COVID-19 in Children: The Present, The Future and The "Long Haul"

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Pediatric Health Network
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A few notes about today's Grand Rounds

- All lines are muted throughout the presentation.
- Please use the Q&A to ask questions or make comments.
- We will be recording the session.
- Today's recording and materials will be posted to the PHN website 3 business days following the presentation:

https://pediatrichealthnetwork.org/

Today's Speaker

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Disclosures: None

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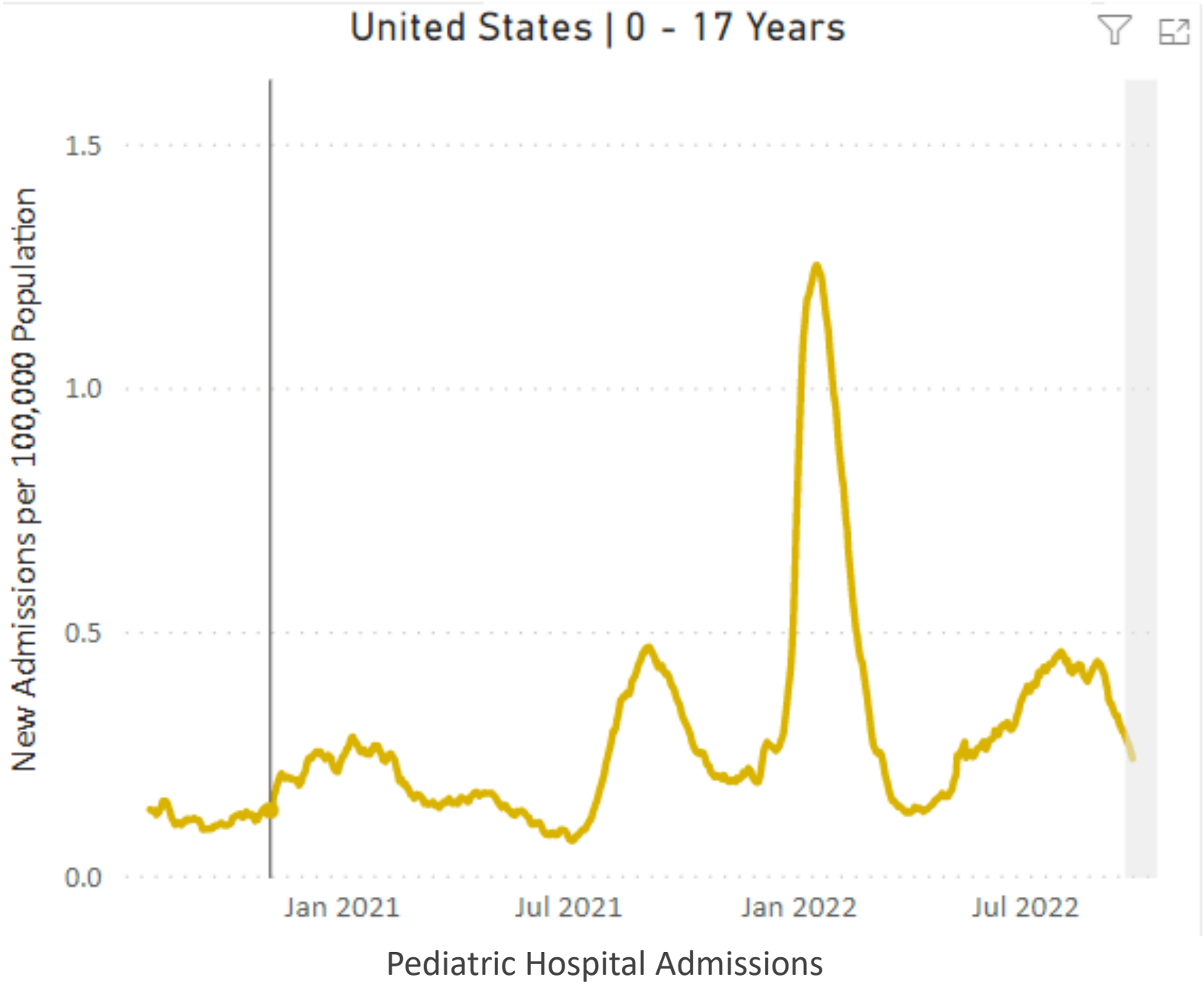
Learning Objectives

- Review **current epidemiology** and trends in COVID in the pediatric population
- Provide **overview of Post-Acute Sequelae in COVID (PASC)/aka "long COVID"** in children and adolescents, including epidemiology, proposed pathophysiology and most common presentations
- Give general pediatricians **tools** for monitoring, early evaluation of PASC and when to refer for additional evaluation
- Overview of the **Children's National Post COVID Program Clinic** for children and adolescents with PASC/long COVID and information on the referral process
- Summarize **current COVID vaccine recommendations** for pediatric patients

Trends in COVID-19 Disease in Children, September 2022



Pediatric Hospital Admissions

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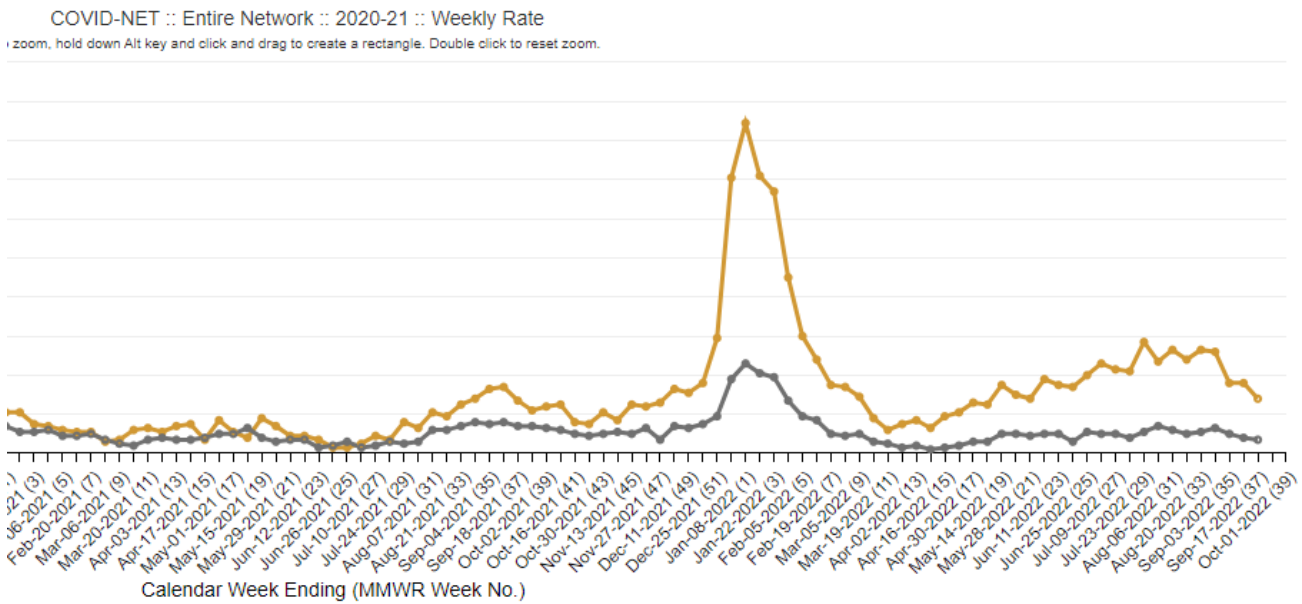
Infants and children <18 years of age:
18.4% of all COVID-19 cases in the U.S.
(~15 million cases) and 1,760 deaths



United States | 0 - 17 Years

159,232

Total Admissions

Aug 01, 2020 - Sep 25, 2022

175

Current 7-Day Average

Sep 19, 2022 - Sep 25, 2022

216

Prior 7-Day Average

Sep 12, 2022 - Sep 18, 2022

914

Peak 7-Day Average

Jan 10, 2022 - Jan 16, 2022

-18.8%

Percent change from prior 7-day avg. of Sep 12, 2022 - Sep 18, 2022

-80.8%

Percent change from peak 7-day avg. of Jan 10, 2022 - Jan 16, 2022

Multisystem Inflammatory Syndrome in Children

TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*	TOTAL MIS-C DEATHS MEETING CASE DEFINITION
8,862	72

*Additional patients are under investigation. After review of additional clinical data, patients may be excluded if there are alternative diagnoses that explained their illness.

