Document 6

Briefing

Rapid Review of COVID-19 Antiviral Effectiveness

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To:	Hon Dr Ayesha Verrall, Minister of Health		
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Contact for telephone discussion

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Minister's office to complete:

☐ Approved ☐ Decline ☐ Noted

☐ Needs change ☐ Seen ☐ Overtaken by events

☐ See Minister's Notes ☐ Withdrawn

Comment:

Rapid Review of COVID-19 Antiviral Effectiveness

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To:	Hon Dr Ayesha Verrall, Minister of Health		

Purpose of report

1. This briefing responds to your request for an analysis of the effectiveness of antiviral treatment of COVID-19, with particular focus on the oral antivirals paxlovid and molnupiravir.
2. It includes a rapid review of international literature, initial evidence regarding effectiveness, and a summary of the planned in-depth evaluation and data analysis expected in March 2023.
3. This report discloses all relevant information.

Context

4. Oral antivirals paxlovid and molnupiravir have been available in Aotearoa New Zealand since 5 April 2022 and 5 May 2022 respectively.
5. Note that remdesivir, an intravenous antiviral, is also available however, its use is more limited than oral antivirals as it as unapproved (available through section 25 of the Medicines Act 1981) and more logistically difficult to administer. Oral antivirals are the focus for this briefing.
6. Therapeutics TAG met several times to consider the evidence available in terms of safety profiles and efficacy and the groups of people who are most likely to benefit from using antivirals.
7. The Pharmac criteria for access to antivirals were introduced on 31 March 2022 and have been reviewed and updated as required (Appendix 1).
8. At the time the oral antivirals were approved, real world data was limited. However, this data is now emerging.
9. The Public Health Agency is currently preparing an in-depth evaluation based on New Zealand data of the effect of therapeutics and vaccination on the risk of hospitalisation, taking into account other factors that may also influence hospitalisation risk, such as age, sex, ethnicity, deprivation and underlying health conditions This analysis is due to be delivered in March, however, this document presents some of the preliminary data.

International literature review of oral antivirals used in Aotearoa New Zealand

10. The Public Health Agency has commissioned a rapid review of the literature, focused on the effectiveness of oral antivirals in a real-world setting.

11. In general, although oral antivirals were demonstrated to have reduced the risk of hospitalisation and death, the evidence base was primarily clinical trial data of unvaccinated populations. Therefore, it is important to evaluate how oral antivirals have performed for vaccinated populations in a real-world setting.

Paxlovid (nirmatrelvir and ritonavir)

12. In clinical trial data, paxlovid is reported to reduce the risk of progression to severe COVID-19 in unvaccinated, high-risk people by 89% compared to placebo during a period of Delta dominance.[1]

13. Observational real-world evidence suggests that paxlovid remains effective against Omicron variants (including BA.4 and BA.5) in vaccinated, high-risk populations. [2,3,4,5] This included reduced relative risks of hospitalisation ranging from 44%[2] to 54%[5] in paxlovid treated, high risk people compared to placebo.

Molnupiravir (Brand name Lagevrio®)

14. Clinical data (the MOVe-OUT trial) reported interim results that suggested molnupiravir use resulted in a 50% reduction of hospitalisations and deaths compared to placebo in unvaccinated adults during the Delta period.[6] This reduced to 30% at the time of publication.**Error! Bookmark not defined.**

15. A large, open label trial (PANORAMIC) completed during an Omicron period found molnupiravir did not reduce hospitalisations or deaths among higher risk, vaccinated (three doses) adults with COVID-19 in the community.[7]

16. The PANORAMIC study reported promising results for secondary endpoints, including a faster time to recovery (by four days on average) and reduced viral load (undetectable viral load at day 7 in 21% of treatment group comparted to 3% in the control).

17. In the PANORAMIC study, less than 6% of participants were over 75 years old and 51% were <50 years old. Similarly, in the MOVe-OUT trial, 83% of participants were <60 years old. This makes it hard to extrapolate any meaningful data in relation to an older population.

18. Observational studies[8,9,10] have suggested molnupiravir reduces the chance of high-risk people dying, especially older people (noting the definition of older varies between studies).

[1] https://www.nejm.org/doi/full/10.1056/NEJMoa2118542 Accessed 9 Feb 2023
[2] https://www.medrxiv.org/content/medrxiv/early/2022/11/05/2022.11.03.22281881.full.pdf Accessed 9 Feb 2023
[3] https://www.medrxiv.org/content/medrxiv/early/2022/09/15/2022.09.12.22279866.full.pdf Accessed 9 Feb 2023
[4] https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e2.htm#suggestedcitation Accessed 9 Feb 2023
[5] https://academic.oup.com/cid/article/76/3/e342/6599020 Accessed 9 Feb 2023
[6] https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/ Accessed 9 Feb 2023
[7] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02597-1/fulltext Accessed 9 Feb 2023
[8] https://www.sciencedirect.com/science/article/pii/S1473309922005072 Accessed 9 Feb 2023
[9] https://www.nejm.org/doi/full/10.1056/NEJMoa2204919 Accessed 9 Feb 2023
[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9400562/ Accessed 9 Feb 2023

19. Manatū Hauora officials and members of the Therapeutics TAG met on 3 February 2023 with PANORAMIC authors to discuss the findings of this study. One consideration was that the population in this study may not be reflective of those who could benefit from molnupiravir within the Aotearoa New Zealand context (e.g., 51% of participants were <50 years old, 94% white).

