Briefing

The effect of COVID-19 oral antivirals on hospitalisation and mortality in Aotearoa New Zealand

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To:	Hon Dr Ayesha Verrall, Minister of Health		
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Minister's office to complete:

☐ Approved	☐ Decline	☐ Noted
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☐ See Minister's Notes	☐ Withdrawn	

Comment:

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The effect of COVID-19 oral antivirals on hospitalisation and mortality in Aotearoa New Zealand.

Security level:	IN CONFIDENCE	**Date:**	6 April 2023
To:	Hon Dr Ayesha Verrall, Minister of Health		

Purpose of report

1. This report provides information relating to the analysis of the effectiveness of oral antiviral treatments for COVID-19, Paxlovid and molnupiravir, in Aotearoa.
2. The briefing provides:
    a. A brief overview of the antiviral roll-out, including describing the eligibility criteria.
    b. An overview of international literature regarding effectiveness.
    c. A summary of the trends in hospitalisation and mortality from COVID-19 in relation to changing antiviral prescribing criteria and uptake for Aotearoa.
3. This briefing discloses all relevant information.

Summary

4. **International evidence** on the effectiveness of Paxlovid and molnupiravir, the main oral antiviral treatments for COVID-19, in **real-world observational studies has been inconsistent**. Furthermore, **most studies are not applicable to Aotearoa New Zealand**, being often based on younger populations, unvaccinated people, and lacking ethnic diversity.
5. **This analysis of Aotearoa data** on antiviral dispensing, hospital admissions, and mortality due to COVID-19 **has shown no evidence of reduced risk for hospital admission based on antiviral uptake.**
    a. A comparison of time trend in dispensing, case reports and hospital admissions did not show any change in the ratio of cases to hospital admissions with increasing antiviral dispensing.
    b. An assessment of individual risk among those dispensed Paxlovid or molnupiravir compared with no treatment also did not detect a reduction in the risk of hospital admission.
6. However, there was **consistent evidence of a beneficial effect of antivirals on the risk of mortality** due to COVID-19.
    a. Population time trends indicate that with substantially increased dispensing from October, during the December/January case wave, mortality did not increase as much as would have been expected compared with previous waves.
    b. Individual level analyses show a beneficial effect of Paxlovid and molnupiravir for most age groups; with overall estimates of between a **40-60% reduction in mortality risk** when compared with no antiviral treatment.

7. **Findings from these analyses were very similar** when comparing trends and risks **for those aged 65 years and over, with those for Māori and Pacific people aged 50 years and over.**

8. This review and preliminary analysis has not yet had input from Health New Zealand or the Māori Health Authority; sharing these findings and receiving feedback is an important next step.

Recommendations

We recommend you:

a)	**Note** the information outlined in this report regarding evidence relating to antiviral effectiveness in reducing hospitalisations in Aotearoa and how this compares internationally.	**Noted**

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Te Pou Hauora Tūmatanui | Public Health Agency

Date: 5 April 2023

Hon Dr Ayesha Verrall

Minister of Health

Date:

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Background and context

Antivirals for COVD-19 became available in Aotearoa New Zealand in 2022

9. Oral antivirals Paxlovid and molnupiravir have been available in Aotearoa since 5 April 2022 and 5 May 2022 respectively.

10. Paxlovid has always been the first line antiviral treatment recommended in Aotearoa in patients without contraindications.

11. Molnupiravir and the intravenous antiviral remdesivir were both second line treatments in 2022. In February 2023, remdesivir was prioritised as the preferential second line treatment and molnupiravir moved to third line, based on international evidence.

12. Current Pharmac access criteria for COVID-19 antivirals are shown in Appendix 1

13. The oral antivirals, Paxlovid and molnupiravir, are the primary focus for this memo. These two antivirals constitute 98% of all COVID-19 antivirals dispensed up until 20 March 2023.

International evidence of effectiveness of oral antivirals

Evidence used to support the initial approval of oral antivirals

14. When oral antivirals were approved in Aotearoa, real-world data on effectiveness were limited and specific to unvaccinated populations against pre-Omicron variants.

    a. In February 2022, a randomised controlled trial in the United States (MOVe-OUT,), reported that molnupiravir had a 30% reduction of hospitalisations and death compared with placebo in unvaccinated adults against Delta (median age of participants 43 years, range 18 – 90 years).[1]

    b. In April 2022, a randomised control trial (EPIC-HR, also in the United States), reported an 89% reduction in patients at high-risk of progression to severe COVID-19 in unvaccinated people treated with Paxlovid compared with placebo during a period of Delta dominance (median age 46, range 18 to 88 years old).[2]

Emerging evidence relevant in an Aotearoa New Zealand context

15. In Aotearoa, 89% of people aged 12 years or older have received at least two vaccination doses as of 21 March 2023.[3] Additionally, Omicron and it sublineages have been predominant in Aotearoa since January 2022, prior to oral antivirals being available in Aotearoa. Therefore, it has become increasingly important to evaluate how oral antivirals perform in highly vaccinated populations in a real-world setting, in the presence of vaccine- and infection-induced immune response, as well as evidence relating to infection with the Omicron variant.

16. Emerging real-world evidence suggests that Paxlovid remains effective against Omicron variants (including BA.4 and BA.5) in vaccinated people in populations at high risk of severe

[1] https://www.nejm.org/doi/full/10.1056/NEJMoa2116044 Accessed 24 March 2023
[2] https://www.nejm.org/doi/full/10.1056/NEJMoa2118542 Accessed 24 March 2023
[3] https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-vaccine-data Updated 21 March 2023

COVID-19.[4,5,6,7] Estimates of hospitalisation risk reduction ranged from 44%[4] to 54%[7] in Paxlovid-treated, high-risk people compared with placebo. Post-hoc subgroup analyses suggested a trend by age (i.e., older groups may receive more benefit from Paxlovid than younger groups). However, sample sizes were small, and the data were subject to the usual confounding associated with observational studies. Additionally, analyses of older people were not primary, pre-specified objectives of these studies.

