Effectiveness of community-based oral antiviral treatments against severe COVID-19 outcomes in people 70 years and over in Victoria, Australia, 2022: an observational study

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Summary

Background Oral Antiviral (OAV) COVID-19 treatments are widely used, but evidence for their effectiveness against the Omicron variant in higher risk, vaccinated individuals is limited.

Methods Retrospective study of two vaccinated cohorts of COVID-19 cases aged ≥70 years diagnosed during a BA.4/5 Omicron wave in Victoria, Australia. Cases received either nirmatrelvir-ritonavir or molnupiravir as their only treatment. Data linkage and logistic regression modelling was used to evaluate the association between treatment and death and hospitalisation and compared with no treatment.

Findings Of 38,933 individuals in the mortality study population, 13.5% (n = 5250) received nirmatrelvir-ritonavir, 51.3% (n = 19,962) received molnupiravir and 35.2% (n = 13,721) were untreated. Treatment was associated with a 57% (OR = 0.43, 95% CI 0.36–0.51) reduction in the odds of death, 73% (OR = 0.27, 95% CI 0.17–0.40) for nirmatrelvir-ritonavir and 55% (OR = 0.45, 95% CI 0.38–0.54) for molnupiravir. Treatment was associated with a 31% (OR = 0.69, 95% CI 0.55–0.86) reduction in the odds of hospitalisation, 40% (OR = 0.60, 95% CI 0.43–0.83) for nirmatrelvir-ritonavir and 29% (OR = 0.71, 95% CI 0.58–0.87) for molnupiravir. Cases treated within 1 day of diagnosis had a 61% reduction in the odds of death (OR = 0.39, 95% CI 0.33–0.46) compared with 33% reduction for a delay of 4 or more days (OR = 0.67, 95% CI 0.44–0.97).

Interpretation Treatment with both nirmatrelvir-ritonavir or molnupiravir was associated with a reduction in death and hospitalisation in vaccinated ≥70 years individuals during the Omicron era. Timely, equitable treatment with OAVs is an important tool in the fight against COVID-19.

Funding There was no funding for this study.

Keywords: COVID-19; Antiviral treatment; Australia

Introduction

Since the emergence of SARS-CoV-2, the virus which causes COVID-19, there have been greater than 768 million reported infections and 6.9 million recorded deaths world-wide, with actual infections and deaths likely to be many times higher.[1] COVID-19 has led to high rates of hospitalisation, mortality, post-acute sequalae, and long-term impacts on quality of life.[2,3] New tools to prevent, detect and treat COVID-19 have been rapidly developed and deployed with a focus on reducing the severity of illness for those most at risk.[2,4] Several therapeutics for COVID-19 including

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Research in context

Evidence before this study

Oral antivirals (OAV) nirmatrelvir-ritonavir and molnupiravir are among the pharmaceutical interventions available for preventing severe COVID-19 in individuals at greater risk. There has been widespread use of OAV in high-income countries following industry-sponsored, multi-centred placebo-controlled randomised controlled trials conducted prior to the emergence of Omicron sub-variants in unvaccinated individuals. These trials showed a reduction in the risk of hospitalisation and death for both nirmatrelvir-ritonavir and molnupiravir. Several real-world effectiveness studies conducted in Hong Kong, the United States, Poland and Israel during the Omicron era concluded both OAVs reduced the risk of severe outcomes such as hospitalisation and death. A more recent open-label randomised trial compared molnupiravir to usual care in the United Kingdom in a vaccinated population who were mostly under 70 years of age and did not find a reduction in hospitalisation and deaths, despite reducing time to recovery.

Added value of this study

By linking notified cases of COVID-19 in Victoria, Australia with prescriptions of nirmatrelvir-ritonavir and molnupiravir, and with hospitalisation and death records, we were able to assess real-world effectiveness. Receiving any of these OAVs was associated with a 57% reduction in the odds of death, and 31% decrease in hospitalisation. Nirmatrelvir-ritonavir was more effective than molnupiravir in preventing mortality (73% vs 55%) and hospitalisation (40% vs 29%) compared to no treatment. Effectiveness in preventing death relative to no treatment decreased, as time from diagnosis to treatment initiation increased, from 61% (95% CI 54%–67%) to 33% (95% CI 3%–56%) for patients treated within 1 day of diagnosis and after 4 days of diagnosis, respectively.

Implications of all the available evidence

Several clinical trials and observational studies showed nirmatrelvir-ritonavir and molnupiravir reduce the risk of hospitalisation and death in people diagnosed with COVID-19. The present study adds to this evidence. Nirmatrelvir-ritonavir is recommended as first-line, but where contraindicated or unsuitable, molnupiravir should be considered. Treatment should be initiated as early as possible while ensuring equity of access in the community. Ongoing research, including clinical trials and observational studies are needed to assess the ongoing effectiveness, role and eligibility criteria for community-based OAVs for reducing severe COVID-19 and post-acute sequalae.

anti-inflammatory agents, antivirals and neutralising antibodies have been shown to reduce mortality, disease progression and/or hospitalisation largely in hospitalised or critically ill patients.[5] Ensuring equity of access to therapeutics remains an ongoing challenge at the global and local level.[6]

Two oral antivirals (OAV), nirmatrelvir-ritonavir (Paxlovid)® and molnupiravir (Lagevrio)®, have become widely used in high-income countries for community-based treatment following industry sponsored double-blind randomised controlled trials that showed their benefit in reducing hospitalisation and death.[7,8] These clinical trials were conducted prior to the emergence of the Omicron variant, in unvaccinated, non-hospitalised adults with mild to moderate COVID-19, at high risk of severe disease. Both drugs were shown to be effective in preventing hospitalisation and death.[5] Evidence has been emerging on the effectiveness of OAV in the Omicron era and in vaccinated populations. Real-world effectiveness studies conducted in several settings including Hong Kong, United States, Poland and Israel have demonstrated an association between OAV and a reduction in the risk of hospitalisation and death.[9–17] As the risk of severe COVID-19 outcomes increases independently with age from the sixth decade and markedly for people over 70 years, older age groups have been a priority for OAV access world-wide.[18]

