Long COVID Evidence Update

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Document Summary

- The New Zealand definition of long COVID was outlined in the Clinical Rehabilitation Guideline for People with long COVID in Aotearoa New Zealand on 15 September 2022. [1] Long COVID is defined as signs and symptoms consistent with COVID-19, that develop during or after an infection, continues for more than 12 weeks and are not explained by an alternative diagnosis.
- The range of symptoms experienced by individuals who develop long COVID is broad, with studies indicating that over 100 symptoms have been associated with long COVID. [2, 3]
- Various studies have reported a wide range of estimates for long COVID prevalence, ranging from single digits to at least 80%. [2, 4] In a global meta-analysis published in April 2022, hospitalised and non-hospitalised patients had estimates of 0.54 (95% CI, 0.44-0.63) and 0.34 (95% CI, 0.25-0.46) respectively, indicating that a significant proportion of patients may develop long COVID, particularly if they were hospitalised during the acute infection. [5] The prevalence of long COVID is difficult to determine for several reasons. For example, studies may use different definitions of long COVID, focus on different groups of people, assess different time periods post-infection, and use different methods to collect data.
- The prevalence of long COVID in Aotearoa New Zealand is currently unknown, however some recently funded studies will help give a better picture following the development of clinical codes for long COVID. [6]
- While data is still emerging, it is likely that Māori will be disproportionately affected by long COVID. Māori continue to experience inequities in vaccination rates and incidence of severe illness requiring hospitalisation[*], both of which are associated with a higher likelihood of developing long COVID.
- The aetiology of long COVID is complex and there is likely to be more than one mechanism that contributes to its development. Evidence continues to emerge on the molecular contributors to long COVID, which may inform advice for management and treatment. SARS-CoV-2 is not just a virus that affects the respiratory system; it can cause widespread tissue damage and inflammation, leading to multisystem disruption, systemic inflammation, and immune dysfunction. [8, 9]
- Many healthcare professionals and researchers have compared the experience of long COVID to other post-viral conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). [10-12] Similarities include a pattern of long-term illness triggered by acute viral infection, comparable symptoms/demographics, and a poor understanding of underlying mechanisms.

[*] Māori also have a greater risk of COVID-19 mortality compared with European and Other groups. 7. Ministry of Health. COVID-19 Mortality in Aotearoa New Zealand: Inequities in Risk 2022 [Available from: https://www.health.govt.nz/publication/covid-19-mortality-aotearoa-new-zealand-inequities-risk.

- A range of factors associated with an increased risk of developing long COVID have been identified. Some of these include older age, being female, multiple early symptoms, obesity, and some pre-existing conditions such as asthma. A range of immunological factors may also play a role.
- Reinfection with SARS-CoV-2 is becoming more common due to waning of immunity and increased immune evasion from emerging new variants. The translation of COVID-19 reinfections to long COVID incidence is currently unknown and difficult to quantify, however it reflects the unique position of Aotearoa New Zealand which had a highly vaccinated population prior to community transmission of Omicron and subsequent variants. Emerging research overseas is generally showing the acute and lingering symptoms for an Omicron infection to be less severe than with earlier variants. [13]
- Vaccination remains the most accepted form of prevention from long COVID. There is a substantial amount of literature emerging that supports the hypothesis that getting vaccinated prior to infection reduces the risk of long COVID. [14-24] The exact effect of vaccination on pre-existing long COVID remains uncertain and contentious. Anecdotal reports and studies suggest a variety of experiences following COVID-19 vaccination ranging from improvement, deterioration, and no change in long COVID symptoms. [15, 17, 23, 25-27]
- There are no specific tests used by healthcare professionals to diagnose long COVID. Diagnosis is instead based on presentation of long COVID symptoms following a known or suspected SARS-CoV-2 infection. There are a wide range of symptoms that can present for long COVID, many of which are common to a multitude of other conditions, making them hard to decipher or confirm as long COVID. [28]
- Diagnostic techniques are emerging, most use immune profiling techniques and machine learning to identify biomarkers associated with inflammation. It remains clinically unproven if tests differentiate between long COVID and other similar conditions. One paper has found cortisol levels appear to be the most significant predictor of long COVID. [29]
- Multiple potential long COVID therapeutics are in development, however none so far are clinically proven. Clinical trials investigating long COVID treatments are currently limited by having small sample sizes, sub-optimal control groups and target specific symptoms. Some potential therapeutic options being explored include Paxlovid, SNG001 (by Synairgen), antihistamines and dietary supplements. [30-33]
- Globally the development and implementation of policies relating to the funding, development, and maintenance of services to treat long COVID is ongoing.

Introduction

In the early stages of the pandemic, most attention was focused on the acute health impacts of SARS-CoV-2 infection. [34] It was initially thought that although some people have a prolonged and complicated hospital stay, most people recover from 'mild' infections within two weeks and from more serious disease within three weeks. [35] However, it has become clear that for some people COVID-19 can lead to persistent illness, with ongoing and often debilitating symptoms. [35-37]

This document is a summary of the current evidence known about the long-term health impacts of COVID-19, often referred to as long COVID, and the experiences of people living with long-term complications of COVID-19. It is a collation of expert opinion and the latest scientific and technical research exploring the ongoing nature or long-term presentation of signs and symptoms that appear or continue to occur after the acute phase of COVID-19, and discusses aetiology, epidemiology, issues related to the impact of vaccination and new emerging variants. Additionally, it includes developments in international guidance from peak bodies on diagnosis, management, support, and rehabilitation pathways. It reflects current knowledge at the time of writing (November 2022). New evidence in this update will be in red text. This evidence brief consolidates the information previously provided.

Limitations

This evidence brief has some notable limitations. The document aims to give an overview of currently available evidence on various aspects of long COVID. While comprehensive, it is not a systematic review and as such some relevant material may have been inadvertently missed. Long COVID is still a relatively new condition, and many questions remain to be answered. Research is ongoing to better understand the causes, risk factors, clinical course, and possible treatments. Clinical trials investigating long COVID-19 treatments currently are limited by often having small sample sizes, sub-optimal control groups and investigate impact on specific symptoms, such as fatigue or thrombotic events.