[CDC COVID Data Tracker: Hospital Admissions]

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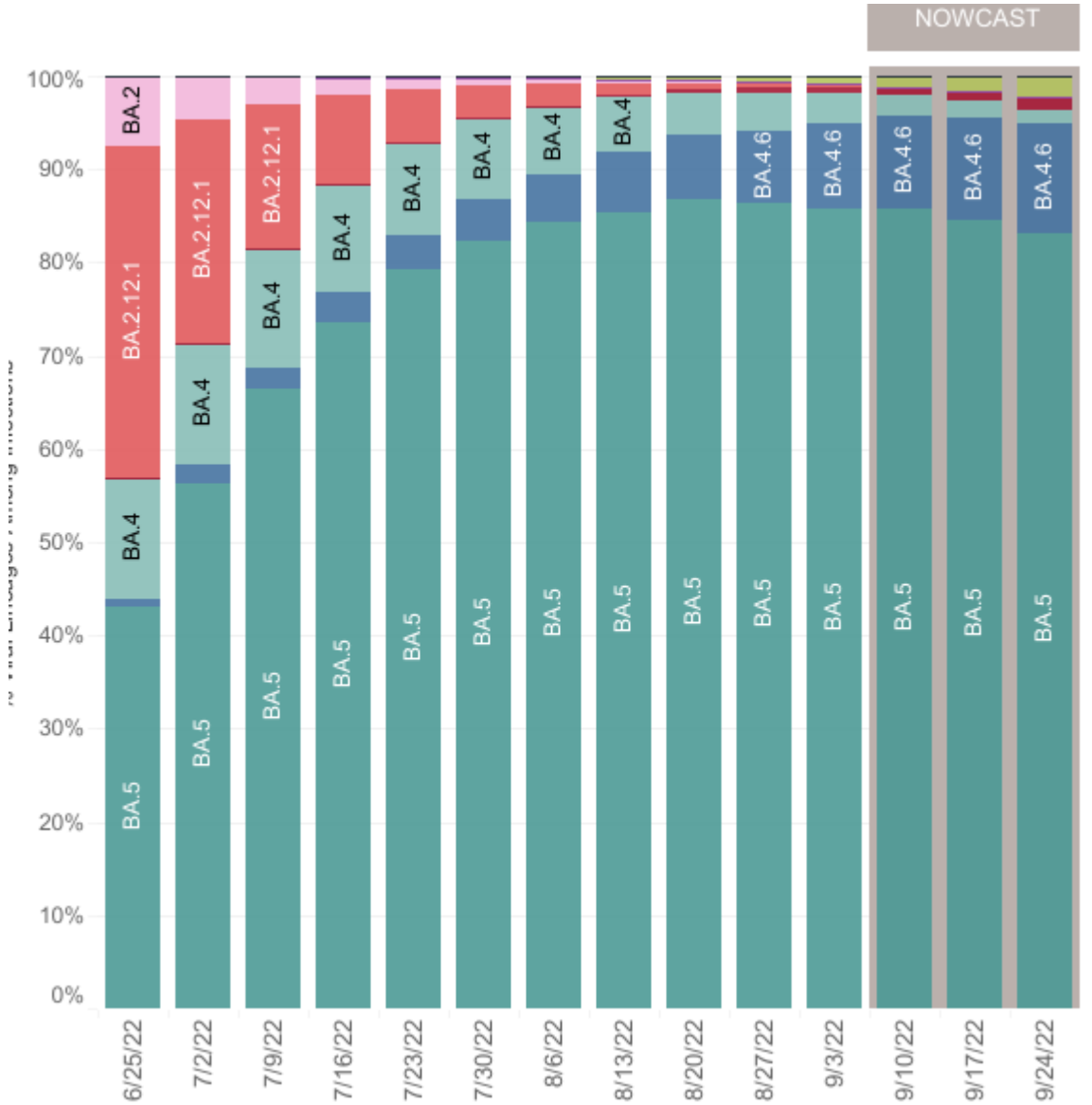
https://covid.cdc.gov/covid-data-tracker/#demographics – as of 28 Sept 2022

Variant Proportions

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	83.1%	81.3-84.7%
	BA.4.6	VOC	11.9%	10.6-13.4%
	BF.7	VOC	2.3%	1.7-3.0%
	BA.4	VOC	1.4%	1.3-1.5%
	BA.2.75	VOC	1.4%	0.9-2.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.2	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%



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Pediatric Post Acute Sequelae of COVID-19/ Long COVID

Definition of Post COVID Conditions

WHO Definition

- A **Post COVID-19 condition** is:
- Symptoms lasting for at least 2 months
- Starting or continuing 12 weeks from the onset of COVID-19
  - **May fluctuate or relapse over time**
- Impact on everyday functioning
- History of probable or confirmed SARS-CoV-2 infection
- cannot be explained by an alternative diagnosis.

Stephenson et al. Arch Dis Child. 2022

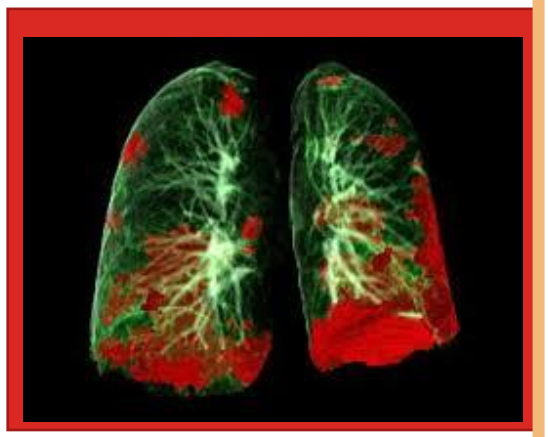
CDC Definition

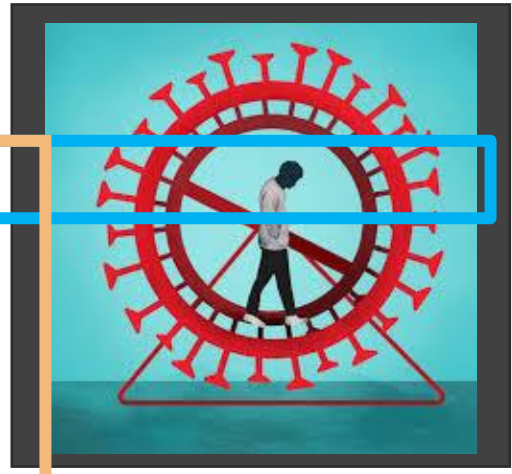
- New, returning or ongoing health problems
- Occurring > 4 weeks after SARS-CoV-2 infection

CDC.gov

Kompaniyets et al. MMWR. 2022.

Spectrum of Post-COVID Conditions





Post-Acute Persistent Symptoms

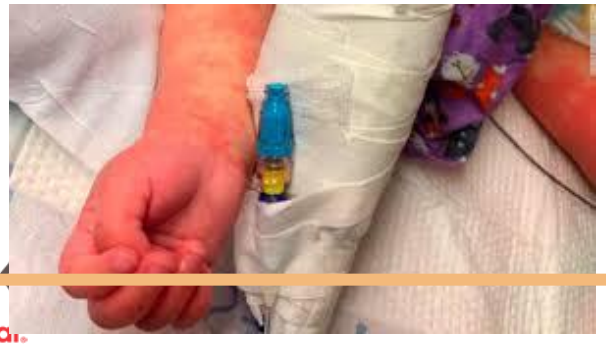
New-Onset Late Sequelae

Persistent and New Chronic Symptoms

4-12 weeks

>12 weeks

MIS-C



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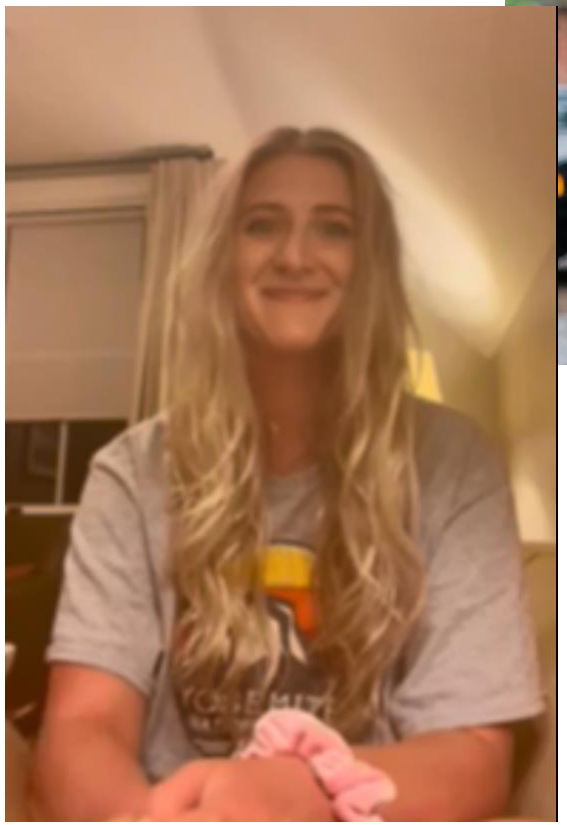
Epidemiology

Prevalence of Pediatric PASC

- Early incidence estimates broad
  - 4-66% of children with COVID
- Lopez Leon meta-analysis, 2022
  - 21 studies, 80,000 children
  - ~**25%** incidence at 4 weeks
- Funk et al (ED based), 2022
  - 5-10% SARS-CoV-2 infected with PASC symptoms compared to 3-5% control
  - Differential: **2-5%**
- Rao et al, 2022 (EHR cohort)
  - **3.7%** differential incidence



