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Extending the interval of COVID-19 vaccine regimens in individuals aged 80 years or older

Published Online
August 19, 2021
https://doi.org/10.1016/
S2666-7568(21)00205-1

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More than 100 SARS-CoV-2 vaccines are in clinical and preclinical research stages,[1] and some are approaching full approval by regulatory bodies. Lessons from the COVID-19 pandemic continue to extend our understanding of vaccine biology. Age-specific mortality from and immunity to SARS-CoV-2 infection have emphasised the vulnerability of older adults to COVID-19 and the higher case fatality in this population compared with younger people.[2] To achieve optimum efficacy, most of the advanced SARS-CoV-2 vaccines must be given in two doses,[1] although some, such as the BNT162b2 mRNA vaccine (tozinameran; developed by Pfizer–BioNTech) and the ChAdOx1 nCoV-19 adenovirus-vector vaccine (Oxford University–AstraZeneca), have shown efficacy after the first dose.[3,4] These findings were obtained from studies done in younger individuals, and attempts to expand them into groups aged 80 years or older have been lacking. Increasing the interval between the first and second doses of the vaccine can help to stretch vaccine supplies; however, implementing such regimens should be based on a firm understanding of the immune responses and efficacy in the most vulnerable populations. Further exploration of human immune senescence in people aged 80 years or older should be adequately addressed to allow better monitoring of this group's immune responses to SARS-CoV-2 vaccines.

In two Articles in *The Lancet Healthy Longevity*, Helen Parry and colleagues[5] and Gokhan Tut and colleagues,[6] as part of the Paul Moss research group at the University of Birmingham, report on their investigations of the immunogenicity of a single dose of the BNT162b2 or ChAdOx1 nCoV-19 vaccines in individuals aged 80 years or older.[5,6] In the complementary Articles, immune responses were explored in people aged 80 years or older living independently (n=165), and in residents (n=35; median age 87 years [IQR 77–90]) and staff (n=89; 48 years [35·5–56]) of long-term care facilities (LTCFs). Encouragingly, single doses of either the BNT162b2 or ChAdOx1 nCoV-19 vaccine reliably elicited humoral immunity in older people in both studies. In Tut and colleagues' study,[6] humoral immune responses to the vaccines in participants without serological evidence of previous SARS-CoV-2 infection were slower to peak in LTCF residents than in LTCF staff, with the apparent correlation between age and spike-specific IgG antibody titre disappearing only in the subset of samples taken more than 42 days since vaccination. The effect of the slow increase in spike-specific antibodies in this population should be further investigated.

Additionally, Tut and colleagues' study provided a preliminary indication of the diminished responses of older people to some of the circulating SARS-CoV-2 variants, and should alert us to the possibility that the slow kinetics of responses to vaccines in this population might hinder the protection of such individuals against future variants of SARS-CoV-2. The use of adjuvants to more rapidly and fully stimulate humoral immune responses in older people might help efforts to protect this population.

The two studies also examined cellular immune responses to the vaccines. Cellular immune responses were weaker and slower to develop than humoral immunity and positive spike-specific T-cell responses were found only in a small subset of vaccinated individuals in both studies, although those with evidence of previous SARS-CoV-2 infection in Tut and colleagues' study all showed positive T-cell responses. At 5–6 weeks post vaccination, the ChAdOx1 nCoV-19 vaccine induced a higher level of cellular responses than did the BNT162b2 vaccine.[5]

These Articles address a crucial concern regarding the interval between the first and second doses of vaccine in older people. Extending the vaccine interval permits the acceleration of vaccine population coverage during the pandemic. The findings might support extending the interval to up to 7 weeks in individuals aged 80 years and older.

Evidence of previous natural infection with SARS-CoV-2 was found in 12 (34%) of 35 residents of LTCFs,[6] suggesting the possibility of bias in this population and limiting the generalisability of the results to people living independently, in whom rates of previous infection differ. A single dose of vaccine is effectively a booster in people who have previously

been infected, and both antibody titres and cellular immunity were significantly higher in such individuals. Additionally, randomisation and group sizes represent a significant challenge in conducting studies in individuals aged 80 years and older, which limits the significance of study conclusions. Another limitation of the study is the measure of functional immune responses to vaccination; functional humoral responses and correlates of immune protection are not fully understood for vaccination in all age groups. However, given the greater fatality rate of SARS-CoV-2 infection in people aged 80 years and older, and the proximity of this age to average life expectancy, a simple follow-up measure of greater duration of survival might provide insight into a functional immune response in vaccinated individuals.

Perhaps the most surprising finding in Tut and colleague's study was the levelling effect of previous infection on the overall immune responses of older versus younger participants. Older participants with serological evidence of previous SARS-CoV-2 infection had robust immune responses to the vaccine and their antibodies were of higher concentration and perhaps greater functionality for neutralising the virus compared with older people who had not previously been infected. These data further support the importance of vaccination in people with previous exposure to SARS-CoV-2 and suggest further expansion of the immune response can occur in older adults who were previously infected. Further studies should aim to enhance our understanding of how the timing of vaccination post infection could benefit older adults.

The influence of SARS CoV-2 variants of concern on vaccine protection has been actively evaluated in younger populations. The observation that antibody inhibition of spike–ACE2 binding by the B.1.351 (beta) and P.1 (gamma) variants of concern were low in samples from older adults without evidence of previous infection in Tut and colleagues' study is of keen interest,[6] and suggests that the limitations of vaccine protection against variants of concern might be substantial in this population, especially considering the modest cellular immune response elicited by a single dose of vaccine in this group. Exactly how extended-interval dosing might protect against future variants of concern is an important consideration and additional studies could help to better define dose regimens in people aged 80 years and older. Collectively, these observations highlight the potential greater vulnerability of vaccinated older adults to infection by variants of concern compared with younger people.

We declare no competing interests.

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1 WHO. COVID-19 vaccine tracker and landscape. July 23, 2021. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed Aug 14, 2021).
2 O'Driscoll M, Ribeiro Dos Santos G, Wang L, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* 2021; **590:** 140–45.
3 Polack FP, Thomas S, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.
4 Voysey M, Clemens SAC, Madhi SA, et al. 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.
5 Parry H, Bruton R, Tut G, et al. Immunogenicity of single vaccination with BNT162b2 or ChAdOx1 nCoV-19 at 5–6 weeks post vaccine in participants aged 80 years or older: an exploratory analysis. *Lancet Healthy Longev* 2021; published online Aug 11. https://doi.org/10.1016/S2666-7568(21)00169-0.
6 Tut G, Lancaster T, Krutikov M, et al. Profile of humoral and cellular immune responses to single doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines in residents and staff within residential care homes (VIVALDI): an observational study. *Lancet Healthy Longev* 2021; published online Aug 19. https://doi.org/10.1016/S2666-7568(21)00168-9.