



Long COVID in Children: From skeptics to true believers



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Conflict of interest: none declared

Case Report

On November 30th, 2020, E', 15 y, arrived at our Long-COVID clinic.

Previously participated in competitive sports (Basketball league)

Symptoms impaired daily activity.

Fatigue, muscle ache, breathlessness that worsens during activity, dizziness, palpitations, concentration difficulty and memory loss, hair loss, diarrhea and weight loss.



Background

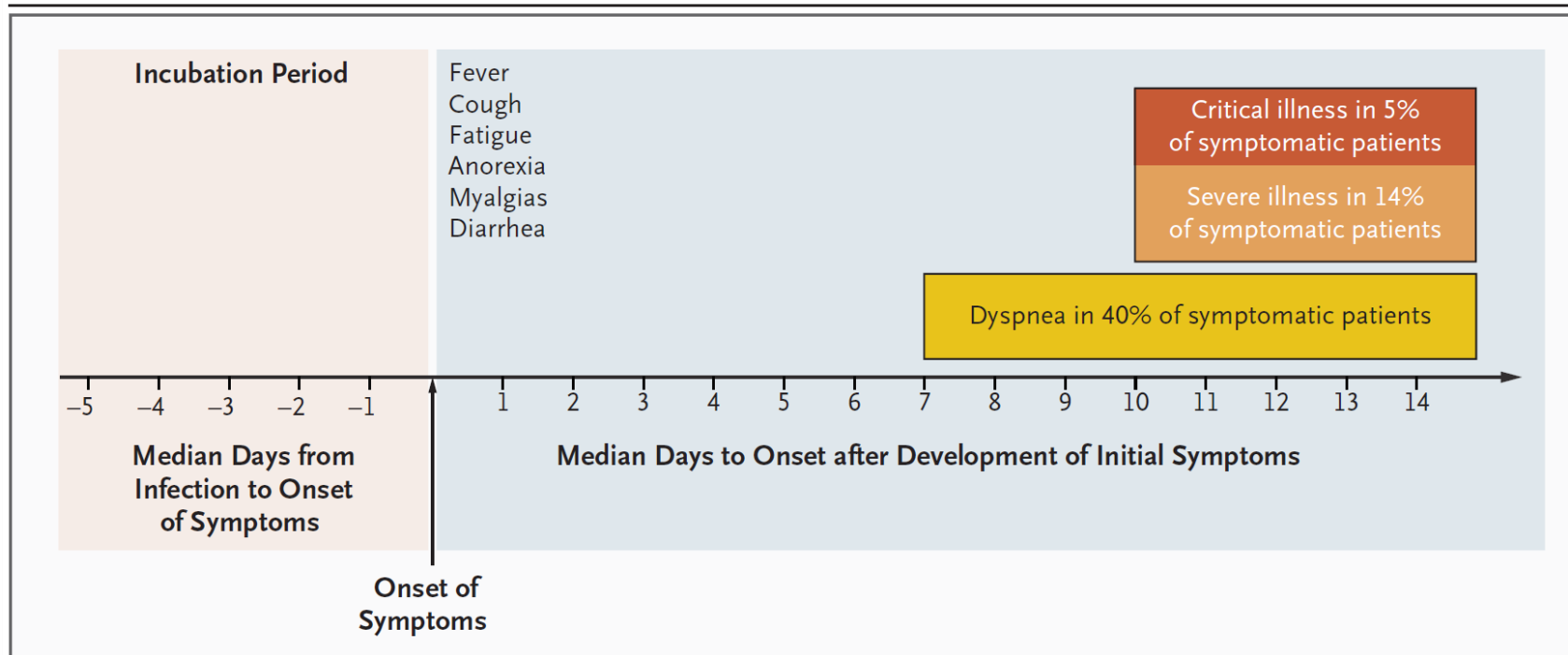
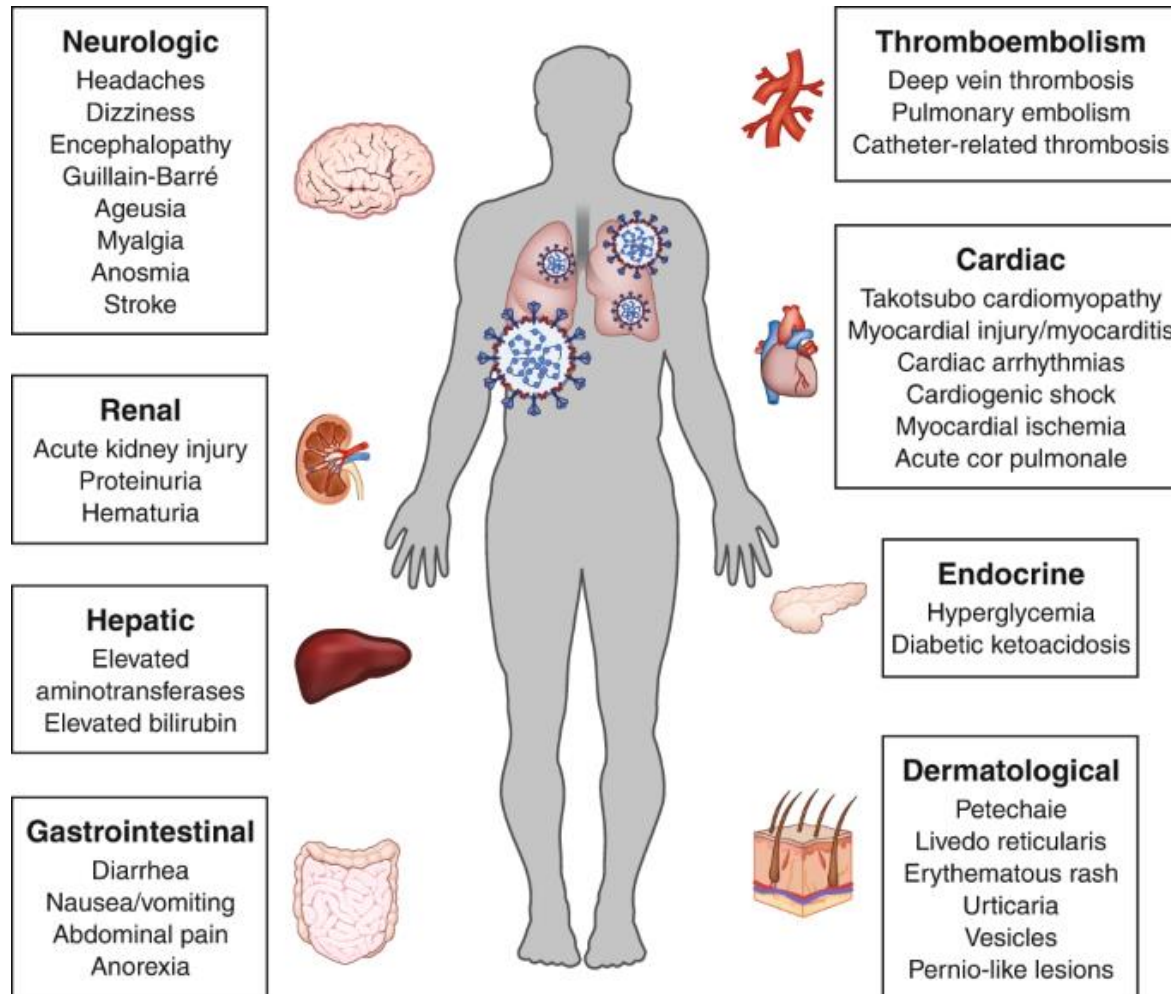


Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

The left border of the colored boxes shows the median time to onset of symptoms and complications. There is wide variation in the duration of symptoms and complications. Adapted from Zhou et al.² and the Centers for Disease Control and Prevention.¹



Background



Gupta, A., Madhavan, M.V., Sehgal, K. *et al.* Extrapulmonary manifestations of COVID-19. *Nat Med* **26**, 1017–1032 (2020).

<https://doi.org/10.1038/s41591-020-0968-3>

Background



Unanswered questions

Definition

Incidence

Risk factors

Healthcare burden

Spectrum of symptoms

Impact on daily function

Medical evaluation

Disease Course



Unanswered questions

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Definition

NICE National Institute for Health and Care Excellence

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Read about [our approach to COVID-19](#)

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We are reviewing these guidelines as new evidence, policy and practice emerges: [give us your feedback](#).

COVID-19 rapid guideline: managing the long-term effects of COVID-19

NICE guideline [NG188] Published date: 18 December 2020

Acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks.

Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks.

Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.



Definition

A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021



Domain number	Domain name
1	History of SARS-CoV-2 infection
2	SARS-CoV-2 laboratory confirmation
3	Minimum time period from onset of symptoms (or from date of positive test for asymptomatic) <u>3 months</u>
4	Minimum duration of symptoms <u>at least 2 months</u>
5	Symptoms and/or impairments: cognitive dysfunction, fatigue, shortness of breath , others
6	Minimum number of symptoms
7	<u>Clustering of symptoms</u>
8	Time-course nature of symptoms: (<u>fluctuating</u> , increasing, <u>new onset</u> , persistent , relapsing)
9	Sequelae of well-described complications of COVID-19 (stroke, heart attack, etc.)
10	Symptoms cannot be explained by an alternative diagnosis
11	Application of definition to different populations: <i>Include separate definition for children, others</i> <i>Impact on everyday functioning</i>

Post COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.**

Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others which generally have an **impact on everyday functioning.**

Symptoms may be **new onset**, following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time. A separate definition may be applicable for children.



Literature search



Received: 3 November 2020

R

ember 2020

DOI: 10.1111/apa.15673

REGULAR ARTICLE

ACTA PÆDIATRICA
NURTURING THE CHILD

WILEY

Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19

Jonas F. Ludvigsson^{1,2,3,4} 

- 5 children with potential long COVID , median age of 12 years (9–15).
- All 5 had fatigue, dyspnea, heart palpitations or chest pain
- 4 had headaches, difficulties concentrating, muscle weakness, dizziness and sore throat.
- The systematic review identified 179 publications with no information on long COVID in children.