The prevalence of long COVID is difficult to establish for many reasons. [2, 38-40] It can be difficult to reliably compare studies of different types and populations, partly because the prevalence of long COVID may vary greatly depending on the groups studied. For example, studies of patients who were hospitalised for COVID-19 tend to find significantly higher rates of long COVID than studies of patients who were not hospitalised. Other complicating factors include:

- Studies may use different definitions of long COVID, focus on different groups of people, assess different time periods post-infection, and use different sample sizes
- There is no specific test to diagnose long COVID, and people may have a wide variety of symptoms that could be related to other health problems
- Published studies may not be representative of everyone who has long COVID
- The ways in which responses are elicited can impact estimated prevalence (e.g., app users are self-selected and responsible for recording symptoms, which can result in sampling and

recording biases). Surveys that investigate symptoms retrospectively may be at particular risk of recall bias

- Most long COVID studies lack control groups, making it difficult to draw a causal link between COVID-19 infection and the reported symptoms.

Long COVID in children remains not well described. There are many limitations which directly affect the strength of outcomes and comparability between studies. These limitations include a lack of a clear case definition, arbitrary follow up time points, subjective assessment, lack of control groups, small population size and low response rates. Often in studies which include young children and infants' data is collected through questioning from parents and caregivers which can also create recall bias. [41-44]

With respect to the impact of vaccination on long COVID, the lack of randomised controlled trials and predominance of observational studies means that causality cannot be determined easily. Long COVID studies exploring the impact of vaccination have generally been small, with self-selected participants and sub-optimal control cohorts. [19] Many studies exclude hospitalised patients, and therefore conclusions may not apply to people who had severe disease. The effect of different vaccines, doses, and dosing schedules on long COVID is also difficult to disentangle. Varying levels of prior exposure and natural immunity between populations, as well as waning immunity and evolving definitions of vaccination status, are further complicating factors.

Long COVID terminology and definitions

Ongoing symptoms are common following many viral and bacterial infections, including other coronaviruses. The term 'long COVID' is generally used to describe persistent or developing signs and symptoms following acute COVID-19. Symptoms may persist for weeks or months causing significant impact on affected individuals, their family and whānau.

Throughout international literature, long COVID is referred to by many names, including post-COVID-19 syndrome, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection, long-term effects of COVID, and chronic COVID.

There is no internationally agreed definition of the long COVID condition yet.

Aotearoa New Zealand will have a unique long COVID profile due to the early successes in transmission reduction in the pandemic. The low prevalence of COVID-19 in Aotearoa New Zealand prior to Omicron has resulted in a proportionally low incidence of long COVID prior to 2022. However, with the arrival of Omicron and its sub-lineages and Aotearoa New Zealand now having had over 1.83 million reported cases of COVID-19, an increase in long COVID cases is expected.

It has been agreed to adopt the clinical case definitions from the joint guideline used by the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) to distinguish between acute and long COVID cases, as follows: [45]

- Acute COVID 19:
    - Signs and symptoms for up to 4 weeks
- Ongoing symptomatic COVID-19:
    - Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks
- Post-COVID-19 syndrome:
    - Any signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. Presentation may include clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body
    - Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed
    - In addition to the clinical case definitions, the term 'long COVID' is commonly used to describe the signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). [46]

A clinical rehabilitation guideline for people with long COVID in Aotearoa New Zealand was released by the Ministry of Health on 15 September 2022. [1] This establishes a clear and standardised definition and supports diagnosis of long COVID in the local context. Clinical codes are now available across primary and secondary care in Aotearoa New Zealand. By coding individuals with a condition, it is possible to determine the prevalence more accurately. This will lead to consistent data collection, analysis, and reporting which is essential for an accurate estimate of the prevalence of long COVID in the population and to allow a better understanding of the impacts of long COVID in Aotearoa New Zealand.[46]

Other widely used international definitions have been developed by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC). Definitions have also been developed for sub-populations of interest including children using the Delphi method, aligning with the WHO guidelines. [47] The resulting definition was outlined as

> "*Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID infection, and may fluctuate or relapse over time*".

Symptoms and Signs

There are **a range of signs and symptoms** that have been associated with long COVID. These vary greatly, with studies indicating that over 100 symptoms have been associated with long COVID. [2, 3]

Symptoms can be respiratory, cardiopulmonary, neurological, or generalised, as detailed in Table 1 below. [48]

The most reported symptoms of long COVID are fatigue or general malaise, headaches, cognitive impairment or attention disorders, or respiratory symptoms. [2, 49]

Table 1: Commonly reported symptoms of long COVID

Cardiopulmonary • Difficulty breathing or shortness of breath • Cough • Chest pain, tightness, or heaviness[†] • Palpitations **Neurological** • Cognitive impairment ('brain fog', loss of concentration or memory issues) • Headache • Sleep disturbance • Peripheral neuropathy symptoms (pins and needles, numbness) • Ongoing changes to smell or taste • Dizziness • Delirium (in older populations) **Musculoskeletal** • Muscle aches and pains • Muscle weakness[‡] • Joint pain **Psychological/ psychiatric symptoms[§]** • Symptoms of depression • Symptoms of anxiety	**Generalised symptoms** • Fatigue • Fever • Pain • Reduced exercise capacity **Gastrointestinal** • Abdominal pain • Nausea • Diarrhoea • Anorexia and reduced appetite (in older populations) **Ear, nose, and throat** • Tinnitus • Earache • Sore throat • Dizziness **Other** • Skin rashes (including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities) • Metallic or bitter taste • Metabolic disruption (such as poor control of diabetes) • Thromboembolic conditions

[†] Clinical assessment is required to investigate the specific cause

[‡] Muscle weakness can be a reported symptom, and may also be clinically measured

[§] The WHO has noted that the association between long COVID and psychiatric disorders is likely bidirectional

Evidence indicates that people experiencing long COVID generally fall into one of two symptom groups: those experiencing ongoing respiratory symptoms (including coughing and shortness of breath) combined with fatigue and headaches; and those experiencing multi-systemic symptoms, affecting the heart, brain, and gut (for example, palpitations and 'brain fog'). [50] A report from the CDC (September 2022) suggests that people who have had COVID-19 have twice the risk of respiratory conditions or developing pulmonary embolism than those who have not had COVID-19. Furthermore, respiratory conditions had the highest risk ratios reported of conditions associated with long COVID. [49, 51]

In addition to the wide range of possible symptoms, some of the key features of long COVID include:

- Concurrence of multisystem, fluctuating and often overlapping 'clusters' of symptoms
- Symptoms that vary in severity and site over time, including symptom-free periods followed by relapses
- Symptom severity may range from mild to incapacitating
- Worsening of symptoms after physical or mental activity
- Relapses may occur in an irregular pattern or in response to specific triggers (e.g., physical, or mental activity, stress, menstruation, heat, or alcohol)
- People may experience new symptoms that were not present during the acute phase of their COVID-19 infection. [35, 37, 52]

COVID-19-associated cognitive impairment often includes impaired function relating to concentration, processing information speed, attention, and memory. [53] Evidence suggests that mild cases of COVID-19 could lead to prominent neuroinflammation, causing physical damage to the white matter in the brain. This disrupts regular cellular processes, similar to damage which occurs during chemotherapy. [54] This damage appears to contribute to the lingering neurological symptom(s) (often termed 'brain-fog') reported by many with long COVID or undergoing chemotherapy. A positive association is the potential for cancer therapy related treatments to provide insight into appropriate treatments for long COVID-induced neurological symptoms. [54]

There is also evidence of COVID-19 infections leading to persistent cardio-renal inflammation and activation of the haemostatic pathways, which have implications for reduced pulmonary and lung function. [55, 56]

Omicron

Studies suggest that while the individual risk of developing long COIVD from Omicron infections is lower than for previous variants, continued high case rates indicate that long COVID cases are expected to increase, leading to a potentially widespread impact on health systems. [57, 58]

The UK's Office for National Statistics (ONS) suggests that despite Omicron having lower case severity there is still significant long COVID burden, largely driven by the high case numbers. [59]

BA.5 continues to be the prevalent Omicron sub-lineage across New Zealand as of November 2022 however, this proportion is decreasing as the proportion of new sub-variants increases. The effect on long COVID incidence as a result from infection with these new sub-variants is currently unknown, however literature suggests that these variants are capable of increased immune evasion due to mutations in the surface spike proteins. [60] Internationally it is estimated that second and third waves of infection due to new sub-variants are likely to increase the prevalence of long COVID, particularly amongst those in high exposure environments such as healthcare. [61]

There is no published evidence, grey literature or media reports suggesting a decline in demand for health services with Omicron, with the number of people self-reporting persistent symptoms beyond four weeks in the UK has been reported to have decreased to 2.1 million from an approximate 2.3 between September and October 2022, which may have impacted demand. However, the number reporting persistent symptoms beyond 12 weeks increased from 1.6 to 1.8 million. [62]

Epidemiology

Prevalence

Various studies and meta-analyses have reported widely varying estimates of long COVID prevalence, ranging from single digit estimates[**] to at least 80% of people following SARS-COV-2 infection. [2, 4] Some have reported at least half of people experience at least one ongoing symptom during the 6-12 months after infection. [63, 64] In a meta-analysis published in April 2022, global estimated pooled prevalence of post-COVID-19 condition was 0.43 (95% CI, 0.39-0.46). [5] Hospitalised and non-hospitalised patients had estimates of 0.54 (95% CI, 0.44-0.63) and 0.34 (95% CI, 0.25-0.46) respectively. Regional prevalence estimates were highest for Asia (0.51; 95% CI, 0.37-0.65), Europe (0.44; 95% CI, 0.32-0.56), and United States of America (0.31; 95% CI, 0.21-0.43). Global prevalence for 30, 60, 90, and 120 days after infection were estimated to be 0.37 (95% CI, 0.26-0.49), 0.25 (95% CI, 0.15-0.38), 0.32 (95% CI, 0.14-0.57), and 0.49 (95% CI, 0.40-0.59), respectively[††]. Some recent studies have reported a prevalence of closer to 20%. For example, a cross-sectional survey carried out during the BA.5 surge in the US found that an estimated 21.5% (95% CI ,18.2-24.7) of respondents with a SARS-CoV-2 infection more than four weeks prior reported long COVID symptoms. [65]

A study published in August 2022 is unique in that it corrected for symptoms present before SARS-CoV-2 infection, as well as controlling for symptom dynamics in age and sex-matched controls. [66] The occurrence of 23 symptoms were assessed in COVID-19-positive participants at 90–150 days after

[**] This meta-analysis incorporated 54 studies and 2 medical record databases with data for 1.2 million individuals (from 22 countries) who had symptomatic SARS-CoV-2 infection. In the modelled estimates, 6.2% (95% uncertainty interval [UI], 2.4%-13.3%) of individuals who had symptomatic SARS-CoV-2 infection experienced at least one of the three long COVID symptom clusters in 2020 and 2021 (after adjusting for health status before COVID-19).

[††] The higher prevalence at 120 days was noted to possibly be due to the predominance of studies with patients who had been hospitalised.

infection and compared with occurrence before infection and with matched controls. It was concluded that in 12.7% of patients, ongoing symptoms could be attributed to COVID-19, as 381 (21.4%) of 1782 COVID-19-positive participants versus 361 (8.7%) of 4130 COVID-19-negative controls had at least one of these core symptoms substantially increased to at least moderate severity at 90–150 days after COVID-19 diagnosis or matched timepoint.

The way in which long COVID is defined and measured will affect prevalence estimates. [39, 40]. The broader the definition, the more people will fall under this category. The severity of ongoing symptoms may vary widely. For example, the ONS in the UK estimated that as of 3 November 2022, an estimated 2.1 million people living in private households in the UK (3.3% of the population) were experiencing self-reported long COVID (symptoms continuing for more than four weeks after the first confirmed or suspected coronavirus (COVID-19) infection that were not explained by something else). Long COVID symptoms adversely affected the day-to-day activities of 1.6 million people (73% of those with self-reported long COVID), with 330,000 (16%) reporting that their ability to undertake their day-to-day activities had been "limited a lot".[59]

Despite the limitations of studies investigating long COVID prevalence (as discussed above), there is increasing evidence that a significant number of people experience long COVID, with the potential to greatly affect health system capacities worldwide. [63] In September 2022, WHO/Europe reported on modelling that showed that an estimated 17 million people in the European Region met the WHO criteria for long COVID in 2020 and 2021. [67] The modelling indicates that there was a 307% increase in new long COVID cases identified between 2020 and 2021, driven by the rapid increase in confirmed COVID-19 cases from late 2020 and throughout 2021.