17. A large, open-label, randomised controlled trial (PANORAMIC) completed during Omicron dominance in the United Kingdom, found no evidence that molnupiravir reduced hospitalisations or deaths in populations at high risk of severe COVID-19 (50 years of age or older, or 18 years and older with specific co-morbidities), who had been vaccinated (three doses) and who had tested positive for COVID-19 in the community.[8] Additional information about this study includes:

    a. Manatū Hauora officials and representatives of the Therapeutics TAG met on 3 February 2023 with PANORAMIC authors to discuss the findings of this study; it was noted that the study participants may not be representative of those who could benefit from molnupiravir in the Aotearoa (e.g., 51% of participants were <50 years old, 94% pākeha).

    b. Further findings from this study, regarding the impact of molnupiravir on long COVID, and a similar study on the effect of Paxlovid are not expected to be available for at least six months.

Impacts of antiviral dispensing on hospitalisation and mortality in Aotearoa

Methods: Data sources

18. Data were extracted for antiviral dispensing, case counts, hospitalisation, and mortality, covering the period 1 January 2022 to 20 March 2023; data included all dates, type of antiviral, length of hospital admission, vaccination details, type of antiviral and demographics such as age and ethnicity.

Methods: Time series analysis

19. Data were analysed as a **time series, comparing the 7-day rolling average of counts for absolute numbers of antiviral dispensed, reported cases, all COVID-related hospital admissions and all deaths** due to COVID-19.

    a. **These data were not analysed on an individual level, and few restrictions were applied to the analyses.** For example, the analysis included hospitalisations with any length of inpatient admission, and patients who reported as a case on or after admission. Therapeutics dispensed included dispensing that may have occurred after the clinical guideline being within 5 days of symptom onset.

[4] https://www.medrxiv.org/content/medrxiv/early/2022/11/05/2022.11.03.22281881.full.pdf Accessed 24 March 2023
[5] https://www.medrxiv.org/content/medrxiv/early/2022/09/15/2022.09.12.22279866.full.pdf Accessed 24 March 2023
[6] https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e2.htm#suggestedcitation Accessed 24 March 2023
[7] https://academic.oup.com/cid/article/76/3/e342/6599020 Accessed 24 March 2023
[8] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02597-1/fulltext Accessed 9 Feb 2023

20. Time series data were analysed in three groups: **those aged 75 years and over; those aged 65-74 years; and Māori and Pacific peoples only aged 50 and over.**

    a. These groups broadly corresponded to the different eligibility criteria over the time period: See Appendix 2 for details.

    b. These results were presented as time series graphs with vertical lines to indicate when changes in eligibility occurred. These cover the Omicron dominant period, including a period prior to antivirals being introduced, and a period after each change in antiviral eligibility.

Methods: Age stratified risks and regression estimates

21. Analyses at an individual level were undertaken to evaluate the impact of antivirals on the risk of hospitalisation and mortality due to COVID-19. Unlike the timeseries analysis, specific eligibility criteria were used for these analyses. **Only those patients whose antivirals were dispensed within two days of case report were defined as having been dispensed antivirals**[9]. Hospital **admission of at least six hours duration** and deaths due to COVID-19 were included, **limited to the window from two to 28 days after case report**.[10] This method was adapted from Drysden-Peterson, *et al,* 2022.[11]

    a. Tables of risk per 1000 cases, by age group, were produced for:

        i. all people 65 years and over,

        ii. Māori and Pacific peoples 50 years and over,

        iii. people 65 years and older who **have had a vaccination dose** within the last 120 days, and

        iv. people 65 years and older **who have not had a vaccination** dose within the last 120 days (this was restricted to those who had at least 2 doses)

22. These individual level data were then analysed using Poisson regression to produce adjusted risk ratios. Risks were adjusted for age, reinfection, vaccination status and comorbidities.

    a. Estimates were produced for those aged 65 years and over, and for Māori and Pacific peoples aged 50 years and over.

    b. Regression was also used to estimate the likelihood of having an antiviral dispensed by ethnicity after adjusting for age.

    c. These were preliminary models, and the full results are not presented here.

[9] Further dispensing after two days in the community, or in hospital, may have occurred, including in those considered to have not had antivirals, however this was outside of the definition of early treatment.
[10] As measures of risk start from two days after report date, those who were hospitalised or died on the day of report or the day after report are excluded.
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9753458/pdf/aim-olf-M222141.pdf Accessed 30 March 2023

Results: Trends in antiviral dispensing, case reports, hospital admissions and deaths due to COVID-19 over time

23. Figure 1 shows time trends among those aged 75 years or more and Figure 2 shows trends in Māori and Pacific peoples aged 50 years or more. Trend for those aged 65-74 years are presented in Figure 3 which can be found in Appendix 3.

24. Figure 1 and Figure 2 both show that despite the increase in dispensing relative to cases in the December/January wave, the ratio of cases to hospitalisations did not decrease. However, there was some evidence of a decrease over this period in the ratio of cases to deaths.

    a. There was no substantial difference in the patterns for those aged 75 years or more when compared with Māori and Pacific aged 50 years or more. The trend was also consistent for those aged 65-74.

    b. Note that the ratio of case reports to dispensing cannot be compared between these figures, as they cover different age-ranges.

