Long COVID in children

In their recent article,[1] Molteni et al. conclude that "symptomatic SARS-CoV-2 infection in UK children aged 5–17 years is usually of short duration with low symptom burden" and that "prolonged illness can occur but is infrequent." Their study was based on parents logging symptoms for their children on the Zoe app and given important methodological limitations, we believe their results do not support their conclusions.

First, parents were only asked about a limited number of the symptoms commonly reported in long COVID[1]. Other symptoms were captured only if parents entered them as free text. Given that logging of symptoms regularly, particularly with free text, is quite laborious, this method is not well-placed for systematic assessment of persisting symptoms for longer periods of time. Some important symptoms, such as 'brain fog' and low mood, were added to the list only later in the study. Though they were found in 11%, and 15% of older children, respectively, they were not included in the primary analysis and we do not know how many children has persistent additional symptoms.[1]

Second, the study did not account adequately for the well-known relapsing and remitting nature of long COVID. Children with any gap in symptoms longer than one week were excluded.[1] Thus, any child whose symptoms temporarily resolved for more than a week and then recurred, was not counted as a child with long covid. [1]

Third, users of the Zoe app are not representative of the UK population, and to our knowledge no attempt was made to reweight the sample.[1] Participants were predominantly white and more affluent than average,[1] the latter characteristic being associated with a lower risk of long COVID.[2,3] Amongst all users of the app, only 25% of all children with positive tests had data logged regularly by parents and met eligibility criteria for the study.[1] Thus, those with complete data are unlikely to be representative, even of the selective cohort of app users. Selection, reporting and response bias can severely compromise the validity of estimates derived from symptom surveys.[4]

Fourth, the duration estimates for long COVID are based on parents either reporting their child as asymptomatic with no subsequence symptoms for a week, or the last symptomatic report if parents stopped using the app.[1] We have already discussed the issue with not fully accounting for relapsing-remitting nature of the illness above. The latter method of using the last logged symptom data is unlikely to be valid, and the data point should have been censored instead (as is usual in survival analyses). As responses are dependent on parents logging symptoms for their child, one could expect response rates to reduce over time. It is quite possible that some of the drop off in reporting is related to ongoing illness in the children and the demands of managing it. This is an important concern as the rates of incomplete reporting were higher for children with confirmed infection (10.6%) compared to children who had tested negative (3.5%).[1] Further the percentage of users who ceased logging symptoms while still having ongoing symptoms was 9.7% in those who reported <28 days of symptoms and 28.6% in those who reported for 28 or more days (**Table 1**). This affects both the duration estimates of persisting symptoms and prevalence estimates of long COVID. Given these data are likely missing not at random, excluding them (as in the sensitivity analysis carried out) would not improve the accuracy of the estimates and would also underestimate duration of symptoms. Even if we assume that ceasing symptom logging means symptom resolution, we would expect this to happen at similar rates in those who tested negative and those who tested positive. This is not the case and if we recalculate the rates assuming any additional cessation of symptom logging in cases over and above the level in controls was due to symptom persistence, this would give an estimated prevalence of long COVID at >28 days of 11% rather than the authors' reported prevalence of 4% at 4 weeks (**Appendix**).

Collectively, these factors all introduce bias in a single direction, namely to an underestimation of the incidence and duration of long COVID. In combination this underestimation might be quite considerable, which could easily explain why Molteni et al.'s estimates are at least 2-4 times lower than in prospective studies that collected data on children systematically over time (**Table 2**). The ONS survey reported a prevalence of 7-8% in this age group at 12 weeks (4-fold higher).[3] Radtke et al.,[5] reported a prevalence of 3.7%, (2-fold higher). Buonsenso et al.,[6] assessed 41 symptoms systematically and their estimates are 10 times higher, although these may be overestimates - unfortunately their case ascertainment methodology was unclear.

Miller et al. (preprint)[7], reported similar rates to the authors' but their study also suffers from a lack of representativeness and no systematic assessment of symptoms, and is based on retrospective assessment.

In summary, the methodological limitations of Molteni *et al.* mean that estimates of prevalence and duration of long COVID in children are likely biased substantially downwards, which may explain why they are lower than other studies. The ONS estimates on long COVID from 5th August 2021[8] suggest that 34,000 children in the UK had symptoms lasting 4 weeks and 7,000 children in the UK have had symptoms for more than 1 year. At the very most, Molteni et al's estimates should be considered only as a lower bound for the incidence of long COVID in children.

References

1. Molteni E SC, Canas LS, Bhopal SS, Hughes RC, Antonelli M. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *The Lancet Child and Adolescent Health* 2021.
2. Whitaker M EJ, Chadeau-Hyam M, Riley S, Darzi A, Cooke G, Ward H, Elliott P. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people, 2021.
3. Statistics OfN. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 April 2021.
4. Bradley VC, Kuriwaki S, Isakov M, Sejdinovic D, Meng XL, Flaxman S. Are we there yet? Big data significantly overestimates COVID-19 vaccination in the US. MedRxiv. 2021
5. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. *JAMA* 2021.
6. Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. *Acta Paediatr* 2021; **110**(7): 2208-11.
7. Miller F NV, Navaratnam AMD Shrotri M, Kovar J, Hayward AC. Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales. *MedRxiv* 2021.
8. ONS. All data related to Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 5 August 2021. 2021.

