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.

the human common cold coronaviruses was understood to be short-lived and fragile;[10] however, in the case of SARS-CoV-2, it was hoped that protection would be increased by highly effective vaccine platforms. If we now appreciate that even hybrid immunity to SARS-CoV-2 infection is (differentially, depending on previous immune experience) poorly durable[11] and annual debates on booster strategy are required, how should we move forward? The dataset from Singapore reminds us that suggesting the booster strategy will simply involve tweaking vaccines annually, as for influenza, seriously underestimates the complexity of the current challenge. The long-term strategy will require considerable effort towards the development of both next-generation vaccines (targeting neutralising epitopes that are truly conserved and disadvantageous for viral mutations) and vaccine platforms that provide durable, local protection in the nasal mucosa, thereby blocking viral transmission.[12]

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Real-world use of nirmatrelvir–ritonavir: who benefits?

The oral antiviral combination nirmatrelvir–ritonavir has become a first-line therapy in many countries for non-hospitalised adults with COVID-19. A trial done from July to December, 2021, showed that, when given within 5 days of symptom onset, nirmatrelvir–ritonavir reduced the risk of COVID-19-related hospitalisation compared with placebo among unvaccinated patients at high risk of serious illness.[1] Since nirmatrelvir–ritonavir was authorised in the USA in December, 2021, the landscape of the pandemic has changed: omicron lineage variants have emerged, and there has been widespread vaccination and SARS-CoV-2 infection, lessening the likelihood that patients will progress to severe disease. The number of hospitalisations, admissions to intensive care units, and deaths due to Omicron variants is only a small fraction of that associated with the delta variant (in June–December, 2021).[2] In these circumstances, whether treatment with nirmatrelvir–ritonavir confers a substantial treatment benefit—particularly when omicron subvariants are the dominant circulating variants and among patients who are vaccinated, or who have been previously infected—has arisen as a key question for clinicians and policy makers.

In *The Lancet Infectious Diseases*, Joseph A Lewnard[3] and colleagues report data for use of nirmatrelvir–ritonavir among outpatients with COVID-19 in the Kaiser Permanente Southern California health-care system between April 8 and Oct 7, 2022, a time when omicron lineages (BA.2, BA.2.12.1, BA.4, and BA.5) were dominant. In this retrospective cohort study, outpatients with a positive PCR test for SARS-COV-2 (their index test) who were dispensed nirmatrelvir–ritonavir (n=7274) were


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matched with outpatients who also tested positive for SARS-COV-2 but were not given nirmatrelvir–ritonavir (n=126 152). 90 129 (67·5%) of 133 426 patients' index test was within 5 days of symptom onset, and 114 208 (85·6%) had received at least two COVID-19 vaccine doses. The authors used Cox proportional hazard models to calculate the treatment effectiveness of nirmatrelvir–ritonavir in preventing 30-day all-cause hospital admission and death. Treatment effectiveness was 79·6% (95% CI 33·9–93·8) when nirmatrelvir–ritonavir was dispensed within 5 days of symptom onset, but only 53·6% (6·6–7·7) when it was dispensed at any time irrespective of symptom onset. It is important to note the low frequency of 30-day hospitalisation (641 [0·5%]) or death (164 [0·1%]) among untreated patients. Thus, there might be limited potential for absolute treatment benefits in a highly vaccinated population infected with omicron variants of SARS-CoV-2, with a number needed to treat of 100–200 to prevent one hospitalisation or death. The rates of 30-day hospitalisation and death reported by Lewnard and colleagues are notably lower than those reported for a subgroup of vaccinated patients with more than one risk factor for progression in the EPIC-SR trial, which was terminated early because of the low event rate.[4]

Lewnard and colleagues use data from an integrated health system to provide valuable insights into the use of nirmatrelvir–ritonavir in a real-world context. Importantly, these are the first observational data that include timing of symptom onset—a key limitation of previous studies.[5,6] Although the reliability of responses entered at the time of test order could be limited by factors such as recall and ascertainment bias, the clear relationship between duration of symptoms and the effectiveness of nirmatrelvir–ritonavir supports the premise that earlier antiviral treatment is associated with greater clinical benefit, highlighting the need for accessible rapid test-to-treat programmes. Furthermore, Lewnard and colleagues' data show that real-world prescribing differs substantially from that in trial settings and the current authorisation criteria. 1802 (24·8%) patients to whom nirmatrelvir–ritonavir was dispensed had symptoms for more than 5 days or were asymptomatic—populations in which nirmatrelvir–ritonavir has no proven benefit and in which the US Food and Drug Administration has not authorised the treatment's use. The investigators accounted for health care use in the previous year (including outpatient visits and vaccination status for other respiratory infections) in their estimates to attenuate bias related to care-seeking behaviors. However, the requirement of a positive SARS-COV-2 test for study inclusion could have introduced substantial selection bias, because other studies show that up to 80% of patients who receive treatment have missing tests in electronic health records.[5]

