



# Burnet Institute

Medical Research. Practical Action.

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PATRON-IN-CHIEF – The Honourable Linda Dessau AC, Governor of Victoria

Thank you for the opportunity to make a submission to the long COVID inquiry. As well as providing this written submission, Professor Margaret Hellard AM, Burnet Institute Deputy Director was also interviewed as a witness to the inquiry on the Wednesday 12<sup>th</sup> October 2022.

## Summary of Key Points, Conclusions and Recommendations

1. In the absence of a national long COVID database, estimates of its prevalence in Australia rely on studies conducted both here and overseas. These studies report a broad range of prevalence, but we believe that a safe estimate in Australia would be between 5% and 10% three months after infection. That equates to between 500,000 and 1 million Australians who have or have had long COVID. The condition may persist for at least two years.
2. Research suggests that long COVID is due to a sustained inflammatory response which has no correlation with the severity of the initial COVID-19 illness. There is also a reduction in cortisol, which plays a major anti-inflammatory role in the body.
3. Research indicates that females, people aged between 30 and 49, ethnic minorities and the socio-economically disadvantaged are at higher risk of long COVID. In addition, smokers, the overweight and obese, and those with certain pre-existing conditions, such as chronic lung disease are also at higher risk.
4. There is good evidence that a third dose (booster) of a COVID-19 vaccine reduces the risk of long COVID by up to 50%.
5. Data from the US and UK demonstrate the significant impact of low COVID on the labour workforce. Extrapolating to Australia, up to 300,000 Australians could be out of work due to long COVID.
6. Currently, there is no evidence-based specific treatment for long COVID. WHO guidelines recommend a multi-disciplinary approach by a combination of primary care providers, specialists and allied health professionals, such as physiotherapists.
7. There is uncertainty around the prevalence of long COVID following COVID infection and the prevalence of long COVID in people who contract COVID-19 following vaccination. We also acknowledge the variation in severity and symptom length in people who have long COVID.
8. However, given there have been more than 10,355,000 million COVID-19 infections in Australia as of the 4 November 2022, noting the uncertainties, even if the proportion of people who experience long COVID following their COVID-19 infection is very low, the total number of Australian's who experience long COVID would be very high. For example, using the estimate of 5% of people with COVID developing long COVID (a prevalence supported by a significant amount of literature), means over 500,000 Australian's will have developed long COVID.

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9. The inquiry is exploring a number of important issues about long COVID, but perhaps the most important issue to be explored is in Item 6 – Best practices to prevent long COVID – as it is commonly recognised that *prevention is better than cure*.
10. Put simply – the best way to prevent long COVID is to reduce the number of people getting COVID infection. This is done through a combination of vaccination, and other public health prevention measures, particularly when cases are rising, and treatment.
11. COVID-19 anti-viral treatments are not only critical to reducing severe disease in acute COVID but also reduce the risk of long COVID, with emerging data on the role of treatment.
12. Public health measures promoting community-wide protective behaviours to prevent infection are under-utilised and under-emphasised in Australia and critical tools in addition to vaccination. These include encouraging the use of high-quality face masks or respirators in indoor settings, clean air (ie ventilation and air filtration), working from home where possible, isolating if you have symptoms consistent with COVID infection or if tested positive, and testing for COVID prior to attending large events or locations where there are people at significant risk of COVID-19 infection.

#### **Recommendations**

1. There is a need to have a standard definition of long COVID in Australia that is consistent across all jurisdictions. The definition of long COVID should include prolonged symptoms as well as post-acute conditions (eg cardiovascular conditions, neurological conditions and diabetes. This definition will need to be used for surveillance and research purposes, including to document the contribution of post-acute COVID to hospitalisation and deaths. Such a definition will inform better use of the ICD-10 diagnosis code for post-acute COVID, (U09.9 Post COVID-19 condition, unspecified) and the medical certification cause of death (MCCD).
2. Australia is currently lacking a clear and coherent national plan for dealing with the ongoing COVID-19 pandemic. It is more likely than not that we will experience ongoing waves of infection from past or new variants every 3-4 months, for a number of years. Australia's COVID-19 plan should include a clear strategy of communication and engagement with the public, so they understand that COVID-19 pandemic is ongoing, and to avoid ongoing high levels of disease and deaths and social and economic disruption arising from the pandemic there is a need for ongoing vaccination and public health measures, particularly during waves of infection. This includes avoiding infection to prevent long COVID
3. Establish a national monitoring system or surveillance approach to accurately estimate the prevalence and extent of the disease burden caused by long COVID-19, which could be modelled on the systems employed by the US National Centre for Health Statistics and the UK Office for National Statistics. This is critical to understanding the true numbers and impact of long COVID and our ability to respond accordingly
4. Generously fund research across the spectrum of discovery science, prevention, treatment, and care and the health, social and economic impact of long COVID as well as studies that evaluate

treatment and management approaches, including clinical trials of promising drugs and other interventions. National coordination of research is required to ensure research priorities are met and there is no duplication of effort (value for money).

5. Given the complexity of the diagnosis and management of long COVID, the current length of routine GP consultations reimbursed by Medicare is not adequate. Consider establishing a specific Medicare item for consultations (especially initial diagnosis) for long COVID.
6. Fund the expansion of public long COVID specialty clinics given that current clinics, especially in Sydney and Melbourne, have waiting lists many months long. Establish such clinics in regional centres and capital cities across the country.
7. Consider the inclusion of people with debilitating long COVID in the National Disability Insurance Scheme.
8. Develop partnerships with community organisations working with culturally and linguistically diverse communities to educate and promote access to health services for the management of long COVID.