More details about prevalence estimates from some key sources, systematic reviews, and meta-analyses can be found in earlier versions of this evidence brief (see particularly 17 October 2022).

Prevalence of long COVID in Aotearoa New Zealand

Currently, the prevalence of long COVID in Aotearoa New Zealand is unknown. However, it is likely that some groups will be disproportionately affected given the varying rates of acute COVID-19 infection. Preliminary results from the Ngā Kawekawe o Mate Korona study suggest that the prevalence may vary across groups. Of 65 Māori participants, 43% (28/65) reported symptoms for more than one month, and of these participants, 75% (21/65) reported experiencing long COVID symptoms for more than three months post-infection. In comparison, of the 405 participants who were non-Māori, 47% (190/405) reported symptoms for more than one month, and of these individuals, 65% (124/405) reported symptoms which lasted more than three months. [68] While similar proportions reported ongoing symptoms overall, slightly more Māori participants reported symptoms for three months or longer. It is not possible to draw conclusions about the overall prevalence of long COVID given that participants were self-selected into the study and there was a particular focus on recruiting Māori participants.

In Aotearoa New Zealand, Māori may have an increased risk of developing long COVID given the higher rates of COVID-19 in this group, and lower vaccination rates. The potential inequitable impact

of long COVID on Māori is concerning and is receiving recent media attention. [69] While data is still emerging, it is likely that Māori will be disproportionately affected by long COVID. Māori continue to experience inequities in vaccination rates and incidence of severe illness requiring hospitalisation, both of which are associated with a higher likelihood of developing long COVID. Māori are also at greater risk of COVID-19 mortality compared with European and Other groups. [7]

With clinical codes now established for use in Aotearoa New Zealand, it will be possible to gain a clearer picture of the number of people affected. The Ministry of Health is funding several new research projects related to COVID-19, including some on long COVID in Aotearoa New Zealand, which will help give an indication of the prevalence of long COVID. One of these studies seeks to establish a registry of long COVID. [6]

Aetiology

Long COVID is complex and there is likely to be more than one mechanism that contributes to its development. Evidence continues to emerge on the molecular contributors to long COVID, which may inform advice for management and treatment. SARS-CoV-2 is not just a virus that affects the respiratory system; it can cause widespread tissue damage and inflammation, leading to multisystem disruption, systemic inflammation, and immune dysfunction. [8, 9] There are currently a few broad theories as to what causes long COVID symptoms. [9, 70] These factors are not mutually exclusive[#], and include:

- persistent virus or viral antigens causing chronic inflammation [29, 71-73]
- autoimmunity triggered by SARS-CoV-2 infection [29, 74, 75]
- dysbiosis (changes in the microbiome) and viral reactivation (reactivation of viruses other than SARS-CoV-2 in the context of COVID-19 infection) [29, 76, 77]
- unrepaired tissue damage from the original infection (including endothelial dysfunction) [9, 70, 76]
- dysregulated immune reaction or immune abnormalities [29, 76, 77]
- changes to the endocrine system. [29, 78, 79]

Similarities between long COVID and ME/CSF

Many healthcare professionals and researchers have compared the experience of long COVID to other post-viral conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). [10-12] The most striking similarities between long COVID and ME/CSF include:

- a pattern of long-term illness being triggered in some people by acute infection of a virus [10]

[#] For example, patients may have some degree of any or all of these contributing factors. It is possible there may be some sub-groups of patients in which one factor is more important than others. It is also possible that the relative importance of these factors could vary depending on the strain of the virus.

- symptoms of fatigue, brain fog, headaches, pain in organs and tissues, and disturbances of the autonomic nervous system which regulates functions such as blood pressure, respiration, digestion, and sleep [11]
- they affect a similar demographic [11]
- poorly understood potential mechanisms with evidence of cellular damage, inflammation, and changes to the immune and endocrine systems. [29]

ME/CFS has a history of being poorly understood and neglected by medical establishments due to the complicated presentation of symptoms and poorly defined aetiology. [11] There remain multiple case definitions of ME/CFS and relatively little research has been carried out on the topic. Until recent years, those with ME/CFS may have had issues accessing care and support as it was considered to be a psychosomatic illness. Recent studies have now debunked this idea and molecular studies have identified it to be a complex biomedical illness that involves immune system dysfunction. [11] Immunological research is underway in New Zealand, including investigation of whether long COVID and ME/CSF share common biomarkers. [11]

Risk factors

There is a growing body of evidence on which groups are at greatest risk of developing persistent symptoms. Long COVID appears to be more common among people who have had severe COVID-19 symptoms during their acute illness but can also affect those who initially had mild or moderate COVID-19. Even people who initially were asymptomatic may go on to develop long COVID. [80] Some factors that may be associated with increased chance of developing long COVID symptoms include:

- older age [5, 50, 81]
- having more than one underlying chronic medical condition or pre-existing condition [82]
- pre-existing asthma [5]
- a higher body mass index (obesity) [82]
- being female[§§] [82-85]
- hospitalisation during acute COVID-19 [5, 86] - duration of long COVID symptoms may also be longer among hospitalised individuals compared to those who were not hospitalised [4]
- multiple early symptoms [87, 88]
- SARS-CoV-2 variant – there is some evidence that the risk of long COVID is less after Omicron infection compared with Delta [58]
- levels of psychological distress before SARS-CoV-2 infection [89]

[§§] An elevated immune response is one proposed explanation for why long COVID appears to be more common in female patients.

- other immunological factors, [87] such as: greater viral load during early stages of infection; the presence of autoantibodies; [78] imbalances or compositional alterations in the gut microbiome, [78, 90]; vaccination status; [21] or previous Epstein-Barr virus infection or a reactivation of latent viruses during initial infection. [78, 91]

Risk of long COVID after reinfection

Reinfection with SARS-CoV-2 is becoming more common due to waning of immunity and increased immune evasion from emerging new variants. Although it is currently unknown to what extent reinfection puts someone at risk of worsening symptoms, it seems likely that another infection increases the risk of developing long COVID.

Anecdotal descriptions suggest that reinfection with SARS-CoV-2 can lead to worsening symptoms of long COVID. A survey published by Long COVID Support and Long COVID Kids (UK) has provided some real world evidence on the effect of reinfection. [92] It surveyed people from 30 countries and indicated that in 80% of respondents, reinfection worsened the symptoms of long COVID. However, it is important to note the potential for overestimation due to reporting bias in surveys.

