Record of the COVID Treatments Advisory Group Meeting held on 30 May 2023

The role of Advisory Groups and records of meetings

Note that this document is not necessarily a complete record of the COVID Treatments Advisory Group meeting; only the relevant portions of the meeting record relating to COVID Treatments Advisory Group discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

The COVID Treatments Advisory Group may:

(a). recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule; or

(b). defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c). recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule; or

(d). recommend that Pharmac discontinue funding of a pharmaceutical currently on the Pharmaceutical Schedule.

Advisory Groups give advice to Pharmac, including recommendations', based on the Groups' different, if complementary, roles, expertise, experience, and perspectives. Recommendations made by the COVID-19 Treatments Advisory Group are in the context of COVID-19 treatments only. Pharmac is not bound to follow the recommendations made below.

The record of this Advisory Group meeting will be reviewed by PTAC at an upcoming meeting.

Excerpt from
Record of the COVID Treatments Advisory Group Meeting held on 30 May 2023

Attendance

Present

Chair – Dr Jane Thomas
Dr Ajay Makal
Professor Brian Anderson
Dr Gillian Hood
Dr Graham Mills
Dr Nigel Raymond
Dr Robyn Manuel
Professor Stephen Munn
Dr Tim Cutfield

Apologies

Eamon Duffy
Dr Justin Travers
Dr Kerry Benson-Cooper
Associate Professor Marius Rademaker

Long COVID

Application

1.1. The Advisory Group reviewed information on COVID-19 antivirals and other treatments for the treatment of long COVID.

1.2. The Advisory Group took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

1.3. The Advisory Group **deferred** its recommendation regarding long COVID treatments until further evidence is available.

1.4. The Advisory Group considered the following in making this recommendation:

- People with long COVID experience a decreased health-related quality of life and increased risk of death.
- The evidence to support the use of pharmaceutical treatments at the time of COVID-19 infection may result in lower incidence of long COVID, but, as yet, this evidence is limited.
- The evidence to support the use of currently available treatments to treat established long COVID symptoms is not yet available.

Discussion

Māori impact

1.5. The Advisory Group discussed the impact of funding treatments for long COVID on Māori health areas of focus and Māori health outcomes. The Group considered that limited local data suggests that long COVID symptoms may occur at similar frequency in Māori and non-Māori in New Zealand. The Group noted that the overall prevalence of long COVID in

New Zealand reported in the Ngā Kawekawe o Mate Korona study was higher than reported in epidemiological literature internationally and may be an overestimate due to a low response rate. The Group considered that Māori and younger people have higher incidences of COVID-19 infection, which is a pre-requisite for long COVID. The Group considered that there are likely to be disproportionately more long COVID cases in Māori, when taking into consideration the cumulative incidence of COVID-19 cases over time.

Background

1.6. The Advisory Group noted its previous consideration of long COVID at its February 2023 meeting:

1.6.1. The Group considered that effectiveness of treatments to reduce 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.

1.6.2. The Group considered that there are other respiratory infections that also have extended recuperation periods, particularly for people who have had severe illness. The Group considered that it is possible recuperation from COVID-19 infection may impact some people more than anticipated from other respiratory infections.

Health need

1.7. The Advisory Group considered that the definition of long COVID varied across different jurisdictions:

1.7.1. The Group noted the Ministry of Health - Manatū Hauora definition of long COVID in New Zealand is 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 (Ministry of Health. 2022. Wellington: Ministry of Health).

1.7.2. The Group noted that the World Health Organization (WHO) and the England/Wales National Institute of Clinical Excellence (NICE) definition of long COVID is *a post COVID-19 condition occurring in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis*.

1.7.3. The Group noted that the Centre for Disease Control and Prevention (CDC) in the United States has noted 'long COVID' is an umbrella term for a wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection.

1.8. The Advisory Group considered that long COVID symptoms are found in a variety of body systems including central nervous system, gastrointestinal tract, coagulation system, vascular (endothelial) system, reproductive system, and the kidneys, liver, and spleen.

1.9. The Advisory Group considered that the breadth of symptoms with long COVID is similar to chronic fatigue syndrome (CFS). The Group was aware of the reported experience of some people with long COVID that following exercise their health deteriorates. The Group noted that the treatment for CFS was delivered by a multi-disciplinary team to treat symptoms and increase exercise capacity.

1.10. The Advisory Group noted that people with long COVID experience decreased health-related quality of life (HRQoL) compared to people without long COVID when measured by SF-36 total scores (Líška et al. Front Public Health. 2022;10:975992). The Group

noted case-control evidence that compared those with post-COVID-19 condition (as per CDC definition) to those without COVID-19 infection, where there was a higher reported mortality at 12 months in those with a post-COVID-19 condition (DeVries et al. JAMA Health Forum. 2023;4:e230010).