Our responses to the specific terms of reference (1, 3, 4, 5, 6) of the inquiry are outlined below.

### **1. The patient experience in Australia of long COVID and/or repeated COVID infections, particularly diagnosis and treatment.**

A key point to highlight is there is no reason to think that the patient experience of long COVID in Australia would be any different to that experienced in other countries. Whilst Australians had a high level of vaccination prior to the vast majority of COVID-19 infections occurring in the community, there is clear evidence of long-COVID occurring post vaccine even if less frequent and severe. There is also no conclusive evidence that the risk of long COVID is higher with previous variants. However, given the high levels of transmission with omicron and reduction in public health measures, the absolute numbers of long COVID will be greater in the omicron era.

The best treatments are currently uncertain but likely to be a combination of antivirals and anti-inflammatories. A single pre-print publication has demonstrated that nirmatrelvir reduced the risk of long COVID by 26%, in addition to reducing the risk of post-acute hospitalisation and death. The role of expanded criteria and access to antivirals needs to be urgently explored through research on effectiveness and cost-benefit.

### **3. Research into the potential and known effects, causes, risk factors, prevalence, management, and treatment of long COVID and/or repeated COVID infections in Australia**

This section of the submission summarises the findings of research that relate to section 3 of the terms of reference. This includes research conducted in Australia and in other countries, where it is relevant. The section is organised to describe the findings of research on the following topics:

1. Prevalence (or frequency) of long COVID or Post-Acute COVID-19 Syndrome (PACS)
2. Effects of long COVID on
  - a. The health of individuals
  - b. The impact of reinfections on long COVID
  - c. Social and economic well-being
3. Possible causes of long COVID
4. Diagnosis, management, and treatment of long COVID

A critical issue to note prior responding to this question in detail is to highlight that there should be no “exceptionalism” in Australia. Australia is not a special case where the nature or prevalence of long COVID will be different to other countries. The notion that Australia won’t experience significant amounts of long COVID is not based in science, even after accounting for high levels of vaccination prior to many people experiencing their first COVID-19 infection.

### **Definition of long, or post, COVID by the World Health Organization<sup>1</sup>**

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that 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 onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

#### **1. Prevalence (or frequency) of long COVID or Post-Acute COVID-19 Syndrome (PACS)**

##### **Global data**

1. A large follow up “meta-analysis” study of more than 1.2 million people diagnosed with symptomatic COVID-19 (both hospitalised and non-hospitalised) was published on 10 October 2022<sup>2</sup>. The analysis was based on 54 studies and 2 medical record databases (from 22 countries). Of the 54 studies, 44 were published and 10 were collaborating cohorts.

The study analysed the proportion of individuals with at least 1 of the 3 self-reported long COVID symptom clusters (persistent fatigue with bodily pain or mood swings; cognitive problems; or ongoing respiratory problems) 3 months after SARS-CoV-2 infection in 2020 and 2021.

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<sup>1</sup> [https://www.who.int/publications/i/item/WHO-2019-nCoV-Post\\_COVID-19\\_condition-Clinical\\_case\\_definition-2021.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1)

<sup>2</sup> [https://jamanetwork.com/journals/jama/fullarticle/2797443?guestAccessKey=7e302e44-286b-4021-ab2a-d60b4c7783fb&utm\\_source=silverchair&utm\\_campaign=jama\\_network&utm\\_content=covid\\_weekly\\_highlights&utm\\_medium=email](https://jamanetwork.com/journals/jama/fullarticle/2797443?guestAccessKey=7e302e44-286b-4021-ab2a-d60b4c7783fb&utm_source=silverchair&utm_campaign=jama_network&utm_content=covid_weekly_highlights&utm_medium=email)

In the modelled estimates, **6.2%** (95% uncertainty interval, 2.4%-13.3%) of individuals who had symptomatic SARS-CoV-2 infection experienced at least 1 of the 3 long COVID symptom clusters 3 months after their infection.

The long COVID symptom clusters were more common in women aged 20 years or older (10.6%) at 3 months than in men aged 20 years or older (5.4%). Both sexes younger than 20 years of age were estimated to be affected in 2.8% of infections.

The estimated mean long COVID symptom cluster duration was 9.0 months among hospitalised individuals and 4.0 months among non-hospitalised individuals. Among individuals with long COVID symptoms 3 months after infection, an estimated 15.1% continued to experience symptoms at 12 months.

Extrapolated to the Australian COVID-19 caseload, we could expect **more than 600,000 Australians with Long COVID at 3 months and 90,000 at 12 months.**

#### **Australian data**

1. A study by ANU<sup>3</sup>, released on 10 October 2022, found that nearly one-third of Australian adults diagnosed with COVID-19 have had symptoms that lasted for longer than four weeks - a definition of long COVID employed by the Commonwealth Department of Health<sup>4</sup>. This equates to just over 14% of the entire adult population in Australia. In addition, nearly five per cent of Australian adults have had COVID-19 symptoms lasting three months or more.
2. A study by the Kirby Institute followed 94% of all COVID-19 cases diagnosed in NSW between January and May 2020 (sample size = 2904) using 3-4 weekly telephone interviews and linkage to hospitalisation and death data to determine if they had recovered from COVID-19 based on symptom resolution<sup>5</sup>.

The study found that 5% still had symptoms at three months. This was more common in women than men and those aged 30-49 were most likely to have long COVID.