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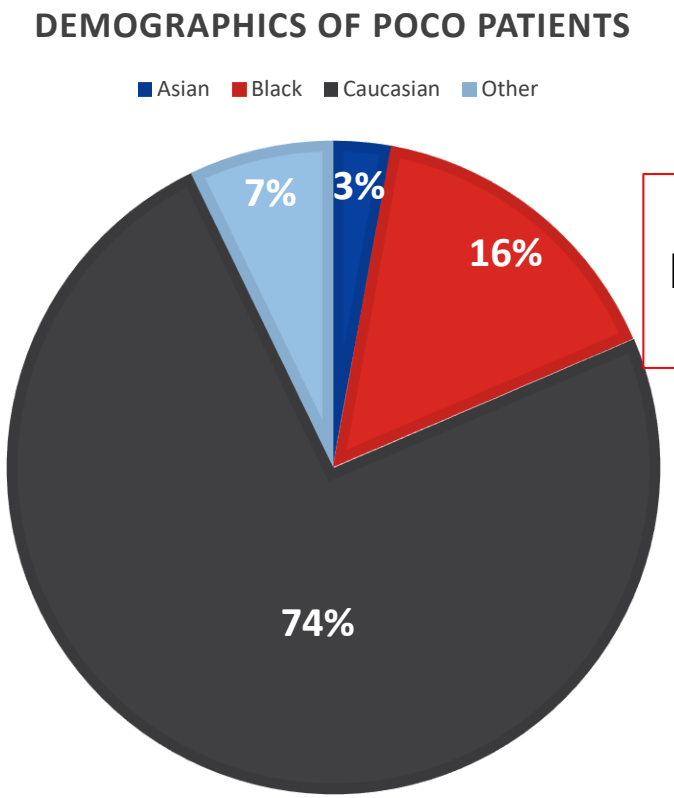
Post COVID Program Clinic by the numbers

- **103 new patients** seen as of 9/14/22
  - 250+ referrals/inquiries
  - 6-10 new referrals per week
  - Booking into 2023
- Average age: 12 years (range 2-20 years)
- Female > Male (55%)
- Most patients from DMV, but also patients from FL, TX, NM, NC, CA, DE, OH
- Ave days from disease onset= 219
  - Range 34-714
- Average number of symptoms per patient = 10
  - Range 2-25

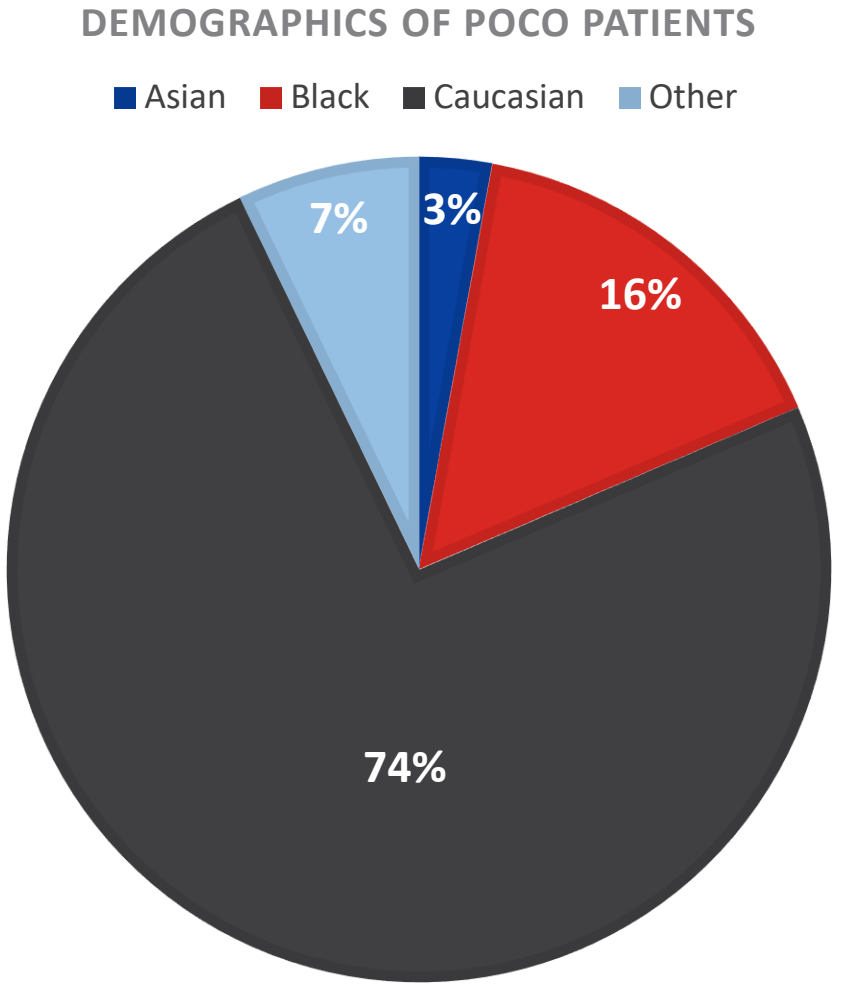


16% Hispanic/Latinx (n=11)

Unpublished data

A note about health care disparities…

- Disproportionately high prevalence of Caucasian patients presenting to clinic
- Anecdotally reported by other PASC clinics (pediatric and adult) in the region/nationally
- Similar to what has been seen with ME/CFS historically



16% Hispanic/Latinx
(n=11)

Unpublished data

Risk Factors

More severe acute COVID-19

- Hospitalized **9.8%** (7.4,13.0) vs **4.6%** (3.6,5.8) in non-hospitalized children
- aOR **2.67 (1.63-4.38)**

Greater number of initial symptoms (>4)

- aOR **2.35** (1.28-4.31)

Age > 14 years

Female

History of allergic or chronic disease

Funk. JAMA. 2022.

Osmanov. Eur Respir J. 2021.

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From adult studies:

- Female
- Comorbidities (mental health, obesity chronic illness, etc)
- Su et al (Cell): Type 2 DM, Higher viral load, autoantibodies and prior EBV infection

Su Y et al. Cell. Jan 2022

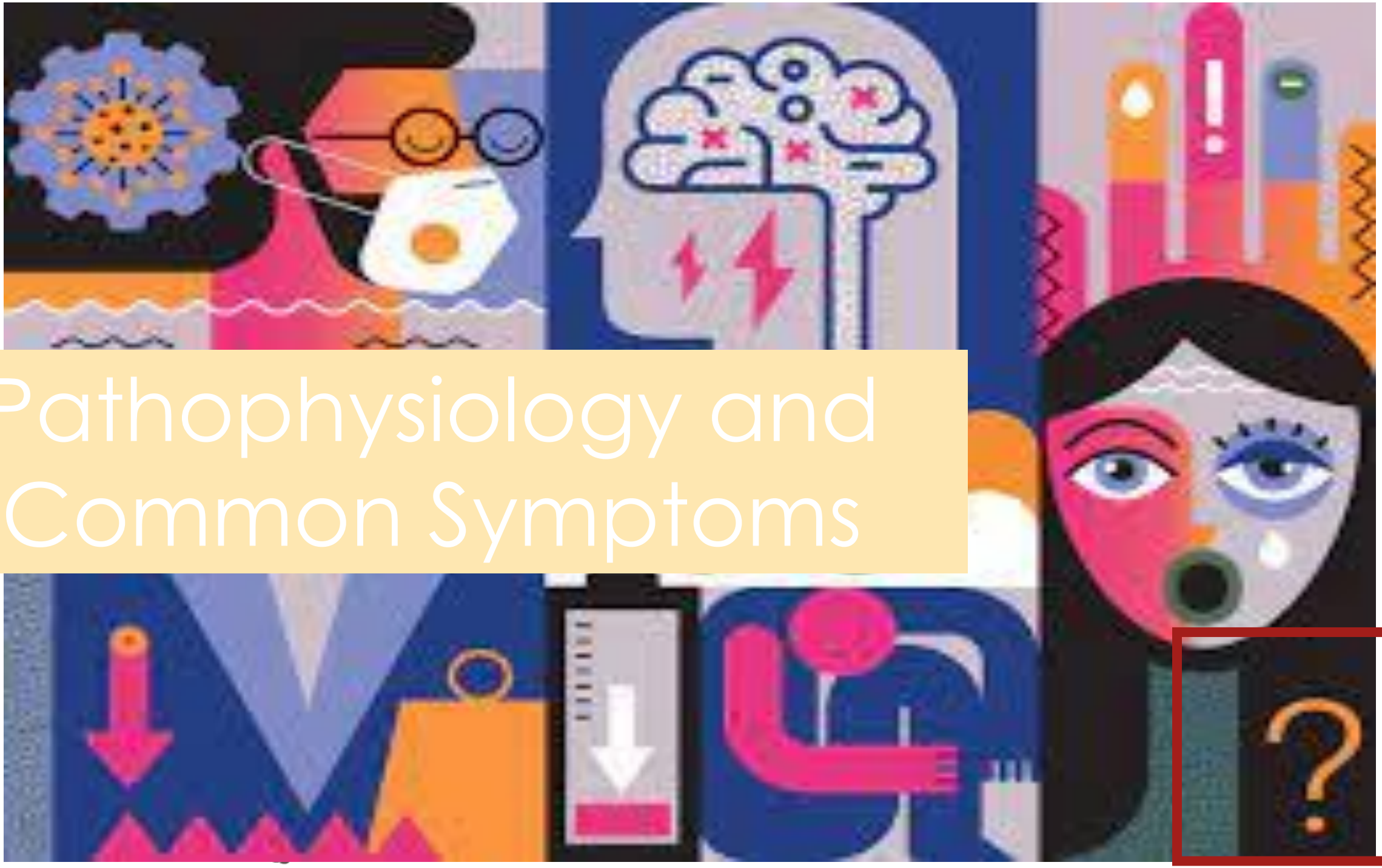
Antonelli et al. Lancet. Jan 2022

Al-Aly. Nature. May 2022.

