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Assessing the impact of the pandemic in children and adolescents: SARS-CoV-2 infection and beyond

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See Articles pages 230 and 240

Acute SARS-CoV-2 infection in children and young people is usually asymptomatic (65% of cases)[1] or mild.[2] Whether children develop post-COVID-19 syndrome[3] (also known as long COVID[4]) and, if so, its clinical features and natural history, are challenging questions.

In *The Lancet Child & Adolescent Health,* Terence Stephenson and colleagues[1] report their findings from CLoCk, a cohort study of non-hospitalised SARS-CoV-2-positive adolescents (cases) matched for month of test, age, sex, and geographical location with SARS-CoV-2-negative adolescents (controls) aged 11–17 years, drawn from the Public Health England database. The reason for testing varied between the two groups (eg, school surveillance in 26% of cases *vs* 71% of controls). 3 months after testing, participants self-completed online questionnaires, including recalled time-of-testing and current symptoms. Response rates were similar in cases (13·3%) and controls (13·5%).

These findings showed high symptom prevalence, increasing markedly from time of testing to 3 months in both groups (35·4% to 66·5% in cases and 8·3% to 53·3% in controls).[1] Overall prevalence of symptoms was greater in cases than controls, although when parsed by symptom burden, this difference was significant only for those with more than five symptoms. Some individual symptoms were more common in cases, including headache, tiredness (assessed as a specific symptom), and anosmia. However, there was no difference in mental health scores, wellbeing, or fatigue (using the 11-item Chalder Fatigue Questionnaire). At 3 months, a symptom cluster was evident in both groups, which included tiredness, headache, dyspnoea, and dizziness. This cluster was more common in cases than controls, and in girls, older children, and those with poorer baseline physical and mental health, irrespective of test status.

Also in the journal, Selina Kikkenborg Berg and colleagues[5] report the findings from LongCOVIDKidsDK, a retrospective, cross-sectional study of Danish adolescents aged 15–18 years testing positive for SARS-CoV-2 within the preceding year, matched for sex and age at test with controls (test-negative or not-tested), drawn from a complete national health database. Symptoms (potentially up to 12 months previously) were assessed using validated questionnaires, along with ancillary questions, including 23 possible long COVID symptoms. Response rates differed between cases (27·3%) and controls (22·3%), and more participants were female (57·6%) than male (42·4%).

LongCOVIDKidsDK[5] also found a high prevalence of symptoms lasting more than 2 months in all young people (61·9% of cases and 57·0% of controls reported at least one symptom). In both groups, more female than male participants reported symptoms lasting more than 2 months. Several symptoms were more common in the case group, including trouble breathing, cough, and sore throat (but not fatigue). However, new symptom burden was low (possibly correlated with initial illness severity) and seemed to decrease over time. The cases had lower symptom scores than controls, and higher quality of life across multiple domains (physical, emotional, social, and school functioning).

These data contrast with other studies, including our own.[2] We did a prospective, real-time, citizen-science study using proxy-logged data from 1734 school-aged, test-positive children, matched for age, gender, and week of testing with 1734 test-negative controls, assessing 19 researcher-determined symptoms (derived from adult data) along with free text. Symptomatic illness lasting 4 weeks or longer was uncommon (4·4%) and lasting 8 weeks or longer was rare (1·8%). As in adults[4] and in LongCOVIDKidsDK,[5] children with symptomatic illness lasting 4 weeks or longer had higher symptom burden acutely, and were more likely to be female and older than children without lasting symptomatic illness.[2] Our figures concord with UK Office for National Statistics (ONS) data from a large, randomly selected population survey assessing 12 symptoms (including fever, headache, tiredness, dyspnoea, and anosmia) from April, 2020, to August, 2021. ONS reported symptom prevalence 4–8 weeks after infection of 3·3% in primary school-aged children (*vs* 3·6% in negative controls) and 4·6% (*vs* 2·9%) in secondary school-aged children.[6]

