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.

9 Epling BP, Rocco JM, Boswell KL, et al. Clinical, virologic, and immunologic evaluation of symptomatic coronavirus disease 2019 rebound following nirmatrelvir/ritonavir treatment. *Clin Infect Dis* 2022; published online Oct 6. https://doi.org/10.1093/cid/ciac663.

10 Miller SR, McGrath ME, Zorn KM, Ekins S, Wright SH, Cherrington NJ. Remdesivir and EIDD-1931 interact with human equilibrative nucleoside transporters 1 and 2: implications for reaching SARS-CoV-2 viral sanctuary sites. *Mol Pharmacol* 2021; **100:** 548–57.

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

Flickr - Kansara

Published **Online** February 10, 2023 https://doi.org/10.1016/S1473-3099(23)00056-7

See **Articles** page 696

relation to the optimal timing of oral antiviral initiation, as evidence has shown that late receipt of nirmatrelvir–ritonavir (>5 days after symptom onset) was associated with a considerable decrease in treatment effectiveness against hospitalisation and death.[7]

At the time of writing, emerging and recombinant variants of omicron continue to pose an imminent threat to public health, especially XBB.1.5 and BQ.1.1, which have even greater immune evasion capabilities than BA.5. While in-vitro evidence has shown susceptibility of BQ.1.1 and XBB to remdesivir, molnupiravir, and nirmatrelvir similar to omicron BA.2 and BA.5,[8] real-world studies are needed to evaluate relative effectiveness in different populations and health-care settings. This need is particularly relevant in the assessment of cost-effectiveness for different therapeutic strategies and their prioritisation for various patient populations, as the number needed to treat to prevent one case of severe COVID-19 might also increase in view of the growing population immunity.[5,9] Further research is needed to investigate the COVID-19 rebound phenomenon and its associated clinical consequences among oral antiviral users and non-users infected with emerging or recombinant variants, as higher incidences of COVID-19 rebound infections and symptoms after nirmatrelvir–ritonavir treatment have been observed in a patient cohort with omicron BA.5 patient cohort compared with a cohort with BA.2.12.1.[10] Finally, active pharmacovigilance programmes and monitoring of any viral mutations that might confer resistance to existing antivirals remain crucial.

We declare no competing interests.

*Carlos K H Wong, Kristy T K Lau, Gabriel M Leung
carlosho@hku.hk

Department of Pharmacology and Pharmacy (CKHW, KTKL), Department of Family Medicine and Primary Care, School of Clinical Medicine (CKHW), and WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health (GML), Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; Laboratory of Data Discovery for Health, Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China (CKHW, GML)

1 Aggarwal NR, Molina KC, Beaty LE, et al. Real-world use of nirmatrelvir–ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study. *Lancet Infect Dis* 2023; published online Feb 10. https://doi.org/10.1016/S1473-3099(23)00011-7.
2 Amani B, Amani B. Efficacy and safety of nirmatrelvir/ritonavir (paxlovid) for COVID-19: a rapid review and meta-analysis. *J Med Virol* 2022; **95:** e28441.
3 Cheema HA, Jafar U, Sohail A, et al. Nirmatrelvir–ritonavir for the treatment of COVID-19 patients: a systematic review and meta-analysis. *J Med Virol* 2023; **95:** e28471.
4 Zheng Q, Ma P, Wang M, et al. Efficacy and safety of paxlovid for COVID-19: a meta-analysis. *J Infect* 2023; **86:** 66–117.
5 Schwartz KL, Wang J, Tadrous M, et al. Real-world effectiveness of nirmatrelvir/ritonavir use for COVID-19: a population-based cohort study in Ontario, Canada. *medRxiv* 2022; published online Nov 5. https://doi.org/10.1101/2022.11.03.22281881 (preprint).
6 Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 in a large US health system: a population-based cohort atudy. *Ann Intern Med* 2023; **176:** 77–84.
7 Lewnard JA, McLaughlin JM, Malden D, et al. Effectiveness of nirmatrelvir–ritonavir against hospital admission or death: a cohort study in a large US healthcare system. *medRxiv* 2023; published online Jan 10. https://doi.org/10.1101/2022.10.02.22280623 (preprint).
8 Imai M, Ito M, Kiso M, et al. Efficacy of antiviral agents against omicron subvariants BQ.1.1 and XBB. *N Engl J Med* 2022; **388:** 89–91.
9 Savinkina A, Paltiel AD, Ross JS, Gonsalves G. Population-level strategies for nirmatrelvir/ritonavir prescribing—a cost-effectiveness analysis. *Open Forum Infect Dis* 2022; **9:** ofac637.
10 Wang L, Volkow ND, Davis PB, Berger NA, Kaelber DC, Xu R. COVID-19 rebound after paxlovid treatment during omicron BA.5 *vs* BA.2.12.1 subvariant predominance period. *medRxiv* 2022; published online Aug 6. https://doi.org/10.1101/2022.08.04.22278450 (preprint).

Potential for improvement in governance and national action plans to overcome antimicrobial resistance

Flickr - MarcoVerch Professional

Published **Online** January 16, 2023 https://doi.org/10.1016/S1473-3099(22)00826-X

See **Articles** page 706

With more than 1·2 million deaths directly attributable to infections with resistant bacteria in 2019,[1] the constantly increasing burden of antimicrobial resistance is a leading cause of death, disability, and economic loss in every region and country globally. Antimicrobials are a global public good that need protection from a "tragedy of the commons".[2] Protecting people from overuse of antibiotics, misuse of antibiotics, and infections, particularly infections with resistant bacteria, requires both global action and nationally targeted responses. However, antimicrobial resistance is a complex multisectoral and multifactorial process. Interventions should be coordinated via overarching plans that are sustained by robust governance frameworks. For example, member countries of WHO endorsed the Global Action Plan (GAP) on antimicrobial resistance in 2015, which explicitly requests countries develop national action plans (NAPs), identify priorities, allocate resources for NAP implementation, and establish national and local governance arrangements.

In *The Lancet Infectious Diseases*, Jay Patel and colleagues[3] developed and measured governance