In 2022, this would be the **equivalent of 500,000 adults** with long COVID at 3 months after infection.

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<sup>3</sup> <https://www.anu.edu.au/news/all-news/more-than-one-in-10-aussies-have-had-long-covid-anu-study>

<sup>4</sup> <https://www.health.gov.au/health-alerts/covid-19/symptoms>

<sup>5</sup> [https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065\(21\)00102-4/fulltext](https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(21)00102-4/fulltext)

3. The ADAPT study in NSW published in March 2021 found that 19% of people diagnosed with COVID-19 had not recovered at 8 months. There was an increased risk in females and the 40–50-year age group<sup>6</sup>.

This is equivalent to almost **2 million cases** of long COVID in Australia in 2022.

4. A Monash University study published in November 2021 looked at COVID survivors in 30 Australian hospitals<sup>7</sup>. At 6 months, **42/108 (38.9%) responding survivors reported a new disability** that they did not have before being infected.
5. The Burnet-Doherty Optimise Study (August 2022 see attached) has followed a cohort of around 700 Victorians since September 2020. A rapid survey was conducted between 12 and 21 August 2022 to assess the proportion of Optimise participants who had experienced long COVID, participants' concerns about long COVID and any behaviours they used to mitigate the risk of developing long COVID. There was an optional additional section of the survey completed only by participants who reported having/having had long COVID, asking about their experiences.

Of the 653 Optimise study participants invited to complete the survey, 499 (76%) responded. The survey defined long COVID as the person experiencing new health problems that have persisted for more than one month after being infected with COVID-19.

### Survey findings

- Forty-nine per cent (243/499) of participants had been infected with COVID-19 at least once since the beginning of the pandemic (December 2019).
- Twelve per cent (61/499) of participants reported that they have/have had long COVID.
- Sixty-one per cent (302/499) of participants had friend/s or family member/s who had experienced long COVID. Forty-two per cent (128/302) of these participants reported providing support to friend/s or family member/s with long COVID.

This highlights the broader impact of long COVID on the community, not just the individual experiencing long-COVID.

### US Data

1. A large study published by **the US Centres for Disease Control** in May 2022 followed a large number of people who had been diagnosed with COVID-19 (n = 353,164) in 50 states during

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<sup>6</sup> <https://www.medrxiv.org/content/10.1101/2021.03.29.21254211v1>

<sup>7</sup> <https://ccforum.biomedcentral.com/articles/10.1186/s13054-021-03794-0>

March 2020–November 2021 and compared them with a control group (n = 1,640,776) who had not been infected with the virus<sup>8</sup>. Data were derived from an electronic patient database.

The study looked at the occurrence of 26 clinical conditions previously attributed to post-COVID illness based on a review of the scientific literature. Case-patients or control patients with a previous history of one of the included conditions in the year before the index encounter were excluded (478,072 patients).

Among all patients aged ≥18 years, 38.2% of case-patients and 16.0% of controls experienced at least one incident condition. Among persons aged ≥65 years, 45.4% of case-patients and 18.5% of controls experienced at least one incident condition. So, in adults aged ≥ 18 years **24.2% of those who reported at least one condition** could be attributed to a previous COVID infection.

The most common incident conditions in both age groups were respiratory symptoms, including a twofold increase in pulmonary embolus, and musculoskeletal pain. The study did not assess the duration of symptoms.

Extrapolated to the Australian caseload, up to **two million adults aged 18** and over could experience post-COVID conditions.

2. A **September 2022 report by the U.S. National Centre for Health Statistics** was based on the Household Pulse Survey<sup>9</sup>. Among all American adults over the age of 18 years, 14% had ever had Long COVID for at least 3 months. Among women it was 17.5% compared to 11% among men. The highest rate was among 40–49-year-olds.

In the same report, among respondents who had ever had COVID-19, 29.6% had Long COVID at 3 months (35% among women, 24% among men). The highest rate was among 50–59-year-olds. There was a very large variation between states.

If this figure was extrapolated to Australia, there would be **3 million affected by long COVID** at 3 months.

## UK Data

1. Data released from the Office for National Statistics in October 2022 show that an estimated **2.3 million people** had symptoms of long COVID more than 4 weeks after the initial infection<sup>10</sup>.

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<sup>8</sup> <https://www.cdc.gov/mmwr/volumes/71/wr/mm7121e1.htm#contribAff>

<sup>9</sup> [https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm?utm\\_campaign=wp\\_to\\_your\\_health&utm\\_medium=email&utm\\_source=newsletter&wpsrc=nl\\_tyh](https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm?utm_campaign=wp_to_your_health&utm_medium=email&utm_source=newsletter&wpsrc=nl_tyh)

<sup>10</sup>

<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddisea>

Of people with self-reported long COVID, **1.8 million people (80%)** had symptoms at least 12 weeks previously, 1.1 million (46%) at least one year previously, and 514,000 (22%) at least two years previously.

**Long COVID symptoms adversely affected the day-to-day activities of 1.6 million people** (72% of those with self-reported long COVID), with 342,000 (15%) reporting that their ability to undertake their day-to-day activities had been “limited a lot”.

**Fatigue continued to be the most common symptom** reported as part of individuals’ experience of long COVID (69% of those with self-reported long COVID), followed by difficulty concentrating (45%), shortness of breath (42%), and muscle ache (40%).

As a proportion of the UK population, the prevalence of self-reported long COVID was greatest in people aged 35 to 69 years, females, and people living in more deprived areas.