Literature search

Open Forum Infectious Diseases

REVIEW ARTICLE

IDSA
Infectious Diseases Society of America

hivma
hiv medicine association

OXFORD

Postacute COVID-19: An Overview and Approach to Classification

Eva M. Amenta,¹ Amy Spallone,^{2,3} Maria C. Rodriguez-Barradas,^{2,3} Hana M. El Sahly,^{2,4} Robert L. Atmar,² and Prathit A. Kulkarni^{2,3}

¹General Internal Medicine, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA, ²Infectious Diseases Section, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA, ³Medical Care Line, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA, and ⁴Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas, USA

Acute SARS-CoV-2 infection

Asymptomatic

Mild

Moderate

Severe

Critical

>3 weeks from
suspected infection

>3 weeks from
symptom onset

Time of hospital discharge (if
>3 weeks after symptom onset)

Post-acute COVID-19

MIS

Persistent symptoms



Organ dysfunction



Unanswered questions

Definition

Incidence

Risk factors

Healthcare burden

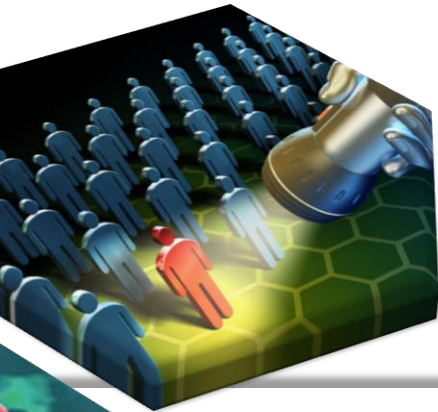
Spectrum of symptoms

Impact on daily function

Medical evaluation

Disease Course





Incidence and risk factors

Preliminary Evidence on Long COVID in children

Danilo Buonsenso, MD^{1,2,3}; Daniel Munblit, MD, PhD^{4,5,6}; Cristina De Rose, MD¹, Dario Sinatti, MD¹, Antonia Ricchiuto, MD¹, Angelo Carfi, MD⁷; Piero Valentini^{1,3}

¹ Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

- 129 SARS-Cov-2 positive children, mean age of 11 ± 4.4 years.
- Assessed after 162.5 ± 113.7 days
- 30% at least one persisting symptom even after 120 days



Incidence and risk factors



Osmanov, et al. *European Respiratory Journal* , 2021 (Russia)

518 hospitalized children: 25% of children had persistent symptoms months after hospitalization. Older age and allergic diseases were associated with higher risk of persistent symptoms at follow-up.

Molteni, et al. *Lancet Child Adolesc Health*, 2021 (UK)

1734 children who tested positive for SARS-CoV-2: 4.4% had illness duration of at least 28 days, more commonly in older than younger children (5.1% of older children vs 3.1% of younger children; $p=0.046$). 1.8% had symptoms for > 56 days.

Office for National Statistics (ONS) Survey, 10/2021 (UK)

Among 297,743 >2 y, the prevalence of self-reported long COVID (> 4 weeks from diagnosis) is 0.2% of children aged 2–11 years and 0.9% of children aged 12–16 years.



Miller, et al. *The Virus Watch study*, Preprint, 2021 (UK)

1.7% (80/4678 children) and 4.6% (8/174) of children with evidence of SARS-CoV-2 infection had persistent symptoms lasting more than 4 weeks. Higher in girls, teenagers and children with long-term conditions.



Israeli Ministry of Health Survey, 9/2021

13,834 children who tested positive for SARS-CoV-2: 11.2% residual symptoms. Following 6 months, 1.8% in 3-6 years, 2.4% in 6-12 years and 4.6% in 12-18 years, had symptoms. RF- age and symptomatic disease.

Blankenburg, et al. PrePrint, 2021, Mental health of Adolescents in the Pandemic: Long-COVID19 or Long-Pandemic Syndrome? (Germany)

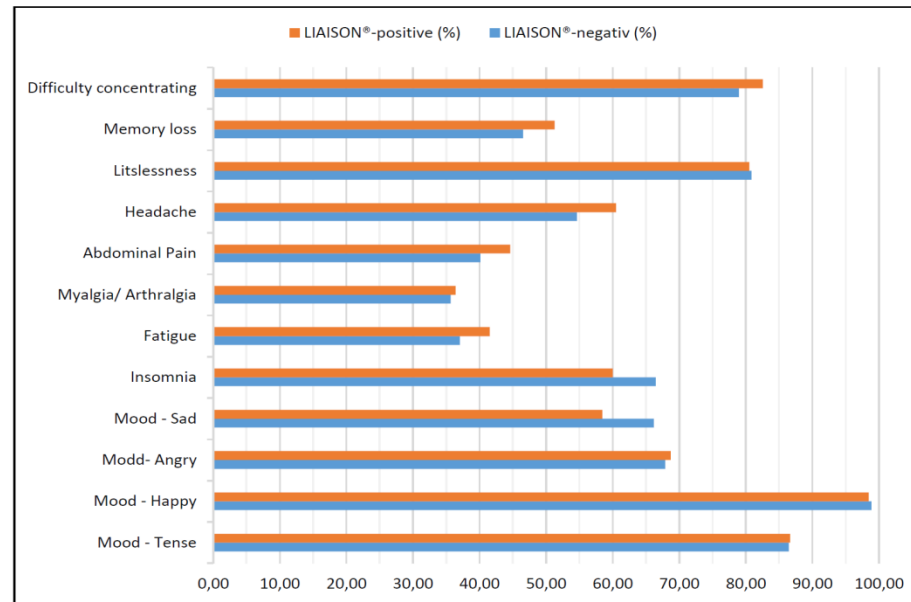
188 Seropositive and 1365 seronegative adolescents (8th-12th grade).

12-Q-survey for symptoms in the past week.

Lack of differences comparing the reported symptoms between seropositive and seronegative students.



Supplementals - Figure 1) Prevalence of neurocognitive, pain and mood symptoms in LIAISON®-negative and positive study participants (Fisher's exact test: n = 1553, * significant at level 0.05)



Stephenson, et al. The CLoCk Study. *BMJ Open*. (UK)

3065 COVID positive vs. 3739 negative, 11-17 years, 3 months post-testing, 30.3% vs. 16.2%, had 3+ symptoms. → any definition of Long COVID should consider multiple symptoms.

