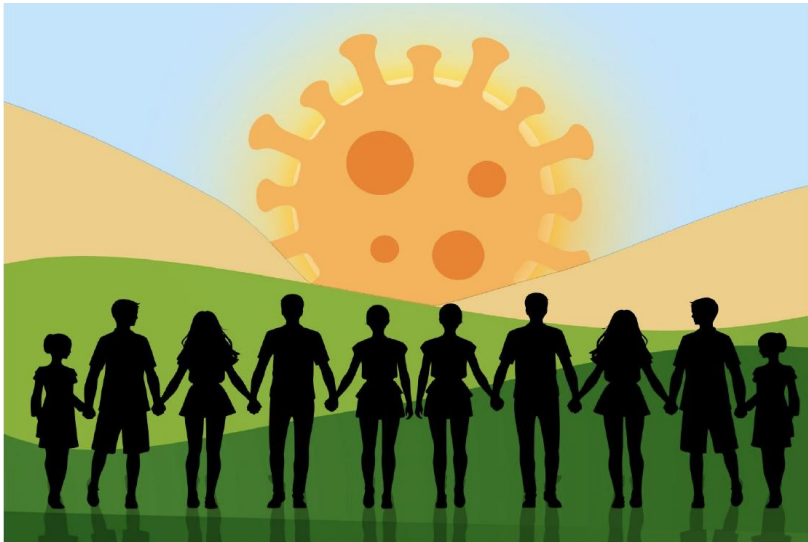




Pediatric Long COVID



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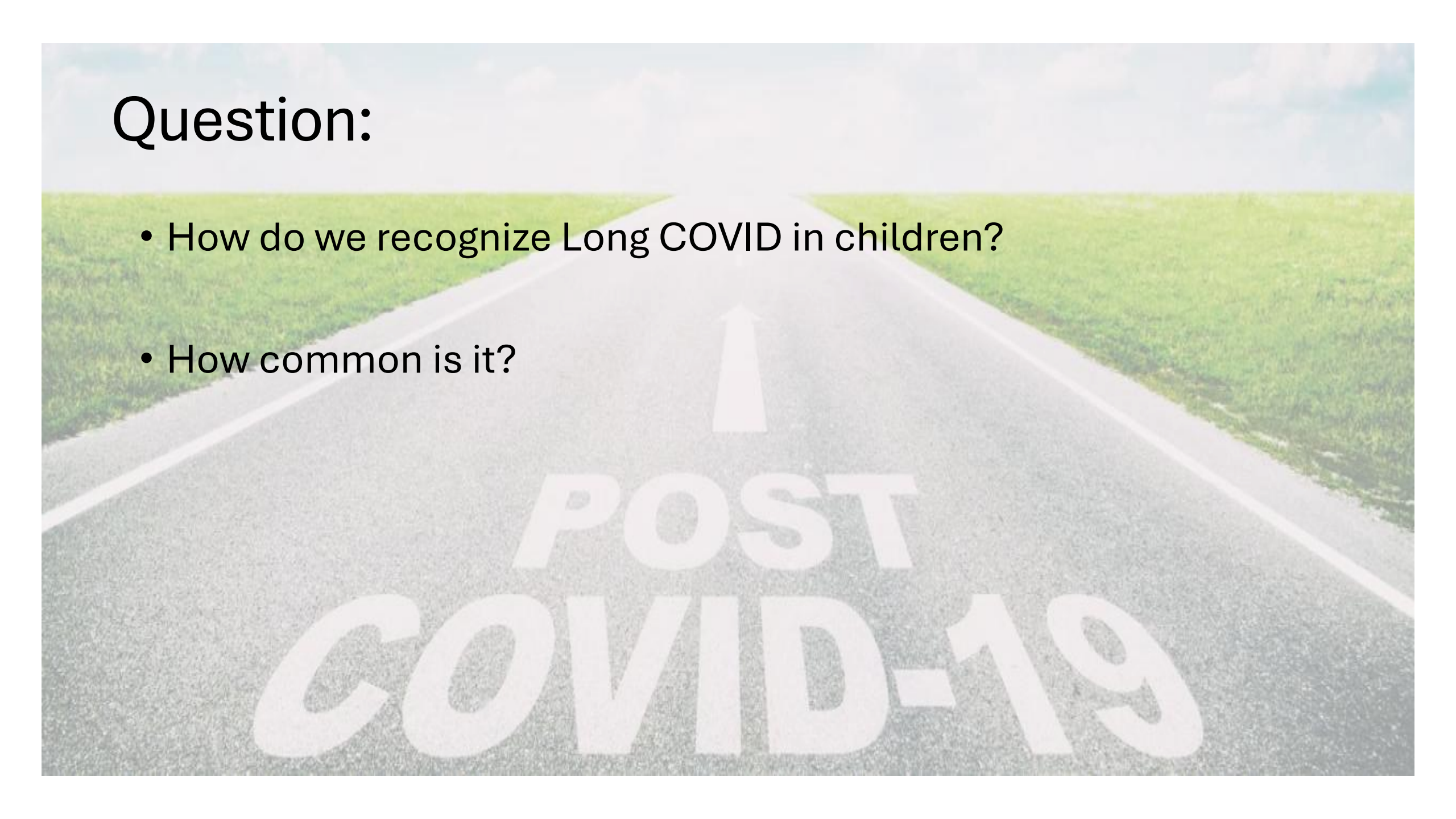
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Question:

- How do we recognize Long COVID in children?
- How common is it?

A photograph of a straight asphalt road stretching into the distance under a blue sky with clouds. The road is flanked by green grass. In the foreground, the words "POST COVID-19" are painted in large, white, bold, sans-serif capital letters on the road surface. Above the text, a white arrow is painted on the road, pointing directly forward towards the horizon.

**POST
COVID-19**

Challenges in diagnosing long COVID

- Likely under recognized
 - Social stigmata: Kids with Long COVID worry that:
 - People don't think Long COVID is a real disease
 - Long COVID is a sign of weakness
 - Kids are embarrassed due to physical limitations
 - Kids feel different from others due to Long COVID

Buonsenso D et al, Children, 9/2023

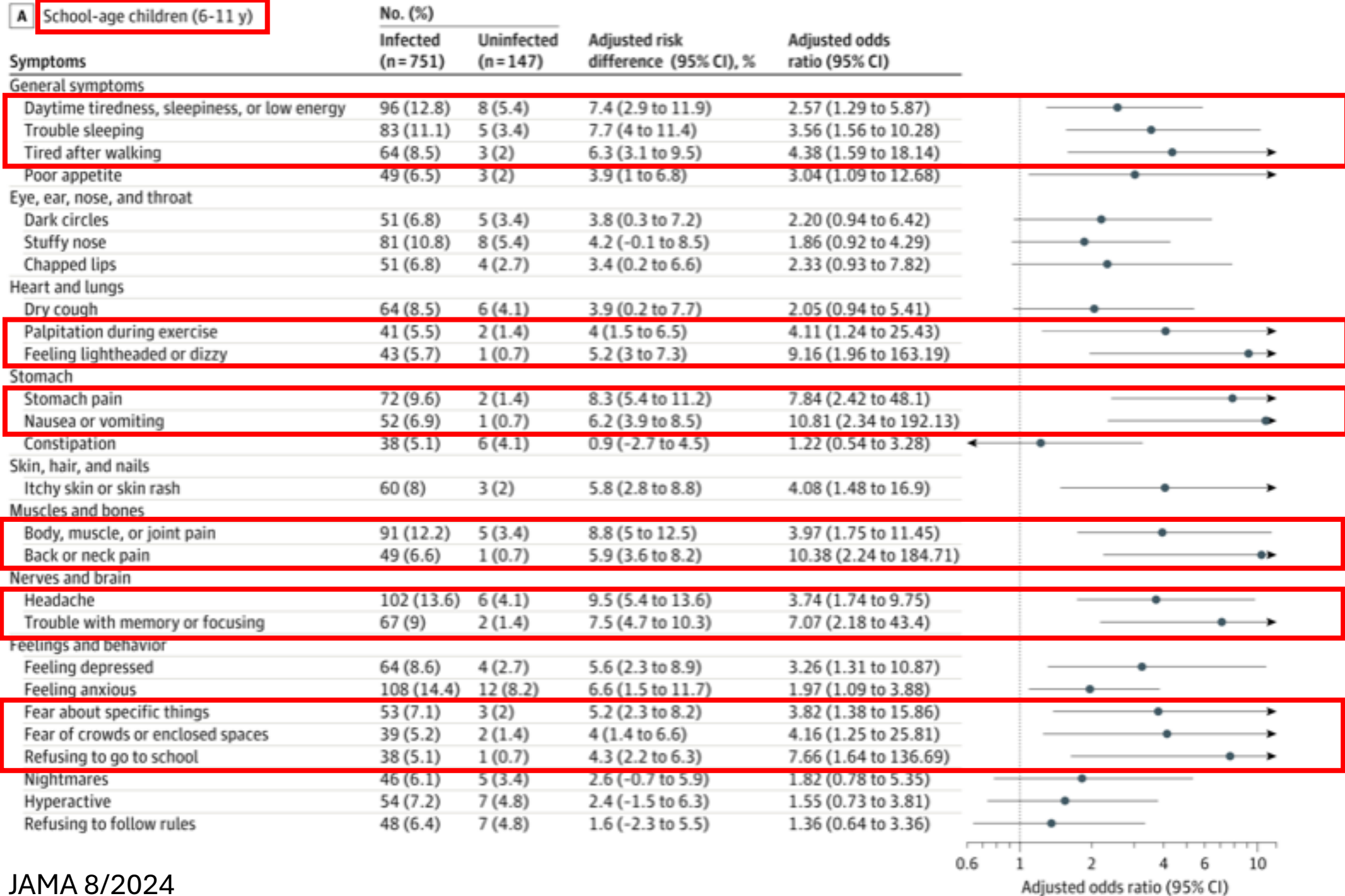
- Overlap with other etiologies
- Unclear benefit of diagnosing with Long COVID