In Australia, nirmatrelvir-ritonavir and molnupiravir were provisionally approved by the Therapeutic Goods Administration (TGA) in January 2022 for the treatment of COVID-19 in non-hospitalised patients at increased risk of severe disease. The medications were subsidised under the Pharmaceutical Benefits Scheme (PBS) for dispensing in community pharmacies after following prescription by a medical or nurse practitioner in March (molnupiravir) and May (nirmatrelvir-ritonavir) 2022. Eligibility criteria for PBS-subsidised OAV was initially restricted to individuals at increased risk of severe disease over 18 years and expanded to additionally include all individuals aged 70 and over without risk factors and with confirmed COVID-19 from July 11, 2022.[19–21] Nirmatrelvir-ritonavir is recommended as the first line treatment in Australia, with molnupiravir recommended in patients where nirmatrelvir-ritonavir is contraindicated or unsuitable.[21]

As part of the pandemic response in Victoria, Australia, the Victorian Department of Health (DH) established data linkage between notified COVID-19 cases and vaccination, hospitalisation, death datasets and OAV prescription data. We aimed to assess the effectiveness of molnupiravir and nirmatrelvir-ritonavir in preventing hospitalisation and death among people aged 70 years and over during a COVID-19 wave where Omicron sub-variants predominated in a highly COVID-19 vaccinated population in Victoria, Australia.

Methods

We conducted a retrospective cohort study involving individuals aged 70 and above who were diagnosed with COVID-19 and reported to the Victorian DH from 11 July to 31 October, 2022. We selected this study period due to several factors: it started on the date of expansion of OAV eligibility, the legal requirement for individuals to report positive SARS-CoV-2 tests until October 12, 2022, and the timing of Victoria's third wave of transmission in 2022 characterised by the dominance of the BA.4 and BA.5 Omicron subvariants.[22,23]

Study setting and procedures

Victoria is Australia's second largest state (population 6.5 million) with the majority of residents (4.9 million) living in Melbourne.[24] In 2021, there were 772,281 Victorians over the age of 70 (12.6%). Following a positive Rapid Antigen Test (RAT) for SARS-CoV-2 individuals were legally required to report their result to the DH via a webform. Pathology providers were required to electronically report SARS-CoV-2 polymerase chain reaction (PCR) results. This notification triggered mobile phone text messages to individuals with a survey to determine risk, facilitating linkage to treatment, care and other supports, including via the DH COVID Positive Pathways program.[25] Public communication and media campaigns were conducted to inform the public that COVID medicines were available, check their eligibility and see their doctor if they test positive.

Oral antivirals were most commonly prescribed in the community by a general practitioner (GP), with several alternative options including community health clinics, nurse practitioners, private specialist clinics, and telehealth services such as the Victorian Virtual Emergency Department. Individuals then provided their prescription to a community pharmacy for dispensing. The National Medical Stockpile (NMS) supplied a smaller amount of COVID-19 treatments, including OAVs, to state and territory governments for dispensing through hospital pharmacies. From February 2022, both OAVs from the NMS were pre-placed in Aboriginal Community Controlled Health Services and molnupiravir in residential aged care facilities (RACFs) due to its long shelf life and suitability in people with potential contraindications to nirmatrelvir-ritonavir.[20] The PBS, NMS, primary care (GPs) and residential aged care facilities were supported by the Australian Government, Department of Health and Aged Care.

In March 2022, a fourth (booster) dose of a COVID-19 vaccine was recommended for anyone aged 65 years and above, residents of aged or disability care, people with severe immunocompromise (over 16 years) and Aboriginal or Torres Strait Islander people over the age of 50.[26] Legal requirements and recommendations for other public health and social measures (such as masks) did not change over the study period. The study was conducted during a period of high vaccination coverage (>95% 2-dose, 94% 3-dose, 70% 4-dose), for individuals aged 70 and above in Victoria. Only those with severe immunocompromise would have been eligible for 5 doses and were excluded. Between the start of the pandemic and the start of the study, in Victoria 2,154,163 people were notified with COVID-19 (6.1% 70 years and over), 177,137 were hospitalised (10.0% 70 years and over) and 4549 died (87.1% 70 years and over). Further details of the health system, model of care, access to medications, and treatment guidelines are available in the Supplementary material–Appendix 1.

Data sources and definitions

The Victorian Department of Health conducted systematic data linkage as an enhanced real-time public health surveillance activity. The Transmission Response Epidemiology Victoria Information System (TREVI) brings together several datasets for case, contact and outbreak management and surveillance. Case records were systematically linked with vaccination records from the Australian Immunisation Registry (AIR, Australian Government), COVID-19 associated hospitalisation data from the Victorian Nosocomial Infection Surveillance System (VICNISS) and COVID-19 associated mortality data from the Victorian Deaths Index. Additional linkage was performed for COVID-19 treatment data from the PBS (Australian Government) and the NMS (Victorian DH) and hospitalisation history from the Victorian Admitted Episodes Dataset (VAED). We performed multi-stage, deterministic data linkage using name, initials, unique public health identification number (Medicare), unique hospital admission identification number, address, and birth date when available. We only performed linkage where this data was not missing and therefore could be linked. Where we did not have a record of the Sex of a case, we removed these cases from the analysis, as the logistic regression performs case wise deletion in the case of a missing value for Sex and this was a very small number of cases for the mortality analysis (n = 555, 1.4%), and hospitalisation analysis (n = 446, 1.4%). We performed an additional analysis which suggested that this subset of missing cases was not systematically different from complete cases (see Supplementary material–Appendix 3).

The resulting dataset was deidentified and exported into R version 4.1.2 for cleaning and analysis. Permission for data linkage was obtained from the relevant data custodians within the Victorian and Australian governments. Approval from a Human Research Ethics Committee was not applicable as the analysis was conducted by the Victorian Department of Health as part of its public health function pursuant to the Public Health and Wellbeing Act 2008 (Vic) and the Health Records Act 2001 (Vic).

