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COVID-19

# Immune readouts from the Oxford COVID-19 vaccine

> a two-dose regimen for the vaccine is more effective at promoting immunity to SARS-CoV-2 and also likely to be well tolerated … the booster dose should still be effective if delivered at 8 weeks

The vast majority of COVID-19 candidate vaccines are designed to target the SARS-CoV-2 spike (S) protein, but the precise vaccine-mediated immune correlates of protection remain to be determined. Two recent reports from the Oxford COVID-19 vaccine team detail the immune outcomes observed in a phase I/II trial of their ChAdOx1 nCoV-19 vaccine, in which volunteers received a single standard dose or various two-dose regimens.

The ChAdOx1 nCoV-19 vaccine comprises a non-replicating chimpanzee adenovirus vector (ChAdOx1) that is genetically modified to express the full-length S protein of SARS-CoV-2. Trial participants were healthy adults aged between 18 and 55 years, with the paper by Ewer et al. describing the immune responses seen in 88 individuals who received either a single dose of ChAdOx1 nCoV-19 or a control vaccine. The paper by Barrett et al. details immune responses in 52 volunteers who were vaccinated with a standard dose of ChAdOx1 nCoV-19 and then received a standard dose ($n = 20$) or half-dose ($n = 32$) booster 56 days later. Previously published data on trial participants who received two standard doses 28 days apart were also included for comparison.

A key finding in the single-dose paper is that a sole vaccination induced S-protein-reactive $CD4^+$ T and $CD8^+$ T cells with a T helper 1 ($T_H1$)-type cytokine bias as well as $CD8^+$ T cells with a cytotoxic phenotype. This is important as $T_H1$-type immunity is thought to mediate protective antiviral immunity whereas $T_H2$-type responses have been linked with potentially adverse vaccine effects. Robust B cell activation and proliferation were also observed after a single dose and anti-S protein IgG (predominantly the $T_H1$-associated IgG1 and IgG3 isotypes) were detected by day 14 and maintained at day 56. Notably, these antibodies showed neutralizing activity against SARS-CoV-2 and their avidity for the S protein increased between days 28 and 56. A single vaccination also induced S protein-specific IgM and IgA. No sex-specific or age-related differences in vaccine responses were observed.

The two-dose paper shows that a second vaccination enhances the titres of anti-S antibodies and their neutralizing activity and further promotes $T_H1$-type T cell responses. Moreover, the booster dose enhances the functional capacity of anti-S antibodies to support antibody-dependent phagocytosis, complement deposition and natural killer cell activation, which have been linked with protective immunity in preclinical studies and with better survival of hospitalized patients with COVID-19. Boosting with a half dose was found to be less effective than a standard dose boost, but giving a second standard dose at day 56 had a similar immune-enhancing effect to a second standard dose given at day 28. Importantly, the second dose of the vaccine was shown to be safe and, in fact, better tolerated than the prime dose. This contrasts to what has been observed for booster shots with other COVID-19 vaccines.

The authors conclude that a two-dose regimen for the vaccine is more effective at promoting immunity to SARS-CoV-2 and also likely to be well tolerated. Moreover, these data suggest that the booster dose should still be effective if delivered at 8 weeks after the initial vaccination.

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**ORIGINAL ARTICLES** Barrett, J. R. et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. *Nat. Med.* https://doi.org/10.1038/s41591-020-01179-4 (2020) | Ewer, K. J. et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. *Nat. Med.* https://doi.org/10.1038/s41591-020-01194-5 (2020)