

Long COVID Evidence Update - 11 August 2022

This evidence brief is up to date as of 11 August 2022.

Long COVID Evidence Update - 11 August 2022	1
Key Points	2
Introduction	4
Long COVID terminology and definitions	4
Symptoms and Signs	6
Table 1: Commonly reported symptoms of long COVID	6
Omicron	8
Long COVID in children	10
Epidemiology	12
Prevalence and incidence	12
Prevalence of long COVID in Aotearoa New Zealand	16
Aetiology	16
Risk Factors	17
Prevention	18
Vaccination	19
The impact of vaccination prior to infection on long COVID	19
The impact of vaccination after infection on long COVID	21
Vaccine injury	24
Other preventions – a holistic approach to long COVID	24
The association between long COVID and other post-viral conditions	24
Impacts	25
Psychosocial impacts	25
Social and economic impacts	25
Diagnosis, Treatment, Management and Support	26
Diagnosis	26
Models of care	27
Evaluations of services	28
International guidelines on rehabilitation and management	29
Policy Responses	32

Key Points

- No international definition has been agreed upon for ongoing symptoms following acute SARS-CoV-2 infection, and the time period of ongoing symptoms varies from 4 weeks to 12 weeks and onwards.
- The New Zealand Ministry of Health has received recommendations from the Long COVID Expert Advisory Group and agreed to adopt a consistent clinical case definition for long COVID to use in Aotearoa New Zealand. The joint guideline by the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) will be adopted to distinguish between ongoing COVID and long COVID cases. This definition differentiates acute COVID-19 (signs and symptoms up to 4 weeks) from ongoing symptomatic COVID-19 (4 weeks to 12 weeks) from Post-COVID-19 syndrome (from 12 weeks).
- A definition of long COVID in children and young people has been developed using the Delphi method: *“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”*.
- There are a range of signs and symptoms that have been associated with long COVID. Symptoms can be respiratory, cardiopulmonary, neurological, or systemic. They can be concurrent, fluctuating and overlapping. Symptoms vary in severity and site over time, including symptom-free periods followed by relapses. The most reported symptoms of long COVID are fatigue or general malaise, headaches, cognitive impairment or attention disorders, and respiratory symptoms.
- Long COVID in children is not well described, and prevalence estimates vary widely. There is some emerging evidence that signs and symptoms or clinical presentation may differ for children, with NICE in the UK noting cardiac and respiratory symptoms were less common in children than adults. A study published on 22 July found 9.8% of hospitalised children and 4.8% of discharged children infected with SARS-CoV-2 and tested in emergency departments went on to report post-COVID-19 conditions (PCCs) 90 days later. The report also indicated that persistent, new or reoccurring health problems were reported in 60% of children who had reported PCCs at 90 days. The most common reported symptoms were respiratory (eg, cough, difficulty breathing, or shortness of breath) and systemic (general fatigue and fever). Risk factors for reporting PCCs included the number of acute symptoms, length of hospitalisation, and older age of child.
- The prevalence of long COVID is difficult to establish for a range of reasons, however preliminary studies suggest that approximately 30% of people who test positive for COVID-19 experience symptoms for 12 weeks or longer. (1)
- Evidence continues to emerge on the cause/s of long COVID. A range of factors have been suggested to contribute including effects of the virus on the body (particularly on the nervous and vascular systems) or persistent virus or virus fragments lingering and causing inflammation; autoimmunity triggered by SARS-CoV-2 infection; changes in the microbiome and viral reactivation; or unrepaired tissue damage from original infection.
- Long COVID appears to be more common among people who have severe COVID-19 symptoms during acute illness, but it can also affect those who initially had mild or moderate COVID-19. Some factors that have been associated with an increased risk of long COVID include increased age, poor pre-pandemic general and mental health, asthma, having underlying health conditions, a higher body

mass index, and being female. Vaccines are important in preventing long COVID and are effective prior to infection and post-infection.

- 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 ([link](#)).
- One case-control study from the UK has found that the risk of ongoing symptoms or long COVID after Omicron infection is approximately half of the risk after Delta infection. Although the percentage of Omicron infections leading to long COVID were lower, the absolute numbers are still expected to be greater than for Delta due to the increased numbers that were infected by Omicron, and therefore the impact on the health system could still be significant. Evidence is still emerging on the potential impact of BA.4 and BA.5 (the latest and now dominant sublineages of Omicron) for long COVID. Initial literature suggests these variants are capable of increased immune evasion due to mutations in the surface spike proteins and increases in transmissibility and infection are likely to increase prevalence of long COVID. There is no published evidence, grey literature or media reports suggesting a decline in demand for services with Omicron, however the number of people self-reporting persistent symptoms beyond four weeks in the UK reduced from approximate 2million to 1.8million between May and July, which may have impacted demand. However, the number reporting persistent symptoms beyond 12 weeks remained stable at 1.4million ([link](#)).
- The effect of vaccination on pre-existing long COVID remains uncertain and contentious, though most studies comparing long COVID symptoms before and after vaccination reported an improvement in symptoms after vaccination, either immediately or over several weeks. Analysis evaluating differences between COVID-19 vaccine types and long COVID outcomes found minor difference between vaccines on preventing long COVID, however those who received Moderna were more likely to report fatigue, myalgia and chest pain than those who received AstraZeneca.
- There has been some discourse suggesting vaccine injury may lead to long COVID symptoms. Some small-scale research has been undertaken however it was inconclusive in its findings, and no causative link was found.
- Long COVID patients are reporting multiple psychosocial impacts, including mental health related impacts, affecting the ability of some patients to work.
- While the fiscal impacts of the COVID-19 pandemic, in general, is well known and reported on across jurisdictions, the fiscal impacts of long-term health impacts and long COVID are less well known but could include decreased productivity from a reduction of participants in the workforce, to costs incurred by an individual, including healthcare costs, lost wages, lost savings, and accrued debt.
- Preliminary analysis from Ngā Kawekawe o Mate Korona has found that 45% of Māori with long COVID say their usual activities have been affected to a moderate or extreme level; about 20% have severe pain and about 10% have difficulty moving.
- There are currently several limitations and challenges in diagnosing long COVID, the most significant being the current lack of consensus on the definition.
- As long COVID has emerged, many healthcare professionals and researchers have compared the experience to other post-viral conditions such as myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) due to the similarities in symptoms and affected demographic, and therefore many researchers are postulating that long COVID may be a sub-type of ME/CSF.
- Due to the wide-ranging and multi-organ nature of symptoms, the treatment and rehabilitation options vary for people with long COVID. There is an emerging consensus on best practice which

points to the need for multidisciplinary, multispecialty approaches to assessment with case management tailored to how the disease manifests for each patient, and development of an individualised management plan.

- There are an increasing number of international guidelines available for clinical management of patients with long COVID which are briefly presented here. Currently, there are no collated Aotearoa New Zealand resources for symptom management.
- 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, 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.
- A new section on service evaluation has been added.

Introduction

In the early stages of the pandemic, most attention was focused on the acute health impacts of SARS-CoV-2 infection. (2) 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. (3) However, it has become clear that for some people COVID-19 can lead to persistent illness, with ongoing and often debilitating symptoms. (3-5)

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, as well as aetiology, epidemiology, issues related to the impact of vaccination and new emerging variants. Developments in international guidance from peak bodies on diagnosis, management, support, and rehabilitation pathways will also be explored. It reflects current knowledge at the time of writing (August 2022). It is a live and working document which will be updated as new evidence emerges, with an updated report scheduled to be shared every eight to twelve weeks with the Chief Allied Health Professions Office (CAHPO), Ministry of Health, Aotearoa New Zealand.

Long COVID terminology and definitions

Ongoing symptoms are common following many viral and bacterial infections, including other coronaviruses. The term ‘long COVID’ is commonly used to describe signs and symptoms that continue or develop after acute COVID-19 (up to four weeks from the initial infection); however, some definitions consider long COVID to be ongoing symptoms from 12 weeks onwards. Symptoms may last for weeks or months after the acute illness. The presence of lingering symptoms may have a significant impact on the daily lives of those who are affected, their family and whānau. Given the numbers of people who have been or will be infected with SARS-CoV-2 worldwide, the public health impact of long COVID could be significant.

Across the international literature, long COVID may be 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 sublineages and Aotearoa New Zealand now having had nearly 1.7 million confirmed cases of COVID-19, an increase in long COVID cases is expected to be seen.

It has been identified that it is clinically important to establish a clear and standardised definition for long COVID in Aotearoa New Zealand. This will lead to more 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.

The Ministry of Health has received recommendations from the Long COVID Expert Advisory Group and agreed to adopt a consistent clinical case definition for long COVID to use in Aotearoa. This includes the following recommendations that:

- the definition is specific and provides exact timeframes that differentiate between ongoing systematic COVID-19 and long COVID; and,
- allows for inclusion in the diagnosis irrespective of COVID-19 test result, allows treatment for people who may have had a false negative result, were unable to access testing, and/or have a test conducted.

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 ongoing COVID and long COVID cases.

This definition is as follows:

- 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:
 - 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. It usually presents with 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-10 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).(6)

Other widely used international definitions include those from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), as defined below.

The [WHO](#) published the following clinical case definition (created by Delphi consensus) in October 2021:

“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 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 which 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. A separate definition may be applicable for children.”

The [CDC](#) in the US uses the term ‘post-COVID conditions’ to describe long COVID, defined as a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19.

A study published online on 17 June 2022 aimed to develop a long COVID definition in children and young people (CYP) using the Delphi method. (7) After three rounds of surveys and a consensus meeting, ten statements were collected, with five meeting the threshold for inclusion into the research definition. 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”*. This definition aimed to align itself with the WHO clinical case definition for adults. The positive COVID-19 test result referred by this definition can be either an PCR test, lateral flow antigen test (‘rapid antigen test’) or antibody test.

Symptoms and Signs

There are **a range of signs and symptoms** that have been associated with long COVID. Signs and symptoms can vary greatly, and one systematic review and meta-analysis completed in early 2021 found 55 long-term effects noted across 15 studies. (8) Another review conducted in November 2021 looked at 50 studies and found more than 100 persistent symptoms reported. (9) Symptoms can be respiratory, cardiopulmonary, neurological, or generalised, as it detailed in Table 1 below. (10)

Table 1: Commonly reported symptoms of long COVID

<p>Cardiopulmonary</p> <ul style="list-style-type: none"> <input type="checkbox"/> Difficulty breathing or shortness of breath <input type="checkbox"/> Cough <input type="checkbox"/> Chest pain, tightness, or heaviness ¹ <input type="checkbox"/> Palpitations 	<p>Generalised symptoms</p> <ul style="list-style-type: none"> <input type="checkbox"/> Fatigue <input type="checkbox"/> Fever <input type="checkbox"/> Pain <input type="checkbox"/> Reduced exercise capacity
<p>Neurological</p> <ul style="list-style-type: none"> <input type="checkbox"/> Cognitive impairment (‘brain fog’, loss of concentration or memory issues) <input type="checkbox"/> Headache 	<p>Gastrointestinal</p> <ul style="list-style-type: none"> <input type="checkbox"/> Abdominal pain <input type="checkbox"/> Nausea <input type="checkbox"/> Diarrhoea

¹ Clinical assessment is required to investigate the specific cause

<input type="checkbox"/> Sleep disturbance <input type="checkbox"/> Peripheral neuropathy symptoms (pins and needles, numbness) <input type="checkbox"/> Ongoing changes to smell or taste <input type="checkbox"/> Dizziness <input type="checkbox"/> Delirium (in older populations)	<input type="checkbox"/> Anorexia and reduced appetite (in older populations)
Musculoskeletal <input type="checkbox"/> Muscle aches and pains <input type="checkbox"/> Muscle weakness ² <input type="checkbox"/> Joint pain	Ear, nose, and throat <input type="checkbox"/> Tinnitus <input type="checkbox"/> Earache <input type="checkbox"/> Sore throat <input type="checkbox"/> Dizziness
Psychological/ psychiatric symptoms³ <input type="checkbox"/> Symptoms of depression <input type="checkbox"/> Symptoms of anxiety	Other <input type="checkbox"/> Skin rashes (including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities) <input type="checkbox"/> Metallic or bitter taste <input type="checkbox"/> Metabolic disruption (such as poor control of diabetes) <input type="checkbox"/> Thromboembolic conditions

Some research indicates that people experiencing long COVID tend to 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'). (11) A report from the CDC (May, 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. (12)

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. (1, 3, 5)

The most reported symptoms of long COVID are fatigue or general malaise, headaches, cognitive impairment or attention disorders, or respiratory symptoms. One meta-analysis concluded that the effects largely corresponded with clinical symptoms including fatigue (58%), headache (44%), attention disorder or cognitive impairment/brain foginess (27%), hair loss (25%) and dyspnea (24%) (shortness of breath). (8)