From the study population, separate analyses were conducted for the mortality and hospitalisation cohorts, with different inclusion criteria, displayed in Figs. 1 and 2, respectively. The study sample for both cohorts was restricted to COVID-19 cases notified to DH that had received 1 or more doses and less than 5 doses of a TGA-approved vaccine at least 14 days prior to their diagnosis date. The exposure of interest was dispensing of nirmatrelvir-ritonavir or molnupiravir as a first and only antiviral treatment and was ascertained through the PBS (n = 24,685, 97.9%) and a small number through the NMS (n = 577, 2.1%). Treatment initiation was defined as the date the script was dispensed by a pharmacist. The NMS database only included medications dispensed via health service and did not include pre-placed stock in Aged Care. As the NMS treatments were primarily dispensed in hospital (n = 382) rather than the community, they were excluded from the hospitalisation analysis. Cases who received other treatments–remdesivir and tixagevimab/cilgavimab–were excluded from both analyses. The outcomes assessed were COVID-19 associated mortality and hospitalisation due to any cause within 35 days from a COVID-19 diagnosis. Mortality was defined as per the Victorian DH surveillance definition—COVID-19 listed as a primary or contributing cause of death on the medical death certificate, or a death within 35 days of diagnosis, excluding trauma/accidents and suicide. The mortality analysis included both community and in-hospital diagnoses. Our post-hoc sensitivity analysis (Supplementary material–Appendix 3) explored the effect of section bias. It concluded that if cases who were diagnosed or treated close to the outcome (hospitalisation or death) were included, selection bias would be introduced, and treatment effectiveness would be increased. To address this, we applied criteria to select a cohort where case ascertainment is as equivalent as possible between treated and untreated groups. First, we recoded people treated the day prior to or the day of hospitalisation or death as untreated. This allowed inclusion of people receiving treatment where there was sufficient time for the drug to have effect (>24 h) and the greatest chance of equivalent ascertainment between treated and untreated groups. Second, we excluded people diagnosed the day prior to or the day of hospitalisation or death as inclusion of this group may disproportionately select for untreated cases with severe disease relative to treated cases.

Hospitalisation was defined through a VICNISS flag in the case database, TREVI, which involved hospital clinicians reporting all COVID-19 cases admitted to hospital during their infectious period, defined as 7 days following an initial positive COVID-19 PCR or RAT, or assessed as infectious ('active COVID-19'), regardless of the reason for admission. Cases were excluded from the hospitalisation analysis if diagnosed 1 day before, the day of, or after hospitalisation for the same reason as exclusion from the mortality analysis (Supplementary material–Appendix 3). Cases residing in Residential Aged Care Facilities (RACF) were excluded from the hospitalisation analysis to reduce bias, as reason for hospital admission in this population may not

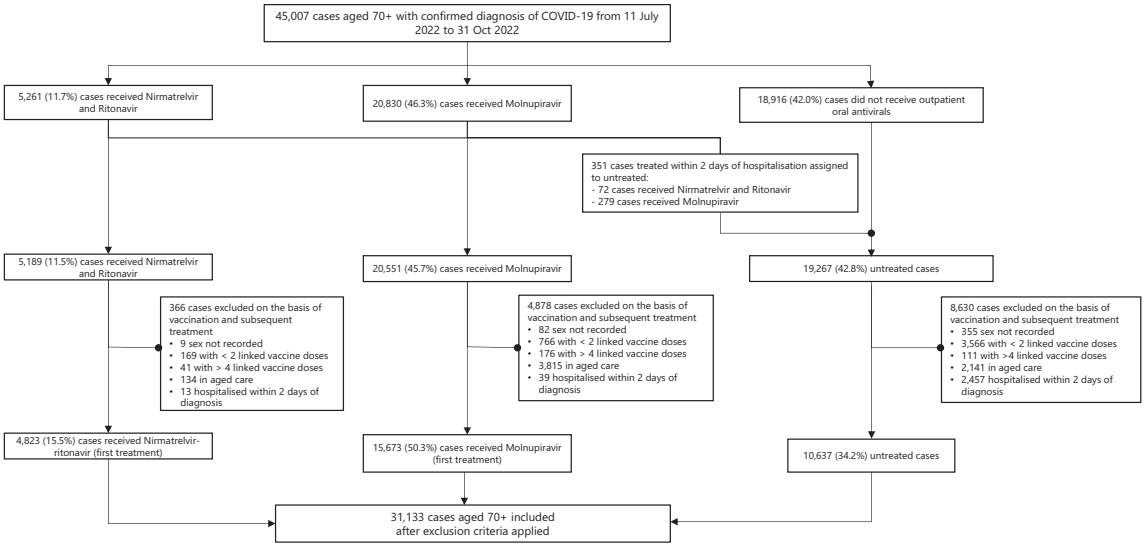

Fig. 1: Retrospective cohort participant inclusion for mortality analysis, Victoria, Australia.

