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.

antimicrobial stewardship perspective, and strikingly similar to the pooled value reported in a recent meta-analysis (62%), again despite a low pooled frequency of bacterial infections in this meta-analysis (6%).[4] Although some encouraging steps forward have been made, a lot of ground is still left to cover.

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SARS-CoV-2 rebound with and without antivirals

As the COVID-19 pandemic continues, interventions for preventing SARS-CoV-2 transmission and progression to severe disease remain priorities. Vaccines against COVID-19 have an important role in preventing symptomatic infections that would otherwise lead to hospitalisation and death, but are less effective in preventing transmission. In addition, monoclonal antibodies have substantially reduced effectiveness against recently emerged strains,[1] and should be tailored to the variants. Therefore, antiviral compounds, specifically nirmatrelvir–ritonavir, molnupiravir, and remdesivir, when used promptly at the onset of SARS-CoV-2 infection, are currently the most effective drug therapies for inhibiting viral replication.

Targeting the early replication stage of SARS-CoV-2 is pivotal to prevent progression to severe COVID-19, especially in immunocompromised and older individuals. In the outpatient setting, both nirmatrelvir–ritonavir and molnupiravir administered for 5 days have led to greater reductions in the relative risk of hospitalisation or death versus placebo in unvaccinated patients at high risk of severe COVID-19, with an associated decrease in nasopharingeal viral load.[2,3]

However, recently reported cases of virological rebound after completion of a 5-day course of nirmatrelvir–ritonavir have raised concerns around the real world effectiveness of antivirals against SARS-CoV-2.[4]

In *The Lancet Infectious Diseases*, Wong and colleagues[5] assessed the incidence of viral burden rebound, and evaluated associated risk factors and clinical outcomes, in a retrospective cohort of consecutive hospitalised patients with non-oxygen-dependent COVID-19 during the omicron BA.2.2 wave (from Feb 26 to July 3, 2022) in Hong Kong. Outcomes were compared between patients receiving and not receiving oral antivirals. Viral burden rebound was defined as a reduction in cycle threshold (Ct) value larger than or equal to 3 between two consecutive measurements, with this decrease sustained in at least an immediately subsequent Ct measurement for patients with three or more measurements.

Among 4592 patients, 213 (4·6%) were reported to have viral burden rebound. Rebound occurred in 16 (6·6%) of 242 patients receiving nirmatrelvir–ritonavir, 27 (4·8%) of 563 patients receiving molnupiravir, and 170 (4·5%) of 3787 patients who did not receive oral antivirals (control group). No significant difference in the incidence of viral burden rebound was found among the three groups. Additionally, a composite clinical outcome of invasive mechanical ventilation initiation, intensive care unit admission, and mortality from day 5

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of follow-up was not significantly associated with viral burden rebound across the three groups.

As expected, immunocompromised status was associated with increased odds of viral burden rebound, regardless of the use of SARS-CoV-2 antivirals. Of note, in the nirmatrelvir–ritonavir group, patients with high comorbidity burden (Charlson Comorbidity Index >6) and those taking corticosteroids had increased odds of rebound; and in the molnupiravir group, patients taking corticosteroids had increased odds of rebound. Surprisingly, the odds of viral burden rebound in patients receiving nirmatrelvir–ritonavir were significantly reduced in individuals who were not fully vaccinated (defined as those who had received less than two doses of BNT162b2 or less than three doses of CoronaVac). Additionally, in patients receiving nirmatrelvir–ritonavir and in those receiving molnupiravir, individuals aged 18–65 years had higher odds of viral burden rebound than individuals aged 65 years or older. A limitation of the study was that no sequencing was performed, making it difficult to differentiate between relapse with the same strain and recurrence of reinfection by a different strain than the one responsible for the initial infection episode.

These rates of viral rebound from a real-world study[5] are consistent, although higher, than the rates reported in the EPIC-HR trial, in which viral load rebound occurred in 23 (2·3%) of 990 patients receiving nirmatrelvir–ritonavir and 17 (1·7%) of 980 patients receiving placebo, without significant difference between these groups.[6] Collectively the data show that COVID-19 rebound is rare but possible, with or without completion of a SARS-CoV-2 antiviral course. In the case of rebound following antiviral treatment, immune evasion due to early viral suppression has been hypothesised as a cause,[7] and this could also partially explain why in the study by Wong and colleagues,[5] fully vaccinated individuals were at increased risk of rebound.

Conversely, in one patient with COVID-19 recrudescence, Carlin and colleagues identified a robust antibody and T-cell immune response,[8] accounting for a mild infection with a low risk of disease progression.

