PHARMACEUTICAL SCHEDULE APPLICATION

To: COVID-19 Treatments Advisory Group

From: Funding Application Advisor

Date: February 2023

Further consideration of groups for funding for COVID-19 antivirals

QUESTIONS TO ADVISORY GROUP

Note to Advisory Group members: These questions have been identified by Pharmac staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

1. Should the populations listed below be included in the criteria as a single criterion for access to COVID-19 antivirals?

    1. Disability Support Services recipients
    2. People with rare disorders
    3. People with severe respiratory conditions (asthma, bronchiectasis, COPD and cystic fibrosis)
    4. People with any prior hospital identified/based comorbid condition/s
    5. People previously hospitalised due to COVID-19
    6. People with multiple COVID-19 infections
    7. People with long covid or post-acute sequelae of SARS-CoV-2 infection (PASC)
    8. People with a high risk of severe long-term effects or high-risk conditions

2. To what extent does the Advisory Group consider that the health need of the populations above are already addressed by the current access criteria?

3. Where the Advisory Group does not consider that any of the conditions above should be included as a single criterion for access to COVID-19 antivirals, does the Advisory Group consider that they should nonetheless be included instead as a 'high risk medical condition' for access to antivirals?

    3.1. If Yes, which groups would take priority?

4. How could a criterion for rare disorders be drafted into the criteria to capture the desired groups, without creating an opportunity for open access?

5. Following the 31 October 2022 meeting does the Advisory Group consider that cystic fibrosis should be included as a single criterion for access to COVID-19 antivirals?

6. Are those with previous hospitalisations relating to COVID-19, excluding those who have been Critical Care or High Dependency care directly as a result of COVID-19, at higher risk of severe COVID-19 upon re-infection?

    6.1. Should previous hospitalisation(s) directly due to COVID-19 be included in the criteria?

7. Are there any additional populations or groups that should be considered by Pharmac?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Advisory Group regarding additional populations and or conditions that should be included in the access criteria for immediate access to COVID-19 antiviral treatments

DISCUSSION

BACKGROUND

Current antiviral criteria (nirmatrelvir with ritonavir, molnupiravir)

Access to funded COVID-19 antivirals (nirmatrelvir with ritonavir, molnupiravir, remdesivir) since 14 September 2022, as detailed in the Pharmac antiviral Access Criteria, relevant to nirmatrelvir with ritonavir and to molnupiravir, have been:

> Access criteria – from any relevant practitioner.
> Approvals are valid for patients where the prescriber confirms the patient meets the following criteria and has endorsed the prescription accordingly:
> All of the following:
>
> 1. Patient has confirmed (or probable) symptomatic COVID-19, or has symptoms consistent with COVID-19 and is a household contact of a positive case;
>   **AND**
> 2. Patient's symptoms started within the last 5 days ~~(if considering nirmatrelvir with ritonavir or molnupiravir) or within the last 7 days (if considering remdesivir)~~;
>   **AND**
> 3. Patient does not require supplemental oxygen#;
>   **AND**
> 4. **ANY** of the following**:**
>   - 4.1. Patient is immunocompromised* and not expected to reliably mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection, regardless of vaccination status; or
>   - 4.2. Patient has Down syndrome; or
>   - 4.3. Patient has sickle cell disease; or
>   - 4.4. Patient has had a previous admission to Critical Care or High Dependency care directly as a result of COVID-19; or
>   - 4.5. Patient is aged 65 years or over; or
>   - 4.6. Patient is Māori or Pacific ethnicity AND aged 50 years or over; or
>   - 4.7. Patient is aged 50 years or over AND has not completed a primary course^ of COVID-19 vaccination; or
>   - 4.8. Patient has any combination of three or more high risk medical conditions for severe illness from COVID-19 identified by the Ministry of Health**;
>
>   **AND**
> 5. Not to be used with other COVID-19 antiviral treatments.
>
> **Notes:**
> Consider molnupiravir or remdesivir if nirmatrelvir with ritonavir is unsuitable or unavailable
> * As per Ministry of Health criteria of 'severe immunocompromise' for third primary dose of COVID-19 vaccine
> ** People with high risk medical conditions identified by the Ministry of Health
> ^ 'Primary Course' defined as receiving at least two courses of vaccination against COVID-19
> # Supplemental oxygen to maintain oxygen saturation >93% or at or above baseline for patients with chronic resting hypoxia

Previous considerations of access criteria for antivirals

The access criteria for COVID-19 antivirals have been considered by the Advisory Group on a number of occasions. Ongoing reviews of the access criteria are intended to ensure that the latest information and evidence is considered and the access criteria enable people considered at high risk of severe illness following COVID-19 infection to access treatment. Previously the Advisory Group has considered that the funded group able to access antivirals was wider than their recommendation.

In addition to the groups included in the current criteria, those with Cystic Fibrosis and people living rurally have been considered by the Group. These have not been recommended for funding by the Advisory Group to date due to equity considerations compared to similar conditions (Cystic Fibrosis) or limited evidence of benefit (those living rurally).

DISCUSSION

Populations for consideration

This section contains information on populations to be considered for inclusion in the antiviral access criteria to enable access to nirmatrelvir with ritonavir, molnupiravir and remdesivir. The selection of these populations is based on public or other Government entities' interest and on previous advice from the Advisory Group. Each population group section includes readily available information as to the population's experience of COVID-19 and any information relating to benefit of use of antivirals in these populations, where it is available.

1. Disability Support Services recipients

There are an estimated 1.1 million disabled people living in New Zealand. Disability Support Services' (DSS) recipients are a relatively small subgroup of less than 45,000 disabled people who are substantially more likely to be highly vulnerable with complex impairments. DSS is often used to describe a range of support that may be available to disabled people and their community. It includes:

- Disability information and advisory services
- Environmental support
- Child development services
- Ongoing support available through the Needs Assessment Service Coordination (NASC) framework such as household management and personal care, respite, individualised funding, supported living, behaviour support and residential support.

Eligible people are likely to have a physical, sensory, intellectual disability or autism which has been identified before the age of 65 and not the result of an accident. DSS recipients are likely to have more complex impairments and co-morbidities than the wider disabled community.

In 2018 there were 38,342 disabled people allocated one or more funded disability support services with a median age of 26 years. Generally, only people aged under 65 are eligible for DSS services, hence the lower numbers of people in the over-65 age groups compared with the general population. The proportion of clients with very high and high support package allocation levels is increasing, while the proportion of those with medium, low and

very low levels are decreasing. Disability support services are varied including supported living, carer support services, aged and community residential care and respite services (Ministry of Health. 2019. Demographic Report for Clients Allocated the Ministry of Health's Disability Support Services: 2018 update. Wellington: Ministry of Health).

We are aware that Te Whatu Ora and Whaikaha are preparing specific modelling and information regarding the disease burden of COVID-19 and its impact on the disabled population in New Zealand. Detail of these findings is yet to be published, therefore the information presented above is the most recently available information specific to New Zealand. Pharmac staff understand that preliminary findings will indicate DSS recipients have been at substantially greater risk of severe outcomes (hospitalisation and death) once they have become infected with COVID-19, with four times the age-adjusted risk of COVID-19 hospitalisation compared with non-DSS recipients, and higher mortality differentials (not further adjusted for other factors such as sex, ethnicity, comorbidities, or vaccination status).

The current list of medical and other conditions, listed on the covid19.govt.nz website (linked to by note ** in the Pharmac antiviral criteria), includes people with a disability (1) who have underlying medical conditions, (2) with less access to public health information, or (3) whose living situation increases their chance of infection. This to date has not been included in Pharmac's proposed list of high-risk conditions (see other paper).

Living with disability with multiple conditions and/or frailty (but not limited to living in supported accommodation) is one of Australia's risk factors in its eligibility criteria for oral COVID-19 treatments.

International evidence suggests that disabled people have been particularly affected by the COVID-19 pandemic and subsequent lockdowns due to three key factors:

1. increased risk of poor health outcomes from catching COVID-19 itself
2. reduced access to essential routine health care and rehabilitation; and
3. adverse social/psychological impacts of efforts to mitigate the pandemic.

Whilst defining who is disabled, and international comparisons, can be difficult, globally disabled people are recognised as a vulnerable group who are likely to be at higher risk of contracting SARS-CoV-2 and experiencing severe COVID-19 related health outcomes.

A Canadian retrospective study reported that after adjustment, disabled people were 77% more likely to be hospitalised and had 36% longer hospital stays than those without disabilities (Brown et al. CMAJ 2022;194(4):E112-E21 (see Appendix 1)). In the United States, the Centres for Disease Control (CDC) reported that for the period of January 2020 to November 2021 within the sub-population of Medicare beneficiaries, COVID-19 hospitalisation rates for disabled people were 50% higher than non-disabled people (Yuan Y et al. MMWR Morb Mortal Wkly Rep. 2022;71(24):791-6 (see Appendix 1)).

A Scottish study reported that people with intellectual disabilities (ID) had a mortality ratio of 3.26 (95% CI 2.19 to 4.32) and that overall adults with ID had more COVID-19 infections, and worse outcomes once infected, particularly adults under 65 years (Henderson et al. J Epidemiol Community Health. 2022;76(6):550-5 (see Appendix 1)).

A population-based cohort study from the NHS England assessing the association between learning disability and risk of hospital admission from COVID-19 in adults and children including 90,307 adults 16 years and older on the disability register. Electronic medical records of approximately 40% of the total population (including 14,312,023 adults in this

analysis) were used to compare those on the disability register to those not on the register found that the hazard ratios for COVID-19 related hospital admission was 5.3 (95% CI, 4.9-5.8) and for COVID-19 related death HR, 8.2 (95% CI, 7.2-9.4) during wave 1 (1 Mar 2020 to 31 Aug 2020) with similar estimates calculated for wave 2 (1 Sept 2020 to 8 Feb 2021). After excluding people aged ≥65 years and those with defined comorbidities, the estimated hazard of COVID-19 related hospital admission was 4.1 (95% CI, 3.3 to 5.2) after adjustment for age, sex, ethnicity, and geographical location, with little change after adjustment for deprivation or residential care status. Slightly attenuated associations were seen in wave 2 (3.0, 2.5 to 3.5) after adjustment for age, sex, ethnicity, and geographical location. Down's syndrome and cerebral palsy were associated with increased hazards (10-fold and 1.27-fold once adjusted, respectively) for both COVID-19 related hospital admissions and death. Patterns were similar in children, but hospital admissions and deaths are rare. Among 9298 children on the learning disability register during wave 1, there were five or fewer (≤0.05%) COVID-19 related hospital admissions. Among 9429 children on the learning disability register during wave 2, there were 20 (0.2%) covid-19 related hospital admissions. In total, across both waves, there were nine non-covid deaths among children on the register and 151 non-covid deaths among children not on the register. It was reported that Public Health England found a 6.3-fold increased risk of mortality in those on the learning disability register than the general population up to June 2020 (Williamson et al. BMJ. 2021;374:n1592 (see Appendix 1)).

Another cohort study assessing COVID-19 related mortality by self-reported disability status during the first two waves in England considered those over 30 years old including 29,293,845 adults, 10% of which reported a limiting disability (3,038,772 people). During follow-up 58% of those who died were disabled. A number of variables were considered when adjusting hazard ratios including age, residence type, population density, ethnicity, highest qualification, deprivation decile, household characteristics (house and family size and composition, key worker), individual and household exposure to disease, and health status (pre-existing health conditions, body-mass index, and number of admissions to hospital and days spent in hospital over the previous 3 years). When adjusted for age analyses showed higher mortality involving COVID-19 among disabled people who were limited a lot (HR 3.05 [95% CI 2.98–3.11] for men; 3.48 [3.41–3.56] for women) and disabled people who were limited a little (HR 1.88 [1.84–1.92] for men; 2.03 [1.98–2.08] for women) than among non-disabled people. Adjustment for residence type, geography (population density and local authority), sociodemographics (ethnicity, highest qualification, deprivation decile), and health conditions reduced but did not eliminate the associations between disability and death involving COVID-19 (HR 1.35 [1.32–1.38] for men who were limited a lot; 1·21 [1·18–1·23] for men who were limited a little; 1.55 [1.51–1.59] for women who were limited a lot; and 1.28 [1.25–1.31] for women who were limited a little). The measure of disability (limited a little or a lot) was self-reported and noted as a subjective assessment as it did not include information from clinical records. Risks experienced by disabled people with mental or physical conditions were not able to be distinguished (Bosworth et al. Lancet Public Health. 2021;6(11):e817-e825 (see Appendix 1)).