Extrapolating to Australia, this would mean **700,000 people with long COVID at 3 months and 420,000 at 12 months.**

### Scottish study

1. A Scottish study, published on 12 October 2022, followed up 33,281 laboratory-confirmed SARS-CoV-2 infections and 62,957 never-infected individuals via 6, 12 and 18-month questionnaires and linkage to hospitalisation and death records<sup>11</sup>.

Of those who completed questionnaires at both 6- and 12-months follow-up, the breakdown by no, partial and full recovery was 295 (8%) 1766 (47%), and 1683 (45%) at six months and 303 (8%), 1705 (46%) and 1736 (46%) at 12 months.

Having not recovered was associated with hospitalised infection, younger age, female sex, deprivation, respiratory disease, depression and multi-morbidity.

Compared to those who were never infected with COVID-19, previous symptomatic infection resulted in poorer quality of life, impairment across all daily activities and 24 persistent symptoms including breathlessness, palpitations, chest pain, and confusion.

**Asymptomatic infection was not associated with adverse outcomes.** Vaccination was associated with reduced risk of seven symptoms.

Extrapolated to the Australian caseload, **800,000 Australians would experience symptoms of Long COVID** at 6 and 12 months after infection.

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<https://www.burnet.edu.au/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6october2022>

<sup>11</sup> <https://www.nature.com/articles/s41467-022-33415-5?s=03>



## 2. Effects of long COVID:

- **The health of individuals**
- **The impact of reinfections on long COVID**
- **Social and economic effects**

### Health of affected individuals

1. A study by Melbourne University published in August 2022 looked at the impact of Long COVID on Disability Adjusted Life Years lost as a result of the Omicron B.1 wave between December 2021 and April 2022<sup>12</sup>. A total of 51,000 DALYs were lost, equivalent to 2.4% of all DALYs during that period. This is similar to DALYs lost during that period due to dementia and drug use disorders, demonstrating a major impact on the health status of Australians.
2. In the **Scottish study** cited earlier<sup>13</sup>, people with previous symptomatic Covid infections reported certain persistent symptoms, such as breathlessness, palpitations and confusion or difficulty concentrating, at a rate roughly **three times as high as uninfected people** in surveys from six to 18 months later. Those patients also experienced elevated risks of more than 20 other symptoms relating to the heart, respiratory health, muscle aches, mental health and the sensory system. After changes in smell and taste, the largest effect sizes were observed for symptoms that were potentially cardiovascular in origin (breathlessness, chest pain and palpitations) and confusion (or brain fog).
3. In the **US CDC study** cited earlier<sup>14</sup>, among patients aged  $\geq 65$  years, the risks were higher among COVID case-patients than among non-COVID controls for all 26 incident conditions, with relative risks (RR) ranging from 1.2 (substance-related disorder) to 2.2 (acute pulmonary embolism). Among patients aged 18–64 years, the risks were higher among case-patients than among controls for 22 incident conditions, with RRs ranging from 1.1 (anxiety) to 2.1 (acute pulmonary embolism); no significant difference was observed for cerebrovascular disease, or mental health conditions, such as mood disorders, other mental conditions, and substance-related disorders. Among case-patients, the RRs for 10 incident conditions were significantly higher among those aged  $\geq 65$  years than among those aged 18–64 years; these conditions were renal failure, thromboembolic events, cerebrovascular disease, type 2 diabetes, muscle disorders, neurologic

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<sup>12</sup> <https://www.medrxiv.org/content/10.1101/2022.08.01.22278219v1>

<sup>13</sup> <https://www.nature.com/articles/s41467-022-33415-5?s=03>

<sup>14</sup> <https://www.cdc.gov/mmwr/volumes/71/wr/mm7121e1.htm#contribAff>

conditions, and mental health conditions (including mood disorders, anxiety, other mental conditions, and substance-related disorders).

4. The authors of a paper published in July 2021 conducted an online survey of people with suspected and confirmed COVID-19, distributed via COVID-19 support and social media<sup>15</sup>. Data were collected from September 6, 2020 to November 25, 2020. They analysed responses from 3762 participants with confirmed or suspected COVID-19, **from 56 countries**, with illness lasting over 28 days and onset prior to June 2020.

For the majority of respondents (>91%), the time to recovery exceeded 35 weeks. During their illness, participants experienced an average of 56 symptoms, across an average of 9 organ systems. The most frequent symptoms after month 6 were **fatigue, post-exertional malaise, and cognitive dysfunction**.

Almost 86% of participants experienced relapses, primarily triggered by exercise, physical or mental activity, and stress. **45% of respondents required a reduced work schedule** compared to pre-illness, and an additional 22% were not working at the time of survey due to illness. Cognitive dysfunction or memory issues were common across all age groups (88%).

5. In addition to numerous studies of post-COVID conditions that fit the WHO definition of long COVID, there is increasing evidence of other one-off events after a COVID infection affecting mainly the cardiovascular and nervous systems.

A study published in February 2022 used national healthcare databases from the US Department of Veterans Affairs to build a cohort of 153,760 individuals with COVID-19, as well as two sets of control cohorts with 5,637,647 (contemporary controls) and 5,859,411 (historical controls) individuals, to estimate risks more than 30 days after the initial infection and 1-year burdens of a set of pre-specified incident cardiovascular outcomes<sup>16</sup>.

The findings included a 50% increased risk of a stroke (compared to the non-infected controls); a 70-80% increase in cardiac arrhythmias; a 20% increase in pericarditis and a twofold increase in myocarditis; a 70% increase in ischaemic heart disease; an almost threefold increase in pulmonary embolus; and a 70% increase in other cardiovascular disorders, such as heart failure.

