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Covid-19: Fourth dose of mRNA vaccines is safe and boosts immunity, study finds

Gareth Iacobucci

Fourth doses of covid-19 mRNA vaccines are safe and provide a substantial boost to antibody concentrations and cellular immunity when given more than six months after a third dose of Pfizer's vaccine, a study has found.

The latest findings from the UK Cov-Boost study, published in *Lancet Infectious Diseases*,[1] compared antibody and T cell responses after a fourth dose of an mRNA covid-19 vaccine with immune responses after a third dose. Giving a fourth dose of Pfizer's and a half dose of Moderna's vaccine was effective at increasing antibody levels and cellular immunity up to and above the baseline and peak levels seen after third dose boosters, the results show.

Although pain at the vaccination site and fatigue were the commonest side effects, there were no vaccine related serious adverse events, and the fourth doses were safe and well tolerated, the authors said.

Some study participants maintained high antibody levels and cellular responses even before the fourth dose and had limited boosting from a fourth dose. Researchers said this trend was also noted in participants with previous infection, which indicated that a fourth dose may not boost immunity if baseline levels are high.

Speaking at a Science Media Centre briefing, Saul Faust, the trial lead and clinical research facility director at University Hospital Southampton NHS Foundation Trust, said that the results underlined the benefits of giving fourth doses to the most vulnerable people this spring as a precautionary strategy.

"The fourth doses of either Pfizer or half dose of Moderna are safe and appear to be effective," he said. "They boost over and above the third dose. But there is a hint from some of the people in the trial that it might reach a ceiling. That will depend on the vaccine, the host immunity, and the dose."

The researchers randomised 166 people who had received a third dose of the Pfizer vaccine (after initial doses of Pfizer or AstraZeneca vaccines in June 2021) to receive either a full dose of the Pfizer (n=83) or a half dose the Moderna (n=83) as a fourth dose. These were given approximately seven months after their third dose.

In the Pfizer group, the geometric mean anti-spike protein IgG concentration at day 28 after the third dose was 23 325 (95% confidence interval 20 030 to 27 162) enzyme linked immunosorbent assay laboratory units (ELU)/mL, which rose to 37 460 (31 996 to 43 857) ELU/mL at day 14 after the fourth dose, representing a significant fold change (geometric mean 1.59 (1.41 to 1.78)). There was a significant increase in the geometric mean anti-spike protein IgG concentration from 28 days after the third dose (25 317 (20 996 to 30 528) ELU/mL) to 14 days after a fourth dose of Moderna (54 936 (46 826 to 64 452)), with a geometric mean fold change of 2.19 (1.90 to 2.52).

The fold changes in anti-spike protein IgG titres from before (day 0) to after (day 14) the fourth dose were 12.19 (10.37 to 14.32) in the Pfizer group and 15.9 (12.92 to 19.58) in the Moderna group. T cell responses were also boosted after the fourth dose. The fold changes for the wild type variant from before to after the fourth dose were 7.32 (3.24 to 16.54) in the Pfizer group and 6.22 (3.90 to 9.92) in the Moderna group.

The study, funded by the UK Vaccine Taskforce and the National Institute for Health and Care Research, will help inform the UK Joint Committee on Vaccination and Immunisation's decision whether to recommend fourth doses to a wider group of people later this year.

"That's the fundamental question that the JCVI are going to be assessing, using data from this study and from a broad range of other studies from the UK and abroad," Faust said. "The key data are going to be severe infection, hospitalisations, and deaths in people who have received either two or three doses, and that's a UK Health Security Agency dataset."

The authors reported several limitations with the study, including the relatively small number of participants in each subgroup. The strengths includes being the first to report on mixed schedule fourth dose data from a randomised trial.

A JCVI spokesperson said the agency was continuing its rolling review of the UK booster programme and will issue advice on an autumn booster programme "in due course."

1 Munro A, Feng S, Janani L, etal. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 covid-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial. *Lancet Infect Dis* 2022. doi: 10.1016/S1473-3099(22)00271-7.