Response rate was 13.4%. Tiredness, headache and shortness of breath vs. tiredness, headache and “other” in test negatives.

No difference in the distribution of mental health scores.

Incidence and risk factors

Roessler, et al. Preprint. 2021 (Germany)

11,950 children COVID-positive vs matched controls;

96 outcomes aggregated into 13 symptom complexes; physical & mental health.

3 months post testing, for all health outcomes, incidence rates (IRs) in the COVID-19 cohort were significantly higher than in the control cohort.

Physical health (IRR=1.31, 95%-CI=[1.24-1.38]); mental health (IRR=1.39, 95%-CI=[1.28-1.52]);

Stratified estimations for the age groups 0-11 and 12-17 yielded similar IRRs.

Malaise/fatigue/exhaustion

(IRR=2.28, 95%-CI=[1.71-3.06])

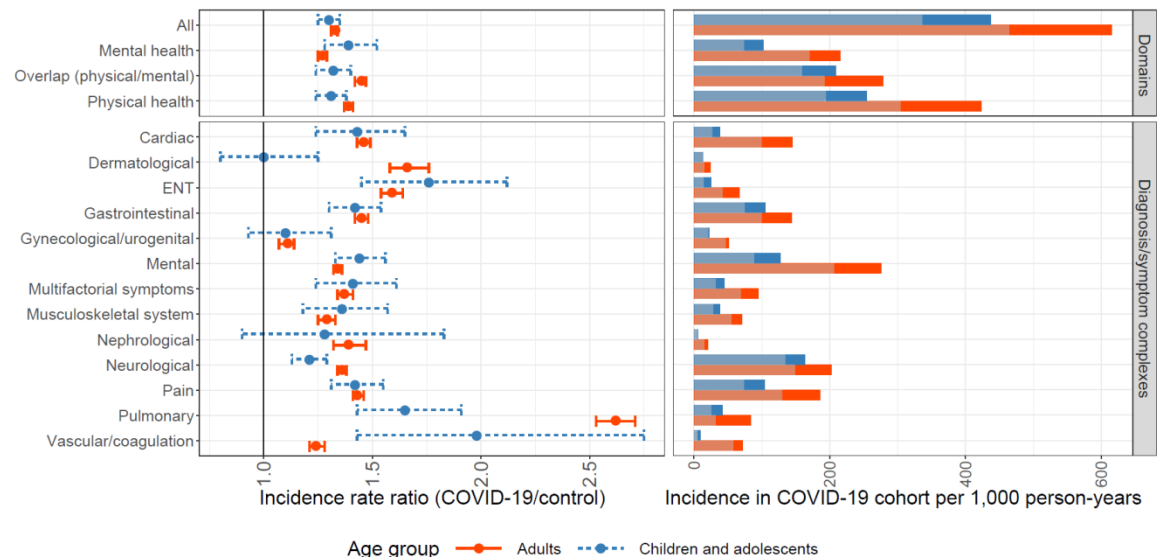
Cough

(IRR=1.74, 95%-CI=[1.48-2.04])

Throat/chest pain

(IRR=1.72, 95%-CI=[1.39-2.12])

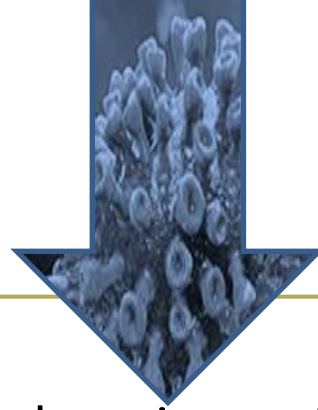
Incidence rates in children < than in adults.



‘In summary, our findings demonstrate that post COVID-19 cannot be dismissed among children and adolescents’



Incidence and risk factors



Taking the studies together, there is consistent evidence that some children will have persisting symptoms after testing positive for SARS-CoV-2.

