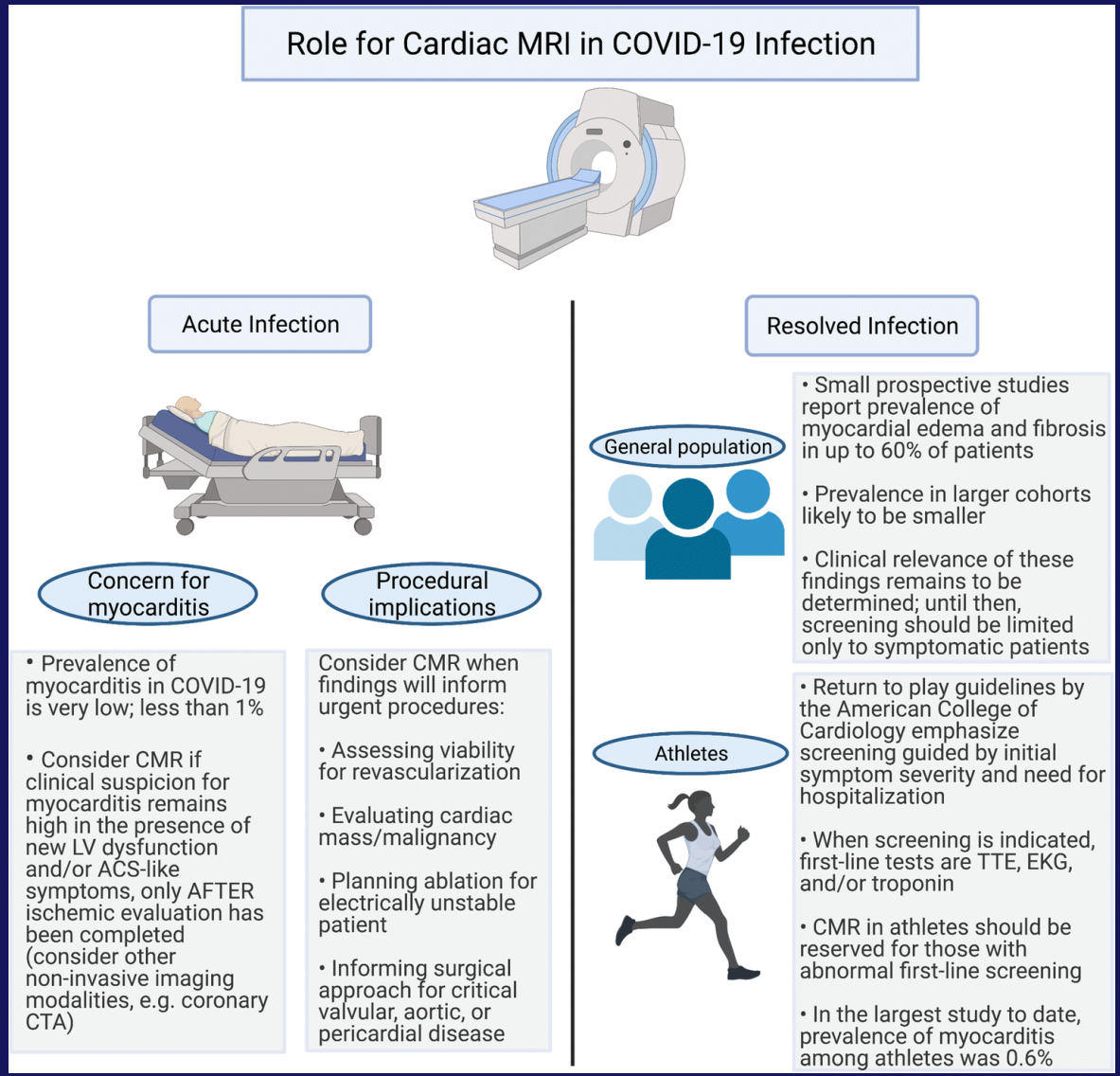
Rubin et al. JAMA Network Open April 23, 2021.
Garcia-Zamora et al. Pacing Clin Electrophysiol. April 23, 2021.
Pierre et al. Pediatr Emerg Care. May 1, 2021.