A systemic review by the Centre for Disease Control (CDC) on the association between disabilities and severe COVID-19 outcomes considered the association between composite physical, developmental and intellectual disabilities and individual disabilities. Overall, intellectual and developmental disabilities, disability (composite), learning disability, Down syndrome, spinal cord injuries, dependence, and activities of daily living are associated with

an increase in mortality among people with COVID-19. Intellectual and developmental disabilities, learning disability, Down syndrome, cerebral palsy, and congenital malformations, and attention-deficit/hyperactivity disorder are associated with an increase in hospitalisation in people with COVID-19. Most investigated disabilities had limited information available on hospitalisation or mortality and information on ICU admission, intubation and ventilation were commonly not reported or had limited information (So et al. CDC COVID-19 Scientific Brief on Disabilities and Severe COVID-19 outcomes. 2021).

2. People with rare disorders

Evidence relating to the impact of COVID on outcomes in those with rare disorders is limited. A broad literature search was conducted by Pharmac staff to investigate the impact of COVID-19 infection on those with rare disorders. The Pharmac definition of a rare disorder is that the disorder is a clinically defined disorder that affects an identifiable and measurable patient population of less than 1:50,000 in New Zealand.

The impact of the COVID-19 pandemic on the care of people with rare or undiagnosed diseases has impacted and delayed the delivery of services (eg surgical, medical, physical therapy services). It is reported that many people reduced their interaction with healthcare services to reduce the risk of becoming infected with COVID-19. In the context of rare diseases this presents a risk of acute decompensation due to greater clinical vulnerability of those with rare diseases Other concerns include the potential interaction between gene therapy for rare diseases (as part of a clinical trial) and vaccination for COVID-19 (Chowdhury et al. Front. Public Health. 2021;9:640282 (see Appendix 1)).

A study on the mood, therapy adherence and COVID-infection in those with Fabry Disease (FD) reported that those with FD were more resilient to the negative psychological effects of lockdown. These patients usually receive their enzyme replacement therapy in hospital, but authors noted that at least half received their therapy at home with moderate adherence. Of the participants 37.8% had been infected with COVID-19. These people were usually young to middle-aged (36.6 ± 12.4 years) and female (60%) in majority. Most patients reported a mild experience however, five patients were hospitalised, all of whom were not vaccinated (Karca et al. Orphnet J Rare Dis. 2022;17(1):338 (see Appendix 1)).

The effects of COVID-19 potentially worsen rare disease related conditions due to several factors, including cytokine storm, cardiovascular damage or failure and neurological effects. In addition, those living with intellectual disability face potential challenges in managing a COVID-19 infection. Recommendations for the treatment of these patients include care for those with COVID-19 to align with current COVID-19 guidelines, education to raise awareness of those with rare diseases in the context of the pandemic, psychological support and avoidance of discontinuation chronic medication to reduce overall morbidity and mortality (Boudjelal et al. J Infect Dev Ctries 2021; 15(4):450-462(see Appendix 1)).

Participants with rare disorders who tested positive for SARS-CoV-2 in the Genomics England 100k Genomes projects had increased risk of COVID-19 related death compared to their unaffected relatives during the first wave of the pandemic in UK, although the increase was not significant after accounting for age and numbers of COVID-19 related comorbidities. An increased risk of COVID-19 related death was reported in those with pre-existing neurology and neurodevelopment disorders in both univariable and multivariable analysis. It was reported that overall, for those over 60 years had a higher risk of mortality (adjusted

odds ratio (aOR) 9.95 (95% CI, 3.52, 28.17)) when adjusted for having at least 2 comorbidities expected to increase risk of COVID-19 related mortality and being affected by rare diseases. Specific disorders that were found to have statistically significant increased risk of COVID-19 related mortality are neurological and neurodevelopmental disorders (aOR 4.22 (95% CI, 1.60, 11.08)), early onset dystonia (aOR 26.64 (95% CI, 2.01, 352.67)), Parkinson's disease (aOR 11.99 (95% CI, 1.25, 114.71)) and intellectual disability (aOR 8.10 (95% CI, 1.11, 59.00)) (Zhang et al. Orphanet J Rare Dis. 2022; 17(1):166 (see Appendix 1)).

Inherited metabolic disease

A survey of clinicians treating those with inherited metabolic (IMD) disease to March 2021, most commonly reported treating lysosomal storage disorders (LSD), carbohydrate, fatty acid oxidation and ketone bodies disorders (C-FAO), amino and organic acids-related disorders (AOA), and disorders of pyruvate metabolism, mitochondrial oxidative phosphorylation, thiamine transport and metabolism, and Krebs cycle defects (PM-MD). These disorders are generally considered at high risk of metabolic decompensation, cardio-respiratory complications, and frequent exacerbation induced by infections, so they may be more vulnerable also to COVID-19-induced complications. Clinicians reported that in general, asymptomatic or mild COVID-19 was the most common presentation in their patients. Over 60% of surveyed clinicians had no adult patients with severe COVID-19 in hospital and over 80% reported no paediatric patients with severe COVID-19 in hospital. The authors noted that this aligned with the general population demographics as that those paediatric patients were less likely to have severe outcomes from COVID-19. It was hypothesised by the authors that LSD could be protective against COVID-19 infection, as SARS-CoV-2 involves lysosomal trafficking; however, this was in contrast to the observations from this survey (Paneghetti et al. Orphanet J Rare Dis. 2022;17(1):109 (see Appendix 1)).

Gaucher Disease

Gaucher Disease (GD) is defined by decreased acid β-glucosidase activity and leads to the accumulation of inflammatory glycosphingolipids and chronic myeloid cell immune activation which could predispose patients to the most severe effects of COVID-19. A study of 181 GD patients reported that among patients who were COVID-19 antibody-positive, quantitative titres indicated moderate to high antibody response. In GD adults, male gender, older age, increased BMI, comorbidities, GBA genotype, prior splenectomy and treatment status were not associated with the probability of reporting symptoms or testing positive. No study participant required COVID-19-specific treatments and there were no deaths. In contrast to *in vitro* reports, glucosylceramide synthase inhibitors (eliglustat) were not found to be protective as those people taking these medicines did not report fewer symptoms or had a decreased probability of testing positive compared to those receiving ERT. The authors considered that GD does not confer a heightened risk for severe effects of SARS-CoV-2 infection feared based on the known chronic inflammatory state in these patients (Fierro et al. Mol Genet Metab. 2021 Jan;132(1):44-48 (see Appendix 1)).

Alpha 1-antitrysin deficiency

Alpha 1-antitrypsin deficiency (AATD) is a genetic disorder that causes an imbalance in proteinase activity, which may lead to premature emphysema and COPD or other diseases (commonly liver diseases). An observational study considered the risk of severe COVID-19

in those with AATD. It was reported that a higher frequency of SARS-CoV-2 infection in the study cohort (3.8%) compared to national data regarding infection, thus giving severe AATD a relative risk of 8.8 (95% CI 5.1-20,0; *P*<0.0001) for symptomatic SARS-CoV-2 infection. Moreover, the relative risk (RR) was higher in AATD patients with pre-existing lung diseases (RR 13.9; 95%CI 8.0-33.6; *P*<0.001), but with a similar death rate (1 in 8, 12.5%) compared to the general population (13.9%; RR 0.9). (Ferrarotti et al. Respir Med. 2021;183:106440 (see Appendix 1)).

Amyloidosis

The amyloidoses are a rare grouping of protein deposition diseases, often presenting with systemic involvement of vital organs including the heart, nerves, kidneys, and GI tract. A Canadian study considered 15 COVID-19 positive amyloidosis patients of whom four patients (26.6%) required hospital admission for COVID-19 infection. All the patients who required hospital admission had cardiac amyloid involvement. One (0.07%) unvaccinated patient died of a COVID-19 infection. Overall mortality rates in those with ATTR and AL were increased during the pandemic compared to pre-pandemic (2018 and 2019). The authors suggest that amyloidosis patients are likely at a high risk for severe COVID-19 infection and mortality, especially those of advanced age, those on an active treatment with chemotherapy, and those with concomitant B-cell or plasma cell disorder. (Lewis et al. Ann Hematol. 2022 Oct;101(10):2307-2315 (see Appendix 1)).

Correspondence with Rare Disorders NZ

To support the review of access to COVID-19 antivirals for people with rare disorders, Rare Disorders NZ has provided correspondence to Pharmac. This letter raised concerns about inequitable access to COVID-19 antiviral treatments in New Zealand for people with rare disorders and requested that access to COVID-19 antivirals is widened to include all people living with a rare disorder in New Zealand where their clinician considers it is appropriate. Rare Disorders NZ noted concerns that many people with rare disorders in New Zealand are unable to access COVID-19 antivirals because they do not meet the current criteria, despite having a similar health risk to eligible populations. This letter was accompanied by an additional letter from Genetic Health Service New Zealand requesting access to antiviral treatments for people with intellectual disabilities. Copies of these letters have been included in Appendix 2.

> *We request that the Advisory Group review these letters as part of the consideration of access to COVID-19 antivirals for people with rare disorders*

3. People with severe respiratory conditions

Asthma

In New Zealand, the prevalence of asthma is reported as 11.4% in the total population with prevalence in Māori estimated 17.2% and prevalence in Pacific peoples estimated to be 13.4% as reported in the New Zealand Health Survey (Ministry of Health. 2022. Annual Data Explorer 2021/22: New Zealand Health Survey [Data File]. (Accessed 1 Feb 2022)). Māori aged 5–34 years were more likely than non-Māori aged 5–34 years to be hospitalised for asthma. In 2014–16, Māori were over twice as likely as non-Māori to be hospitalised for asthma. This inequity is reported to be increasing as rates of hospitalisation for Māori are stable while hospitalisation in non-Māori, non-Pacific peoples has decreased over time

(Ministry of Health. 2019. Wai 2575 Māori Health Trends Report. Wellington: Ministry of Health).

An CDC review reported that there was inconsistent and inconclusive evidence of increased risk of mortality and intubation resulting from COVID-19 infection in people with asthma. However, it was reported there was evidence to support an increased risk of ICU admission and hospitalisation, however most reported wide confidence intervals or inclusion of the null and at least a moderate threat to interval validity. Evidence to support an association between asthma severity and increased risk of mortality, ICU admission and ventilation with COVID-19 was inconsistent. An increased risk of hospitalisation was reportedly supported by evidence however the definitions used in supporting studies were different (Okasako-Schmucker et al. CDC COVID-19 Scientific Brief on Asthma and Severe COVID-19 outcomes. 2021).

The reported risk of hospitalisation or mortality for those with asthma was not consistent. A systemic review and meta-analysis considered those with asthma and their risk of infection and hospitalisation using data from 51 studies from 1 December 2019 and 11 July 2021. The pooled prevalence of diagnosed COVID-19 in people with asthma was 8.08% (95% CI 6.87-9.30%). For people with asthma there was no statistically significant difference in the reported risk ratio of hospitalisation (1.18 (95% CI 0.98-1.42, *P*=0.08)), for ICU admission (1.21 (95% CI 0.97-1.51, *P*=0.09)); for ventilator use (1.06 (95% CI 0.82-1.36, *P*=0.65)); and for mortality (0.94 (95% CI 0.76-1.17, *P*=0.58)). Of the studies included there was considerable heterogeneity in reported results in all outcomes (Sunjaya et al. Eur Respir J. 2022; 59(3): 2101209 (see Appendix 1)). Another observation study has reported that there is an increased risk of hospitalisation as severity of asthma increases (defined by medication use (type and frequency), exacerbation history, and type 2 inflammation (atopy history and blood eosinophil count)). Those with asthma with a significant association with COVID-19 hospital admission were those who regularly used inhaled corticosteroids plus add-on (inhaled long-acting β-agonist, oral leukotriene receptor antagonist, oral theophylline) therapy or those with frequent exacerbations (Bloom et al. Am J Respir Crit Care Med. 2022; 205(1): 36–45 (see Appendix 1)). In contrast, a retrospective study reported that asthma is not a risk factor for severe COVID-19 disease and that the association between medication use and hospitalisation risk not supported (Eggert et al. Allergy. 2022; 77(1):173-185 (see Appendix 1)). Further a longitudinal study on the burden of long COVID from the United Kingdom found that pre-existing asthma was associated with prolonged symptoms post-COVID (Thompson et al. Nat Commun. 2022; 13: 3528 (see Appendix 1)).