Estimation of ~1%

Designated Pediatric Clinic, Schneider Children's, Israel

~160 children, mean age 11 ± 4 years, (range:1-19), 30%: 5-11 years

Background illness: none in 76%

Competitive sports: 12%

Acute COVID-19: Mild, symptomatic in 87%

Non were vaccinated against COVID-19



Unanswered questions

Definition

Incidence

Risk factors

Healthcare burden

Spectrum of symptoms

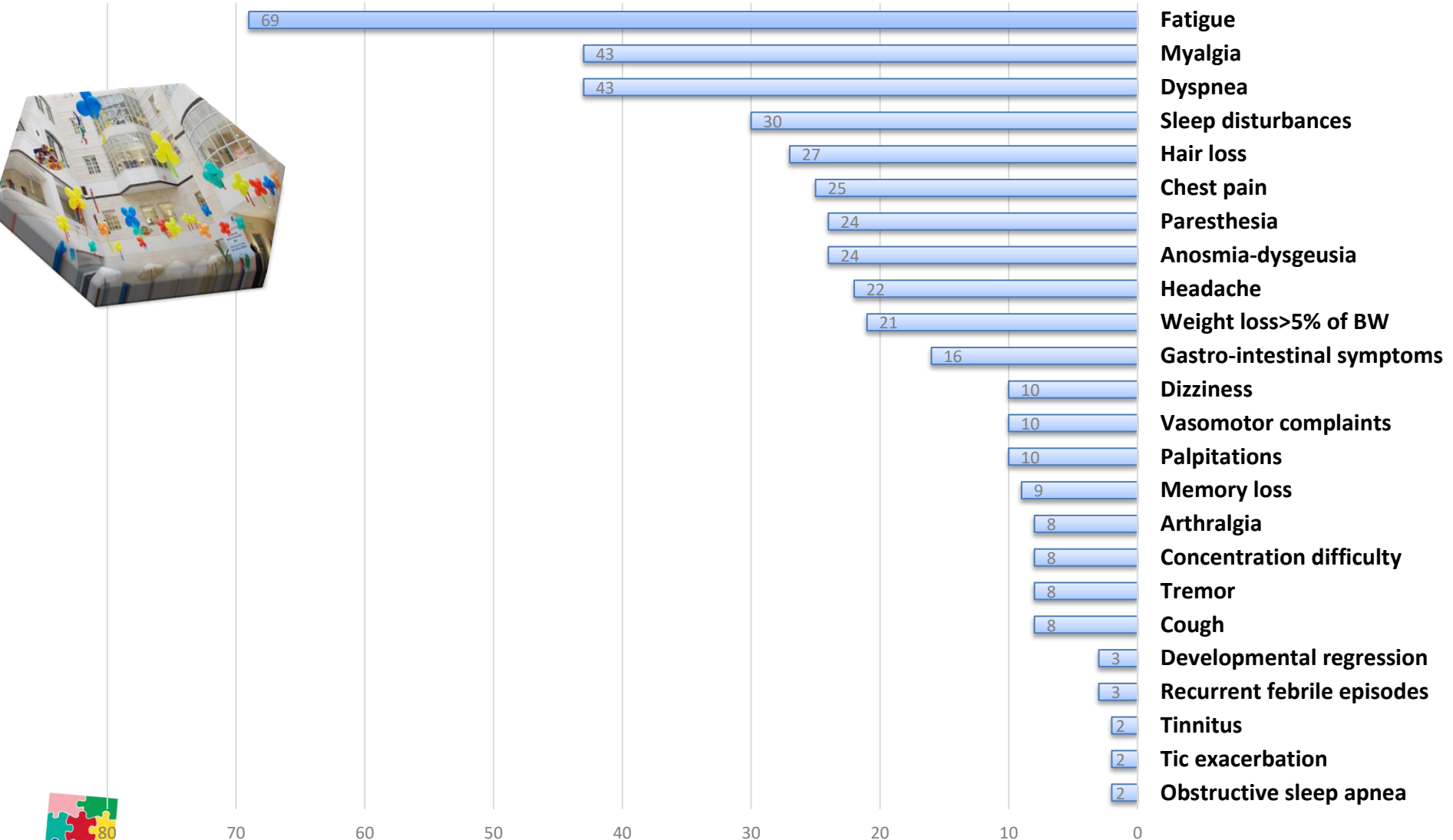
Impact on daily function

Medical evaluation

Disease Course



Spectrum of physical symptoms



Spectrum of physical symptoms

Buonsenso D, et al. *Acta Paediatr.* 2021

Fatigue, muscle and joint pain, headache, insomnia, respiratory problems and palpitations.

Brackel et al. *Pediatr Pulmonol.* 2021

National survey among Dutch pediatricians
89 children, aged 2–18 years

Stephenson, et al. *BMJ Open.* (UK)

Among 3065 COVID positive, tiredness, headache and shortness of breath were most common

TABLE 1 Results – Patient characteristics, survey

Total number of children	89	
The median age of children	13 (IQR: 9–15)	
Age range	2–18	
Positive PCR tests	47	52.8%
Positive serology tests	31	34.8%
Positive medical histories	34	38.2%
Unknown	8	9.0%
Complaints		
Fatigue	77	87%
Dyspnea	49	55%
Concentration difficulties	40	45%
Headaches	34	38%
Thoracic pain complaints	31	35%
Stomach ache	29	33%
Myalgia	25	28%
Diarrhea	21	24%
Memory loss	12	13%
Cardiac palpitations	16	18%
Skin irritation/lesions	6	7%
Dizziness	3	3%
Brain fog	2	2%
Weight loss	2	2%
Loss of appetite	2	2%
Persistent fever	2	2%

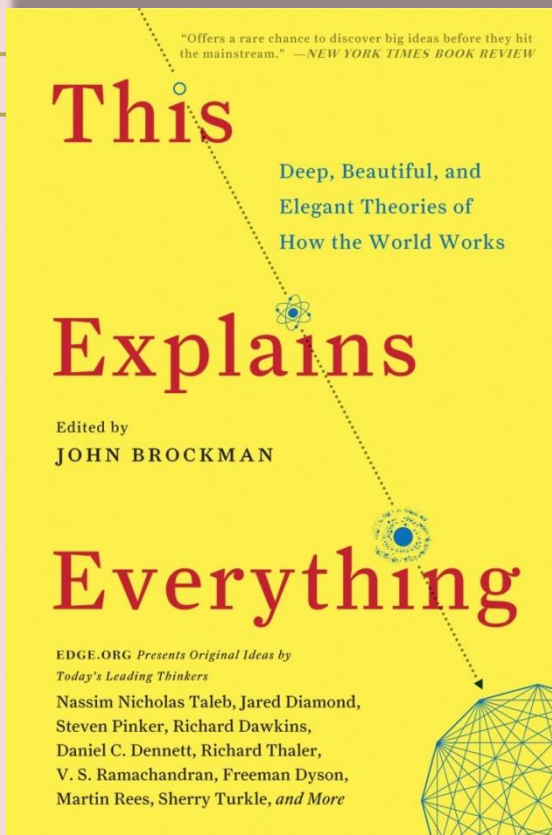
Brackel, CLH, et al. Pediatric long-COVID: An overlooked phenomenon? *Pediatric Pulmonology*. 2021; 56: 2495- 2502.

