Record of the COVID Treatments Advisory Group Meeting held on 10 May 2022

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.

Attendance

Present
Chair – Dr Jane Thomas
Professor Brian Anderson
Eamon Dufy
Dr Gillian Hood
Dr Graham Mills
Dr Jessica Keepa
Dr Kerry Benson-Cooper
Associate Professor Marius Rademaker
Professor Stephen Munn
Dr Tim Cutfield

Apologies
Dr Justin Travers
Dr Nigel Raymond
Dr Robyn Manuel

1. Presentation of Auckland hospitalisation data from Dr Colin McArthur

Discussion

Acknowledgement

1.1. The Advisory Group acknowledged again the particular impact of COVID-19 on Māori and Pacific people, older people, people who are immunocompromised, people with premorbid conditions (eg. lung disease, diabetes, heart disease, etc), and/or disabled people.

Māori impact

1.2. The Advisory Group noted that Māori were 30% more likely to be hospitalised than non-Māori when adjusting for age and vaccination status. The Group noted that age was the major factor for determining risk of hospitalisation. The Group noted that two other important factors were vaccination status and ethnicity.

Discussion

1.3. The Advisory Group noted that Dr Colin McArthur is an intensive care specialist and head of research for critical care at Auckland Hospital. He presented data on the hospitalisation and intensive care admissions in Northern DHBs (Auckland, Waitemata, Counties Manukau and Northland DHBs).

1.4. The Advisory Group noted that the data compared hospitalisation and intensive care admissions against a COVID-19 case dataset including data on age band, New Zealand deprivation, ethnicity, vaccination status and gender. The Group noted that there were roughly 265,000 notified cases from 11 January to 6 April 2022. The Group noted the hospital admission dataset of 100,000 patients had 1978 admissions within 14 days of case notification or diagnosed on the day following admission so likely community

acquired infection. The Group noted that those identified as a hospitalised COVID-19 case were not able to be further stratified by whether cases were hospitalised for a COVID-19 related reason or unrelated reason. The Group noted it was assumed that the relative risks were not impacted by this. The Group noted that a multivariate logistic regression on age, vaccination status and ethnicity was used in the analysis.

1.5. The Advisory Group noted that the risk of hospitalisation increases with increasing age and strong risk factor after 60-65 years old when adjusted for ethnicity and vaccination status. The Group noted that the risk of hospitalisation is increased in unvaccinated and partly vaccinated individuals compared to those who have received 2 doses or more of vaccine when adjusted for age and ethnicity. The Group noted the lowest risk of hospitalisation was in those that had received a booster vaccination. The Group noted that the risk of hospitalisation was increased for Māori and Pacific peoples compared to non-Māori or Pacific peoples when adjusted for age and vaccination rate. The Group noted that the odds ratio for hospitalisation risk associated with age was higher than the influence of vaccination and ethnicity. However, the risk for those unvaccinated being hospitalised was still 5 times that of other vaccination statuses, and Pacific peoples and Māori were at 50% and 30% higher risk of hospitalisation from COVID-19 respectively when adjusting for age and vaccination status.

1.6. The Advisory Group considered the risk profiles of the groups and the application of these to the access criteria for giving those with the highest risk of hospitalisation (suggested as those with a risk of >10%) access to COVID-19 treatments. The Group noted that the influence of vaccination status was less impactful in those <40 years and >65 years suggesting that age is a more important risk factor for hospitalisations, followed by vaccination status. The Group noted that comorbidities were not reported on in this presentation. The Group noted that this would likely have an impact on the hospitalisation risk. The Group noted that distinction of these comorbidities would be important as not all comorbidities are at equal risk of hospitalisation from COVID-19.

1.7. The Advisory Group considered the impact of age being a risk factor for hospitalisation across all indications and the lack of clarity between admissions related to COVID-19- and admissions for other reasons where COVID-19 was only coincidental. The Group considered that this would be due to the lower threshold for admission of older people than younger people for physiological and social reasons. The Group considered that more older people would be hospitalised with COVID-19 without pneumonitis than younger people. The Group considered the impact of the treatments available on COVID-19 related admissions in older people to be unknown. The Group considered that the risk of hospitalisation and the risk of death would be similar, with similar risk factors, and that the impact of COVID-19 treatments on risk of death is also unknown.

1.8. The Advisory Group considered the potential impact of admission of less than 24 hours (very short admission) on risk and the definition of admission given a recent unpublished Northern Region Health Coordination Centre (NRHCC) report suggesting that a significant number of admissions were confined to overnight. The Group noted that this was taken into account by excluding those admissions that were less than 12 hours or until the next calendar day (considered to be observed and then discharged home) depending on the available data from each DHB. The Group noted that the total hospital

admissions (100,000) excluded short stays on this basis. The Group considered the impact of admissions and discharges based on capacity and stays under 24 hours could be substantial and that the reported risk of hospitalisation could not indicate this.

1.9. The Advisory Group considered it was important to have an adjusted ratio to determine cost-effectiveness of the treatments and the benefit of using COVID-19 treatments to prevent hospitalisation. The Group considered that it was likely that the community reported cases were lower than the actual number of community cases. The Group noted that although that was the case, only those with a positive test were able to access COVID-19 treatments so is likely reflective of those eligible for treatment.