6. A study published in August 2022<sup>17</sup> analysed de-identified data between January 20, 2020, and April 13, 2022 from health-care records of approximately 89 million patients collected from hospital, primary care, and specialist providers (mostly from the USA, but also **Australia**, the UK, Spain, Bulgaria, India, Malaysia, and Taiwan). The analysis compared psychiatric and

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<sup>15</sup> <https://pubmed.ncbi.nlm.nih.gov/34308300/>

<sup>16</sup> <https://www.nature.com/articles/s41591-022-01689-3>

<sup>17</sup> [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(22\)00260-7/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(22)00260-7/fulltext)

neurological outcomes of people diagnosed with COVID-19 (n = 1,487, 712) with a non-infected comparison cohort (approximately equal).

Risks of common psychiatric disorders returned to baseline after 1–2 months (mood disorders at 43 days, anxiety disorders at 58 days). By contrast, risks of cognitive deficit (known as brain fog), dementia, psychotic disorders, and epilepsy or seizures were still increased at the end of the 2-year follow-up period.

This study demonstrated that the increased incidence of mood and anxiety disorders post-COVID was transient, with no overall excess of these diagnoses compared with other respiratory infections. In contrast, the increased risk of psychotic disorder, cognitive deficit, dementia, and epilepsy or seizures persisted throughout.

The fact that neurological and psychiatric outcomes were **similar during the delta and omicron waves** indicates that the burden on the health-care system might continue even with variants that are less severe in other respects.

### **The impact of reinfections on long COVID**

1. A number of studies have shown that the number of reinfections with the Omicron variant has been far higher than with Delta and other earlier variants.

The UK Office for National Statistics has estimated that the risk of reinfection with Omicron is five times higher than with Delta<sup>18</sup>. A large proportion of reinfections in the Omicron dominant period had first infections in the Alpha (37.9%) and Delta (37.1%) dominant periods. A small proportion of people have had a first and second infection during the same variant dominant period, but the rate is highest for those in the Omicron dominant period (14.6%).

2. A study of US veterans compared 257,427 people with a first infection with the virus that causes COVID-19 to a group of 38,926 people who had a second or later infection, and then to 5.4 million people who never were infected<sup>19</sup>.

The researchers followed the veterans over 6 months. They compared people who had one, two, three, or more infections to the non-infected group. Among those with reinfection, about 13% had two infections, 0.76% had three infections, and .08%, or 246, people had four or more infections.

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<sup>18</sup>

<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveycharacteristicsofpeopletestingpositiveforcovid19uk/20july2022#:~:text=higher%20viral%20load,-,People%20are%20now%20around%20five%20times%20more%20likely%20to%20be,more%20likely%20to%20be%20reinfected>

<sup>19</sup> <https://www.researchsquare.com/article/rs-1749502/v1>

They showed that compared to people with one infection, reinfection contributed additional risks of all-cause mortality, hospitalisation, and adverse health outcomes in the pulmonary and several extra-pulmonary organ systems (cardiovascular disorders, coagulation and haematologic disorders, diabetes, fatigue, gastrointestinal disorders, kidney disorders, mental health disorders, musculoskeletal disorders, and neurologic disorders).

Compared to veterans with a first coronavirus infection, **those who got a reinfection had more than double the risk of dying from any cause.**

3. Another study, published in September 2022, was based on a survey sent to people with long COVID in 30 countries including the UK, US, France and Canada between 4 April 2022 and 19 June 2022<sup>20</sup>. Responses were received from 484 adults and 112 children and young people who'd had at least two COVID-19 infections.

The results were similar across adults and young people. Overwhelmingly, reinfection worsened the symptoms of long COVID in most people who were still symptomatic. In those who still had long COVID at the time of reinfection, 80% saw their symptoms worsen vs. 10% who saw their symptoms improve. Around 85% saw old symptoms return or new additional symptoms vs. 10% who had a resolution or improvement of symptoms.

In 60% of people who were in recovery or remission with long COVID, reinfection caused a recurrence of long COVID.

### 3. Possible causes of long COVID

While there is so far no clear consensus on the cause of long COVID – there may be several pathways – research so far suggests it results from changes in the immune system that lead to a “hyper-inflammatory” attack on numerous organs of the body.

1. In Australia, scientists at the Kirby Institute (UNSW) have found that unvaccinated people with long COVID – even those whose initial infection was mild or moderate – have a sustained inflammatory response for at least eight months following their infection, suggesting that long COVID is very different to other infections<sup>21</sup>.

The team examined blood samples from people with and without long COVID for a variety of ‘immune biomarkers’. These are biological characteristics which can help define a medical condition in an accurate and reproducible way. They compared these to people who had not had COVID-19, and found persistently elevated levels of Type I and Type III interferons – types of protein that cells make in response to the presence of a virus. These interferons generally

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<sup>20</sup> <https://www.longcovidkids.org/post/a-world-first-effect-of-covid-reinfection-on-people-living-with-long-covid>

<sup>21</sup> <https://www.nature.com/articles/s41590-021-01113-x>

disappear after an infection clears, but in patients with long COVID they were present for an extended period.

They found that there was **no correlation** between these immunological changes and the severity of the initial COVID-19 illness. They found that even when the virus has completely left the body, the immune system remains switched on. If the same thing is measured after a standard cough or cold, which they did in this study through one of their control groups, this signal is not there. It's unique to sufferers of long COVID.

