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Age and frailty in COVID-19 vaccine development

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See Articles page 1979

Older adults, particularly those who are frail or living in long-term care facilities, have been disproportionately affected by the COVID-19 pandemic.[1] Vaccines that are safe and effective in this population have been eagerly anticipated. In *The Lancet*, Maheshi Ramasamy and colleagues present results of the safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine in older adults (those older than 55 years).[2]

Their results are part of a larger single-blind, randomised, controlled, phase 2/3 trial of the ChAdOx1 nCoV-19 vaccine (which is a replication-defective chimpanzee adenovirus-vector vaccine) with a MenACWY meningococcal vaccine comparison group. The study design was complex, with participants randomly assigned using block randomisation to one of ten different groups, and older adults were only enrolled after initial determination of safety in the youngest age group (aged 18–55 years). Participants in the two older age groups (aged 56–69 and ≥70 years) were further randomly assigned to receive either one dose (day 0) or two doses (day 0 and a boost dose on day 28) of vaccine. The ChAdOx1 nCoV-19 groups were also sequentially recruited to receive either a low dose or (after demonstration of safety) a standard dose of the vaccine. In this immunogenicity subgroup of the larger study, 560 healthy adults were included, distributed among the three age groups (160 participants aged 18–55 years, of whom 100 received the COVID-19 vaccine; 160 aged 56–69 years, of whom 120 received the COVID-19 vaccine, and 240 aged ≥70 years, of whom 200 received the COVID-19 vaccine). 280 (51%) of 552 analysed participants were female and the median age in the 18–55 years group was 43·0 years (IQR 33·6–48·0), in the 56–69 years group was 60·0 years (57·5–63·0), and in the 70 years and older group was 73·0 years (71·0–76·0). For 7 days after each dose, participants completed diary cards for solicited local and systemic adverse events. Serious adverse events were recorded and will be monitored for 1 year. Severity of reactions and adverse events was graded as mild, moderate, or severe, depending on their effect on daily activities. Immune responses were measured using assays of anti-spike protein IgG and neutralising antibody titres for humoral immunity and IFN-γ enzyme-linked immunospot (ELISpot) for cell-mediated immunity.

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In this Article, the authors focus on safety and immunogenicity in older adults; reporting on efficacy outcomes is pending. They found that both local and systemic reactions were more common with ChAdOx1 nCoV-19 than with MenACWY, but decreased with increasing age. For example, in those who received the ChAdOx1 nCoV-19 two standard-dose regimen, 43 (88%) of 49 participants aged 18–55 years, 22 (73%) of 30 aged 56–69 years, and 30 (61%) of 49 aged 70 years and older reported at least one local reaction (most commonly injection-site pain and tenderness) and 42 (86%) of 49 participants in the 18–55 years group, 23 (77%) of 30 in the 56–69 years group, and 32 (65%) of 49 in the 70 years and older group reported at least one systemic reaction (most commonly fatigue, headache, feverishness, and myalgias; these were graded as severe in seven [5%] of 128 participants after the prime dose and one [1%] of 127 participants after the boost dose). 13 participants had serious adverse events during the study period, none of which were judged to be due to study vaccine. The decrease in local and systemic reactions with increasing age might be explained by the anti-inflammatory response to low-grade chronic inflammation, and suppression of acute inflammatory processes.[3] Immunogenicity was robust and similar across age groups, as long as a boost dose was provided.

Anti-spike protein IgG responses at 28 days after the boost dose were similar among the three age groups (in the standard-dose groups: 18–55 years, median 20 713 arbitrary units [AU]/per mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; ≥70 years, 17 561 AU/mL [9705–37 796], n=47; p=0·68), and 208 (>99%) of 209 participants in the boost dose groups had neutralising antibodies by day 14 after the last vaccination. In IFN-γ ELISpot assays enumerating antigen-specific T cells done for those in the prime-boost standard-dose group, T-cell responses peaked at 14 days after a single standard dose and did not increase significantly after a boost dose (18–55 years, median 1187 spot forming cells [SFCs] per million peripheral blood mononuclear cells [IQR 841–2428], n=24; 56–69 years, 797 SFCs [383–1817], n=29; and ≥70 years 977 SFCs [458–1914], n=48; p=0·46). The authors state that these results based on IFN-γ ELISpot will be followed up with a more detailed analysis of other measures of cell-mediated immunity.

