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

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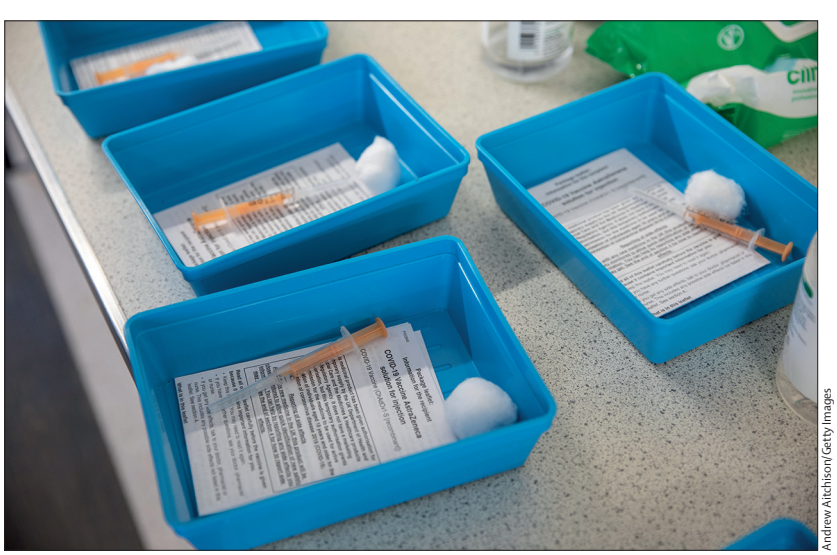
Supply and availability issues for government-approved vaccines, together with worries about rare side-effects (such as thrombotic thrombocytopenia), have necessitated the switch to heterologous COVID-19 vaccination schedules—an approach commonly known as mixing vaccines. Several studies have addressed 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 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



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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).

I declare no competing interests.

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