2. In addition to the immunological changes found in long COVID patients by the Australian study, another study in the US found other abnormalities in 215 patients<sup>22</sup>. They included unexpected increases in antibody responses directed against non-SARS-CoV-2 viral pathogens, particularly Epstein-Barr virus. They observed that levels of cortisol were uniformly lower among participants with long COVID relative to matched control groups.

Cortisol is a steroid hormone that is produced by the adrenal glands. When released into the bloodstream, cortisol can act on many different parts of the body and can help reduce inflammation.

3. Neurological conditions that occur after the initial COVID-19 infection are not believed to be caused by persistence of the virus in the brain and spinal cord. Research has found that these conditions are caused by cytotoxic amyloid clumps formed from fragments of protein from SARS-CoV-2<sup>23</sup>. These amyloid clumps are highly toxic to nerve tissues and have been observed in certain neurodegenerative disorders, such as Alzheimer's Disease, dementia, and Parkinson's disease.

### **Risk factors for long COVID**

1. One of the most comprehensive studies of the outcomes and risk factors for long COVID was conducted in the UK and published in July 2022<sup>24</sup>. The study analysed 486,149 adults with confirmed SARS-CoV-2 infection and 1,944,580 matched adults with no recorded evidence of SARS-CoV-2 infection. The risk factor analysis included 384,137 individuals infected with SARS-CoV-2 with a minimum of 12 weeks of follow-up. When using the WHO definition of long COVID, several sociodemographic and clinical risk factors were significantly associated with the incidence of long COVID.

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<sup>22</sup> <https://www.medrxiv.org/content/10.1101/2022.08.09.22278592v1>

<sup>23</sup> <https://www.nature.com/articles/s41467-022-30932-1>

<sup>24</sup> <https://www.nature.com/articles/s41591-022-01909-w#:~:text=Smokers%20and%20former%20smokers%20were,those%20who%20had%20never%20smoked>

Women were at 50% increased risk compared to men. Older age above 30 years was associated with a higher risk of reporting long COVID symptoms in the initial analysis; however, after adjusting for baseline variables, **older age was associated with a lower risk**, with those aged 30–39 years having a 6% lower risk (0.94, 0.90–0.97) and those aged ≥70 years having a 25% lower risk (0.75, 0.70–0.81) **compared to those aged 18–30 years**.

There were associations between the risk of reporting long COVID symptoms and certain ethnic minority groups, with a 20% increased risk in Black Afro-Caribbean ethnic groups, 14% in mixed ethnicity and a 6% increased risk in other minority ethnic groups of patients with Native American, Middle Eastern or Polynesian origin as compared to white ethnic groups.

The risk also increased with increasing levels of socioeconomic deprivation, with a 11% increased risk in those who were most socioeconomically deprived compared to those least deprived.

Smokers and former smokers were at increased risk of reporting long COVID symptoms (12% and 8%, respectively), compared to those who had never smoked. Baseline BMI in the overweight or obese range was also associated with a 10% increased risk of persistent symptoms, compared to those with a non-elevated BMI.

A wide range of pre-existing conditions at baseline was also associated with an increased risk of long COVID symptoms. The comorbidities with the largest increases were 55% for chronic obstructive pulmonary disease, 39% for benign prostatic hyperplasia, 37% for fibromyalgia, 35% for anxiety and 31% for depression.

#### **4. Diagnosis, management and treatment of long COVID**

##### **Diagnosis of long COVID**

Currently, the diagnosis of long COVID is based on clinical criteria described in a range of definitions. In this submission, we refer to the WHO definition. With up to 200 symptoms in 10 organ systems described within the post-acute COVID syndrome, the diagnosis is challenging given that clinicians need to exclude other causes of these symptoms<sup>25</sup>.

To help clinicians address the expected growing burden, researchers at **Perth's Murdoch University** have been working on a tool that can identify molecular biomarkers for long COVID – without the need to detect the disease itself – and be easily deployed in medical practices across the world, at low cost<sup>26</sup>.

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<sup>25</sup> [https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(21\)00299-6/fulltext](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00299-6/fulltext)

<sup>26</sup> <https://www1.racgp.org.au/newsgp/clinical/progress-made-on-long-covid-diagnostic>

The technology works by using a specially designed set of radio pulses to extract signals from inflammatory glycoprotein markers and fats bound to lipoproteins that gives a rapid diagnosis in approximately a minute.

The principal researcher said that ‘The next step is the clinical deployment of the technology in a real setting to generate the sort of validation data needed to appropriately license this technology for diagnostic use.’

### **Management and treatment**

Thus far, there have been no published clinical trials evaluating long COVID management strategies. A number of guidelines exist, including by the World Health Organization<sup>27</sup> and the Royal Australian College of GPs<sup>28</sup>. These clinical guidelines have been developed through consensus among specialist physicians.