The strengths of the study include a large sample with a wide age range, and a robust trial design. The inclusion of measures of cell-mediated immunity is important given the limitations of relying solely on antibody titres in older adults.[4,5] The main study limitations were its single-blind design, the inclusion of few participants older than 80 years, and exclusion of people with substantial underlying chronic illnesses and frailty. Overall, Ramasamy and colleagues summarise that the ChAdOx1 nCoV-19 vaccine is better tolerated in older adults than younger adults and has similar immunogenicity across all age groups after a boost dose; both conclusions are well supported by their results.

How might the results be applied to the true target populations for COVID-19 vaccines? The current UK Joint Committee on Vaccination and Immunisation top priority groups are: older adults living in care homes and care home workers, all those aged 80 years and older, and health-care and social-care workers, and all those aged 75 years and older.[6] Frailty is common to each, and gives a more holistic understanding than comorbidities alone of susceptibility to adverse outcomes.[7] The concept of immunosenescence (waning of immune responses) is important for understanding vaccine responses in older adults. There is increasing evidence that immunosenescence is not universally or evenly experienced with biological ageing but is part of what contributes to the variability in susceptibility that is seen with frailty and an increasing burden of health conditions.[5,8] So the story is more complex than simply older age brings immunosenescence. Frailty is increasingly understood to affect older adults' responses to vaccines for infections such as influenza, shingles, and pneumococcus.[9–11] Even when a measure of frailty has not been included in a study upfront, generation of a robust frailty measure using data already collected is possible.[10,12]

A plan for how to consider frailty in COVID-19 vaccine development is important. Involving geriatricians could bring a key lens to assist with planning these ongoing studies focusing on older adults and interpreting the results. Consideration of the dosing would be important. In this study, the low-dose regimen appeared to be as good or at least nearly as good as the standard-dose regimen, which could be useful for antigen and dose sparing as production ramps up. However, frail older adults might benefit from a higher dose of vaccine and we would not be able to assess this effect unless frailty was specifically queried in immunogenicity studies.

It is encouraging that more studies in older adult populations are underway and will hopefully bring opportunities to implement nuanced analyses of how underlying health status and frailty affect vaccine safety, reactogenicity, immunogenicity, and efficacy in older adults in real-world settings. Older adults (across the full spectrum of frailty) and those who care about them are eagerly awaiting this progress towards safe and effective COVID-19 vaccines.

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Is it time for injectable antiretroviral therapy for HIV?

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See **Articles** page 1994

Long-acting injectable antiretroviral therapy (ART) offers the convenience of reduced dosing frequency and, for the combination of the long-acting rilpivirine and cabotegravir, provides an additional two-drug ART option. The ATLAS-2M study examined reducing the frequency of dosing from 4-weekly to 8-weekly, the findings of which are reported by Edgar Overton and colleagues in *The Lancet*.[1] They compared the safety and efficacy of two injectable dosing strategies to maintain virological suppression in people with HIV without previous treatment failure. Preliminary data from the LATTE-2 study provided evidence that 8-weekly dosing is feasible.[2]

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The ATLAS-2M study recruited a third of its participants from those completing 52 weeks of the ATLAS study,[3] which enrolled people virologically suppressed for at least 6 months on oral ART to monthly injections of long-acting cabotegravir and rilpivirine or maintenance of their oral regimen. The other two-thirds of participants satisfied the same entry criteria for ATLAS. Individuals with previous treatment failure or interruption, a history of HIV drug resistance, or clinically significant comorbidities such as cardiovascular disease and mental health disorders were excluded.

ATLAS-2M is an ongoing, randomised, multicentre (Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the USA), open-label, phase 3b, non-inferiority study of the week-48 antiviral efficacy of cabotegravir plus rilpivirine long-acting maintenance therapy administered intramuscularly every 8 weeks or every 4 weeks to treatment-experienced adults living with HIV-1. 1045 participants were randomly assigned to the every 8 week (n=522) or every 4 week (n=523) group; 37% (n=391) transitioned from every 4 weeks long-acting cabotegravir plus rilpivirine in ATLAS. Median participant age was 42 years (IQR 34–50; 27% [n=280] female at birth; 73% [n=763] white race).