Bronchiectasis

An estimated 8,053 or 162 per 100,000 people are living with severe bronchiectasis in New Zealand with ethnicity and socio-economic status displaying significant inequity for hospitalisation rates (Barnard & Zhang. Asthma and Respiratory Foundation NZ. 2020). For Māori males the rate of hospitalisation has increased by 15% from 2001/03 to 2011/13 (from 34.2 events per 100,000 people to 39.3 per 100,000 people). Conversely, there was a decrease in the rate of hospitalisation for Māori females (41.9 events per 100,000 people in 2001–03 to 34.6 per 100,000 people in 2011–13) (Ministry of Health. 2019. Wai 2575 Māori Health Trends Report. Wellington: Ministry of Health).

Information on the relationship between pre-existing bronchiectasis and severe COVID-19 is limited. Observational studies and case reports make up most of the evidence available at

time of writing. The CDC reviewed evidence on the association with bronchiectasis and mortality or ICU admission, intubation or hospitalisation. Evidence was limited but suggested an increased risk mortality and ICU admission while evidence for intubation or hospitalisation was limited (Stone et al. CDC COVID-19 Scientific Brief on Bronchiectasis and Severe COVID-19 outcomes. 2021). A South Korean cohort study considered the association between those with COVID and bronchiectasis and receiving oxygen, ICU admission, mechanical ventilation, ECMO, mortality and severe COVID-19. It was reported that there was a statistically significant increased risk of receiving oxygen therapy, ECMO, having severe COVID-19 and mortality (P <0.05). Authors noted, that considering similar ICU admission rates, COVID-19 patients with bronchiectasis revealed worse clinical course finally than those without bronchiectasis although both groups had similar severity when admitted to ICU initially. Impaired mucociliary clearance and chronic inflammation in the airway of patients with bronchiectasis is likely to increase their susceptibility to and severity of COVID-19. The authors also noted that those with bronchiectasis were significantly older and more likely to have other pulmonary or extra-pulmonary comorbidities, (Choi et al. Ther Adv Respir Dis. 2021;15:1753466621995043(see Appendix 1)). An observational study following up non-cystic fibrosis bronchiectasis patients for 12 months, during 2020. A decrease in the absolute value of FEV1 and an increase in the number of acute exacerbations however, no hospitalisations were reported after analysis of 30 patients. Only two patients were diagnosed with COVID-29 during the follow-up period with the impact of disruption to service provision for those with bronchiectasis (Qin et al. J Clin Med. 2022;11(6):1727(see Appendix 1)).

Chronic Obstructive Pulmonary Disease (COPD)

In 2014, COPD was estimated to affect 2.3% of New Zealanders aged 45 years and over with an estimated total population prevalence of 0.97%. Age-standardised population prevalence was highest for Māori, at 2.50%, followed by Pacific peoples, at 2.44%, and trailed by non-MPA (Māori, Pacific or Asian people) at 0.83% and Asian peoples at 0.35% respectively. The average age of those with COPD is as follows: Māori 61.3 years, compared with 62.6 for Pacific peoples, 65.7 for Asian peoples, and 70.7 for non-MPA, who would be funded under the current access criteria. Ethnic inequity in hospitalisation disproportionately favours non-Māori and non-Pacific peoples with Māori being 4 times as likely to be hospitalised due to COPD with the inequity increasing over the period 2001-03 to 2011-13 (Ministry of Health. 2019. Wai 2575 Māori Health Trends Report. Wellington: Ministry of Health).

Evidence assessing the risk of ICU admission and mortality from the Global Initiative for Chronic Obstructive Lung Disease (GOLD Report 2023), reported that COPD patients were found to be at slightly higher risk of ICU admission (aOR 1.28; 95% CI 1.08, 1.51) and mortality (aOR 1.41; 95% CI, 1.37,1.65). Those with decreased lung function, being underweight, depression and prior COPD treatment in inpatient or secondary care are considered factors in predicting severe COVID-19 (Halpin et al. Am J Respir Crit Care Med. 2021; 203(1): 24–36 (see Appendix 1)). A systematic review of patients with COPD and COVID-19 reported increased odds of hospitalisation (OR 4.23, 95% CI, 3.65–4.90), ICU admission (OR 1.35, 95% CI 1.02–1.78) and mortality (OR 2.47, 95% CI 2.18–2.79). The reported odds ratios for hospitalisation are higher than reported by the GOLD report and were not adjusted. The authors noted that surrogate measures of severity were reported

such as mechanical ventilation or ICU admission but not consistently and the heterogeneity of the studies would have likely contributed to overall bias (Gerayeli et al. EClinicalMedicine. 2021; 33: 100789 (see Appendix 1)).

Cystic Fibrosis

At its meeting on 31 October 2022 the Advisory Group considered the funding of antiviral treatments for COVID-19. At the time the Advisory Group deferred its recommendation on the addition of CF to antiviral access criteria until issues of severe comorbidities in general in people aged under 50 years were considered. In reaching this recommendation, the Group considered the following

- people with severe cardiovascular, renal and lung conditions would have similar risk of hospitalisation due to COVID-19 as people with CF, and were also likely to require a combination of three or more high-risk medical conditions in order to access funded community COVID-19 treatments, and
- although there is a high overall health need for people with CF, other conditions also resulted in declines in and reduced in lung function including COPD and non-CF bronchiectasis and these conditions disproportionately affect Māori and Pacific peoples, and
- other conditions specified in the criteria (Down syndrome and sickle cell disease) have good disease-specific evidence for health need for these conditions, but evidence for health need and benefit in CF is of poor quality and strength.

Now that a wider range of comorbidities have been presented, including a range of respiratory conditions we seek the Advisory Groups views on whether people with Cystic Fibrosis would have a similar risk of severe illness of following COVID-19 as these groups for inclusion in the access criteria for COVID-19 antivirals.

4 People with severe comorbid condition/s

Currently, cases are eligible if they have 3 or more high-risk medical conditions listed on the covid19.govt.nz website (linked to by note ** in the Pharmac antiviral criteria). These conditions are being discussed in another agenda item in this meeting. This does not allow for patients with serious comorbidity occurring in less than three named conditions.

There may be a need to include people at risk with having any prior hospital identified/based comorbid condition/s. The Ministry's September 2022 covid mortality analysis COVID-19 Mortality in Aotearoa New Zealand: Inequities in Risk (health.govt.nz) reported a 4.7 age/ethnicity/vaccination-adjusted residual relative case fatality rate for cases having any prior hospital identified/based comorbid condition. That is, after adjusting for other risk factors, having hospital-defined comorbidity increased case fatality rates 4.7 times. See Table 5 of that analysis.

Staff seek the Advisory Group's views on including having any (one or more) prior hospital identified/based comorbid conditions.

5 People previously hospitalised due to COVID-19

The current access criteria include where people have had a previous admission to Critical Care or High Dependency care directly as a result of COVID-19, implying severe need previously. The issue arises, in light of possibly extending access to other groups, whether access should be extended to all patients admitted to hospital directly as a result of COVID-19.

Pharmac staff do not have supporting evidence for this to hand. Staff consider however that, from a practical perspective, and considering the above variable evidence that subsequent SARS-CoV-infections may or may not have increased severity, that such patients may be at a higher risk of being hospitalised in part based on their previous history of hospitalisation. This is where past hospitalisation directly due to COVID-19 implies and is a possible direct proxy for previous infection being severe, and hence clinicians may be more wary and have lower thresholds to referral and then admission to hospital, all things else being equal.

We note the intent of providing community access to antivirals had included, to a large part, reding hospitalisation risk and its consequences to the health system (particularly overload through high case numbers). Clinician thresholds are arguably a non-disease health sector factor affecting hospitalisation risk.

In Australia, people are eligible for oral COVID-19 treatments when they have had past hospitalisation due to COVID-19 if they are aged 50 years and over, or are First Nations people aged 30+ years. A past COVID-19 infection episode resulting in hospitalisation is one of Australia's risk factors in its eligibility criteria.

We seek the Advisory Group's views.

6 People with multiple COVID-19 infections

Manatū Hauora - Ministry of Health defines COVID-19 re-infection as a case reported at least 29 days after the last times a person received a positive test for COVID-19. Prior to 30 June 2022 this was defined as a reported case at least 90 days after a positive test. In the week ending 18 December 2022 reinfections accounted for 29.7% of all reported cases increasing from 18% in the weeks prior. Cumulatively, reinfections have made up 4.7% of total cases reported in 2022. The proportion of cases that are reinfections is expected to increase over time (Public Health Agency. 2022. COVID-19 Trends and Insights Report. Wellington: Ministry of Health).

A French study on the risk of re-infection and severity of these infections reported that there was no difference in the first infection and subsequent re-infections, defined as an infection >90 days after initial infection, in terms of severity. The authors noted that in most cases each infection in each patient was likely caused by different COVID-19 variants and variant pathogenicity is known to be different (i.e Delta v Omicron). It is therefore difficult to evaluate the respective roles of the responsible virus variants and the possible effect of a previous infection in terms of protection or potential facilitating effect. Nevertheless, when comparing patients experiencing the first infection to those sustaining a reinfection with a similar variant, hospitalisation rates were similar, and depended on patient age only. Those over 60 years old were 10.64 times more likely to be hospitalised by re-infection than those under 60 years

(95% CI, 2.01-56.32 *P* =0.005) (Nguyen et al. Emerg Microbes Infect. 2022; 11(1): 894–901 (see Appendix 1)).

In contrast, another French study reported that of 46 patients 27.8% got worse in the second episode, and 8.1% were admitted in ICU or died, 29.5% got better and 42.6% presented the same clinical status for both episodes. However, only the difference in those presenting with mild to moderate symptoms was statistically significant (94.8% v 78.7% *P*= 0.044) with more severe presentations not statistically significant (*P* >0.05) (Brougui et al. Eur J Clin Invest. 2021; 51(5): e13537 (see Appendix 1)).

An American study using data from US Veterans Affairs database reported that, compared with no reinfection, reinfection contributed additional risks of death (hazard ratio (HR) = 2.17, 95% CI, 1.93–2.45), hospitalisation (HR = 3.32, 95% CI 3.13–3.51) and clinical sequelae including pulmonary, cardiovascular, haematological, diabetes, gastrointestinal, kidney, mental health, musculoskeletal and neurological disorders. The risks were evident regardless of vaccination status. The risks were most pronounced in the acute phase but persisted in the post-acute phase at 6 months. Compared to noninfected controls, cumulative risks and burdens of repeat infection increased according to the number of infections. Previous exposure to the virus may be expected to hypothetically reduce risk of reinfection and its severity; however, COVID-19 is mutating rapidly and new variants and subvariants are replacing older ones every few months. Evidence suggests that the reinfection risk is especially higher with the Omicron variant, which was shown to have a marked ability to evade immunity from previous infection. Any protection from previous infection (against reinfection and its severity) also wanes over time; evidence suggests that protection from reinfection declined as time increased since the last immunity-conferring event in people who had previously been infected with SARS-CoV-2, regardless of vaccination status. (Bowe et al. Nat Med. 2022; 28(11): 2398-2405 (see Appendix 1)).

7 People with long covid or post-acute sequelae of SARS-CoV-2 infection (PASC)

The Ministry of Health defines long COVID as “Any signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. Presentation may include clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body”. Currently, the prevalence of long COVID in Aotearoa New Zealand is unknown. The Ministry of Health Long COVID evidence update reports that a global pooled estimated prevalence of post-COVID-19 condition was 0.43 (95% CI, 0.39-0.46) and for hospitalised and non-hospitalised patients estimated as 0.54 (95% CI, 0.44-0.63) and 0.34 (95% CI, 0.25-0.46), respectively.

Preliminary results from the Ngā Kawekawe o Mate Korona study suggest that the prevalence may vary across groups. Of 65 Māori participants, 43% (28/65) reported symptoms for more than one month, and of these participants, 75% (21/65) reported experiencing long COVID symptoms for more than three months post-infection. In comparison, of the 405 participants who were non-Māori, 47% (190/405) reported symptoms for more than one month, and of these individuals, 65% (124/405) reported symptoms which lasted more than three months. Reported risk factors include: older age, having more than 1 underlying chronic medical condition, pre-existing asthma, higher BMI, female sex,

hospitalisation during acute COVID-19, multiple early symptoms, variant infected with (Omicron potentially less risk than Delta), psychological distress pre-infection and other immunological factors. The effect of re-infection on long COVID risk is not well understood and difficult to quantify. Vaccination looks to have a positive effect on risk of long COVID. Ministry of Health has reported Paxlovid as a pipeline treatment option for those with long COVID based on in vitro evidence but note there are no clinical trials currently investigating this (Ministry of Health. Long COVID Evidence Update. November 2022. [accessed 7 Feb 23]). Current Ministry of Health guidelines suggest symptom management, such as sleep aids, as medications for long COVID are not yet validated (Ministry of Health. 2022. Clinical Rehabilitation Guideline for People with Long COVID (Coronavirus Disease) in Aotearoa New Zealand: Revised December 2022. Wellington: Ministry of Health).

