Project report: Evidence synthesis on Long-Covid

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Overview and Summary of Project
This project aimed to conduct a systematic evidence synthesis on long-term sequelae of SARS-CoV-2 infections to inform policy decisions on essential health care services provision, to improve risk communication to health professionals and the general population, and to strengthen cooperation between epidemiological and clinical research on mechanisms and effective preventions and treatments.

The project aimed to answer the following questions:
1. What is the existing evidence on long-term health outcomes and the resulting impact on daily life activities following SARS-CoV-2 infection? Studies were mapped, and results were stratified according to the following variables: study design, length of follow-up, population characteristics, main health outcomes, preexisting health conditions and health determinants, among others.
2. How were children and adolescents affected by long-term health consequences of SARS-CoV-2 infections impacting healthy development, health-related quality of life, ability to conduct activities of daily living and needs for health care services use?

Study Protocol from OSF
Detailed description of the initial protocol and subsequent amendments can be found at the OSF project site (https://osf.io/b7dwy/)

Article 1
Long-term health symptoms and sequelae following SARS-CoV-2 infection: an evidence map
Post-Covid-19 conditions, also known as Long-COVID, describe a long and more complex course of illness than acute covid-19 with no widely accepted uniform case definition. We aimed to map the available evidence on persistent symptoms and sequelae following SARS-CoV-2 in children and adults.

We searched the Cochrane COVID-19 Study Register and WHO COVID-19 Global literature on Coronavirus disease database on November 5th 2021. We included longitudinal and cross-sectional studies and we extracted their characteristics, including the type of core outcomes for post-Covid-conditions.

We included 565 studies (657 records). Most of the studies were uncontrolled cohort studies (85%). The median follow-up was 13 weeks (range 2-84, IQR 9-24). 72% of studies were conducted in high-income countries, 93% included unvaccinated adults with mild-to-critical disease, only 10% included children and adolescents, and less than 5% children up to five years. Regarding health outcomes, most of the included studies focused on health symptoms, including respiratory symptoms (71%), neurological symptoms (57%), fatigue (54%), pain (50%), mental functioning (43%), cardiovascular functioning (40%), and post-exertion symptoms (28%), cognitive function (26%). Fewer studies assessed other symptoms such as overall recovery (24%), the need for rehabilitation (18%), health-related quality of life (16%), changes in work/occupation and study (10%), or survival related to Long Covid (4%). Most studies (83%) reported multiple outcomes.

Concluding, there is a need for controlled cohort studies with long-term follow-up and focus on overall recovery, health-related quality of life and ability to perform daily tasks. Studies need to be extended to later phases of the pandemic and countries with low resources. Choosing adequate controls will get increasingly difficult as the pandemic proceeds, with more and more people getting infected. This will require careful assessment of infection and immunisation status as well as health status/health determinants before infection. In addition to controlled cohort studies, case comparison (control) studies may be valuable based on a refined clinical case definition of Long COVID. This requires intensive work on a consented clinical case definition, systematic identification of cases (case registers), and identification of valid controls.
Article 2

Short and long-term wellbeing of children following SARS-CoV-2 infection: a systematic review

To describe the findings of studies assessing key outcomes related to global wellbeing and recovery in children and adolescents, we searched the Cochrane COVID-19 Study Register and WHO COVID-19 Global literature on coronavirus disease database on 5 November 2021 and created a comprehensive evidence map of longitudinal and cross-sectional studies on COVID-19 related symptoms and sequelae.

We selected those studies from the map and tracked emerging data from the identified ongoing studies that included children and adolescents with a follow-up greater than 12 weeks and focused on quality of life, recovery, school attendance and resource use/rehabilitation. We assessed their methodological quality with the JBI tool for prevalence studies. Due to the heterogeneity across studies, we did not conduct a meta-analysis and prepared a narrative synthesis of the results.

We included 25 studies (21 longitudinal - 6 retrospective and 4 cross-sectional, six with a control group, of which one was a controlled cross-sectional study) with over 68 thousand unvaccinated children and adolescents with mostly asymptomatic or mild disease. Most of the studies had important limitations due to the use of a convenience sample, a poor description of their study population and heterogeneous definitions for the main outcomes of this review. Based on four studies, quality of life was not largely affected in adolescents following COVID-19, but there might be greater impairment in young children and those with more severe forms of the disease (Paediatric Inflammatory Multisystem Syndrome). Based on five studies, there might be an impairment in daily activities and increased school absenteeism following COVID-19, but the findings were highly variable. Regarding recovery and duration of symptoms, 22 studies provided highly variable estimates based on heterogeneous definitions of overall persistence of symptoms, ranging from 0 to 67% at 8-12 weeks and 8 to 51% at 6-12 months. We found limited data on resource use and the need for rehabilitation. One controlled study indicated that the quality of life of infected children and adolescents might not substantially differ from controls. All controlled studies found a higher burden of persistent symptoms in COVID-19 cases compared with test-negative controls or cases of influenza. Only seven studies (28%) reported multiple outcomes.

Concluding, there is to date limited evidence on the short and long-term well-being of children following SARS-CoV-2 infection. The findings from these first studies indicate that long-term symptoms may be present in children, but the burden estimates were based on heterogeneous estimates and studies with methodological limitations. High-quality longitudinal studies with control groups are needed to describe the outcomes in this population, especially in the later stages of the pandemic following the implementation of vaccination and the emergence of new variants as well as reinfections.

Appendix 1: List of excluded studies after full-text screening and reasons for exclusion

Detailed description of the excluded studies with the reasons for exclusion can be found at the OSF project site (https://osf.io/b7dwy/)

Appendix 2: Data extraction table with results and Risk of Bias information from included studies

Detailed description of the data extraction table and risk of bias assessment of included studies can be found at the OSF project site (https://osf.io/b7dwy/)