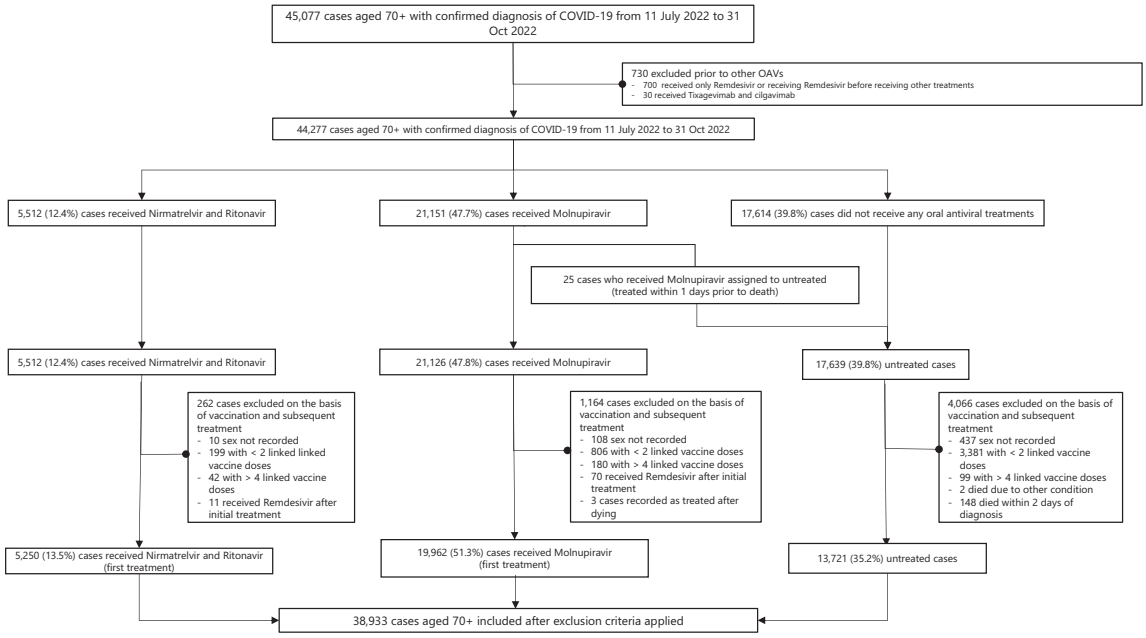

Fig. 2: Retrospective cohort participant inclusion for hospitalisation analysis, Victoria, Australia.

necessarily correlate with severe disease. For example, the medical decision or patient preference (advanced care directive) may be to accept treatment but not be hospitalised, regardless of severity—which would make treatment look more effective.

Additional variables collected were age, sex, vaccination status, hospitalisation history, socioeconomic status, RACF status and date of diagnosis and treatment initiation. Socioeconomic status was defined using the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), specifically, the Index for Relative Socioeconomic Disadvantage (IRSD),[27] assigning individuals to a decile group (low: deciles 1–3, medium: deciles 4–7, or high: deciles 8–10) based on their residential postcode. As co-morbidities were unavailable, history of hospitalisation was used as proxy and was defined as the number of hospital admissions between 1st January 2018 and 31st December 2020, grouping cases into those with minimal (less than two) vs more substantial (two or more) admissions. Whether an individual resided in a RACF was defined using address matching. We adjusted our estimates for mortality and hospitalisation by including these variables in our analysis to address any relationship between treatment and the exposure of interest which may be due to these characteristics.

Statistical analysis

All analyses were performed in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), using the tidyverse (version 2.0.0) for data processing, the stats package (version 4.1.2) for modelling, and ggplot2 (version 3.4.2) for producing visualisations. A binary logistic regression model was used to estimate the association between OAV and the outcomes of interest for each cohort (mortality and hospitalisation). For each outcome, we ran two models: i) treatment as a binary categorical variable (not treated/treated) ii) treatment as a three-level categorical variable with treatment defined as having received either of the two drugs. A third model was run for the mortality analysis only with time from diagnosis to treatment as the exposure of interest (untreated, 0–1, 2–3, 4+ days). All models included covariates for sex, vaccination status, hospitalisation history, socioeconomic status, and for the mortality analysis, RACF status. The Supplementary material–Appendix 2 contains detailed information on model specification. Results are presented as adjusted Odds Ratios (OR), with 95% confidence intervals, and p-values at 0.05 level (2-tailed tests), with the threshold for treatment coefficients adjusted for multiplicity using Holm-Bonferroni correction for the mortality (3 models) and hospitalisation (2 models) cohorts respectively. All models satisfied the assumptions underlying logistic regression. No violations of multicollinearity were observed; inspection of the Generalised Variance Inflation Factor (GVIF) showed all predictors had values very close to 1. We did not include any continuous predictors, so the linearity assumption between these and the log-odds of the outcomes do not apply. Finally, each of our predictors had large sample sizes. We performed post-hoc sensitivity analyses to

examine how changes in the definition of diagnosis prior to the outcome of interest, and treatment prior to the outcome of interest, impacted on estimates of treatment effectiveness (Supplementary material–Appendix 3).

Results

The characteristics of the mortality and hospitalisation cohorts are detailed in Tables 1 and 2, respectively. The treated and untreated groups in both cohorts were well matched in median age and had high levels of vaccination with >92% of cases having 3 or more doses. Median time from vaccination to diagnosis was 105 days (IQR 71–165 days). Observation of Tables 1 and 2 shows treated cases were more likely to be female, live in areas of higher socioeconomic advantage (SEIFA 8–10), be vaccinated with 4 doses of covid vaccination, have a history of hospitalisation, and (in the mortality analysis) live in a RACF. Cases who received molnupiravir were slightly older than untreated cases and those receiving nirmatrelvir-ritonavir. Most (96.5%) treatments occurred within three days of diagnosis. Cases who received molnupiravir were more likely to have prior hospitalisation compared to those that received nirmatrelvir-ritonavir and no treatment.

Modelling results are reported in Table 3 (also see Supplementary material–Appendix 3, Supplementary Figs. S4–S8 for forest plots). Compared to untreated cases, receiving either OAV was associated with a 57% (OR = 0.43, 95% CI 0.36–0.51) reduction in the odds of death. This reduction was 73% (OR = 0.27, 95% CI 0.17–0.40) for nirmatrelvir-ritonavir and 55% (OR = 0.45, 95% CI 0.38–0.54) for molnupiravir. Initiating treatment within a day of diagnosis was associated with a 61% reduction in the odds of death (OR = 0.39, 95% CI 0.33–0.46) which reduced to 55% if treatment was commenced two to three days post diagnosis (OR = 0.45, 95% CI 0.35–0.57). Receiving treatment four or more days post-diagnosis was not associated with a