1.10. The Advisory Group considered the inclusion of co-morbidities to be useful for assessing risk profile of patients. The Group noted that this was not assessed in the analysis but that the assumption that comorbidities could be broken down into none, one, two or 3 and over co-morbidities and risk increases as number of co-morbidities increase.

2. Treatments for persistent/relapsing SARS-CoV-2 infection

Application

2.1. The Advisory Group considered information regarding the use of treatments for COVID-19 in the treatment of persistent/relapsing SARS-CoV-2 infection.

Recommendation

2.2. The Advisory Group considered information regarding the use of treatments for COVID-19 in the treatment of persistent/relapsing SARS-CoV-2 infection.

Initial Application – (treatment of persistent SARS-CoV-2 infection)
Any relevant practitioner. Approvals valid for 1 week for all applications meeting the following criteria:
All of the following:

1. Patient has evidence of persistent SARS-CoV-2 infection (≥20 days); and
2. Patient is immunocompromised; and
3. Patient is not expected to mount an adequate immune response to SARS-CoV-2 infection, regardless of vaccination status; or has confirmed deficiency of a (neutralising) serological response; and
4. A multidisciplinary team (including an infectious disease physician) considers the treatment to be appropriate

2.3. The Advisory Group recommended that the above access criteria be included for all treatments funded for COVID-19 to allow them to be used if required in the treatment of persistent SARS-CoV-2 infection.

Discussion

2.4. The Advisory Group noted that persistent SARS-CoV-2 infection is rare amongst people infected with COVID-19 however, it can be a complication amongst the extremely immunocompromised, particularly people with B-cell depletion.

2.5. The Advisory Group noted that the availability of evidence for the treatment of persistent/remitting SARS-CoV-2 infection is limited because cases are rare.

2.6. The Advisory Group considered available clinical evidence for the treatment of people with persistent/remitting SARS-CoV-2 infection.

2.7. The Advisory Group noted a case report Choi B et al N Engl J Med 2020. The authors reported that although most immunocompromised people effectively clear SARS-CoV-2 infection there is the potential for persistent infection and accelerated viral evolution associated with an immunocompromised state.

2.8. The Advisory Group noted a case report Avanzato VA et al. Cell. 2020. regarding an immunocompromised individual with chronic lymphocytic leukaemia and acquired hypogammaglobulinemia infected with SARS-CoV-2. The authors reported that the patient remained infectious for 70 days following initial diagnosis.

2.8.1. The Advisory Group noted that the patient did not appear to benefit from intravenous immunoglobulin therapy (IVIG) but did appear to clear SARS-CoV-2 infection following two doses of convalescent plasma, with a demonstrable increase in anti- SARS-CoV-2 antibodies.

2.9. The Advisory Group noted a case report Buckland MS et al. Nat Commun. 2020. Regarding a patient with COVID-19 and the prototypic genetic antibody deficiency X-linked agammaglobulinaemia who, despite evidence of complement activation and a robust T cell response, developed persistent SARS-CoV-2 pneumonitis, without progressing to multi-organ involvement. The authors reported that the patient had an initial clinical improvement following treatment with remdesivir but was unable to clear the virus. The authors concluded that re-treatment with remdesivir, followed by two doses of convalescent plasma resulted in the SARS-CoV-2 infection being cleared.

2.10. The Advisory Group noted a preprint case report publication Nussenblatt V et al. medRxiv; 2021. regarding persistent/remitting SARS-CoV-2 infection in a patient with post-treatment B-cell aplasia. The authors reported that the patient remained infected with SARS-CoV-2 for 355 days and SARS-CoV-2 infection was cleared following treatment with remdesivir and high-titre convalescent plasma.

2.11. The Advisory Group noted a retrospective cohort study Pommeret F et al. Ann Oncol. 2021 involving patients with SARS-CoV-2 immune escape mutations and secondary clinical deterioration in COVID-19 patients with B-cell malignancies. 34 cancer patients presenting with a mild to moderate COVID-19 were treated with bamlanivimab with etesevimab within five days of symptom onset. The authors reported that patients with B-cell malignancies (n = 5, 15%) displayed a worse clinical evolution, with delayed COVID-19 symptoms from day 14 to day 30 following treatment with bamlanivimab with etesevimab All of the patients with B-cell malignancies required hospitalisation after day 14. Four of the patients cleared SARS-CoV-2 infection following treatment with convalescent plasma and one patient died.

2.11.1. The Advisory Group noted that bamlanivimab with etesevimab is not available for use in the treatment of COVID-19 in New Zealand and supply is not currently being sourced by Pharmac.

2.12. The Advisory Group considered that the authors conclusions suggest that patients with B-cell malignancy may be particularly at risk of developing viral escape variants that result in persistent, post-treatment SARS-CoV-2 infection.