² Muscle weakness can be a reported symptom, and may also be clinically measured

³ The WHO has noted that the association between long COVID and psychiatric disorders is likely bidirectional

Neurological symptoms, including persistent cognitive impairment, appear to be affecting as many as one-in-four people recovered from COVID-19. (13) COVID-associated cognitive impairment often includes impaired function relating to concentration, processing information speed, attention, and memory. (13) In an investigation of the mechanisms leading to this, a study led by the Stanford University School of Medicine found that even mild cases of COVID-19 could lead to prominent neuroinflammation (or more specifically, brain inflammation). This causes physical damage to the white matter in the brain that resembles damage seen after cancer chemotherapy, including disruption to the same cell types and processes. (14) This damage appears to contribute to the lingering neurological symptom (often termed ‘brain-fog’) reported by many with long COVID or undergoing chemotherapy. One positive from this association is that cancer therapy related treatments could provide insight into appropriate treatments for long COVID-induced neurological symptoms. (14)

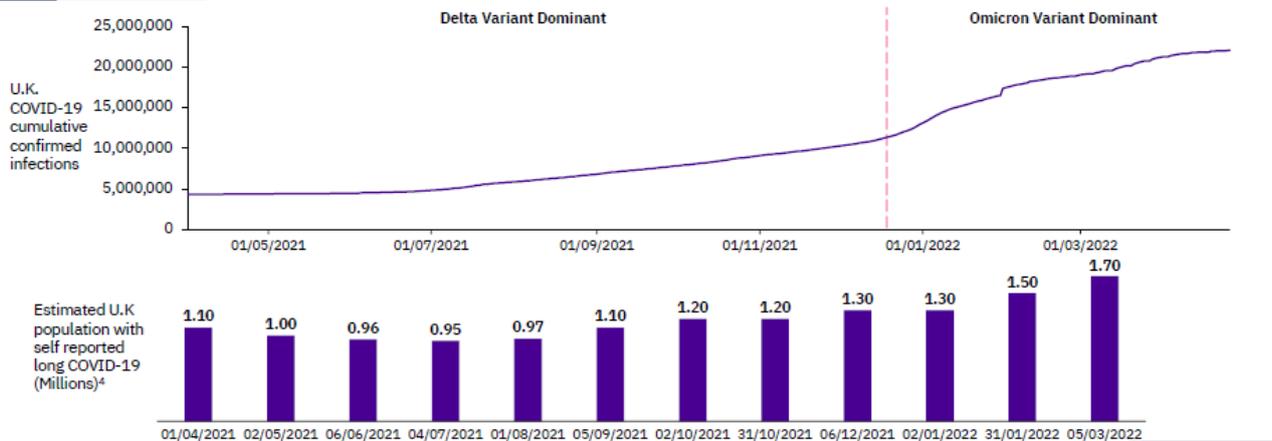
Another study found COVID-19 infections lead to persistent cardio-renal inflammation and activation of the haemostatic pathways which have implications to lung function. The impacts on multisystem injury pathways during SARS-CoV-2 infection could be considered to inform clinical guidelines in preventative measures for long COVID and support measures targeting preventative therapies. (15)

A systematic review and meta-analysis published in mid-April 2022 found over 60 physical and psychological signs and symptoms with wide variation in prevalence estimates reported across 39 studies, although, notably, most studies had a high or moderate risk of bias. The most reported symptoms were weakness (41%; 95% CI 25% to 59%), general malaise (33%; 95% CI 15% to 57%), fatigue (31%; 95% CI 24% to 39%), concentration impairment (26%; 95% CI 21% to 32%) and breathlessness (25%; 95% CI 18% to 34%). Thirty-seven percent (95% CI 18% to 60%) of patients reported reduced quality of life and 26% (10/39) of the studies presented evidence of reduced pulmonary function.(16) In May 2022 the CDC reported that in people with previous COVID-19 diagnosis, one in five individuals between 18-64 years reported at least one incidence of 26 conditions attributed to long COVID. This was even more common in people over 65 years, with one in four. (12)

There is limited evidence on any association between how symptom presentation of long COVID may differ between variants of SARS-CoV-2, and this could be confounded by a variety of factors such as the vaccination rollout, changes in treatment, as well as changes in detection and testing capacities and levels of community prevalence. With the high rates of community transmission of Omicron, and increased asymptomatic transmission, there is less detection of Omicron occurring, compounded by the shift to relying on rapid antigen tests. One early observational study found the Alpha variant was more likely to cause persistent cognitive symptoms when compared to the original Wuhan variant, though these could have been influenced by a range of causes. In this same study the Alpha variant appeared less likely to cause impaired hearing or a loss of sense of smell compared with the original variant. (17)

Omicron

There is limited data available on Omicron, however initial evidence from the UK’s Office for National Statistics (ONS) suggests that despite lower case severity with Omicron, these variants are still presenting a significant long COVID burden, which appears to be largely driven by the higher number of cases. ([link](#), visualisation by Airfinity).



The UK's [ONS](#) conducted a study using self-reported data from COVID-19 cases to explore the impact of Omicron BA.1 or BA.2 variants on long COVID. The data suggested that:

- For vaccine boosted adults, there was not statistically significant difference in the risk of self-reported long COVID between first infections with the Delta variant and with either Omicron BA.1 or Omicron BA.2.
- For boosted adults, the odds of reporting long COVID symptoms four to eight weeks after infection were 21.8% higher after Omicron BA.2 than Omicron BA.1.
- For those with only a vaccine primary course of two doses, the survey found that the odds of reporting long COVID symptoms after infection were 49.7% lower in Omicron B.A1 infections than the Delta variant.

A June 2022 study has found that the risk of ongoing symptoms or long COVID after Omicron infection is approximately half of the risk after Delta infection. (18) In this UK based case-control study, the odds of symptoms 4 weeks or more post-infection (as per NICE definition) were compared in patients with Omicron (n=56,003 people, 55% female, mean age 53 years) and Delta (n=41,361, 59% female, mean age 53 years). In the Delta-infected cohort, 10.8% experienced ongoing symptoms compared to 4.5% in the Omicron cohort. Although the percentage of Omicron infections leading to long COVID were lower, the absolute numbers are still expected to be greater than for Delta due to the increased numbers that were infected by Omicron, and therefore the impact on the health system could still be significant. The study was unable to estimate the incidence of ongoing symptoms or long COVID in children nor did it compare vaccination statuses. (18)

BA.4 and BA.5 are two of the latest variant sub-lineages of the Omicron strain. These variants are currently the most prevalent within the New Zealand community as of August 2022. The implications towards long COVID incidence as a result from infection with these new sub-variants is currently unknown. The literature suggests that these variants are capable of increased immune evasion due to mutations in the surface spike proteins. (19) Internationally it is estimated that second and third waves of infection due to new sub-variants are likely to increase prevalence of long COVID, (20) particularly amongst those in high exposure environments e.g. healthcare workers. (20)

There is no published evidence, grey literature or media reports suggesting a decline in demand for services with Omicron, however the number of people self-reporting persistent symptoms beyond four weeks in the UK reduced from approximate 2million to 1.8million between May and July, which may have impacted

demand. However, the number reporting persistent symptoms beyond 12 weeks remained stable at 1.4million ([link](#)).

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 (such as a lack of a clear case definition, arbitrary follow up time points, subjective assessment, lack of control groups, and low response rates). (21, 22) Evidence is predominantly limited to select populations without control groups. (23) Relatively few studies have focused on SARS-CoV-2 infection sequelae in children and adolescents, and large, harmonised longitudinal studies are needed. (24) Persistent illness in children has been noted in some studies and in patient support groups, but its prevalence, characteristics and duration are unclear. (25, 26) As is described above, a definition of long COVID for children and young people has been developed using the Delphi method.

Estimates of the prevalence of long COVID in children vary widely. (22) The variability in prevalence estimates could be due to a range of factors, such as initial SARS-CoV-2 infection severity, different methodological approaches (clinical assessment vs self-report), definition of cases (diagnosed vs suspected), variable follow-up times, and prevalence of pre-existing clinical conditions. (23) In the US, a large long-term study of the impacts of COVID-19 on children has recently begun. It will track up to 1,000 children and young adults and evaluate the impacts on their physical and mental health over three years. (24)

Some studies suggest that long COVID in children is less common and tends to be less protracted than in adults. (27) 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 diagnosis less likely. One report suggests that over half the children and adolescents 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 on children and adolescents. (28)

There is some emerging evidence that signs and symptoms or clinical presentation may differ for children, with [NICE in the UK noting](#) cardiac and respiratory symptoms were less common in children than adults. The NICE panel noted that common presentation in children is a lack of concentration, short-term memory loss, and/or difficult doing everyday tasks ≥ 4 weeks after acute COVID-19 illness.

Some of the studies of long COVID in children include:

- A review of studies of long COVID in children and adolescents identified 14 heterogeneous studies (4 cross-sectional, 10 prospective cohort) investigating long COVID symptoms in a total of 19,426 children and adolescents. The prevalence of long COVID symptoms varied from 4% to 66%, and there was also large variation in the reported frequency of different symptoms. Zimmerman et al (2021) note that all the studies in their review were likely to have been conducted before the Delta variant became dominant, which may have a different risk of long COVID.(22)
- A pre-print from a German study of 157,134 individuals (11,950 children/adolescents and 145,184 adults) with confirmed COVID-19.(29) The COVID-19 and control cohorts were well-balanced regarding covariates. For all adverse health outcomes combined, incidence rates (IRs) in the COVID-19 cohort were significantly higher than those in the control cohort in both children/adolescents. Incidence rate ratio (IRR) estimates were similar for the age groups 0-11 and 12-17. Incidence rates

- in children/adolescents were consistently lower than those in adults. Among the specific outcomes with the highest IRR and an incidence rate of at least 1/100 person-years in the COVID-19 cohort in children and adolescents were malaise/fatigue/exhaustion, cough, and throat/chest pain.
- The UK Office of National Statistics found that 9.8% of children aged 2-11 years and 13% aged 12-16 years reported at least one ongoing symptom five weeks after a positive diagnosis, whereas 25% of adults aged 35-69-years had symptoms five weeks after a positive diagnosis. (30, 31)
 - A paper describing data from the UK COVID Symptom Study (a citizen science project with data collected via an app, which has some associated limitations) found that of 1,734 children aged 5-17 years who were symptomatic at the time of their positive test and reported symptoms regularly for at least 28 days, 4.4% had an illness duration of at least 28 days.(25) Ongoing symptoms for at least 28 days was less common in younger children aged 5-11 years (3.1%, p=0.046). Over 98% of 1,379 children had recovered by 56 days.(25) However, there may be some bias as using apps is likely to select participants from higher socio-economic background, who have a lower risk of poor outcomes. (22)
 - One of the earliest studies on long COVID in children (a cross-sectional study of 129 children in Italy who were diagnosed with COVID-19 between March and November 2020) reported that 42.6% of children surveyed had one or more symptoms >60 days post infection.(32) This included children with mild or asymptomatic initial infection.
 - A cohort study of 136 children (most of whom had mild or asymptomatic COVID-19) in Melbourne in 2020 observed that 8% of children had post-acute symptoms. They found that full recovery occurred within weeks of acute symptom onset and reported symptoms were mild in severity but noted this was a young cohort (median age three years).(27)
 - A national, cross sectional study in Denmark has investigated the prevalence of ongoing symptoms of long COVID symptoms in children (0-14 years). It found that compared with controls, older children experiencing long COVID had lower quality-of-life scores relating to social and emotional functioning. (33) However, this study also has found that long-lasting symptoms associated with COVID-19 occurred frequently in children, regardless of whether they had a SARS-CoV-2 infection or not. This is an import observation as it outlines that symptoms in children come and go frequently and although they can persist for months they may not have an obvious cause. (33)
 - A national cohort study using data from the Public Health England database looked at adolescents aged 11 to 17 years who tested positive between January and March 2021, who were then matched by month of test, age, sex, and geographical region to adolescents who tested negative. Three months after testing, 2038 (66.5%) who tested positive and 1993 (53.3%) who tested negative had any symptoms, and 928 (30.3%) from the test-positive group and 603 (16.2%) from the test-negative group had three or more symptoms. At 3 months after testing, the most common symptoms among the test-positive group were tiredness (1196 [39.0%]), headache (710 [23.2%]), and shortness of breath (717 [23.4%]), and among the test-negative group were tiredness (911 [24.4%]), headache (530 [14.2%]), and other (unspecified; 590 [15.8%]). Overall the study concluded that adolescents who tested positive for SARS-CoV-2 had similar symptoms to those who tested negative, but had a higher prevalence of single and, particularly, multiple symptoms at the time of PCR testing and 3 months later.(34)
 - A further study in the US described a paediatric multidisciplinary post COVID-19 rehabilitation clinic model as well as a case series of patient presentations. The most common symptoms among

patients <21 years of age who presented to the clinic were fatigue, headaches, difficulty with schoolwork, brain fog and dizziness/lightheadedness. (35)

Long-term SARS-CoV-2 infection-associated symptoms can be difficult to distinguish from pandemic-associated symptoms. (21, 22) Some studies have found that children who tested negative for COVID-19 have had similar symptoms, which are common after other viral infections, and could also be due to the experience of lockdown and other social restrictions.(36, 37) 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.(22) 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.(24)

In summary, “the relative scarcity of studies of long COVID and the limitations of those reported to date mean the true incidence of this syndrome in children and adolescents remains uncertain. The impact of age, disease severity and duration, virus strain, and other factors on the risk of long COVID in this age group also remains to be determined.”(22) However, even if the proportion of children experiencing post-acute impacts is relatively low, if transmission is widespread (as has been with Omicron), then the impact of persisting symptoms will be considerable.

