



Delaying the second dose of covid-19 vaccines

Concerns remain about effectiveness in older adults

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On 30 December 2020, the UK announced a deviation from the recommended protocol for the Pfizer-BioNTech covid-19 vaccine, prolonging the interval between doses from 3 to 12 weeks.^{1,2} Similar decisions were made for the Oxford-AstraZeneca vaccine, for which a longer gap between doses had been shown to improve efficacy in some age groups.³

The stated intention was to maximise benefit with limited supplies and to minimise hospital admissions and deaths. For the Pfizer-BioNTech vaccine, the decision to delay the second dose was based on extrapolations from phase III trial data showing an efficacy of 89% 15–21 days after the first dose.^{4,5} At the time, Pfizer did not support the decision, stating that high efficacy could not be guaranteed.⁶

Efficacy in elderly people seems excellent after two doses of the Pfizer-BioNTech vaccine.⁷ A longer gap between doses may improve the long term immune response, as seen with AstraZeneca's vaccine.^{3,8} However, as many people in priority subgroups have not yet received a second dose, any substantial waning of protection during the 12 week interval will create problems as the UK starts to reopen.

This is of particular concern for older adults. The phase II trial of the Pfizer-BioNTech vaccine reported a reduced antibody response among participants aged 65–85 compared with those under 55.⁵ Recent data from Public Health England showed efficacy against symptomatic disease was 57% among adults over 80 after a single dose, increasing to 85% after the second dose.⁹

This is consistent with antibody surveillance data from the React-2 study,¹⁰ which showed IgG positivity 21 days after one dose of Pfizer-BioNTech vaccine in 80% of adults under 60, but in only 49% and 34% of those aged over 70 and 80, respectively. IgG positivity increased to 93% and 88%, respectively, after a second dose, suggesting that the second dose is critical in these vulnerable age groups. Data from Public Health Scotland showed that effectiveness against hospital admission waned from 35 days after the first dose,¹¹ although as results were not reported by age it remains unclear whether these are age cohort effects or related to waning immunity, or both.

Real world data (as yet not peer reviewed) suggest promising efficacy of the Pfizer-BioNTech vaccine among older adults. In Israel, where most people over 60 have already received two doses of the vaccine, surveillance data show a marked divergence in the rates of hospital admission and death between vaccinated and unvaccinated age groups.^{12,13}

Variant threats

New variants of SARS-CoV-2 complicate this picture. A study published as a preprint¹⁴ found a neutralising antibody response against the B.1.1.7 variant (first discovered in the UK) in eight of 15 participants over 80 years, 21 days after one dose of the Pfizer-BioNTech vaccine, compared with 100% in those under 80.

In a preprint subanalysis of 256 participants who tested positive for covid-19 during the phase II/III AstraZeneca vaccine trial, the vaccine seemed to remain highly effective against the B.1.1.7 variant,¹⁵ but the efficacy of single and double doses was once again not reported by age. This is a substantial gap in our understanding for both vaccines.

Taken together, current evidence suggests legitimate concern about the efficacy of these vaccines in older adults after a single dose, including about the durability of the immune response.

Even less evidence is available about the effectiveness of these vaccines against the B.1.351 variant (first identified in South Africa) or newer variants identified in the UK that also express the E484K mutation associated with immune escape. Early data from Novavax,¹⁶ Johnson & Johnson,¹⁷ AstraZeneca,¹⁸ Pfizer-BioNTech, and Moderna¹⁹ suggest the vaccines may be less effective against the B.1.351 variant, at least for mild to moderate disease. These findings highlight the threat posed by virus adaptation and emergence of escape mutations. A single dose strategy may exacerbate this threat, according to some modelling studies.²⁰

Governments currently rolling out vaccinations should mitigate the uncertainty associated with deviations from recommended vaccine protocols by delivering vaccines within a robust trial framework. This would help address the lack of data, provide an early warning of potential harms, and allow rapid modification of vaccination programmes globally if necessary.

At the same time, studies must be done to identify the correlates of immunity among vaccinated people over time, so policies can be adapted quickly to ensure adequate protection. Greater transparency around data for older adults is also required since all vaccines are currently deployed primarily in these age groups.

As potential vaccine resistant variants continue to circulate in the UK, the need for a clear exit strategy from the pandemic has never been greater. Effective suppression of transmission remains key to preventing the emergence and spread of new variants able to escape vaccine acquired immunity. Measures such as testing, tracing, and supported isolation,

coupled with mass vaccination and tight border controls, are the only logical way to ensure this third lockdown is truly the UK's last.

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