The results of a study using the US Veteran Affairs database report that in the post-acute phase of COVID-19, there was increased risk of an array of incident neurologic sequelae including ischemic and haemorrhagic stroke, cognition and memory disorders, peripheral nervous system disorders, episodic disorders (for example, migraine and seizures), extrapyramidal and movement disorders, mental health disorders, musculoskeletal disorders, sensory disorders, Guillain–Barré syndrome, and encephalitis or encephalopathy. The estimated that the hazard ratio of any neurologic sequela was 1.42 (95% confidence intervals 1.38, 1.47) and burden 70.69 (95% confidence intervals 63.54, 78.01) per 1,000 persons at 12 months. The risks and burdens were elevated even in people who did not require hospitalisation during acute COVID-19 (Xu et al. Nat Med. 2022; 28:2406-2415 (see Appendix 1)).

A cohort study on the impact of nirmatrelvir on the risk of developing positivet-acute sequelae of COVID-19 (PASC) used healthcare databases to identify users of the health system who had a COVID-19 positive test between March 1, 2022 and June 30, 2022, were not hospitalised on the day of the positive test, had at least 1 risk factor for progression to severe COVID-19 illness and survived the first 30 days after COVID-19 diagnosis. Those who were treated with oral nirmatrelvir within 5 days after the positive test (n=9217) and those who received no COVID-19 antiviral or antibody treatment during the acute phase of infection (control group, n= 47,123). Outcomes measured include ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, shortness of breath and cough. Predefined covariates included age, race, sex, body mass index (BMI), smoking status (current, former, and never), prior history of COVID-19 infection, use of steroids, use of long-term care, eGFR, blood pressure, cancer, chronic lung disease, dementia, diabetes, hyperlipidaemia and immune dysfunction. Compared to the control group, treatment with nirmatrelvir was associated with reduced risk of PASC (hazard ratio 0.74 95% CI (0.69, 0.81), absolute risk reduction 2.32 (1.73, 2.91) per 100 persons at 90 days) including reduced risk of 10 of 12 post-acute sequelae. Nirmatrelvir was associated with reduced risk of PASC in people who were unvaccinated (HR 0.68 (95% CI, 0.57,0.74)), vaccinated (0.69 (0.64,0.75)), and boosted (0.79 (0.72, 0.86)), and in people with primary COVID-19 infection (0.75 (0.70, 0.81)) and reinfection (0.75 (0.66, 0.84)). Nirmatrelvir was associated with reduced risk of PASC in people with 1 to 2 (HR 0.77(95% CI, 0.67, 0.88)), 3 to 4 (0.77 (0.72, 0.83)), and 5 or more (0.70 (0.61, 0.80)) baseline risk factors. The authors noted use of data from US Veteran Affairs electronic medical databases, with a significant white male population, limit the potential generalisability of the reported findings (Xie et al. Preprint. 2022 (Supplementary information available in Appendix 1 in addition to full text)).

Case reports on the effect of oral nirmatrelvir on long COVID symptoms provide some anecdotal evidence to suggest further study for the use of antivirals for the treatment of long COVID is warranted. Four separate cases were included, each with different risk of severe COVID-19 upon initiation of nirmatrelvir with ritonavir for acute COVID-19, in subsequent weeks after initial symptoms have not resolved or have become worse or during the acute phase of a COVID-19 re-infection (Peluso et al. Pathog Immun. 2022;7(1):95-103 (see Appendix 1)).

A prospective study assessing the prevalence and risk factors for long-covid syndrome and followed up for at least six months in Italy of patients hospitalised and affected by COVID-19 between 10 March 2020 and 15 January 2021. Of those admitted 449 patients were included with 322 diagnosed with long-covid in 1-month post-discharge (visit 1) and 206 at 6 months post-discharge (visit 2). In multivariate analysis, intensive care unit (ICU) admission (OR 2.551; 95% CI, 1.998, 6.819; *P*= 0.019), time of hospitalisation (OR 2.255; 95% CI, 1.018, 6.992; *P*= 0.016) and treatment with remdesivir (OR 0.641; 95% CI, 0.413, 0.782; *P* <0.001) were independent predictors of long-covid. Of those included in the study the median age was 65 years and 78% were male, the most frequent comorbidities were cardiovascular diseases (14.2%), diabetes (15.8%) and chronic neurological conditions (7.3%), 13.8% required ICU admission and 42% received CPAP/NIV. Remdesivir was received by 36.3% of participants and corticosteroids given to 86.8%. At visit 2, the most common long-covid symptoms were loss of smell (53.7%), sleeping disorders (53.6%), taste disturbance (49.8%) and 'brain fog' (43.9%), persistence of breathlessness (38.2%) and fatigue syndrome (34.7%) (Boglione et al. QJM. 2022;114(12):865-871 (see Appendix 1))

8 Multifactorial analyses of people with a high risk of severe long-term effects or high-risk conditions

A gap in the current knowledge of risk factors for severe COVID-19 disease including hospitalisation (health sectors' key concerns at the peak of the Omicron waves of the pandemic) is the lack of comparability across populations, where limited numbers of risk factors are reported in isolation. This is mitigated, in part, by population-based studies of large numbers of cases that assess and weight (via multivariate analysis) a number of risk factors, within the same source populations of cases, rendering relative risks that are comparable across risk factors. Such studies for COVID-19 case severity inlcude:

Hippisley-Cox et al. BMJ 2021;374:n2244 (see Appendix 1)
This prospective, UK national population-based cohort study using the QResearch database linked to data on covid-19 vaccination, SARS-CoV-2 results, hospital admissions, systemic anticancer treatment, radiotherapy, and the national death and cancer registries. The primary outcome was covid-19 related death, and the secondary outcome was covid-19 related hospital admission. Outcomes were assessed from 14 days after each vaccination dose. Of 6,952,440 vaccinated patients in the derivation cohort, 5,150,310 (74.1%) had two vaccine doses. Of 2031 covid-19 deaths and 1929 covid-19 hospital admissions, 81 deaths (4.0%) and 71 admissions (3.7%) occurred 14 days or more after the second vaccine dose. Mortality hazard ratios (and reported hospitalisation risk), adjusted for age, body mass index and background SARS-CoV-2 infection rate at the time of vaccination, were highest for:

- patients with Down's syndrome (mortality HR 12.7 (95% CI 4.68, 34.38), hospitalisation HR 2.55 (0.63, 10.28)),

- kidney transplantation (mortality HR 8.07 (3.34, 19.54), hospitalisation HR 12.82 (7.65, 21.47))
- sickle cell disease (mortality HR 7.73 (1.07, 55.83)),
- care home residency (mortality HR 4.14 (3.66, 4.68), hospitalisation HR 1.69 (1.43, 2.01)),
- chemotherapy, grade C (mortality HR 4.30 (1.06, 17.51), hospitalisation HR 1.16 (0.16, 8.35)),
- HIV/AIDS (mortality HR 3.29 (1.05, 10.29)),
- liver cirrhosis (mortality HR 2.96 (2.02, 4.34), hospitalisation HR 1.79 (1.13, 2.83)),
- rare neurological conditions (mortality HR 2.63 (1.69, 4.08), hospitalisation HR 2.30 (1.44, 3.65)),
- recent bone marrow transplantation or a solid organ transplantation ever (mortality HR 2.49 (0.69, 10.08), hospitalisation HR 6.81 (3.18, 14.56)),
- dementia (mortality HR 2.23 (1.98, 2.50), hospitalisation HR 2.07 (1.79, 2.39)), and
- Parkinson's disease (mortality HR 2.23 (1.79, 2.78), hospitalisation HR 1.47 (1.06, 2.03)).

Conditions with a statistically significant, increased risk (HR >1.1) of hospitalisation (not listed above) are CKD stage 3, 4 or 5 with or without dialysis, chemotherapy grade B, type 2 diabetes with HbA1c <59mmol/mol or ≥59mmol/mol, blood cancer, COPD, coronary heart disease, stroke, atrial fibrillation, congestive cardiac failure, epilepsy, schizophrenia or bipolar disorder. The second dose of vaccination did not change the association with the previously mentioned conditions, but absolute risks were reduced.

The authors note that the deployment of drug and non-drug interventions to protect individuals with residual vulnerability after vaccination needs to be considered in the context of absolute risks of severe outcomes at the time of making predictions. Absolute risks are related to both the prevalence of SARS-CoV-2 infection in the population and the likelihood of SARS-CoV-2 exposure in a vaccinated adult population.

This study used a risk prediction tool (Qcovid3 risk model from 8 Dec 2020 to 15 Jun 2021) and compared the predicted mortality and hospitalisation risk to the observed risk in the derivation cohort. For example, it shows that 78.7% of deaths occurred in individuals in the top 5% for predicted absolute risk of covid-19 death (predicted absolute risks at 70 days above 0.06%). Individuals in the top 20% for predicted absolute risk of death accounted for 98.9% of deaths. Although these algorithms have been designed to inform UK health policy and interventions to manage COVID-19 related risks, they are also claimed to have international potential, subject to local validation.

Bergman et al. Eur J Epidemiol. 2021; 36(3):287-98(see Appendix 1)

This Swedish case control study considered the risk factors for COVID-19 diagnosis, hospitalisation and all-cause mortality nationwide during 2020. The risk factors associated with non-ICU hospitalisation and ICU hospitalisation for those with any comorbidity or taking any medication the adjusted odds ratio (aOR) for non-ICU hospitalisation was 2.39 (95% CI, 2.23–2.57) and ICU hospitalisation was aOR 2.17 (95% CI, 1.88, 2.50). Those with the following conditions were reported to be at higher risk of hospitalisation and ICU hospitalisation:

- immune disorder
- diabetes
- COPD

- asthma
- renal failure/CKD
- liver disease
- dementia/Alzheimer's
- down syndrome
- influenza
- solid organ transplant
- those taking antithrombotics, proton-pump inhibitors, corticosteroids or opioids.

The following were also reported to increase the risk of all-cause mortality; cardiovascular disease, hypertension, cancer, autoimmune disease, diabetes, COPD, renal failure/CKD, liver disease, dementia/Alzheimer's disease, down syndrome, pneumonia, sepsis, alcohol intoxication, anti-thrombotic, corticosteroid and opioid use. It was noted that 90% of hospitalised patients had one or more comorbidities or medication use. Age was reported as the strongest individual risk factor for severe COVID-19. The authors noted limitations are not necessarily causal and may have residual confounding, the presence of medical conditions may be underestimated due to the dataset used and the testing rate is subject to a number of factors.

Kompaniyets et al. Prev Chronic Dis. 2021;18:E66 (see Appendix 1)
This study from the USA considered underlying medical conditions and their attributable risk to severe illness in people hospitalised with COVID-19. Data from more than 800 hospitals from March 2020 to March 2021 were included. Of those hospitalised with COVID-19 (540,667 patients) 94.9% had at least 1 comorbidity 249,522 (46.2%) had an ICU admission, 76,680 (14.2%) received invasive mechanical ventilation (IMV), and 80,174 (14.8%) died. The strongest risk factors for death were obesity (adjusted risk ratio [aRR] = 1.30; 95% CI, 1.27–1.33), anxiety and fear-related disorders (aRR 1.28; 95% CI, 1.25–1.31), and diabetes with complication (aRR 1.26; 95% CI, 1.24–1.28), as well as the total number of conditions, with aRRs of death from 1.53 (95% CI, 1.41–1.67) for patients with 1 condition, 2.55 (95% CI, 2.32–2.80) for patients with 2-5 conditions, 3.29 (95% CI, 2.98–3.63) for patients with 6-10 conditions and 3.82 (95% CI, 3.45–4.23) for patients with more than 10 conditions (compared with patients with no conditions). Of the underlying medical conditions considered in those 18-39 years, those associated with ICU admission were obesity, diabetes with complication, essential hypertension, anxiety and fear-related disorders, asthma and tobacco-related disorders. Of those 40 years and over conditions associated with ICU admission were diabetes with complication, obesity, anxiety or fear-related disorders, chronic kidney disease, coronary atherosclerosis and heart disease, COPD and bronchiectasis and aplastic anaemia.