Emergence of SARS-CoV-2 resistance as a cause of viral rebound is unlikely, considering that in previous studies on COVID-19 rebound, resistance mutations have not been identified.[9] Other noteworthy hypotheses include the proposal that antiviral exposure might be insufficient due to individual pharmacokinetics,[8] or that SARS-CoV-2 persists in viral sanctuaries—sites where viruses can persist and potentially remain transmissible after drug treatments such as antivirals.[10] In the case of SARS-CoV-2 persistence, perhaps a 5-day course of antivirals could be insufficient to eradicate SARS-CoV-2 in individuals with immunocompromised status or comorbidities, or in those taking steroids.

Given that no association was found between oral antiviral treatment and viral burden rebound, the study by Wong and colleagues emphasises the importance of continuing to offer antivirals to individuals with COVID-19 who are at increased risk of progression to severe COID-19. A major advance from this study is the identification of risk predictors of viral burden rebound. These predictors were immunocompromised status and concomitant use of corticosteroids for all patients; and high comorbidity burden in patients receiving nirmatrelvir–ritonavir. Further studies are needed to better define the causes of viral rebound in patients with COVID-19, and to understand how to tailor the administration of SARS-CoV-2 antivirals in accordance with patient pharmacokinetics.

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Real-world effectiveness of nirmatrelvir–ritonavir against BA.4 and BA.5 omicron SARS-CoV-2 variants

Over the past year of the COVID-19 pandemic, populations worldwide have been facing the constant threat of the SARS-CoV-2 omicron variant and its sublineages, and the high transmissibility and substantial immune evasion properties of the variants have contributed to considerable numbers of hospitalisations and deaths. Nevertheless, with the increasing availability and access to novel oral antiviral drugs (eg, nirmatrelvir–ritonavir and molnupiravir) and hybrid immunity induced by infection and COVID-19 prime-boost vaccines, the risk of progression to severe disease, hospitalisation, or death has reduced.

In *The Lancet Infectious Diseases*, Neil R Aggarwal and colleagues[1] reported the real-world use of nirmatrelvir–ritonavir among high-risk outpatients with COVID-19 during the omicron BA.2 and BA.2.12.1 (from March 26 to June 18, 2022) and BA.4 and BA.5 (from June 19 to Aug 25, 2022) waves in Colorado, USA. This retrospective cohort study used nirmatrelvir–ritonavir order in the non-hospitalised setting as the time of exposure, and designated the SARS-CoV-2 positive test date as the index date (assumed to be 1 day before the recorded nirmatrelvir–ritonavir order date if the positive test date was missing). After propensity-score matching, 7168 patients treated with nirmatrelvir–ritonavir and 9361 untreated controls were included for analysis. Outpatient use of nirmatrelvir–ritonavir was associated with significantly reduced odds of 28-day all-cause hospitalisation (adjusted odds ratio 0·45, 95% CI 0·33–0·62), the primary outcome of this study. Such clinical benefit was consistently observed during both omicron BA.2 and BA.2.12.1 and BA.4 and BA.5 predominant periods. Treatment with nirmatrelvir–ritonavir was also associated with significantly reduced odds of 28-day all-cause mortality. Additionally, reduced odds of emergency department visits after nirmatrelvir–ritonavir administration were observed among patients who were treated, compared with their untreated counterparts, suggesting that clinically significant rebound requiring urgent medical care was not observed more frequently among users of oral antivirals.

This study has provided timely information on the effectiveness of nirmatrelvir–ritonavir against different sublineages of the omicron SARS-CoV-2 variant in a population with high COVID-19 vaccination coverage (over 78% of patients had received at least one dose, and over 57% had been boosted). Although several meta-analyses concluded similar reductions in the risk of hospitalisation or death with nirmatrelvir–ritonavir use, the studies included were primarily done during the predominance of the delta variant (the pivotal EPIC-HR trial) or omicron BA.1 and BA.2 (most observational studies);[2–4] hence, this study by Aggarwal and colleagues has added information on the real-world use of nirmatrelvir–ritonavir against omicron BA.4 and BA.5 sublineages, which are prevailing in some parts of the world. Another preprint cohort study has identified similar protection against hospitalisation and death with nirmatrelvir–ritonavir use during a period characterised by the growth of omicron BA.5, yet its effectiveness appeared to have attenuated slightly compared with the pre-BA.5 period.[5] Two more observational studies showed similar clinical benefits of early nirmatrelvir–ritonavir use in outpatients with COVID-19 against various omicron sublineages, including BA.4 and BA.5; however, the results were not stratified to confirm the oral antiviral effectiveness against BA.4 and BA.5.[6,7]

Acknowledging the absence of a SARS-CoV-2 positive test date for the majority of their patients treated with nirmatrelvir–ritonavir, Aggarwal and colleagues[1] did a sensitivity analysis using a 3-day difference between the oral antiviral order date and assumed positive test date, and obtained similar results. Notably, symptom duration before the nirmatrelvir–ritonavir order date was also not available, and the missingness of these data might preclude accurate interpretation of the findings in

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