Reinfection at the time of writing is often from an Omicron infection occurring after infection with a previous variant such as Delta or Alpha. Omicron reinfections after a previous Omicron infection are less common, although have been shown to occur and may become more common with emerging new variants that are more immune evasive. The translation of COVID-19 reinfections to long COVID is difficult to quantify currently and reflects the unique position of Aotearoa New Zealand which has a highly vaccinated population (>95%) and the Omicron and subsequent variants being the dominant infections in New Zealand (>93%). Emerging research overseas demonstrates the acute and lingering symptoms of an Omicron infection to be less severe than with earlier variants. [13]

It is important to note that reinfection in New Zealand is likely to become more common as time goes on, which reinforces the importance of vaccination, including boosters, for the best defence against COVID-19.

A recent study (November 2022) that used the US Veterans Affairs national healthcare data reported an increased risk of death, hospitalisation, and sequelae with reinfection compared to no reinfection. [93] These results have been widely reported; however, the results should be interpreted very carefully as the follow-up time after symptom onset is not the same in the comparison groups (no reinfection group and the reinfection group). Furthermore, it is not surprising that people who have had a reinfection recently have more symptoms than those who had one infection earlier.

Long COVID in children

Long COVID in children is not well described, and the studies to date have generally been of poor quality, with some significant limitations as described above. [41-44] Persistent illness in children has

been noted in some studies and in patient support groups, but its prevalence, characteristics, and duration are currently unclear. [94, 95]

Studies indicate that the length of time a child is symptomatic varies, with reports ranging from 28 days to 3 months. [42, 94] The most prevalent long COVID symptoms within children's cohorts are fatigue or weakness, shortness of breath, cough, headaches, muscle and body aches, and fever. The most common types of activity impairments were inability to walk or exercise as much as before, sleeping more than usual, and difficulty focusing and completing schoolwork. [96-99]

Estimates of the prevalence of long COVID in children vary widely, with studies reporting rates of 4% to 66%. [42, 99-106] A systematic review and meta-analysis conducted in the US reported the estimated prevalence of long-COVID in children from 16 studies to be 25%, noting estimates range from 2% to 66%. [106] The variability in prevalence estimates have been linked to various factors including initial SARS-CoV-2 infection severity and variant type, different methodological approaches (clinical assessment vs self-report), definition of cases (diagnosed vs suspected), variable follow-up times, prevalence of pre-existing clinical conditions, size of study population and definitions used for control groups. [42, 43, 107, 108] One report suggests that over half the children and adolescents studied reported psychological and physical symptoms related to long COVID, irrespective of whether they received a positive SARS-CoV-2 diagnosis or not, though this is difficult to interpret and highlights the impact of the pandemic itself on children and adolescents. [109] There is also difficulty in interpreting results from the existing literature, as defining control groups within a population with high levels of COVID-19 infection can result in bias.

Some studies suggest that long COVID in children is less common and tends to be less protracted than in adults. [104] Other experts argue that accurately establishing how many children and adolescents experience long COVID is difficult and likely underestimated. This may be because acute SARS-CoV-2 infection is less severe in children, often making an initial definitive diagnosis less likely. [105] Long-term SARS-CoV-2 infection–associated symptoms can be difficult to distinguish from pandemic-associated symptoms. [41, 42] Studies have found that children who tested negative for COVID-19 have had similar symptoms, which are also common after other viral infections, and could also be due to the experience of lockdown and other social restrictions. [110, 111]

Given that acute COVID-19 generally poses a low risk to children, an accurate determination of the risk of long COVID is important in the debate about the risks and benefits of vaccination in this age group. [42] Similar to adults, it is likely that long COVID in children may have a greater impact on those from socioeconomically disadvantaged areas and ethnic minority groups. [44]

Prevention through vaccination

Much of the discussion on prevention of long COVID currently focuses on the role of vaccination. Collectively, findings from various studies suggest that vaccination against COVID-19 might reduce the population prevalence of long COVID by reducing the risk of:

- continuing to experience persistent symptoms in those who already have symptoms when vaccinated
- developing persistent symptoms after breakthrough infections
- being infected in the first place
- transmitting the virus after infection. [18]

In Aotearoa New Zealand, most people are vaccinated with Pfizer and have received two or more doses. Additionally, a large proportion of people had received a complete primary vaccination course prior to community spread of COVID-19.

There continues to be no data in children about the level of protection provided by vaccination against the incidence of long COVID.

Vaccination prior to infection

There is a substantial amount of literature emerging that supports the hypothesis that getting vaccinated prior to infection reduces the risk of long COVID. [14-24]

Studies have suggested the following themes:

1. **The incidence of long COVID is lower in people with breakthrough infection following vaccination than in unvaccinated controls**. [18] A UK community-based matched cohort study (September 2022) reported that persistent symptoms were seen in 9.5% of breakthrough cases compared to 14.6% in the unvaccinated controls. [18]
2. **Vaccinated people are less likely to report symptoms than unvaccinated or partially vaccinated people**. [14-23] In general, vaccinated people were less likely to report the following symptoms in the medium to long term: fatigue, persistent muscle pain, headache, hair loss, weakness in arms and legs, shortness of breath, dizziness, anosmia, interstitial lung disease, myalgia, and other pain. [17] Papers reporting on this can be split into those that investigated the effect from one dose, [23] at least two doses, [21, 22], or at least 3 doses. [21-24] Only one paper identified reported that they found no difference in symptoms between vaccinated and unvaccinated people. [112]
3. **Evidence likely underestimates the effect of vaccination prior to infection on long COVID.** This is because it cannot account for all infections that were completely avoided due to vaccination.

