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This is a revised, written version with bibliography of my testimonial for the patient perspective panel held on Friday 12 May 2023.

I rapidly go through the working definition for Long Covid in view of research, pathophysiology, and lived experience. I highlight the current definition in bold in the following text.

Overall, I think the working definition is a good and inclusive definition as a starting point.

“Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection.”

This is appropriate as we know, scientifically, that a vast range of symptoms, signs, and conditions are associated with Long Covid (*below*). It would be useful to clarify that a positive PCR, RAT, or antibody test are not necessary for diagnosis. A clinical diagnosis of Covid–Long Covid should be enough. Many do not have access to such tests. Moreover, the risk of false negatives is relevant under certain circumstances, such as timing of administration, type of testing, and individual immune response to infection [1] [2] [3].

“The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection”

I broadly agree with the four week threshold as a starting point [4] although I acknowledge there are different perspectives, including the WHO definition of post Covid condition. I also note: There can be delayed onset of symptoms, signs and conditions after [the acute phase of the disease–four weeks], including potentially after asymptomatic–subclinical–pauci-symptomatic–mild onset of Covid [4] [5] [6] [7] [8]. Long Covid can be the outcome of different levels of disease severity in the acute phase, from asymptomatic–pauci-symptomatic, to life-threatening Covid that required hospitalization [5] [6] [9] [10] [11]. Long Covid can affect patients of all ages, genders, ethnicities, and prior health statuses.

“Long Covid may be multisystemic; and may present with a relapsing–remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection”

These are strong points [12] which must be maintained, including the mention of severe and life-threatening events far from infection (e.g. stroke, thromboembolism, myocarditis—pericarditis, etc). The existence of such events and conditions is proven by lived experience, case reports [6] [7] [13] [14] [15] [16], and data on mortality and increased risk for death in Long Covid [17] [18] [19] [20] [21]. Awareness around this point is fundamental to save lives. While it is possible (but not assured) the highest risk of death and severe events in Long Covid is closer to infection in some patients, we cannot forget people are being reinfected.

I would add “and lifelong disability.” We already know some outcomes of SARS-CoV-2 infection do not have a cure in view of current medical knowledge, or are irreversible (e.g. amputations, transplants [22] [23] [24]). We do not have any certainty that a cure for Long Covid will be found (leading to full disease resolution).

“Long COVID is not one condition.”

I note that Long Covid can present with many associated conditions affecting, basically, all organs and body systems e.g. [5] [8] [18] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37]. The extent of pathology and disease severity can vary from individual to individual, and over time. The kinds of organs and body systems affected can also vary from person to person and across the disease course [26] [38].

“Long Covid represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes.”

This is a valid point and noted in the literature. [I reserve to comment further if more clarity is available about what “entities” mean in this context].

I add below some further comments, which can help the committee to address some pressing issues.

Recognize not everyone has access to the best diagnostic investigations.

Recognize some damage to organs and tissues can be identified only, or primarily, via procedures such as autopsies, (which were critical to early discoveries on pathophysiology) e.g. [39] [40], or sophisticated diagnostics, which are often available only in research settings e.g. [29] [37]. It is also possible some damage cannot even be identified with existing tools.

Damage to specific organs and body systems, therefore, can be present, even when a patient do not have evidence of it on paper.

This shouldn't preclude people with impairments, physical limitations, symptoms, etc. from receiving support, such as disability benefits, sick leave, additional, more sophisticated clinical investigations, and even treatment when needed and possible.

Yet, we must be careful with 1. “Hasten” diagnoses – namely, diagnoses made too fast [4]; 2. Restrictive, too specific clinical case definitions, for example based on a few synonyms only, which could exclude people from a diagnosis of Long Covid and any potential diagnostics or treatments; 3. too “firm”, not flexible classification in sub-types (such as phenotypes and endotypes), when not everything is known about Long Covid, each patient might have their own challenges, and not everyone has access to adequate investigations.

Billions of people have now likely been infected with SARS-CoV-2. Only a small minority has been analysed for Long Covid. We don't know everything.

An inclusive clinical case definition shouldn't preclude, however, support, treatment, and specific sub-diagnoses and research endpoints under Long Covid (e.g. thromboembolism, diabetes, dysautonomia, coagulopathy, pericarditis, heart failure, chronic kidney disease, immune dysfunction, etc.), when the evidence for such conditions is found in a patient. Many conditions and complications have already been linked to Long Covid in the literature e.g. [5] [16] [17] [18] [19] [20] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [41] [42]. Long Covid does not mean "vague symptoms" or an "ill defined syndrome".

Personalized and interdisciplinary approaches are key, given how broad and heterogeneous Covid itself is [4] [38]. This heterogeneity across the patient population can be reflected, obviously, in the "long" tail of the disease. Not all patients will necessarily present exactly with the same symptoms, signs and sequelae in Long Covid.

Please consider different disease pathways [4]. The natural history and development of Covid–Long Covid can vary from patient to patient e.g. [5] [6] [8] [24] [43].

Hospitalization alone should not be used as an indicator of Covid–Long Covid severity. Many factor—including gender, race, ethnicity, bed availability in hotspots— can play a significant role in access to care [4]. There are people who were not hospitalized in acute Covid and died beyond four weeks e.g. [7] [13], while people with milder acute disease and apparent resolution of symptoms are reported to have been hospitalized in the acute phase e.g. [44]. Others are hospitalized in Long Covid but not in acute Covid e.g. [5] [6].

Many people with mild disease at onset have developed Long Covid.

Early treatment should be fundamental to avoid deterioration. This is really difficult to get, however, for many people. The provision of early diagnosis and treatment should be an area of utmost urgency.