Preventative Factors

Vaccination appears to be (somewhat) protective

- UK Study (Jan 2022): 50% reduction in risk of PASC
- VA Study (May 2022): 15% reduction in risk of PASC
- Meta-analysis (Notarte et al, eClinical Medicine 2022)
  - **Mixed results; inconclusive**



Pathophysiology and Common Symptoms

Long COVID Kids Survey

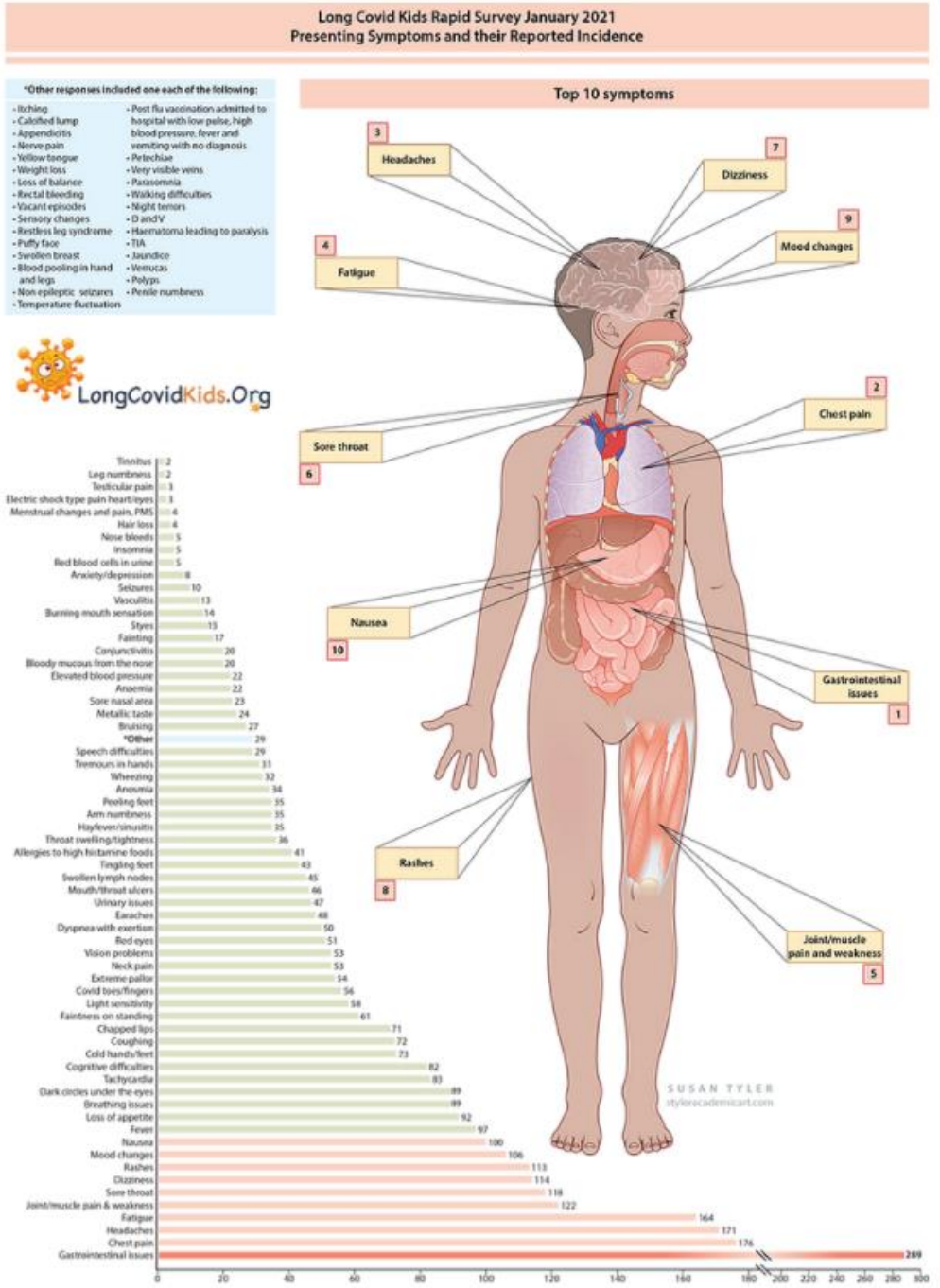
Survey of 510 families of children who were diagnosed with COVID-19 between Jan 2020-Jan 2021

Mean symptomatic period of 8.2 months (SD 3.9)

- 25% with persistent acute symptoms
- 49% with initial recovery and then later symptom onset
- 95% reported 4 or more symptoms

Top reported symptoms

- **Fatigue (87%)**
- **Headache (78%)**
- **Abdominal pain (76%)**
- **Muscle/joint pain (60%)**



Buonsenso, D. et al. Clinical Characteristics, Activity Levels and Mental Health Problems in Children with Long COVID: A Survey of 510 Children. *Preprints* **2021**,

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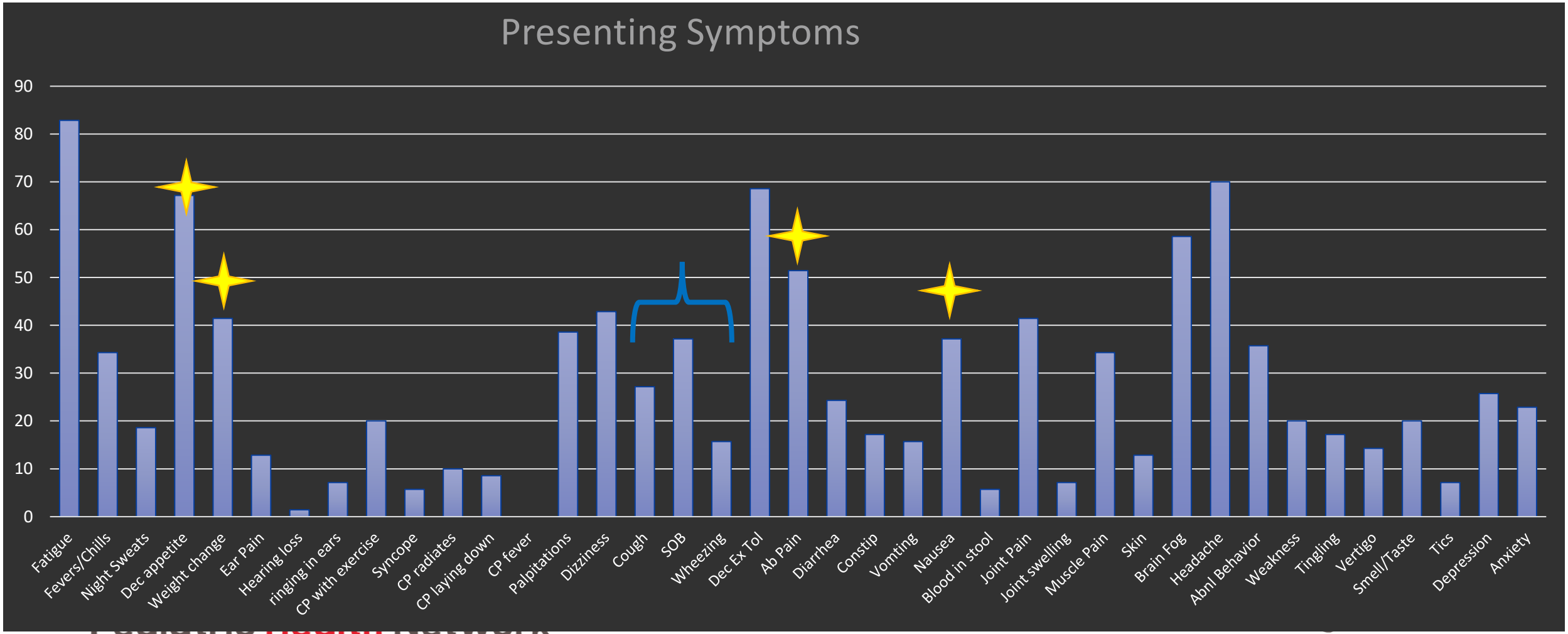
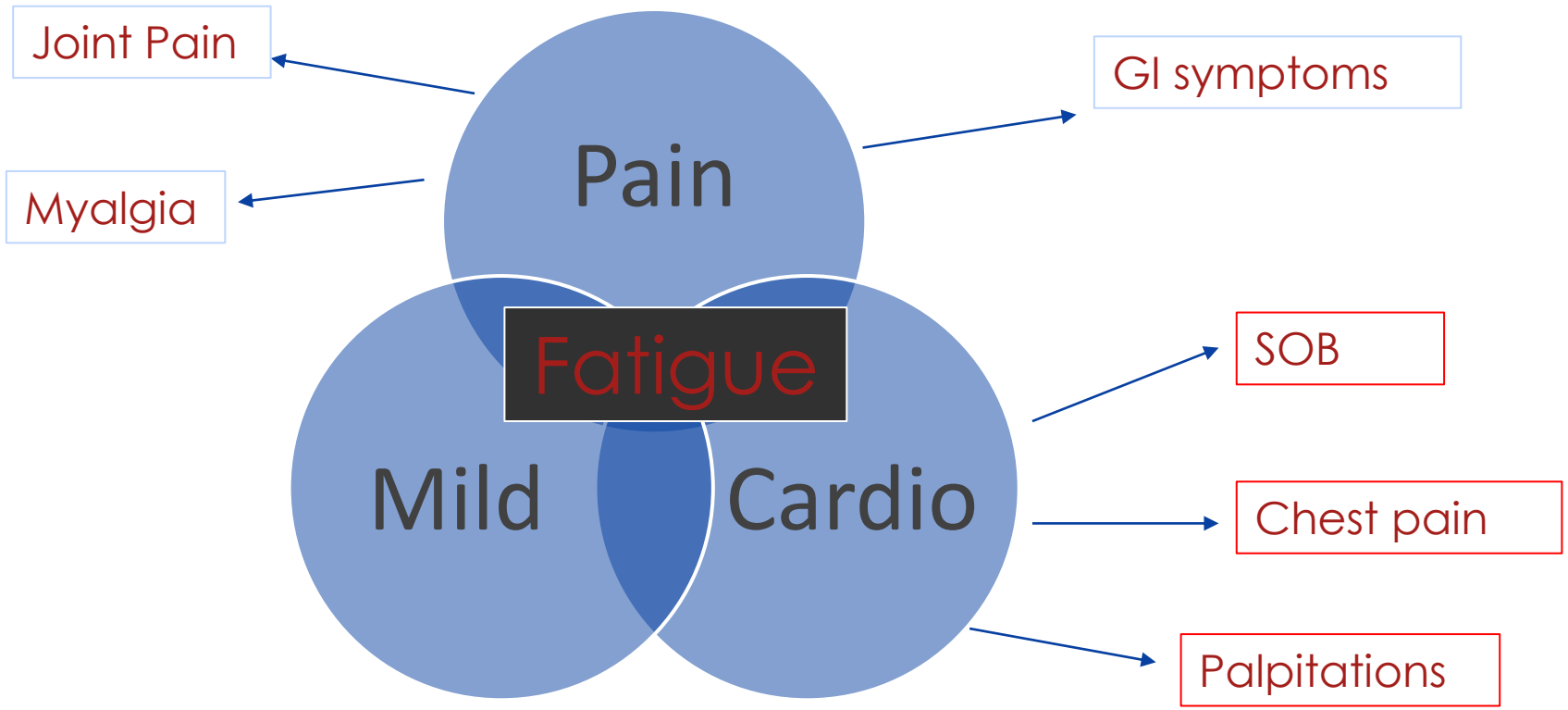
Presenting Symptoms (at intake)