Vaccination after infection

The exact effect of vaccination on pre-existing long COVID remains uncertain and contentious. Anecdotal reports and studies suggest a variety of experiences following COVID-19 vaccination ranging from improvement, deterioration, and no change in long COVID symptoms. [15, 17, 23, 25-27]

A UK Health Security Agency rapid evidence brief (January 2022) reviewed multiple studies and reported that vaccination after infection seems to be more often correlated with long COVID symptoms improving than with them worsening. However, it was most common for there to be no

change in long COVID symptoms following vaccination. [15, 17] In some cases, as high as 70% of people reported no change. [15] A review (July 2022) reported that nine studies indicated vaccination likely improves the effects of long COVID, one saw a negative association between vaccination and long COVID, one saw mixed results depending on the symptoms, and one paper found no association between vaccination after infection and long COVID. [14]

Evidence relating to vaccination after infection tends to relate to the following themes:

1. **The timing of vaccination following infection:** It has been reported that people who were vaccinated sooner were less likely to report long COVID symptoms than unvaccinated people. [15, 23] People who were vaccinated within 4 weeks of infection reported four to six times less long COVID symptoms and people vaccinated between 4-8 weeks following infection reported three times less symptoms. [23] Additionally, protection is reported from vaccination as long as 12 weeks after infection. [23]
2. **Changes in long COVID symptoms after vaccination:** There are many studies that compare changes in symptoms, however these have many limitations and are hard to compare directly. A large study published in *Nature Medicine (*May 2022) used the US Veterans Affairs databases for an analysis that included more than 13 million people. [86] This reported that vaccination lowers the risk of long COVID after infection by about 15%. [26] A community-based cohort study (May 2022) of 28,356 participants from the UK's COVID-19 Infection Survey examined the trajectory of long COVID symptoms following COVID-19 vaccination. [18, 19, 113]
   In this:
   - a single dose was associated with an initial 12.8% decrease in the odds of long COVID, however this was not sustained over the next 12 weeks
   - a second vaccination was associated with an 8.8% decrease in the odds of long COVID, and this was sustained over the next nine weeks [18, 113]

   In another study, improvement to symptoms of long COVID was reported in 23.2% of vaccinated people, compared to 15.4% in the unvaccinated cohort while a worsening of symptoms was reported in 5.6% of vaccinated people compared to 14.3% in the unvaccinated cohort. [15]
3. **Vaccine specific data:** A review of literature comparing different vaccine types has reported that most studies did not find any difference in efficacy in preventing long COVID symptoms between vaccine types. [14, 114] One study (April 2022) found a significant difference in the symptoms of long COVID reported by participants that received the Moderna vaccine compared to AstraZeneca with more reporting fatigue, myalgia, and chest pain in the Moderna cohort. [14] A report found that people who received mRNA vaccines after infection tended to report larger levels of improvement compared to adenovector vaccines. [27]

In general, it is accepted that vaccination leads to no worsening of symptoms or quality of life with some statistically significant improvements. [15] Therefore, it is widely recommended that after a COVID-19 infection, people should start or continue their vaccination schedule after three months from diagnosis with the acute illness, to allow for some time for recovery.

Vaccine injury

There is a theory that suggests in rare occasions vaccine injury may lead to long COVID symptoms. Some small-scale research has been undertaken however there have been no conclusive findings to suggest that the vaccine may be causing rare and lasting health problems in some people. Avidra Nath, the clinical director at the National Institute of Neurological Disorders and Stoke reported that the people had "temporal association" between their faltering health and vaccination, however it was unclear if there was "an etiological association." In general, there was a correlation, but no defined causation between the vaccination and the long COVID symptoms. [115]

Impacts

Psychosocial impacts

The functional impairment experienced by some people with long COVID and the toll managing symptoms has on quality of life is becoming clearer. Studies are reporting an overall reduction in quality of life through the onset of multiple psychosocial impacts/outcomes from long COVID including post-traumatic stress disorder (PTSD), major depressive disorder, anxiety disorders, sleep disorders, phobias, fears with avoidant behaviours, health anxieties, obsessive-compulsive disorder (OCD) and adjustment disorder related to living with long COVID-19 symptoms, social exclusion and addictions (as a form of coping), and neuropsychiatric disorders. [116-118] Researchers have also found in a systematic review that people with long COVID have increased reported rates of neuropsychiatric sequelae however, the risk of incident neuropsychiatric manifestations varied among studies. [118]

Further research into the new-onset neuropsychiatric symptoms are required to determine evidence of a causal relationship. In the Ngā Kawekawe o Mate Korona study, 43% of Māori and 52% of non-Māori reported not feeling understood by their healthcare professional, and 61% and 76% respectively reported having concern about not knowing when their symptoms would end. [68]

Social and economic impacts

The financial impact of long COVID is widespread but hard to quantify given the wide variety of variables involved including decreased productivity due to a reduction in workforce, to the increased associated individual costs, including healthcare costs, lost wages, lost savings, and accrued debt. Additionally, long COVID has an impact on the ability of some patients to work. Studies have found that people with ongoing symptomatic COVID-19 or long COVID have reduced work schedules, report increased absence from work/education, reduced performance in education, and often require extra support and recovery time. [52, 119] Long COVID therefore limits the ability of people to return to work and to socialise, not only potentially further affecting their mental health, but also having economic consequences for them, their whānau, and society. [37] There is also widespread international concern regarding the long-term economic consequences of long COVID related

neuropsychiatric sequelae. Young individuals who develop these neuropsychiatric conditions as the result of long COVID may have reduced ability to attend school or higher education as well as the ability to find and maintain employment. [52, 119] This could potentially lead to a widespread economic burden for future generations. [120]

Further work to fully assess the financial impact of long COVID is required as research and reporting regarding the overall financial impact and financial effects of long COVID is currently scarce. The social and economic burden of long COVID will likely affect Māori and Pacific peoples to a greater degree, as they have accounted for a greater proportion of cases during Aotearoa New Zealand's COVID-19 outbreaks.

Management and Support

Diagnosis

Currently, there are no specific tests that can be used by healthcare professionals to diagnose long COVID. Diagnosis is instead based on presentation of long COVID symptoms following a known or suspected SARS-CoV-2 infection. There are a wide range of symptoms that can present for long COVID, many of which are common to a multitude of other conditions, making them hard to decipher or confirm as long COVID. Additionally, symptoms can be diverse with multi-organ involvement, may fluctuate, vary widely, and will affect people in different ways. [28] Compounding the lack of clear diagnostic tools, due to the relative newness of the condition, there may be a limited amount of knowledge of the condition among healthcare professionals.