A study published on 22 July (38) assessed the proportion of children infected with SARS-CoV-2 tested in emergency departments, that then reported post-COVID-19 conditions (PCCs) 90 days later. (38) The results found that 9.8% of hospitalised children and 4.6% of discharged children reported PCCs. The report also indicated that persistent, new or recurring health problems were reported in 60% of children who had reported PCCs at 90 days. The most common reported symptoms were respiratory (eg, cough, difficulty breathing, or shortness of breath) and systemic (general fatigue and fever). (38) The report also indicated that the main risk factors for reporting PCCs included the number of acute symptoms, length of hospitalization, and older age of child.

Epidemiology

Prevalence and incidence

The prevalence of long COVID is difficult to establish for a range of reasons, including: (8, 39, 40)

- Studies of long COVID have used different measurement criteria and different inclusion criteria, so they cannot be reliably compared. Studies also often differ in the way they collect data.
- Studies have focused on different groups of people, different symptoms, and time intervals, and used different sample sizes.
- Most studies report the frequency of at least one symptom (not necessarily the same symptom), rather than a cluster of symptoms.
- Published studies may not be representative of everyone who has long COVID, especially with individuals of different cultures and ethnicities considered within samples. New Zealand specific samples need to include Māori, Pacific peoples, people with disabilities, older adults and those living in remote and rural communities.

- Difficulties in accessing COVID-19 testing in different countries may mask the true number of long COVID cases if studies require testing confirmation of the initial infection. In addition, testing policies vary between countries.
- 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). In addition, many studies use retrospective self-reported symptoms.
- Some tools validated for other diseases may not be appropriate for use in long COVID patients.
- The prevalence of long COVID may also vary greatly depending on the groups studied (for example, app users vs population studies vs studies of patients who were hospitalised).
- The definition of long COVID currently is linked to over 200+ symptoms (41) therefore, studies must have sufficiently large populations to be representative of the range of long COVID symptoms. Otherwise, it is unlikely that estimates of prevalence and incidence will be accurate ([link](#)).
- The method of diagnosis of long COVID in national databases also currently appears to rely on self-classification and self-reporting.
- Despite these limitations, there is increasing evidence that a significant proportion of people experience long COVID, and there are concerns that these long-term effects may occur on a scale that “could overwhelm existing health care capacity, particularly in low- and middle-income countries.”(17)

Please see the below table for an overview of prevalence estimates from some key sources, systematic reviews, and meta-analyses.

Paper	Population / Aim/ Number of studies	Key findings
Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 4 August 2022 . The Office for National Statistics UK.	1.8 million people (self-reported)	An estimated 1.8 million people living in private households in the UK (2.8% of the population) were experiencing self-reported long COVID (symptoms persisting for more than four weeks after the first suspected coronavirus infection that were not explained by something else) as of 2 July 2022. This figure is based on symptoms and not a clinical diagnosis, and only 1.4 million (81%) had had COVID-19 at least 12 weeks previously.
A systematic review and meta-analysis published in mid-April 2022(42): Chen, C., et al., <i>Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review</i> . The Journal of Infectious Diseases, 2022.	50 studies were included and 41 were part of the meta-analysis.	As of 16 April 2022, the global estimated pooled prevalence of post COVID-19 condition was 0.43 (95% CI: 0.39,0.46), or 200 million individuals. - Regional prevalence estimates were Asia— 0.51 (95% CI: 0.37,0.65), Europe— 0.44 (95% CI: 0.32,0.56), and North 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. -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.

Paper	Population / Aim/ Number of studies	Key findings
		<p>- Denmark has the highest estimate of Long COVID-19 per 100,000 people (defined in this case as at least one symptom of COVID-19 up to 120 days after infection), with 23,558, followed by Andorra (23,329), and Israel (23,194).</p> <p>-The United States has the highest absolute number of Long COVID-19 cases, with 25,141,186, followed by India (22,824,713), and France (12,526,469).</p>
<p>Systematic review and meta-analysis published in August 2021 (8): Lopez-Leon, S., et al., <i>More than 50 long-term effects of COVID-19: a systematic review and meta-analysis</i>. Scientific Reports, 2021. 11(1): p. 16144.</p>		<p>Estimated that the number of people with SARS-CoV-2 who developed one or more long-term symptoms could be as high as 80% of patients.</p>
<p>October 2021 systematic review (17): Groff, D., et al., <i>Short-term and Long-term Rates of Post-acute Sequelae of SARS-CoV-2 Infection: A Systematic Review</i>. JAMA Network Open, 2021. 4(10): p. e2128568-e2128568.</p>	<p>The mean age was 54.4 years, and 79% were hospitalised during acute COVID-19. High-income countries contributed 79% of the studies.</p>	<p>The median (IQR) proportion of COVID-19 survivors experiencing at least 1 post-acute sequelae of COVID-19 (PASC) was 54.0% (45.0%-69.0%; 13 studies) at 1 month (short-term), 55.0% (34.8%-65.5%; 38 studies) at 2 to 5 months (intermediate-term), and 54.0% (31.0%-67.0%; 9 studies) at 6 or more months (long-term). That is, more than half of COVID-19 survivors experienced PASC 6 months after recovery.</p>
<p>Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ (2021) Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 18(9): e1003773. (43)</p>	<p>A retrospective cohort study based on linked electronic health records (EHRs) data from 81 million patients including 273,618 COVID-19 survivors.</p>	<p>Among COVID-19 survivors (mean [SD] age: 46.3 [19.8], 55.6% female), 57.00% had one or more long-COVID feature recorded during the whole 6-month period (i.e., including the acute phase), and 36.55% between 3 and 6 months.</p> <p>Findings showed that the highest prevalence is in Asia, followed by Europe and North America.</p> <p>The data is limited due to being self-reported with the studies definitions of long COVID varying from 4 to 12 weeks.</p>

Paper	Population / Aim/ Number of studies	Key findings
Long COVID: Household Pulse Survey . CDC	US Census Bureau survey	40% of the total adult population has contracted COVID-19, and from this population, the estimated prevalence of long COVID (ongoing symptoms for three months or longer) is 1 in 5 adults.
Zeng, N., Zhao, YM., Yan, W. et al. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action. <i>Mol Psychiatry</i> (2022). (44) https://doi.org/10.1038/s41380-022-01614-7	A meta-analysis of survivors' health consequences and sequelae for COVID-19. A total of 151 studies were included involving 1,285,407 participants from thirty-two countries.	At least one sequelae symptom occurred in 50.1% (95% CI 45.4-54.8) of COVID-19 survivors for up to 12 months after infection. The most common investigation findings included abnormalities on lung CT (56.9%, 95% CI 46.2–67.3) and abnormal pulmonary function tests (45.6%, 95% CI 36.3–55.0), followed by generalised symptoms, such as fatigue (28.7%, 95% CI 21.0–37.0), psychiatric symptoms (19.7%, 95% CI 16.1–23.6) mainly depression (18.3%, 95% CI 13.3–23.8) and PTSD (17.9%, 95% CI 11.6–25.3), and neurological symptoms (18.7%, 95% CI 16.2–21.4), such as cognitive deficits (19.7%, 95% CI 8.8–33.4) and memory impairment (17.5%, 95% CI 8.1–29.6). The findings suggest that after recovery from acute COVID-19, half of survivors still have a high burden of either physical or mental sequelae up to at least 12 months.
A global systematic analysis of the occurrence, severity, and recovery pattern of long COVID in 2020 and 2021 (45) https://doi.org/10.1101/2022.05.26.22275532	10 ongoing cohort studies in 10 countries. They pooled data from the contributing studies, two large medical record databases in the United States, and findings from 44 published studies using a Bayesian meta-regression tool. Analyses are based on detailed information for 1906 community infections and 10526 hospitalized patients from the ten collaborating cohorts, three of which included children.	Globally, in 2020 and 2021, 144.7 million (95% uncertainty interval [UI] 54.8–312.9) people suffered from any of the three symptom clusters of long COVID. This corresponds to 3.69% (1.38–7.96) of all infections. The fatigue, respiratory, and cognitive clusters occurred in 51.0% (16.9–92.4), 60.4% (18.9–89.1), and 35.4% (9.4–75.1) of long COVID cases, respectively. Those with milder acute COVID-19 cases had a quicker estimated recovery (median duration 3.99 months [IQR 3.84–4.20]) than those admitted for the acute infection (median duration 8.84 months [IQR 8.10–9.78]). At twelve months, 15.1% (10.3–21.1) continued to experience long COVID symptoms.

Prevalence of long COVID in Aotearoa New Zealand

At this time the prevalence of long COVID in Aotearoa New Zealand is unknown. However, preliminary results from the Ngā Kawekawe o Mate Korona study suggest that the prevalence may vary across groups. Importantly, participants in this study were self-selected into the study. Furthermore, there was an emphasis on recruiting Māori participants, and therefore for these reasons it is not possible to draw firm conclusions regarding prevalence. The researchers reported that of 65 Māori participants, 43% (N=28) reported symptoms for more than one month, and of these participants, 75% (N=21) reported experiencing long COVID symptoms for more than three months post-infection. In comparison, of the 405 participants who were non-Māori, 47% (N=190) reported symptoms for more than one month, and of these individuals, 65% (N=124) reported symptoms which lasted more than 3 months ([link](#)). While similar proportions reported ongoing symptoms overall, slightly more Māori participants reported symptoms for three months or longer.

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. (46, 47) As described in a Goodfellow Unit webinar in April 2022, there are currently four broad theories as to what causes long COVID symptoms. (47) These factors are not mutually exclusive⁴, and include:(47)

- 1) **Persistent virus or viral antigens causing chronic inflammation:** In some patients, SARS-CoV-2 viral antigens can be found in tissue months after acute infection. For example, one study reported expression of SARS-CoV-2 RNA in the gut mucosa ~7 months after mild acute COVID-19 in 32 of 46 patients with inflammatory bowel disease. (48) Post acute COVID-19 symptoms were reported from the majority of patients (66%) with viral antigen persistence, but not from patients without viral antigen persistence. It was not possible to culture virus in any participants. Additionally, a pre-print case study with two long COVID patients, found viral antigen in the breast and appendix tissue at 6 and 15 months following infection. There was also evidence of negative strand RNA which is indicative of ongoing replication. It was noted however that live virus was not able to be cultured in these patients. (49)
- 2) **Autoimmunity triggered by SARS-CoV-2 infection:** Autoantibodies have been found in some patients with long COVID. However, determining the significance of these can be difficult as some may be involved in the disease process and some may be non-functional 'bystanders'. There is some evidence that patients who are better at making antibodies against SARS-CoV-2 are less likely to have autoantibodies detected. It is also unclear whether the autoantibodies were triggered by COVID-19 or whether they were there prior and only now became evident. Looking at antibody

⁴ 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.

isotypes can provide insights. Auto-antibodies can precede disease by months or years so this may be a way to identify patients at higher risk of long COVID. (50)

- 3) **Dysbiosis (changes in the microbiome) and viral reactivation (reactivation of viruses other than SARS-CoV-2 in the context of COVID-19 infection):** These are two ways that microbes outside of SARS-CoV-2 may plausibly contribute to long COVID. A number of studies investigating what happens in the microbiome (especially oral) of patients with long COVID have found decreased microbial diversity, increased pathogenic bacteria and decreased beneficial bacteria. In terms of viral reactivation, work is underway to look at whether reactivation of EBV or other herpes viruses may contribute to long COVID. (51)
- 4) **Unrepaired tissue damage from the original infection (including endothelial dysfunction):** A study performed in hamsters found that SARS-CoV-2 infection resulted in pathologies leading to long COVID. The study found when compared to Influenza A, SARS-CoV-2 had a greater likelihood to permanently damage the lungs and kidneys and impacted both the olfactory bulb and epithelium of the hamsters. A month after viral clearance, within the olfactory bulb and epithelium there was activation of T-cells and myeloid cells, production of proinflammatory cytokines and interferon responses. These responses were correlated to behavioural changes including increased compulsive behaviours and anxiety. (52) These sustained transcriptional changes could also be corroborated from tissue isolated from individuals who recovered from COVID-19. These data highlight a molecular mechanism for persistent COVID-19 symptomology and provide a small animal model to explore future therapeutics linked to the onset of long COVID. However, the link between the severity of symptoms, degree of cellular damage and the impact this has on risk of developing long COVID will require further research. (47)

More research is needed to better understand the potential immunological mechanisms contributing to the development of long COVID. Some people with long COVID are experiencing similar symptoms to myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), which has been noted after other viral infections such as SARS-CoV-1 and MERS (Middle East Respiratory Syndrome). (53) There is a similar pattern of long-term illness being triggered by acute infection by these viruses in some people. (54) Current research suggests that cellular damage and inflammation from these viral infections is linked to symptoms similar to ME/CFS. There is continued research underway to investigate how long COVID may be related to other post-viral conditions.