	No treatment *n* = 13,721	Molnupiravir *n* = 19,962	Nirmatrelvir-ritonavir *n* = 5250	Received treatment *n* = 25,212	Overall *n* = 38,933
Age	77 (73, 84)	78 (74, 85)	76 (72, 81)	78 (73, 84)	77 (73, 84)
Sex					
Female	7181 (52.3%)	11,231 (56.3%)	2966 (56.5%)	14,197 (56.3%)	21,378 (54.9%)
Male	6540 (47.7%)	8731 (43.7%)	2284 (43.5%)	11, 015 (43.7%)	17,555 (45.1%)
Days from diagnosis to treatment					
0–1 days	NA	15,099 (76.6%)	4065 (78.2%)	19,164 (76.9%)	19,164 (76.9%)
2–3 days	NA	3925 (19.9%)	992 (19.1%)	4917 (19.7%)	4917 (19.7%)
4+ days	NA	694 (3.5%)	140 (2.7%)	834 (3.4%)	834 (3.4%)
No treatment or treatment prior to diagnosis					
No treatment	13,721	NA	NA	NA	13,721
Prior	NA	244	53	297	297
Socioeconomic decile (IRSD)					
1–3	3026 (22.1%)	3567 (17.9%)	715 (13.6%)	4282 (17.0%)	7308 (18.8%)
4–7	4923 (35.9%)	6796 (34.0%)	1600 (30.5%)	8396 (33.3%)	13,319 (34.2%)
8–10	5772 (42.1%)	9599 (48.1%)	2935 (55.9%)	12,534 (49.7%)	18,306 (47.0%)
Vaccination status					
1–2 doses	1132 (8.3%)	839 (4.2%)	200 (3.8%)	1039 (4.1%)	2171 (5.6%)
3 doses	4298 (31.3%)	4197 (21.0%)	982 (18.7%)	5179 (20.5%)	9477 (24.3%)
4 doses	8291 (60.4%)	14,926 (74.8%)	4068 (77.5%)	18,994 (75.3%)	27,285 (70.1%)
Aged-care resident					
No	11,689 (85.2%)	16,107 (80.7%)	5110 (97.3%)	21,217 (84.2%)	32,906 (84.5%)
Yes	2032 (14.8%)	3855 (19.3%)	140 (2.7%)	3995 (15.8%)	6027 (15.5%)
Hospitalisation history					
<2 Hosp between 2018 and 2020	7624 (55.6%)	9805 (49.1%)	2973 (56.6%)	12,778 (50.7%)	20,402 (52.4%)
^{3}2 Hosp between 2018 and 2020	6097 (44.4%)	10,157 (50.9%)	2277 (43.4%)	12,434 (49.3%)	18,531 (47.6%)
Hospitalised					
Not hospitalised	12,086 (88.1%)	19,266 (96.5%)	4955 (94.4%)	24,221 (96.1%)	36,307 (93.3%)
Hospitalised	1635 (11.9%)	696 (3.5%)	295 (5.6%)	991 (3.9%)	2626 (6.7%)
Death					
Alive	13,259 (96.6%)	19,616 (98.3%)	5221 (99.4%)	24,837 (98.5%)	38,096 (97.9%)
Dead	462 (3.4%)	346 (1.7%)	29 (0.6%)	375 (1.5%)	837 (2.1%)

Table 1: **Characteristics of individuals diagnosed with COVID-19, July 11–October 31, 2022, Victoria, Australia: mortality analysis.**

	No treatment n = 10,637	Molnupiravir n = 15,673	Nirmatrelvir-ritonavir n = 4823	Received treatment n = 20,496	Overall n = 31,133
Age	75.0 (72.0, 80.0)	77.0 (73.0, 82.0)	75.0 (72.0, 80.0)	76.0 (73.0, 81.0)	76.0 (73.0, 81.0)
Sex					
Female	5299 (49.8%)	8433 (53.8%)	2733 (56.7%)	11,166 (54.5%)	16,465 (52.9%)
Male	5338 (50.2%)	7240 (46.2%)	2090 (43.3%)	9330 (45.5%)	14,668 (47.1%)
Socioeconomic decile (IRSD)					
1–3	2246 (21.1%)	2581 (16.5%)	613 (12.7%)	3194 (15.6%)	5440 (17.5%)
4–7	3856 (36.3%)	5268 (33.6%)	1445 (30.0%)	6713 (32.8%)	10,569 (33.9%)
8–10	4535 (42.6%)	7824 (49.9%)	2765 (57.3%)	10,589 (51.7%)	15,124 (48.6%)
Vaccination status					
1–2 doses	782 (7.4%)	583 (3.7%)	140 (2.9%)	723 (3.5%)	1505 (4.8%)
3 doses	3387 (31.8%)	3291 (21.0%)	843 (17.5%)	4134 (20.2%)	7521 (24.2%)
4 doses	6468 (60.8%)	11,799 (75.3%)	3840 (79.6%)	15,639 (76.3%)	22,107 (71.0%)
Hospitalisation history					
<2 Admissions between 2018 and 2020	6390 (60.1%)	8037 (51.3%)	2801 (58.1%)	10,838 (52.9%)	17,228 (55.3%)
^{3}2 Admissions between 2018 and 2020	4247 (39.9%)	7636 (48.7%)	2022 (41.9%)	9658 (47.1%)	13,905 (44.7%)
Hospitalisation					
Not hospitalised	10,452 (98.3%)	15,478 (98.8%)	4777 (99.0%)	20,255 (98.8%)	30,707 (98.6%)
Hospitalised	185 (1.7%)	195 (1.2%)	46 (1.0%)	241 (1.2%)	426 (1.4%)

Median (IQR); n (%).

Table 2: **Characteristics of individuals diagnosed with COVID-19, July 11–October 31, 2022, Victoria, Australia: hospitalisation analysis.**

large reduction in the odds of death (OR = 0.67, 95% CI 0.44–0.97).

Treatment with either OAV was also associated with a 31% reduction in the likelihood of hospitalisation compared to untreated cases (OR = 0.69, 95% CI 0.55–0.86), 40% (OR = 0.60, 95% CI 0.43–0.83) for nirmatrelvir-ritonavir and 29% (OR = 0.71, 95% CI 0.58–0.87) for molnupiravir. Males and those previously hospitalised were more likely to be hospitalised, whereas those in higher SEIFA deciles, and who received 4 doses of vaccine were less likely to be hospitalised (Table 3).

The sensitivity analyses (Supplementary material–Appendix 3) show that treatment effectiveness is highly sensitive to the choices around inclusion criteria, particularly for the hospitalisation analysis, but that our cohort definitions were chosen to reduce possible inflation of treatment effectiveness due to selection bias favouring selection of treated or untreated people.