Other populations, for consideration by the Advisory Group at a later stage

There are other groups who could be considered, described below. They relate to extending the age, ethnicity, vaccination status, medical conditions criteria and some others at high risk. **Time will not permit their consideration at this meeting**; however, they are listed below as context to the groups the Advisory Group will be discussing above.

The current access criteria include all cases aged 65 years and over, Māori and Pacific cases aged 50+ years, and cases not having received 2 or more COVID vaccine doses if aged 50+ years. Other groups are eligible if they have 3+ high risk conditions.

As background, we note the 21,761 COVID-19 hospitalisations in 2022 compared with 2,101,038 cases recorded that year. This provided a rate of 1.04% hospitalisations/cases (not accounting for time lags between case notification and hospitalising with progressed disease). Hospitalisation/case rates varied 73-fold by age group and ethnicity, with eg. a 18% hospitalisation/case rate for Māori/Pacific aged 90+ years.

COVID-19 cases recorded

Year-mont (Multipl Year = 2022

cases	ethnicit		
Age gro	Māori or P	other ethr	Total
0 to 9	60900	134421	195321
10 to 19	83924	200161	284085
20 to 29	101266	254087	355353
30 to 39	80966	279523	360489
40 to 49	61572	243248	304820
50 to 59	48213	212996	261209
60 to 69	28466	153722	182188
70 to 79	11007	91814	102821
80 to 89	3311	40629	43940
90+	444	10299	10743
Unknown	9	60	69
Total	**480078**	**1620960**	**2101038**

All COVID-19 admissions

Year 2022

hosp	ethnicit		
Age gro	Māori or P	other ethr	Total
0–9	763	1067	1830
10–19	321	502	823
20–29	565	889	1454
30–39	585	1093	1678
40–49	616	1058	1674
50–59	883	1462	2345
60–69	955	2032	2987
70–79	797	3045	3842
80–89	470	3381	3851
90+	81	1196	1277
Total	**6036**	**15725**	**21761**

Proxy case-hospitalisation rates (no. hospitalisations / no. cases)

Year	2022				
Age group	Māori or Pacific	other ethnicities	Total	RR age cf 10-19	RR MP vs. other
0–9	1.25%	0.79%	0.94%	3.2	1.6
10–19	0.38%	0.25%	0.29%	1.0 (ref)	1.5
20–29	0.56%	0.35%	0.41%	1.4	1.6
30–39	0.72%	0.39%	0.47%	1.6	1.8
40–49	1.00%	0.43%	0.55%	1.9	2.3
50–59	1.83%	0.69%	0.90%	3.1	2.7
60–69	3.35%	1.32%	1.64%	5.7	2.5
70–79	7.24%	3.32%	3.74%	12.9	2.2
80–89	14.20%	8.32%	8.76%	30.3	1.7
90+	18.24%	11.61%	11.89%	41.0	1.6
Total			1.04%		

current eligibility for antivirals

Depending on the COVID-19 morbidity risk with other groups, future options to extend the age/ethnicity/vaccination status/demographic/conditions groups could include:

Harmonising with the current criteria for COVID-19 vaccine 2nd booster eligibility, ie.

1. all aged 50+ years (ie ages 50-64 increment)
2. Māori/Pacific aged 40+ years (ie ages 40-49 increment for Māori/Pacific)
3. healthcare, aged care and disability workers aged 30+

Lowering age thresholds for cases not having received 2+ COVID vaccine doses, ie.

4. aged 40+ for cases who have received <2 COVID vaccine doses, where this group is currently aged 50+ (ie ages 40-49 increment for <2 vaccinations). The current age 50+ for <2 vaccine doses is the same as the current age 50+ for all Māori/Pacific (see 2. above)
5. Māori/Pacific aged 30+ with <2 COVID-19 vaccine doses (ie extending both 2. and 4. above, same age as 3. above)

Other

6. Māori and Pacific ethnicity (all ages) who are either (1) not yet vaccinated, (2) have co-existing medical conditions (1 or more), and/or (3) difficulties accessing healthcare. The current list of medical and other conditions, listed on the covid19.govt.nz website (linked to by note ** in the Pharmac antiviral criteria), includes this group. This to date has not been included in Pharmac's proposed list of

high-risk conditions (see other paper). In Australia, First Nations people aged 30+ are eligible for oral COVID-19 treatments with 1 additional risk factor for developing severe disease.

7. People living remotely in rural areas. Living remotely with reduced access to higher level healthcare is one of Australia's risk factors in its eligibility criteria for oral COVID-19 treatments.
8. Aged 50+ years with 2+ high risk conditions (currently 3). In Australia, people aged 50+ are eligible for oral COVID-19 treatments when they have 2 additional risk factors for developing severe disease.

International Recommendations – included in Appendix 3 for reference

Advisory Group Recommendations

We seek the advice of the Group as to the inclusion and priority of the following groups to the Antiviral Access Criteria under criterion 4. Note, these are in the order they appear in the paper and are not in any order of priority.

ANY of the following:

- **4.1 Disability Support Services recipients**
- **4.2 People with rare disorders expected to be at risk of severe COVID-19 as a result of their disorder**
- **4.3 People with severe respiratory conditions expected to be at risk of severe COVID-19**
- **4.4 People with any prior hospital identified/based comorbid condition/s expected to increase the risk of severe COVID-19**
- **4.5 People previously hospitalised due to COVID-19**
- **4.6 People with multiple COVID-19 infections and previous experience of severe COVID-19 associated outcomes**
- **4.7 People with long covid or post-acute sequelae of SARS-CoV-2 infection (PASC)**
- **4.8 People with a high risk of severe long-term effects from COVID-19**

APPENDICES

Appendix 1: **Included papers**

- Brown et al. 2022
- Yuan et al. 2022
- Henderson et al. 2022
- Williamson et al. 2021
- Bosworth et al. 2021
- Chowdbury et al. 2021
- Karca et al. 2022
- Boudjelal et al. 2021
- Zhang et al. 2022
- Paneghetti et al. 2022
- Fierro et al. 2021
- Ferrarotti et al. 2021
- Lewis et al. 2022
- Sunjaya et al. 2022
- Bloom et al. 2022
- Eggert et al. 2022
- Thompson et al. 2022
- Choi et al. 2022
- Qin et al. 2022
- Haplin et al. 2021
- Geraveli et al. 2021
- Nguyen et al. 2022
- Brouqui et al. 2021
- Bowe et al. 2022
- Xu et al. 2022
- Xie et al. Preprint. 2022
- Xie et al. Supplementary information
- Peluso et al. 2022
- Boglione et al. 2022
- Hippisley-Cox et al. 2021
- Bergman et al. 2021
- Kompaniyets et al. 2021

Appendix 2: **Correspondence**

Letter from Genetic Health NZ

Letter from Rare Disorders NZ

Appendix 3: International recommendations

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The impact on the health outcomes of population groups experiencing health disparities

HEALTH BENEFITS

- The health benefit to the person
- Consequences for the health system

PHARMACEUTICAL SCHEDULE APPLICATION

To: COVID-19 Treatments Advisory Group

From: Funding Application Advisor

Date: May 2023

COVID-19 antivirals (and any other medicines) for the prevention and treatment of long COVID

QUESTIONS TO ADVISORY GROUP

Note to Committee members: These questions have been identified by Pharmac staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

Need

1. Considering the currently available treatments for long COVID, is there an unmet health need? If so, why?
2. What are the Advisory Group's views on the people who are most at risk of long COVID. Can these groups be easily identified?

   2.1. What is the strength and quality of current evidence for these needs?
3. What is the Advisory Group's view on possible numbers of people with long COVID, is there particular information that would be helpful for Pharmac staff to estimate these numbers?
4. Does long COVID disproportionally affect, and what is the impact on each group's health outcomes for:
   - Māori?
   - Pacific people?
   - Other groups already experiencing health disparities relative to the wider New Zealand population (eg NZ Dep 9-10 deprivation, refugees/asylum seekers)?

   4.1. What is the strength and quality of evidence for these?

Health benefit

5. Does the Advisory Group consider that any pharmaceutical treatment options for long COVID offer any health benefit or create any risks?
6. What benefits or risks does the Advisory Group consider could be expected to result from treating people during the acute phase of COVID-19, especially those people at risk of developing long COVID, with treatments aiming to prevent long COVID?
7. What benefits or risks does the Advisory Group consider could be expected to result from treating people with established long COVID?
8. What does the Advisory Group consider would be meaningful benefit from the treatment of long COVID?

9. Which patient population would benefit most from treatment against or as a result of long COVID? What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from pharmaceutical prevention or treatment of long COVID? Please provide a high-level appraisal of the current evidence (eg study design, population, endpoints).

General

10. Is there any data or information missing from the discussion paper, in particular clinical trial data and commentary?

Recommendations

11. Should the access criteria for any currently available treatments for COVID-19 be extended to include the treatment of long-COVID?

12. Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.

    - What is the potential impact of this proposal on Māori health outcomes?

13. Should any treatments that are currently under development be considered by Pharmac for the treatment of long COVID-19?

18. Does the Committee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is provide the COVID-19 Treatments Advisory Group with an update on current literature for long COVID and seeks advice regarding the pharmaceutical prevention of long COVID and possible treatments, including antivirals .

This is the first paper specifically on long COVID that has been prepared for consideration by the COVID-19 Treatments Advisory Group.

We expect that further discussion on this topic is likely to be required at future meetings as new evidence and information becomes available.

DISCUSSION

BACKGROUND

Previous consideration of long COVID

Pharmac staff have previously provided the following observational studies to the Advisory Group for consideration of health need of people with long COVID and the possible health benefit associated with the use of antiviral treatments, as follows:

- Xu et al. Nat Med. 2022; 28:2406-2415
  A retrospective cohort study using the US Veteran Affairs database, reporting in the post-acute phase of COVID-19 an increased risk of an array of incident neurologic sequelae (compared with historic controls).
- Boglione et al. QJM. 2022;114:865-871
  A prospective longitudinal observational study assessing the prevalence and risk factors for long-COVID syndrome, in Italy of patients hospitalised and affected by COVID-19 and followed for at least six months.
- Xie et al. Preprint. 2022
  A retrospective cohort study assessing the association of nirmatrelvir treatment on the risk of developing post-acute sequelae of COVID-19 (PASC), using healthcare databases to identify users of the health system. *This is now published, with reported results in* ***Table 1****.*
- Peluso et al. Pathog Immun. 2022;7:95-103
  Four case reports of oral nirmatrelvir and associations with risk of long COVID symptoms.

As in the draft record(s) from the February 2023 meeting, the following was discussed:

- *The Advisory Group noted a preprint retrospective cohort study in US Veterans (Xie et al. Preprint. 2022) reported that there was a reduction in post-acute death of 48%, post-acute hospitalisation 30% and post-acute sequelae 26%. The Group noted that there were limitations of this study, including that this was a non-experimental observational cohort study rather than a randomised controlled trial; that it included only those that were considered at high risk of severe outcomes; and that the definition of post-acute sequelae (long COVID) was different to New Zealand definitions of long COVID.*

- *The Advisory Group also considered that the definition of long COVID was not clear and that there are many people presenting post COVID-19 with fatigue-like syndromes. The Group considered that a decrease in the severity of illness associated with Omicron variant infection could also mean there is a decrease in morbidity of post-acute sequelae (long COVID) but considered this was not currently supported by evidence.*

- *The Advisory Group considered that efficacy of nirmatrelvir with ritonavir in reducing morbidity associated with long COVID would be difficult to assess, due to lack of confidence in diagnosis of long COVID, different definitions of long COVID, and difficulties with assessing a more subjective endpoint. The Group considered that there are other viral infections that have extended recuperation periods, particularly for those who have had severe illness. The Group considered that recuperation from COVID-19 infection impacts some people more than they would normally expect from other viral illnesses.*

Need

The health need of the person

The Ministry of Health defines long COVID as “Any signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. Presentation may include clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body”. Long COVID is a multifaceted condition, and its’ resulting impact may include debilitating sequalae, impairments that impact on quality of life, capacity to return to work, and social and holistic effects on people. An impairment can be intellectual, psychiatric, physical, neurological, or sensory, and can be temporary, intermittent, or ongoing.