Risk Factors

There is a growing body of evidence about which groups are at greatest risk of developing persistent symptoms. A study published in June 2022 investigated long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. Increasing age, female sex, white ethnicity, poor pre-pandemic general and mental health, overweight/obesity, and asthma were associated with prolonged symptoms in both sources of data. (55)

Long COVID appears to be more common among people who have severe COVID-19 symptoms during acute illness but can also affect those who initially had mild or moderate COVID-19. Even people who initially had no symptoms may go on to develop long COVID. (56) Long COVID is seen in all age groups, however, it appears to be less common in children and adolescents than in adults.

Some factors that may be associated with increased chance of having long COVID symptoms have been identified, and these include:

- older age (4, 11, 57) ([link](#))
- having more than one underlying chronic medical condition or pre-existing conditions (57)
- a higher body mass index (obesity) (57)
- being female (57-59)([link](#))
- hospitalisation during acute COVID-19 (60)
- multiple early symptoms (61, 62)
- SARS-CoV 2 variant type.(18)

Data from the UK Coronavirus (COVID-19) Infection Survey (7 July) indicates that as a proportion of the UK population, the prevalence of self-reported long COVID was greatest in people aged 35 to 69 years, females, people living in more deprived areas, those working in social care, health care, or teaching and education, and those with another activity-limiting health condition or disability. ([link](#)) In the UK's Coronavirus (COVID-19) Infection Survey, prevalence of self-reported long COVID was greatest in people aged 35 to 49 years, females, people living in more deprived areas, those working in social care, teaching and education or health care, and those with another activity-limiting health condition or disability. Notably, this was self-reported rather than from clinical diagnosis. ([link](#)) A review published in June 2022(59) found that the likelihood of having long COVID syndrome was significantly greater among females (OR = 1.22; 95% CI: 1.13–1.32) The authors commented that if an elevated immune response is involved in long COVID, this may be a potential explanation for why long COVID appears to be more common in female patients.(59) Research indicates that females mount faster and more robust immune responses, and sex differences in immune response have also been reported in other viral and bacterial infections with chronic sequelae.(59)

Other factors that may immunologically predispose people to a greater risk of long COVID have been noted,(61) and these include having a greater viral load during early stages of infection, the presence of autoantibodies, (63) imbalances or compositional alterations in gut microbiome,(63, 64) and vaccination status.(65) Previous Epstein-Barr infection or a reactivation of latent viruses during initial infection has also been noted.(63, 66)

Recent studies have found that there is a correlation between COVID-19 variant type and the risk of developing long COVID. A UK based study published in June has indicated that the risk of developing long COVID from Omicron (4.4%) is roughly half the risk from Delta infections (10.8%).(18) These studies do however note the risk of developing long COVID still remains of significant concern as the rising Omicron incidence rates indicate that the absolute numbers of people with long COVID will be large, and therefore a burden on the health system.

Prevention

Much of the discussion on prevention of long COVID currently focuses on the role of vaccination. Collectively, findings from various early studies suggest that vaccination against COVID-19 might reduce the population prevalence of long COVID by reducing the risk of: (a) continuing to experience persistent symptoms in those who already have symptoms when vaccinated; (b) developing persistent symptoms

after breakthrough infections; (c) being infected in the first place; and (d) transmitting the virus after infection. (67) However, vaccination before infection likely confers only partial protection against development of long COVID, and so reliance on it as a sole mitigation strategy may not optimally reduce long-term health consequences of SARS-CoV-2 infection. (60)

Other contributors to prevention of long COVID are not well studied, however it is widely accepted that resting during the acute COVID infection phase and living a generally healthy lifestyle are likely to help recovery from COVID-19 and may prevent long COVID.

Vaccination

The effectiveness of vaccination against long COVID is a critical area of research, but significant uncertainties remain. Much of the evidence to date points to a protective effect of vaccination. However, the lack of randomised controlled trials and predominance of observational studies mean that causality cannot be easily determined (67) and it is difficult to truly know the effect of vaccination. A BMJ editorial published in May 2022 notes that benefits of vaccination against long COVID are possible, but more evidence is needed, along with a mechanism of action. (68) Early research suggests that long COVID symptoms are less common following breakthrough infections, but the effectiveness of vaccination on pre-existing long COVID is less clear. (67)

A key resource on the topic at this time is a review by the UK Health Security Agency (UKHSA), which was published in February 2022. (69) The review included 15 observational studies published up until mid-January 2022. Overall, the review indicated that people who have had one or more doses of a COVID-19 vaccine are less likely to develop long COVID than those who remain unvaccinated. (70) However, as all the studies were observational, it is possible that differences other than vaccination may contribute to the results. In addition, the definition of long COVID varied between studies. (71)

Another review (July, 2022) evaluated differences between various COVID-19 vaccine types and whether the vaccines used has an impact on long COVID outcomes. This review also showed most studies has reported vaccination led to participants being less likely to develop long COVID (67, 68, 72, 73) or to experience an improvement to long COVID symptoms, however two studies still reported vaccination as increasing the risk of long COVID. (72, 74) Most studies did not find any difference in efficacy between vaccine types. (74) However one study (April, 2022) found a significant difference in the symptoms of long COVID reported by participants that received Moderna vaccine, compared to AstraZeneca, with more reporting fatigue, myalgia and chest pain in the Moderna cohort. (74, 75) Due to the observational nature of this study, better randomised controlled trials would be required to more definitively identify differences between vaccination types, however a trial such as this would be difficult due to the high rates of vaccination now.

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 ([link](#)).

The impact of vaccination prior to infection on long COVID

UKHSA collated evidence from eight studies which investigated the effectiveness of vaccination against long COVID prior to infection. (69) Findings from six of the eight studies suggested that vaccinated people (those who have had one or two doses) were less likely to develop symptoms of long COVID following infection compared with unvaccinated people. (71) This was seen in short (4 weeks), medium (12-20 weeks), and long

(6 months) term timeframes after infection. In two of the eight studies, participants that were fully vaccinated 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.(69) As all eight of the studies only included participants who had COVID-19, the effect of vaccination on reduced incidence of COVID-19 is not accounted for. Therefore the studies likely underestimate the effectiveness of vaccines to prevent long COVID.

A review (July 2022) had the following table summarising studies that investigated the effects of vaccination on long COVID in patients that were vaccinated prior to a COVID-19 infection. A table taken from this review is shown below. (74) In this it shows Simon et al. (76) reported that vaccination significantly decreased the risk of developing long COVID symptoms after just a single dose. This was also seen in Antonelli et al. where a population that received two doses were half as likely to have symptoms after 28 days. (65) In contrast Tarquet et al. found no difference in long COVID prevalence between people who were vaccinated prior to infection and an unvaccinated control group. (77)

Table 2. Effects of vaccination on long COVID in patients who were vaccinated before getting infected with COVID-19.

Author	Total Participants	Vaccinated (n)	Vaccine Used	Single Dose (n)	Double Dose (n)	Participants Who Developed COVID-19 (n)	Participants Who Developed Long COVID-19	Differences between Vaccines	Vaccination Effects on Long COVID	Symptoms Effected
Antonelli et al. [18]	4740	2370	(Pfizer, Astrazeneca Moderna)	-	2370	not specified	50% less than those with one dose or unvaccinated	None	Half as likely to have symptoms > 28 days	Respiratory, ENT, MSK, CVS, GI, Neurological, Psychiatric, Fever, Fatigue
Taquet et al. [19]	18,958	9479	65.1% were vaccinated with 'Pfizer/BioNTech', 9.0% with Moderna, 1.6% with Janssen', and 24.4% with unspecified subtype	N/A	N/A	not specified	N/A	no outcomes on long COVID	Less likely to exhibit 5 symptoms of long COVID	Anosmia, Fatigue, Hairloss, Myalgias, ILD
Simon et al. [20]	240,648	20,188	Pfizer, Jansen, Moderna	2392	17,796	not specified	90,319	not reported	Less likely to have any symptom of long COVID (OR 0.22)	Respiratory, ENT, MSK, CVS, GI, Neurological, Fever, Fatigue
Blumberg et al. [21]	43	15	Pfizer	2	13	not specified	not specified	N/A	Less likely to have symptoms of long COVID.	Respiratory, CVS
n (Total)	n = 264,389	n = 32,052								

N/A: not applicable.

Figure: Image from Mumtaz et al. (74). References in the image relate to the following 18=(65), 19=(77), 20=(76) , 21= (78).

A UK nested case-control study (65) included in the UKHSA review (deemed medium quality) found that fully vaccinated participants were approximately half as likely to have symptoms lasting at least 28 days as unvaccinated participants.(71) However, no statistically significant benefit was found for those who were partially vaccinated compared to those who were unvaccinated. The UK [Office for National Statistics](#) reported similar results in January 2022 (based on data to 30 November 2021). In a sample of UK adults aged 18-69 years, receiving two doses of a COVID-19 vaccine was associated with a 41.1% decrease in the odds of self-reported long COVID at least 12 weeks later (compared to socio-demographically similar study participants who were not vaccinated when infected).

A research letter (July 2022) reported on an observational cohort study of workers from nine Italian healthcare facilities. (79) Data was collected from March 2020 to April 2022, where the workers were tested every 1 or 2 weeks to identify symptomatic and asymptomatic COVID-19 infections. All workers were required to receive 3 doses of the Pfizer vaccine with a clearly defined dosing schedule (first and second doses January-February 2021 and booster November-December 2021). All participants completed a survey which included a list of SARS-CoV-2 symptoms during infection, co-morbidities, and other demographics. The study defined long COVID as one or more SARS-CoV-2 symptom after 4 weeks. People hospitalised from COVID were also excluded to avoid any bias related to severe disease. Of the 2,560 participants, 739 (29%) had a COVID-19 infection, including 89 asymptomatic infections. From the participants that had a COVID-19 infection, 229 (31%) presented with long COVID. This long COVID prevalence was different between waves, with 48.1% in wave one, 35.9% in wave 2 and 16.5% from wave 3. The number of vaccination doses was associated with the prevalence of long COVID, with a 41.8% prevalence in unvaccinated patients, 30.0% after 1 dose, 17.4% after 2 doses and 16.0% after 3 doses. Additionally, older age, higher BMI, obstructive lung disease and allergies were associated with long COVID. A limitation to this study was that COVID duration and symptoms were self-reported. Additionally, the exclusion of hospitalised patients means that these conclusions do not represent people who had severe disease. (79)

There continues to be no data in children about the level of protection provided by vaccination against the incidence of long COVID (in addition to protection against infection) in those who have become infected after vaccination.

The impact of vaccination after infection on long COVID

It is widely recommended that after a COVID-19 infection, people should start or continue their vaccination schedule after 3 months from diagnosis with the acute illness, to allow for some time for recovery.