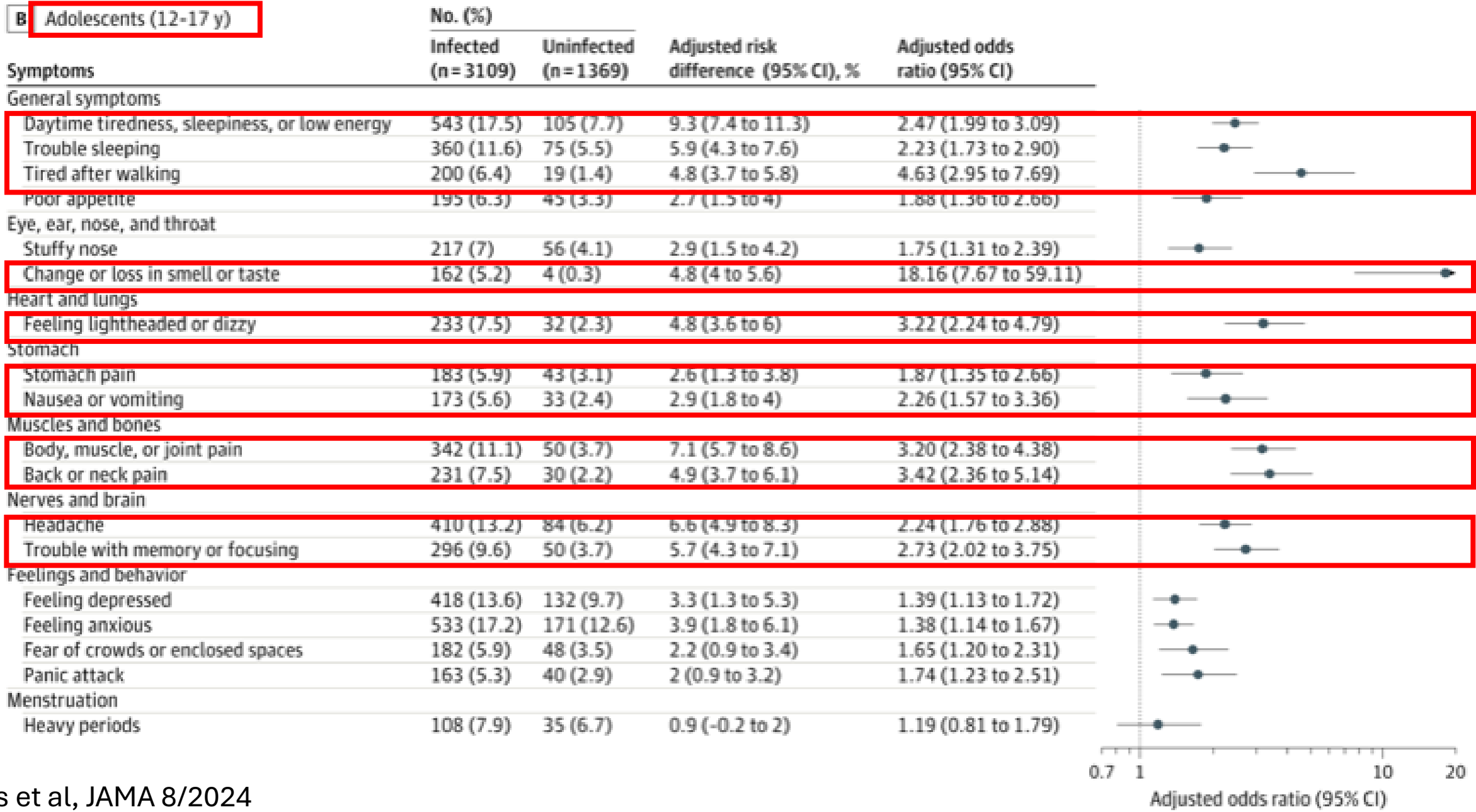
Characterizing Long COVID in Children

- RECOVER-pediatrics study
- 5367 children sent survey between March 2022 and December 2023
- Infected vs not infected (confirmed by nucleocapsid)
 - Infected group: >500 days post infection
- Symptoms compared across cohorts
- **1 in 5 children experience symptoms of long COVID**

A School-age children (6-11 y)



B Adolescents (12-17 y)



Characterizing Long COVID in Infants/Toddlers

- RECOVER-pediatrics study
- 472 infants/toddlers ages 0-5 years, between March 2022 and July 2024
- No blood confirmation of infection
- Symptoms compared across cohorts
- Infected children ~twice as likely to experience prolonged symptoms

Table 2. The Long COVID (LC) Research Index^a

Age group	Symptom	Log odds ratio	Score
Infants/toddlers (0-2 y)	Poor appetite	0.47	5.0
	Trouble sleeping	0.34	3.5
	Wet cough	0.32	3.5
	Dry cough	0.27	3.0
	Stuffy nose	0.05	0.5
Preschool-aged children (3-5 y)	Daytime tiredness/sleepiness or low energy	0.64	6.5
	Dry cough	0.28	3.0

^a To fit a logistic regression model to identify which symptoms could be used to identify which participants have LC-probable vs LC-unspecified status, least absolute shrinkage and selection operator (LASSO) was used, resulting in these log odds ratio estimates. In this model, the symptoms were the exposures, and the outcome was infection status. The log odds ratio estimates were divided by 0.10 and rounded up to the nearest 0.5 to calculate individual