Discussion

Our study found a significant association between OAV treatment and a reduction in death and hospitalisation compared to no treatment, in a cohort of highly vaccinated individuals aged 70 years and over during an Omicron sub-variant (BA.4 and BA.5) wave, in Victoria, Australia. The benefit relative to no treatment appeared greater for people who received nirmatrelvir-ritonavir than those that received molnupiravir. Our results suggest that timely treatment is paramount—cases treated within three days of diagnosis had a lower likelihood of death than those that were treated four or more days after diagnosis.

A strength of our study is that we analysed all notified cases in Victoria during the study period. All Victorians aged 70 and over were eligible for treatment and all cases were required to notify DH of their diagnosis (until October 12, 2022), minimising reporting bias. We followed the STROBE guidelines for reporting observational studies. This is the first real world observational effectiveness study of OAVs in Australia. The study is relevant to other similar settings with an older population, high levels of vaccination, where both OAV were available and as it was conducted during the dominance of the Omicron variant. Our methods and sensitivity analyses support the robustness of our findings, particularly for the mortality analyses.

Our findings are limited by the observational nature of our study whereby unobserved confounders may bias estimates of treatment effectiveness. Of primary concern in our hospitalisation analysis is reporting bias, where individuals seeking treatment may be more likely to report their diagnosis. If present, this potentially results in an under-ascertainment of untreated non-hospitalised infections in our cohort, leading to bias towards treatment effectiveness. We attempted to mitigate this via our cohort selection criteria and modelling approach and quantify their effect via post-hoc sensitivity analysis (Supplementary material–Appendix 3). We excluded cases who were diagnosed in the community on the same day or the day prior to hospitalisation, as they are more likely to have severe

Model	Unadjusted odds ratio (95% CI) mortality	p-value	Adjusted odds ratio (95% CI) mortality	p-value	Unadjusted odds ratio (95% CI) hospitalisation	p-value	Adjusted odds ratio (95% CI) hospitalisation	p-value
Treatment								
3 doses			0.66 (0.51, 0.85)	0.001			0.83 (0.57, 1.26)	0.37
4 doses			0.45 (0.36, 0.57)	<0.0001			0.59 (0.41, 0.88)	0.007
Male			1.34 (1.16, 1.54)	<0.0001			1.26 (1.04, 1.53)	0.02
RACF resident			6.67 (5.78, 7.70)	<0.0001				
SEIFA decile 4–7			0.80 (0.66, 0.96)	0.016			0.76 (0.58, 0.98)	0.035
SEIFA decile 8–10			0.81 (0.68, 0.97)	0.022			0.72 (0.57, 0.93)	0.011
2+ Admissions 2018–2020			1.89 (1.63, 2.19)	<0.0001			2.76 (2.26, 3.40)	<0.0001
Treatment[a]	0.43 (0.36, 0.51)	<0.0001	0.43 (0.36, 0.51)	<0.0001	0.67 (0.55, 0.82)	<0.0001	0.69 (0.55, 0.86)	<0.0001
Treatment type								
3 doses			0.65 (0.51, 0.84)	0.001			0.83 (0.57, 1.26)	0.37
4 doses			0.45 (0.36, 0.57)	<0.0001			0.59 (0.41, 0.88)	0.007
Male			1.34 (1.16, 1.54)	<0.0001			1.26 (1.04, 1.52)	0.021
RACF resident			0.80 (0.66, 0.96)	0.017				
SEIFA decile 4–7			0.82 (0.68, 0.98)	0.026			0.76 (0.58, 0.98)	0.036
SEIFA decile 8–10			6.42 (5.55, 7.42)	<0.0001			0.73 (0.57, 0.94)	0.013
2+ Admissions 2018–2020			1.88 (1.63, 2.18)	<0.0001			2.75 (2.25, 3.39)	<0.0001
Molnupiravir[a]	0.51 (0.44, 0.58)	<0.0001	0.45 (0.38, 0.54)	<0.0001	0.71 (0.58, 0.87)	0.001	0.71 (0.58, 0.87)	0.003
Nirmatrelvir-ritonavir[a]	0.16 (0.11, 0.23)	<0.0001	0.27 (0.17, 0.40)	<0.0001	0.54 (0.39, 0.75)	0.0002	0.60 (0.43, 0.83)	0.001
Time from diagnosis to treatment								
3 doses			0.67 (0.52, 0.87)	0.002				
4 doses			0.46 (0.36, 0.58)	<0.0001				
Male			1.35 (1.17, 1.55)	<0.0001				
RACF resident			0.81 (0.67, 0.98)	0.031				
SEIFA decile 4–7			0.83 (0.69, 1.00)	0.046				
SEIFA decile 8–10			6.74 (5.83, 7.79)	<0.0001				
2+ Admissions 2018–2020			1.89 (1.63, 2.20)	<0.0001				
0–1 days[a]	0.38 (0.32, 0.44)	<0.0001	0.39 (0.33, 0.46)	<0.0001				
2–3 days[a]	0.49 (0.38, 0.61)	<0.0001	0.45 (0.35, 0.57)	<0.0001				
4+ days[a]	1.03 (0.69, 1.49)	0.044	0.67 (0.44, 0.97)	0.044				

Binary logistic regression was used to estimate the Odds Ratio (OR) of mortality and hospitalisation given treatment status. OR of outcome reported for unadjusted models, and models adjusted for covariates of vaccination status, sex, RACF status (mortality only), socioeconomic status (SEIFA decile), hospitalisation history. Estimates are relative to baseline reference categories: 1–2 doses, Female, non-RACF resident, SEIFA deciles 1–3, <2 Admissions 2018–2020, and No treatment (for each of the treatment categories). Adjusted Odds Ratios for treatment are multiplicity corrected using the Holm-Bonferroni method in the same order as they appear in the table for each cohort. [a]Denotes treatment categories in each model and analysis.