Arrhythmias and Cardiac Arrests

- **Overdose-associated Fatal US Cardiac Arrests Were Elevated 42.1% in 2020 during the COVID Pandemic,** especially in socioeconomically disadvantaged and racial/ethnic minority communities.
- **COVID-associated Arrhythmias and Sudden Cardiac Death: The Relationship of Large City Out-of-Hospital Cardiac Arrests (OHCA) and the Prevalence of COVID-19.** A >20% increase in OHCA in 2020 and 59% in April 2020, they increased >100% in cities with higher COVID incidences. A direct association between COVID and the frequency of OHCA in Europe and the US. Suggests OHCA is a direct consequence of COVID. An underestimate since most patients were pronounced dead without COVID testing.

Friedman et al. JAMA Psychiatry. May 26, 2021.
McVaney et al. EClinicalMedicine. April 7, 2021.

Review of the Role and Indications for Cardiac Magnetic Resonance (CMR) Imaging in Acute and Resolved Infection, Both in the General Population and More Specifically in Athletes



Chilazi M et al. Coronary Heart Disease. May 13, 2021.

COVID Cardiac Involvement Among Young Competitive Athletes Has a Low Prevalence and Low Short-term Risk of Clinical Events

- National Cohort (ORCCA Investigators at 42 Colleges with 19,378 athletes [3018 COVID+]).
- <1% had signs of possible, probably, or definite **myocarditis (21/3018, 0.7%)**.
- Those with myocarditis were more likely to have had moderate COVID and/or cardiopulmonary symptoms.
- There were no myocardial infarctions but there was **one cardiac arrest**.

Moulson et al. Circulation. April 17, 2021.

Consensus Care Recommendations

1. **Asymptomatic or mildly symptomatic** athletes fully recovered from COVID **do not require cardiac testing prior to returning to sport.**
2. Athletes with **moderate or worse symptoms, and/or cardiopulmonary symptoms**, cardiac evaluation inclusive of **ECG, troponin, echo, and CMR** (for myocarditis, inflammation, injury) should be considered prior to return to play.

Further understanding of COVID heart disease is essential as cardiac involvement could portend increased risk for short- and long-term adverse cardiovascular events.

Moulson et al. Circulation. April 17, 2021.

CDC says Vaccine Link to Heart Inflammation is Stronger than Previously Thought. Rare but Higher-Than-Expected

CDC is investigating 226 cases of myocarditis and pericarditis reported to its Vaccine Adverse Event Reporting System (VAERS) in late May.

- There were 789 reported cases.
- 573/789 were after the second dose, median time after symptoms was 3 days after the first dose and 2 days after the second dose, but symptoms started as far as 33 days after the first dose and 80 days after the second dose.
- Over half (475/789) were among those ≤30 years.
- **Only 226/475 have met the CDC working case definition of myocarditis or pericarditis but that does not mean these were caused by the vaccines.**
- Most of these **(81%) had a documented full recovery**.
- The rest had ongoing symptoms (41 with 15 still hospitalized and 3 in ICUs) or lack of follow-up.

CDC Reported Patients Characteristics

- **Males under** 30 may face heart problems after getting vaccinated.
- Myocarditis and Pericarditis share the same symptoms of fever, fatigue, dyspnea on exertion, and chest pain. The 475 reported had **chest pain, elevated cardiac enzymes, ST or T wave changes, dyspnea, and abnormal echocardiography/imaging**.
- Myocarditis following vaccination in younger teens and men in their early 20s. There were **79 cases of myocarditis/pericarditis in 16-17 yos after a second vaccine dose with the expected number being 19 cases**. 18-24 yos: 196 cases/8-83 expected.
- Treatment for myocarditis can be solved with **over-the-counter medication** (anti-inflammatory drugs such as ibuprofen, or **resolve itself**. More than 80% got better on their own. Some were given IVIG.