<https://doi.org/10.1002/ppul.25521>

Buonsenso D, et al. Preliminary evidence on long COVID in children. *Acta Paediatr.* 2021 Jul;110(7):2208-2211. doi: 10.1111/apa.15870.

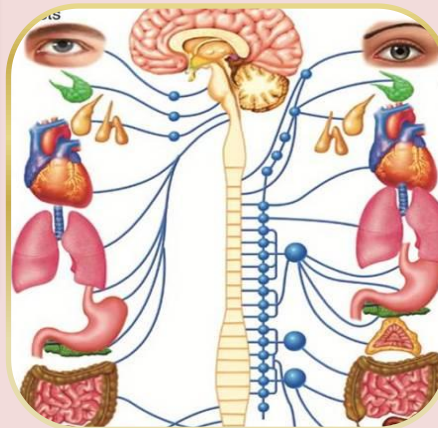
Epub 2021 Apr 18. PMID: 33835507; PMCID: PMC8251440.





Hyperventilation: A Possible Explanation for Long-Lasting Exercise Intolerance in Mild COVID-19 Survivors?

Justina Motiejunaite^{1,2*}, Pauline Balagny^{1,3}, Florence Arnoult¹, Laurence Mangin^{1,4}, Catherine Bancal¹, Marie-Pia d'Ortho^{1,2} and Justine Frija-Masson^{1,2}



Clinical Medicine 2021 Vol 21, No 1: e63–7

COVID-19 RAPID REPORT

Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies

Authors: Melanie Dani,^A Andreas Dirksen,^B Patricia Taraborrelli,^B Miriam Torocastro,^C Dimitrios Panagopoulos,^D Richard Sutton^E and Phang Boon Lim^F

Hyperventilation induced hypocapnia -> disabling symptoms such as:
dyspnea, tachycardia, chest pain, fatigue, dizziness and syncope at exertion



Unanswered questions

Definition

Incidence

Risk factors

Healthcare burden

Spectrum of symptoms

Impact on daily function

Medical evaluation

Disease Course



Impact on daily function



Brackel et al. *Pediatr Pulmonol.* 2021

National survey among Dutch pediatricians

89 children, aged 2–18 years, suspected of long-COVID with various complaints.

Of these children, 36% experienced severe limitations in daily function.

Total admitted to the hospital because of long-COVID ^b	16	18%
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Limitations in daily functioning

No limitations	7	8%
Mild limitations in daily functioning ^c	43	48%
Severe limitations in daily functioning ^d	32	36%

^aLike coughing (1%), myocarditis (1%), and anosmia (1%).

^bFor unknown reasons.

^cFor example, can go to school but excessively tired.

^dFor example, less or no school possible.



Impact on daily function



Buonsenso, et al. *Acta Paediatr.* 2021

~40 children: 42.6% being distressed by these symptoms

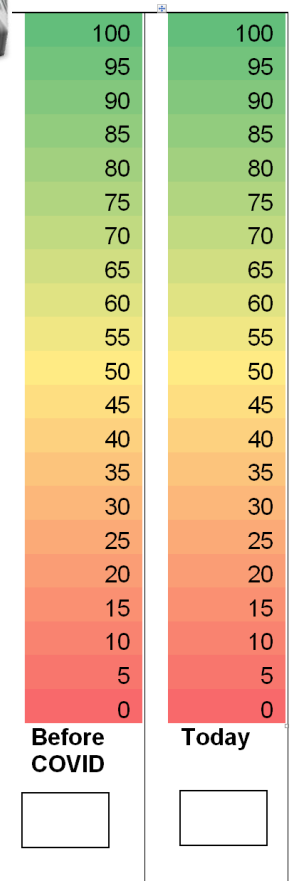
Δ QoL-6 points

Ashkenazi-Hoffnung et al. *Ped Infect Dis J.* 2021 and unpublished data

160 children: 40% moderate/severe limitation in ADL

60% limitation in physical activity

Δ QoL- Decrease of 29 (SD 25) points by parents; 52 (SD 20) points by children



Buonsenso D, et al. Preliminary evidence on long COVID in children. *Acta Paediatr.* 2021 Jul;110(7):2208-2211. doi: 10.1111/apa.15870. Epub 2021 Apr 18. PMID: 33835507; PMCID: PMC8251440.

Ashkenazi-Hoffnung, et al. Long COVID in Children, *The Pediatric Infectious Disease Journal*: August 5, 2021 - Volume - Issue - doi: 10.1097/INF.0000000000003285

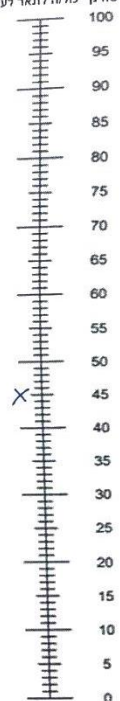
Impact on daily function



- בבקשה סמן/י X על הסולם בכדיי לציין את המצב הבריאותי של ילדך כיום.

- כעת, כתוב/י את המספר שסימנת בסולם המדידה בריבוע מטה.

המצב הבריאותי הטוב ביותר
שהינך יכולה לתאר לעצמך.



המצב הבריאותי הרע ביותר
שהינך יכולה לתאר לעצמך.