How do Lewnard and colleagues' findings affect use of nirmatrelvir–ritonavir? The results of the UK-based PANORAMIC platform trial (ISRCTN30448031), in which nirmatrelvir–ritonavir has reportedly been provided to more than 6000 people, are eagerly awaited. Further randomised trials of nirmatrelvir–ritonavir are unlikely given the question of equipoise and the substantial time and cost of such trials. In the absence of new trial data, several real-world studies[5–7] have suggested that nirmatrelvir–ritonavir is associated with a reduced risk of progression to severe disease across several omicron variants. However, it has become clear that the absolute reduction in risk provided by treatment has decreased substantially, which greatly increases the cost of preventing one hospitalisation. Studies of whether nirmatrelvir–ritonavir affects additional patient-centred outcomes, such as post-COVID-19 condition (also known as long COVID), are planned and could affect the cost-effectiveness of the intervention and whether continued widespread use is merited as the pandemic evolves. Characterisation of patients who most benefit from treatment with nirmatrelvir–ritonavir and studies of when treatment is most effective are needed.

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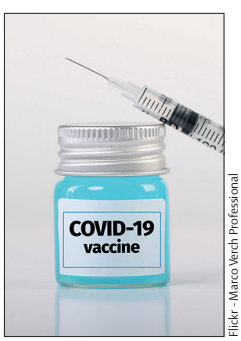
The ups and downs of observational vaccine research



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In *The Lancet Infectious Diseases,* Chemaitelly and colleagues[1] estimate the relative long-term effectiveness of a third (booster) dose of COVID-19 mRNA vaccine compared with receiving only two doses in preventing SARS-CoV-2 infection and severe disease. Using rich national data from Qatar, the authors perform the estimation in various subgroups, finding that the relative effectiveness is higher in individuals more clinically vulnerable to COVID-19. Estimating the effectiveness over time, the authors found that by 6 months after receipt of the booster, relative effectiveness had mostly waned. The importance of these findings, and particularly of the heterogeneous relative effectiveness in different subgroups, is evident.

This study joins a long line of important observational vaccine studies done during the COVID-19 pandemic. Soon after the vaccines were first introduced in late 2020 following successful phase 3 clinical trials, a deluge of acute scientific questions arose, some of which include: how effective are the vaccines in specific subgroups of high clinical vulnerability (eg, immunosuppression and chronic kidney disease)? How effective are they in pregnancy? How effective are they against emerging variants? Are there safety concerns that were too uncommon to be detected in the clinical trials? Randomised clinical trials, which are by nature slower to be performed and usually limited to specific populations, were not able to provide the necessary answers in time. Observational studies, based on national data or specialised cohorts, rushed in to fill the gap, contributing important knowledge and aiding in formulating public health policy worldwide.[2] It would probably be reasonable to say that observational epidemiological studies have never been as important as during the COVID-19 pandemic.

However, despite the proliferation of observational studies, researchers must never forget the high risk of bias inherent in them. A specific example from the study by Chemaitelly and colleagues[1] could serve as a good example of this, as the authors estimate negative relative effectiveness starting 6 months after boosting, concluding that immune imprinting from pre-omicron vaccines is probably harming the immune response to omicron variants. Although this conclusion is possible, one must be cognisant of the many possible biases. For example, it is possible that the adjustment performed did not fully account for the differences between the boosted cohort and cohort that did not receive a booster, resulting in residual confounding. Further, it is possible that the cohort that did not receive a booster was less frequently tested if ill, resulting in differential outcome misclassification; it is possible that the use of discrete-time hazards conditioned on survival at least 6 months after vaccination results in selection bias was due to depletion of susceptibles from the cohort that did not receive a booster.[3] All of these biases are reasonable explanations for the finding of negative relative effectiveness, probably even more so than the possibility of actual immune imprinting. In fact, considering all these possible biases through a careful lens, I would surmise that the negative relative effectiveness observed in the study, after most of the effect from boosting has waned, is in fact a failed test for a negative control outcome,[4] pointing to possible bias in the rest of the study findings. Although the authors cite evidence from the immunological literature that supports their assertion, other immunological studies oppose it, instead claiming that the ancestral strain is sufficiently antigenically similar to the omicron variants so that cross-reactivity from the original vaccine is beneficial.[5]

As I mentioned above, observational epidemiology has been instrumental for generating important scientific evidence during the COVID-19 pandemic. But this new-found importance has not lessened its difficulties. Even as the field progresses and becomes more rigorous with the greater application of formal causal inference,[6] and novel techniques such as target trial emulation,[7] valid estimation remains highly challenging. With this in