Multi-Center Children's Hospitals Myocarditis Experience

Similar to a report published in *Pediatrics* this past week describing 7 adolescent (14-19 yo) boys who developed **myocarditis several days after receiving their second dose of the Pfizer**/BioNTech COVID vaccine.

- All 7 boys fully **recovered rapidly**.
- The temporal association of these cases with vaccination warrant investigation as to causality.

The Causal Versus Coincidental Relationship Between the Vaccines and These Conditions in Adolescents Remains in Question and to be Determined

Cause and effect associations/coincidence are **challenging to determine**:

1. >300 million US vaccine doses given (130 million Americans fully vaccinated with either Pfizer or Moderna) and <300 reported cases of myocarditis/pericarditis.
2. Countless illnesses and events occur daily.
3. Myocarditis affects thousands of US people and >3 million worldwide annually, it is still rare compared to COVID vaccinations.
4. Most myocarditis is mild and un-diagnosed.
5. Severe cardiac issues, including myocarditis, have been found during and after COVID infections, even in young healthy athletes where 2.3% have myocarditis without noticeable symptoms.
6. Myocarditis can be caused by any type of virus, is more common in spring and summer (now), and normally affects this age group and sex.

COVID Vaccination Must Continue

- Surgeon General, FDA, CDC, AAP, AHA Strongly Conclude Officially: **Heart conditions due to COVID infection much riskier than heart condition after vaccines**.
- • AHA **recommends vaccination specifically "including people with cardiovascular risk factors such as high blood pressure, obesity, and type 2 diabetes, those with heart disease, and heart attack and stroke survivors, because they are at much greater risk of an adverse outcome from COVID than they are from the vaccine**."
- • June 18, 2021 CDC ACIP emergency meeting will review.