1.11. The Advisory Group noted the reported results from the Ngā Kawekawe o Mate Korona study that of its 990 survey participants, 21.9% (n=217) met the WHO criteria for long COVID, including 33 Māori, four Pacific peoples, and 181 from other ethnic groups, reporting at least one symptom lasting three months or more (Russell et al. 2022. Wellington: Victoria University of Wellington).

1.11.1. The Group noted that overall, Pacific peoples participants were less likely to report symptoms lasting more than three months than Māori and other ethnic group participants, who were equally likely to report long-lasting symptoms.

1.11.2. The Group considered that the prevalence of long COVID in survey participants reported by Russell et al. was high compared with epidemiological estimates internationally. The Committee considered that anecdotal evidence from New Zealand clinicians suggests actual burden to be lower. Members considered this higher reported rate may have been due to either the high rate of re-infection observed in New Zealand, cases arising in the pre-Omicron era, or to distortion from the types of cases that responded. The Committee considered that the survey perhaps had inadvertently selected for cases with proportionately longer-lasting disease (where 990 people participated, but invitations were delivered to 8012 cases).

1.11.3. The Group considered that time since acute infection is an important factor to consider in the interpretation of these data, as over time symptoms of long COVID decrease (Mizrahi et al. BMJ. 2023; 380:e072529) and this is would affect the proportion of cases with long COVID stable over longer terms.

1.12. The Advisory Group considered that international evidence suggests that 10% of those previously infected with COVID-19 will experience long COVID. The Group considered that the prevalence of long COVID will likely wane over time (Mizrahi et al. 2023). Members considered that the burden of long COVID has been less than initially expected.

1.13. The Advisory Group noted that the LOGIC study had 6 weeks of consecutive follow up with 8 months and 15 months further follow up investigating the incidence of long COVID in New Zealand and that this is yet to be published.

1.14. The Advisory Group noted that it is reported that long COVID is less likely in those infected with Omicron compared with previous SARS-CoV-2 variants, and more likely in those who have had multiple COVID-19 infections compared to those having had only one infection (Thaweethai et al. JAMA. 2023;329:1934-64). The Group considered that those who are unvaccinated, have had severe or repeated COVID-19 infection or were infected with earlier variants of the virus (pre-Omicron) would be at higher risk of developing long COVID.

1.15. The Advisory Group noted that many New Zealanders had had at least one COVID-19 infection. The Group noted that Māori and Pacific peoples and younger people have higher incidences of COVID-19 infection, which is a pre-requisite for long COVID. The Group considered that limited local data indicates long COVID symptoms occur at similar frequency in each ethnic group in New Zealand, following each new COVID-19 infection. The Group considered that there are likely to be disproportionately more long COVID cases in Māori and Pacific peoples and younger people, when taking into consideration the cumulative incidence of COVID-19 cases over time.

1.16. The Advisory Group considered that the strength of the evidence for this health need to be high, and the quality of the evidence to be moderate.

Health benefit

1.17. The Advisory Group considered that there were some potential therapies for treatment and/or prevention of long COVID including COVID-19 antivirals (nirmatrelvir with ritonavir, molnupiravir or remdesivir), naltrexone, metformin, anti-coagulants, sulodexide and pycnogenol.

1.18. The Advisory Group noted evidence for use of nirmatrelvir with ritonavir during the acute phase of COVID-19 preventing long COVID:

1.18.1. The Group noted a retrospective cohort study that reported a decrease in the risk of developing post-COVID-19 when treated with nirmatrelvir compared to no treatment to day 180 (relative risk (RR) 0.74, 95% CI 0.72-0.77; absolute risk reduction (ARR) 4.51%, 95% CI 4.01-4.99) (Xie et al. JAMA Intern Med. 2023:e230743). The Group considered that the size of the population used (treatment group = 35,717; control group = 246,076) and the use of inverse probability weighted survival models meant that the risk of bias within this cohort study was reduced. The Group considered that the absolute risk reduction from treatment with nirmatrelvir (the 4.51%) was small, with a number needed to treat (NNT) of 22.

1.18.2. The Group noted the following studies related to the effectiveness of nirmatrelvir with ritonavir:

- Bajema et al. [Preprint]. 2022
- Lasagna et al. Cancers (Basel). 2023;15:1269
- Bertuccio et al. Infection. 2023:1–12

1.19. The Advisory Group noted evidence for use of remdesivir during the acute phase of COVID-19 preventing long COVID:

1.19.1. The Group noted a cohort study that reported a lower prevalence of long COVID syndrome in people previously hospitalised with COVID-19 who had been treated with remdesivir compared to those not treated (odds ratio (OR) = 0.64, 95% CI 0.41-0.78; *P*<0.001) (Boglione et al. QJM, 2022;114:865-71). The Group considered that multivariate analysis indicated that remdesivir patients were under-represented, suggesting an advantage of prior treatment. The Group considered that this study did not capture of all treated and untreated people to determine the differential prevalence of long COVID.