While these guidelines are broad and address particular symptom clusters, they do have in common a number of approaches:

- Multidisciplinary rehabilitation teams; continuity and coordination of care; and people-centred care and shared decision-making.
  - A workforce for the rehabilitation of adults with post COVID-19 condition may include but is not limited to physiotherapists, occupational therapists, nurses, psychologists, speech and language therapists, physicians and social workers.
  - Early referral of adults with post COVID-19 condition for appropriate rehabilitation services is suggested when experiencing symptoms and impairments that have an impact on everyday functioning.
  - For the clinical rehabilitation management of breathing impairment in adults with post COVID-19 condition use a combination of education and skills training on self-management strategies such as nasal breathing and pacing approaches – physical exercise should be employed with caution as it may induce severe symptoms.
  - For the clinical rehabilitation management of cognitive impairment in adults with post COVID-19 condition use a combination of education, skills training on self-management strategies and cognitive exercises.
1. **In the UK**, a set of recommendations for GPs on the recognition, diagnosis and management of long COVID was developed by a two-stage Delphi consensus process with a panel of primary and secondary care doctors<sup>29</sup>. Over two rounds of Delphi testing, panellists indicated their

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<sup>27</sup> <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>

<sup>28</sup> <https://www.racgp.org.au/getattachment/8c5b3936-5551-4b94-81d4-614e2b69da51/Caring-for-patients-with-post-COVID-19-conditions.aspx>

<sup>29</sup> <https://bjgp.org/content/71/712/e815>

agreement with each recommendation (using a five-point Likert scale) and provided comments. Recommendations eliciting a response of 'strongly agree', 'agree', or 'neither agree nor disagree' from 90% or more of responders were taken as showing consensus.

Thirty-three clinicians representing 14 specialties reached consensus on 35 recommendations. Chiefly, GPs should consider long COVID in the presence of a wide range of presenting features (not limited to fatigue and breathlessness) and exclude differential diagnoses where appropriate. Rehabilitation should be individualised, with careful activity pacing (to avoid relapse) and multidisciplinary support.

2. In an article published in *Nature* in August 2022, the author notes that although at least 26 randomised clinical trials of long-COVID therapies are under way, many are too small or lack the necessary control groups to give clear results<sup>30</sup>. However, in the next year, key trials could yield results for drugs that target the immune system, blood clots or lurking fragments of the coronavirus itself.

Those that have reached Phase III trials include anti-inflammatory and anti-thrombotic drugs and steroids. Uncertainty about the root causes of long COVID could dissuade researchers from launching trials. Another obstacle is that some of the most common symptoms, such as fatigue and brain fog, are difficult to measure objectively.

But some researchers have pushed ahead. Several trials try to tame errant immune responses. Some of these rely on familiar drugs, such as colchicine, an anti-inflammatory drug that treats gout and is often prescribed to people with long COVID. Other trials are using drugs that have shown some success in treating severe acute COVID-19, including steroids and other immunosuppressants, such as sirolimus, which is used to prevent organ rejection after a transplant. Antihistamines have also showed promise.

Some of the most logical candidate drugs for long COVID are still not being tested in trials. Several antivirals are used against acute COVID-19. Some researchers think these drugs could ease the symptoms of long COVID, too — particularly as evidence grows that a lingering SARS-CoV-2 reservoir could trigger the condition. But there are still no registered studies directly looking at whether these antivirals — which are expensive and in relatively short supply compared with generic drugs — could ease long-COVID symptoms.

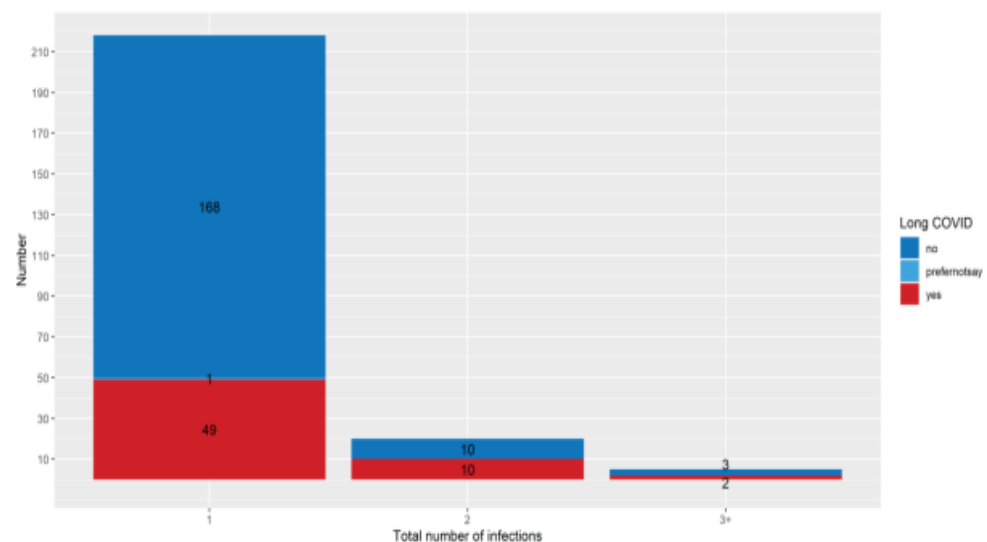
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<sup>30</sup> <https://www.nature.com/articles/d41586-022-02140-w>



The graph below suggests that long COVID may be associated with repeated infections.

**Figure 1: Number of people with long COVID by number of infections**



**4. The health, social, educational and economic impacts in Australia on individuals who develop long COVID and/or have repeated COVID infections, their families, and the broader community, including for groups that face a greater risk of serious illness due to factors such as age, existing health conditions, disability and background;**

As there is no national database on Long COVID in Australia and no accurate estimate of its prevalence, there are few published studies on the social and economic impact of long COVID in this country. There is clear evidence however, that COVID-19 is more likely to impact people with social and structural disadvantage and people with previous health issues.

There is also increasing evidence that people with previous issues with their health may be at greater risk of developing long COVID.