Figure 1 Trends in antiviral dispensing, case reports, hospital admissions and deaths due to COVID-19 in those aged 75 years and over, 1 January to 20 March 2023

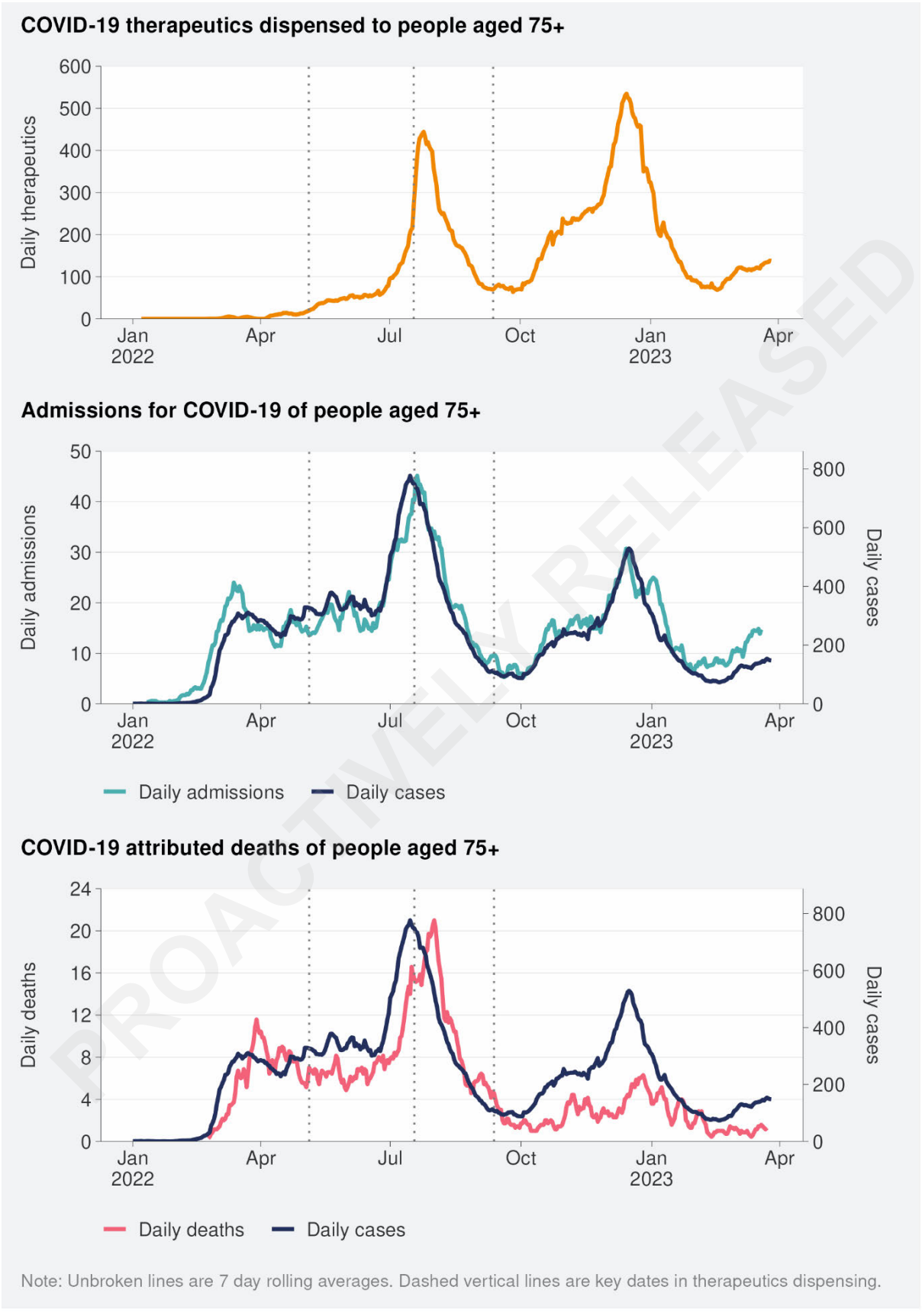
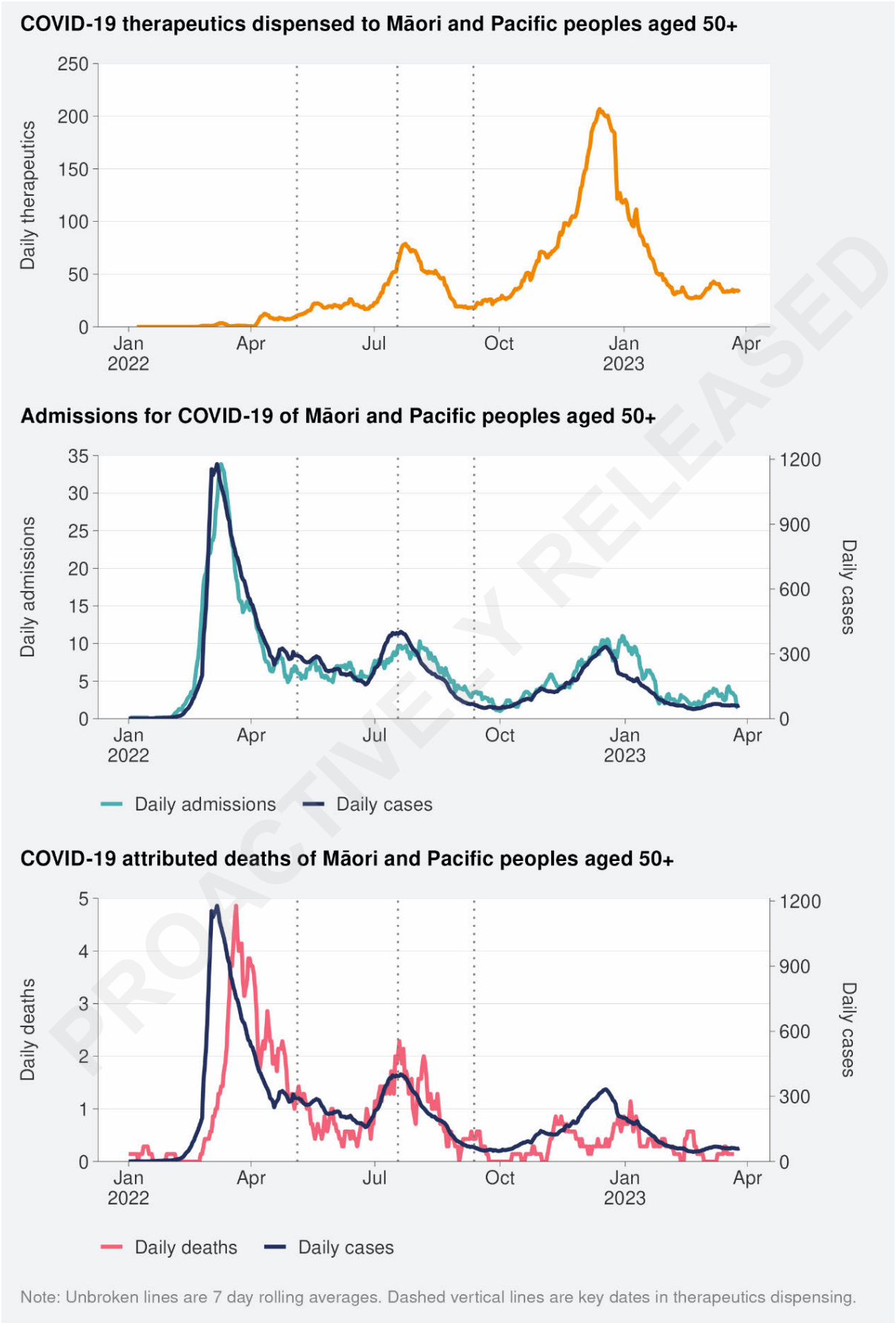