1.19.2. The Group noted the interim results of an open-label follow-up of a randomised trial that reported no difference between those treated with remdesivir and those not treated (RR 0.94, 95% CI 0.47-1.90), when considering potential long COVID symptoms (Nevalainen et al. Nat Commun.2022;13:6152). The Group considered that this suggested that remdesivir had no protective effect against developing long COVID.

1.19.3. The Group considered that these two reports were conflicting, but considered the methodology used by Nevalainen et al. was stronger.

1.20. The Advisory Group noted the evidence for the use of molnupiravir during the acute phase of COVID-19 preventing later long COVID:

1.20.1. The Group noted a cohort study that reported that the treatment of acute COVID-19 with molnupiravir and one risk factor for long COVID was associated with a reduced risk of long COVID (ARR 2.97%, 95% CI 2.31%-3.60%, NNT 34) (Xie et al. BMJ. 2023;381:e074572). The Group noted that the study included participants

treated in 2022 and 2023 and that around 13% were completely unvaccinated. The Group considered the use of accepted methodology (inverse probability weighting) reduced the risk of bias.

1.20.2. The Group noted an unpublished retrospective cohort study that reported that the molnupiravir treated group were more likely to require admission to hospital than controls, especially in the longer term. The Group noted that the study examined a variety of parameters at 6 months post-infection, including malaise and fatigue, and molnupiravir was not reported to be superior to no treatment (Bajema et al. [Preprint] 2022). The Group noted that the participants included in the study were mostly vaccinated (74%) and treated in 2022.

1.20.3. The Group considered that the reported findings from the above two studies were conflicting.

1.21. The Advisory Group considered that treatment with COVID-19 antivirals may reduce the likelihood of people developing long COVID, with nirmatrelvir with ritonavir appearing to have the strongest effect of the funded options. The Group considered that an improvement in HRQoL and reduction in excess mortality would be meaningful benefits in the treatment of long COVID.

1.22. The Advisory Group noted an unpublished randomised control trial assessing the use of early outpatient use of metformin, ivermectin or fluvoxamine, indicating that early use of metformin may prevent later long COVID (Bramante et al. medRxiv [Preprint]. 2022). The Group noted that participants were overweight or obese (median BMI = 29.8 kg/m^2 (Interquartile range (IQR) 27.0-34.2)). The Group considered there was a reasonable number of participants included in the metformin arm (n=564) and relevant control arm (n=561). The Group noted that by 300 days after randomisation there was a significant reduction in the risk of participants reporting themselves developing medically-diagnosed long COVID (hazard ratio (HR) 0.58 (95% CI 0.38-0.88); ARR 4.4% (95% CI 1.1% to 7.6%), NNT 23) when treated with metformin within 7 days' acute COVID-19 symptom onset. The Group considered that treatment with metformin during acute COVID-19 infection, in people who are overweight or obese, may reduce the likelihood developing long COVID. The Group considered that the biological plausibility was not clear but noted that the trial was limited to overweight or obese people.

1.23. The Advisory Group considered that the current evidence for use of COVID-19 antivirals is from retrospective cohort studies, there is biological plausibility for the use of these treatments to prevent long COVID, and nirmatrelvir with ritonavir may possibly be more effective than molnupiravir in preventing of long COVID.

1.24. The Advisory Group considered that further evidence from trials of other treatments (and some that are considered above) which are currently underway may offer other effective treatments for consideration in future. The Group considered however that at the current time these other treatments were not yet proven as treatments for long COVID.

1.24.1. The Group considered that trials of anti-coagulants were in people hospitalised for COVID-19 focussing on major coagulation events, such as deep vein thrombosis, pulmonary embolism or death and none of these trials (HEAL-COVID, ACTION or MICHELLE) evaluated (or prespecified they will evaluate) long COVID incidence. The Group noted a cohort study that assessed triple anti-platelet therapy in people with long COVID but considered the lack of untreated control group meant that understanding the natural history of long COVID symptoms and comparison between treated and untreated groups is more difficult. The Group considered that the evidence to support the use of anti-coagulants for long COVID is not sufficient.

1.24.2. The Group noted a study assessing the effect of pycnogenol on cardiovascular risk factors including endothelial function and microcirculation in people recovering from COVID-19 (Belcaro et al. Minerva Med. 2022;113:300-8). The Group noted

that the outcomes measured were all surrogate markers of cardiovascular risk, the quality-of-life measures including a Karnofsky Scale was statistically significant but overall, the data were low quality. The Group noted that this supplement is used in the treatment of CFS.

1.24.3. The Group considered that the off-label use of naltrexone or aripiprazole may be harmful due to known adverse effects and no published evidence supporting the use for long COVID.

1.25. The Advisory Group did not recommend pharmaceutical prophylaxis (including antivirals) to reduce the likelihood of developing long COVID based on the extent, strength and quality of available evidence, which the Group considered to be very early and confined to few clinical studies. The Group considered data that is robust, practice-changing and supported by international authorities would be helpful for the Group when considering again making any recommendations.