As recommended in the Ministry of Health clinical guidelines (Ministry of Health. 2022. Clinical Rehabilitation Guideline for People with Long COVID (coronavirus disease) in Aotearoa New Zealand: Revised December 2022. Wellington: Ministry of Health), 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. There appears to be no specific time course, symptoms may improve one week and relapse the next. The expected time to recovery from symptoms of COVID-19 are:

- Four weeks for muscle aches, chest pain, and sputum production.
- Six weeks for cough and breathlessness to be significantly improved, if not fully resolved.
- Three months for most other symptoms with residual fatigue.
- Six months for all symptoms unless the patient had a complicated/prolonged admission to intensive care (Grade B, fair evidence but concerns about volume and consistency of evidence available).

It was also recommended that the presentations in the post-acute COVID-19 scenario are likely to be:

- nonspecific post viral symptoms, particularly fatigue, breathlessness chest pain and palpitations.
- specific serious sequelae resulting from the acute infection, or as delayed complications.
- recovery after severe illness that required intensive care management.
- psychosocial effects of prolonged symptoms and functional impairment (Grade C, expert opinion/consensus guideline).

Reported risk factors include: older age, having more than 1 underlying chronic medical condition, pre-existing asthma, higher BMI, female sex, hospitalisation during acute COVID-19, multiple early symptoms, the infecting SARS-Cov-2 variant (Omicron potentially less risk than Delta), psychological distress pre-infection and other immunological factors.

The effect of re-infection on long COVID risk is not well understood and difficult to quantify. Vaccination looks to have a positive effect on risk of long COVID. Ministry of Health has reported Paxlovid as a pipeline treatment option for those with long COVID based on in vitro evidence but note there are no clinical trials currently investigating this (Ministry of Health. Long COVID Evidence Update. November 2022.).

Epidemiology

Currently, the prevalence of long COVID in Aotearoa New Zealand is unknown. Manatū Hauora - Ministry of Health (Ministry of Health. 2022) refers to a global pooled estimated case-prevalence of post-COVID-19 condition (from Chen et al. J Infect Dis. 2022;226:1593-1607) was 43% of cases and for hospitalised and non-hospitalised cases estimated at 54% and 34% respectively; however, the source analysis (Chen et al. 2022) did note that its estimates ranged widely from 9% to 81% prevalence in cases, being affected by interstudy differences in endemic causative subvariants (noting most component studies preceded the Omicron subvariant), sex, region, COVID-19 study population (eg hospitalised vs non-hospitalised), syndromes comprising post-COVID-19 conditions, and follow-up time, and with significant heterogeneity within strata of component studies.

Manatū Hauora has also referred to recent studies reporting lower case-prevalences of long-term symptoms (Ministry of Health. 2022), eg

- Qasmieh et al. medRxiv. 2022:2022.09.04.22279588:
  A population-based cross-sectional survey during the Omicron BA.5 surge in the US mid-June to the beginning of July 2022 (n=3042), reporting that of 527 respondents self-reporting confirmed/probable/possible SARS-CoV-2 infection occurring more than four weeks earlier, 21.5% (95% CI 18.2-24.7%) reported having long COVID symptoms.
- Ballering et al. Lancet. 2022;400:452-61
  A retrospective 'matched observational cohort study' (probably better described as a case control study) in the Netherlands, matching self-reported COVID-19 cases with age/sex-matched controls, thus correcting for symptoms prior to SARS-CoV-2 infection. The study assessed 23 symptoms in 1782 COVID-19-positive participants at 90 to 150 days after infection, comparing with symptom occurrence before infection and with the matched controls. Ongoing symptoms were ascribed to

COVID-19 in 12.7% of cases (with 21.4% (381/1782) of the COVID-19-positive participants experiencing at least one of these core symptoms substantially increasing to at least moderate severity at 90–150 days after COVID-19 diagnosis or matched timepoint, versus 8.7% (361/4130) of negative controls).

Preliminary results from the Manatū Hauora-funded Ngā Kawekawe o Mate Korona study (Victoria University of Wellington (VUW). 2022 [presentation]), analysing to date for 373 people in Aotearoa NZ having COVID-19 before December 2011, suggest in that largely pre-Omicron era some 31% of respondents overall (21+124)/(65+405) had symptoms for at least three months or more.

Manatū Hauora has also recently funded the LOGIC study through the Waikato hospital to better understand of the incidence, duration, severity, and risk factors for Post-COVID Syndrome and other mental and physical health problems and disability after admission to hospital with COVID-19 during the Omicron outbreak, and assessment of the healthcare requirements, costs, and personal impact of these outcomes. A Long Covid registry being established to estimate the clinical, quality of life and economic impacts of Long COVID in Aotearoa New Zealand and providing a means to continually monitor health outcomes and inequities (Ministry of Health. COVID-19 and National Immunisation Programme research projects. Updated 27 April 2023).

The impact on the Māori health areas of focus and Māori health outcomes

Reported results from the Ngā Kawekawe o Mate Korona study (VUW 2022) do not yet suggest clear variation in of long COVID case-prevalence across ethnic groups. Of its 65 Māori participants, 43% (28/65) reported symptoms for more than one month, and of these participants, 75% (21/65) reported experiencing long COVID symptoms for three months or more post-infection, ie 21/65 (32%) still having symptoms at 3+ months. By comparison, of its 405 participants who were non-Māori, 47% (190/405) reported symptoms for more than one month, and of these individuals, 65% (124/405) reported symptoms that lasted three months or more, ie 124/405 (31%) . Note however that Māori continue to experience inequities in vaccination rates and incidence of severe illness requiring hospitalisation, both of which are associated with a higher likelihood of developing long COVID.

The impact on the health outcomes of population groups experiencing health inequities

Pacific peoples

Of 18 Pacific peoples who participated, two were diagnosed with long COVID (OR 0.11 (95% CI 0.03 to 0.50) when compared to European/other ethnic groups. Conversely, COVID-19 disproportionally affected Pacific people through both the Delta and Omicron outbreaks. Therefore, the likelihood Pacific people will also be disproportionally affected by long COVID. The Ngā Kawekawe o Mate Korona study recommended that the barriers to access for primary health care should be reduced for Pacific peoples with long COVID, acknowledging the inequities faced by Pacific peoples (Jeffreys et al. Ngā Kawekawe o Mate Korona - Impacts of COVID-19 in Aotearoa: Technical Report and Supplementary Tables. 2022. Wellington: Te Herenga Waka-Victoria University of Wellington).

Pharmac staff are not aware of any other specific population groups experiencing health disparities who are disproportionately affected by long COVID.

Risk factors for long COVID

Manatū Hauora – Ministry of Health describes current risk factors for long COVID as follows (Ministry of Health. Long COVID Evidence Update. November 2022):

- older age (Perlis et al. [Preprint] estimated OR 1.10, 95% CI 1.01-1.19 for each decade beyond 40 years)
- being female
- having more than one underlying chronic medical condition or pre-existing condition including pre-existing asthma or a higher body mass index (obesity)
- levels of psychological distress before SARS-CoV-2 infection
- multiple early symptoms
- hospitalisation during acute COVID-19; duration of long COVID symptoms may also be longer among hospitalised individuals compared to those who were not hospitalised
- SARS-CoV-2 variant –some evidence that the risk is less after Omicron v Delta
- other immunological factors, such as: greater viral load during early stages of infection; the presence of autoantibodies; imbalances or compositional alterations in the gut microbiome; vaccination status; or previous Epstein-Barr virus infection or a reactivation of latent viruses during initial infection.

A systemic review and meta-analysis evaluated the demographic characteristics and comorbidities that are associated with developing post-COVID condition (PCC) in adults (18 years and over). The meta-analysis reported female sex (OR,1.56; 95% CI, 1.41-1.73), age (40-69 years and ≥70 years v <40 years) (OR,1.21; 95%CI, 1.11-1.33), high BMI (OR,1.15; 95% CI,1.08-1.23), and smoking (OR,1.10; 95% CI, 1.07-1.13) being associated with an increased risk of developing PCC (Tsampasian et al. JAMA Intern Med. 2023:e230750 (see Appendix 1))

Thompson et al considered a number of different factors that could affect the risk of long COVID including: female sex, ethnicity, no higher education, index of multiple deprivation (IMD), current smoking, poor health overall, psychological distress, overweight or obese, comorbid diabetes, hypertension, high cholesterol or asthma by analysing 10 longitudinal studies (LS) and electronic health record data (EHR) on the risk factors for long COVID. Of note at week 4, those with asthma, pre-pandemic psychological distress, poor overall health, deprivation and female sex all reported that a higher risk of long COVID (see Figure 1 below) (Thompson et al. Nat Commun. 2022;13:3528 (see Appendix 1)).

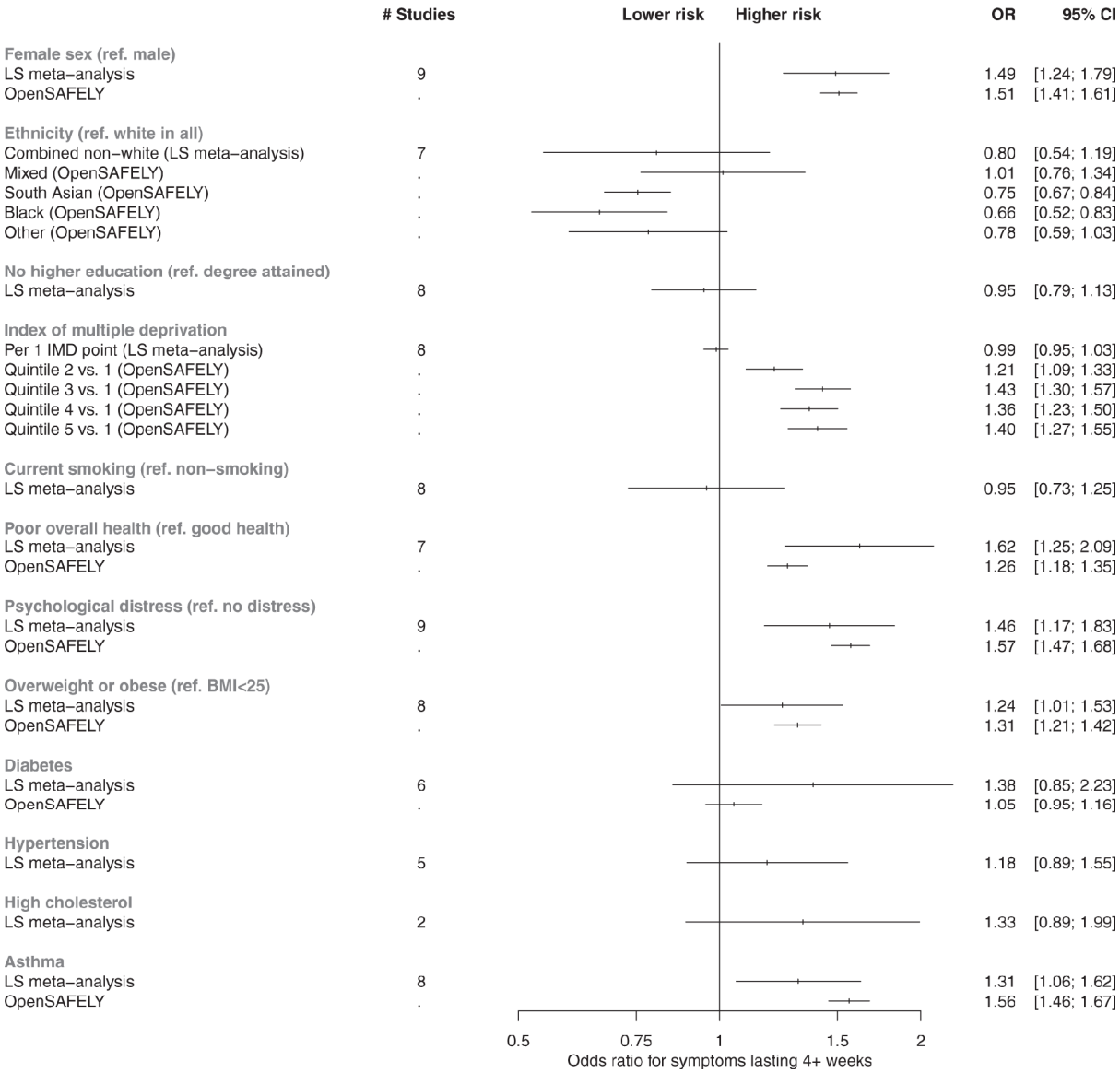

Figure 1: Risk factors associated with long COVID from meta-analyses of LS findings alongside corresponding analyses from EHRs. Source: (Thompson et al. Nat Commun. 2022;13:3528).