Long Covid, as a concept, offers an unifying framework to understand and reflect upon "post covid" pathology [4].

An issue is, do diseases, such as diabetes or autoimmune diseases, post Covid present with the same features of the same diseases pre-pandemic? Namely, if you are diagnosed after Covid with a disease meeting the clinical case definition for, for example, rheumatoid arthritis or diabetes, is it possible such conditions present specific features induced by the trigger (Covid–SARS-CoV-2 infection), or influenced by the patient having had Covid – for example a stronger cardiovascular component, or additional Covid-related comorbidities, such as the sequelae of acute Covid lung pathology? This topic is, actually, already being addressed in research. For example, Rubino et al 2020 wondered in the NEJM whether the type of diabetes triggered by Covid could be a "a new type of diabetes", and about its "natural history", and "management" [45].

This issue has implications for the diagnosis and treatment of many conditions post Covid.

Long Covid, as a concept, also, allows to address features which are, or could be, specific to SARS-CoV-2 infection e.g. [4] [39]; not least viral persistence of SARS-CoV-2 [46]. Some of such

features could be yet to be identified. We need to acknowledge the unknown. We need to be ready to include emerging evidence fast and effectively.

SARS-CoV-2 infection could trigger or drive a change in the whole landscape of our body: metabolic, in the cardiovascular system, the coagulation cascade, how we respond to medication, to medical procedures, etc. This must be addressed urgently.

Recognition of any Covid-specific damage, however, must not preclude access to treatment, where such treatment is appropriate (e.g. for diabetes post Covid). Some conditions associated with Long Covid, such as cardiovascular disease, are particularly worrisome as they can be fatal [7] [13] [14] [15] [19] [20].

Differential diagnosis to identify conditions which aren't Long Covid (e.g. lung cancer when the patient presents with respiratory symptoms) remains critical. Yet, Long Covid shouldn't be a diagnosis of exclusion. Ramifications and complications of Long Covid such as metabolic, cardiovascular, pulmonary, renal etc. disease should be part of clinical diagnosis and research endpoints.

The risk of longest-term sequelae, such as neurodegenerative pathology or cancer, remains to be fully elucidated. Yet, this risk should be addressed in view of emerging evidence e.g. [47], a review with bibliography [48] [49]. We also know other infections and viruses are linked to such conditions [50] [51]. Infections and viruses are also linked to a wide array of sequelae and specific conditions emerging, or becoming apparent, years or decades after infection (for example, multiple sclerosis and the widely discussed link with the Epstein Barr virus [52] [53] [54]; AIDS from HIV infection; post-polio syndrome from poliovirus infection [55].).

Covid–Long Covid is—are some of the most studied diseases in medical history. As of 23 May 2023, a search on the repository for medical papers PubMed under *Covid renders over 356,000 results [56]. There are several thousands of publications on Long Covid alone [57]. We have a lot of knowledge to build on. This is in addition to existing biomedical knowledge from before the pandemic, including around other infections and related conditions like ME/CFS, dysautonomia, viral persistence, etc. [58]. There is evidence of prolonged illness from SARS-COV infection—SARS e.g. [59]. In view of all this, we shouldn't say Long Covid is “mysterious”. People deserve to know about the risks of SARS-CoV-2 infection. Clinicians and researchers should be informed on both existing and emerging biomedical data.

We need, however, more research on Omicron and the effects of multiple infections with SARS-CoV-2, with particular regard to pathophysiology.

As I collaborate with the charity Long Covid Kids, I want to draw attention to pediatric Long Covid. There is increasingly vast evidence of Long Covid in children, and growing research on pathophysiology [5] [6] [41] [60] [61] [62] [63] [64] [65] [66] [67]. However, we need more research to fully elucidate pathophysiology and potential treatments (as is the case for Long Covid in adults). Long Covid in children is an urgent topic, also in the context of repeated infections. The impact of SARS-CoV-2 infection—Covid on pregnancy, the foetus and embryos, is another urgent area to address. This is also in view of growing evidence in this regard e.g. [68] [69].

It is about the future of our children.

Children may face specific challenges to care and diagnostic, such as depending on their caregivers; or poor recognition of Long Covid in pediatric patients.

I conclude by saying that Long Covid is the patient-made and patient-preferred term for the long-term health effects of SARS-CoV-2 infection [4] [12] [70] [71]. I invite the committee to recognize the immense amount of collective, grassroots, international, often unpaid and unrecognized labour the Long Covid community has mobilized to achieve recognition.

There is no time to waste. Long Covid must not be minimized. People living with Long Covid deserve care, support, research, treatment.

There is much more to say but time has gone. Thanks very much for your kind attention. I am happy to answer any further questions: elisaperego78@yahoo.it

Author and disclaimer

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I am Honorary Research Fellow at University College London, an honorary position, not employment. I am currently too ill to hold a steady job, especially a full-time “9 am–5 pm” one. I am a person living with Long Covid. I have experience of chronic disease and infectious diseases with long-term symptoms from before Covid. I am Long Covid Kids Champion for the charity Long Covid Kids. This is an unpaid, volunteer position to raise awareness about pediatric Long Covid. I present my evidence as an individual patient, researcher, and advocate, and not on behalf of any organisation. I have been widely involved in Long Covid patient-driven advocacy, research, policy, and science communication since early 2020 to the best of my capacity in view of my health. I took part to the WHO meeting of August 2020 that openly recognized Long Covid. I am a researcher, and not a clinician or medical doctor. These recommendations must not be considered medical advice, but as research and advocacy ones. The bibliography is indicative, and not exhaustive. The committee will want to consider strengths and limitations of the various studies cited. No funding supported the preparation of this document. I am grateful to the Long Covid and chronic illness community for extensive discussion on Long Covid.

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