Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Real-world effectiveness of oral antivirals for COVID-19

New orally bioavailable, direct-acting, antiviral therapeutics targeting RNA viruses including SARS-CoV-2 have arrived. Molnupiravir and nirmatrelvir plus ritonavir were granted an emergency use authorisation by the US Food and Drug Administration in December, 2021, for treating outpatients with first-ever SARS-CoV-2 infection confirmed by PCR (aged ≥18 years for molnupiravir and ≥12 years and children ≥40 kg for nirmatrelvir plus ritonavir), on the basis of the analysis of the pivotal randomised, placebo-controlled trials, MOVe-OUT[1] and EPIC-HR.[2] Both studies included unvaccinated outpatients receiving the antivirals within 5 days of symptom onset during the delta (B.1.617.2) surge. Participants were considered at risk for severe COVID-19, although fairly young (82·8% aged <60 years in MOVe-OUT and 87·2% aged <65 years in EPIC-HR), and their main risk factor for severity was overweight (73·7% participants had a BMI >30 kg/m^2 in MOVe-OUT and 80·5% had a BMI >25 kg/m^2 in EPIC-HR). In these populations, both antivirals were associated with a significant decrease in the relative risk of hospitalisation or death: by 30% for molnupiravir and by 89% for nirmatrelvir plus ritonavir. Upon widespread use of these antivirals in 2022, further real-world data were needed to refine these results and to test their effectiveness under various conditions.

Carlos Wong and colleagues[3] report findings from a large-scale, real-world, retrospective cohort study done in Hong Kong during the omicron (B.1.1.529) subvariant BA.2.2 wave. Consistent with local guidelines, the authors included outpatients at risk of severe disease to assess the effectiveness of early administration of molnupiravir and nirmatrelvir plus ritonavir (within 5 days of symptom onset). Data were collected via electronic medical records with cross-reference to vaccination records from the Department of Health, taking advantage of the near-complete coverage of local health data. 4983 molnupiravir users were matched with 49 234 non-users, and 5542 nirmatrelvir plus ritonavir users were matched with 54 672 non-users using a propensity score that was based on age, sex, date of confirmed SARS-CoV-2 infection, Charlson Comorbidity Index score, and vaccination status. All included patients were from the Hong Kong area. Among molnupiravir users, 955 (51%) of 1880 were female and the mean age was 80·8 years. Among nirmatrelvir plus ritonavir users, 462 (50%) of 924 were female and the mean age was 77·2 years. Among controls, 7310 (49%) of 14810 were female and the mean age was 74·3 years. In time-to-event propensity-score-matched models, early molnupiravir use was associated with a reduction in all-cause mortality (the primary outcome; hazard ratio 0·76 [95% CI 0·61–0·95]; p=0·013) but had no significant effect on COVID-19-related hospital admission (0·98 [0·89–1·06]; p=0.·8), and the early use of nirmatrelvir plus ritonavir was associated with a reduction in all-cause mortality (0·34 [0·22–0·52]; p<0·0001) and hospital admission (0·76 [0·67–0·86]; p<0·0001).


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See **Articles** page 1213

Overall, the risk of all-cause mortality was reduced by 24% with molnupinavir and by 66% with nirmatrelvir plus ritonavir. Similar results were obtained in sensitivity analyses through case-control models. Subgroup analyses among fully vaccinated participants showed a reduction in hospital admissions (0·66 [0·42–1·02], p=0·063 for molnupiravir, and 0·71 [0·51–1·01], p=0·056 for nirmatrelvir plus ritonavir), whereas the effect on mortality was not significant for molnupiravir, and not evaluable for nirmatrelvir plus ritonavir because of the low number of fatal events. This study has inherent limitations of observational retrospective studies. Notably, a self-reporting bias was likely to exist, because asymptomatic or mildly symptomatic patients might not have been seeking medical attention, leading to overestimation of antiviral treatment effect.

This study brings relevant data from clinical practice among a large community-dwelling population (85% of participants aged >60 years), in which the efficacy of both antivirals in preventing all-cause mortality was maintained and nirmatrelvir plus ritonavir was associated with a reduction in hospitalisation. Another real-world, large-scale, retrospective study done in Israel concluded that initiating nirmatrelvir plus ritonavir within the first 5 days of SARS-CoV-2 infection was associated with a significantly reduced risk of progression to severe COVID-19 or mortality.[4] Further, the results suggest an antiviral activity of both antivirals during the period of omicrion subvariant BA.2.2 dominance, as previously observed during the subvariant BA.1 surge with nirmatrelvir plus ritonavir[4] and confirmed in vitro.[5,6] Also, in fully vaccinated participants with breakthrough COVID-19, hospitalisation was reduced when receiving the antivirals and was less marked than reported elsewhere for nirmatrelvir plus ritonavir.[4] This finding raises the question of what should be the antiviral of choice for outpatients with breakthrough COVID-19, a frequent occurrence in the context of broad vaccine coverage. Further prospective studies are warranted in the setting of outpatients with breakthrough COVID-19 or in combination trials or when new oral therapeutics become available using these antivirals as comparators. The occurrence of rebound disease following a 5-day course of nirmatrelvir plus ritonavir that has been reported elsewhere[7,8] was not documented here.

Continuing to collect and disseminate data on the effectiveness and safety of COVID-19 antivirals is important for populations at risk of severe disease.

CB reports consulting fees from Da Volterra and Mylan and from 4Living Biotech (member of a data safety monitoring board for a clinical trial [LEONARDO] to investigate the effect of plerixafor in acute respiratory failure related to COVID-19), which are all unrelated to the topic of this Comment. FA declares no competing interests.

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Safeguarding children's health in a changing global environment

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Children are exquisitely vulnerable to environmental hazards.[1] This sensitivity reflects children's unique exposures, their immaturity, and the great complexity of early human development. Exposures during prenatal windows of susceptibility can increase risk for disease in childhood and impair health across the lifespan.