2.13. The Advisory Group noted correspondence published in April 2022 Rockett R, et al. N Engl J Med. 2022 regarding the development of resistance mutations in patients with the Delta variant of SARS-CoV-2 treated with sotrovimab. The authors noted that of the first 100 consecutive patients to receive sotrovimab at health care facilities in the Western Sydney between August and November 2021, 23 patients were identified with persistent SARS-CoV-2 infection following treatment with sotrovimab. Of these 23 patients, respiratory tract specimens pre-and post-sotrovimab treatment were available for eight patients, nearly all of these patients being immune compromised. The authors reported that all but one of the patients developed the S:E340K mutation, which has previously demonstrated the highest resistance to sotrovimab, and noted that mutations generally increased over the course of infection. Patients remained infectious for 14-40 days after treatment with sotrovimab.

2.14. The Advisory Group considered results of a national survey of clinicians in the United Kingdom treating people with persistent/remitting SARS-CoV-2 infection, which was defined as individuals with at least 21 days duration of clinical illness and/or at least 2 episodes of clinical illness.

2.14.1. The Advisory Group noted that the most common issue amongst patients with persistent/remitting SARS-CoV-2 infection was B-cell depletion, as a result of a number of primary and secondary causes, most commonly anti-CD20 therapy.

2.14.2. The Advisory Group noted that the median duration of illness per patient at time of the survey was 64 days, with a maximum recorded illness duration of 300 days.

2.14.3. The Advisory Group noted the results of the survey which indicated that those people who had received combination therapy such as anti-SARS-COV 2 antibodies in addition to antiviral treatments were more likely to clear persistent/remitting SARS-CoV-2 infection than antiviral therapy alone.

2.15. On balance of the available evidence, the Advisory Group considered it was likely that patients with persistent/remitting SARS-CoV-2 infection would require multiple (combined and/or sequential) treatments for COVID-19, such as an antibody treatment in combination with antiviral treatments, and in some instances may require increased dosing or treatment duration, compared to those with more mild or moderate disease.

2.16. The Advisory Group considered that the various treatments that had been funded for COVID-19 in New Zealand were not interchangeable and it would be important for any criteria to enable clinicians to choose the most appropriate treatments available for their patient and the variant of SARS-CoV-2 being treated.

2.17. Noting information provided in the Auckland Regional guidance, the Advisory Group considered that within New Zealand patient groups at high risk of persistent SARS-CoV-19 infection were likely to include:

- anti-CD20 monoclonal antibody therapy (eg rituximab) within the past 6 months.

- treated B-cell haematologic malignancy (eg multiple myeloma, chronic lymphocytic leukaemia, lymphoma) within the past 6 months.
- primary or acquired hypogammaglobulinaemia (IgG <3), even if on replacement immunoglobulin.
- primary immunodeficiency associated with severe B-cell or combined cellular defects.
- solid organ transplant, haematopoietic stem cell transplant, or CAR-T cell therapy within the past 6 months
- graft-versus-host disease currently treated with multi-modal immunosuppressive therapy
- advanced HIV with CD4 <200
- other conditions associated with profound immunocompromise based on combined immunosuppression, functionally equivalent to the above groups.

2.18. The Advisory Group considered that it was difficult to predict the number of people in New Zealand who may require treatment for persistent/remitting SARS-CoV-2 infection. Members noted that in the Auckland region approximately 30 people had been treated so far and suggested nationally there may be between 100 and 200 peopled requiring treatment over a year.

2.19. The Advisory Group considered that cases of persistent/remitting SARS-CoV-2 infection are likely to be complex and would require specialist multidisciplinary teams led from within hospitals to manage them. The Advisory Group considered it was unlikely that these cases could be managed in a primary care setting.

2.20. Noting the likely complexity of patients with persistent/remitting SARS-CoV-2 infection, the Advisory Group considered that it would be important for guidance to be available to multidisciplinary teams.

2.21. The Advisory Group considered that of the COVID-19 antiviral treatments that are currently available, remdesivir would likely be the most preferred, noting its use in the treatment of patients with persistent/remitting SARS-CoV-2 infection internationally. The Group considered molnupiravir would be the least preferred, noting its reduced efficacy in the treatment of COVID-19 compared to the other antiviral treatments currently available.

2.22. The Advisory Group noted that there were currently no monoclonal antibody treatments available in New Zealand effective against the dominant variant of SARS-CoV-2 currently (at the time of the meeting) (Omicron BA.2), however high-titre convalescent plasma was available from the New Zealand Blood Bank and had been used to successfully treat patients with persistent/remitting SARS-CoV-2 infection.

2.23. The Advisory Group noted that tixagevimab with cilgavimab is expected to be available in the New Zealand in the coming months. Noting that this treatment appears to be effective against the BA.2 Omicron subvariant of SARS-CoV-2, the Advisory Group considered that once it becomes available tixagevimab with cilgavimab may be preferred rather than convalescent plasma for these patients.

3. Efficacy of antibodies and antivirals against SARS-CoV-2 variants

Application

3.1. The Advisory Group reviewed the efficacy of antibodies and antivirals against SARS-CoV-2 variants.

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

3.3. The Advisory Group noted that, for the purposes of this discussion, the efficacy of tocilizumab or baricitinib against SARS-CoV-2 variants will not be considered, as these agents do not have direct activity against the virus.