Emerging diagnostic tools

Immune profiling in conjunction with machine learning has been used to show numerous abnormalities and discrepancies between blood samples taken from long COVID patients and control cohorts. Abnormalities include: [29]

- increased cell populations that are associated with elevated inflammatory and antiviral immune responses
- marked differences between myeloid and lymphocyte populations
- evidence of elevated humoral responses against SARS-CoV-2 in long COVID patients
- differences in immune modulators and hormones.

One of the most significant differences identified to date is a pronounced decrease of cortisol which is reduced by approximately half in long COVID patients compared to healthy and convalescent controls. [29] This paper concluded, based on machine learning, that cortisol levels alone appear to be the most significant predictor of long COVID. [29] This is consistent with findings in another paper. [78]

There are a few specific platforms that use biomarkers to assist with the diagnosis of long COVID including the IncellKINE long COVID test, [121] Novel CovGENE PCR Blood Test [122], and Fourier transform-nuclear magnetic resonance (FT-NMR) spectrometer. [123]

Treatment

Multiple potential long COVID therapeutics are in development, however none have been clinically proven at this stage. Clinical trials investigating long COVID treatments often are currently limited by having small sample sizes, sub-optimal control groups, and target specific symptoms, such as fatigue or thrombotic events.

Some pipeline therapeutics for long COVID include:

- **Paxlovid:** an *in vitro* study has provided preliminary evidence that Paxlovid may be used as a treatment for long COVID, however there are currently no clinical trials investigating this in a patient setting. [30]
- **SNG001** (interferon-beta 1a)**:** Phase III data was presented at the Infectious Disease Week 2022 that suggested Synairgen's inhaled antiviral treatment, SNG001, may be beneficial in reducing long COVID symptoms. This included a 35.4% reduction in fatigue/malaise, a 28.3% reduction in dyspnea, and a 61.4% improvement in people who had reported loss of taste and smell. Additionally, it was reported to reduce anxiety and depression. This data was generated in a clinical trial with endpoints focused on acute COVID-19 treatment. Further evidence is required to support the use of SNG001 in long COVID treatment. [31]
- **Antihistamines:** There is some initial evidence from a small study (n=65) that suggests that antihistamines may improve long COVID symptoms. [32]
- **Dietary supplements:** A small US clinical trial (n=51) has identified a nutraceutical formulation (including β-caryophyllene, pregnenolone and seven other compounds) for the treatment of long COVID. When looking at 12 specific symptoms in long COVID patients, the study reported a significant attenuation of symptoms in 72-84% of participants. [33]. Limitations to this study include its small numbers of participants and open-label study design.

Models of care

Currently the mainstay of long COVID management is supportive and holistic care, symptom control, and detection of treatable complications. [124] Evidence for interventions to improve long COVID symptoms is limited, [125] however there is a consensus that the best practice for treatment and rehabilitation of long COVID needs to be a multidisciplinary, multispecialty approach. [35, 37, 124, 126-130] This will support the wide-ranging and multi-organ nature of symptoms. Specific symptom management will usually be pragmatic, with avoidance of over-investigation. [126, 130]

It is proposed that models of care should include an assessment and case management plan that is developed and tailored to match how the disease manifests for each patient [37, 126]. Services should also allow for sufficient time for the clinic visit and have the ability for follow-up. [129] Some patients may find it useful to keep track of their symptoms to help better understand them, identify which impact them most, and identify patterns and changes. [127]

International studies have explored the use of physical activity-based rehabilitation, neurocognitive rehabilitation, as well as physical and psychological re-conditioning. [131] Key services that have been identified as tools for those struggling with fatigue include physical therapy, physiotherapy, and

occupational therapy. Additionally, important specialists may include experts in the fields of internal medicine, infectious disease, pulmonology, cardiology, ophthalmology, psychology, physical medicine, ear, nose and throat, speech pathology, and neurology. [35] Nutritional support has also been important, with lethargy having flow-on effects onto the ability to cook and prepare food, resulting in some struggling with malnutrition. [128] Several of the studies delivered interventions via non-face to face digital means, including telehealth/rehabilitation, [132-135] app based [136, 137] or virtual reality devices. [138, 139]

There are several case reports endorsing supervised exercise and education programmes. The studies advocate for multidisciplinary rehabilitation to reduce disability and improve functionality [140] and quality of life [141]; improvements in six-minute walk test, dyspnoea scores [142] and anxiety scales. [143, 144]

Internationally, many countries are implementing dedicated treatment guidelines, care pathways and useful online resources to support patients with long COVID. This includes:

- opening long COVID clinics as one-stop-shops for treatment and support [35, 145]
- developing online resources such as:
    - informative websites that provide symptom-based suggestions to manage long COVID at home [146]
    - websites (such as Altea Long COVID Network) which provide a meeting place for those affected, relatives, medical professionals, researchers, and other interested parties. [147]
- Creating new frameworks to establish coordinated rehabilitation care pathways across the care continuum specifically targeting in-hospital care, continuing care, and community-based care. (e.g., the Provincial Post COVID-19 Rehabilitation Response Framework in Alberta, Canada). [148]

For children, New Zealand specific resources are available online, including:

- Recovering From COVID – Including long COVID [149]
- Back to Activity and Sport After COVID-19 [150]

Some studies have also explored the role complementary and alternative medicine may have in long COVID management. [125, 154-158] These include the uses of essential oils, oral supplements, aromatherapy, and Traditional Chinese Medicine. The effectiveness of most complementary and alternative medicine interventions still needs evaluation.

Models of care in Aotearoa New Zealand

In September 2022, Aotearoa New Zealand resources for symptom management were published by Te Whatu Ora Waitemāta [159] and Manatū Hauora. [1] Te Whatu Ora Waitemātā have developed Aotearoa New Zealand contextualised patient resources which includes guidance on what long COVID is. It shares tips and tricks for managing long COVID and looking after yourself, ensuring people with long COVID tend to not only their physical health but all aspects of Te Whare Tapa Whā, including

advice for self-care, eating well, and relaxation. Specific guidance on coping with brain fog or cognitive changes is included, as well as guidance on managing fatigue and pacing, headaches, and keeping track of symptoms.