Figure 2 Trends in antiviral dispensing, case reports, hospital admissions and deaths due to COVID-19 in Māori and Pacific peoples aged 50 years or more, 1 January to 20 March 2023



Results: Individual risk of hospital admission and death by treatment status

Age-stratified risk in those aged 65 years and over

25. There were 2,067 hospital admissions among the 260,897 cases who met inclusion criteria of 2 or more days from report to hospital admission or death.
    a. Approximately 32% of these cases had antiviral treatment within two days of report. This percentage has increased over time, from 10% during the period from 5 May to 17 July, to 32% in the period 18 July to 11 September 2022, as the criteria for antivirals widened. Since 12 September, 66% of cases are dispensed antivirals within two days of report.
26. Table 1 and Table 2 show the age-stratified risk for hospital admission and death, respectively, for those aged 65 years or more.
    a. Results for those recently vaccinated (within 120 days of case report) and not recently vaccinated are included in Appendix 3, Table 5 to Table 8.
27. There was **no evidence** in this dataset **of a reduction in individual risk of hospitalisation in those aged 65 years or more** following treatment within two days of report date:
    a. For both Paxlovid and molnupiravir, age-specific risk and overall risk of hospitalisation were similar to, or greater than, those who had not had antivirals (Table 1).
    b. Similar patterns were seen when restricting by time since most recent vaccination (Table 5 and Table 6).
28. By contrast, the **mortality risks were around 2-3 times lower** at all ages for those who were dispensed Paxlovid compared with those who had no antivirals.
    a. For molnupiravir, there appeared to be a protective effect only for those aged 80 or more, but it is important to note that there is substantial uncertainty in the point estimates as demonstrated by the wide 95% confidence intervals (Table 2).
    b. Similar patterns were seen when restricting by time since most recent vaccination (Table 7 and Table 8).

Table 1 Hospital admission risk per 1000 cases by treatment status in those aged 65 years and over, 1 January 2022 to 20 March 2023

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
65–69	242	3.7; 3.3–4.2	53	3.7; 2.8–4.8	46	8.4; 6.3–11.2	0	0; 0–0	341	6.8; 6.2–7.3
70–74	257	5.4; 4.8–6.1	84	6.3; 5.1–7.8	68	11; 8.7–14	0	0; 0–0	409	10.3; 9.5–11.1
75–70	238	8; 7.1–9.1	89	7.6; 6.2–9.4	63	9.9; 7.7–12.6	0	0; 0–0	390	16; 14.9–17.1
80–84	218	11.6; 10.2–13.3	82	11; 8.9–13.6	95	18.3; 15–22.3	2	16.8; 4.2–64.7	397	28.9; 27.1–30.8
≥85	307	17.9; 16.1–20	117	20.7; 17.3–24.8	106	19.4; 16.1–23.4	0	0; 0–0	530	43.3; 41–45.7
Total	**1262**	**7.1; 6.7–7.5**	**425**	**8.1; 7.4–8.9**	**378**	**13.2; 11.9–14.6**	**2**	**2.3; 0.6–9.3**	**2067**	**7.9; 7.6–8.3**

Table 2 Mortality risk per 1000 cases by treatment status in those aged 65 years and over, 1 January 2022 to 20 March 2023

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
65–69	46	0.7; 0.5–0.9	5	0.3; 0.1–0.8	8	1.5; 0.7–2.9	0	0; 0–0	59	6.8; 6.2–7.3
70–74	78	1.6; 1.3–2	11	0.8; 0.5–1.5	11	1.8; 1–3.2	2	8; 2–31.4	102	10.3; 9.5–11.1
75–70	121	4.1; 3.4–4.9	14	1.2; 0.7–2	28	4.4; 3–6.4	0	0; 0–0	163	16; 14.9–17.1
80–84	180	9.6; 8.3–11.1	22	2.9; 1.9–4.5	32	6.2; 4.4–8.7	3	25.2; 8.2–75.2	237	28.9; 27.1–30.8
≥85	631	36.9; 34.1–39.8	69	12.2; 9.7–15.4	88	16.1; 13.1–19.8	4	42.1; 15.9–106.9	792	43.3; 41–45.7
Total	**1056**	**5.9; 5.6–6.3**	**121**	**2.3; 1.9–2.8**	**167**	**5.8; 5–6.8**	**9**	**10.6; 5.5–20.2**	**1353**	**5.2; 4.9–5.5**

Age-stratified risk in Māori and Pacific peoples aged 50 years and over

29. Table 3 and Table 4 show age stratified hospital admission and mortality risks, respectively, for Māori and Pacific peoples aged 50 years or more.

