COVID-19

A 'mix and match' approach to SARS-CoV-2 vaccination

Heterologous dosing with the adenovirus-based ChAdOx1 (AstraZeneca) vaccine followed by an mRNA vaccine induced stronger immune responses than did the homologous ChAdOx1 vaccine series, according to recent immunogenicity studies.

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Despite the development of multiple successful vaccines against the coronavirus SARS-CoV-2, the continued emergence of variants of concern and the sporadic worldwide distribution of vaccines have limited and will continue to limit vaccine effectiveness. A new wrinkle in the global vaccine effort has been the occurrence of rare events such as thrombosis and thrombocytopenia syndrome associated with adenovirus-based vaccines. This triggered cessation of the distribution of AstraZeneca's ChAdOx1 nCoV-19 (ChAd) vaccine in many countries, as well as a surge in vaccine hesitancy in risk-averse populations[1].

In this issue of *Nature Medicine*, studies by Barros-Martins et al.[2] and Schmidt et al.[3] capitalize on the ad hoc heterologous prime–boost vaccination that resulted from the halting of vaccination with ChAd in several European countries, which left partially vaccinated people the option of completing their vaccinations with an mRNA vaccine (BNT162b2 (BNT), from Pfizer–BioNTech); or mRNA-1273, from Moderna).

Barros-Martins et al. report that, compared with results obtained by homologous ChAd–ChAd dosing, the ChAd–BNT dosing strategy resulted in significantly greater immunoglobulin G (IgG) and IgA immune responses directed against the SARS-CoV-2 spike protein and robust, 20- to >60-fold greater titers of neutralizing antibody against the Alpha (B.1.1.7), Beta (B.1.351) and Gamma (P.1) SARS-CoV-2 variants of concern[2]. These neutralizing titers were approximately threefold higher than those in serum from the groups dosed with BNT–BNT (albeit with differing intervals between dose 1 and dose 2), with higher titers of the IgG and IgA subclasses. Similarly, Schmidt et al. show significantly higher titers of IgG antibodies directed against the SARS-CoV-2 spike protein and receptor-binding domain after ChAd–mRNA (either BNT162b2 or mRNA-1273) or mRNA–mRNA vaccination than after homologous ChAd–ChAd vaccination[3]. In addition, the participants dosed with ChAd–mRNA demonstrate a greater number of circulating spike protein–specific CD4$^+$ and CD8$^+$ T cells, as well as cytokine-producing T cells, than that of participants dosed with ChAd–ChAd. Schmidt et al. further demonstrate comparable multifunctional, spike protein–specific CD4$^+$ T cell responses but greater CD8$^+$ T cell responses in the ChAd–mRNA group[3]. A third study, published recently in *Lancet*, provides additional evidence that the heterologous ChAd–mRNA vaccine approach is well tolerated and stimulates a robust IgG and neutralizing-antibody response[4]. Combined, these studies show improved immunogenicity outcomes with heterologous dosing and suggest possible superiority of this strategy over homologous prime–boost regimens for cellular responses and neutralization of variants (Fig. 1).

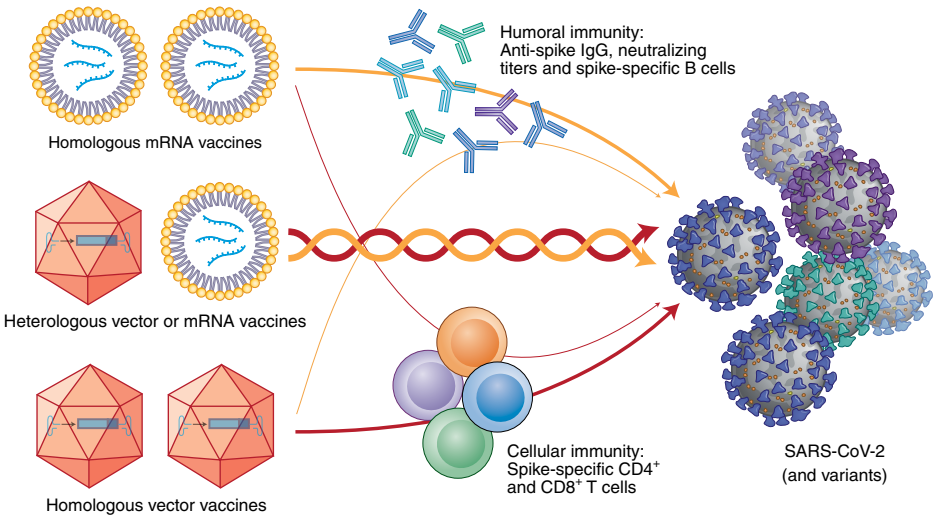

Fig. 1 | A heterologous SARS-CoV-2 vaccine platform induces strong immunity. Heterologous dosing with an adenovirus-based vaccine (ChAd) followed by an mRNA vaccine (either BNT or mRNA-1273) results in more-robust humoral immunity (orange arrow) and cellular immunity (red arrow) than does homologous vaccination with adenovirus-based vaccines. The heterologous vaccine strategy improves the induction of spike protein–specific CD8$^+$ T cells[3] and neutralization of variants[2] beyond that achieved by either of the homologous vaccine-dosing strategies.