Recommendation

3.4. The Advisory Group considered:

- The overall available evidence for antibody and antiviral treatments for SARS-CoV-2 variants is limited to in vitro or in vivo in animal models or early pre-print research, with no clinical studies to date for the Omicron BA.2 variant.
- Antiviral treatments are likely to continue to remain active with current and future variants of SARS-CoV-2.
- Monoclonal antibody treatments are likely to continue to have a limited role with future variants of SARS-CoV-2, however, individual monoclonal antibodies may be useful in targeted situations for small high-risk populations.

Discussion

Background

3.5. The Advisory Group noted that since the initial outbreak of SARS-CoV-2, a number of variants have emerged with different infectivity profiles, clinical characteristics, and sensitivity to treatments. The Advisory Group noted that currently the BA.2 subvariant of Omicron is the dominant strain of SARS-CoV-2 in New Zealand, and there is growing evidence to suggest some treatments may not be effective against Omicron BA.2. It was noted that this is of particular concern for antibody treatments as these generally target the spike protein, which is highly susceptible to mutation (Omicron BA.1 has 37 spike mutations; Omicron BA.2 has 31).

3.6. The Advisory Group noted the eight pharmaceuticals that have to date been funded explicitly for the treatment of SARS-CoV-2 in New Zealand (New Zealand's COVID-19 Treatments Portfolio).

Discussion

3.7. The Advisory Group noted the following evidence on the efficacy of antibodies and antivirals against SARS-CoV-2 variants:

3.7.1. An *in vitro* study of the efficacy of antibodies and antiviral drugs against SARS-CoV-2 variants (Takashita et al. N Engl J Med. 2022;386:995-8; Takashita et al.

N Engl J Med. 2022;386:1475-7). The Advisory Group noted that the results suggested casirivimab plus imdevimab (Ronapreve) lost inhibitory capability against Omicron B.1.1.529 but did inhibit Omicron BA.2. It was noted that tixagevimab with cilgavimab (Evusheld) inhibited Omicron B.1.1.529 and BA.2, but with a FRNT50 (the titre of monoclonal antibodies required for a 50% reduction in the number of infectious foci) substantially higher than for Beta or Gamma variants. It was noted that sotrovimab inhibited Omicron B.1.1.529, but with a FRNT50 substantially higher than for Beta or Gamma variants and had lower neutralizing activity for BA.2. It was also noted that the susceptibility of Omicron B.1.1.529 to remdesivir (Veklury) and molnupiravir (Lageviro) was similar to older variants, and that the susceptibility of Omicron BA.2 to remdesivir, molnupiravir, and nirmatrelvir was similar to older variants.

3.7.2. An *in vitro* study of the antiviral activity of remdesivir, molnupiravir, and nirmatrelvir against SARS-CoV-2 variants of concern (prior to BA.2) (Vangeel et al. Antivral Res. 2022;198:105252). The Advisory Group noted that the results suggested all agents had equipotent antiviral activity against the ancestral virus and the Alpha, Beta, Gamma, Delta, and Omicron variants. It was noted that the authors concluded that the target proteins of these antivirals are highly conserved, and that there is a high probability that new variants of concern will remain sensitive to these antiviral agents.

3.7.3. An *in vitro* study of the antigenic properties of Omicron BA.1 and BA.2, including analysis of the neutralising ability of 19 monoclonal antibodies (Iketani et al. Nature. 2022;604:553-6). The Advisory Group noted that the results showed BA.2 exhibited marked resistance to 17 of 19 antibodies tested, including sotrovimab, which retained activity against BA.1 and BA.1+R346K, but its activity against BA.2 dropped 27-fold. It was noted that tixagevimab with cilgavimab retained activity against BA.2, and that only bebtelovimab had adequate activity against all sublineages of Omicron tested.

3.7.4. A study that evaluated the sensitivity of BA.1 and BA.2 isolates to nine therapeutic antibodies *in vitro* and then directly measure the neutralising activity of the antibodies in sera from 29 immunocompromised individuals who had received casirivimab plus imdevimab and/or tixagevimab with cilgavimab (Bruel et al. Nat Med. 2022; doi: 10.1038/s41591-022-01792-5. Online ahead of print). The Advisory Group noted that bamlanivimab, etesevimab, casirivimab, sotrovimab, adintrevimab, regdanvimab and tixagevimab were inactive against BA.2. It was noted that BA.2 was sensitive to cilgavimab and partly inhibited by imdevimab, and that the combination of tixagevimab with cilgavimab was not more effective than cilgavimab alone. It was noted that sera from casirivimab with imdevimab recipients did not neutralize BA.1 and poorly neutralised BA.2. It was noted that neutralisation of BA.1 and BA.2 was detected in 19 and 29 out of 29 tixagevimab with cilgavimab recipients, respectively. It was noted that four breakthrough Omicron infections were reported among the 29 individuals, suggesting antibody treatment did not fully prevent infection.