30. There were 697 hospital admissions and 160 deaths among the 96,637 cases who met inclusion criteria of two or more days from report to hospital admission or death; with 18% of cases having had antiviral treatment within two days of report.

    a. Over this time period, this percentage treated within two days of report has increased from 8% during the period between 5 May to 17 July, to 18% between 18 July to 11 September 2022, as the eligibility criteria was expanded. Since 12 September, this has increased to 48%.

31. Consistent with the age-stratified patterns of risk for everyone aged 65 years and over, there was **no evidence** in this dataset of a reduction in **individual risk of hospitalisation** following treatment within two days of report date:

    a. For both Paxlovid and molnupiravir age-specific risks and overall risk of hospitalisation were similar to those who had not had antivirals (Table 3).

32. Similar to age-stratified patterns of mortality risk for everyone aged 65 years and over, the **mortality risks** were around **two times lower** at all ages, for those who were dispensed Paxlovid compared with those who had no antivirals (Table 4).

Table 3 Hospital admission risk per 1000 cases by treatment status among Māori and Pacific peoples aged 50 years or more, 1 January 2022 to 20 March 2023

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
50–59	208	4.6; 4–5.2	20	4.9; 3.2–7.6	18	12; 7.6–19	0	0; 0–0	246	6.8; 6.2–7.3
60–69	176	7.1; 6.1–8.2	11	3.2; 1.7–5.7	15	8.7; 5.3–14.4	0	0; 0–0	202	10.3; 9.5–11.1
70–79	108	12.8; 10.6–15.5	24	12.8; 8.6–19	18	14.5; 9.1–22.8	0	0; 0–0	150	16; 14.9–17.1
80–89	54	23.2; 17.8–30.1	10	18.8; 10.1–34.6	14	29.7; 17.6–49.5	1	142.9; 19.7–580.8	79	28.9; 27.1–30.8
90+	16	58; 35.8–92.6	2	26; 6.5–98.3	2	26; 6.5–98.3	0	0; 0–0	20	43.3; 41–45.7
Total	562	6.9; 6.4–7.5	67	6.7; 5.3–8.5	67	13.4; 10.5–17	1	6.1; 0.9–42	697	7.2; 6.7–7.8

Table 4 Mortality risk per 1000 cases by treatment status among Māori and Pacific peoples aged 50 years or more, 1 January 2022 to 20 March 2023

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
50–59	13	0.3; 0.2–0.5	2	0.5; 0.1–2	0	0; 0–0	0	0; 0–0	15	6.8; 6.2–7.3
60–69	33	1.3; 0.9–1.9	0	0; 0–0	1	0.6; 0.1–4.1	0	0; 0–0	34	10.3; 9.5–11.1
70–79	31	3.7; 2.6–5.2	4	2.1; 0.8–5.7	4	3.2; 1.2–8.5	0	0; 0–0	39	16; 14.9–17.1
80–89	46	19.7; 14.8–26.3	5	9.4; 3.9–22.4	2	4.2; 1.1–16.8	1	0; 0–0	54	28.9; 27.1–30.8
90+	13	47.1; 27.5–79.5	3	39; 12.6–114.3	2	26; 6.5–98.3	0	0; 0–0	18	43.3; 41–45.7
Total	136	1.7; 1.4–2	14	1.4; 0.8–2.4	9	1.8; 0.9–3.5	1	0; 0–0	160	1.6; 1.4–1.9

Adjusted risk ratios from preliminary regression models

33. There was **no evidence** of a protective effect for **individual risk of hospital admission** following treatment within two days of report date, based on regression models that adjusted for age, reinfection, vaccination status and comorbidities.

    a. A regression model accounting for age group, along with evidence of comorbidities (the pharmacy dispensing and hospital-based comorbidity indices) and time since vaccination, also found no evidence of a protective effect. The adjusted risk ratios for Paxlovid and for molnupiravir (compared with no antiviral) were slightly in favour of the untreated group, however, confidence intervals were wide.[12]

[12] The adjusted relative risks for hospital admission were 1.22 (95% CI 1.10-1.37) for Paxlovid and 1.38 (95% CI 1.22-1.56) for molnupiravir for those aged 65 years or more when compared with no treatment within two days of case report.

b. Findings were very similar for Māori and Pacific people aged 50 years or more, with adjusted risk ratios for Paxlovid and for molnupiravir both close to 1 and wide confidence intervals.[13]

34. However, similar to evidence from comparison of time trends and age-stratified tables, regression analysis estimates suggest a **60% and 40% reduction in mortality risk for the Paxlovid- and molnupiravir-treated patients aged 65 years and over, respectively**.[14]

35. There was also evidence of a protective effect for **Māori and Pacific people aged 50 years** or more. The adjusted risk ratios suggested an **approximate 40% reduction in mortality risk for the Paxlovid-treated patients and a 60% reduction in mortality risk for molnupiravir-treated patients**. However, the findings for Paxlovid were not statistically significant, and also noting that the results from over 65 year-olds and the Māori and Pacific people cohorts cannot be compared directly due to several potential factors including the age differences in the cohorts.[15]

36. While not directly related to the protective effect of antivirals, the **likelihood of antiviral dispensing** is an important aspect when considering equity. In this cohort of people who had been followed up from two days to 28 days after case report, after taking age into account, **among cases who were aged 65 year and over, Māori and Pacific peoples were 5% and 34% less likely, respectively, to be dispensed antivirals compared with European and other.**

Discussion

37. International evidence from multiple studies has consistently shown that Paxlovid reduces the risk of hospitalisation and death. The evidence for molnupiravir is not as clear. The above analyses did not detect a protective effect of antivirals against hospitalisation in Aotearoa, but does suggest a protective effect against mortality for both Paxlovid and molnupiravir in those aged 65 and over (57% and 38% reduction in risk, respectively). However, there is a substantial risk of bias in the data as discussed below.

