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## The COVID-19 continuum of illness



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Published Online  
June 15, 2022

[https://doi.org/10.1016/S2213-2600\(22\)00219-3](https://doi.org/10.1016/S2213-2600(22)00219-3)

This online publication has been corrected. The corrected version first appeared at [thelancet.com/respiratory](https://www.thelancet.com/respiratory) on June 29, 2022

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On Oct 6, 2021, WHO recognised the need to codify the post-COVID-19 condition and formalised the cataloguing of diverse symptoms and multisystem sequelae after COVID-19. Symptoms of post-COVID-19 condition include fatigue, shortness of breath, cognitive dysfunction, and symptoms interfering with daily functioning. These symptoms can remit or relapse over time, but persist for at least 2 months and occur 3 months after the initial COVID-19 illness.<sup>1</sup>

This seminal cataloguing of symptoms has been supplanted by the urgency to develop a core outcome set (COS) to ensure uniform capture of critically important symptoms for post-COVID-19 clinical research studies. Daniel Munblit and colleagues,<sup>2</sup> using a rigorous Delphi consensus methodology and prespecified criteria for outcome inclusion, have developed a COS for symptoms of the post-COVID-19 condition that include: fatigue; pain; post-exertion symptoms; work or occupational and study changes; survival; “functioning, symptoms, and conditions” for each of cardiovascular, respiratory, nervous system, cognitive, mental health, and physical outcomes; and recovery. A strength of their study was the recruitment of a diverse and multidisciplinary investigator group and inclusion of those with lived experience of post-COVID-19 condition and their carers. Munblit and colleagues’ strong foundational work, including the multisource development of an exhaustive a-priori list of candidate post-COVID-19 symptoms, and methodology ensure robust validity.

Despite the laudable rigour and importance of this work, there are some limitations that warrant discussion. The participant sample for the Delphi procedure might challenge the generalisability of the findings because their characteristics (ie, country of origin, age, sex, and ethnicity) might not be wholly representative of these same stakeholder groups worldwide, particularly in relation to at-risk groups. COVID-19 has highlighted the central role of social determinants of health in the development and exacerbation of long-term morbidity.<sup>3</sup> Purposive recruitment, including people of colour, political refugees, migrants, the immunocompromised, older people, at-risk young people, those residing in low-income and middle-income countries, and those who are socially disadvantaged, is crucial to capture and contextualise reported symptoms as part of

core outcomes. Munblit and colleagues clearly went to great lengths to recruit a representative study sample, but due to compromised access to health care, limited education, poor health advocacy and literacy, institutionalised racism, and poverty, many people are still systematically not represented. We need to urgently address these challenges to ensure that the COS has broad validation and evaluation in the most at-risk populations.

Looking ahead, it is imperative that we understand the interrelatedness and responsiveness of the COS across the severity of COVID-19-related illness. The determination of both shared and unique symptom distributions across illness severity has important implications for mapping to clinical outcomes, development of a standardised follow-up scheme, and ongoing interprofessional and multidisciplinary longitudinal intervention. Some examples are seen in the Wuhan cohort that was followed for 1 year after recovering from COVID-19.<sup>4</sup> Almost half of patients across the illness spectrum reported at least one symptom at the 1-year follow-up, although symptom prevalence varied by COVID-19 severity. By contrast, reports of pain and discomfort, anxiety, or depression were similarly represented regardless of illness severity. The entire critically ill group was distinct and reported more dyspnoea and had poorer lung function and worse functional outcomes at 1 year than did patients with less severe illness. This finding highlights the dominant contribution of acute respiratory distress syndrome (ARDS) and critical illness sequelae,<sup>5</sup> and the difficulty in discerning what is solely attributable to COVID-19 rather than post-intensive care syndrome.<sup>6</sup> The COS will require validation across the spectrum of COVID-19 severity of illness.

As Munblit and colleagues discuss, a crucial next step is to mesh the symptom-based COS with clinical outcomes that are important for patients and their families. COVID-19 is a multisystem disease, necessitating the adoption of a robust suite of clinical outcomes that capture end-organ injury and facilitate identification of pre-existing and novel clinical phenotypes. The outcomes used in many COVID-19 cohorts with 1-year follow-ups already recapitulate the outcomes previously studied in severe ARDS,<sup>5</sup> severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome

(MERS).<sup>7-9</sup> Identifying commonalities and differences from previous work in coronaviruses is informative, but it is imperative to further extend candidate outcomes through comprehensive biological and tissue sampling. The COS must be mapped to a spectrum of clinical outcomes that promote a fuller understanding of innate host susceptibility and resilience across organ systems through foundational genetics, and basic and translational science.<sup>10</sup>

The COS requires evaluation within the care continuum, incorporating interprofessional and multidisciplinary perspectives, to understand individual patients' long-term health trajectories and how COVID-19 modifies baseline health status and long-term outcomes, and contributes to high-cost health-care users. Patients with SARS and MERS had important and persistent decrements in multidimensional outcomes and compromised health-related quality of life up to the 2-year follow-up. Critically ill patients who survive severe ARDS experience persistent disability and increased health-care use for 5 or more years after their illness.<sup>11,12</sup> The sequelae of COVID-19 warrant priority on the basis of the sheer number of surviving patients around the world, the enormous burden placed on underfunded specialty, rehabilitation, and mental health services, and the urgent need to inform public policy and health-care planning.

Family outcomes in caregivers and their children also need to be prioritised for core outcomes. Families of patients with COVID-19 have reported difficulty in establishing relationships with the intensive care unit (ICU) team and felt powerlessness, unreality, and abandonment with their loved ones.<sup>13</sup> Post-traumatic stress disorder (PTSD) has been reported in 35% of caregivers and independently associated with COVID-19-related ARDS.<sup>14</sup> Younger children are rarely studied but are at considerable risk for PTSD.<sup>15</sup> COVID-19 illness was often clustered within families, leading to multiple family members in hospital or the ICU simultaneously. In some cases, several family members died within a short period of time and some children were orphaned.

Building on this important initial work, we need to further validate symptoms with broad representation across the COVID-19 spectrum of illness and within our most susceptible and diverse patient groups in developing countries and across varied health-care systems. We need to map symptoms to outcomes important for patients and their families, informed by

genetic and translational work to explicate differential innate vulnerabilities, multisystem injury, and resilience. We need to embrace an illness episode as part of a continuum of care and recovery, and endorse the necessity of long-term follow-up. COVID-19 illness affects the entire family and health-care team—caregivers, children, and health-care providers must be included in all studies and planned interventions going forward.

MSH participated in the WHO Delphi consensus study and was also a participant in the Delphi exercise and member of the broader steering committee (PubMed indexed) of the Post-COVID-19 Condition Core Outcome Set study by Munblit and colleagues. ÉA declares lecture fees from Alexion and Sanofi; in addition, his hospital has received research grants from Baxter, Alexion, Fisher Payckle, and Merck Sharp & Dohme.

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