symptom scores. An individual's LC research index is calculated by summing the scores for each prolonged symptom a participant reported. A prolonged symptom is defined as a symptom that the participant experienced for at least 4 weeks since the beginning of the COVID-19 pandemic and is still experiencing at the time of enrollment. The index is derived separately for infants/toddlers and preschool-aged children.

Long COVID happens when a child continues to have symptoms ≥ 3 months after having a COVID-19 infection.

Sometimes symptoms change, or symptoms may reappear after feeling better.



Signs and symptoms of long COVID are variable in children of different ages.

Infants and toddlers (0-2 y)

- Trouble sleeping
- Poor appetite
- Stuffy nose
- Dry or wet cough

Preschool-aged children (3-5 y)

- Daytime tiredness or sleepiness
- Low energy
- Dry cough

School-aged children (6-11 y)

- Trouble with memory or focusing
- Feeling lightheaded or dizzy
- Back or neck pain
- Headaches
- Trouble sleeping
- Stomach pain
- Nausea or vomiting
- Fear of specific things
- Refusing to go to school
- Itchy skin or rash

Adolescents (12-17 y)

- Trouble with memory or focusing
- Feeling lightheaded or dizzy
- Back or neck pain
- Headaches
- Change or loss in smell or taste
- Body, muscle, or joint pain
- Daytime tiredness or sleepiness
- Low energy
- Tired after walking



There is no cure for long COVID, but physicians may recommend medicine to help with some symptoms and guidance on avoiding symptom flares.