Health Benefit

Early preventive treatments during acute COVID-19 disease to reduce the incidence of later long COVID

There are currently no pharmaceutical options available specifically for the treatment or prevention of long COVID, however a number of guidelines have been developed to assist with its management.

In **Table 1**, information relating to current evidence relating to the use of COVID-19 antivirals and the subsequent reported reduction in incidence of long COVID is included with additional information below.

Later treatments for established long COVID

The tables below detail that a number of studies have been completed or are underway to investigate the effectiveness of currently available funded antivirals in the prevention or treatment of long COVID. **Table 2** also identifies a number of novel agents (and those currently funded) being investigated for the treatment of long COVID.

Manatū Hauora – Ministry of Health guidelines

Current Manatū Hauora guidelines suggest symptom management, such as sleep aids, as medications for long COVID are not yet validated. It is suggested that symptom management eg with sleep medications for sleep disturbance, could be used if appropriate. The Ministry states the majority of interventions that are currently recommended for long COVID are non-pharmacological ie physiotherapy, occupational therapy, psychologist or dietitian rehabilitation (Ministry of Health. Clinical Rehabilitation Guideline for People with Long COVID (coronavirus disease) in Aotearoa New Zealand: Revised December 2022. Wellington: Ministry of Health).

International Recommendations

England/Wales

It was recommended there are established treatments for managing the common symptoms often seen with ongoing symptomatic COVID-19 and post-COVID-19 syndrome, as set out in current national and local guidance, which can be followed for symptomatic relief. However, there is a lack of evidence for pharmacological interventions to treat the condition itself (NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. Version 1.20. March 2022).

Australia

Guidelines are adapted from the NICE guidelines above. Specific symptomatic treatment is based on effective treatment already available eg physiotherapy or medicine for symptom relief. It is recommended that in patients with continuing symptoms after COVID-19, that unproven therapies outside of guidelines or randomised trials should not be used without appropriate ethical approval. Those that are specifically noted in the guidelines to only be used in research settings are naltrexone and hyperbaric oxygen therapy (Australian National Clinical Evidence Taskforce. 2023. Australia Guidelines for the Clinical Care of People with COVID-19.).

Canada

The research on post–COVID-19 condition treatment and management is emerging, but to date is characterised predominantly by case reports/series. There are fewer studies of other designs, evidence syntheses, or qualitative studies; no economic analyses were identified. The majority of the identified evidence has looked at certain types of treatment or management for post–COVID-19 condition, such as vaccination. There appears to be limited evidence regarding certain types of indication/diagnosis, such as haematological conditions, and population groups, including children and those without symptoms during initial infection

(CADTH Health Technology Review. Post–COVID-19 Condition Treatment and Management Rapid Scoping Review. December 2022).

Literature Search

Pharmac staff conducted a PubMed search on 11 May 2023 and identified the following publications regarding COVID-19 antivirals for long COVID.

Table 1: Literature search results from PubMed for long COVID prevention or treatment with nirmatrelvir with ritonavir, remdesivir or molnupiravir (see Appendix 1)

Nirmatrelvir with ritonavir 33 results (4 relevant) Search terms: ((long COVID) OR (post-acute sequelae)) AND (nirmatrelvir)		
Study and citation	**Design**	**Outcomes and results**
Association of treatment with nirmatrelvir and the risk of post–COVID-19 condition (PCC). Xie et al. JAMA Intern Med. 2023:e230743 (formal publication of the earlier Xie et al. Preprint. 2022 preprint version)	A retrospective cohort study of 281,793 people under the US Department of Veterans Affairs (VA) (mean [SD] age 61.99 years [14.96]; 242 383 [86.0%] male) with SARS-CoV-2 infection who had at least one risk factor for progression to severe COVID-19 illness, with 35,717 treated with nirmatrelvir with ritonavir in the acute phase of COVID-19 infection compared to 246,076 with no treatment. Inverse probability weighted survival models were used to estimate the association of nirmatrelvir (vs control) with post–acute death, post–acute hospitalisation, and a prespecified panel of 13 post–acute COVID-19 sequelae (components of PCC) and reported in relative scale as relative risk (RR) or hazard ratio (HR) and in absolute scale as absolute risk reduction in percentage at 180 days (ARR).	Compared with the control group (ie non-treated cohort) , nirmatrelvir was associated with reduced risk of post-COVID-19 condition (PCC) (RR, 0.74; 95% CI, 0.72-0.77; ARR, 4.51%; 95% CI, 4.01-4.99) including reduced risk of 10 of 13 post-acute sequelae. Nirmatrelvir was also associated with reduced risk of post–acute death (HR 0.53 (95% CI, 0.46-0.61); ARR 0.65% (95% CI, 0.54-0.77), and post–acute hospitalisation (HR 0.76 (95% CI, 0.73-0.80); ARR 1.72% (95% CI, 1.42-2.01)). Nirmatrelvir was associated with reduced risk of PCC in people who were unvaccinated, vaccinated, and boosted, and in people with primary SARS-CoV-2 infection and reinfection.
Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among U.S. Veterans: target trial emulation studies with one-month and six-month outcomes. Bajema et al. [Preprint]. 2022	Three retrospective target trial emulation studies (ie respective cohort studies) comparing matched patient cohorts who received nirmatrelvir-ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir-ritonavir versus molnupiravir in the Veterans Health Administration (VHA). Participants were 90% male with median age 67 years and 26% unvaccinated, at risk of severe COVID-19, treated in the outpatient setting during January 2022 and February 2022. Participants included were treated with nirmatrelvir-ritonavir (n=1,639) compared to not treated (n=103,353) OR treated with molnupiravir (n=922) compared to not treated (n=111,233) OR nirmatrelvir-ritonavir treated (n=1,637) compared to molnupiravir treated (n=795). Primary outcomes included all-cause 30-day hospitalisation or death and 31-180-day incidence of acute or long-term care admission, death, or post-	Long term outcomes (day 31-180) of statistical significance as reported: • Incidence of acute or long-term care admission was 123.0 events per 1000 persons in the molnupiravir arm compared with 82.5 events per 1000 persons in the no treatment arm (subhazard ratio [SHR] 1.48, 95% CI 1.11 to 1.99). • Compared to the no treatment arm, the nirmatrelvir-ritonavir arm had a lower incidence of renal conditions (44.2 v 65.1 events per 1000 persons, SHR 0.68, 95% CI 0.48 to 0.95).

	COVID-19 conditions. For post-COVID conditions, 6-month incidence was only in matched groups without prevalent conditions and who were alive at day 31. For 30-day outcomes, unadjusted risk rates, risk differences, and risk ratios were calculated. For 31-180-day outcomes, unadjusted time-to-event analyses were used. Subhazard ratios (SHR), derived from proportional hazards regression accounting for the competing risk of death, are presented for acute long-term care admissions and post-COVID outcomes.	• Compared to molnupiravir arm, nirmatrelvir-ritonavir had a lower incidence of renal conditions (39.2 v 90.2 events per 1000 persons, SHR 0.42, 95% CI 0.22 to 0.80). • There were otherwise no significant differences between groups regarding the incidence of post-COVID conditions.
Long-COVID in patients with cancer previously treated with early anti-SARS-CoV-2 therapies in an out-of-hospital setting: a single-center experience. Lasagna et al. Cancers (Basel). 2023;15:1269	Observational study of 97 medical oncology patients (under treatment for solid tumours) identified as having COVID-19 estimating their incidence of long COVID symptoms , with telephone survey of patients at least 12 weeks after their COVID-19 diagnosis (from January to September 2022 (Omicron surge)). Secondary outcomes were the incidence of long COVID symptoms according to WHO case definition, the time to COVID-19 symptoms resolution and the time to nasal swab viral clearance in the two groups (Long COVID vs. No Long COVID).	Twelve patients (12.4%) reported long COVID. No significant difference between early anti-COVID-19 therapies and long COVID (P = 0.443) was seen. The female sex (P = 0.024) and diabetes mellitus (P = 0.014) were significantly associated with long COVID. No statistically significant difference between the two groups (Long COVID vs. No Long COVID) according to the time to nasal swab viral clearance (p = 0.078).
The impact of early therapies for COVID-19 on death, hospitalization and persisting symptoms: a retrospective study. Bertuccio et al. Infection. 2023:1–12	A retrospective cohort study, including all outpatients evaluated from April 2021 to March 2022 in Brescia, Lombardy, northern Italy. Patients were stratified in three groups: treated with mAbs, treated with antivirals drugs and controls (patients eligible but refused treatment). A total of 649 patients were included in the study, of which 242 (37.3%) were treated with mAbs, 197 (30.3%) with antiviral drugs and 210 (32.4%) were not treated. Data were collected at baseline and at month 1 and 3 (data on self-reported symptoms were collected using a telephone-administered questionnaire). Authors assessed early COVID-19 therapies effectiveness in preventing hospitalisation, death at 1 or 3 months and persisting symptoms at 3 months after the onset of SARS-CoV-2 infection.	Data on long COVID at 3 months were available for 323 (49.8%) patients. Inverse associations were found for treatment groups as compared to the control group: • Participants treated with antiviral drugs for any symptoms (OR 0.43, 95% CI 0.21–0.87) • Participants treated with mAbs for any neuro-behavioural symptoms (OR 0.48, 95% CI 0.25–0.92) Authors also reported a positive association for the diagnosis of long COVID in females compared to men, with an OR of 2.14 (95% CI 1.30–3.53) for any symptoms.

Remdesivir 182 results (3 relevant) Search terms: ((long COVID) OR (post-acute sequelae)) AND (remdesivir)		
Study	**Design**	**Outcomes and results**
Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect? Boglione et al. QJM. 2022;114:865-71	A prospective observational study of all hospitalised patients affected by COVID-19 at our centre of Infectious Diseases (Vercelli, Italy) admitted between 10 March 2020 and 15 January 2021 for at least 6 months after discharge. Two follow-up visits were performed: after 1 and 6 months after hospital discharge.	Long COVID Syndrome (LCS) was diagnosed in 322 subjects at Visit 1 (71.7%) and in 206 at Visit 2 (45.9); according to the post-COVID-19 functional status scale we observed 147 patients with values 2–3 and 175 with values >3 at Visit 1; at Visit 2, 133 subjects had the score between 2–3 and 73 > 3. In multivariate analysis, treatment with remdesivir (OR = 0.641; 95% CI=0.413–0.782; *P*<0.001) was reported as independent predictors of LCS. Statistically significant differences were reported when comparing the group of patients treated with remdesivir against those untreated we observed that at Visit 1, 123 subjects were not affected by LCS vs. 81 without remdesivir treatment. Patients with a score between 2 and 3 were 27 and 120 in the two groups, respectively; patients with a score >3 were 13 and 85, respectively. All the differences in the two groups were statistically significant (*P* < 0.001).
Effect of remdesivir post hospitalisation for COVID-19 infection from the randomised SOLIDARITY Finland trial (1 year follow up) Nevalainen et al. Nat Commun. 2022;13:6152.	Interim results from the first long-term open-label follow-up of a randomised trial (NCT04978259) of remdesivir for hospitalised acute COVID-19, assessing remdesivir associations with one-year recovery (primary outcome) and other patient-important outcomes (n=208 in the RCT, 181 completing one-year follow up).	At one year: • Self-reported recovery occurred in 85% in remdesivir and 86% in standard of care (SoC) (RR 0.94, 95% CI 0.47-1.90). • Of the 21 potential long-COVID symptoms, patients reported moderate/major bother from fatigue (26%), joint pain (22%), and problems with memory (19%) and attention/concentration (18%) and there was no reported statistically significant difference between groups. • Authors inferred no convincing difference between remdesivir and SoC in quality of life or symptom outcomes