Limitations

20. Limits to these studies often include small sample sizes or sub-optimal treatment or control groups. In some cases it is hard to differentiate between hospitalisation with or from COVID-19. Additionally, it is difficult to make comparisons in trials that occurred during different variant waves (i.e., Omicron or Delta) or with participants with different vaccination statuses.

Risk Analyses based on New Zealand data

Rapid analysis

21. The Public Health Agency has prepared the below rapid analysis of risk mediated by use of antiviral medication in cases of COVID-19.

22. The use of antivirals has increased over the past 6 months (see Table 1). For example, in December 2023 there were approximately 12,000 prescriptions for molnupiravir and 23,000 prescriptions for paxlovid dispensed, for a total of 35,000 prescriptions. This was an increase from approximately 21,000 the previous month. In addition, the proportion of prescriptions dispensed by a pharmacy, as opposed to GP, has also increased over time. In January, approximately 15% of prescriptions were via a pharmacist-initiated supply or supplied as a pharmacist-only medicine, with the remaining 85% coming from general practice.

Table 1 Number of prescriptions dispensed for molnupiravir and paxlovid over the previous 6 months in Aotearoa New Zealand

Month	Category	Molnupiravir	Paxlovid	Total	% Total antiviral dispensed via pharmacy (i.e., not GP)
Aug'22	Total Antiviral dispensed	3809	5500	9309	3.7%
Sep'22		1787	3180	4967	7.8%
Oct'22		4136	7785	11921	9.6%
Nov'22		7186	13649	20835	11.5%
Dec'22		12021	22713	34734	15.8%
Jan'23		4454	8326	12780	14.8%

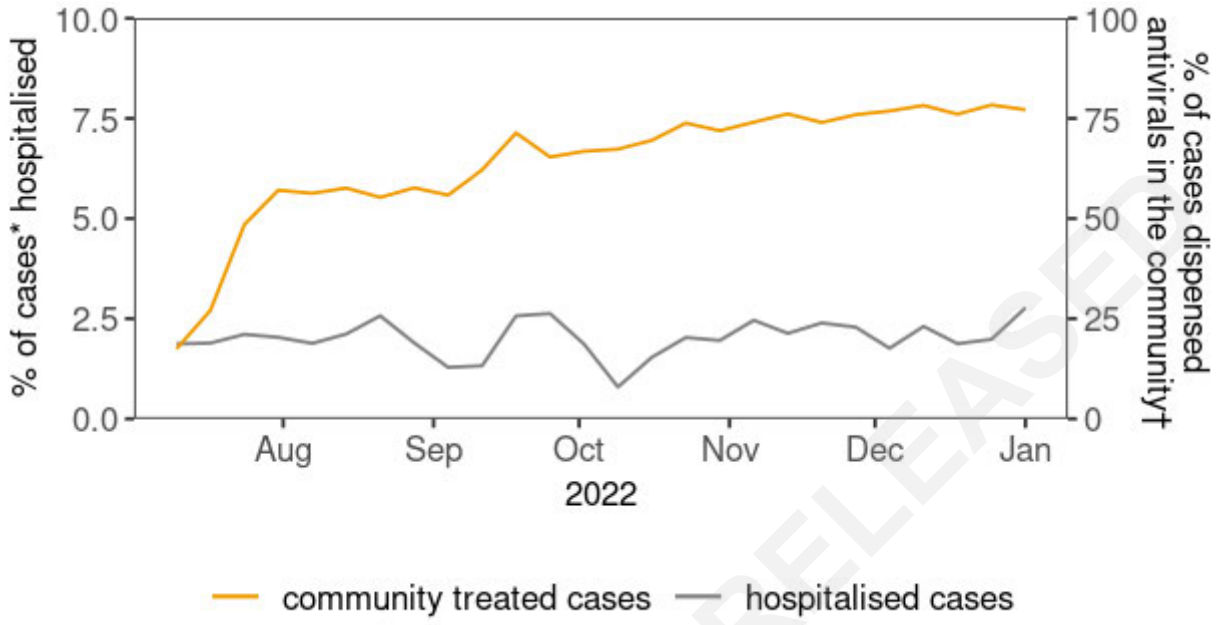
23. Since 18 July all cases of COVID-19 in those age 75 or more years have been eligible for antivirals; around 7.5% of all cases have been in this age group, but they make up 40% of hospitalisations to date.