As indicated by these new studies, validating the immunogenicity and reactogenicity of 'mix and match' dosing with different approved vaccines may offer a solution that could help mitigate supply shortages and interruptions. The improved immunogenicity outcomes also suggest that a heterologous vaccine approach may overcome limitations of the individual vaccine platforms. Immunogenicity in response to adenovirus-vectored vaccines is limited by pre-existing neutralizing antibodies to common adenovirus serotypes to which humans are exposed, and may compromise the ability to mount an immune response to the SARS-CoV-2 spike protein,

as was noted with the CanSino Biologics–Beijing Institute of Biotechnology's adenovirus type 5–vectored formulation[5]. Using a non-human adenoviral vector, such as Astra Zeneca's ChAd vaccine[2], or using heterologous recombinant adenovirus serotypes (rAd26 followed by rAd5), as seen for the Russian Gamaleya Sputnik V vaccine[6], enables adenovirus-based vaccine platforms to deliver the SARS-CoV-2 spike protein in a way that will generate an enhanced immune response. Nevertheless, adenovirus-based vaccine platforms are limited in that they induce strong T cell responses but are less effective at developing neutralizing antibody responses.

Extensive pre-clinical and early-phase clinical studies, particularly in the development of vaccines against human immunodeficiency virus, have long demonstrated the potential immunological advantages of heterologous prime–boost vaccination strategies. Neutralizing spike protein–specific antibodies are capable of preventing infection with SARS-CoV-2 in animal models, and these antibodies have served as the marker for a protective vaccine response, although precise thresholds have not been confirmed in humans[7]. Although seroconversion is more readily assessed, T cell responses also contribute to viral clearance after infection; these may generate a more-robust response to recently emergent variants, and may be generated even in the absence of detectable antibody responses in immunocompromised transplant recipients[8,9]. Incorporating vaccines that elicit mainly humoral responses (e.g., protein-based vaccines) and those that elicit strong cellular responses (e.g., viral vector–based vaccines) into heterologous prime–boost platforms may therefore improve the breadth of immunity to SARS-CoV-2[10]. Animal studies suggest that heterologous vaccination against SARS-CoV-2 improves spike protein–specific type 1 helper T cell responses, as well as levels of spike protein–specific IgA antibodies[11]. Mounting evidence demonstrates that an adenovirus-vectored prime followed by an mRNA boost at an interval of 6–12 weeks is safe and provides greater humoral and cellular immune responses than does the homologous ChAd–ChAd dose strategy. Studies are ongoing in the UK, and more recently in the US, to investigate the 'mix and match' strategy in a prospective manner. These heterologous vaccine strategies may add further resilience to SARS-CoV-2 vaccinations against the backdrop of continually emerging variants.

The probability that booster vaccines may be required, either to stimulate waning immunity or to expand the breadth of immunity to SARS-CoV-2 spike protein lineage variants, further highlights the importance of optimizing the immunogenicity of vaccines. Thus far, mRNA vaccines have demonstrated continued efficacy against the B.1.1.7 variant, with reduced but ongoing efficacy against the B.1.351 and P.1 circulating variants[12]. This suggests that the robust neutralizing antibody response induced by the mRNA platform may provide the amplitude of humoral immune response needed to overcome the genetic mutations within the SARS-CoV-2 variants. This contrasts with the performance of the AstraZeneca vaccine, which, despite generating a robust T cell response, has been shown to perform poorly against the B.1.351 variant[13]. Given the ongoing threat of current and future circulating variants, studies exploring alternative sequence booster strategies (e.g., viral vector after nucleic acid platform), additional vaccine doses after a complete SARS-CoV-2 vaccine series (wild-type boost), or variant booster doses after wild-type primary vaccination are ongoing or in development. Additionally, the interval between prime and boost probably has a critical role.

These strategies may be of particular importance in enhancing immune responses in immunocompromised patients—including those with malignancies or transplants or otherwise on immunosuppressive medications. Solid-organ transplant recipients and patients with hematological malignancies have shown lower humoral responses to approved vaccines against COVID-19[9,14]. The combination of two vaccine strategies that offer complementary stimulation of different immune pathways may more effectively induce long-lasting B cell responses and potent T cell responses.

Although triggered by the unfortunate interruption in the use of adenovirus-based vaccines, cross-platform mixed-dosing strategies have demonstrated advantageous immunogenicity outcomes, as measured by both humoral responses and cellular responses to the original SARS-CoV-2 and its variants. These innovative vaccine-dosing schedules may be required both as proof against vaccine supply interruptions and for maximizing immune responses, which in turn will help to reduce the transmission of emerging variants and protect immunocompromised people. ❐

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