Unpublished data

Heterogeneity of Long COVID



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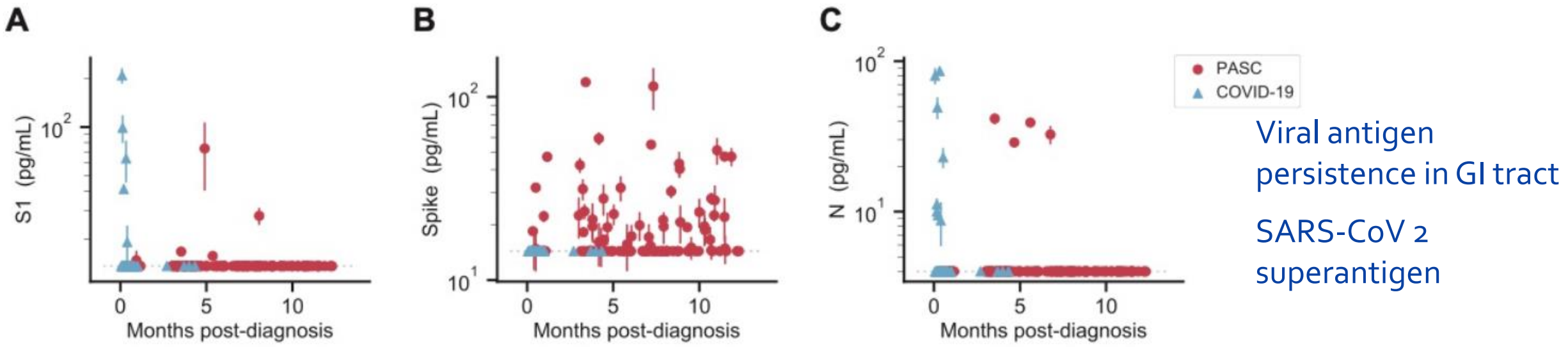
Kenny et al. Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms. OFID. Mar 2022.

Viral Antigen Persistence



S1

Spike

N protein

Viral antigen persistence in GI tract

SARS-CoV 2 superantigen

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Swank et al 2022

Endovascular Dysfunction and Microclots

Inflammatory microthromboses

- Labs in South Africa, Germany and UK (US pending)
- Definitive testing limited to research setting

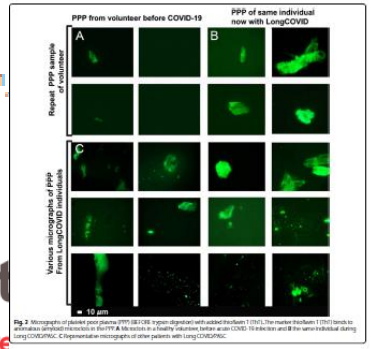
Pretorius et al. Cardiovasc Diabetol (2021) 20:172
https://doi.org/10.1186/s12933-021-01359-7

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin

Etheresia Pretorius[1*], Maré Vlok[2], Chantelle Venter[1], Johannes A. Bezuidenhout[1], Janami Steenkamp[1,4] and Douglas B. Kell[1,5,6*]



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Endovascular dysfunction/endotheliopathy

- Can study with current clinically available labs

Received: 8 June 2021 | Accepted: 9 August 2021
DOI: 10.1111/jth.15490

jth

BRIEF REPORT

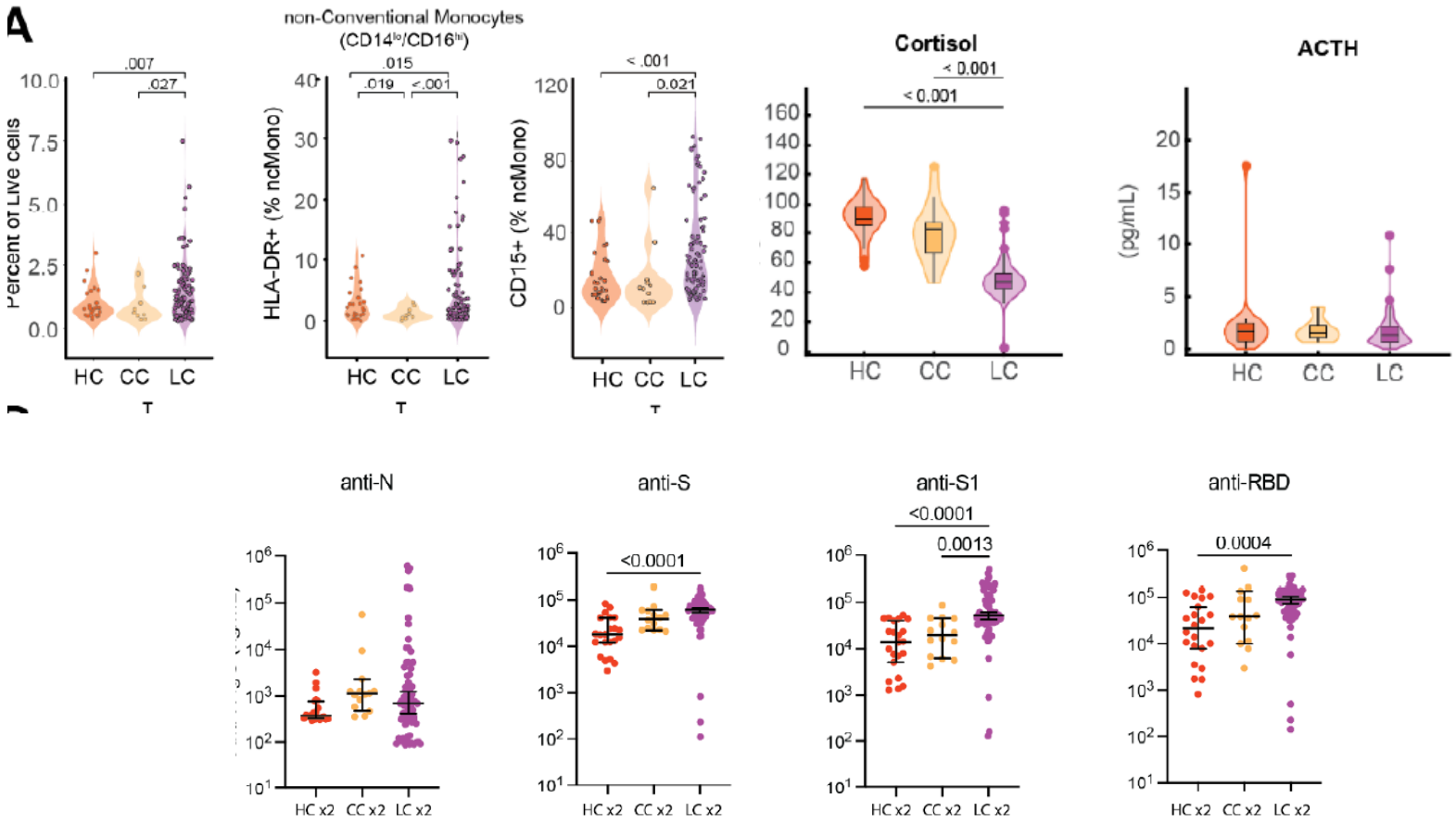
Persistent endotheliopathy in the pathogenesis of long COVID syndrome

