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malaria, are at higher risk of severe anaemia. Therefore, SCA should be diagnosed as early as possible, to target these children for malaria-preventive interventions.

In conclusion, although sickle cell disease is one of the oldest known haemoglobinopathies, it has not received adequate attention by funders and African governments. Funding for research into this important disease should be a priority, as appropriate interventions to improve the life expectancy of children with SCA are urgently needed.

We declare no competing interests.

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1 Piel FB, Hay SI, Gupta S, Weatherall JD, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013; **10**: e1001484.

- 2 Billo MA, Johnson ES, Doumbia SO, et al. Sickle cell trait protects against *Plasmodium falciparum* infection. *Am J Epidemiol* 2012; **176** (suppl 7): S175–85.
- 3 Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun* 2010; **1**: 104.
- 4 Allison AC. The distribution of sickle cell trait in East Africa and elsewhere, and its apparent relationship to the incidence of subtertian malaria. *Trans R Soc Trop Med Hyg* 1954; **48**: 312–18.
- 5 Williams TN, Obaro SK. Sickle cell disease and malaria morbidity: a tale with two tails. *Trends Parasitol* 2011; **27**: 315–20.
- 6 Luzzatto L. Sickle cell anaemia and malaria. *Mediterr J Hematol Infect Dis* 2012; **4**: e2012065.
- 7 Uyoga S, Olupot-Olupot P, Connon R, et al. Sickle cell anaemia and severe *Plasmodium falciparum* malaria: a secondary analysis of the Transfusion and Treatment of African Children Trial (TRACT). *Lancet Child Adolesc Health* 2022; published online July 1. [https://doi.org/10.1016/S2352-4642\(22\)00153-5](https://doi.org/10.1016/S2352-4642(22)00153-5).
- 8 McAuley CF, Webb C, Makani J, et al. High mortality from *Plasmodium falciparum* malaria in children living with sickle cell anemia on the coast of Kenya. *Blood* 2010; **116**: 1663–68.
- 9 Agaba BB, Anderson K, Gresty K, et al. Molecular surveillance reveals the presence of *pfhpr2* and *pfhpr3* gene deletions in *Plasmodium falciparum* parasite populations in Uganda, 2017–2019. *Malar J* 2020; **19**: 300.
- 10 Berhane A, Anderson K, Mihreteab S, et al. Major threat to malaria control programs by *Plasmodium falciparum* lacking histidine-rich protein 2, Eritrea. *Emerg Infect Dis* 2018; **24**: 462–70.

## Difficult questions about long COVID in children

The COVID-19 pandemic is likely to leave long-lasting marks on a generation of children and young people, mainly from indirect effects, including those of school closures, social isolation,<sup>1–3</sup> and a so-called immunity debt resulting from 2 years with reduced exposure to common pathogens.<sup>4</sup> A small proportion of children have had serious sequelae of SARS-CoV-2 infection itself, with the most dramatic being multisystem inflammatory syndrome in children (MIS-C).<sup>5</sup> Furthermore, a less well-defined entity, termed long COVID or post-COVID-19 condition, has been suggested, referring to children with long-lasting symptoms after SARS-CoV-2 infection that are not explained by another disease.<sup>6</sup> In contrast to MIS-C, the symptoms attributed to long COVID are non-specific and occur frequently in otherwise healthy children; headache, mood swings, abdominal pain, and fatigue are all common, and, although they can be symptoms of a disease, they often are not.<sup>7</sup> Accordingly, the occurrence of these symptoms after infection with SARS-CoV-2 does not necessarily mean that they are caused by the infection.

Paediatricians frequently meet children with non-specific symptoms. Since the pandemic started, parents have occasionally considered whether a child's symptoms

could be caused by COVID-19 occurring in the preceding months. Therefore, Selina Kikkenborg Berg and colleagues should be applauded for their study, published in *The Lancet Child & Adolescent Health*, assessing whether non-specific symptoms are more frequent in children after infection with SARS-CoV-2 than in children who have never had the infection.<sup>8</sup>

The first finding of the study<sup>8</sup> is that long-lasting symptoms, defined in the primary analysis as those lasting for at least 2 months, occurred frequently in children, regardless of whether or not they had had COVID-19. Although this finding might not be surprising to child health workers, it is an important observation: symptoms in children come and go frequently, often without an obvious cause; sometimes they persist for many months, and usually they eventually wane.

