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.

been identified and accounted for. Such immunity was likely to be prevalent in Brazil and Scotland because both countries had had several substantial waves of COVID-19 before 2021. Third, the estimates of vaccine effectiveness and the magnitude of waning protection (ie, RRs in this study) should be interpreted with caution owing to challenges in estimating risk of infection and severe outcomes among vaccinated and unvaccinated individuals in observational studies.[4,5]

Notwithstanding these methodological limitations, the finding that protection with ChAdOx1 nCoV-19 wanes is crucial, because ChAdOx1 nCoV-19 is one of the most widely used vaccines and its effectiveness against the omicron variant has yet to be characterised. Preliminary data show that the antibodies from a three-dose course of mRNA vaccines neutralise omicron, although all the studies report a notable drop in neutralising antibody titres compared with earlier variants such as delta.[6,7] These data suggest that the effectiveness of mRNA vaccines against severe disease and death might be retained. However, there are limited data about the effectiveness of other vaccines against omicron, let alone data about heterologous vaccination and boosters. Better understanding about waning protection of different vaccines[8,9] would help inform the design and update of vaccination policy, especially for LMICs and in anticipation of further emergence of new VOCs.

We declare no competing interests.

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Mixing mRNA, adenoviral, and spike-adjuvant vaccines for protection against COVID-19

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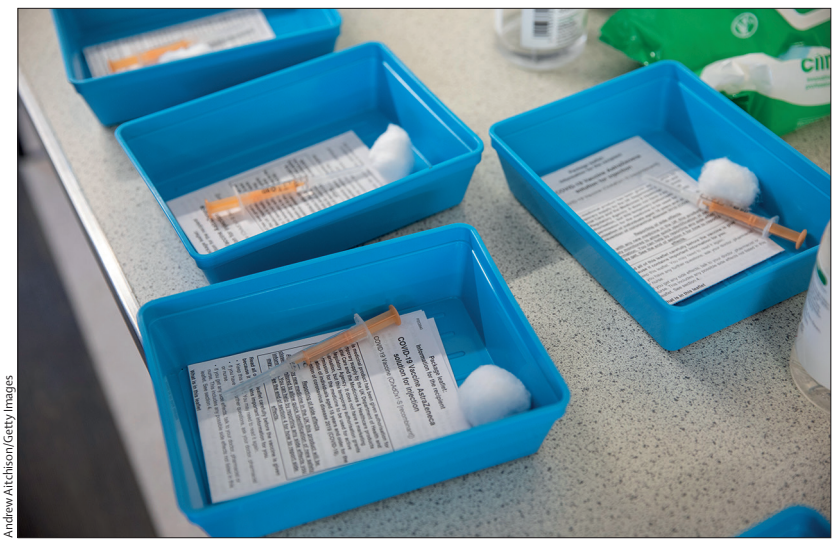
Supply and availability issues for government-approved vaccines, together with worries about rare side-effects (such as thrombotic thrombocytopenia), have necessitated the switch to heterologous COVID-19 vaccination schedules—an approach commonly known as mixing vaccines. Several studies have addressed the efficacy and safety of this practice in the battle against SARS-CoV-2 and its variants.[1–9] Adding to this evidence base, an Article in *The Lancet* by Arabella Stuart and colleagues reports the findings of the Com-COV2 Study Group, a multicentre survey network of nine institutions in the UK.[10]

The study participants (1072 individuals, 42·1% women, and ranging in age from 50 years to 78 years) received either homologous or heterologous prime-boost vaccination schedules against COVID-19 with chimpanzee non-replicating adenovirus (ChAdOx1 nCoV-19, hereafter referred to as ChAd), Pfizer–BioNTech mRNA (BNT162b2, referred to as BNT), Moderna mRNA (mRNA-1273, referred to as m1273), or Novavax Matrix M-adjuvanted recombinant S protein (NVX-CoV2373, referred to as NVX) vaccines. This study is a follow-up of another report published by the same group,[1] and the findings support previous data



Andrew Aitchison/Getty Images

suggesting that ChAd homologous schedules are less immunogenic than a ChAd prime followed by a mRNA-based vaccine boost. The present Article extends results from the previous paper by including boosts with the m1273 and NVX vaccines. The protocol consisted of priming with either ChAd (540 participants) or BNT (532 participants) vaccines, followed 8–12 weeks later with boosts of ChAd, BNT, m1273, or NVX vaccines. Serological testing was done 28 days later. Antibody levels against S protein were measured by ELISA. Levels of neutralising antibodies directed against live SARS-CoV-2 (Victoria 01/2020) and vesicular stomatitis virus pseudotypes were also reported for the different vaccine combinations. Cellular immune response following stimulation of cryopreserved peripheral blood mononuclear cells (PBMCs) with purified S protein was quantitated by measuring interferon-γ release in ELISPOT assays.