1. The COVID-19 Impact Monitoring Survey Series, by the ANU Centre for Social Research and Methods has published data from their August 2022 survey<sup>31</sup>.

Of those who reported COVID-19 symptoms that lasted for more than 4 weeks, 22.5% said that it reduced their ability to carry-out day-to-day activities compared with the time before they

<sup>31</sup> [https://csm.cass.anu.edu.au/sites/default/files/docs/2022/10/The\\_experience\\_of\\_COVID-19\\_in\\_Australia\\_-\\_For\\_web.pdf](https://csm.cass.anu.edu.au/sites/default/files/docs/2022/10/The_experience_of_COVID-19_in_Australia_-_For_web.pdf)

had COVID-19 'a lot', with 63.3% saying it reduced their ability 'a little'. This was quite similar for those who had symptoms for 3 months or more (21.6% and 64.3%).

Compared to a short (less than 4 weeks) bout of COVID-19, those who experienced long COVID had significantly and substantially lower life satisfaction, than prior to the pandemic.

2. In the **United States**, data published by the Brookings Institute in August 2022 found that more than 4 million Americans were out of work due to long COVID<sup>32</sup>. This is equivalent to **more than 300,000 Australians out of work due to long COVID**. The annual cost of those lost wages in the US is around US\$170 billion a year (and potentially as high as US\$230 billion).

This was up from 1.6 million full-time equivalent workers estimated to be out of work due to long Covid in January 2022. With 10.6 million unfilled jobs at the time, long Covid potentially accounted for 15% of the US labour shortage. The August revision followed the Census Bureau adding four new questions about long Covid to its Household Pulse Survey, giving researchers a better understanding of the condition's prevalence.

3. In **the UK**, a paper published in March 2022, described an online survey that followed people who self-reported having long COVID and had not been hospitalised during the first two weeks after infection<sup>33</sup>. The study analysed data from 2,550 participants with a median duration of illness of 7.6 months. The most common symptoms that persisted were exhaustion, chest pressure/tightness, shortness of breath and headache. Cognitive dysfunction and palpitations became more prevalent later in the illness.

One third (32%) reported they were unable to live alone without any assistance at six weeks from start of illness. **16.9% reported being unable to work** solely due to COVID-19 illness. 37.0% reported loss of income due to illness, and 64.4% said they were unable to perform usual activities/duties.

4. In a paper published in July 2022, the authors analysed the impact of long COVID on the UK workforce<sup>34</sup>. They used data from the Office for National Statistics' COVID Infection Survey (CIS), which showed that approximately 1.4 million people aged 17–69 suffered from persistent COVID symptoms for more than four weeks in the four weeks leading up to the 5 March 2022. This corresponds to 3.1% of the population in this age group. Just below an estimated 1 million people of this age group had long COVID for an extended period of more than 12 weeks.

The proportion of people of working age who have long COVID and are limited in their daily activities as a consequence, has remained relatively stable at around 19%. The authors estimated

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<sup>32</sup> <https://www.brookings.edu/research/new-data-shows-long-covid-is-keeping-as-many-as-4-million-people-out-of-work/>

<sup>33</sup> <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0264331>

<sup>34</sup> <https://www.tandfonline.com/doi/full/10.1080/13504851.2022.2098239>

that in the four weeks ending 5 March 2022 this equated to **around 269,000 individuals** or 0.61% of the UK working-age population.

An estimated 11.4% of those 17–69-years-old who were in work prior to the pandemic and reported to have long COVID between November 2020 and September 2021 had left employment. This compares to 7.7% in a comparison group who did not have long COVID.

In a speech in May 2022, a member of the **Bank of England monetary committee** estimated that the total UK workforce shrank by 440,000 people up to February 2022, compared to the fourth quarter of 2019, just before the pandemic<sup>35</sup>. While due to a number of factors, such as BREXIT, there was also a marked drop in participation rates, especially among people aged 50 to 64, most of which was due to long-term sickness, such as long COVID.

He also noted that the share of the population who did not want a job because of long-term sickness was at a record high of almost 4.5%, and that there had been “an especially sharp rise” in the number of women not working for that reason.

#### **5. The impact of long COVID and/or repeated COVID infections on Australia’s overall health system, particularly in relation to deferred treatment, reduced health screening, postponed elective surgery, and increased risk of various conditions including cardiovascular, neurological and immunological conditions in the general population; and**

There is a definite need for a national approach to collection of data to enable a greater understanding of long COVID, its impact on communities especially those at greater risk, and the impact on the health sector more broadly.

#### **6. Best practice responses regarding the prevention, diagnosis and treatment of long COVID and/or repeated COVID infections, both in Australia and internationally**

As outlined at the beginning of our response the best way to prevent long COVID is to reduce the number of COVID infections circulating in the community. These means having a clear and ongoing national COVID response plan that includes regular vaccinations, the introduction of public health measures and strong stakeholder communications as infections begin to rise to dampen the impact of waves of infection.

Vaccination is not fully protective of getting COVID-19 or developing long COVID but there is some evidence that it affords some protection. For example, a recent UK study reported that patients

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<sup>35</sup> <https://www.bankofengland.co.uk/speech/2022/may/michael-saunders-speech-at-the-resolution-foundation-event>

who are fully vaccinated (yet who still suffer a breakthrough SARS-CoV-2 infection) appear less likely to experience Long COVID, reporting an odds ratio of 0.51 (95% CI 0.32–0.82;  $p=0.0060$ ).<sup>19</sup>

As outlined in previous sections, evidence is increasing on the benefits of treatment for long-COVID.