38. It is difficult to interpret findings from the Aotearoa data and to compare them to international findings. This is because there are differences between countries, as well as inherent risk of biases in datasets. There are few analytical options available to account for these biases without inadvertently introducing other biases. Some issues around bias are:

a. In order to avoid a bias towards an overestimate of effect of antivirals (due to people with less severe COVID-19 having more time to receive treatment than those rapidly hospitalised or dying) we used a method where all individuals had the same time available (two days) in which to receive treatment. However, this also means

[13] The adjusted relative risks for hospital admission were 0.90 (95% CI 0.70-1.17) for Paxlovid and 1.17 (95% CI 0.89-1.53) for molnupiravir for Māori and Pacific people aged 50 years and over when compared with no treatment within two days of case report.

[14] The adjusted relative risks for mortality were 0.43 (95% CI 0.35-0.52) for Paxlovid and 0.61 (95% CI 0.52-0.73) for molnupiravir for those aged 65 years and over when compared with no treatment within two days of case report

[15] The adjusted relative risks for mortality were 0.63 (95% CI 0.37-1.08) for Paxlovid and 0.40 (95% CI 0.20-0.80) for molnupiravir for Māori and Pacific people aged 50 years and over when compared with no treatment within two days of case report

that people who received antivirals later, and may have benefited from them, were classified as having not received antivirals in this analysis.

b. The proportion of cases reported (case ascertainment) likely varied over time and is also likely associated with severity of symptoms, individual health (e.g., comorbidities), health behaviour, and health care access. This will introduce bias. For example, if those most at risk of severe disease are more likely to report a positive test and to seek antivirals, results will be biased towards showing that those who have received antivirals have worse outcomes. In Aotearoa, estimates of *relative* case ascertainment (relative to the levels of case ascertainment during April 2022) for the whole population have been calculated based on wastewater and case reporting comparisons. These estimates suggest that the case ascertainment has declined since April 2022, and has fluctuated substantially. In October, when cases were low, the case ascertainment was about half that observed in April; but in February 2023 the case ascertainment rose to be about 75% of the rate in April 2022. However, there is substantial uncertainty associated with these estimtates. It is not known if these relative case ascertainment trends are representative of those aged over 65 years, or how changes in levels of case ascertainment are related to the severity of infection and underlying health of individuals.[16]

c. Biases may be created by the likelihood of an individual being prescribed, dispensed and adhering to antiviral treatments. For example, while it was possible to stratify analyses by age group to address some issues surrounding eligibility, other eligibility criteria are based on underlying conditions and risk for severe disease. This level of detail is not available in the National Collections. There are many unmeasured potential confounders. Therefore, potentially the analysis does not provide a sound comparison of treated and untreated people who have (unknown) differing levels of risk of severe disease.

d. Biases are likely to be created by the ability and tendency to *access* hospital care. These abilities and tendencies may not only be related to individuals, but also to the health system and capacity. For example, if hospitals are close to capacity, less severe cases may not be admitted when they might have been if the hospital had lower occupancy

39. The Aotearoa findings need to be interpreted in the context. In particular:

a. Mortality data is less complex than hospitalisation data in several respects, and likely does not suffer from as many biases as hospitalisation data. There was evidence of a substantial reduction in risk of mortality from antiviral treatment.

b. Potential biases could underestimate the protective effect of antivirals.

Equity

40. Previous evidence has indicated that Māori and Pacific peoples are at greater risk of severe outcomes following COVID-19 infection than other ethnicities. This evidence has informed the decisions around the eligibility criteria and the lower age threshold for Māori and Pacific peoples (50 years) compared to other groups (65 years).

[16] https://www.esr.cri.nz/our-expertise/covid-19-response/covid19-insights/wastewater-surveillance-dashboard/

41. We conducted a separate analysis focussing on Māori and Pacific peoples, which evaluated the protective effect of oral antivirals on hospitalisation risk and mortality risk for COVID-19. The results were similar to the general population, in that no protective effect was observed for hospitalisation risk, but there were benefits observed for mortality risk. Treatment with antivirals were associated with a halving of the mortality risk in Māori and Pacific peoples, compared with untreated patients.

42. Overall, analyses found that among Māori and Pacific peoples aged 50 years or more, the trends were very similar to that for all ethnicities aged 65-74 and 75 years and over.

43. However, we also found that in those aged 65 years and over, Māori and Pacific peoples were 5% and 34% less likely, respectively, to be dispensed antivirals within two days of case report compared with European and other.

    a. This likelihood of antiviral dispensing did not take into account underlying conditions; generally, comorbidities are more prevalent, and at younger ages, in Māori and Pacific peoples than other ethnicities. This would suggest that there is greater inequity in antiviral dispensing than indicated by this preliminary comparison. Further work evaluating these inequities is warranted.

Next steps

44. The Intelligence, Surveillance and Knowledge (ISK) team within the Public Health Agency will continue to monitor trends and emerging data relating to therapeutics, as well as hospitalisation and mortality trends, both nationally and internationally.

ENDS.

Appendix 1: Pharmac Access Criteria for COVID-19 Antivirals

Current criteria (updated on 14 September 2022)

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[17];
   AND
4. **ANY** of the following:
    1. Patient is immunocompromised[18] 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[19] 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[20];**
       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

[17] Supplemental oxygen to maintain oxygen saturation >93% or at or above baseline for patients with chronic resting hypoxia

[18] As per Manatū Hauora - Ministry of Health criteria (link) of 'severe immunocompromise' for third primary dose of COVID-19 vaccine

[19] 'Primary Course' defined as receiving at least two courses of vaccination against COVID-19

[20] People with high risk medical conditions (link) identified by Manatū Hauora - Ministry of Health

