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Pandemic moves and countermoves: vaccines and viral variants

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In the past few months, the results of several phase 3 studies showing high vaccine efficacy against SARS-CoV-2 and the subsequent rapid regulatory approval and roll-out of several vaccines have ignited much optimism. However, this optimism has been dampened by the emergence of several new virus variants that are more transmissible and less sensitive to vaccine-induced antibodies.[1–6] The extent to which emerging variants affect the efficacy of vaccines appears to vary considerably between vaccines and variants. In *The Lancet*, Katherine Emary and colleagues[7] show that the Oxford–AstraZeneca ChAdOx1 nCoV-19 vaccine does retain meaningful efficacy against the B.1.1.7 variant that originated in the UK,[8] although efficacy is probably somewhat reduced compared with that against the original virus strain.

The study draws on emerging data from the COV002 trial (NCT04400838), an ongoing phase 2/3 trial assessing the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in the UK. The vaccine was previously reported to have 70·4% efficacy against virologically confirmed symptomatic COVID-19.[9] For the current exploratory analysis, Emary and colleagues exploited the co-circulation of the B.1.1.7 strain and the original strain during the course of the trial to assess the efficacy against each variant separately. From a cohort of 8534 individuals aged 18 years and older (6636 [78%] aged 18–55 years, 5065 [59%] female, 7863 [92%] White), they analysed the viral sequences from 311 participants who tested positive for SARS-CoV-2 more than 14 days after receiving two doses of the ChAdOx1 nCoV-19 vaccine or a meningococcal conjugate control vaccine. Vaccine efficacies against symptomatic infection were 70·4% (95% CI 43·6 to 84·5) for the B.1.1.7 variant and 81·5% (67·9 to 89·4) for the other variants. Although based on small case numbers, a larger difference in efficacy was observed for SARS-CoV-2 infections with no or unreported symptoms (28·9% [–77·1 to 71·4] for B.1.1.7 and 69·7% [33·0 to 86·3] for other variants). The levels and duration of viral RNA detection were lower in participants who received ChAdOx1 nCoV-19 than those who received the control vaccine, irrespective of the infecting virus strain, but viral loads appeared higher in ChAdOx1 nCoV-19 vaccinees infected by the B.1.1.7 variant than in those infected by other variants. Given the wide CIs in these exploratory analyses, no firm conclusions can be drawn on the precise clinical efficacy against the B.1.1.7 variant and, importantly, how this efficacy compares with efficacy against the original circulating variants. However, the results point towards lower efficacy, which also seems consistent with the nine-times reduction in neutralising activity against the B.1.1.7 variant compared with non-B.1.1.7 variants in the serum samples from vaccinees in this study.

Graver concerns about potential reductions in vaccine efficacy are presented by emerging variants other than B.1.1.7.[1] The Glu484Lys spike mutation, present in the P.1 and B.1.351 strains originating in Brazil and South Africa[10,11] and several other emerging strains, was not observed in the sequences analysed by Emary and colleagues because it was not circulating widely in the UK during the time of analysis. The Glu484Lys mutation is particularly important because it substantially reduces the neutralisation activity of monoclonal antibodies and serum samples from vaccinees or individuals infected with non-variant viruses.[2–5] The ChAdOx1 nCoV-19 vaccine had low efficacy in a phase 2 trial in South Africa where B.1.351 variants predominate,[6] which could point to a further loss of vaccine efficacy when variants harbouring Glu484Lys become dominant. Importantly, B.1.1.7 sublineages containing the Glu484Lys mutation have emerged in the UK and elsewhere.

The two desirable effects of COVID-19 vaccines are to prevent severe disease to reduce mortality and alleviate the strain on health systems, and to prevent infection and transmission in order to stop the pandemic. Most of the vaccines in use appear to retain meaningful efficacy in preventing severe disease caused by some of the emerging strains. However, the extent to which prevention of infection and spread is affected receives less attention. In this respect, the low efficacy in preventing asymptomatic infections with the B.1.1.7 variant reported by Emary and colleagues might be concerning, especially in combination with observed higher viral loads in these vaccinees compared with vaccinees infected with other variants. Infection and virus replication in the presence of

partial immunity might result in evolution towards escape from vaccine-induced immunity. Reductions in vaccine efficacy rendered by circulating variants of concern might thus facilitate the emergence and spread of progressively resistant variants, especially when delaying or waiving second vaccine doses, with potential consequences for pandemic control.[12–14]

In summary, the early findings reported by Emary and colleagues suggest a meaningful degree of efficacy against the B.1.1.7 variant, which is encouraging. However, additional data are clearly needed to fully appreciate the potential impact of this and other variants of concern on current and future vaccine efficacy, and to provide conclusive evidence that will inform important policy projections and decisions. The COV002 study is ongoing and we eagerly await further data during this anxious time.

RWS declares no competing interests. MDdJ reports personal fees from Janssen Pharmaceuticals, Roche, Cidara Therapeutics, and Vertex, outside the area of work commented on here. RWS and MDdJ's institution, Amsterdam University Medical Centers, has filed a patent application on SARS-CoV-2 antibodies.

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Newer versus older antiseizure medications: further forward?

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Since 1990, many new antiseizure medications have been launched. Many have been licensed on the basis of evidence from add-on therapy in resistant epilepsies; there have been few head-to-head comparative data in patients who are newly diagnosed.[1] Findings from Standard and New Antiepileptic Drugs (SANAD) I, the first SANAD trial, provided the first comprehensive data to address this question; lamotrigine was shown to be superior to carbamazepine, gabapentin, oxcarbazepine, and topiramate in time to treatment failure,[2] and valproate was a clinically and cost-effective alternative to lamotrigine or topiramate.[3] However, since these trials were done, other medications have been licensed for use, and levetiracetam has been increasingly considered a safe alternative in the treatment of both focal and generalised epilepsies, despite few head-to-head comparative data,[4] specifically with the increasing concern about the effect of valproate in pregnancy on the unborn child.

In *The Lancet*, Anthony Marson and colleagues[5,6] report the results of SANAD II—two pragmatic, open-label, randomised trials providing useful data in addressing this issue. In the study of patients with newly diagnosed focal epilepsy,[5] 990 patients (43% women, mean age 39·9 years) were recruited. Levetiracetam did not meet non-inferiority in the intention-to-treat analysis of time to 12-month remission from seizures (hazard ratio *vs* lamotrigine 1·18 [97·5% CI 0·95–1·47]), which was calculated as days from randomisation to the first date at which a period of 12 months had elapsed without any seizures. In the per-protocol analyses, lamotrigine showed superiority and better cost-effectiveness over levetiracetam and zonisamide. In the second