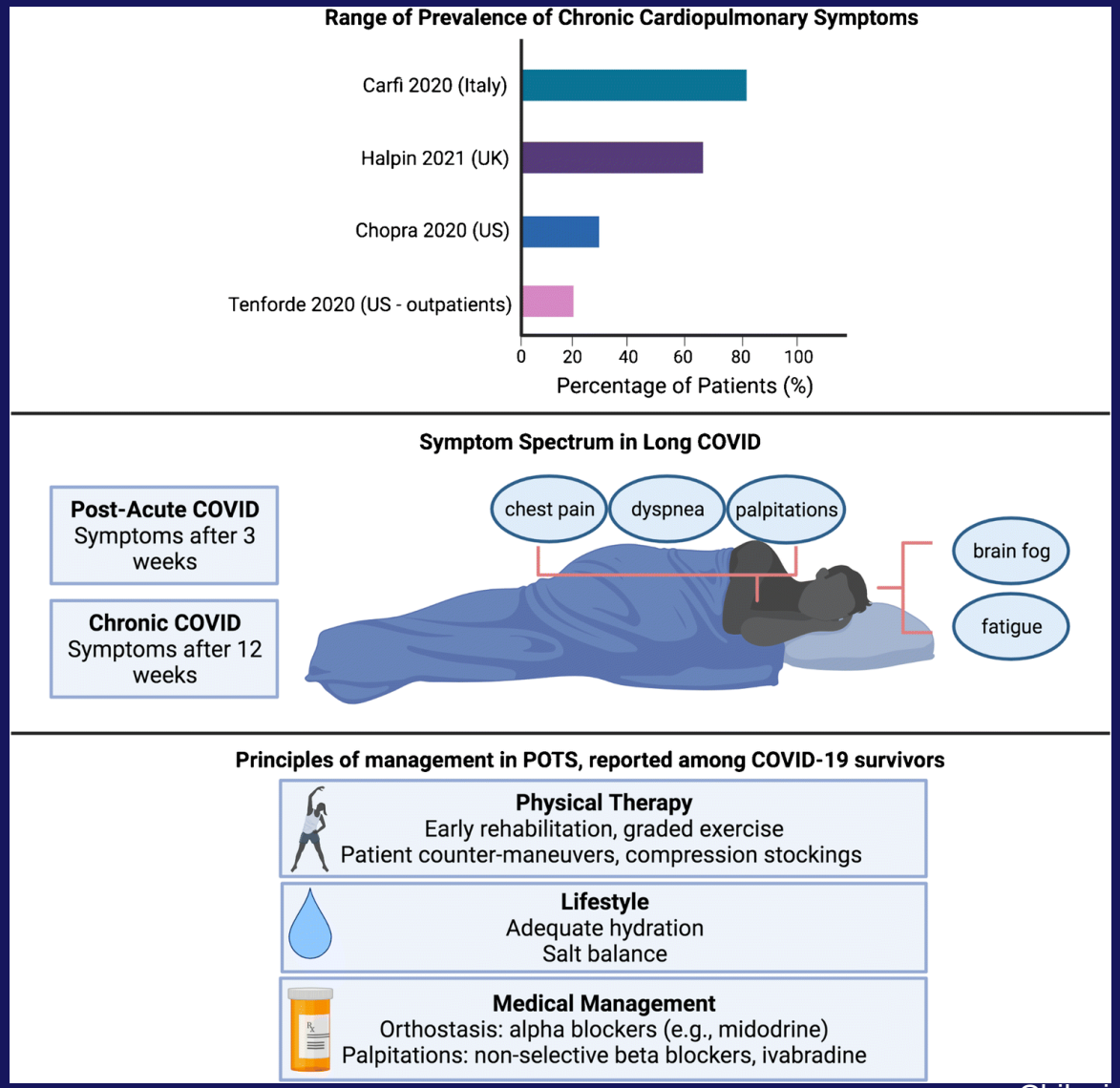
Spencer C. June 14, 2021. Lee BY. June 14, 2021. Shimabukuro T, CDC Immunization Safety Office. June 10, 2021. Marshall M, et al. Pediatrics. June 2021. O'Leary S and Maldonato Y. Pediatrics June 2021. Cohen E. CNN. June 13, 2021. Jenco M. AAP News. June 10, 2021. Korioth T. AAP News. June 11, 2021.

Myocarditis with mRNA Vaccines – March - May 2021

- **Pfizer/Moderna mRNA Vaccine Associated Mild Myocarditis** (Heart Inflammation) in Male Adolescent/Young Adults Within 4 Day After the Second Dose in the US and Europe.
- CDC Advisory Committee on Immunization Practices (ACIP) and the COVID-19 Vaccine Safety Technical Work Group said **the figures are the same as expected baseline rates of myocarditis** (10-20 cases per 100K population after reviewing >200 million vaccine doses) and there is **no evidence that the vaccines caused myocarditis**. Hypotheses include that the **vaccines set off an immune response that results in the production of anti-heart antibodies where the vaccine antibodies designed to target the COVID virus also indirectly bind to and injure heart muscle cells in the process**. Many missed or never diagnosed so this information has been provided to clinicians to enhance early recognition and appropriate management. Report cases to VAERS (Vaccine Adverse Event Reporting System).
- Israel's Health Ministry and the US Department of Defense are also examining 27 cases of heart inflammation in 5.4 million people who had received the first dose of Pfizer's vaccine and 121 cases after the second dose of 5 million recipients. Most cases were hospitalized for up to 4 days only and 95% had a "mild" illness. More common in 16-19 yos. June 1 recommendations were to vaccinate 12 and older to reduce the risks of severe COVID-19 or long-haul symptoms.

CDC ACIP Meeting-COVID-19 VaST Work Group Technical Report – May 17, 2021. Cohen E. CNN Health. June 9, 2021.

Review of the Prevalence of Long COVID, Definitions and Symptomatic Manifestations, and Current Principles of Management for Potential COVID/Postural Orthostatic Tachycardia Syndrome Overlap



Chilazi M et al. Coronary Heart Disease. May 13, 2021.