The Broad Street Pump

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Long COVID – Knowledge gaps, research needs and a way forward

Professor Tania C. Sorrell, AM

University of Sydney, Australia

Introduction

After the health, social and economic impost of the COVID-19 pandemic, Long COVID has emerged as a major concern with implications for individual, population and societal health, for public health practice and for health systems planning and resourcing. Long COVID lasting more than twelve weeks is estimated to affect 5–10% of Australians who have had COVID-19[1], but lower rates following SARS-CoV-2 infections since 2022 have recently been reported in the United Kingdom (4.0% of first infections in adults, 2.4% of re-infections)[2]. Even so, this amounts to potentially hundreds of thousands of cases in Australia and more than 65 million worldwide. The true prevalence/incidence in Australia is unknown, as national population data have not been collected systematically and a standardised definition, though urgently needed, has not been developed (either here or overseas).

The Australian Government response

In recognition of the potential scale of the problem and the lack of knowledge about Long COVID, the Australian Government has nominated it as a key focus in Australia's COVID-19 response, alongside COVID-19 vaccines and treatments (National COVID-19 Health Management Plan 2023)[3]. A parliamentary Committee of Enquiry into Long COVID and repeated COVID Infections chaired by Dr Mike Freelander, MP, was established in late 2022. More than 600 submissions were made to this committee by multiple stakeholders, including one from the Australian Academies of Science and of Health and Medical Sciences. These Academies also convened an interactive Roundtable of experts with the parliamentary committee at Parliament House Canberra, chaired by Tania Sorrell, in February, 2023. The Roundtable documents and discussion are available in Hansard and form the basis of this paper. The final parliamentary committee report was released in May 2023[4].

Inside this issue

Professor Tania C. Sorrell, AM

University of Sydney

CIDM centre for infectious diseases & microbiology Public Health

NSW Government Health Western Sydney Local Health District

The University of Sydney

Long COVID, what is it, knowledge gaps, research and research needs, and the way forward.

History: The term "Long COVID" was first used by affected individuals and introduced via Twitter by Dr Elisa Perugo in May 2020[5]. Since then, it has been widely adopted by the community and authorities alike. However, providing a case definition for a complex and heterogenous condition like Long COVID, to meet the needs of different end-users has been problematic. Challenges include the following:

(1) Different "end users" require a case definition that is clear and appropriately nuanced to facilitate:
- Research needed to understand, diagnose and manage Long COVID so as to ultimately improve health outcomes,
- Surveillance to understand the nature, extent and distribution of the condition,
- Clinical care, rehabilitation and social support,
- Public health and health policy development,
- Health system planning (for patients, impacted workforce and future needs),
- High quality evidence to inform resourcing by government and other funders.

(2) Long COVID is a heterogeneous condition that is influenced not only by underlying biological mechanisms but also the individual's psycho-social context, socioeconomic and cultural circumstances and the available social support.

(3) There is evidence for multiple underlying pathophysiological mechanisms. However, there is no single, simple/definitive diagnostic test, nor is there likely to be. Efforts are being directed toward identifying a minimum set of characteristic diagnostic and/or prognostic bio/physiological/imaging markers/correlates.

(4) A working, functional definition must evolve with new information, but a standardised, operational definition is needed now for clinical purposes and impactful research outcomes.

The challenge of Long COVID as an entity is perhaps best encapsulated by health systems expert and academic, Professor Martin Hensher, in a recent Editorial entitled "Long COVID in Australia: achieving equitable access to supportive health care"[6] viz " Long COVID is precisely the kind of challenge the current Australian health system finds most difficult: a non-fatal, chronic condition manifested as complex combinations of symptoms, without a simple diagnostic test or definitive pharmacotherapy, and causing distress to people with the disorder, who may need considerable face-to-face and other contact care".

The WHO definition of Long COVID is used most commonly, world-wide, but has limitations. It was developed for clinical purposes using Delphi methodology[7].