Question:

- What causes Post acute sequelae of COVID
 - ***(or what do we know so far)
- What can kids teach us?

POST
COVID-19

Table 1 | Identification of SARS-CoV-2 RNA and protein after COVID-19

SARS-CoV-2 Viral Reservoirs

	RNA	Protein	PASC symptoms	Location
Tissue (biopsy)				
Goh et al. ³⁹	✓	S, N	✓	Appendix, skin and breast tissues 163 and 426 d after COVID-19
Zollner et al. ³⁸	✓	N	✓	Gut mucosa/epithelium tissue ~7 months after COVID-19
deMelo et al. ²⁷	✓	N	✓	Olfactory neuroepithelium tissue 110–196 d after COVID-19
Gaebler et al. ³³	✓	N	No	Intestinal tissue ~4 months after COVID-19
Cheung et al. ¹¹⁴	✓	S, N	NM	Colon, appendix, ileum, hemorrhoid, liver, gallbladder and lymph nodes 9–180 d after COVID-19
Hany et al. ²⁹	NM	N	NM	Gastric and gallbladder tissues 274–380 d after COVID-19
Miura et al. ³⁰	✓	N	No	Adenoid tonsil, adenoid tissue, nasal cytobrush and nasal wash from children with no documented COVID-19 or upper airway infection in the month before collection
Xu et al. ³⁷	✓	NM	No	Child adenoid and tonsil tissue up to 303 d after COVID-19
Peluso et al. ²⁴	✓	NM	✓	Colorectal lamina propria tissue 158–676 d after COVID-19
Yao et al. ²⁵	✓	S, N	✓	Fungiform papillae tongue tissue 6–63 weeks after COVID-19
Tissue (autopsy)				
Stein et al. ³¹	✓	N	NM	Dozens of human body and brain tissue types at least 31 d and up to 230 d after COVID-19
Roden et al. ³²	✓	NM	NM	Lung tissue up to 174 d after COVID-19
Rendiero et al. ²⁶	NM	S	NM	Lung tissue up to 359 d after COVID-19
Stool				
Natarajan et al. ¹¹⁵	✓	NM	✓	Stool up to 230 d after COVID-19
Yonker et al. ⁸⁴	✓	S, N	✓	RNA in stool of children with MIS-C 13–62 d after COVID-19, S and N protein in plasma
Jin et al. ¹¹⁶	✓	S	NM	Neonatal stool in infants born to mothers whose COVID-19 symptoms resolved more than 10 weeks before delivery
Blood				
Schultheiß et al. ⁴⁰	NM	S1	✓	Plasma at a median time of 8 months after COVID-19
Swank et al. ⁴¹	NM	S, S1, N	✓	Plasma up to 12 months after COVID-19
Peluso et al. ⁴⁴	NM	S1, N	✓	Plasma neuron-derived EVs 35–84 d after COVID-19
Peluso et al. ⁴²	NM	S1, S, N	✓	Plasma up to 16 months after COVID-19
Craddock et al. ⁴⁵	✓	S	✓	Spike linked to EVs in samples obtained at least 8–12 weeks (up to 1 year) after COVID-19
Tejerina et al. ¹¹⁷	✓	NM	✓	Plasma at a median time of 55 d after COVID-19 (also found in stool/urine at the same median time point)