Appendix 2: Changes to the Pharmac Access Criteria for COVID-19 Antivirals

Version	Date	Key Changes
01	31 March 2022	• Criteria to cover Paxlovid and molnupiravir once available. • Patient needed all of the following: 1. Patient has confirmed (or probable) symptomatic COVID-19 2. Patient's symptoms started within the last 5 days 3. Either: 3.1. 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 3.2. Patient has at least five of the following: 3.2.1. Any combination of the risk factors for severe COVID-19 disease identified by the Ministry of Health (with each individual condition counting as one risk factor) 3.2.2. Māori or any Pacific ethnicity 3.2.3. Patient is aged 65 years and over, or is 50 years and over and has not completed a full course of vaccination, and 4. Either: 4.1. Patient does not require supplemental oxygen (to maintain oxygen saturation >93%); or 4.2. Patient does not require supplemental oxygen to maintain oxygen saturations at or above baseline (for patients with chronic resting hypoxia); and 5. Not to be used in conjunction with other oral COVID-19 antiviral treatments. • Full criteria available on Pharmac website.[21]
02		Criteria also to include remdesivir. Eligibility extended to include people: • with Down Syndrome • with Sickle cell disease • over 65 years old who have not completed full (two doses) COVID-19 vaccination course Full criteria available on Pharmac website.[22]

03	18 July 2022	Eligibility extended to include people: • aged 75 years and over • who have been previously admitted to intensive care units from a COVID-19 infection • Māori and Pacific peoples who have at least FOUR other risk factors (compared to five other risk factors for other ethnicities) Criteria calculated to include populations groups with an estimated 10% risk of hospitalisation following COVID-19 infection. Full criteria available on Pharmac website.[23]
04	14 September 2022	Eligibility extended to include: • Anyone 65 years or over • Anyone of Māori or Pacific ethnicity who is 50 years or over • Anyone 50 years or over who hasn't completed their primary course of vaccination (at least two doses) • Anyone else with three or more high-risk medical conditions (as defined on here[24]) Full criteria available on Pharmac website.[25]

[21] https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2022-03-31-decision-on-access-criteria-for-two-oral-covid-19-treatments/?keyword=antiviral%20COVID-19&type=all&page=1 Accessed 24 March 2023
[22] https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2022-04-28-decision-oral-covid-treatment-widened-access/ Accessed 24 March 2023
[23] https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/july-2022-access-criteria-updated-covid-19-antivirals/ https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2022-03-31-decision-on-access-criteria-for-two-oral-covid-19-treatments/?keyword=antiviral COVID-19&type=all&page=1 Accessed 24 March 2023
[24] https://covid19.govt.nz/prepare-and-stay-safe/people-at-higher-risk-of-severe-illness-from-covid-19 Accessed 24 March 2023
[25] https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2022-09-12-decision-to-simplify-access-for-antiviral-covid-19-treatments/?keyword=antiviral&type=all&page=1 Accessed 24 March 2023

Appendix 3: Additional time trend and individual risk results

Figure 3 Trends in antiviral dispensing, case reports, hospital admissions and deaths due to COVID-19 in those aged 65-74 years, 1 January to 20 March 2023

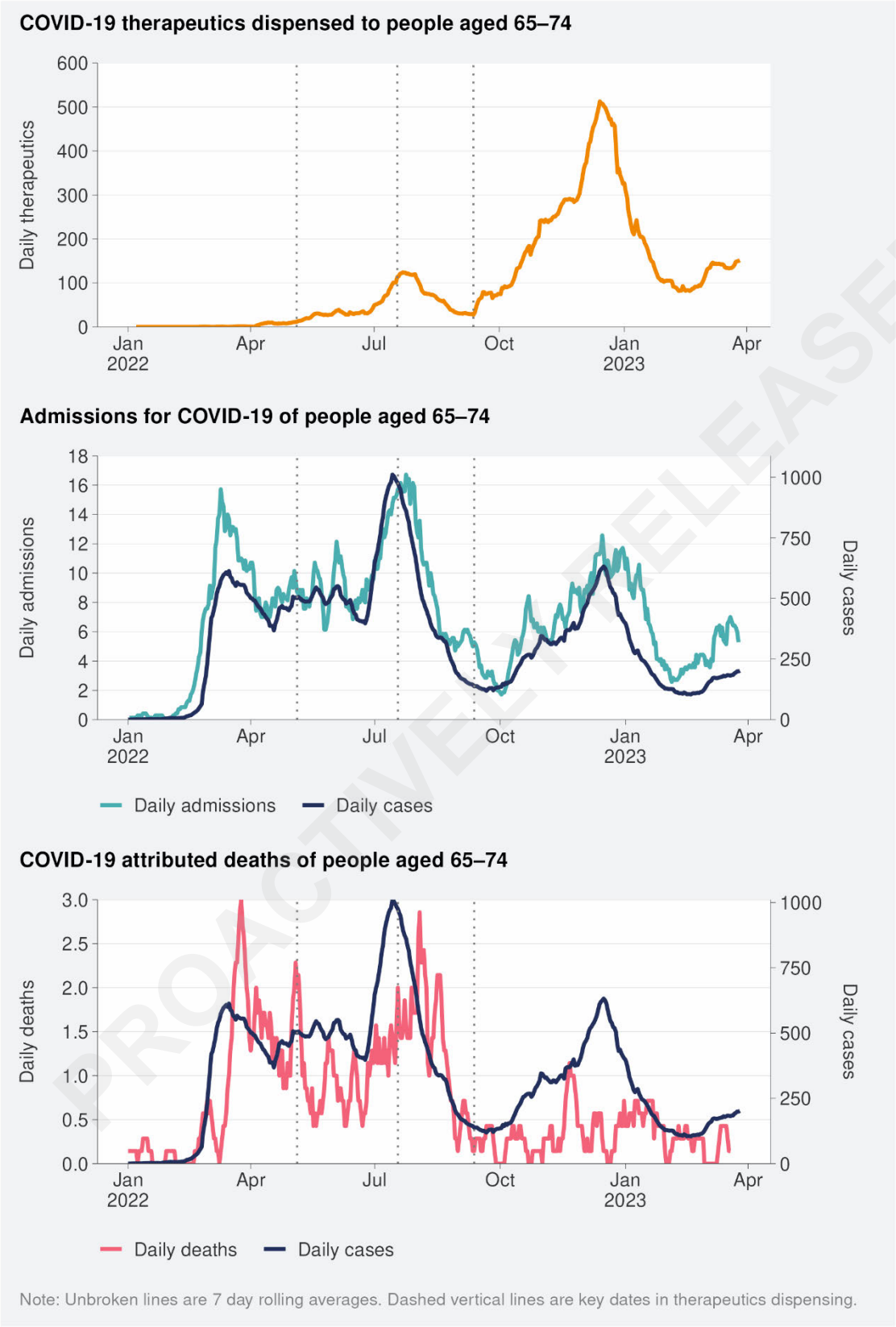


Table 5: Hospital admission risk per 1000 cases by treatment status among those who had their most recent vaccination dose in the 120 days prior to case report, 1 January 2022 to 20 March 2023