Second, the study found that symptoms of any kind were slightly more frequent in children who had been infected with SARS-CoV-2 (ie, cases). The absolute differences were small, and for most individual symptoms there was no statistically significant difference. For example, among children aged 4–11 years, 125 (2.5%) of 5023 cases had stomach aches over a period of at least 2 months, compared



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with 477 (2.6%) of 18 372 controls; 176 (3.5%) cases had trouble remembering or concentrating for at least 2 months, compared with 760 (4.1%) controls; and 263 (5.2%) cases had mood swings for at least 2 months, compared with 1332 (7.3%) controls. Overall, marginally but statistically significantly more cases than controls had any long-lasting symptom: for children aged 4–11 years, 1912 (38.1%) cases reported any symptoms lasting for at least 2 months, compared with 6189 (33.7%) controls; similar findings were observed with any symptoms lasting for at least 3 months. When considering a longer duration of symptoms, the differences between cases and controls diminished.

Interpretation of these data is challenging. The findings might have been influenced by selection bias. The proportion of parents who responded to the survey was low in cases (29%) and controls (22%), and it is probable that parents whose children had symptoms after COVID-19 would be more likely to respond to a questionnaire about the subject, thereby inflating the proportion of children with long-lasting symptoms among cases. This bias could have been overcome by using registry data, as done in a Norwegian study, which found higher use of primary but not secondary care for children in the first months after having COVID-19.<sup>9</sup> However, in both studies,<sup>8,9</sup> recall bias is possible: at the time of the study, relatively little was known about COVID-19, and substantial public awareness was paid to its severity and complications. In this context, some parents might have been more likely to note minor symptoms in their children after COVID-19.

It is plausible that, in some cases, SARS-CoV-2 infection might indeed cause long-lasting symptoms, as seen after other viral infections.<sup>10</sup> Not addressed by these studies<sup>8,9</sup> is whether symptoms following COVID-19 are more severe or longer lasting than those occurring after infection with other respiratory viruses, such as respiratory syncytial virus, rhinovirus, or influenza virus. Until it is clarified whether COVID-19 differs from other respiratory infections in this way, it seems excessive and premature to establish multi-professional clinics specifically for children with long COVID, as suggested by Kikkenborg Berg and colleagues in the Article.<sup>8</sup>

Third, the study reveals small but significantly higher quality-of-life scores on some scales of the Pediatric

Quality of Life Inventory (PedsQL) in some age groups of children who had COVID-19. This finding seems paradoxical given that cases also reported more long-lasting symptoms, but is reassuring for children with COVID-19.

Fourth, the study reports that “long COVID symptoms” occur in around a third of children after infection. This reporting is problematic: as confirmed by the study itself, symptoms were almost as frequent in children without COVID-19. This finding emphasises that a temporal association with an infection (or other event) does not necessarily imply causality. Furthermore, although the study refers to the WHO case definition when defining long COVID, the WHO definition further requires the exclusion of other causes of the symptoms, which is not possible using a questionnaire.

Research in COVID-19 is like trying to hit a moving target. The present study is already somewhat historical because the children surveyed were infected with a different strain of SARS-CoV-2 than is currently dominant, and more recent strains appear to cause less severe symptoms. Additionally, since the majority of children in Denmark have immunity from previous infection, they might have milder symptoms if infected with SARS-CoV-2 again, limiting the future generalisability of the findings.

The differences found in Kikkenborg Berg and colleagues’ study<sup>8</sup> are small and probably of limited clinical relevance. Because most symptoms were mild, and the small excess of non-specific symptoms was accompanied by a paradoxical higher quality of life in children who have had COVID-19, the study findings can be considered reassuring. On a population level, the overall impact on children of having had COVID-19 is probably small, and less than the indirect effects of the pandemic. For most children with non-specific symptoms following COVID-19, the symptoms are more likely to be caused by something other than COVID-19 and, if they are related to COVID-19, they are likely to pass with time.

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1 Poulain T, Meigen C, Kiess W, Vogel M. Wellbeing, coping with homeschooling, and leisure behavior at different COVID-19-related lockdowns: a longitudinal study in 9- to 16-year-old German children. *JCPP Adv* 2022; 2: e12062.

For the WHO case definition of post-COVID-19 condition see [https://www.who.int/publications/i/item/WHO-2019-nCoV-Post\\_COVID-19\\_condition-Clinical\\_case\\_definition-2021.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1)

- 2 Corrigan C, Duke G, Millar J, et al. Admissions of children and adolescents with deliberate self-harm to intensive care during the SARS-CoV-2 outbreak in Australia. *JAMA Netw Open* 2022; **5**: e2211692.
- 3 Barbieri V, Wiedermann CJ, Kaman A, et al. Quality of life and mental health in children and adolescents after the first year of the COVID-19 pandemic: a large population-based survey in South Tyrol, Italy. *Int J Environ Res Public Health* 2022; **19**: 5220.
- 4 Cohen R, Ashman M, Taha M-K, et al. Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap? *Infect Dis Now* 2021; **51**: 418–23.
- 5 Nygaard U, Holm M, Hartling UB, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. *Lancet Child Adolesc Health* 2022; **6**: 459–65.
- 6 WHO. Coronavirus disease (COVID-19): post COVID-19 condition. [https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-\(covid-19\)-post-covid-19-condition](https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition) (accessed May 17, 2022).
- 7 Rask CU, Olsen EM, Elberling H, et al. Functional somatic symptoms and associated impairment in 5–7-year-old children: the Copenhagen Child Cohort 2000. *Eur J Epidemiol* 2009; **24**: 625–34.
- 8 Kikkenborg Berg S, Palm P, Nygaard U, et al. Long COVID symptoms in SARS-CoV-2-positive children aged 0–14 years and matched controls in Denmark (LongCOVIDKidsDK): a national, cross-sectional study. *Lancet Child Adolesc Health* 2022; published online June 22. [https://doi.org/10.1016/S2352-4642\(22\)00154-7](https://doi.org/10.1016/S2352-4642(22)00154-7).
- 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.
- 10 Kneyber MCJ, Steyerberg EW, de Groot R, Moll HA. Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr* 2000; **89**: 654–60.

## Elimination of race-based medicine: a call to action

In a recently published American Academy of Pediatrics (AAP) policy statement<sup>1</sup> on eliminating race-based medicine, the authors write about “...the elimination of race-based medicine as part of a broader commitment to dismantle the structural and systemic inequities that lead to racial health disparities”. In this, we hear a cry for action. Extensive research and dialogue reaffirms the fact that race is a sociopolitical construct. Racism is a risk factor, induces trauma and epigenetic changes, and negatively influences the social determinants of health. Race itself is not a tool for making clinical decisions. Beyond undoing the damage of the inclusion of race-based care in clinical guidelines,<sup>1–3</sup> we must also ask how we teach medicine; how clinicians, researchers, and policy makers work together to prevent racism in health care; and how we are all held accountable for doing this work. The policy recommendations in the statement are strong and applicable across all roles in health care. In this Comment, we expand on some of these theories and provide a blueprint for what must come next.

Clinical guidelines serve as the standard of care for hospitals throughout the USA and, in the case of some guidelines, throughout the world. The work of examining clinical guidelines for inequities and racism is key to moving towards achieving more equitable care and outcomes, and we applaud the AAP for this work. However, it is necessary for us to interrogate not just the guidelines as they exist, but also the process by which we create guidelines. The output of a project or guideline is only as good as the input provided; if we are not asking the right questions, particularly as they pertain to health equity, we might be missing the mark.

Among the generalised processes that are typically used in clinical guideline creation, it is time we included an examination of whether the guideline being produced is appropriately using the concept of race as a social identity, not a biological one, and is interrogating the influence of racism, considering social determinants of health, and critically examining the social conditions that might be influencing poor outcomes for health conditions, all through a critical race lens.<sup>4,5</sup> By being diligent in the production of guidelines, we move closer to practices that further health equity.

Building on the AAP authors’ call to action,<sup>1</sup> we assert that it is essential—but not sufficient—to remove race-based calculations in clinical guidelines. Addressing these inaccuracies will require a methodical approach to educating current and future clinicians and researchers. A comprehensive strategy to educate the next generation of the health-care workforce should begin with re-examining early childhood education and parental education, given research suggests that infants show preference for particular skin colours at as early as 3 months of age.<sup>6</sup> Within our immediate purview as medical educators, we feel compelled to embed into every course and rotation the understanding that race-based medicine is flawed and ultimately harmful to our patient populations.

We must teach our learners the history of how race-based medicine became mainstream and the evidence behind the assertion that race is a social, not a biological, construct.<sup>7</sup> In doing so, we can remove knowledge gaps, avoid furthering stereotypes, and perhaps spur innovation toward more creative research



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