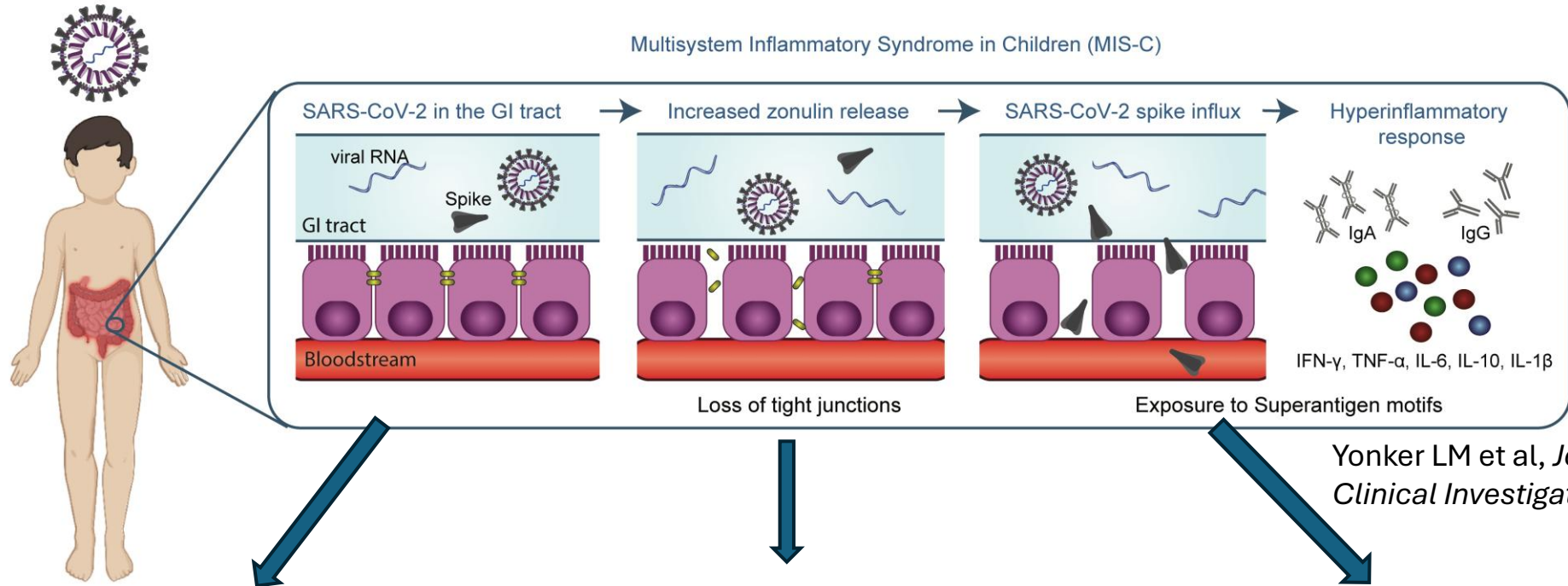
✓, identified; No, not present; NM, not measured; S and S1, spike protein.

Proal et al, Nat Immunology, 2024

Post-Acute Sequelae of COVID spectrum:

MIS-C ←————→ **Long COVID**

Exposure to SARS-CoV-2



Yonker LM et al, *Journal of Clinical Investigation*, 7/2021

Multiple studies show
SARS-CoV-2 in gut
in PASC

Can last >1 year

Proal et al, *Nature Imm*, 2023

Every unit increase in
zonulin = 44% increased
risk of PASC

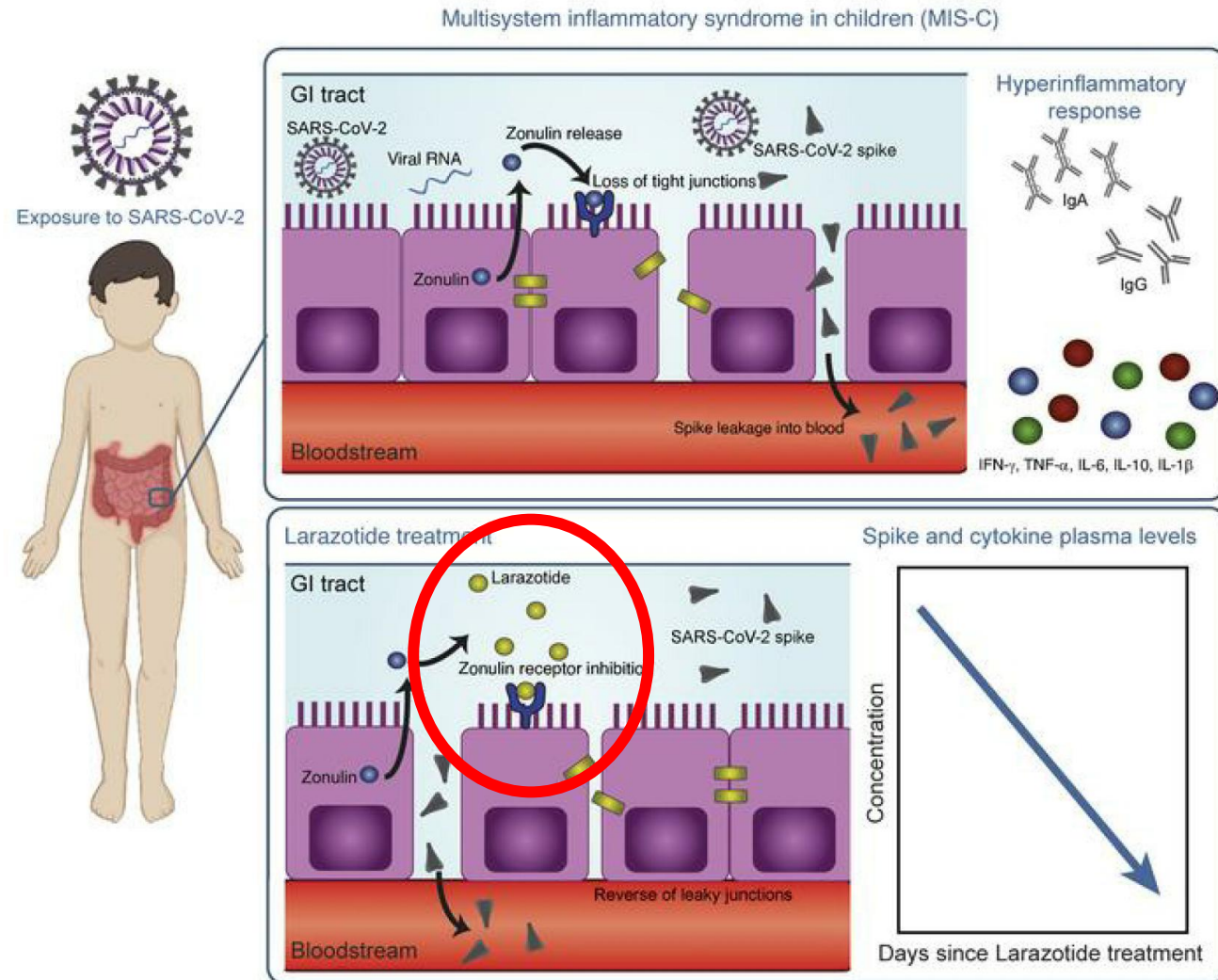
Mouchati et al, *Front Imm*, 2023

Spike proteins detected
in blood of adults with
PASC

Swank et al, *JID*, 2023
Swank et al, *Clin Microb Inf*, 2024

Long COVID

Larazotide treatment for MIS-C: 1) Open Label 2) Double Blind placebo controlled trial