3.7.5. A study that evaluated the *in vitro* catalytic activity and potency of nirmatrelvir against the main protease of prevalent variants of concern/interest: Alpha, Beta, Delta, Gamma, Lambda, Omicron, as well as the original Washington or wildtype strain (Greasley et al. J Biol Chem. 2022;298:101972). The results suggest that nirmatrelvir plus ritonavir (Paxlovid) has the potential to maintain plasma concentrations of nirmatrelvir many-fold times higher than the amount required to stop the SARS-CoV-2 variants of concern/interest, including Omicron, from replicating in cells.

3.7.6. A pre-print study that assessed the efficacy of molnupiravir against the earlier Alpha, Beta and Delta variants of concern and Omicron in the Syrian hamster COVID-19 model (Rosenke et al. bioRxiv [preprint]. 2022). The data suggests that molnupiravir treatment inhibits virus replication in the lungs and upper and lower respiratory tract.

3.8. The Advisory Group also noted that recent data suggest the emergence of several Omicron subvariants which may have a growth advantage over BA.2. The Advisory Group noted that Ministry of Health SARS-CoV-2 Variants update, published 27 April 2022 provides an overview of recent identified Omicron sub-variants, and that BA.4 and BA.5 are thought to have some growth advantage over BA.2. It was noted that reports from South Africa indicate BA.4 and BA.5 are becoming predominant (Tegally et al. Medrxiv [preprint]; 2 May 2022), and that the BA.4 variant has recently been detected in New Zealand. The Advisory Group noted that preliminary data suggests BA.4 and BA.5 may partially evade Omicron BA.1 infection generated immunity and exhibit stronger neutralization escape form the plasma of 3-dose COVID-19 vaccinees (Khan et al. bioRxiv [preprint]; 1 May 2022; Cao et al. bioRxiv [preprint]; 2 May 2022). The Advisory Group also considered the importance of regularly reviewing the Living guidance for clinical management of COVID-19 (World Health Organization) for the most current information on treatment guidelines for variants of concern.

3.9. The Advisory Group considered that the evidence for available treatments with new variants is currently limited to in vitro or *in vivo* studies using animal models or early pre-print research, with no clinical studies were identified for the BA.2 variant. It was considered however that the strength of evidence is good and that there is consistency throughout the evidence provided. The Advisory Group also considered that the total number needed to treat to prevent one hospitalisation or death increases as variants with a lower risk of severe disease emerge. The Advisory Group considered the cost effectiveness of monoclonal antibodies in low-risk groups is unfavourable and that such treatments would be more appropriate for use in the immunocompromised population, depending on the variant of concern.

3.10. The Advisory Group considered that monoclonal antibody treatments including casirivimab plus imdevimab, cilgavimab, and sotrovimab have reduced activity against BA.1 and BA.2 in community prevention of severe disease. Members considered that cilgavimab and bebtelovimab retain activity against BA.2, and also have activity against BA.4 and BA.5. Given the trend of BA.4 and BA.5 variants reported in South Africa, Members considered that it may be beneficial to retain use of such monoclonal antibodies in the immunocompromised population. Overall, the Advisory Group

considered is likely that the monoclonal antibody treatments would continue to have a limited role with future variants of SARS-CoV-2, however, may be useful in targeted situations for small high-risk populations.

3.11. The Advisory Group considered that antiviral treatments including nirmatrelvir plus ritonavir, remdesivir, and molnupiravir retained activity against BA.1 and BA.2. The Advisory Group considered that antiviral treatments are likely to remain active with current and future variants of SAR-CoV-2 given they target proteins which are well preserved. The Advisory Group considered antiviral treatments are appropriate for use in the general population. The Advisory Group considered there are a number of candidate anti-viral treatments under development, however that the evidence is in this area is limited.

4. Future planning for the next SARS-CoV-2 infection wave

Application

4.1. The Advisory Group reviewed presented information relating to future planning for the potential next wave of SARS-CoV-2 infection.

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

Discussion

Māori impact

4.3. The Advisory Group noted that the risk of hospitalisation for Māori was higher than that of non-Māori. The Group considered that under the current access criteria eligible population groups were not accessing the treatments at rates that could be expected based on available data.

4.4. The Advisory Group noted that access for Māori is lower than expected and noted the challenges in facilitating access for Māori. The Group noted feedback received by Pharmac that the updated access criteria disadvantaged Māori and Pacific peoples in younger age groups compared to older people (of all ethnicities). The Group considered the current access criteria for COVID-19 treatments targeted the correct group of people at high risk of hospitalisation following SARS-CoV-2 infection and considered and that the distribution mechanisms for the treatments were impacting access and update.

Discussion

4.5. The Advisory Group noted an analysis of the first wave of SARS-CoV-2 infections. The Group noted that by 27 February 2022, during the COVID-19 Omicron variant wave, the number of new cases had increased each day over the previous 7 days across the country and in the Auckland region there had been an increase in the number of COVID-19 positive hospital admissions. The Group noted that this point was 9 days before the number of new cases peaked and the 12 days before number of active cases peaked and 2 to 3 weeks until COVID-19 positive hospital admissions peaked.

4.6. The Advisory Group noted that between August 2021 and March 2022 there were 779,608 cases and 6,270 hospital admissions. The Group noted that those who were unvaccinated were admitted at a rate of 3,354 per 100,000 cases compared to partially vaccinated 2,536 per 100,000 cases, fully vaccinated 752 per 100,000 and boosted 660 per 100,000 as reported by the Ministry of Health at the time.

4.7. The Advisory Group noted British Columbia (BC) data on Omicron admissions from December 2021 to late January 2022. The Group noted that the risk of hospitalisation was associated with increasing age and increasing comorbidities and completion of the primary course of vaccination was reported to be protective against hospitalisation. The Group noted that, when using the BC data as a model for New Zealand, the estimate for the population of people eligible for antiviral treatment if access was widened to those with an admission risk >10% would be 300,000 people and >5% admission risk would be an estimated 415,000 people. The Group noted that these estimates incorporated comorbidity and ethnicity data from Pinnacle PHO, where 447,000 patients are enrolled.

4.8. The Advisory Group noted that at this time there were 120,000 antiviral courses available for use. The Group noted that Pharmac staff estimated the Number Needed to Treat (NNT) for those with a 10% risk of admission was 11 for nirmatrelvir with ritonavir and 33 for molnupiravir, for those with a 5% risk of admission was 22 for nirmatrelvir with ritonavir and 66 for molnupiravir, and a 2.5% risk of mortality was 66 for nirmatrelvir with ritonavir and 132 for molnupiravir.

4.9. The Advisory Group considered the difference between a surge in the number of cases and a change in severity of disease. The Group considered that the risk of hospital admission would remain the same in a surge of cases and a proportional increase in the number of people requiring COVID-19 treatments relative to the size of the surge would be expected.

4.10. The Advisory Group considered that a change in severity could be measured as the proportion of ICU admissions compared to cases, as a surrogate marker. The Group considered this would be an appropriate indicator signalling a need to reconsider the access criteria. The Group considered that in the case of a change in severity the NNT may also change, decreasing as severity increased and increasing as severity decreased.

4.11. The Advisory Group considered that increasing access to treatments without evidence of benefit is unlikely to improve hospitalisation rates and that treatments are not without potential harm or risk. The Group considered the current access criteria to be appropriate in the context of New Zealand's current COVID-19 environment and if there was a change in severity or surge that they could reconsidered the criteria at that point.

4.12. The Advisory Group noted data from Waikato hospital outlining the proportion of those presenting to the emergency department (ED) stratified by age from March 2022 to May 2022. The Group noted that during times of surge, children presenting to ED as COVID-19 positive peaked while older people was much lower and remained stable regardless of the peak in new or active cases. The Group considered that the trend of increasing cases may not affect older people and those affected by the peaks are more likely to be younger. The Group considered there could be benefits from treatment in the older

person group as the impact of the pandemic in this group has been extended for a longer time compared with other age groups.

4.13. The Advisory Group noted that national data from February 2022 to April 2022 showed an initial surge in those aged 10 to 29 years then reducing with a smaller peak in cases in those 30 to 40 years (Ministry of Health 2022). The Group considered the data needed to be carefully interpreted as the data was presented as percentages of total cases not absolute number of cases. The Advisory Group considered the estimated proportion of the population who had had COVID-19 at the time of the meeting and noted that there was still a significant proportion of the population who could be infected with COVID-19 which could prolong the pandemic.

4.14. The Advisory Group considered that evidence for efficacy of COVID-19 antivirals in older people and against Omicron variants was lacking. The Group considered that evidence-based treatment was preferred as the NNT should be kept low to moderate, and that evidence for use is not strong if extending treatment to lower risk groups. The Group noted that the NNT decreased as the risk of hospitalisation increased, and again that people with a 5-10% risk of COVID-related hospital admission would have a corresponding estimated NNT of 11-22 for that outcome if they were treated with nirmatrelvir with ritonavir. The Group considered this scale of NNT to probably be the upper limit reasonable, given the incremental health gains versus relative broad costs of treatment in this setting.

4.14.1. The Group considered that the clinical severity of circulating variants' COVID-19 disease would affect the baseline rate of hospitalisation and therefore proportionally the NNT; and that as such the NNT would depend in part on age, COVID-19 vaccination status, ethnicity, immunocompromise, and co-morbidity.

4.15. The Advisory Group noted feedback received by Pharmac that the updated access criteria was disadvantaging Māori and Pacific peoples in younger age groups compared to older people (of all ethnicities). The Group considered that these treatments had the potential to harm and there was risk to the individual in terms of side effects and, in the case of nirmatrelvir with ritonavir, potential for a person's regular medicines to be interrupted or drug-drug interactions causing negative outcomes.

4.16. The Advisory Group considered the emerging evidence about prolonged viral shedding with nirmatrelvir with ritonavir and the impact of this on the spread of COVID-19 to others. The Group considered the impact of COVID-19 on hospital services and staffing to be important because higher COVID-19 hospitalisations cause resources to be diverted as well as absence of staff members with COVID-19 delaying normal services. The Group considered that although this was not able to be included in a NNT it was a major consideration when hospitalisation is the preventable outcome.