Table 3: **Outcomes for COVID-19 oral antiviral treatment effectiveness Victoria, Australia, 11th July 2022–31st October 2022: model results for mortality and hospitalisation analyses.**

illness and less likely to receive treatment and their inclusion would increase estimates of treatment effectiveness. Our surveillance definition of hospitalisation was any-cause whilst infectious with COVID-19, which means our hospitalised cohort could comprise a mix of patients with COVID-19 as a primary admission diagnosis, a secondary or contributing diagnosis or an incidental diagnosis. Data was not available to link and analyse admission diagnosis in our study. Given our selection criteria excludes diagnoses in hospital, outcome misclassification bias may be introduced by people who received community-based OAV but were hospitalised for another cause. Operational insights from health services during the study period indicates that incidental COVID-19 was a small proportion of admissions. We were unable to include medical co-morbidities, which may act as a confounder as they could be associated with both exposure (treatment) and the outcome; people may be more likely to test, access care, and be hospitalised. We may partially account for this by including a proxy, history of hospitalisation, as a covariate in the model but acknowledge this will not completely block the confounding effect of severity and is a limitation of our study. We were unable to measure adherence to medications once prescribed. However, as patients had accesses to a medical practitioner, supports including COVID positive pathways (that provide remote support and reminders) and treatment was only for a short duration, this is unlikely to be a major limitation.

Our findings are consistent with the existing literature. Firstly, the direction and magnitude of the treatment effect is similar to the two clinical trials in the pre-Omicron era.[7,8] A recent open-label multi-centre randomised control trial (PANORAMIC) in the UK showed that while molnupiravir use is associated with a reduction in viral load, time to symptom resolution, and medical care access frequency after 28 days, it did not reduce the risk of all-cause hospitalisation and mortality relative to standard of care.[28] It is important to note that the study population were relatively young (86% were 50–70 years) and the rates of death and hospitalisation in a highly vaccinated population were substantially lower than our older cohort. Therefore, the study may not have adequately assessed the potential benefit for molnupiravir in the over-70 age group.

Secondly, most real-world effectiveness studies, which were conducted in the Omicron era support the effectiveness of OAV in reducing mortality and hospitalisation, with some evidence for a larger reduction seen with nirmatrelvir-ritonavir relative to no treatment, than molnupiravir.[9–11,16] In Hong Kong, nirmatrelvir-ritonavir was consistently associated with a larger risk reduction than molnupiravir in reducing the risk of hospitalisation (14–33% vs no effect), in-hospital disease progression (13–62% vs 24–57%), and death (48–78% vs 5–39%).[9] However, nirmatrelvir-ritonavir is not suitable for some individuals with underlying conditions such as severe chronic kidney or liver disease or when there are drug–drug interactions that cannot be managed. In these individuals, molnupiravir is a suitable option and preferable to no treatment, given its favourable safety profile. This supports the current Victorian clinical treatment guidelines for COVID-19 and may be why molnupiravir was more frequently prescribed than nirmatrelvir-ritonavir in this older population.

Benefits of OAV may extend beyond reducing acute mortality and hospitalisation. Recent observational data from a US veterans cohort has reported effectiveness of both nirmatrelvir-ritonavir[29] and molnupiravir[17] in reducing the risk of post-acute sequalae of COVID-19 or long COVID. Clinical trials are ongoing and OAV may be an important tool in the prevention of long COVID, a condition with major potential health and societal consequences with limited current management options.[30] Surveillance and ongoing research on treatment effectiveness will allow for monitoring the impact of new variants and for the potential emergence of antiviral resistance. The significance of mutations induced by molnupiravir is uncertain and requires further research.[31]

In Australia, pandemic responses saw a focus on engagement and response in priority communities—including residents of aged care facilities, people living with disability, culturally and linguistically diverse (CALD) communities and Indigenous Australians. Despite this, Australians with lower socioeconomic status, who are more likely from these communities, are more likely to be hospitalised with or die from COVID-19.[32] A recent publication from Victoria demonstrated that cases from the lowest IRSD quartile were 15% (95% CI 13–17%) less likely to receive OAV than the top quartile.[19] Addressing structural barriers in the health system, improving health literacy, ensuring accessibility and acceptability, and developing strategies to increase antiviral uptake, particularly for those who bear the greatest burden of COVID, will aid in mitigating these inequities.

A key lesson from our study is the importance of enhanced and real-time surveillance, which includes population-wide data linkage. Such data linkage work has routinely been undertaken for research purposes rather than embedded in public health responses. During the COVID-19 response in Victoria, the linkage of databases was prioritised as a key public health activity to inform policy and action. Victoria has an established specialist data linkage unit and the capability for this function. Establishing systematic national data linkage and expansion to other data sets that assist in addressing inequity such as CALD status, disability, and co-morbidities, would greatly benefit the public health response to infectious diseases and other health issues.

In Victoria's Omicron BA.4 and BA.5 wave in 2022, early community-based initiation of OAV in people diagnosed with COVID-19 aged 70 years and over, who had high levels of vaccination, reduced their likelihood of death and hospitalisation. This effect was seen for both nirmatrelvir-ritonavir and molnupiravir, with greater reductions of these poor outcomes observed among those receiving nirmatrelvir-ritonavir. Further research is needed to assess the effectiveness of OAV in different settings, sub-populations and at-risk groups, not only for the outcomes of mortality and hospitalisation, but also post-acute sequalae. Real-world effectiveness studies are an important addition to the evidence base during a public health emergency, alongside well-designed clinical trials. OAV are an important vital additional tool as part of a multi-layered response to COVID.[2] While the COVID-19 public health emergency has been declared over, COVID-19 remains an established and ongoing health concern that is a leading cause of death, morbidity and ongoing epidemic waves.[33] A sustained response to COVID-19 is required that aims to reduce community transmission, mitigate the risk of illness in priority and high-risk populations, and protect health systems; while research and innovation aims to deliver more effective tools, including optimising access to existing and novel therapeutics.

Contributors

CVH: conceptualisation, data curation, software, formal analysis, visualisation, methodology, writing—original draft, reviewing and editing, project administration.

SSM: supervision, conceptualisation, methodology, writing—original draft, writing—review and editing, project administration.

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Data sharing statement

Individual participant data from this study are not able to be shared by the authors. A request to receive data may be made to the Victorian Department of Health and Australian Department of Health and Aged Care. All proposals will be reviewed by the relevant data custodians to ensure that the proposed use aligns with participant consent. To initiate a data request, please contact the corresponding author or health departments directly. A data dictionary and the analytical code is available on request from the authors.

Declaration of interests

No conflicts of interest or relevant disclosures existed for the authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100917.