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

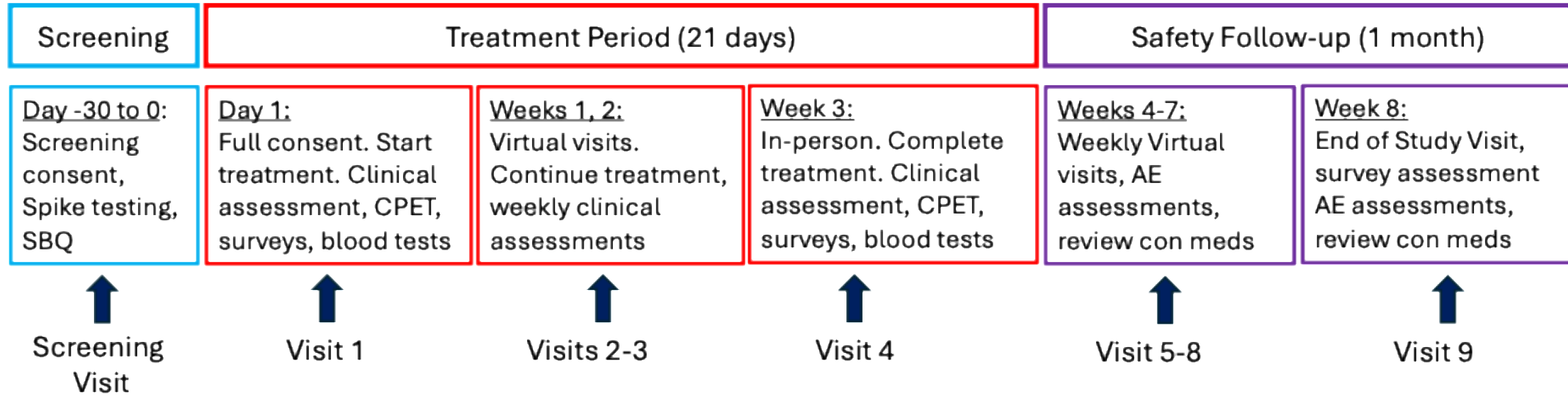
CORONAVIRUS

Viral spike antigen clearance and augmented recovery in children with post-COVID multisystem inflammatory syndrome treated with larazotide

Lael M. Yonker^{1,2,3*}, Abigail S. Kane^{1,2}, Zoe Swank^{3,4,5}, Lena Papadakis¹, Victoria Kenyon^{1,2}, Samuel Han^{3,4,5}, Rosiane Lima^{1,2}, Lauren B. Guthrie^{1,2}, Bryan Alvarez-Carcamo^{1,2}, Manuella Lahoud-Rahme^{1,3}, Duraisamy Balaguru^{1,3}, Ryan W. Carroll^{1,3}, Josephine Lok^{1,3}, Chadi El Saleeby^{1,3}, David R. Walt^{3,4,5}, Alessio Fasano^{1,2,3,6}

Larazotide for Long COVID: Study design

- Goal: enroll 150 patients
- Mass General Hospital
 - Ages 7-50 years
- 2:1 randomization
- 21-day treatment period + 28-day follow up period
 - Two in-person visits: Day 1 and Day 21



Equity in Research: A Global Consensus Statement on the Urgency of Including Children in Long COVID Trials



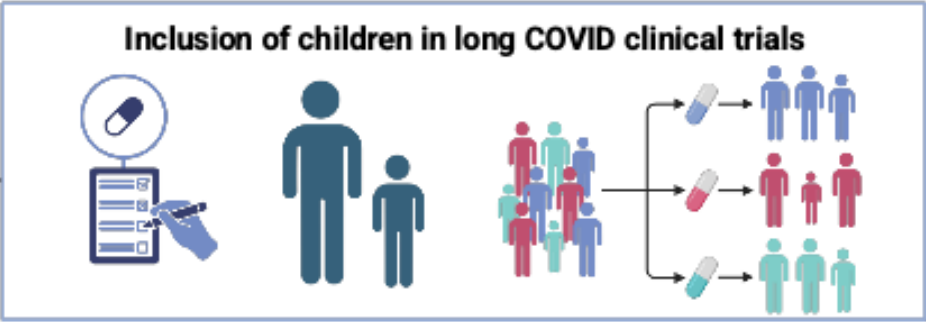
EUROPEAN RESPIRATORY *journal*

OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

RATIONALE

SOLUTIONS

Similar long COVID symptoms in children and adults Persistent SARS-CoV-2 reservoirs Dysregulated inflammation in children and adults Significant impact on health and well being in children



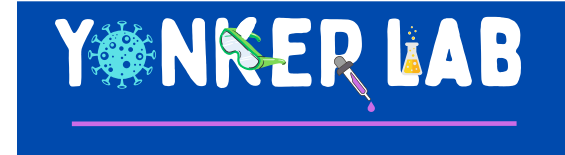
Pediatric adaptable PROs Pediatric subgroup analyses Determine if established safety profile in children Pharmacokinetics Allometric scaling

Mandate proposals include children Facilitate regulation and funding for trials including children

Equity in Research: A Global Consensus Statement on the Urgency of Including Children in Long COVID Clinical Trials

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Thank you!



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**Long COVID
Larazotide study:**

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more info!**



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