4.17. The Advisory Group considered that treatment for COVID-19 is best given as promptly as possible for the best efficacy and that this presents challenges for equitable delivery and administration of COVID-19 in New Zealand, and particularly for oral antiviral treatments which are available in the community and have a reduced window for administration compared to other treatments. The Group also considered that in the case of a vaccine resistant strain of SARS-CoV-2 treatments would need to be easily available to those at

high risk. The Group considered the current access criteria for COVID-19 treatments was targeting the appropriate group of people at high risk of hospitalisation and severe illness following SARS-CoV-2 infection and that the distribution mechanisms for treatments may be negatively affecting access and uptake.

Correspondence & matters arising

5. Inpatient use of remdesivir discussion (SOLIDARITY trial results)

Recommendation

5.1. The Advisory Group recommended that remdesivir be funded for treatment of COVID-19 subject to the following access criteria:

Access criteria – from any relevant practitioner.
Approvals are valid for patients where the prescribing clinician 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. ANY of the following:
    - 3.1. The patient meets ONE of the following:
        - 3.1.1. 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
        - 3.1.2. Patient has Down syndrome; or
        - 3.1.3. Patient has sickle cell disease; or
        - 3.1.4. Patient has had a previous admission to ICU directly as a result of COVID-19; or
        - 3.1.5. Patient is aged 75 years or over; or
    - 3.2. Patient is of Māori or Pacific ethnicity and has at least FOUR of the following factors:
        - 3.2.1. Any combination of high-risk medical conditions for severe illness from COVID-19 identified by the Ministry of Health** (with each individual condition counting as one factor)
        - 3.2.2. Patient is under the age of 50 and has not completed their primary course^ of vaccination (counts as one factor)
        - 3.2.3. Patient is aged between 50 and 64 years (counts as one factor, or four if patient has not completed a primary course^ of vaccination)
        - 3.2.4. Patient is aged between 65 and 74 years (counts as two factors, or four if patient has not completed a primary course^ of vaccination); or
    - 3.3. Patient is of another ethnicity and has at least FIVE of the following factors:
        - 3.3.1. Any combination of high-risk medical conditions for severe illness from COVID-19 identified by the Ministry of Health** (with each individual condition counting as one factor)
        - 3.3.2. Patient is under the age of 50 and has not completed their primary course^ of vaccination (counts as one factor)
        - 3.3.3. Patient is aged between 50 and 64 years (counts as one factor, or two if patient has not completed a primary course^ of vaccination)
        - 3.3.4. Patient is aged between 65 and 74 years (counts as two factors, or five if patient has not completed a primary course^ of vaccination); and
4. Not to be used in conjunction with other COVID-19 antiviral treatments.

5.2. The Advisory Group **recommended** that remdesivir be funded for treatment of COVID-19 subject to the following Access Criteria for Section H of the Pharmaceutical Schedule:

Initiation – COVID-19 in hospitalised patients
Therapy limited to 5 doses
All of the following:
1 Patient is hospitalised with confirmed (or probable) symptomatic COVID-19; and

2 Patient is considered to be at high risk of progression to severe disease; and
3 Patient's symptoms started within the last 7 days; and
4 Patient does not require, or is not expected to require, mechanical ventilation; and
5 Not to be used in conjunction with other funded COVID-19 antiviral treatments; and
6 Treatment not to exceed five days.

5.3. In making this recommendation, the Advisory Group considered the moderate strength, moderate quality evidence that remdesivir provides a significant health benefit to those with COVID-19 requiring supplemental oxygen.

Discussion

5.4. The Advisory Group noted that remdesivir has been available for use in New Zealand since September 2020, and that remdesivir access criteria were recently aligned (5 May 2022) with the oral antiviral access criteria.

5.5. The Advisory Group reviewed the final results of the SOLIDARITY trial and meta-analyses of mortality in all relevant trials to date (WHO Solidarity Trial Consortium. Lancet 2022;399:1941-53). The Advisory Group noted that the SOLIDARITY trial was a large, simple, international, open-label, randomised trial which previously reported the interim mortality analyses of four repurposed antiviral drugs in 14,221 adults recently hospitalised with COVID-19. It was noted that hydroxychloroquine, lopinavir, and interferon (IFN)-β1a were discontinued for futility but randomisation to remdesivir continued.

5.6. The Advisory Group noted that the deaths reported in the SOLIDARITY trial in those assigned to remdesivir and those assigned to the control group was 42.1% versus 38.6% in those already ventilated (mortality rate ratio [RR] 1.13, CI 0.89 to 1.42, *P*=0.32), 14.6% versus 16.3% in those not ventilated but on oxygen (RR 0.87, CI 0.76 to 0.99, *P*=0.03), and 2.9% versus 3.8% in those not on oxygen initially (RR 0.76, CI 0.46 to 1.28, *P*=0.30), respectively. It was noted that the non-prespecified composite outcome of death or progression to ventilation occurred in 19.6% versus 22.5% participants (RR 0.84, CI 0.75 to 0.93, *P*=0.001), respectively. The Advisory Group noted that a meta-analysis of mortality in all randomised trials to date of remdesivir versus no remdesivir was also conducted.