> *Long COVID is defined by "a history of probable or confirmed SARS CoV-2 infection, with symptoms present usually 3 months from the onset of COVID-19, which last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, but also others, and generally have an impact on everyday functioning. Symptoms may be new in onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time".*

This definition provides a useful clinical framework but contains ambiguities, and for epidemiological and other research studies in particular, risks being over-inclusive and hence non-discriminatory.

Individual symptoms are common to many conditions. More than 200 symptoms have been reported post-acute COVID-19, with three symptom clusters, which can also overlap, being the most common (see Figure 1 below), though the range of diagnoses is reduced when symptom severity is associated with inability to perform usual work or activities of daily living.

Figure 1 [8]

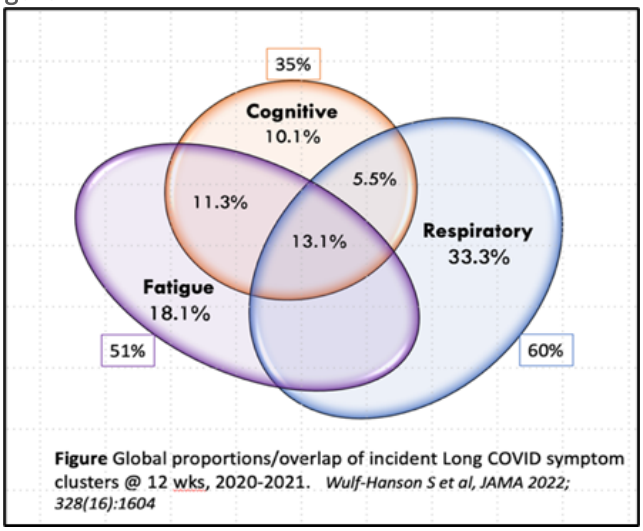


Figure Global proportions/overlap of incident Long COVID symptom clusters @ 12 wks, 2020-2021. *Wulf-Hanson S et al, JAMA 2022; 328(16):1604*

Other relatively common symptoms include abdominal pain, altered smell/taste, anxiety, blurred vision, chest pain, cough, depression, dizziness, intermittent fever, gastrointestinal issues - diarrhoea, constipation, acid reflux, menstrual problems, joint pain, muscle pain, headache, neuralgia, paraesthesiae, post-exertional malaise, sleep disorders, tachycardia/palpitations, new onset allergies, tinnitus and other hearing issues. In meeting the WHO criterion of "probable Long COVID" we now face the added uncertainty of the acute COVID diagnosis created by the current marked decline in community testing for/reporting acute COVID.

Ambiguous wording: Ambiguities in the WHO wording, highlighted by italics in the definition (see Box 1 above) are problematic for research in particular as they have the potential for significant overcall of the diagnosis and hence reduction in the reproducibility and value of research findings. In addition, published studies of incidence/prevalence are difficult to compare because investigators have tried to streamline the WHO definition, for example, by nominating different times of onset post-acute COVID. Many studies are also subject to additional biases, not least of which are a reliance on self-reporting of symptoms, lack of controls, and an initial focus on hospitalised patients.

A "living definition": In an evolving pandemic, any definition must evolve with new evidence (new understanding of the pathophysiology, indicative prognostic and diagnostic tests, functional assessment tools, validated treatments, social support pathways). Most importantly, any definition must be easily understood and meaningful to all stakeholders including the general public, First Nations Peoples, culturally and linguistically diverse communities and people with limited health literacy. It must be co-developed/modified in collaboration with people with lived experience, clinical and diagnostic discipline experts; researchers; public health and health planners and align with an international definition (i.e. developed with international colleagues)

Knowledge gaps and research required (Boxes 2 and 3)

Many issues were discussed during the Roundtable, which was comprised of expert clinicians, epidemiologists, academic researchers, and representatives of priority populations, community organisations and those with lived experience. Specific disciplines represented included infectious diseases, microbiology, epidemiology, modelling, immunology, genomics, proteomics and metabolomics, mental health, allied health, psychiatry, neurology, cardiology, respiratory medicine, primary care, aged care and rehabilitation, vaccinology, social science and communication, public health, health systems and health policy).

Box 2. Knowledge gaps

- The impacts on the progression of long COVID of natural infection, vaccination and treatments given during the acute COVID phase.
- The most effective treatments and management strategies.
- How surveillance and monitoring most effectively and efficiently be undertaken, analysed and promulgated.
- The prevalence and impact of long COVID on Aboriginal and Torres Strait Islander peoples, CALD communities, people with disabilities and other priority populations.
- How long COVID impacts children under 10 years of age.
- The role of biomarkers in diagnostics and further research
- Evidence-based models of care and support.
- Long COVID patient access to, and inequities in, the health system including longer-term support.
- How to support patients to manage their condition, where they can actively do so.
- How to help the health workforce understand long COVID and be equipped to deal with it.

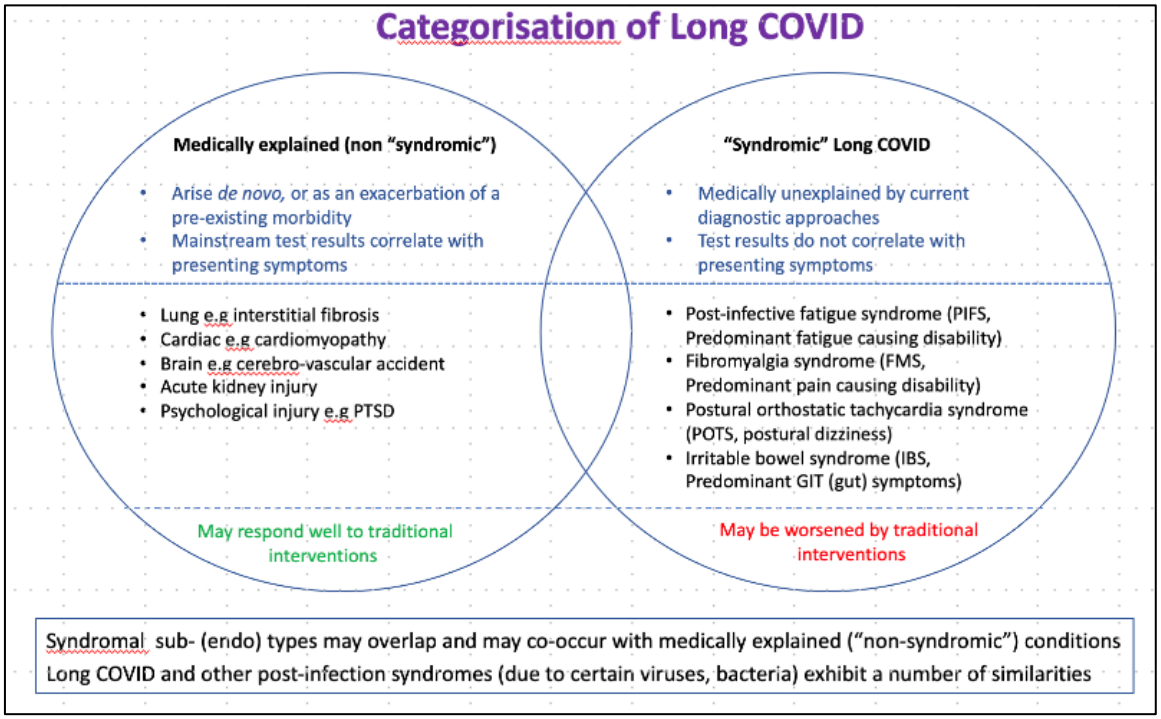
Box 3. Research to address knowledge gaps

- Determine the most effective, centralized, integrated national data warehousing, surveillance/ monitoring/analysis systems that also capture priority populations (Aboriginal and Torres Strait Islander peoples, CALD communities, people with disabilities, immune-suppressed etc. and improve public health predictions/ interventions eg an Australian CDC.
- Impacts of natural infection, viral variants, vaccination, antiviral/other treatments in acute phase.
- More specific diagnostics and corroborative tests (laboratory and clinical/functional), role of biomarkers for diagnosis/endotyping/risk assessment.
- Validation of new treatments/other interventions eg rehabilitation, mental health, social support, self-management with equitable access to clinical trials.
- Adequate and sustained research infrastructure, platforms (eg biobanks) and networks.
- Informed public (including communications tailored to First nations, CALD, other key populations).
- Up to date, cognate workforce – education, training and communication.
- Adequate clinical workforce, public health, clinical /basic researchers, health planners.
- Co-development of research with people with lived experience.

Boxes 2 and 3[9]

Categorising Long COVID to better understand the extent and impact of the condition, its relationship to other post-viral syndromes and to generate an integrated health system response.

Figure 2 illustrates a practical categorisation of Long COVID that distinguishes two main categories or subgroups[9,10].



Linking Long COVID categories with underlying pathophysiology.

Mechanisms proposed to explain the pathophysiology of Long COVID can be grouped into those causing organ damage associated with the initial acute infection and long-term "inflammatory" mechanisms. Hypotheses for the genesis of these "phenotypes" are under active investigation and include one or more of viral persistence (or persistence of components of the virus), impaired oxygen delivery due to micro-clotting associated with endothelial dysfunction; microvascular dysregulation and vasculo-proliferative processes initiated by prior hypoxia; disruption of cellular energy metabolism and other metabolic pathways, collectively designated as the metabolic phenotype[11] immune dysregulation with or without reactivation of latent pathogens such as the herpes viruses EBV and HHV-6; autoimmunity and immune priming from molecular mimicry; alterations in the gut microbiome (dysbiosis), and dysfunctional signalling in the brainstem and/or vagus nerve [10,12,13].

A detailed understanding of the different pathologies will facilitate refining diagnostic and prognostic markers for this complex and perplexing condition.

A nationally coordinated research program

Recommendation 4 of 9 put forward by the parliamentary committee to the Minister for Health and Aged care proposes *that Australian Government establish a nationally coordinated research program, led by the Department of Health and Aged Care (and preferably linked into pending Australian Centre for Disease Control), to coordinate and fund COVID-19 and long COVID research and that:*

- This funding should be longer term, be nationally coordinated and aim to better integrate research by fostering greater collaboration rather than fragmentation.
- There be adequate representation from Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse populations and other vulnerable groups including the elderly, children, people with disability and the immunosuppressed.
- Research programs should span basic science, clinical trials, models of care, health promotion and implementation science and be adequately funded.

MRFF funding announced.

Upon release of the parliamentary committee report the Hon Mark Butler announced an allocation of AUD $50 million for research into long COVID from the Medical Research Future Fund (MRFF) with an initial call for applications expected later this year[14].

The ministerial and governmental response to the additional eight recommendations is under active consideration. A framework for better and more equitable outcomes, which would see a fundamental change in health care delivery for chronic and complex conditions like long COVID, is summarised in a solicited Editorial in the Medical Journal of Australia, written by three members of the Roundtable group of Experts[6].

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Staff Profile

Dr Xiaomei Zhang

Dr Xiaomei Zhang is currently undertaking a NHMRC TB-CRE postdoctoral fellowship in Mycobacterial Genomics under the supervision of Professor Warwick Britton, at the Centenary Institute and the Centre for Infectious Diseases and Microbiology – Public Health (CIDM-PH), Westmead. Since completing her PhD in Microbiology and Immunity at the evolutionary microbiology lab (Lanlab), University of New South Wales, in March 2022, her research has focused on the rapid detection and identification of bacterial pathogens using genomics. She has successfully transitioned into the field of mycobacterial genomics, employing advanced techniques to the complex dynamics of tuberculosis (TB) transmission and drug resistance.

In her current role, Xiaomei's research primarily focuses on investigating local transmission patterns and drug resistance in TB in NSW, Australia. By utilizing routine Whole Genome Sequencing (WGS) data obtained from clinical isolates, she aims to evaluate the added value of Mtb WGS in drug susceptibility testing and explore benchmarks for assessing TB control programs using WGS, particularly in low incidence settings. Xiaomei investigates drug-resistant within-host sub-populations and the frequency of resistance-conferring mutations in minority variants. Her work provides an important assessment of drug-resistant minority variants with potential for improving patient outcomes, considering the growing utilization of high-resolution sequencing-based methods for TB surveillance and care, in regions with a high burden of TB. Xiaomei is also focused on the development of targeted next-generation sequencing assays for detecting drug resistance. Her goal is to contribute to the advancement of diagnostic tools that can facilitate the timely and accurate identification of drug-resistant TB strains directly from clinical samples.

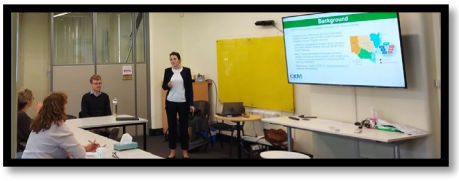
Dr Xiaomei Zhang
Centenary Institute / CIDM-PH
xiaomei.zhang@sydney.edu.au

News & Events

CIDM-PH and Sydney ID were recently joined by delegates from Duke-National University Singapore, Ministry of Health Indonesia, and Research Institute for Tropical Medicine Philippines, for a two-day workshop on **"Developing decision trees for pathogen genomics"** with the aim to develop practical tools to assist countries in Asia to help prioritize efforts for integrating genomics sequencing within national surveillance programs.

Developing Decision Trees for Pathogen Genomics Workshop

CIDM-PH hosted its first workshop in the **"Trial of Genomic Surveillance"** with the Western Sydney Public Health Unit on 15 & 19 May 2023. The aim of this workshop is to assess the impact of integrated genomic surveillance across the continuum of public health care involving public health units. Workshops with Far West and Western NSW, and Murrumbidgee and Southern NSW are scheduled for later in the year.



Trial of Genomic Surveillance Workshop

CONTACT US

CIDM-PH

Centre for Infectious Diseases and Microbiology Public Health

Westmead Hospital, ICPMR Building,
Level 3, Cnr Hawkesbury & Darcy Roads,
Westmead NSW 2145

PHONE:

(612) 8890 9870

WEBSITE:

www.wslhd.health.nsw.gov.au/CIDM-PH

E-MAIL:

WSLHD-CIDM-PH@health.nsw.gov.au

SYDNEY ID

Sydney Institute for Infectious Diseases

Westmead Hospital, Block K, Level 5

Cnr Hawkesbury & Darcy Roads
Westmead NSW 2145

WEBSITE:

www.sydney.edu.au/infectious-diseases-institute

E-MAIL:

infectious.diseases@sydney.edu.au

UPCOMING EVENTS

Sydney ID Distinguished Lecture
Prof Peter Hotez

The deadly rise of antiscience – vaccines, neglected tropical diseases and climate change

15 June 2023

9.30am – 10.30am (AEST)

Register

SAVE THE DATE…

PROGRAM & REGISTRATION COMING SOON

CIDM-PH Webinar

Unravelling Hot Topics in Infectious Diseases

21 July 2023

1.00pm – 4:00pm (AEST)

Online – Registrations open soon

CIDM-PH Annual Colloquium

24 November 2023

9.00am – 5:00pm (AEST)

WECC, Westmead Hospital, Westmead NSW

Event Enquiries:

WSLHD-CIDM-PH@health.nsw.gov.au

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