The concentrations of S antibody titres and efficacy of neutralising antibodies for the different vaccine schedules could be ranked as (from highest to lowest): BNT/m1273, ChAd/m1273, BNT/BNT, BNT/NVX, ChAd/NVX, and ChAd/ChAd. The ranking for cellular response and interferon-γ secretion from the different schedules was: ChAd/NVX, ChAd/m1273, BNT/m1273, BNT/BNT, ChAd/ChAd, and BNT/NVX. Clearly, mRNA vaccine approaches were more advantageous in terms of producing neutralising antibodies, but the ChAd adenovirus-based vaccine—and to a lesser extent, NVX—appeared to help stimulate interferon-γ production from PBMCs, which could correlate with longer periods of immunological protection or memory.

Similar neutralising antibody and interferon-γ cellular response assays were also done with serum samples and PBMCs from people infected with the beta and delta SARS-CoV-2 variants of concern. A greater response was shown with the neutralising antibodies against the Victoria strain than with those against the variants, but the S protein-stimulated cellular response results were similar to and consistent with the preceding results against the Victoria strain.

To my knowledge, this study constitutes the first randomised controlled trial of heterologous COVID-19 vaccination schedules incorporating m1273 and S protein-subunit boosts. Although there are just a few randomised clinical trials in the literature involving heterologous vaccination schedules, many observational studies support the value of this approach, including studies of the ChAd/BNT, BNT/ChAd, ChAd/m1273, Ad26/Ad5, ChAd/BBV152, Coronavac/ChAd, Coronavac/Convidecia, and Ad26/BNT schedules.[3–10] The baculovirus-derived NVX vaccine has been submitted to WHO for emergency use and its safety and efficacy have been documented, but randomised clinical trials are limited in number.[11,12] The NVX vaccine is produced in the baculovirus–insect cell system using the Wuhan sequence containing two prolines that stabilise trimer formation.[11] The vaccine contains a saponin-based Matrix-M adjuvant. A trial in the USA and the UK indicates that a homologous prime-boost of NVX elicits 89·7% protection against the original Wuhan strain and 86·3% against the alpha (UK B.1.1.7) variant.[12] The results of the new study by Stuart and colleagues indicate that NVX increases the cellular immune response of the ChAd vaccine but does not equal the humoral response of the mRNA vaccines.

The study possesses some minor limitations in terms of survey design. The population comprised older adults (age 50–78 years) with 90–95% of the participants self-identifying as White. BNT-primed participants had twice the number of respiratory and diabetic comorbidities as those in the ChAd-primed groups, and this difference could have influenced immune status. Not all permutations of heterologous vaccines were investigated—for example, NVX and m1273 priming was not considered. Longitudinal testing, reflecting immune memory response, has not yet been reported but is in progress. The study does not provide information on

vaccine effectiveness in terms of protection against actual infection; instead, effectiveness was inferred from immunogenicity. Cellular immunity was only studied in 60% of the participants, and aspects of memory B and T cell response are beyond the scope of this study, although staining of intracellular cytokines during preliminary flow cytometry of T cells indicated that heterologous vaccines favoured a T-helper-1 response.

Overall, the paper is dense with data and the results are important and highly relevant to current vaccination programmes. Schedules containing at least one mRNA dose produced the highest neutralising antibody responses, with BNT/m1273 generating a greater humoral immune response than the homologous BNT/BNT schedule, probably reflecting the higher mRNA content in the m1273 vaccine. Mixed vaccines should be recognised for certification during travel, and heterologous vaccination could enhance deployment of vaccines in poorer regions of the world. It also remains to be seen how effective the heterologous vaccines are in preventing disease or reinfection against newer variants, such as the Omicron variant (B.1.1.529).

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Anticoagulation in COVID-19

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Thrombotic complications (arterial and venous) are common in patients admitted to hospital with COVID-19 and are an independent predictor of poor outcome.[1] Microvascular thrombi also contribute to organ dysfunction, including acute respiratory distress syndrome. The pathogenesis of thrombosis in COVID-19 is intimately linked with the inflammatory response to the virus, endothelial infection, activation, and injury as well as hypercoagulability.[2] Recognition that thrombosis is a key contributor to clinical deterioration and death has led to global interest in whether escalated anticoagulation dose or extended duration improves patient outcomes. Early in the COVID-19 pandemic, published guidelines were heterogeneous with some, in the absence of evidence, recommending increased anticoagulation doses (particularly in critical care), stratifying dose by D-dimer results, or extended post-discharge thromboprophylaxis, or both.[3] Since then, randomised controlled trials have focused on all phases of illness—from the community, to hospital admission, when critically ill, and post-hospital discharge—so that high-quality evidence is now informing clinical practice. From these trials, it has become clear that efficacy and safety of antithrombotic treatments depend on timing with respect to illness severity and dose, and that the mechanism of action might also be important.

For non-critically ill patients hospitalised with COVID-19, therapeutic-dose heparin appears beneficial, with a high probability of reducing the need for organ support and the progression to intubation and death, regardless of D-dimer results.[4] Results from two subsequent randomised controlled trials