The effect of vaccination on pre-existing long COVID remains uncertain and contentious, as published studies have generally been small and with self-selected participants. (68) Anecdotal reports and some studies (69, 80) suggest a range of experiences following COVID-19 vaccination ranging from improvement, deterioration, and no change in long COVID symptoms. In the UKHSA review, 3 of 4 studies comparing long COVID symptoms before and after vaccination suggested that more cases reported an improvement in symptoms after vaccination, either immediately or over several weeks. (69) However, some cases in all studies did report a worsening in symptoms after vaccination. (69) In three of the five studies reporting on symptom changes following vaccination of people with long COVID, there was a higher proportion of people with long COVID who reported unchanged symptoms following vaccination (up to 70%) than people whose symptoms improved or worsened. (69)

Some studies have suggested that vaccination after infection can significantly reduce the likelihood of long COVID. For example, a large study which analysed self-reported data from 1.2 million UK smartphone users found that two doses of a COVID-19 vaccine halved the risk of long COVID. (65) However, some recently published studies suggest that the protective effect may not be as great as initially thought. (81)

A large study published in *Nature Medicine* in May 2022 used the US Veterans Affairs databases for an analysis that included more than 13 million people. (60) This reported that vaccination lowers the risk of long COVID after infection by about 15%. (81) Symptoms such as brain fog and fatigue were compared in vaccinated and unvaccinated participants for up to six months after they tested positive for SARS-CoV-2. No difference was found in the type or severity of symptoms between vaccinated and unvaccinated groups. Limitations of this study are the relatively small numbers of women included and suboptimal schedules for

vaccination. (79) Additionally, this was completed prior to the emergence of Omicron and its sublineages so may not be representative of current circulating variants.

The UKHSA rapid evidence briefing also reported on 3 studies which compared people with long COVID who were infected with SARS-CoV-2 and then subsequently vaccinated, to participants with long COVID that remained unvaccinated following infection. All three studies reported that the cohort who received the vaccinations were significantly less likely to experience long COVID symptoms shortly after vaccination and over longer periods. (69)

One of the largest studies on this topic to date (published May 2022) is a community-based cohort study of 28,356 participants (mean age 46 years, 56% female, 89% white) from the UK's COVID-19 Infection Survey examined the trajectory of long COVID symptoms following COVID-19 vaccination. Participants were aged 18 to 69 years who received at least their first vaccination after test-confirmed infection. The study had a median follow-up of 141 days from first vaccination (among all participants) and 67 days from second vaccination (84% of participants). The principal finding was a decrease in the likelihood of experiencing long COVID symptoms after a second vaccine dose. First vaccination was associated with an initial 12.8% decrease (95%CI: -18.6% to -6.6%) in the odds of long COVID but increasing by 0.3% (-0.6% to +1.2%) per week after the first dose. Second vaccination was associated with an 8.8% decrease (-14.1% to -3.1%) in the odds of long COVID, with the odds subsequently decreasing by 0.8% (-1.2% to -0.4%) per week. There was no statistical evidence of heterogeneity in associations between vaccination and long COVID by socio-demographic characteristics, health status, whether hospitalised with acute COVID-19, vaccine type (adenovirus vector or mRNA), or duration from infection to vaccination. (67) Similar findings to this have been reported in multiple other studies. (82, 83)

As part of a federated research study with the COVID-19 Patient Recovery Alliance, Arcadia Data Research (Arcadia.io) performed a retrospective analysis of the medical history of 240,648 COVID-19-infected persons to identify factors influencing the development and progression of long COVID. Data were captured directly from electronic health record (EHR) systems, practice management systems. This analysis revealed that patients who received at least one dose of any of the three COVID vaccines available in the US (Pfizer, Moderna or Janssen) prior to their diagnosis with COVID-19 were 7-10 times less likely to report two or more long-COVID symptoms compared to unvaccinated patients. Furthermore, unvaccinated patients who received their first COVID-19 vaccination within four weeks of SARS-CoV-2 infection were 4-6 times less likely to report multiple long-COVID symptoms, and those who received their first dose 4-8 weeks after diagnosis were 3 times less likely to report multiple long COVID symptoms compared to those who remained unvaccinated. The study authors argue that this relationship supports the hypothesis that COVID-19 vaccination is protective against long COVID and that effect persists even if vaccination occurs up to 12 weeks after COVID-19 diagnosis. (76)

Additionally, one small study with 44 vaccinated and 22 matched unvaccinated participants, assessed the timing of vaccination following COVID diagnosis in people that were hospitalised. This study found that in both vaccinated and unvaccinated people following infection, most people (up to 70%) reported no change to long COVID symptoms after vaccination. (72) Additionally, it concluded that people who were vaccinated sooner were likely to report less long COVID symptoms than unvaccinated people. However, in the vaccinated cohort, 23.2% (n=10) reported symptoms of long COVID to be improving compared to 15.4% (n=3) in the unvaccinated. Additionally, 14.3% reported symptoms of long COVID to be worsening in the unvaccinated, while only 5.6% of the vaccinated cohort reported this. Overall, this study concluded that

vaccination led to no worsening of symptoms or quality of life with some statistically significant improvements. (72)

A study in the UK surveyed 900 people living with long COVID and evaluated the impact of their first COVID-19 vaccination on their symptoms. In this, 57.9% of people reported an improvement to symptoms, 24.2% no change and 17.9% reported deterioration. The report also stated that people who received mRNA vaccines tended to report larger levels of improvement compared to adenovector vaccines. This is the largest survey to date of people living with long COVID, however due to the self-reporting nature of the survey, it is noted that a randomised controlled trial would be required to confirm any direct links between that observed between vaccination and improvement to long COVID symptoms. (82)

A review (July 2022) had the following table summarising studies that investigated the effects of vaccination on long COVID in patients that were vaccinated after a COVID-19 infection. (74) In the table it reported that nine studies indicated vaccination likely improves the effects of long COVID, one saw a negative association, one saw mixed results depending on the symptoms, and one saw no association between vaccination after infection and long COVID.

Life 2022, 12, 1066

3 of 13

Table 1. Effects of vaccinations on pre-existing COVID-19 symptoms.

Author	Total Participants	Vaccine Given	Unvaccinated (n)	Vaccinated (n)	Single Dose (n)	Double Dose (n)	Participants Who Developed Long COVID (n)	Differences between Vaccines Reported	Vaccination Effects on Long COVID	Symptoms Effected
Arjun et al. [6]	487	Covaxin	119	368	81	287	142	N/A	More likely to develop long COVID symptoms (aOR = 2.32)	Fatigue, Fever, Chills, ENT, Respiratory
Arnold et al. [7]	66	Pfizer, AstraZeneca	22	44	N/A	N/A	66	no difference	50% less likely to develop long COVID symptoms	Respiratory, ENT, MSK, CVS, GI, Neurological Fatigue
Ayoubkhani et al. [8]	28,356	Pfizer, Moderna, Adenoviral vector vaccine	0	28,356	N/A	N/A	6729	no difference	Less likely to develop all long COVID symptoms (OR = 0.91)	Respiratory, ENT, MSK, CVS, GI, Neurological, Psychiatric, Fever, Fatigue
Gaber et al. [9]	77	Pfizer, Moderna	10	67	-	-	-	no difference	Less likely to develop 1 or more long COVID symptoms	Fatigue, Anxiety, Shortness of Breath
Kuodi et al. [10]	951	Pfizer, Moderna	317	634	340	294	337	-	36–73% less likely to develop long COVID symptoms	Fatigue, headache, MSK, Dermatological, insomnia, LOC
Nehme et al. [11]	1596	Pfizer, Moderna	825	771	424	347		no difference	Less likely to develop any one symptom (aOR 0.60)	Fatigue, Neurological, ENT, Respiratory
Peghin et al. [12]	479	Pfizer, Moderna, AstraZeneca Johnson & Johnson	347	132	N/A	N/A	201	no difference	More likely to develop ocular symptoms, less likely to develop hair loss	Hair Loss, Ocular symptoms
Scherlinger et al. [13]	567	Pfizer, Moderna, Adenoviral vector vaccine	170	397	255	142	380	no difference	22% of patients felt an improvement in long COVID Symptoms	Respiratory, GI, Neurological, CVS, Psychiatric, MSK, ENT, Pruritis, Bruising, Fever, Chills
Senjam et al. [14]	773	N/A	407	366	173	193	0	N/A	Less likely to develop long COVID symptoms	ENT, Neurological, MSK, Dermatological, Fatigue, Respiratory

Table 1. Cont.

Author	Total Participants	Vaccine Given	Unvaccinated (n)	Vaccinated (n)	Single Dose (n)	Double Dose (n)	Participants Who Developed Long COVID (n)	Differences between Vaccines Reported	Vaccination Effects on Long COVID	Symptoms Effected
Strain et al. [15]	812	Astrazeneca, Pfizer, Moderna	0	812	698	114	812	MRNA superior	57% of participants reported an improvement in symptoms	Respiratory, ENT, MSK, CVS, GI, Neurological, ANS dysfunction, Rash, Fever, COVID toes
Tran et al. [16]	910	Pfizer, Moderna, AstraZeneca, Johnson & Johnson	455	455	N/A	N/A	not specified	no difference	More likely to experience remission of all long COVID symptoms (HR = 1.97)	Respiratory, ENT, MSK, CVS, GI, Neurological, Dermatological, ANS dysfunction, Psychiatric, Fatigue
Wisnivesky et al. [17]	453	Pfizer, Moderna, Jansen	129	324	N/A	N/A	not specified	no difference	No association	
	n = 35,527		n = 2801	n = 32,726			n = 8667			

N/A: not applicable.

Figure: Image from Mumtaz et al. (74). References in the image relate to the following for this documents: 6=(84),7= (72), 8= (67), 9= (85),10= (86), 11=(87), 12=(88), 13=(89), 14=(90), 15=(82), 16=(83), 17=(91).

Vaccine injury

There has been some discourse suggesting vaccine injury may lead to long COVID symptoms. A news article published in Science (Jan, 2022) discussed the experience on an individual. who received a dose of AstraZeneca vaccine as part of a clinical trial, having never had COVID-19. (92) By the evening she became disorientated and had blurred vision. Her multiple symptoms rapidly worsened, including heart rate fluctuation. Eventually she spent most of her time in a darkened room, with little energy for basic tasks such as brushing her teeth. As a result, she was diagnosed by her doctor with anxiety. (92)

By January 2021, the National Institute of Health (NIH) began to receive more reports like this. Some small-scale research has been undertaken however it was inconclusive in its findings relating to whether 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 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. (92)

Other preventions – a holistic approach to long COVID

Although it is largely agreed that the best way to prevent long COVID is to prevent the initial SARS-CoV-2 infection itself, more information is required to truly understand how to prevent long COVID after infection has occurred. Other strategies in prevention of long COVID are not well studied, however it is generally accepted that resting during the recovery of acute infection and healthy lifestyle can help recovery viral infections. Given the range of symptoms and general lack of understanding in the mechanisms leading to long COVID, many experts believe a “holistic” approach with personal care, relevant to the patient is the best way to prevent it. A community-based study, completed in France 2020, indicated that an interaction between long COVID and smoking. (93)

The association between long COVID and other post-viral conditions

As long COVID has emerged, many health care professionals and researchers have compared the experience to other post-viral conditions such as myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) due to the similarities in symptoms and affected demographic, and therefore many researchers are postulating that long COVID may be a sub-type of ME/CSF. (94) Of note people with ME/CSF experience 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. (94)

ME/CFS has a history of being maligned and neglected by medical establishments, likely due to the complicated presentation of symptoms and poorly defined aetiology. (94) There remain multiple case definitions of ME/CFS and relatively little research has been carried out on it. Until recent years, ME/CFS research and medical care suffered from many believing it 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 an immune system dysfunction. (94)

In New Zealand, research by University of Otago Emeritus Professor Warren Tate has mapped key changes in important physiological and biochemical pathways and systems in ME/CSF patients. The molecular level changes can be used to explain the diverse symptoms and ongoing disease course. Tate has been awarded funding from Brain Research New Zealand, which is being used to compare the molecular signals in people diagnosed with ME/CSF with those with long COVID. (94) Additionally, research by New Zealand Immunologist, Dr. Anna Brooks, based at the University of Auckland is also studying the 'immunity and molecular studies of SARS-CoV-2 infection, post-viral conditions and COVID-19 vaccination'. Both Brooks and Tate hope to determine if the two disease share common biomarkers. (94)

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. An early patient-led study of 3,762 self-described long haulers in 56 countries found 45.2% (42.9% to 47.2%) reported requiring a reduced work schedule compared to pre-illness and 22.3% (20.5% to 24.3%) were not working at the time of the survey due to their health conditions.(41)

Long COVID patients are reporting multiple psychosocial impacts, including mental health related impacts. This includes reporting experiences of feeling depressed, anxious, or worried. (95) Another article considering guidance to support patients experiencing long COVID found several specific mental health challenges, 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.(96) 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 ([link](#)).