24.

25. **Figure** 1 depicts the case hospitalisation rates over time for those aged 75 and over (gray). This includes cases that are diagnosed in the community and excludes cases diagnosed in the hospital setting. The graph also depicts the percent of cases with antivirals dispensed in the community i.e., prior to hospitalisation, if applicable (orange).

While there has been an increase in the proportion of cases where antivirals were dispensed, the case hospitalisation rate has remained close to 2.5%.

Figure 1 Percent of cases hospitalised compared with the percent of cases* that were dispensed any antiviral in the community† weekly; for those aged 75 years or more, July- December 2022*



** Limited to cases detected in the community, excludes cases first detected in a hospital.*

† Does not include dispensing that occurred only after hospitalisation. Antivirals include primarily paxlovid and molnupiravir, but this preliminary analysis also includes some other antiviral therapies, e.g., remdesivir.

26. The trends in

27. **Figure** 1 could be explained by, for example, a reduction in case ascertainment (this is not possible to explore directly). The trends could also be confounded by differences in underlying health status of cases over time and/or between those who have or have not been dispensed antivirals.

28. With regards to changes in case ascertainment, the case hospitalisation rate for the community-detected cases in those aged under 65 years – the majority of whom were not eligible for antivirals – increased over the second half of 2022. This supports the idea that as case ascertainment has declined, the relative proportion of reported cases requiring hospitalisation has increased. Whether this trend would have been seen in over 75 years olds in the absence of antivirals is unknown.

29. Overall, the complexity and assumptions involved in interpreting population level trends demonstrates that a more considered analysis of the impact of antivirals is needed; ecological comparisons of trends over time may lead to incorrect conclusions.

Evaluation and Risk Analysis of Hospitalisation

30. Using Aotearoa specific data, the Public Health Agency is undertaking an evaluation of hospitalisation, evaluating the role that antivirals, vaccines, demographics and other factors play in the risk of hospitalisation for COVID-19.

31. An analysis of the effectiveness of both vaccination and antiviral use with respect to hospitalisations during the three Omicron waves in 2022 is currently being undertaken; preliminary results are expected by the end of February.

32. The analysis will include a description of the patterns of hospitalisation and antiviral dispensing among cases eligible for antivirals. The independent effectiveness (after accounting for potential differences in age, vaccination status and underlying health issues among those who did/did not receive treatment) will also be evaluated.

Equity

33. Internationally, COVID-19 has disproportionately affected many vulnerable populations and exacerbated existing inequities. This includes people who are chronically ill, have disabilities, are low income, minority groups or who have mental health conditions.

34. Evidence has indicated the Māori and Pacific peoples are at greater risk of developing severe COVID-19 than other ethnicities. Therefore, the access criteria for COVID-19 antivirals has a lower age threshold for Māori and Pacific peoples (>50 years old) compared to other groups (>60 years old).

35. While the primary aim of a more fulsome evaluation would be to provide an independent estimate of the risk reduction associated with therapeutics, ethnicity and deprivation will be explored, and whether therapeutics have had an impact on the inequitable risk of hospitalisation experienced by Māori and Pacific peoples.

Next steps

36. The Public Health Agency is currently preparing an in-depth evaluation the effect of therapeutics such as vaccination and antivirals in the risk of hospitalisation, taking into account other factors that may also influence hospitalisation risk, such as age, sex, ethnicity, deprivation and underlying health conditions.

37. The Public Health Agency will continue to monitor emerging evidence in the literature and can provide more information at your request.

Recommendations

We recommend you:

a) **Note** the initial analysis and literature review outlined in this paper. **Noted**

b) **Note** that further in-depth analysis and risk evaluation is being prepared and will be shared with you in March 2023. **Noted**

Dr Andrew Old
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Date:

Hon Dr Ayesha Verrall
Minister for Health
Date:

Appendix 1:

Antiviral Access Criteria were introduced on 31 March 2022 and were updated on 5 May 2022, 18 July 2022 and 12 September 2022.

Antiviral 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:
    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
    2. Patient has Down syndrome; or
    3. Patient has sickle cell disease; or
    4. Patient has had a previous admission to Critical Care or High Dependency care directly as a result of COVID-19; or
    5. Patient is aged 65 years or over; or
    6. Patient is Māori or Pacific ethnicity AND aged 50 years or over; or
    7. Patient is aged 50 years or over AND has not completed a primary course^ of COVID-19 vaccination; or
    8. Patient has any combination of three or more high-risk medical conditions for severe illness from COVID-19 identified by Manatū Hauora - 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 Manatū Hauora - Ministry of Health criteria (external link) of 'severe immunocompromise' for third primary dose of COVID-19 vaccine
** People with high risk medical conditions identified by Manatū Hauora - Ministry of Health (external link)
^ '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