References

1 WHO coronavirus (COVID-19) dashboard [internet]. [cited 2023 Jun 28]. Available from: https://covid19.who.int.
2 Sachs JD, Karim SSA, Aknin L, et al. The Lancet Commission on lessons for the future from the COVID-19 pandemic. *Lancet*. 2022;400(10359):1224–1280.
3 Schöley J, Aburto JM, Kashnitsky I, et al. Life expectancy changes since COVID-19. *Nat Hum Behav*. 2022;6(12):1649–1659.
4 Kumari M, Lu RM, Li MC, et al. A critical overview of current progress for COVID-19: development of vaccines, antiviral drugs, and therapeutic antibodies. *J Biomed Sci*. 2022;29(1):68.
5 Murakami N, Hayden R, Hills T, et al. Therapeutic advances in COVID-19. *Nat Rev Nephrol*. 2023;19(1):38–52.
6 Hotez PJ, Batista C, Amor YB, et al. Global public health security and justice for vaccines and therapeutics in the COVID-19 pandemic. *EClinicalMedicine*. 2021;39:101053.
7 Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;386(15):1397–1408.
8 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of covid-19 in Nonhospitalized patients. *N Engl J Med*. 2022;386:509–520.
9 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet*. 2022;400(10359):1213–1222.
10 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. *Lancet Infect Dis*. 2022;22(12):1681–1693.
11 Wai AKC, Chan CY, Cheung AWL, et al. Association of Molnupiravir and Nirmatrelvir-Ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19. *Lancet Reg Health West Pac*. 2022;30:100602.
12 Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of molnupiravir in high risk patients: a propensity score matched analysis. *Clin Infect Dis*. 2022;76(3):453–460. p. ciac781.
13 Flisiak R, Zarębska-Michaluk D, Rogalska M, et al. Real-world experience with molnupiravir during the period of SARS-CoV-2 Omicron variant dominance. *Pharmacol Rep*. 2022;74(6):1279–1285.
14 Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe covid-19 outcomes during the omicron surge [internet]. *N Engl J Med*. 2022;387(9):790–798. Available from: https://www.ncbi.nlm.nih.gov/pubmed/36001529.
15 Shah MM, Joyce B, Plumb ID, et al. Paxlovid associated with decreased hospitalization rate among adults with COVID-19 — United States, April–september 2022 [internet]. *MMWR Morb Mortal Wkly Rep*. 2022;71:1531–1537. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e2.htm.
16 Yip TCF, Lui GCY, Lai MSM, et al. Impact of the use of oral antiviral agents on the risk of hospitalization in community coronavirus disease 2019 patients (COVID-19). *Clin Infect Dis*. 2023;76(3):e26–e33.
17 Xie Y, Bowe B, Al-Aly Z. Molnupiravir and risk of hospital admission or death in adults with covid-19: emulation of a randomized target trial using electronic health records. *BMJ*. 2023;380:e072705.
18 Yanez ND, Weiss NS, Romand JA, Treggiari MM. COVID-19 mortality risk for older men and women. *BMC Publ Health*. 2020;20(1):1742.
19 Allard NL, Canevari J, Haslett N, Cowie BC. Access to oral COVID-19 antivirals in the community: are eligibility criteria and systems ensuring equity? *Med J Aust*. 2023;218(10):438–441. mja2.51949.
20 Sturgiss E, Simpson N, Ball L, Hall Dykgraaf S, Kelly P, Kidd M. Community-based access to oral antiviral treatments for COVID-19 in Australia. *Aust J Gen Pract*. 2023;52(6):409–412.
21 Department of Health, Victoria. *COVID-19 medications for at risk people who do not require oxygen*. Australia: Victoria State Government; 2021.
22 Department of Health Victoria A. Coronavirus update for Victoria - 7 July 2022. State Government of Victoria, Australia [cited 2023 May 23]. Available from: https://www.health.vic.gov.au/media-releases/coronavirus-update-for-victoria-7-july-2022.
23 Department of Health Victoria A. Chief health officer update - 4 November 2022. State Government of Victoria, Australia [cited 2023 May 23]. Available from: https://www.health.vic.gov.au/media-releases/chief-health-officer-update-4-november-2022.
24 2021 Victoria, census all persons QuickStats | Australian Bureau of Statistics [cited 2023 Aug 3]. Available from: https://www.abs.gov.au/census/find-census-data/quickstats/2021/2.
25 Lim SM, Allard NL, Devereux J, et al. The COVID positive pathway: a collaboration between public health agencies, primary care, and metropolitan hospitals in Melbourne. *Med J Aust*. 2022;216(8):413–419.
26 Australian Government Department of Health and Aged Care. ATAGI updated recommendations for a winter dose of COVID-19 vaccine. Australian Government Department of Health and Aged Care [cited 2023 Aug 9]. Available from: https://www.health.gov.au/news/atagi-updated-recommendations-for-a-winter-dose-of-covid-19-vaccine; 2022.
27 Socio-economic Indexes for areas (SEIFA), Australia, 2021 | Australian Bureau of Statistics [cited 2023 May 28]. Available from: https://www.abs.gov.au/statistics/people/people-and-communities/socio-economic-indexes-areas-seifa-australia/latest-release; 2023.
28 Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023;401:281–293.

29 Xie Y, Choi T, Al-Aly Z. Association of treatment with nirmatrelvir and the risk of post–COVID-19 condition. *JAMA Intern Med*. 2023;183(6):554–564 [cited 2023 May 23]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2802878.
30 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133–146.
31 Sanderson T, Hisner R, Donovan-Banfield I, Peacock T, Ruis C. Identification of a molnupiravir-associated mutational signature in SARS-CoV-2 sequencing databases. *Infect Dis (except HIV/AIDS)*. 2023. https://doi.org/10.1101/2023.01.26.23284998. [cited 2023 May 23].
32 Australian Institute of Health and Welfare. Australia's health 2022: data insights [cited 2023 May 23]; Available from: http://www.aihw.gov.au/reports/australias-health/australias-health-2022-data-insights/summary; 2022.
33 Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic [cited 2023 Jun 5]. Available from: https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic.