Submission to the Inquiry into Long COVID and Repeated COVID Infections

House Standing Committee on Health, Aged Care and Sport
16 November 2022

The Peter Doherty Institute for Infection and Immunity (Doherty Institute) is an unincorporated joint venture between the University of Melbourne and The Royal Melbourne Hospital, combining research, teaching, public health and reference laboratory services, diagnostic services and clinical care in infectious diseases and immunity.

We have provided input and comments principally on Term of Reference 3: Research into the potential and known effects, causes, risk factors, prevalence, management, and treatment of long COVID and/or repeated COVID in Australia.

Our submission contains three sections:

1. Doherty Institute Capacity
2. General Recommendations
3. Long COVID Specific Recommendations

1. Doherty Institute Capacity

The Doherty Institute has research expertise and established relationships that are being employed to address long and repeated COVID, with leadership of and involvement in a number of existing projects.

Some of these projects, and their contributions to the understanding of long and repeat COVID include:

- Associate Professor Vicki Lawson is developing pre-clinical animal models for COVID-19, with experience assessing the neurological impact of SARS-CoV-2 infection. In particular, she is leading an MRFF grant exploring the neurological and brain impacts of SARS-CoV-2 variants of concern. The project will develop novel, sensitive and specific biomarkers of virus-induced brain injury (Aim 1) and, identify viral determinants of neurovirulence (Aim 2) to predict the neurological impact of

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newly emerging VOC (Aim 3). Collaborators include researchers from the Doherty Institute and La Trobe University.

- Professor Stephen Kent, Dr Adam Wheatley and Dr Jennifer Juno have a long-standing collaboration with UNSW exploring the immunological consequences of SARS-CoV-2 infection and have contributed to comprehensive analysis of immune responses eight months after SARS-CoV-2 infection. This analysis, using samples from the ADAPT cohort and published in *Nature Immunology*[1], showed that innate immune cells are highly activated in people with long COVID, with a lack of naïve T and B cells and elevated type 1 and type 3 interferons. They are now looking in more detail at the B cell response. The analysed ADAPT cohort includes 147 individuals, 31 with long COVID.

- Dr Katherine Gibney is a lead investigator (together with Professor Margaret Hellard from the Burnet Institute) on the Optimise Study, a research survey study established in 2020 to track the Victorian COVID-19 response. Around 700 high-risk and COVID-impacted participants have been recruited with ethics approval for further contact. A rapid survey on long COVID was conducted in August 2022, with the report available on the study website[2]. Survey findings include support for ongoing public health measures to prevent long COVID, a significant proportion of people experiencing long COVID without any formal diagnosis, and widespread impacts of long COVID on participants' everyday lives. The Optimise study has good engagement with the Victorian Department of Health and has produced bi-monthly reports.

- Dr Irani Thevarajan established the Sentinel Travellers and Research Preparedness Platform for Emerging Infectious Disease (SETREP-ID) study pre-COVID, which was activated to capture biological samples from hospitalised SARS-CoV-2 cases in 2020. This cohort has since undertaken longitudinal follow-up (but with modest numbers). Dr Thevarajan collaborates with immunologists Professors Katherine Kedzierska and Dale Godfrey, with potential to link to additional samples via

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[1] Phetsouphanh C, Darley D, Wilson D, Howe A, Munier CML, Patel SK, Juno JA, Burrell LM, Kent SJ, Dore GJ, Kelleher AD, Matthews G. Immunological dysfunction persists for 8 months following initial mild-moderate SARS-CoV-2 infection. *Nature Immunology* 2022 DOI: **10.1038/s41590-021-01113-x**

[2] https://optimisecovid.com.au/wp-content/uploads/2022/10/Optimise_Long-COVID-Snapshot.pdf

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Associate Professor Sophie Valkenburg. The SETREP-ID cohort is also supporting research looking at clinical sequelae in the context of treatment and vaccination of adults and children who develop long COVID.

- The Australian Partnership for Preparedness Research on InfectiouS disease Emergencies (APPRISE) is based at the Doherty Institute. APPRISE is an NHMRC-funded Centre of Research Excellence that has received an additional grant for continuation via the Commonwealth Department of Health. Professor Sharon Lewin is the chief investigator, with several other Doherty staff involved. The additional grant will fund two large national projects, including one on long COVID. APPRISE is also progressing platform capabilities for infectious disease research, including the establishment of a virtual biobank to link diverse biological specimen collections together for searching in once place (including ADAPT and SETREP-ID).

- Through APPRISE, Professor Jodie McVernon established the Australian 'First Few X' (FFX) study in 2020, including biological sampling and detailed household transmission analysis in the first 28 days following COVID infection, with longer term follow-up for many participants. The study is currently able to recruit in Victoria via the Royal Children's Hospital and the Walter and Eliza Hall Institute. FFX data includes detailed vaccination history, symptom and household contact data in acute COVID, predominantly Omicron cases and could be adapted for long COVID investigation with household controls.

- Virologist Dr Sarah Londrigan has a longstanding collaboration (and approved protocol for research) with Royal Melbourne Hospital respiratory physician Associate Professor Daniel Steinfort – with capacity to sample airway epithelial and immune cells from vulnerable patients, including those with long COVID.

- Professor Jodie McVernon has links to the Patron program of research at the Melbourne Medical School which is a platform capability led by Professor Lena Sanci for primary care surveillance – this platform could be activated to study long COVID including in rural and remote areas.

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2. General Recommendations

Creating and strengthening an ecosystem to support long COVID research

1. Programs that foster collaboration and cross-institution relationships should be prioritised and funded explicitly since established research collaborations can adapt to address new disease challenges and questions.

2. Funding and grant programs and internal Institutional review, promotion and reward programs should develop strategies to measure and reward collaboration as an important contribution to preparedness for future infectious disease challenges.

3. Research platform capabilities that extend across disease areas (and institutions) including physical infrastructure (e.g. PC3 laboratory and animal facilities, biobanking facilities etc.) and digital/administrative infrastructure (e.g. data linkage arrangements, Electronic Medical Record systems, research governance strategies) should be constantly strengthened and prioritised for investment.

4. Successful multidisciplinary disease responses (e.g. Hepatitis B and HIV responses in Australia, integration of clinical research and biobanking into standard clinical care in the UK) should be explored and studied to provide guidance and inspiration for new disease responses. This includes engagement not only across different academic disciplines, but also with community and lived experience organisations, governments and health providers.

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3. Long COVID Specific Recommendations

Filling known evidence gaps

1. Understanding and characterising long COVID in Australia will be an important contribution internationally since most infections have been SARS-CoV-2 Omicron (and subvariants) and have been in a largely vaccinated population.

2. This will require larger, representative and well-characterised cohorts to facilitate understanding and study of the full range of long COVID consequences, including:

    o   Prevalence and incidence in Australia

    o   Clinical symptoms of acute and long COVID

    o   SARS-CoV-2 variant details

    o   Vaccination status

    o   Biological sampling

3. Need to develop animal models of long COVID to test interventions, undertake behavioural studies and further understand the pathogenesis of infection including biomarker identification.

4. Need to understand effective models of care, including action research to identify and strengthen care pathways linking primary care with specialist services.

5. Consider strategies and frameworks to enable the collection of (and research access to) post-mortem tissue, including brain tissue, from people who die following severe acute and long COVID.