Overall, long COVID is having an impact on reported quality of life. An online survey study completed in 2021 found an overall reduction in quality of life, and this was due to a range of the symptoms reported which included sleep quality, breathlessness, physical activity and mental health. (95)

Social and economic impacts

While the fiscal impacts of the COVID-19 pandemic in general is well known and reported on across jurisdictions, the fiscal impacts of long COVID specifically are less well known and scarcely reported on, as the impacts are hard to quantify given the wide variety of variables involved. The impact of long COVID can be looked at from multiple angles: from decreased productivity due to a reduction in workforce, to the costs incurred by an individual, including healthcare costs, lost wages, lost savings, and accrued debt.

Additionally, long COVID has had an impact on the ability of some patients to work. People with ongoing symptomatic COVID-19 or post-COVID-19 syndrome who report increased absence or reduced performance in education or work may need extra support and recovery time. (1) 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. (5)

Preliminary analysis from Ngā Kawekawe o Mate Korona study has found that 45% of Māori with long COVID say their usual activities have been affected to a moderate or extreme level; about 20% have severe pain; and about 10% have difficulty moving ([link](#)).

The Solve Long COVID initiative, a non-profit research and advocacy group in the United States, has estimated that the disability caused by long COVID has cost \$386 billion dollars in the United States alone. Only the personal financial impact on affected individuals was considered, like lost wages, lost savings, and healthcare costs, from the beginning of the pandemic through to January 31 2022 ([link](#)).

Further work to measure the financial impact of long COVID is still required to fully understand its scale. Countries across the globe have committed varying levels of financial resources to diagnose, understand and treat the condition, but research and reporting regarding the overall financial impact and the second and third order financial effects of long COVID is currently scarce.

The social and economic burden of long COVID will affect Māori and Pacific peoples to a greater degree, as they have accounted for a greater proportion of cases during Aotearoa New Zealand's Delta and Omicron outbreaks.

Diagnosis, Treatment, Management and Support

Diagnosis

There are currently several limitations and challenges in diagnosing long COVID, the most significant being the current lack of consensus on the definitions of long COVID (as is detailed above).

Although there are a wide range of symptoms that can present for long COVID, many of these symptoms are common from a multitude of other conditions, making them hard to decipher or confirm as long COVID. Additionally, ongoing symptoms may vary widely and will affect people in diverse ways, and symptoms can be diverse with multiorgan involvement. Long COVID is multi-factorial, and more than one mechanism may be implicated in clinical presentations. (97)

Compounding the lack of clear definitions, due to the relative newness of the condition, there may be a limited amount of knowledge of the condition known by many healthcare professionals.

There are currently no specific tests to aid in the diagnosis.

Preliminary analysis from the Ngā Kawekawe o Mate Korona study has found many patients have faced a number of healthcare access challenges in their long COVID journey, including:

- 32% of Māori and 49% of non-Māori reporting their doctor did not recommend or provide wraparound support
- 50% of Māori and 40% of non-Māori being unable to get good information about vaccines for people with long COVID
- 35% of Māori and 34% of non-Māori not being referred to a specialist, and 13% of Māori and 4% of non-Māori not having their specialist referral accepted
- 52% of Māori and 37% of non-Māori not knowing who to ask for help or support

- 48% of Māori and 44% of non-Māori not feeling listened to
- 32% of Māori and 43% of non-Māori reporting their doctor did not know what to do next ([link](#)).

Models of care

Due to the wide-ranging and multi-organ nature of symptoms, the treatment and rehabilitation options must vary for people with long COVID. There is an emerging consensus therefore on best practice which points to the need for multidisciplinary, multispecialty approaches to assessment with case management tailored to how the disease manifests for each patient, (5) and an individualised management plan developed. (98) Some patients may find it useful to keep track of their symptoms. Keeping a log of symptoms can help better understand them, identify which symptoms impact them most, and identify patterns and changes in their symptoms. (99) Due to the wide-ranging and multi-organ nature of symptoms, the treatment and rehabilitation options must vary for people with long COVID.

Internationally, multidisciplinary teams are working together to tackle the unique symptoms each patient experiences and tailoring treatment to them. (3) Countries are creating dedicated treatment guidelines and care pathways, and the US, UK and Germany have opened post-COVID clinics as one-stop-shops for treatment and support. For example, an Adult Post-Acute COVID clinic at Vanderbilt University brings together specialists from internal medicine, infectious disease, pulmonology, cardiology, ophthalmology, psychology, physical medicine, ear, nose and throat, speech pathology and neurology. (3) Physical therapy, physiotherapy, and occupational therapy have also been key tools used for those struggling with fatigue. 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. (100) Having sufficient time for the clinic visit is another part of current international clinic models for long COVID clinics, with one study endorsing initial visits of longer than 30 minutes and having the ability for follow-up as components of the services. (101)

Specific symptom management will usually be pragmatic, with avoidance of over-investigation. (98, 102)

Currently, there are no collated Aotearoa New Zealand resources for symptom management. The National Institute for Health Innovation has a page on long COVID ([link](#)) which directs patients and health professionals to the NHS (National Health Service, UK) COVID recovery website (below) and has symptom-based suggestions to manage long COVID at home.

The NHS, UK based, self-help site Your COVID Recovery has a page explaining long COVID.

<https://www.yourcovidrecovery.nhs.uk/what-is-covid-19/long-covid/>. On this site there are patient resources to help manage many of the commonly experienced symptoms of long COVID including:

- Managing the effects on your body <https://www.yourcovidrecovery.nhs.uk/managing-the-effects/effects-on-your-body/>
- Managing the effects on your mind <https://www.yourcovidrecovery.nhs.uk/managing-the-effects/effects-on-your-mind/>
- Your wellbeing <https://www.yourcovidrecovery.nhs.uk/your-wellbeing/>

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, 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. ([link](#))

Swiss based Altea Long COVID Network is an online site which focuses on the exchange of information about long COVID. Altea is a meeting place for those affected, relatives, medical professionals, researchers, and other interested parties. ([link](#))

For children, specific resources are available from Long COVID Kids including:

- A support pack ([link](#))
- Cautious Tortoise - a resource for to support decision making for a cautious approach to conditions triggered by a virus ([link](#))
- Pacing Penguins, a resource on energy management ([link](#))

For Aotearoa New Zealand, an equity focus with a co-design approach with key affected communities of those living with long COVID, Māori and Pacific peoples is key. 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. (103) 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.

Complementary medicine studies have also been undertaken to understand the role they may have in long COVID management. Fatigue is the most common long-haul symptom among women who have recovered from an acute COVID-19 infection. One randomised, blinded, controlled clinical trial evaluated an essential oil blend for energy boosting effects. Two weeks of twice-daily inhalation resulted in significant improvements to energy levels as compared to a placebo group. Aromatherapy improves energy levels among women who have recovered from COVID-19 but still experience low energy.(104) There is also evidence that Traditional Chinese Medicine (TCM) medications are effective in the symptom management of COVID-19 patients.(105) There are clinical trials underway exploring safety and efficacy of Ayurvedic interventions and yoga on the long term effects of COVID-19 (106), and osteopathy treatment for fatigue, however the results are not yet reported. (107) Conversely, evidence for the effectiveness of most Complementary and Alternative Medicine interventions still needs evaluation.

[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. (108)

Evaluations of services

A scoping review (109) aimed to identify key concepts and knowledge gaps foong 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: (1) GP uncertainty, (2) listening and empathy, (3) assessment and monitoring of symptoms, (4) coordinating access to appropriate services, (5) facilitating provision of continual and integrated multidisciplinary care and (6) the need to provide or facilitate psychological support. The findings show that GPs can play and have played 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, however GPs need to be well resourced and upskilled to provide clear support.

There are several case reports endorsing supervised exercise and education programmes. The studies advocate for multidisciplinary rehabilitation to reduce disability and improve functionality (110) and quality of life (111); improvements in six-minute walk test, dyspnoea scores (112) and anxiety scales; (113, 114). However, it is noted, some of the studies have been completed on patients prior to 2022 and the widespread Omicron outbreak or on hospitalised patients which does not reflect all patients presenting with long COVID in Aotearoa New Zealand.

The use of virtual rehabilitation (115), telemonitoring (116) and mobile healthcare for rural areas (117) were all identified in the literature as service models for delivery of care in long COVID patients. High patient satisfaction (60, 117) was one of the outcomes from studies utilising these service models.

Olfactory training has also been studied for the treatment of persistent olfactory disorders however the outcomes of the study were not conclusive as beneficial. (118)

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. (5, 119) 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.

Alongside treatment options, support and care services may be needed for people with persistent symptoms. 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. (122) Psychological supports can also help people with the process of recovery and not just the psychological adjustment. Timely access to good quality information to understand their illness, managing expectations of others, as well as positive contact with people who are or previously been through this illness also assist in an individual's recovery. (123)

There are an increasing number of guidelines available for clinical management of patients with long COVID. Some of these are listed below.

Source	Title	Date	Link	Notes
Australian National COVID-19 Clinical Evidence	Australian Guidelines for the clinical care of people with COVID-19: Post COVID-19	Living Guidelines last updated 9 May 2022	https://app.magicapp.org/#/guideline/L4Q5An/saction/jDJJQ	Guidance for clinicians on: <ul style="list-style-type: none"> - Assessing and diagnosing post-COVID conditions - A consensus recommendation of symptoms and signs - Management and care of people with post-COVID-19 condition

National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners (RCGP)	COVID-19 rapid guideline: managing the long-term effects of COVID-19	Version 1.14 published on 01.03.2022	https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742	Guidance for clinicians on: <ul style="list-style-type: none"> - Identification - Assessment - Investigations and referral - Planning care - Management (including self-management or supported management, multidisciplinary rehabilitation, and additional support) - Follow-up, monitoring, and discharge - Sharing information and continuity of care - Service organisation - Common symptoms - Equality considerations
Centres for Disease Control and Prevention (CDC), USA	Interim Guidance on Evaluating and Caring for Patients with Post-COVID Conditions	June 2021	https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html	<p>Includes guidance on general clinical considerations, patient history and physical examinations, assessment, and testing, management, and public health recommendations.</p> <p>The guidelines argue many post-COVID conditions can be managed by primary care providers, with the incorporation of patient-centred approaches to optimise the quality of life and function in affected patients.</p> <p>Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient's well-being; lack of laboratory or imaging abnormalities does not invalidate the existence, severity, or importance of a patient's symptoms or conditions.</p> <p>Healthcare professionals and patients are encouraged to set achievable goals through shared decision-making and to approach treatment by focusing on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia); a comprehensive management plan focusing on improving physical, mental, and social wellbeing may be helpful for some patients.</p>
BMJ Practice Pointer (102)BMJ Practice Pointer (102)	Management of post-acute COVID-19 in primary care	Aug 2020	https://www.bmj.com/content/370/bmj.m3026	Guidance for the management of people with long COVID in primary care.
Royal Australian	Caring for Patients	May 2022	https://www.racgp.org.a	The purpose of this resource is to provide advice and support to GPs and their teams when caring for patients

College of General Practitioners	with Post COVID-19 Syndrome		u/getattachment/8c5b3936-5551-4b94-81d4-614e2b69da51/Caring-for-patients-with-post-COVID-19-conditions.aspx	with post–COVID-19 conditions, and to encourage the development of individualised plans for their ongoing management.
Scottish Intercollegiate Guidelines Network (SIGN) (124) Scottish Intercollegiate Guidelines Network (SIGN) (124)	Managing the long-term effects of COVID-19	Dec 2020	https://www.sign.ac.uk/media/1833/sign161-long-term-effects-of-covid19-11.pdf	This document covers care for people who have symptoms that develop during or after an infection consistent with COVID-19, continue for more than four weeks and are not explained by an alternative diagnosis. It also provides advice on diagnosis and management based both on the best available evidence and the knowledge and experience of the expert panel.
Ontario Health	Post-COVID-19 Condition: Guidance for Primary Care	Dec 2021	https://www.ontariohealth.ca/sites/ontariohealth/files/2021-12/PostCovidConditionsClinicalGuidance EN.pdf	This document includes guidance for primary care on: <ul style="list-style-type: none"> - Assessment - Testing - Diagnosis - Physical examination - Management
Chartered Society of Physiotherapy	COVID-19 Rehabilitation Standards	August 2021	https://www.csp.org.uk/publications/covid-19-community-rehabilitation-physiotherapy-service-delivery	UK guidance for physiotherapy service delivery for adults who are hospitalised due to acute COVID-19 or long COVID

Policy Responses

The full magnitude of the long COVID burden globally is still yet to be known, with countries all at varying stages of their response to COVID-19, with some only having experienced significant outbreaks following the emergence of the Omicron variant, resulting in a lack of first-hand experience in addressing long COVID and undeveloped systems to respond to and report on long COVID.