בריאות ילדי כיום = 45

שאלון איכות חיים

- ברצוננו לדעת עד כמה מצבו/ה הבריאותי של ילדך, טוב או רע בתקופה שלפני מגפת הקורונה לעומת מצבו/ה הבריאותי כיום.

- זהו סולם מדידה הממוספר מ-0 עד 100.

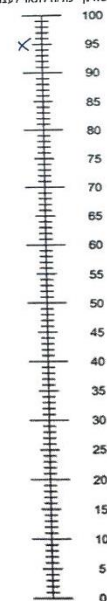
- 100 מבטא את המצב הבריאותי הטוב ביותר שהינך יכולה לתאר לעצמך.

- 0 מבטא את המצב הבריאותי הרע ביותר שהינך יכולה לתאר לעצמך.

- בבקשה סמן/י X על הסולם בכדיי לציין את המצב הבריאותי של ילדך בתקופה שלפני מגפת הקורונה.

- כעת, כתוב/י את המספר שסימנת בסולם המדידה בריבוע מטה.

המצב הבריאותי הטוב ביותר
שהינך יכולה לתאר לעצמך.



המצב הבריאותי הרע ביותר
שהינך יכולה לתאר לעצמך.

בריאות ילדי לפני מגפת הקורונה = 95

15870.



Unanswered questions

Definition

Incidence

Risk factors

Healthcare burden

Spectrum of symptoms

Impact on daily function

Medical evaluation

Disease Course



Medical evaluation results



Normal cardiac investigation in most



Elevated creatine phosphokinase-14%; low ferritin- 40%



Abnormal chest x-ray/ lung function tests- 30%; mild obstructive pattern



Psychologically, parental anxiety, adjustment disorder, PTSD-10%



Unanswered questions

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Disease course



Ludvigsson et al. *Acta Paediatr.* 2021

5 children: Some had improved after 6–8 months, but they all suffered from fatigue and none had fully returned to school.

Say et al. *Lancet Child Adolesc Health.* 2021 (Australia)

12/151 children with mild and asymptomatic disease

Median age 3 years [IQR 1–8]; symptom duration 3-8 weeks.

All children had returned to their baseline health status.

Ashkenazi-Hoffnung et al. unpublished data

160 children: 80% significant improvement/resolution of symptoms in 6-12 months;

6% recurrent COVID-19 infection with long COVID relapse



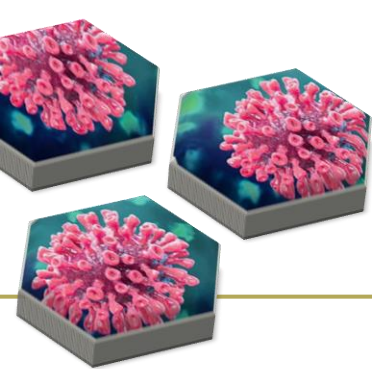
Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatr.* 2021 Mar;110(3):914-921. doi: 10.1111/apa.15673. Epub 2020 Dec 3. PMID: 33205450; PMCID: PMC7753397.

Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health.* 2021;5(6):e22-e23. doi:10.1016/S2352-4642(21)00124-3

In Conclusion



Definition	4 w, 12 w
Incidence	0.2-30%; Estimated ~1% Clinics at tertiary centers: >250
Risk factors	Age, Female
Healthcare burden	IRR ~1.5
Spectrum of symptoms	Wide; Physical ± Mental
Impact on daily function	Variable; Among patients in designated clinics- ~50% mod/severe
Medical evaluation	Mild obstructive airway disease : 30%
Disease Course	Resolution in 6-12 m in most Relapse 6%

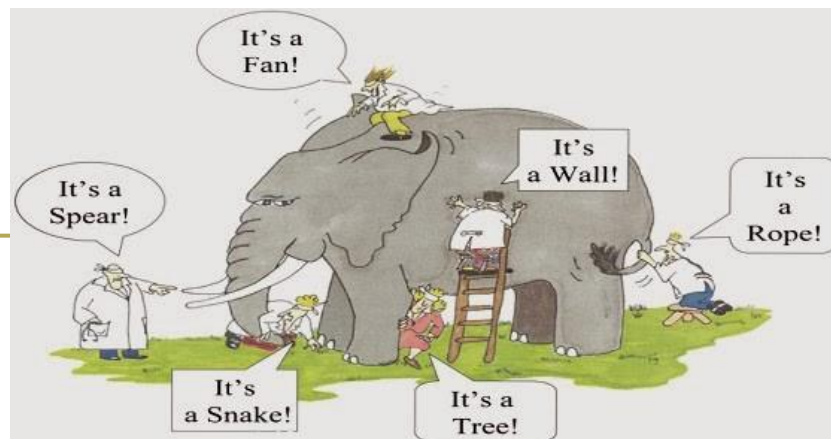
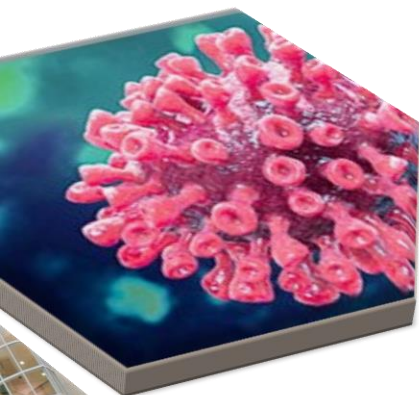


Policy Brief: The Impact of COVID-19 on children

15 APRIL 2020

"Children are not the face of the COVID-19 pandemic. But they risk being among its biggest victims."