5.7. The Advisory Group noted that SOLIDARITY alone, as well as the meta-analyses of all trials, suggest no mortality reduction in already-ventilated patients, but some mortality reduction in patients who are receiving oxygen but are not ventilated.

5.8. The Advisory Group considered that the evidence provided demonstrates that remdesivir offers a modest health benefit for those with COVID-19 who are receiving oxygen, and an insignificant health benefit in those on ventilation. The Advisory Group considered the reduction in the composite endpoint of death or progression to ventilation in those treated with remdesivir represents a meaningful outcome due to the impact it has on those with COVID-19, their family/whānau, and the wider health system. It was considered that remdesivir is not appropriate for use in those with COVID-19 on ventilation in an ICU setting, noting its primary mechanism involves reduction of viral load in the early stages of disease with minimal impact on the inflammatory response. The Advisory Group also considered that it was unclear which day in the course of infection that remdesivir treatment was initiated in trial participants.

5.9. The Advisory Group considered that there is an unmet need in those hospitalised with COVID-19 who have not previously received antiviral treatment and/or require supplemental oxygen. It was considered that those requiring oxygen account for a large proportion of those hospitalised for COVID-19, and that the health benefit of remdesivir in this population group should be considered in current Access Criteria for remdesivir. The Advisory Group therefore considered it appropriate to create additional Access Criteria for remdesivir in Section H of the Pharmaceutical Schedule which does not include the current access criterion "patient does not require supplemental oxygen" to allow for use in this population. The Advisory Group considered that if funded access to remdesivir were to be widened, the number of those eligible for treatment would be expected to increase but not significantly.

6. Baricitinib/tocilizumab combined use (RECOVERY trial)

Recommendation

6.1. The Advisory Group **recommended** that baricitinib be funded for moderate to severe COVID-19 subject to the following Access Criteria:

> **Initial Application – moderate to severe COVID-19**
> Re-assessment required after 14 days
> Prerequisites:
> 1. Patient has confirmed (or probable) COVID-19; and
> 2. Oxygen saturation of < 92% on room air, or requiring supplemental oxygen; and
> 3. Patient is receiving adjunct systemic corticosteroids, or systemic corticosteroids are contraindicated; and
> 4. Baricitinib is to be administered at doses no greater than 4 mg daily for up to 14 days

6.2. The Advisory Group **recommended** that tocilizumab be funded for moderate to severe COVID-19 subject to the following Access Criteria:

> **Initial Application** – **moderate to severe COVID-19**
> *Section B requirements: Applications from any relevant practitioner. Approvals valid for 4 weeks.*
> *Section H requirements: Re-assessment required after 1 dose*
> *Prerequisites*:
> 1. Patient has confirmed (or probable) COVID-19; and
> 2. Oxygen saturation of < 92% on room air, or requiring supplemental oxygen; and
> 3. Patient is receiving adjunct systemic corticosteroids, or systemic corticosteroids are contraindicated; and
> 4. Tocilizumab is to be administered at doses no greater than 8 mg/kg IV for a maximum of one dose

6.3. In making these recommendations, the Advisory Group considered the good strength, moderate quality evidence that the combined use of baricitinib and tocilizumab may provide an additional health benefit for those with moderate to severe COVID-19.

Discussion

6.4. The Advisory Group noted that current hospital access criteria for tocilizumab and baricitinib exclude the combined use of these treatments.

6.5. The Advisory Group reviewed results from the RECOVERY trial, a randomised, controlled, open-label, platform form and updated meta-analysis evaluating the use of baricitinib in 8156 patients hospitalised for COVID-19 (Horby et al. MedRxIV [preprint] March 2022). The Advisory Group noted that patients were randomly allocated to receive standard care plus baricitinib administered 4 mg once daily by mouth for 10 days or until discharge if sooner (n=4148) versus standard care alone (n=4008). It was noted that at randomisation, 95% of patients were receiving a corticosteroid such as dexamethasone, 23% were receiving tocilizumab, and 20% were receiving the antiviral drug remdesivir.

6.6. The Advisory Group noted the RECOVERY trial reported that 12% of those allocated to baricitinib versus 14% of those receiving standard care alone died within 28 days; a reduction of 13% (age-adjusted rate ratio 0.87; 95% confidence interval [CI] 0.77 to 0.98; *P*=0.026). The Advisory Group noted that including the results from RECOVERY into an updated meta-analysis of all 9 completed trials (involving 11,888 randomised patients and 1484 deaths), allocation to baricitinib or other JAK inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0.80; 95% CI 0.71 to 0.89; *P*<0.001).

6.7. The Advisory Group noted that baricitinib was found to reduce deaths significantly, however that the size of benefit was somewhat smaller than that suggested by previous trials. The Advisory Group considered that the combined use of baricitinib and tocilizumab may provide an additional health benefit to those with moderate to severe COVID-19 and does not appear to be harmful. The Advisory Group therefore considered it appropriate to amend the Access Criteria to widen funded access of baricitinib and tocilizumab to allow for combined use for treatment of moderate to severe COVID-19 where appropriate.