Helen Fogarty[1] | Liam Townsend[2,3] | Hannah Morrin[1] | Azaz Ahmad[1] | Claire Comerford[1] | Ellie Karampini[1] | Hanna Englert[4] | Mary Byrne[5] | Colm Bergin[2,3] | Jamie M. O'Sullivan[1] | Ignacio Martin-Loeches[6] | Parthiban Nadarajan[7] | Ciaran Bannan[2] | Patrick W. Mallon[8,9] | Gerard F. Curley[10] | Roger J. S. Preston[1,11] | Aisling M. Rehill[1] | Dennis McGonagle[12,13] | Cliona Ni Cheallaigh[2,3] | Ross I. Baker[14,15] | Thomas Renné[4,16] | Soracha E. Ward[1] | James S. O'Donnell[1,5,11,15] | the Irish COVID-19 Vasculopathy Study (iCVS) investigators

Immune Dysregulation, Autoimmunity and Inflammatory Dysregulation

Klein, Putrino and Iwasaki-
Immune Profiling of Long COVID

- **Low cortisol**
- **Increased circulation of monocytes**
- **Increased anti-spike protein antibodies**



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Dysautonomia and Small Fiber Neuropathy

CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID

Anne Louise Oaklander, MD, PhD, Alexander J. Mills, BS, Mary Kelley, DO, Lisa S. Toran, MD, Bryan Smith, MD, Marinos C. Dalakas, MD,* and Avindra Nath, MD*

Correspondence
Dr. Oaklander
aloaklander@mgh.harvard.edu

Neurol Neuroimmunol Neuroinflamm 2022;9:e1146. doi:10.1212/NXI.0000000000001146

Abstract

Background and Objectives

Recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appears exponential, leaving a tail of patients reporting various long COVID symptoms including unexplained fatigue/exertional intolerance and dysautonomic and sensory concerns. Indirect evidence links long COVID to incident polyneuropathy affecting the small-fiber (sensory/autonomic) axons.

Results

Among 17 patients (mean age 43.3 years, 69% female, 94% Caucasian, and 19% Latino), 59% had ≥1 test interpretation confirming neuropathy. These included 63% (10/16) of skin biopsies, 17% (2/12) of electrodiagnostic tests and 50% (4/8) of autonomic function tests. One patient was diagnosed with critical illness axonal neuropathy and another with multifocal demyelinating neuropathy 3 weeks after mild COVID, and ≥10 received small-fiber neuropathy diagnoses. Longitudinal improvement averaged 52%, although none reported complete resolution. For treatment, 65% (11/17) received immunotherapies (corticosteroids and/or IV immunoglobulins).

Discussion

Among evaluated patients with long COVID, prolonged, often disabling, small-fiber neuropathy after mild SARS-CoV-2 was most common, beginning within 1 month of COVID-19 onset. Various evidence suggested infection-triggered immune dysregulation as a common mechanism.

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Evaluation and Management

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CDC Centers for Disease Control and Preve
CDC 24/7: Saving Lives, Protecting People™

COVID-19

PEDIATRIC ANNALS

aapm&r

EDUCATION QUALITY & PRACTICE ADVOCACY

Long COVID Guidance Statements

- Cardiovascular Complications
  - Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cardiovascular Complications in Patients with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
- Breathing Discomfort
  - Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Breathing Discomfort and Respiratory Sequelae in Patients with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
    - Access all of the tables from the breathing discomfort guidance statement, which include the recommendations, health equity considerations/examples, rehabilitation approaches and more.
- Cognitive Symptoms
  - Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cognitive Symptoms in Patients with Post-Acute Sequelae of SARS-CoV-2 infection (PASC)
    - Access all of the tables (also available in PowerPoint slides) from the cognitive symptoms guidance statement, which include the

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Physical Evaluation: Labs

Initial (4-12 weeks post-COVID)

- CBC with differential +/- iron studies
- CMP
- CRP, ESR, ferritin
- TSH and Free T4
- Vitamin D +/- Vitamin B12
- EBV Antibody Panel
- SARS-CoV-2 Nucleocapsid (N) antibody

Expanded (symptoms > 12 weeks or progressive, organ specific)

- ANA, RF, other rheumatological markers
- D-dimer, fibrinogen
- Troponin
- BNP

Evaluation: Expanded (symptom based)

*CNH Pulmonary Medicine Criteria for CXR/PFT for Post-COVID Conditions:

- Any **respiratory symptoms** during acute COVID
- Any patients who were **hospitalized** for COVID
- **Persistent respiratory symptoms** (even mild) following positive test

** CNH Cardiology Criteria for ECG/Echocardiogram and Referral for non-MIS-C Post-COVID Conditions:

- **Admitted** for COVID
- Palpitations, syncope, dizziness
- Chest pain
  - With **exercise**
  - **Radiates** to back, jaw, L arm, shoulder
  - Increased when **laying down**

CXR*

Pulmonary Function Tests*

ECG **

Echocardiogram**

MRI Brain

Neurocognitive testing

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Evaluation: Assessment Tools

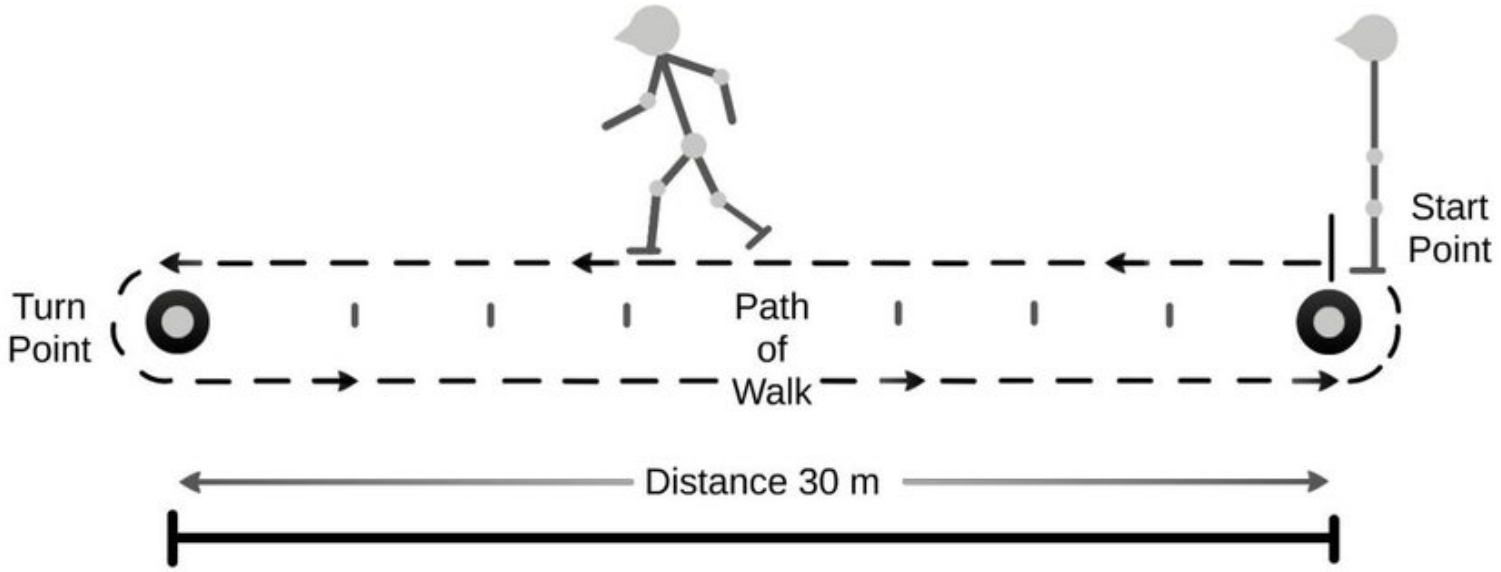
Aerobic Capacity/Endurance testing

- 6-minute walk test

Dysautonomia testing

- Tilt-table testing
- Orthostatic HR assessment

PFTs as needed (separately)



Cardiac evaluation (EKG, Echo, Stress Test, MRI) as needed separately

Psychological Evaluation: Assessment Tools

PROMIS (Patient Reported Outcomes Management Information System)

- Parent Proxy: Children 5-17 years
- Self-Report: Children 8-17 years, Adults 18+

Generates *t*-scores with clinical cut points

Endovascular Dysfunction Evaluation

Suggested laboratory evaluation:

- CBC, retic, LDH, smear review
- PT/PTT, fibrinogen, thrombin time
- BMP and LFT
- **Platelet mapping TEG**
- VWD Diagnostic Evaluation
- **Fibrinolysis Comprehensive Panel** [Alpha-2-Antiplasmin, D-Dimer, Quantitative, Euglobulin Clot Lysis Time, Fibrinogen Degradation Products (FDP), Plasminogen Activator Inhibitor (PAI-1) Ag, Plasminogen Activity, Tissue Plasminogen Activator (TPA), EIA, Fibrin Monomer]
- VW multimer analysis
- ADAMTS-13
- **C3, C4, CH50 and SC5B-9 (MAC complex)**

- For patients with severe fatigue, PEM, palpitations or dyspnea

Current Management Approaches

Gradual, individualized, step-wise, goal directed physical rehabilitation*

- Focus on energy conservation and "the 4 Ps"
  - **Avoid Post Exertional Symptom Exacerbation**
  - **Pacing, Prioritizing, Positioning and Planning**
  - **POTS model/Levine protocol**

Similar gradual titration up to mental/academic activity

Therapy for coping strategies, CBT in some instances

Olfactory Re-training

Symptomatic management (Neuro, GI)

Low risk vitamins and supplements with some suggestion of benefit in the literature

- Magnesium, B vitamin complex, Vitamin D, Coenzyme Q10

Anticoagulation (in select patients)

Specific Management Strategies: Fatigue

- Start an individualized and structured, titrated return to activity program*
- Discuss energy conservation strategies.
- Encourage a healthy diet and hydration.
- Treat, in collaboration with appropriate specialists, underlying medical conditions.

Specific Management Strategies: Fatigue

- Discuss energy conservation strategies.
  - ***P***acing → avoid a push and crash cycle
  - ***P***rioritizing → decide which activities need to get done on specific days and which activities can be postponed
  - ***P***ositioning → modifying activities to make them easier to perform
  - ***P***lanning → plan the day or week to avoid overexertion and to recognize energy windows

Specific Management Strategies: Brain Fog

Graded return to cognitive activity

- Scheduled rest periods
- Reduced expectations re: assignment completion/exams
- Reduced homework assignments

Consider accommodations for where/when/how work is completed

- Use of audio books
- Complete exams in a quiet/low light room
- Extended time for assignments

Stage	Description	Activity level	Criteria to move to next stage
0	No return, at home	Day 1: maintain low-level cognitive and physical activity. No prolonged concentration. Cognitive readiness challenge: as symptoms improve, try reading or math challenge task for 10–30 min; assess for symptom increase	To move to stage 1: student can sustain concentration for 30 min before significant symptom exacerbation and; symptoms reduce or disappear with cognitive rest breaks
1	Return to school, partial days (1–3 h)	Attend one to three classes, with interspersed rest breaks as needed. Minimal expectations for productivity. No tests or homework	To move to stage 2: student symptom status improving, able to tolerate 4–5 h of activity with two to three cognitive rest breaks built into school day
2	Full day, maximal supports required throughout the day	Attend most classes, with two to three rest breaks (20–30 min), no tests. Minimal homework (<60 min). Minimal-to-moderate expectations for productivity	To move to stage 3: number and severity of symptoms improving, needs only one to two cognitive rest breaks built into school day
3	Return to full day, moderate supports provided in response to symptoms during the day	Attend all classes with one to two rest breaks (20–30 min); begin quizzes. Moderate homework (60–90 min). Moderate expectations for productivity. Design schedule for make up work	To move to stage 4: continued symptom improvement, needs no more than one cognitive rest break per day
4	Return to full day, minimal supports (monitoring final recovery)	Attend all classes with zero to one rest breaks (20–30 min); begin modified tests (breaks, extra time). Homework (90+ min), moderate- to-maximum expectations for productivity	To move to stage 5: no active symptoms, no symptoms with cognitive or physical exertion during the full school day
5	Full return, no supports needed	Full class schedule, no rest breaks. Maximum expectations for productivity. Begin to address makeup work at this stage	N/A

N/A: Not applicable.
Adapted with permission from [4] © GA Gioia (2014).

Specific Management Strategies: Fatigue and Brain Fog

Families frequently fall into one of two groups:

- "We are trying to do everything like before."
- "We don't want to do anything until the symptoms resolve."

Both groups need assistance adjusting expectations

Psychology helps families prioritize/attenuate expectations and/or get motivated to mobilize

Brain Fog Next Steps: Neuropsychology

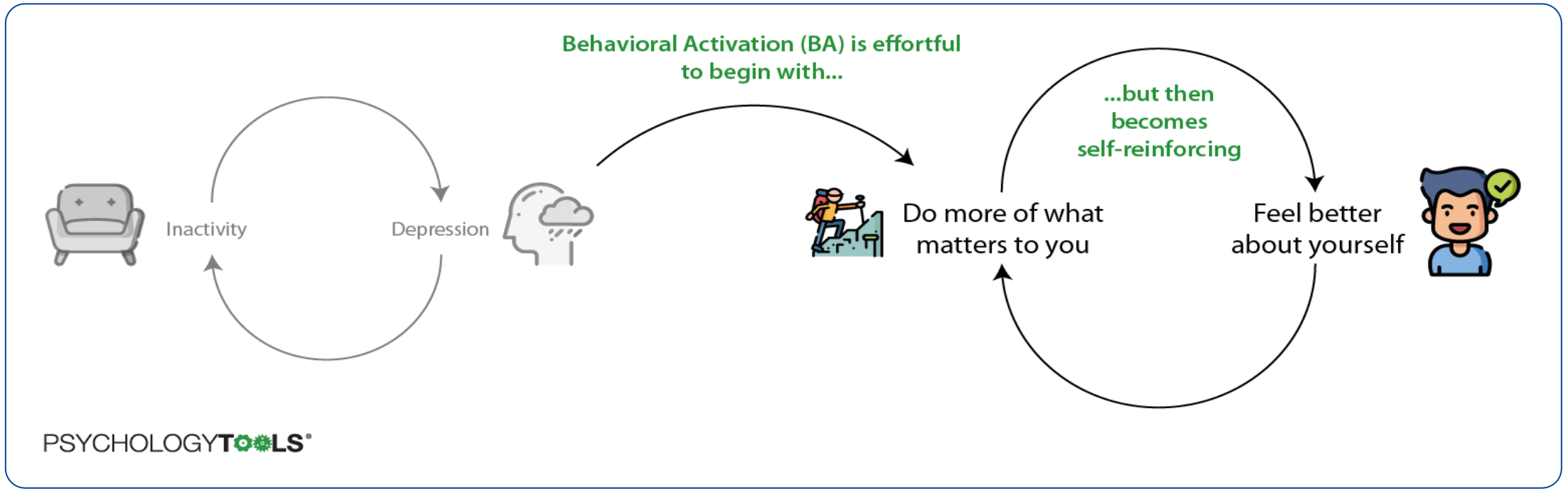
Given the large number of patients with cognitive impairment, we will be implementing

- Executive functioning screener
- Direct referral to neuropsychology

Specific Management Strategies: Depression

Cognitive-Behavioral Therapy

- Behavioral Activation



Children's National Post COVID Program Clinic

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Children's National Post COVID ("PoCo") Program Clinic

AAP News 3/1/22

Open since May 2021

Multidisciplinary clinic

Children/Adolescents (≤ 21 years)

- Prolonged symptoms or New, late-onset symptoms
- > 12 weeks since infection
- Lab confirmed (or lab confirmed contact) COVID
  - **RT-PCR**
  - **Antigen**
  - **Serology***
- **Wednesday** afternoons at Main Campus
  - **~2 hour appointments**

CNH Post COVID Multidisciplinary Clinic

Primary specialties

- Infectious Disease
- Physical Medicine and Rehab
- Psychology
- Hematology*

Additional specialties

- Neurology
- Gastroenterology
- Pulmonology
- Cardiology
- Pain
- Rheumatology

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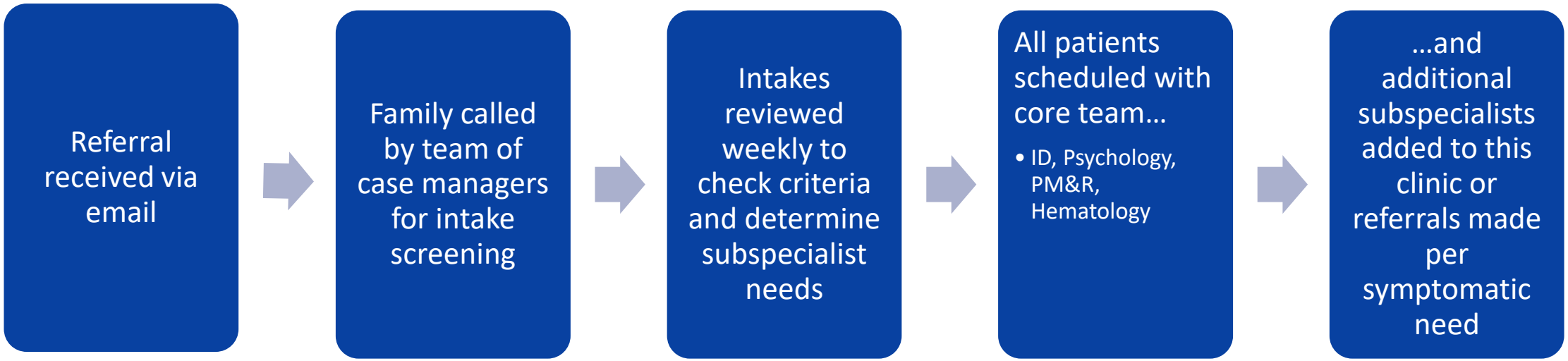
CNH Post COVID Program Clinic (PoCo Clinic)



GI, Neurology, Pain Medicine, Rheumatology, Cardiology and Pulmonary Medicine

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How to Refer

- Please fax any relevant medical records
- "Attn: Post COVID Program, 202-476-3850"
- Current wait time ~ 4 months