Co-authors:
Deepti Gurdasani, Queen Mary University of London, UK
Hisham Ziauddeen, University of Cambridge, UK
Anthony Costello, UCL, UK
Gabriel Scally, University of Bristol, UK
Athena Akrami, UCL, UK
Christina Pagel, UCL, UK
Trisha Greenhalgh, University of Oxford, Oxford, UK
Sarah Rasmussen, University of Cambridge, UK

Susan Michie, UCL, UK
Martin McKee, London School of Hygiene & Tropical Medicine
Kit Yates, University of Bath, UK
Seth Flaxman, Imperial College London, UK
Valerie C. Bradley, University of Oxford, UK

Appendix:

In the study cohort there were 243 children who had not had an asymptomatic report by the time of their last symptom log (symptom resolution not documented). Of those who were SARS-CoV-2 negative, this included 56 out of 1719 who had <28 days of symptom reports, and 4 out of 15 who had ≥ 28 days of symptom reports. For children who tested positive, this included 161 out 1657 with <28 days of reports, and 22 out of 77 of those with ≥ 28 days of reports.

If we assume that parents stopped symptom logging because of symptom resolution, then we would expect parents of both children who tested negative (controls) and positive (cases) to behave similarly. If we consider that all controls with <28 days of logged symptoms stopped logging because of symptom cessation, this would yield a rate of 3.25 % (56/1719). We would therefore expect symptom logging to have ceased for 54 out of the 161 children because of symptom resolution, with the remaining 107 attributable to logging having ceased because of persistent symptoms. This would give a long COVID estimate of 11% ((107+77)/1734). Even if we assume that only half of the remaining 107 who ceased logging did so because of symptom resolution, this still yields a rate of 7.5% ((54+77)/1734). Both these estimates are higher than those of the authors.

Ceased logging	Positive	negative
<28 days	161/1657	56/1719
>28 days	22/77	4/15
	183	60

Table 1: Summary of long COVID prevalence studies in children

	ONS study	**Buonsenso et al.**	**Miller et al.**	**Radke et al.**	**Molteni et al.**
Study design	Community-based sampling from the UK	Community-based, Italy.	Household cohort, England and Wales,	55 randomly selected schools, Switzerland	Symptom based survey using Zoe symptom tracker app
Representativeness	Sampled, and weighted to be representative of UK population	Convenience sample. Children with severe neuro-cognitive impairment excluded	Non-representative, higher socio-economic status	Randomly sampled schools	Poor representation of ethnic minorities. Higher SES

Case ascertainment	Asymptomatic and symptomatic PCR positivity	PCR positivity	PCR positivity and serology	Positive serology	Symptom based, PCR positivity
Sample size	3,489 2-16 yr old with positive PCR test)	129 <=18 years PCR positive > 30 days prior	4,678 (175 with confirmed infection)	1,355 (109 seropositive)	1,734 (PCR or LFD positive) and 1,734 controls
Response rate	In England: 51% households enrolled after original invitation 98% provided 1st swab, and 93% agreed to follow up. Overall response to long COVID questionnaire unclear.	Unclear, convenience sample	Unclear	54%	25%
Symptoms assessed directly	12 symptoms	41 (Assessment by paediatricians)	Open ended only	?8 (unclear)	19 symptoms + free text
Prevalence among infected	At 5 weeks: 9.8% (2-11 yrs) 13% (12-16 yrs) At 12 weeks: 7.4% (2-11 yrs) 8.2% (12-16 yrs)	<=18 years 42.6% at >60 days	<=17 year olds 4.6% at 4 weeks	In 6-16 year olds: 9.4% at 4 weeks 3.7% at 12 weeks	In 5-17 year olds: 4% at 4 weeks, 1.8% at 12 weeks
Prevalence in controls	At 5 weeks: 2.0% (2-11 yrs) 1.7% (12-16 yrs) At 12 weeks: 1.7% (all age gps)	No control group	<=17 year olds 1.7% at 4 weeks	In 6-16 year olds: 9.7% at 4 weeks 2.2% at 12 weeks	In 5-17 year olds: 0.9% at 4 weeks

Gaps allowed	2 consecutive follow ups without symptoms	Unspecified	Unspecified- relapsing and remitting symptoms considered	Unclear in reported methodology	1 week
Follow up	Weekly up to 4 weeks, and monthly up to a year.	Assessed on average 5.4 months later.	Retrospective – recall from February 2020.	Retrospective : 5-7 months previously.	Up to 5 months, Last report considered symptom resolution.
Comments on biases	Limited number of symptoms assessed, recall bias	Possible overestimation, retrospective, lack of controls, ascertainment of cohort unclear, possible selection bias and recall bias.	Likely underestimate Non-representative, retrospective, misclassification bias, no direct assessment of symptoms.	Likely underestimate Misclassification due to serological testing, retrospective nature, recall bias, and limited symptoms reporting.	Likely underestimate Non-representative, poor response, common symptoms not assessed, relapsing and remitting nature not considered.