For an equitable policy response in Aotearoa New Zealand, partnership, and shared decision-making with key affected communities, including those with long COVID, the Māori Health Authority, the Ministry for Pacific Peoples, and the New Ministry for Disabled People.

United Kingdom: The UK government has set up over 80 specialist clinicsⁱ to provide support to those suffering from long COVID, which provide psychological and physiological support services. Further research funding is being provided through grants to NGOs and healthcare providers through the National Institute of Health, to date only around 50 million pounds of funding has been provided for research in to Long COVID. The UK government has made Statutory Sick Payments, Universal Credit or Employment and Support Allowance (ESA) available to people if Long COVID affects how much they can work. Affected individuals can also apply for a Personal Independence Payment if they have difficulty with everyday tasks and getting around.ⁱⁱ 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](#).

United States: As of July 2021, long COVID, also known as post-COVID conditions, can be considered a disability under the Americans with Disabilities Act. President Joe Biden has directed federal agencies 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 as they try to return to jobs while coping with the uncertainties of the malaise.

France: Since the French government identified Long COVID at the end of the first wave of the virus in spring 2020, it has been watching the issue closely to care for those affected and to better understand the disease. On 17 March 2022, the 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 has committed to the establishment of a Germany-wide 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 dealing with Long COVID have established a dedicated national association, with thirteen specialised working groups, to promote research, share information and improve the treatment of patients suffering from Long COVID.

Sweden: The Swedish government has implemented several responses to Long COVID. It 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 Long COVID sufferers. However, the general lack of information about the condition, and awareness of it, as well as the immense pressure on the healthcare system during the pandemic, means that a system for testing and assessment, treatment, and support available to sufferers is not yet fully functioning.

1. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline [NG188] 2021 [updated 11 November 2021]. Available from: <https://www.nice.org.uk/guidance/ng188>.
2. Leung TYM, Chan AYL, Chan EW, Chan VKY, Chui CSL, Cowling BJ, et al. Short- and potential long-term adverse health outcomes of COVID-19: a rapid review. *Emerg Microbes Infect.* 2020;9(1):2190-9.
3. National Institute for Health Research. Living with COVID19 2020 [updated 15 October 2020]. Available from: <https://evidence.nihr.ac.uk/themedreview/living-with-covid19/#Conclusions>
4. The Royal Society. Long Covid: what is it, and what is needed? 2020 [updated 23 October 2020]. Available from: <https://royalsociety.org/-/media/policy/projects/set-c/set-c-long-covid.pdf>
5. World Health Organization (WHO). Policy Brief 39: In the wake of the pandemic - Preparing for Long COVID Copenhagen, Denmark: WHO,; 2021 [Available from: <https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf>.
6. Angamuthu N, Geraldine Gagasa E, Baker D, Tsui J, Evan D'Souza R. Transmission of infection among health care personnel performing surgical tracheostomies on COVID-19 patients. The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland. 2021.
7. Stephenson T, Allin B, Nugawela MD, Rojas N, Dalrymple E, Pinto Pereira S, et al. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. *Archives of Disease in Childhood.* 2022;107(7):674-80.
8. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Scientific Reports.* 2021;11(1):16144.
9. Hayes LD, Ingram J, Sculthorpe NF. More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review. *Frontiers in Medicine.* 2021;8.
10. Cau R, Faa G, Nardi V, Balestrieri A, Puig J, Suri JS, et al. Long-COVID diagnosis: From diagnostic to advanced AI-driven models. *European Journal of Radiology.* 2022;148:110164.
11. COVID Symptom Study. Long COVID: What do we know so far? 2021 [updated 12 April 2021]. Available from: <https://covid.joinzoe.com/post/long-covid-what-we-know>.
12. Bull-Otterson L BS, Saydah S, et al. . Post-COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71:723-17.
13. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Network Open.* 2021;4(5):e2111417-e.
14. Fernández-Castañeda A, Lu, P., et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell.* 2022.
15. Multisystem involvement is common in post-COVID-19 syndrome. *Nature Medicine.* 2022;28(6):1139-40.
16. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. *BMJ Global Health.* 2021;6(9):e005427.
17. Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Network Open.* 2021;4(10):e2128568-e.
18. Antonelli MP, J.C., et al. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *The Lancet.* 2022;399(10343):2263-4.
19. Reynolds CJ, Pade C, Gibbons JM, Otter AD, Lin K-M, Muñoz Sandoval D, et al. Immune boosting by B. 1.1. 529 (Omicron) depends on previous SARS-CoV-2 exposure. *Science.* 2022;377(6603):eabq1841.
20. Pagel C. The covid waves continue to come. *British Medical Journal Publishing Group;* 2022.
21. Murdoch Children's Research Institute (MCRI). Research Brief: COVID-19 and Child and Adolescent Health Victoria, Australia: MCRI,; 2021 [updated 13 September 2021. Version 1:[Available from:

<https://www.mcri.edu.au/sites/default/files/media/documents/covid-19-and-child-and-adolescent-health-140921.pdf>.

22. Zimmermann P, Pittet LF, Curtis N. How Common is Long COVID in Children and Adolescents? The Pediatric Infectious Disease Journal. 2021;40(12).
23. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. JAMA. 2021;326(9):869-71.
24. Munblit D, Sigfrid L, Warner JO. Setting Priorities to Address Research Gaps in Long-term COVID-19 Outcomes in Children. JAMA Pediatrics. 2021;175(11):1095-6.
25. Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. The Lancet Child & Adolescent Health. 2021:708-18.
26. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol 2021 [2021.03.18.21253888]. Available from: <http://medrxiv.org/content/early/2021/03/23/2021.03.18.21253888.abstract>.
27. Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. The Lancet Child & Adolescent Health. 2021;5(6):e22-e3.
28. Zimmermann P, Pittet LF, Curtis N. The Challenge of Studying Long COVID: An Updated Review. The Pediatric infectious disease journal. 2022;41(5):424-6.
29. Roessler M, Tesch F, Batram M, Jacob J, Loser F, Weidinger O, et al. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19 2021 [2021.10.21.21265133]. Available from: <http://medrxiv.org/content/early/2021/10/22/2021.10.21.21265133.abstract>.
30. Office for National Statistics UK. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK 2021 [Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/alldatarelatingtoprevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk>].
31. Lewis D. Long COVID and kids: scientists race to find answers: Nature; 2021 [updated 18 November 2021. Available from: https://www.nature.com/articles/d41586-021-01935-7?utm_source=tw_t&utm_medium=social&utm_campaign=nature].
32. Buonsenso D, Munblit D, De Rose C, Sinatti D, Ricchiuto A, Carfi A, et al. Preliminary evidence on long COVID in children. Acta Paediatrica. 2021.
33. KiKkenborg Berg S, Palm, P. et al. Long COVID symptoms in SARS-CoV-2-positive children aged 0–14 years and matched controls in Denmark (LongCOVIDKidsDK): a national, cross-sectional study. The Lancet Child & Adolescent Health. 2022.
34. Stephenson T, Pinto Pereira SM, Shafran R, de Stavola BL, Rojas N, McOwat K, et al. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLOCK): a national matched cohort study. The Lancet Child & Adolescent Health. 2022.
35. Morrow AKMN, Rowena PhD; Vargas, Gray PhD; Jashar, Dasal Tenzin PhD; Henning, Ellen PhD; Stinson, Nika PT, DPT; Malone, Laura A. MD, PhD. . Postacute/Long COVID in Pediatrics: Development of a Multidisciplinary Rehabilitation Clinic and Preliminary Case Series. American Journal of Physical Medicine & Rehabilitation: December 2021. 2022;100:1140-7.
36. Jason LA, Katz BZ, Shiraishi Y, Mears CJ, Im Y, Taylor R. Predictors of Post-Infectious Chronic Fatigue Syndrome in Adolescents. Health Psychol Behav Med. 2014;2(1):41-51.
37. Katz BZ, Shiraishi Y, Mears CJ, Binns HJ, Taylor R. Chronic fatigue syndrome after infectious mononucleosis in adolescents. Pediatrics. 2009;124(1):189-93.
38. Funk AL, Kuppermann N, Florin TA, Tancredi DJ, Xie J, Kim K, et al. Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. JAMA Network Open. 2022;5(7):e2223253-e.
39. Martin C, Luteijn M, Letton W, Robertson J, McDonald S. A model framework for projecting the prevalence and impact of Long-COVID in the UK. PloS one. 2021;16(12):e0260843-e.

40. Ministry of Health NZ. Long COVID 2021 [updated 21 June 2021. Available from: <https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-health-advice-public/about-covid-19/long-covid>.
41. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact 2021 [2020.12.24.20248802]. Available from: <http://medrxiv.org/content/early/2021/04/05/2020.12.24.20248802.abstract>.
42. Chen C, Hauptert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review. *The Journal of Infectious Diseases*. 2022.
43. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLOS Medicine*. 2021;18(9):e1003773.
44. Zeng N, Zhao Y-M, Yan W, Li C, Lu Q-D, Liu L, et al. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action. *Molecular Psychiatry*. 2022.
45. Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. A global systematic analysis of the occurrence, severity, and recovery pattern of long COVID in 2020 and 2021 2022 [2022.05.26.22275532]. Available from: <http://medrxiv.org/content/early/2022/05/27/2022.05.26.22275532.abstract>.
46. Brooks A. Immunity and Pathology. Long COVID: Journeying together through the fog (webinar): University of Otago, Wellington; 2022.
47. Hurst M. Long COVID (webinar). Goodfellow Unit; 2022.
48. Zollner A, Koch R, Jukic A, Pfister A, Meyer M, Rössler A, et al. Postacute COVID-19 is Characterized by Gut Viral Antigen Persistence in Inflammatory Bowel Diseases. *Gastroenterology*.163(2):495-506.e8.
49. Denise Goh JCTL, Sonia Bilbao Fernández et al. . Persistence of residual SARS-CoV-2 viral antigen and RNA in tissues of patients with long COVID-19, PREPRINT. *Research square*. 2022.
50. Mobasheri L, Nasirpour MH, Masoumi E, Azarnaminy AF, Jafari M, Esmaeili SA. SARS-CoV-2 triggering autoimmune diseases. *Cytokine*. 2022;154:155873.
51. Giannos P, Prokopidis K. Gut dysbiosis and long COVID-19: Feeling gutted. . *J Med Virol*. 2022;94(7):2917-8.
52. Frere JJ, Serafini RA, Pryce KD, Zazhytska M, Oishi K, Golyner I, et al. SARS-CoV-2 infection in hamsters and humans results in lasting and unique systemic perturbations post recovery. *Science Translational Medicine*.0(0):eabq3059.
53. Pustake M, Tambolkar I, Giri P, Gandhi C. SARS, MERS and CoVID-19: An overview and comparison of clinical, laboratory and radiological features. *Journal of Family Medicine and Primary Care*. 2022;11(1):10-7.
54. Newman M. Chronic fatigue syndrome and long covid: moving beyond the controversy. *BMJ*. 2021;373:n1559.
55. Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat Commun*. 2022;13(1):3528.
56. Centers for Disease Control and Prevention (CDC). Post-COVID Conditions: Overview 2021 [updated 9 July 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fclinical-care%2Flate-sequelae.html.
57. Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al. Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK. *medRxiv*. 2021:2021.06.24.21259277.
58. Stewart S, Newson L, Briggs TA, Grammatopoulos D, Young L, Gill P. Long COVID risk - a signal to address sex hormones and women's health. *The Lancet Regional Health – Europe*. 2021;11.