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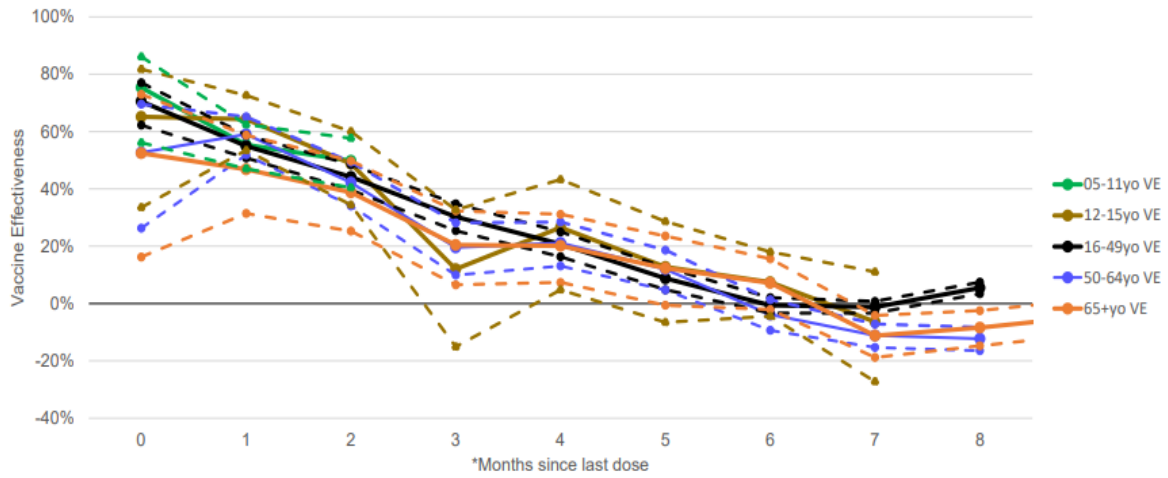
COVID-19 Vaccines in Children and Adolescents, Fall 2022

COVID-19 Vaccines for Pediatric Patients: Current Landscape

Vaccine	Mechanism	Ages	Schedule
Pfizer	mRNA	6 mo -4 years 5 years-17 years	3 dose: D0, D21-56, D112 2 dose + booster: D0, D21-56 + booster*
Moderna	mRNA	6 months and older	2 dose: Day 0 and Day 28-56
Novavax	Protein subunit vaccine	12 years and older	2 dose: Day 0 and Day 21

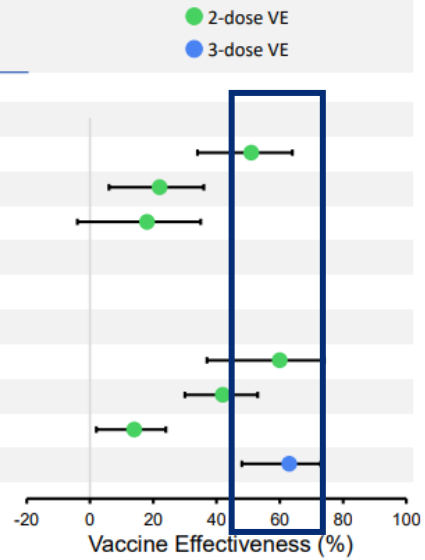
Do COVID-19 Vaccines even still work?

ICATT: mRNA 3 vs. 2-dose relative VE against symptomatic infection during BA.4/BA.5, ages 5+ years



*Vaccination dose dates are collected as month and year. Month 0 represents tests in the same month as last dose (at least 2 weeks after last dose). For all months greater than or equal to 1 the value represents the difference between calendar month of test and calendar month of last dose receipt (at least 2 weeks after last dose).

Vaccination status (days since most recent dose)	Total	SARS-CoV-2 positive, N	Adjusted VE (95% CI)
5-11 years			
Unvaccinated	21,009	1,375	Ref
2 doses (14-59)	1,151	72	51 (34-64)
2 doses (60-149)	4,068	179	22 (6-36)
2 doses (≥150)	1,338	109	18 (-4-35)
12-15 years			
Unvaccinated	7,318	1,443	Ref
2 doses (14-59)	219	27	60 (37-74)
2 doses (60-149)	1,082	196	42 (30-53)
2 doses (≥150)	3,308	587	14 (2-24)
3 doses (≥7)	973	43	63 (48-73)



CDC preliminary unpublished data. Prior infection excluded, other methods based on: Fleming-Dutra KE, Britton A, Shang N, et al. Association of Prior BNT162b2 COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection in Children and Adolescents During Omicron Predominance. *JAMA*. Published online May 13, 2022. doi:10.1001/jama.2022.7493

NEW: Bivalent Booster Vaccines

- **All individuals 12 years of age and older** should receive a bivalent booster at 2 months or more after primary series
  - Bivalent booster (Pfizer, Moderna) contains mRNA of original strain and BA.4/BA.5 omicron strain
  - Monovalent booster discontinued

-Children 5-11 years

- EUA application for (10ug total) bivalent booster submitted by Pfizer on 9/26/22

Upcoming Bivalent Vaccine Studies (Pfizer)

Study	Ages	Vaccine Status	Dose	Projected Enrollment
Substudy A (1/**2/3**)	6 mo-23 months	**Naive**	TBD (3 vs 6 vs 10 mcg)	P1- October 2022 P2/3- Q1 2023
Substudy B	6 mo-4 years	s/p 2 or 3 doses	3 mcg	
Substudy C (1/**2/3**)	6 mo- 4 years	s/p 3 doses	TBD (6 vs 10 mcg)	2023
Substudy D	5 years-11 years	s/ p 2 or 3 doses	10mcg	

How to Claim CME Credit:

1. Navigate here: https://icmes.inova.org/
2. Log in
3. Under Credits, click "Claim CME Activity Credits"
4. Search for and select "2022 Pediatric Health Network Grand Rounds"
5. Click the "Claim" hyperlink next to the presentation title ("Back to School & COVID-19 Vaccines")
6. Complete the evaluation (if available) and click "Submit"

CME must be claimed within 90 days of event!

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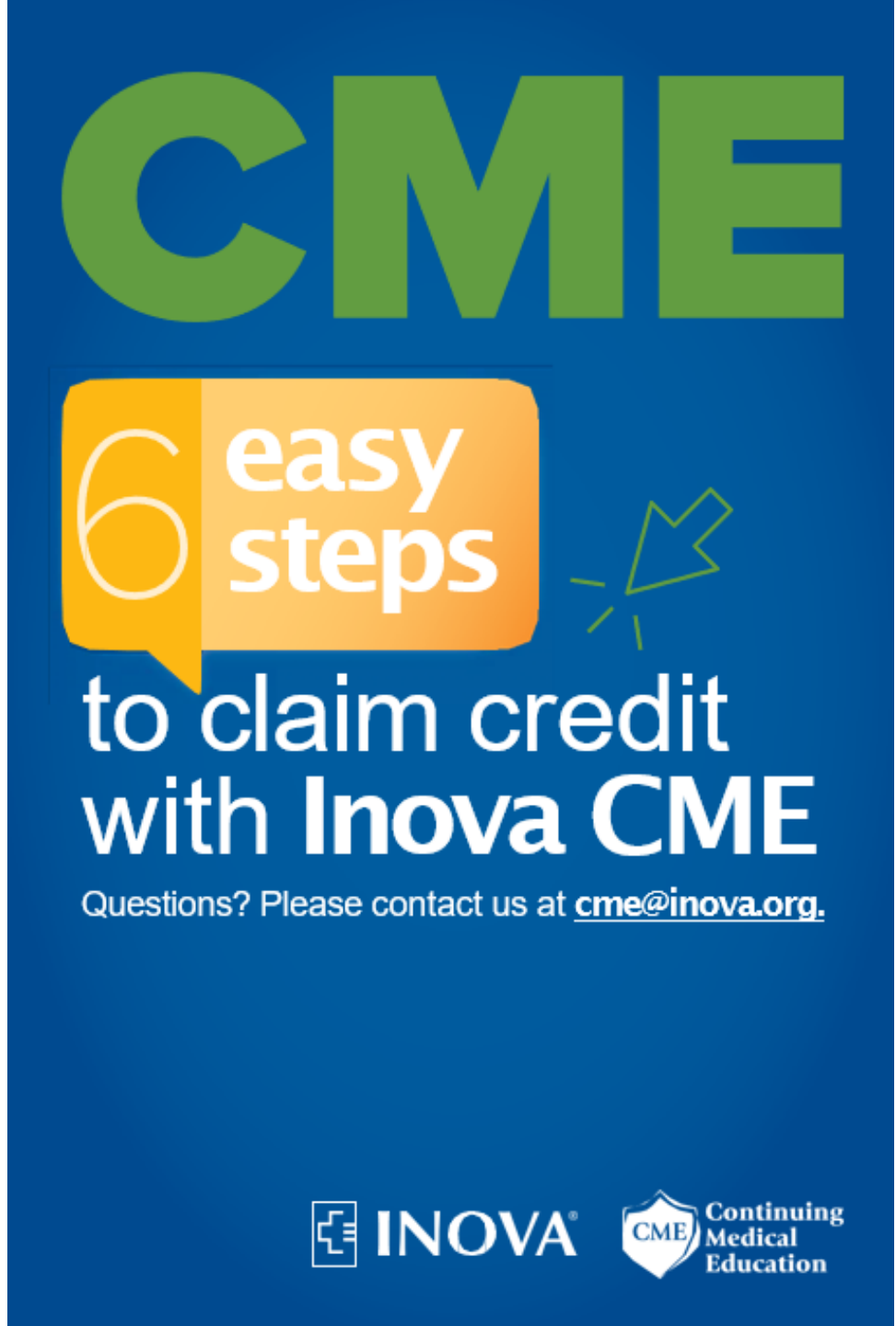

Thank you!

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