Title: Calculating the prevalence of prolonged symptoms following symptomatic SARS-CoV-2 infection in children - Author's Reply

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The Office for National Statistics (ONS) have now updated and corrected their earlier estimates reporting symptom prevalence 4-8 weeks post-infection consistent with ours: 3·3% in primary-school aged children and 4·6% in secondary-school aged, with a matched control group symptom prevalence of 3·6% and 2·9% respectively[1,2].

We openly acknowledged that our cohort is not fully representative of the UK population; hence we compared demographic data with the UK population (Supplementary Information). Gurdasani's statement '25% of cases had data logged' is not strictly correct— these were cases fulfilling pre-hoc defined inclusion and exclusion criteria, which allowed accurate duration calculation.

Both letters suggested our symptom assessment was 'limited'. Our nineteen symptoms encompassed all commonly-reported, and some rarer, COVID-19 symptoms (including the most commonly reported symptoms in the ONS and CLOCK studies). Although some symptoms ('brain fog', 'low mood') were not explicitly asked in all 1,734 children, the median

durations in the 1,439 (83%) children who were explicitly asked were extremely short (1-2 days each), and are therefore unlikely to change our overall results. Free text provided an opportunity to detect symptoms unique to children not captured otherwise; no such symptoms emerged. We are mindful of Bradford-Hill criteria 3 (specificity); considering the ~200 symptoms reported with COVID-19/'Long-COVID'[3]: suggesting not all of these are necessarily causally related.[4]

We disagree that proxy-logging via smartphone is 'laborious', noting here the high assiduousness (mostly daily) and persistence (>90%) of proxy-reporting. We share concern that proxy-logging cessation prior to a healthy report might affect results, hence our sensitivity analyses, which included counting all children with LC28 even if logging subsequently ceased; estimates remained within confidence intervals. When discontinuation occurred, it was mostly at a time concomitant with median illness duration. If all 161 early-cessation children ultimately had LC28 (highly unlikely) our estimates would rise. However, if LC28 rates were proportionate to the >90% children logged until healthy, 7 extra LC28 cases would result, giving LC28 rates of 84/1734 children (4·8%), still within our confidence intervals.

Using one week as our threshold for defining illness continuation was raised. This threshold was as previously published.[5] As wellness periods lengthen between illness episodes it becomes increasingly difficult to attribute with clinical confidence later episodes of illness to initial infection. Here, standardising post-COVID syndromes definition in children will help future research.

We disagree with Gurdasani that our estimates are 'seven-fold' lower than the CLOCK study. The CLOCK study reported 66·5% positively- and 53·4% negatively-tested children had ≥1 symptom 3 months post-infection, a risk ratio of 1·25, an extremely modest risk. If we use the same criteria, at four weeks our risk ratio was 5·1. Importantly, both CLOCK and the ONS showed high symptom prevalence in children testing negative, presumably capturing both effects of other illnesses and the pandemic *per se*.

We reiterate our conclusion that "a holistic approach for all children with persistent illness during the pandemic is appropriate" whether or not due to SARS-CoV-2 infection.

References

1 Office for National Statistics. Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk/26april2020to1august2021.

2 Ayoubkhani D. How common is long COVID? That depends on how you measure it | National Statistical. https://blog.ons.gov.uk/2021/09/16/how-common-is-long-covid-that-depends-on-how-you-measure-it/ (accessed Oct 4, 2021).

3 Characterizing long COVID in an international cohort: 7 months of symptoms and their impact - EClinicalMedicine. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00299-6/fulltext (accessed Oct 1, 2021).

4 Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965; **58**: 295–300.

5 Sudre CH, Murray B, Varsavsky T, *et al.* Attributes and predictors of long COVID. *Nat Med* 2021; **27**: 626–31.