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
65–69	118	3; 2.5–3.6	18	4.2; 2.6–6.6	12	7.3; 4.1–12.7	0	0; 0–0	148	6.8; 6.2–7.3
70–74	159	5.1; 4.3–5.9	20	4.7; 3–7.3	17	8.5; 5.3–13.6	0	0; 0–0	196	10.3; 9.5–11.1
75–70	137	6.9; 5.9–8.2	28	6.2; 4.3–9	14	5.9; 3.5–9.9	0	0; 0–0	179	16; 14.9–17.1
80–84	137	10.9; 9.2–12.9	28	9.3; 6.5–13.5	29	13.8; 9.6–19.8	1	18.9; 2.7–122.1	195	28.9; 27.1–30.8
≥85	170	15.5; 13.4–18	40	16; 11.7–21.7	34	14.8; 10.6–20.7	0	0; 0–0	244	43.3; 41–45.7
Total	**721**	**6.3; 5.9–6.8**	**134**	**7.2; 6.1–8.5**	**106**	**10.2; 8.4–12.3**	**1**	**2.5; 0.3–17.4**	**962**	**6.7; 6.3–7.1**

*Table 6: Hospital admission risk per 1000 cases by treatment status among those who had their most recent vaccination dose more than 120 days prior to case report, 1 January 2022 to 20 March 2023**

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
65–69	93	4; 3.2–4.9	31	3.2; 2.2–4.5	32	9; 6.3–12.6	0	0; 0–0	156	6.8; 6.2–7.3
70–74	73	4.9; 3.9–6.1	60	6.9; 5.3–8.8	49	12.5; 9.5–16.5	0	0; 0–0	182	10.3; 9.5–11.1
75–70	90	10; 8.2–12.3	59	8.5; 6.6–10.9	46	12.1; 9.1–16.1	0	0; 0–0	195	16; 14.9–17.1
80–84	71	12.6; 10–15.9	53	12.3; 9.4–16	61	20.4; 15.9–26.2	1	16.4; 2.3–107.4	186	28.9; 27.1–30.8
≥85	110	19.8; 16.5–23.9	72	23.8; 19–29.9	67	22.1; 17.4–28	0	0; 0–0	249	43.3; 41–45.7
Total	**437**	**7.5; 6.8–8.2**	**275**	**8.4; 7.5–9.5**	**255**	**14.7; 13–16.6**	**1**	**2.4; 0.3–16.5**	**968**	**8.9; 8.3–9.5**

* *Vaccination analyses were restricted to those who had at least 2 doses of vaccination prior to case report*

*Table 7: Mortality risk per 1000 cases by treatment status among those who had their most recent vaccination dose in the 120 days prior to case report, 1 January 2022 to 20 March 2023**

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
65–69	16	0.4; 0.2–0.7	0	0; 0–0	2	1.2; 0.3–4.8	0	0; 0–0	18	6.8; 6.2–7.3
70–74	33	1.1; 0.7–1.5	3	0.7; 0.2–2.2	5	2.5; 1–6	0	0; 0–0	41	10.3; 9.5–11.1
75–70	47	2.4; 1.8–3.2	3	0.7; 0.2–2.1	6	2.5; 1.1–5.6	0	0; 0–0	56	16; 14.9–17.1
80–84	62	4.9; 3.9–6.3	2	0.7; 0.2–2.7	7	3.3; 1.6–7	1	18.9; 2.7–122.1	72	28.9; 27.1–30.8
≥85	213	19.4; 17–22.2	14	5.6; 3.3–9.4	19	8.3; 5.3–12.9	0	0; 0–0	246	43.3; 41–45.7
Total	**371**	**3.2; 2.9–3.6**	**22**	**1.2; 0.8–1.8**	**39**	**3.7; 2.7–5.1**	**1**	**2.5; 0.3–17.4**	**433**	**3; 2.7–3.3**

*Table 8: Mortality risk per 1000 cases by treatment status among those who had their most recent vaccination dose more than 120 days prior to case report, 1 January 2022 to 20 March 2023**

	No antivirals		Paxlovid only		Molnupiravir only		Other/combination		Total	
Age	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**	**N**	**Risk; 95% CI**
65–69	23	1; 0.7–1.5	5	0.5; 0.2–1.2	6	1.7; 0.8–3.7	0	0; 0–0	34	6.8; 6.2–7.3
70–74	38	2.5; 1.8–3.5	7	0.8; 0.4–1.7	4	1; 0.4–2.7	2	15.7; 3.9–60.8	51	10.3; 9.5–11.1
75–70	60	6.7; 5.2–8.6	11	1.6; 0.9–2.9	19	5; 3.2–7.8	0	0; 0–0	90	16; 14.9–17.1
80–84	98	17.4; 14.3–21.2	20	4.6; 3–7.2	24	8; 5.4–12	2	32.8; 8.2–121.8	144	28.9; 27.1–30.8
≥85	348	62.7; 56.7–69.4	49	16.2; 12.3–21.4	63	20.8; 16.3–26.5	4	83.3; 31.6–201.9	464	43.3; 41–45.7
Total	**567**	**9.7; 8.9–10.5**	**92**	**2.8; 2.3–3.4**	**116**	**6.7; 5.6–8**	**8**	**18.9; 9.5–37.3**	**783**	**7.2; 6.7–7.7**

* *Vaccination analyses were restricted to those who had at least 2 doses of vaccination prior to case report.*