Although multiple symptoms have been reported in children and young people after SARS-CoV-2 infection, most studies have been small and uncontrolled. As highlighted recently,[7] coalescing data for ongoing

symptoms after COVID-19 is difficult, with heterogeneity of inclusion criteria, disease definition, assessment methodology, and duration of follow-up. A meta-analysis[8] of five controlled studies found that, in individuals aged 19 years and younger with confirmed or probable SARS-CoV-2 infection and symptoms beyond 4 weeks, few symptoms were more common in cases than controls, with small absolute differences in cognitive difficulties (3%), headache (5%), anosmia (8%), sore throat (2%), and sore eyes (2%), but not in fatigue. These data should not be interpreted as showing that children with SARS-CoV-2 infection do not have these or other long-lasting symptoms; rather, that these symptoms are not confined to SARS-CoV-2 infection. Indeed, the pooled prevalence of fatigue (using 17 studies, both with and without control data) was 47%.[8]

What conclusions can we reach? First, both CLoCK[1] and LongCOVIDKidsDK[5] found a high symptom burden in the control groups, including mental health issues. Few comprehensive paediatric population studies have assessed prevalence of headache, fatigue, and other symptoms before the COVID-19 pandemic; nonetheless, the symptom increase observed in test-negative children in CLoCK suggests an impact of the pandemic on all children, irrespective of infection.

Second, no study is perfect. In addition to study design issues detailed above, our own study[2] did not assess baseline mental health or functional status and was not fully representative of the general population; CLoCK[1] and LongCOVIDKidsDK[5] had low participation rates, differential recruitment, gender imbalance, and required teenagers to recall symptoms over long time periods. A major and unsolvable issue is that children and young people are aware of their SARS-CoV-2 status, and media coverage of long COVID has been extensive. Especially for retrospective studies, it would be surprising if there were not some self-selection towards longer, unresolved presentations, recall bias, and systematic bias due to social measures (eg, school re-opening). Controlled studies have been key in differentiating effects of SARS-CoV-2 infection per se versus pan-population psychosocial stressors, but the omicron (B.1.1.529) wave means that numbers of never-infected children are rapidly decreasing, compromising future recruitment of control groups. Similarly, the social construct of children's lived experience of the pandemic was unique, and we might never have more informative studies than these.

Third, the usefulness of considering post-COVID-19 syndrome as a single entity is unlikely to have empiric validity, and a one-size-fits-all therapeutic approach is unlikely to be appropriate. Management should consider differential or additional diagnoses and the mind–body interaction (highlighted by CLoCK), and integration of mental health professionals in multidisciplinary teams should be seen as a parallel and equally valid process towards the main aim: recovery of wellbeing in the broadest sense. Encouragingly, several studies suggest that children and young people will improve with time.[2,5,9] Last, the scientific and medical communities should listen to children's and families' voices in co-production of future research and service delivery, ultimately informing individualised routes to recovery for all children.

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1 Stephenson T, Pinto Pereira SM, Shafran R, et al. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. *Lancet Child Adolesc Health* 2022; published online Feb 7. https://doi.org/10.1016/S2352-4642(22)00022-0.

2 Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health* 2021; **5:** 708–18.

3 WHO. A clinical case definition of post COVID-19 condition by a Delphi consensus. Oct 6, 2021. https://apps.who.int/iris/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf (accessed Jan 28, 2022).

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

5 Kikkenborg Berg S, Dam Nielsen S, Nygaard U, et al. Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVIDKids-DK): a national, cross-sectional study. *Lancet Child Adolesc Health* 2022; published online Feb 7. https://doi.org/10.1016/S2352-4642(22)00004-9.

6 UK Office for National Statistics. Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: April 26, 2020, to August 1, 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk/26april2020to1august2021 (accessed Jan 28, 2022).

7 Zimmermann P, Pittet LF, Curtis N. How common is long COVID in children and adolescents? *Pediatr Infect Dis J* 2021; **40:** e482–87.

8 Behnood SA, Shafran R, Bennett SD, et al. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: a meta-analysis of controlled and uncontrolled studies. *J Infect* 2021; published online Nov 20. https://doi.org/10.1016/j.jinf.2021.11.011.

9 Magnusson K, Skyrud KD, Suren P, et al. Healthcare use in 700 000 children and adolescents for six months after COVID-19: before and after register based cohort study. *BMJ* 2022; **376:** e066809.