Rongoā Māori (Māori medicine) where ailments are treated in a holistic manner is also of cultural significance for Aotearoa populations. A scoping review is underway to examining the barriers and facilitators for Māori accessing injury and rehabilitation services, and the findings will be of benefit when considering long COVID rehabilitation for the priority populations affected by long COVID. [160]

Equity considerations in models of care

Research was undertaken with an underserved community in the UK which discussed preferences of individuals in relation to their support for self-managed recovery from long COVID. [161] Patient and peer support networks have played a key role in the initial response to long COVID predominantly on social media platforms Facebook and Twitter. Further research was undertaken in the US to study receipt of outpatient rehabilitation services within six months of COVID-19 diagnosis and incidence of long COVID symptoms. [162] The study reported being African American was associated with lower utilisation of out-patient rehabilitation services despite a similar incidence of long COVID symptoms. Further research is needed to better understand barriers to rehabilitation services and address ethnic inequalities in receipt of care. For Aotearoa New Zealand, using an equity lens with a co-design approach with affected communities of those living with long COVID, particularly Māori and Pacific peoples, will be essential.

Evaluation of services

A scoping review [163] aimed to identify key concepts and knowledge gaps for long COVID by conducting a review of literature on the condition's management by United Kingdom GPs. Six key themes were identified which impact on the delivery of services:

- GP uncertainty
- assessment and monitoring of symptoms
- coordinating access to appropriate services
- listening and empathy
- facilitating provision of continual and integrated multidisciplinary care
- the need to provide or facilitate psychological support.

The findings highlight that GPs have a key role in the management of long COVID, and that patient care can be improved through better understanding of patient experiences, standardised approaches for symptom identification and treatment, and facilitation of access to multidisciplinary specialist services when needed. GPs need to be well resourced and upskilled to provide clear support.

The use of virtual rehabilitation, [164] telemonitoring, [165] and mobile healthcare for rural areas [166] were all identified in the literature as service models for delivery of care in long COVID patients. High patient satisfaction was one of the outcomes from studies utilising these service models. [132-135]

Olfactory training has also been studied for the treatment of persistent olfactory disorders however the outcomes of the study were not conclusive as beneficial. [167]

International guidelines on rehabilitation and management

Existing international guidelines propose that the initial management of long COVID should be in primary care and should include a series of investigations both to characterise how the individual is affected and to exclude other conditions that may coexist. Management, referrals, and care pathways should then be tailored to the manifestations of disease, including investigation and referral for signs of involvement of different organ systems. [37, 148]

The patient voice has been critical in shaping awareness of long COVID internationally and within New Zealand, and patient- and whānau-centred care should continue to be the focus. Counselling and psychological support may be needed to address high rates of poor mental health, and many of the post-COVID clinics set up throughout the US and UK contain psychology services or referrals. [168] Timely access to good quality information to understand their illness, managing expectations of others, as well as positive contact with people who have previously been through this illness also assist in an individual's recovery. [124, 169]

There are several guidelines available for clinical management of patients with long COVID, as shown in Table 2 below.

Table 2: International guidelines for clinical management of patients with long COVID

Source	Title	Date
Agency for Clinical Innovation, Australia [170]	Clinical practice guide for assessment and management of adults with post-acute sequelae of COVID-19 Guidance for NSW health clinicians	Original Publication Date 14 May 2022, Review Date 1 August 2022
Centers for Disease Control and Prevention (CDC), USA [171]	Post-COVID Conditions: Information for Healthcare Providers	22 Sept 2022
Chartered Society of Physiotherapy, UK [172]	COVID-19 Rehabilitation Standards	Original version published 14 July 2021 Updated 27 August 2021

Source	Title	Date
National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners (RCGP), UK [45]	COVID-19 rapid guideline: managing the long-term effects of COVID-19	Version 1.20 published on 3.11.2022
Ontario Health, Canada [173]	Post-COVID-19 Condition: Guidance for Primary Care	Dec 2021
Royal Australian College of General Practitioners, Australia [174]	Caring for Patients with Post COVID-19 Syndrome	May 2022
Scottish Intercollegiate Guidelines Network (SIGN), Scotland [175]	Managing the long-term effects of COVID-19	Original version published Dec 2020 Updated November 2021

Policy responses

Globally countries are at varying stages of their response to COVID-19, with some only having experienced significant outbreaks following the emergence of the Omicron variant. This has resulted in a lack of first-hand experience in addressing long COVID and under-developed systems capable of reporting and responding to increasing burden from long COVID.

All COVID-19 related policies in Aotearoa New Zealand require partnership and shared decision-making with key affected communities, including those with long COVID, the Māori Health Authority, the Ministry for Pacific Peoples, and Whaikaha – Ministry for Disabled People.

Australia: An inquiry into the health, social, educational, and economic impacts of long COVID and repeated COVID infections was launched in September 2022 by the House Health Committee. [176]

United Kingdom: 80 clinics focusing on providing support to those suffering from long COVID have been established with a primary focus on psychological and physiological support services. The UK government has made Statutory Sick Payments, Universal Credit or Employment and Support Allowance available to people if long COVID affects the ability to work. Affected individuals also qualify for a Personal Independence Payment if they have mobility difficulties. The UK's response has endeavoured to provide all information in accessible and age-appropriate formats so that people can understand and take part in decisions about their care, as guided by the NICE guidelines on shared decision making and good patient experiences. [177, 178]

United States: As of July 2021, long COVID can be considered a disability under the Americans with Disabilities Act. Federal agencies have been asked to support patients and doctors by providing science-based best practices for treating long COVID, maintaining access to insurance coverage, and protecting the rights of workers.

France: On 17 March 2022, the French Health Minister published a statement recognising long COVID as a health concern in France and acknowledging the necessity for ongoing research into its prevalence, diagnosis, and treatment.

Germany: The German Government intends to a nationwide network of 2,580 competence centres and interdisciplinary outpatient clinics to further research and ensure needs-based care around the long-term effects of COVID-19. German physicians have also established a national association containing thirteen specialised working groups, to promote research and improve long COVID treatment. The Federal Ministry of Health has recently changed the national testing guidelines, as free access to testing for asymptomatic citizens as been removed. [179]

Sweden: The Swedish government has supported research on COVID-19 through funding to the Swedish Research Council and tasked the Swedish Agency for Health and Care Services Analysis with mapping long COVID care across the country. The National Board of Health and Welfare has produced guidelines and statistical reports to support the health and welfare system in meeting the needs of patients with long COVID. However, the systems for testing, assessment, treatment, and support are still being developed and are not yet fully functioning.

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