		(*P*>0.05), and wide confidence intervals included possible benefit and harm.
Anti-nucleocapsid antibody levels and pulmonary comorbid conditions are linked to post-COVID-19 syndrome. Jia et al. JCI Insight. 2022;7:e156713	Adult SARS-CoV-2 reverse transcription PCR–positive (RT-PCR–positive) patients were recruited at Stanford from March 2020 to February 2021. Study participants were seen for in-person visits at diagnosis and every 1–3 months for up to 1 year after diagnosis; they completed symptom surveys and underwent blood draws and nasal swab collections at each visit. Kaplan-Meier plots and log-rank tests were used to evaluate the associations between time to symptom resolution and participant characteristics (ie use of remdesivir).	Reportedly, there was no significant association between time to first symptoms resolution (TTFR), ie acute symptom resolution, and remdesivir treatment (38 vs 40 days for who received vs those who did not receive remdesivir treatment; *P*=0.18). Reportedly, there was no significant association between time to sustained symptom resolution (TTSR), ie long-term symptom relief, and remdesivir treatment (198 vs 197 days for those who received vs those who did not receive remdesivir treatment; *P*=0.2).
Molnupiravir 23 results (1 relevant) Search terms: ((long COVID) OR (post-acute sequelae)) AND (molnupiravir)		
Study	**Design**	**Outcomes and results**
Molnupiravir and risk of post-acute sequelae of COVID-19: cohort study. Xie et al. BMJ. 2023;381:e074572	A retrospective cohort study in people who tested positive for SARS-CoV-2 between 5 January 2022 and 15 January 2023, had at least one risk factor for progression to severe COVID-19, and survived the first 30 days after testing positive (n=229,286). Groups compared were those who were treated with molnupiravir (n=11472) and those who had no COVID-19 antibody or antiviral treatment (n=217,814). The outcomes measured included post-acute death and post-acute hospital admission and a composite of post-acute death or hospital admission. Also examined the risk of developing 13 prespecified post-acute sequelae of SARS-CoV-2 (PASC): incident ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue and malaise, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, dysautonomia, shortness of breath, and cough.	Compared with no treatment, molnupiravir use within five days of a positive SARS-CoV-2 test result was associated with reduced risk of PASC: • relative risk 0.86 (95% confidence interval 0.83 to 0.89); • absolute risk reduction at 180 days 2.97% (95% confidence interval 2.31% to 3.60%) Molnupiravir was associated with reduced risk of eight of the 13 post-acute sequelae: dysrhythmia, pulmonary embolism, deep vein thrombosis, fatigue and malaise, liver disease, acute kidney injury, muscle pain, and neurocognitive impairment. Molnupiravir was also associated with reduced risk of PASC in people who had not received a COVID-19 vaccine, had received at one or two vaccine doses, and had received a booster dose, and in people with primary SARS-CoV-2 infection and reinfection.

	Inverse probability weighting was used to balance the treatment and no treatment groups.	
Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among U.S. Veterans: target trial emulation studies with one-month and six-month outcomes. Bajema et al. [Preprint]. 2022	Three retrospective target trial emulation studies (ie respective cohort studies) comparing matched patient cohorts who received nirmatrelvir-ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir-ritonavir versus molnupiravir in the Veterans Health Administration (VHA). For further information, see above under **nirmatrelvir with ritonavir** section.	Long term COVID-19 outcomes (day 31-180) of statistical significance as reported: • Incidence of acute or long-term care admission was 123.0 events per 1000 persons in the molnupiravir arm compared with 82.5 events per 1000 persons in the no treatment arm (subhazard ratio [SHR] 1.48, 95% CI 1.11 to 1.99). • Compared to the no treatment arm, the nirmatrelvir-ritonavir arm had a lower incidence of renal conditions (44.2 v 65.1 events per 1000 persons, SHR 0.68, 95% CI 0.48 to 0.95). • Compared to molnupiravir arm, nirmatrelvir-ritonavir had a lower incidence of renal conditions (39.2 v 90.2 events per 1000 persons, SHR 0.42, 95% CI 0.22 to 0.80). There were otherwise no significant differences between groups regarding the incidence of post-COVID conditions.

Other pharmaceuticals with emerging possible evidence for long COVID prevention or treatment

Metformin

Bramante et al. COVID-OUT Trial Team. medRxiv [Preprint]. 2022 (see Appendix 1 for full text)
The COVID-OUT trial was an investigator-initiated, multi-site, phase 3, randomised, quadruple-blinded placebo-controlled clinical trial. The design simultaneously assessed three oral medications (metformin, ivermectin, fluvoxamine) and assessed COVID-19 outcomes for up to 10 months to assess, among other things, whether early outpatient treatment of SARS-CoV-2 with metformin, ivermectin, or fluvoxamine may prevent Long Covid (as a secondary outcome measure).

This was a decentralised, remotely delivered trial in the United States involving 1,125 adults, aged 30 to 85 years; self-reported as overweight or obese (median BMI was 29.8 kg/m^2 (IQR 27.0-34.2)); > 7 days of symptoms and enrolled within three days of documented COVID-19 infection; and no known previous COVID-19 infection.

Treatment regimens were as follows:

- Immediate release metformin titrated over 6 days to 1500mg per day, 14 days total
    - Treatment: n = 564
    - Blinded control: n = 561
- ivermectin 430mcg/kg/day for 3 days;
    - Treatment n=361
    - Blinded control n=377
- fluvoxamine, 50mg on day one then 50mg twice daily through 14 days
    - Treatment: n=297
    - Blinded control n=298

Prespecified outcomes were as follows:

- Primary outcome: composite end point of any of hypoxemia (≤93% oxygen saturation on home oximetry), emergency department visit, hospitalisation, or death.
- Secondary outcomes included medical-provider diagnosis of long COVID, reported by participant by day 300 after randomisation (used a time to event approach, with time denoting the time from randomisation)

Primary outcome results and related acute secondary outcome results for acute COVID-19 for the three treatments were published in August 2022 (Bramante et al. COVID-OUT Trial Team. N Engl J Med. 2022;387:599-610), indicating *inter alia* metformin not providing statistically significant benefits for acute disease outcomes.

Pre-print results for the chronic secondary outcome of long COVID were released in December 2022 as Bramante et al. medRxiv [Preprint]. 2022 above, pending peer review, reporting uptake and effects at day 300 that included:

- 86% of metformin group and 81% of blinded controls completed surveys
- For the metformin versus blinded control, the hazard ratio (HR) for developing long COVID was 0.58 (95% CI 0.38 to 0.88); for ivermectin was HR 0.99 (0.59 to 1.64); and for fluvoxamine was HR 1.36 (0.79 to 2.39)

- Cumulative incidence of long COVID was 6.3% (95% CI, 4.2%-8.2%) in the metformin treated group, 10.6% (8.0%-13.1%) in the blinded control group
- The absolute risk reduction for the metformin group was 4.4% (7.6%-1.1%)

Pharmac staff note the Advisory Group's previous decline recommendations regarding ivermectin and fluvoxamine in the treatment of acute COVID-19, and note that metformin is currently fully funded in community and hospital without any restriction.

Pharmac staff note the clear limitations of using simple patient self-reports of physician-diagnosed long COVID as the measure of long covid incidence. However, staff note this form of measurement may possibly cause bias that is non-differential (not differential), ie a bias that applies equally across groups; and that provided there was effective blinding, if anything that non-differential bias would simply dilute/weaken possible true effects, reducing precision but not necessarily the central estimate of effect That is, the 0.58 metformin:control HR could remain reliable, but its 0.38 to 0.88 95% CI may understate true minimal effects (ie the 0.88 upper bound of the 95% CI, may in fact be lower higher, ie the minimum relative hazard reduction of 12% may be higher).

However, the long COVID outcomes in COVID-OUT (to date, as Bramante et al. COVID-OUT Trial Team. medRxiv [Preprint]. 2022) remain to be peer reviewed.

Other

Concurrently, a lay summary article (Ducharme J. Time Magazine. 2023) has claimed some treatments used in myalgic encephalomyelitis/chronic fatigue syndrome may also be effective for long-term COVID effects, including pacing strategy, low dose naltrexone, beta-blockers, antihistamines, and vagal nerve stimulation.

Table 2: Studies identified by Pharmac staff on Clinicaltrials.gov for ongoing trials for pharmaceutical treatments for long-COVID (search terms: Long covid treatment; prevention long covid). **Please note** this is not an exhaustive list.

Study description and intervention	**Outcomes**	**Stage**	**Estimated completion**
Clinical Trial of Efficacy and Safety of Prospekta in the Treatment of Post-COVID-19 Asthenia (NCT05074888) A Multicenter, Double-blind, Placebo-controlled, Parallel-group, Randomized Clinical Trial of Efficacy and Safety of Prospekta in the Treatment of Patients With Post-COVID-19 Asthenia.	Primary outcome: Change in the mean Fatigue Severity Scale (FSS) score (1 indicates "strongly disagree" and 7 indicates "strongly agree") after 4 weeks of treatment based on medical records.	Completed (not published)	June 8, 2022
Phase 2 Study of RSLV-132 in Subjects With Long COVID (NCT04944121) RSLV-132 is an enzymatically active ribonuclease designed to digest the ribonucleic acid contained in autoantibodies and immune complexes and thereby render them biologically inert. A dose of 10 mg/kg will be administered by intravenous infusion on Days: 1, 8, 15, 29, 43, and 57	Primary outcome: PROMIS Fatigue SF 7a T-score	Active, not recruiting	March 2023
Paxlovid (Nirmatrelvir with ritonavir) for Treatment of Long Covid (STOP-PASC) (NCT05576662)	Primary outcomes: Core Symptoms Severity Scale Score [Time Frame: Week 10]	Recruiting	November 2023
SOLIDARITY Finland Long-COVID (Remdesivir Long-term Follow-up Study of COVID Patients) (NCT04978259)	Primary outcomes: Assess the effects of remdesivir + standard of care (SoC) vs. only SoC on long-COVID symptoms (eg fatigue and other neurological inputs) and quality of life (QoL) using questionnaires at one (published and included in **table 1** above) and two years post-discharge.	Recruiting	December 2023
imPROving Quality of LIFe In the Long COVID Patient (PROLIFIC) (NCT05823896) Phase II, interventional, randomised, parallel group, double-blind, placebo-controlled, single-centre study of nirmatrelvir/ritonavir (300/100 mg) or placebo/ritonavir (100mg), administered orally twice daily for 15 days in non-hospitalized patients with post- COVID conditions. Pfizer-sponsored.	Primary outcome: Change from baseline in quality of life at day 16	Not yet recruiting	March 2024

Low-dose Naltrexone for Post-COVID Fatigue Syndrome (NCT05430152) Phase II, randomised parallel group, double-blinded placebo-controlled trial	Primary Outcome: Change in the Fatigue Severity Scale (FSS) total score by 4.7 points or over at 12 and 16 weeks	Not yet recruiting	April 2024
AT1001 (Larazotide) for the Treatment of Long COVID (NCT05747534)	Primary outcomes: Adverse Event Profiling and Time to Symptom Resolution [Time Frame: 8 weeks] Evaluate the safety and efficacy of Larazotide (AT1001) versus placebo in children and young adults 7 to ≤21 years of age who present with symptoms of Long COVID in the presence of SARS-CoV-2 antigenemia.	Recruiting	March 2026
Assessing the Efficacy of Sirolimus in Patients With COVID-19 Pneumonia for Prevention of Post-COVID Fibrosis (NCT04948203) Phase II and III randomised parallel assignment clinical trial	Primary outcomes: Prevalence of patients with >10% pulmonary fibrosis as evidenced by CT scan at 12 weeks	Recruiting	June 2024
PAxlovid loNg cOvid-19 pRevention triAl With recruitMent In the Community in Norway (PanoramicNOR) (NCT05852873) Phase III double-blinded placebo-controlled randomised clinical trial	Primary outcome: Symptoms of long-COVID [Time Frame: 3 months] (A dichotomous variable for presence of any of the three most important long-COVID symptoms: (i) fatigue, (ii) dyspnoea and (iii) cognitive symptoms (defined as memory and/or concentration problems)).	Not yet recruiting	May 2026

In addition to the above studies, the following review was identified relating to pharmacological treatment of long COVID:

Chee et al. J Med Virol. 2023;95:e28289
A systematic review of the current clinical trials considering pharmacological treatment of long-COVID, up to July 2022, being 6 published and 54 ongoing clinical trials. Many different interventions have been considered in this study including colchicine, montelukast, apixaban, atorvastatin, corticosteroids, human serum albumin, intranasal ivermectin, naltrexone and vitamin D (not an exclusive list). The authors categorised these studies by mechanism of action including chronic inflammation and endothelial dysfunction, activation of the coagulation system, chronic inflammation and pulmonary fibrosis, long COVID and the neurological and olfactory systems, repurposed nutraceuticals, and gut dysbiosis and probiotics.

APPENDICES

Appendix 1: Evidence

- Xie et al. 2023
- Bajema et al. [Preprint]. 2022
- Lasagna et al. 2023
- Bertuccio et al. 2023
- Boglione et al. 2022
- Nevalainen et al. 2022
- Jia et al. 2022
- Xie et al. 2023
- Bramante et al. 2022
- Chee et al. 2022

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities

HEALTH BENEFITS

- The health benefit to the person