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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 **[recommended? licensed?]** 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] **[meaning correct? - yes]**

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 trial data showing an efficacy of 89% 15-21 days after the first dose.[4] **[is this a reference to this trial. If not, can we you cite one? Primary sources are always best if available – This is a reference to the extrapolation the JCVI performed on the Phase III Pfizer data, and released only in the format referenced, which is the briefing document]** At the time, Pfizer did not support the decision, stating that high efficacy could not be guaranteed.[5]

Efficacy in elderly people seems excellent after two doses of the Pfizer-BioNTech vaccine.[6] A longer gap between doses may improve the long term immune response**[meaning? improve the long term response?]**, as seen with AstraZeneca's vaccine.[3 7] 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.[8] 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 **[correct?]** 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. **[is this what you mean? Yes, this is in reference to the Israeli experience and referenced]** [12] [13]

Variant threats

New variants of SARS-Co-V-2 complicate this picture. A study published as a preprint **[OK? Should this be singular or plural? You cite only one study]**,[14] found a neutralising antibody response against the B.1.1.7 variant (first discovered in the UK) in 8 of 15 **[Q to A how many?]** participants over 80 years, 21 days after one dose of the Pfizer-BioNTech vaccine, compared with 100% in those under 80. **[OK? - corrected]**

In a preprint sub-study of 256 participants that tested positive for COVID during the Phase II/III AstraZeneca vaccine trial, the vaccine appeared to remain highly effective against the B.1.1.7 variant **[in one trial? Was it a big trial? Peer reviewed? Published?]**,[15] but the efficacy of single and double doses was once again not reported by age **[correct? - confirmed]**. 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 **[correct? - yes]**) or newer variants identified in the UK that also express the E484K mutation associated with immune escape. **[Ok? - yes]** Early data **[unpublished? Can you cite a primary source for these trials, not secondary reports of the trials in the media? -references updated and added to the bottom, you can remove the previous references (16-18), 19 is correct]** from Novavax,[1621] Johnson & Johnson,[1722] AstraZeneca,[18] 23Pfizer-BioNTech, and Moderna[19] 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 non-peer reviewed modelling studies**[OK? – reference updated as has been pubished]**.[2024]

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. **[OK? - yes]**

As potential vaccine resistant variants continue to circulate in the UK **[Ok?-yes]**, 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 **[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.

<eref>1   Covid-19 second-stage vaccinations to be delayed across UK. Guardian 2020 Dec 30. https://www.theguardian.com/world/2020/dec/30/covid-19-second-stage-nhs-vaccinations-delayed-across-uk</eref>

<eref>2   Department of Health and Social Care. Optimising the covid-19 vaccination programme for maximum short-term impact. 2021. https://www.gov.uk/government/publications/prioritising-the-first-covid-19-vaccine-dose-jcvi-statement/optimising-the-covid-19-vaccination-programme-for-maximum-short-term-impact</eref>

<jrn>3   Voysey M, Clemens SAC, Madhi SA, et al; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99-111. doi:10.1016/S0140-6736(20)32661-1. PubMed</jrn>

<eref>4   UK Government. Covid-19 Greenbook. Chapter 14a. Covid-19-SARS-CoV-2. 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961287/Greenbook_chapter_14a_v7_12Feb2021.pdf</eref>

<jrn>5   Iacobucci G, Mahase E. Covid-19 vaccination: what's the evidence for extending the dosing interval? *BMJ* 2021;372:n18. PubMed doi:10.1136/bmj.n18 </jrn>

<jrn>6   Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;383:2603-15. PubMed doi:10.1056/NEJMoa2034577</jrn>

<jrn>7   Wise J. Covid-19: New data on Oxford AstraZeneca vaccine backs 12 week dosing interval. *BMJ* 2021;372:n326. PubMed doi:10.1136/bmj.n326 </jrn>

<unknown>8 Pfizer. Pfizer-BioNTech covid-19 vaccine (BNT162, PF-07302048). Vaccines And Related Biological Products Advisory Committee briefing document, 10 Dec 2020. https://www.fda.gov/media/144246/download **[Q to A please confirm url]**</unknown>

<eref>9   Public Health England. COVID-19: analysing first vaccine effectiveness in the UK. Public health matters, 23 Feb 2021. https://publichealthmatters.blog.gov.uk/2021/02/23/covid-19-analysing-first-vaccine-effectiveness-in-the-uk/</eref>

<prpt>10   Ward H, Cooke G, Whitaker M, et al. REACT-2 Round 5: increasing prevalence of SARS-CoV-2 antibodies demonstrate impact of the second wave and of vaccine roll-out in England. medRxiv 2021;2021.02.26.21252512.[Preprint.] https://doi.org/10.1101/2021.02.26.21252512</prpt>

<eref>11   Vasileiou E, Simpson CR, Robertson C, et al. Effectiveness of first dose of covid-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. SSRN 2021 [Preprint.] https://www.ssrn.com/abstract=3789264 doi:10.2139/ssrn.3789264 </eref>

<jrn>12   Mahase E. Covid-19: Israel sees new infections plummet following vaccinations. *BMJ* 2021;372:n338. PubMed doi:10.1136/bmj.n338 </jrn>

<prpt>13   Chodick G, Tene L, Patalon T, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. medRxiv 2021:2021.01.27.21250612v1. [Preprint.] https://www.medrxiv.org/content/10.1101/2021.01.27.21250612v1</prpt>

<prpt>14   Collier DA, Meng B, Ferreira I, Datir R, et al. Impact of SARS-CoV-2 B.1.1.7 spike variant on neutralisation potency of sera from individuals vaccinated with Pfizer

vaccine BNT162b2. medRxiv 2021;2021.01.19.21249840. [Preprint.] https://doi.org/10.1101/2021.01.19.21249840</prpt>

<eref>15 Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). SSRN 2021. [Preprint.] https://papers.ssrn.com/abstract=3779160</eref>

<jrn>16 Mahase E. Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant. *BMJ* 2021;372:n296. PubMed doi:10.1136/bmj.n296 </jrn>

<eref>17 Zimmer C, Weiland N, LaFraniere S. New analyses show Johnson & Johnson's one-dose vaccine works well. *New York Times* 2021 Feb 24. https://www.nytimes.com/2021/02/24/science/johnson-johnson-covid-vaccine.html</eref>

<eref>18 Boseley S, Murray J. Study shows Oxford Covid vaccine has less protection against South African variant. *Guardian* 2021 Feb 7. https://www.theguardian.com/society/2021/feb/07/covid-vaccine-booster-variants-emerge-minister</eref>

<jrn>19 Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 2021. PubMed doi:10.1038/s41586-021-03398-2</jrn>

<prpt>20 Saad-Roy CM, Morris SE, Metcalf CJE, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. medRxiv. 2021 [Preprint.] https://doi.org/10.1101/2021.02.01.21250944 </prpt>

21: Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial | Novavax Inc. - IR Site [Internet]. [cited 2021 Mar 16]. Available from: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3

22.
Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry. :24.

23.
Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. medRxiv. 2021 Feb 12;2021.02.10.21251247.

24. 1.
Saad-Roy CM, Morris SE, Metcalf CJE, Mina MJ, Baker RE, Farrar J, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. Science [Internet]. 2021 Mar 9 [cited 2021 Mar 16]; Available from: https://science.sciencemag.org/content/early/2021/03/08/science.abg8663