CHRISTMAS 2020: HOUSE OF GOD

To each child their own coronavirus

Laetitia Martinerie,^{1,2} Delphine Bernoux,³ Lisa Giovannini-Chami,^{4,5} Alexandre Fabre^{3,6}

In the ancient Indian parable of the blind men and an elephant, the shape of the animal is appreciated differently by six blind men who conceptualise it only by touching part of its body.¹ In a similar way, children may conceptualise severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in their own unique ways.

Although SARS-CoV-2 infection is less severe in children² (rare instances of multisystem inflammatory syndrome in children notwithstanding^{3,4}), young people have nonetheless been at the forefront of policy makers' concerns.

This year children have been denied access to school,⁵ and infection containment policies have generally involved sidelining them from society.⁶ These fears have contributed to delayed access to care.⁷ Moreover, lockdown restrictions have affected

children both directly, through limitations on social interactions and physical exercise, and indirectly, through the impact these measures have had on their parents and caregivers, leading to anxiety, symptoms of post-traumatic stress disorder, and even child abuse.⁸ The concurrent covid-19 "infodemic" has contributed to a climate of fear centred on the virus itself.⁹

Some of the earliest representations of figures in the Blombos cave in South Africa, Ardales cave in Spain, and Chauvet cave in France are a reminder that drawing is one of the oldest forms of human expression. Drawing could put a face on SARS-CoV-2 and allow for a better grasp of the reality of the pandemic.¹⁰ Twenty children (12 girls and eight boys) aged between 4 and 14 years (mean 7.75 (SD 3.16) years,) were asked to draw a coronavirus as they imagined it, without reference to any model (fig 1).

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⁴ Pediatric Pulmonology and Allergology Department, Hôpitaux pédiatriques de Nice CHU-Lenval, Nice, France

⁵ Université de Nice-Sophia Antipolis, Nice, France

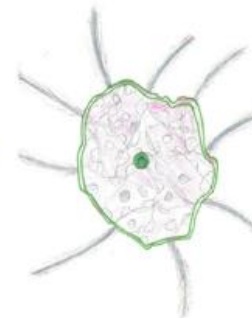
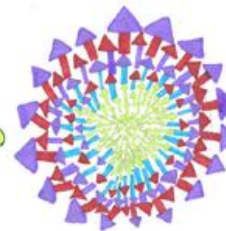
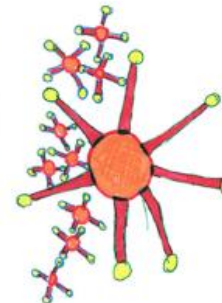
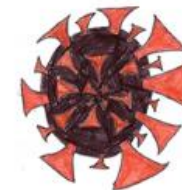
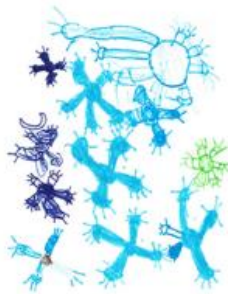
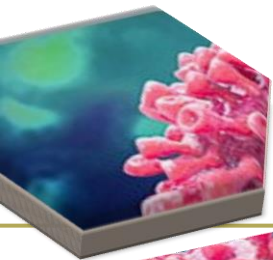
⁶ Aix Marseille Université, INSERM, GMGF, Marseille, France

Correspondence to: A Fabre
alexandre.fabre@ap-hm.fr

Cite this as: *BMJ* 2020;371:m4578
<http://dx.doi.org/10.1136/bmj.m4578>

Published: 16 December 2020





TO EACH CHILD THEIR OWN CORONAVIRUS

The elephant and the blind men: the children of long covid

Frances K Simpson,¹ Amali U Lokugamage²

In response to Martinerie and colleagues' article¹ we note the concerns about the sociological effects of the pandemic on children. We feel, however, that the article's view that SARS-CoV-2 infection is less severe in children is unsubstantiated and, as outlined in our BMJ Opinion piece,² there has been insufficient epidemiological study of long covid in children.

We appreciate art as a therapeutic outlet and means of communication for adults to understand what coronavirus has meant to children. We also appreciate the use of the parable of the blind men and the elephant³ in describing the subjective experiences of coronavirus for children. This important allegory can be extended to include children whose lived experience of the pandemic has been one of chronic illness.

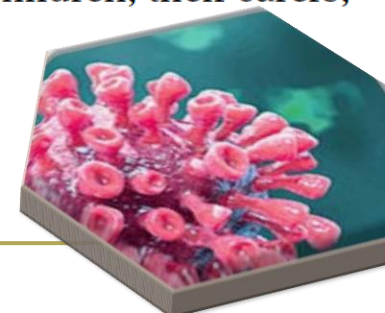
The parable of the elephant and the blind men may also be adopted to offer a useful account of long covid itself—each patient experiencing their own version which has required excellent communication to conceptualise the condition. The recent long covid NICE guideline⁴ is a testament to this process, a demonstration that when all the blind men share their experiences, they do not need to come to blows.

Children's experience of the virus relies on the beneficence and advocacy of adults to be heard. The children from the Long Covid Kids organisation⁵ have made use of film⁶ to express their experiences. Let's ensure that it gets heard and that responses to the pandemic for children are co-produced by children, their carers, and the official organisations that seek to offer assistance.

Competing interests: None declared.



Response at: www.bmj.com/content/371/bmj.m4578/rr.



Pediatric COVID-19 disease burden

Acute illness

PIMS
~150

Long COVID
~1%



Thank-you



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