59. Sylvester SV, Rusu R, Chan B, Bellows M, O'Keefe C, Nicholson S. Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review. *Current Medical Research and Opinion*. 2022;1-9.
60. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nature Medicine*. 2022;28(7):1461-7.
61. Cervia C, Zurbuchen Y, Taeschler P, Ballouz T, Menges D, Hasler S, et al. Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome. *Nat Commun*. 2022;13(1):446.
62. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. *Nature Medicine*. 2021;27(4):626-31.
63. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-95.e20.
64. Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GC-Y, Ng SSS, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. *Gut*. 2022;71(3):544.
65. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *The Lancet Infectious Diseases*. 2022;22(1):43-55.
66. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens*. 2021;10(6):763.
67. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. *BMJ*. 2022;377:e069676.
68. Sivan M, Greenhalgh T, Milne R, Delaney B. Are vaccines a potential treatment for long covid? *BMJ*. 2022;377:o988.
69. UK Health Security Agency. The effectiveness of vaccination against long COVID. A rapid evidence briefing 2022 [Available from: <https://ukhsa.koha-ptfs.co.uk/cgi-bin/koha/opac-retrieve-file.pl?id=fe4f10cd3cd509fe045ad4f72ae0dfff>].
70. UKHSA review shows vaccinated less likely to have long COVID than unvaccinated [press release]. UK Government, 15 Feb 2022 2022.
71. Mahase E. Covid-19: Vaccinated people are less likely to get long covid, review finds. *BMJ*. 2022;376:o407.
72. Arnold DT, Milne A, Samms E, Staddon L, Maskell NA, Hamilton FW. Are vaccines safe in patients with Long COVID? A prospective observational study 2021 [2021.03.11.21253225]. Available from: <http://medrxiv.org/content/early/2021/03/14/2021.03.11.21253225.1.abstract>.
73. Mahase E. Covid-19: Do vaccines work against omicron-and other questions answered. *BMJ* (Clinical research ed). 2021;375:n3062.
74. Mumtaz A, Sheikh AAE, Khan AM, Khalid SN, Khan J, Nasrullah A, et al. COVID-19 Vaccine and Long COVID: A Scoping Review. *Life*. 2022;12(7):1066.
75. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, Rossman J. The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. *Vaccines* (Basel). 2022;10(5).
76. Simon MA, Luginbuhl RD, Parker R. Reduced Incidence of Long-COVID Symptoms Related to Administration of COVID-19 Vaccines Both Before COVID-19 Diagnosis and Up to 12 Weeks After. *medRxiv*. 2021:2021.11.17.21263608.
77. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. *medRxiv*. 2021:2021.10.26.21265508.
78. Blumberg Y, Edelstein M, Jabal KA, Golan R, Perets Y, Saad M, et al. Protective effect of BNT162b2 vaccination on aerobic capacity following mild to moderate SARS-CoV-2 infection: a cross sectional study, Israel, March-December 2021. *medRxiv*. 2022:2021.12.30.21268538.
79. Azzolini E, Levi R, Sarti R, Pozzi C, Mollura M, Mantovani A, et al. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. *JAMA* Published online July 01. 2022.

80. Tsuchida T, Hirose M, Inoue Y, Kunishima H, Otsubo T, Matsuda T. Relationship between changes in symptoms and antibody titers after a single vaccination in patients with Long COVID. *Journal of Medical Virology*. 2022;94(7):3416-20.
81. Reardon S. Long COVID risk falls only slightly after vaccination, huge study shows: *Nature News*; 2022 [updated 25 May 2022. Available from: <https://www.nature.com/articles/d41586-022-01453-0>.
82. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, Rossman J. The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. *Vaccines*. 2022;10(5):652.
83. Tran V-TaP, Elodie and Saldanha, Julia and Pane, Isabelle and Ravaud, Philippe,. Efficacy of COVID-19 Vaccination on the Symptoms of Patients With Long COVID: A Target Trial Emulation Using Data From the ComPaRe e-Cohort in France. Pre-print. *The Lancet*. 2021.
84. Arjun MC, Singh AK, Pal D, Das K, Gajjala A, Venkateshan M, et al. Prevalence, characteristics, and predictors of Long COVID among diagnosed cases of COVID-19. *medRxiv*; 2022.
85. Gaber TA, A. Unsworth, A. Martindale, J. Are mRNA Covid 19 vaccines safe in Long Covid patients? A Health Care Workers perspective. *British Journal of Medical Practitioners*., 2021;14(1).
86. Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Wiegler KB, Jabal KA, et al. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021. *medRxiv*. 2022:2022.01.05.22268800.
87. Nehme M, Braillard O, Salamun J, Jacqueroz F, Courvoisier DS, Spechbach H, et al. Symptoms After COVID-19 Vaccination in Patients with Post-Acute Sequelae of SARS-CoV-2. *Journal of General Internal Medicine*. 2022;37(6):1585-8.
88. Peghin M, De Martino M, Palese A, Gerussi V, Bontempo G, Graziano E, et al. Post-COVID-19 syndrome and humoral response association after 1 year in vaccinated and unvaccinated patients. *Clinical Microbiology and Infection*. 2022;28(8):1140-8.
89. Scherlinger M, Pijnenburg L, Chatelus E, Arnaud L, Gottenberg J-E, Sibilia J, et al. Effect of SARS-CoV-2 Vaccination on Symptoms from Post-Acute Sequelae of COVID-19: Results from the Nationwide VAXILONG Study. *Vaccines*. 2022;10(1):46.
90. Senjam SS, Balhara YPS, Kumar P, Nichal N, Manna S, Madan K, et al. Assessment of Post COVID-19 Health Problems and its Determinants in North India: A descriptive cross section study. *medRxiv*. 2021:2021.10.03.21264490.
91. Wisnivesky JP, Govindarajulu U, Bagiella E, Goswami R, Kale M, Campbell KN, et al. Association of Vaccination with the Persistence of Post-COVID Symptoms. *J Gen Intern Med*. 2022;37(7):1748-53.
92. Couzin-Frankel JV, G. In rare cases, coronavirus vaccines may cause Long Covid-like symptoms. In: *Health SI*, editor. *Science*2022.
93. Barthélémy H, Mougnot E, Duracinsky M, Salmon-Ceron D, Bonini J, Pérez F, et al. Smoking increases the risk of post-acute COVID-19 syndrome: Results from a French community-based survey. *Tob Induc Dis*. 2022;20:59.
94. Hall M. Is Long Covid a new type of chronic fatigue syndrome? RNZ2021 [Available from: <https://www.rnz.co.nz/news/what-you-need-to-know/456714/is-long-covid-a-new-type-of-chronic-fatigue-syndrome>.
95. Faghy MA, Maden-Wilkinson T, Arena R, Copeland RJ, Owen R, Hodgkins H, et al. COVID-19 patients require multi-disciplinary rehabilitation approaches to address persisting symptom profiles and restore pre-COVID quality of life. *Expert Review of Respiratory Medicine*. 2022:1-6.
96. Hussain FA. Facilitating care: a biopsychosocial perspective on long COVID. *British Journal of General Practice*. 2022;72(714):30-1.
97. Maltezou HC, Pavli A, Tsakris A. Post-COVID Syndrome: An Insight on Its Pathogenesis. *Vaccines (Basel)*. 2021;9(5).
98. RACGP. Caring for adult patients with post-COVID-19 conditions East Melbourne, VIC2020 [
99. The National Institute for Health Innovation. Long COVID 2021 [Available from: <https://www.nihi.auckland.ac.nz/long-covid>.

100. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nature Medicine*. 2021;27(4):601-15.
101. Dundumalla S, Barshikar, S, Niehaus, WN, Ambrose, AF, Kim, SY, Abramoff, BA. . A survey of dedicated PASC clinics: Characteristics, barriers and spirit of collaboration. *PM&R*. 2022;14:348- 56.
102. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. 2020;370:m3026.
103. Fowler-Davis S, Young R, Maden-Wilkinson T, Hameed W, Dracas E, Hurrell E, et al. Assessing the Acceptability of a Co-Produced Long COVID Intervention in an Underserved Community in the UK. *International Journal of Environmental Research and Public Health*. 2021;18(24):13191.
104. Hawkins J, Hires C, Keenan L, Dunne E. Aromatherapy blend of thyme, orange, clove bud, and frankincense boosts energy levels in post-COVID-19 female patients: A randomized, double-blinded, placebo controlled clinical trial. *Complementary Therapies in Medicine*. 2022;67:102823.
105. Jeon S-R, Kang JW, Ang L, Lee HW, Lee MS, Kim T-H. Complementary and alternative medicine (CAM) interventions for COVID-19: An overview of systematic reviews. *Integrative Medicine Research*. 2022;11(3):100842.
106. Yadav B, Rai A, Mundada PS, Singhal R, Rao BCS, Rana R, et al. Safety and efficacy of Ayurvedic interventions and Yoga on long term effects of COVID-19: A structured summary of a study protocol for a randomized controlled trial. *Trials*. 2021;22(1):378.
107. Curi ACC, Ferreira APA, Nogueira LAC, Meziat Filho NAM, Ferreira AS. Osteopathy and physiotherapy compared to physiotherapy alone on fatigue in long COVID: Study protocol for a pragmatic randomized controlled superiority trial. *International Journal of Osteopathic Medicine*. 2022.
108. Nelson V LM, Richard L, et al. Examining the barriers and facilitators for Māori accessing injury and rehabilitation services: a scoping review protocol. *BMJ open*. 2022;12(2):e048252.
109. Brennan A, Broughan J, McCombe G, Brennan J, Collins C, Fawsitt R, et al. Enhancing the management of long COVID in general practice: a scoping review. *BJGP Open*. 2022:BJGPO.2021.0178.
110. Güler T, Yurdakul FG, Acar Sivas F, Kiliç Z, Adigüzel E, Yaşar E, et al. Rehabilitative management of post-acute COVID-19: clinical pictures and outcomes. *Rheumatol Int*. 2021;41(12):2167-75.
111. Nopp S, Moik F, Klok FA, Gattinger D, Petrovic M, Vonbank K, et al. Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life. *Respiration*. 2022;101(6):593-601.
112. Soril LJJ, Damant RW, Lam GY, Smith MP, Weatherald J, Bourbeau J, et al. The effectiveness of pulmonary rehabilitation for Post-COVID symptoms: A rapid review of the literature. *Respiratory Medicine*. 2022;195:106782.
113. N Elliott AB, N Heron, C Ranson, J Hull , R Martin, J Elliott. *British Journal of sports medicine* April 23, 2022. [cited 2022]. Available from: <https://blogs.bmj.com/bjism/2022/04/23/graduated-return-to-play-after-sars-cov-2-infection-what-have-we-learned-and-why-weve-updated-the-guidance/>
114. Albu S, Rivas Zozaya N, Murillo N, García-Molina A, Figueroa Chacón CA, Kumru H. Multidisciplinary outpatient rehabilitation of physical and neurological sequelae and persistent symptoms of covid-19: A prospective, observational cohort study. *Disability and Rehabilitation*. 2021:1-8.
115. Harenwall S, Heywood-Everett S, Henderson R, Godsell S, Jordan S, Moore A, et al. Post-Covid-19 Syndrome: Improvements in Health-Related Quality of Life Following Psychology-Led Interdisciplinary Virtual Rehabilitation. *Journal of Primary Care & Community Health*. 2021;12:21501319211067674.
116. Romaszko-Wojtowicz A, Maksymowicz S, Jarynowski A, Jaśkiewicz Ł, Czekał Ł, Doboszyńska A. Telemonitoring in Long-COVID Patients—Preliminary Findings. *International journal of environmental research and public health*. 2022;19(9):5268.
117. Stallmach A, Katzer K, Besteher B, Finke K, Giszas B, Gremme Y, et al. Mobile primary healthcare for post-COVID patients in rural areas: a proof-of-concept study. *Infection*. 2022.
118. Vandersteen C, Payne M, Dumas L, Cancian É, Plonka A, D'Andréa G, et al. Olfactory Training in Post-COVID-19 Persistent Olfactory Disorders: Value Normalization for Threshold but Not Identification. *J Clin Med*. 2022;11(12).

119. Manhas KP, O'Connell P, Krysa J, Henderson I, Ho C, Papathanassoglou E. Development of a Novel Care Rehabilitation Pathway for Post-COVID Conditions (Long COVID) in a Provincial Health System in Alberta, Canada. *Physical Therapy*. 2022.
120. Dahlgren G, Whitehead M. The Dahlgren-Whitehead model of health determinants: 30 years on and still chasing rainbows. *Public Health*. 2021;199:20-4.
121. Diderichsen F, Hallqvist J, Whitehead M. Differential vulnerability and susceptibility: how to make use of recent development in our understanding of mediation and interaction to tackle health inequalities. *International Journal of Epidemiology*. 2019;48(1):268-74.
122. Walter K. An Inside Look at a Post-COVID-19 Clinic. *JAMA*. 2021.
123. Skirrow P, Morris, L. Thoughts that Count [Presentation]. 2022 [Available from: <https://az659834.vo.msecnd.net/eventsairaueprod/production-otago-public/bfb8d575b3b342c7b72be4c5fb221c0c>].
124. Scottish Intercollegiate Guidelines Network. SIGN 161: Managing the long-term effects of COVID-19: National guidance for identification, assessment and management Edinburgh: SIGN; 2020 [updated 18 December 2020. Available from: <https://www.sign.ac.uk/media/1833/sign161-long-term-effects-of-covid19-11.pdf>].

ⁱ British Medical Journal – COVID-19 How Europe is approaching long COVID - <https://www.bmj.com/content/376/bmj.o158> - Accessed 13 May 2022

ⁱⁱ UK Government - Find help and support if you have long COVID - <https://www.gov.uk/guidance/find-help-and-support-if-you-have-long-covid#if-you-have-long-covid-and-are-unable-to-work> – Accessed 13 May 2022