Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Natural immunity helps overcome the age-related decline of SARS-CoV-2 vaccine immunogenicity

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There is an interesting paradox that has become particularly apparent in the study of vaccine-preventable diseases, such as influenza[1] and COVID-19:[2-5] immunity derived from infection (ie, natural immunity)—the very thing we aim to prevent with vaccination—can be tremendously beneficial to vaccine responses and protection against subsequent infection. Regarding SARS-CoV-2, most studies support this idea, with evidence of higher antibody responses in previously infected compared to uninfected vaccinees.[2,4] In line with this, vaccine effectiveness against infection following second dose in previously uninfected adults declines from 85% after 1–2 months to 51% approximately 9 months later, whereas for those previously infected, effectiveness remains around 90% after 9 months.[3] Protection against severe disease also appears to be enhanced,[5] which implicates a beneficial effect of previous infection on the cell-mediated part of the adaptive immune system (eg, CD4 helper and CD8 cytotoxic T-lymphocytes). However, although the study of cell-mediated SARS-CoV-2 vaccine responses are not rare in the literature,[6] whether previous infection effects the frequency and function of these cells remains unclear.

Due to the additive benefit of previous infection and vaccination,[3] broad immunisation for all eligible individuals would be expected to improve overall protection at the population-level. However, knowledge of previous infection through surveillance data and outbreak history might also be exploited in decisions regarding the prioritisation of vaccine delivery. This could be particularly useful in long-term care facilities (LTCF), which are a major COVID-19 hotspot. In Canada, residents of LTCF represent 43% of all COVID-19 deaths, yet only 3% of cases.[7] There are few data to suggest that the beneficial effect of previous infection is maintained with age, or in older adults living with frailty. In *The Lancet Healthy Longevity*, Gokhan Tut and colleagues[8] aimed to fill this knowledge gap. In a cohort of nearly 500 staff younger than 65 years old and residents older than 65 years old (80% of whom were >80-years-old), the authors show that a second dose of either ChAdOx1 nCoV-19 (Oxford–AstraZeneca) or BNT162b2 (BioNTech–Pfizer) substantially boosts anti-spike protein antibody titres and SARS-CoV-2 neutralisation capacity, which is significantly higher in staff compared with residents. However, this was only true for participants that did not show evidence of a previous infection; residents who were anti-nucleocapsid seropositive exhibited similar antibody titres as staff and both groups exhibited nearly 100% viral neutralisation. To assess cell-mediated immunity, the authors first quantified the number of IFN-γ producing peripheral blood mononuclear immune cells, finding nearly identical trends as their antibody-related endpoints, although previous infection appeared to have less of a beneficial effect on staff immunity. Analysis indicated that previous infection was associated with significantly greater secretion of the chemokine CXCL10 and the proinflammatory cytokine TNF following ex vivo stimulation with spike protein. Finally, the authors used intracellular cytokine staining to specifically quantify the frequency of CD4 T cells that produced IFN-γ, IL-2, or both in response to SARS-CoV-2 antigens. Although differences in the frequency of these populations were not apparent based on infection status, the frequency of central memory CD4 T cells were twice as high in those with a previous infection, whereas T-cells featuring a terminally differentiated phenotype were 4-times lower in previously infected compared with previously uninfected individuals.

This study adds important knowledge to our understanding of the ageing immune system and potential clues to the mechanisms by which previous infection supports strong vaccine responses. First, their findings clearly show that older, frail adults are quite capable of generating robust, long-lived memory against SARS-CoV-2 following infection, seemingly to a similar degree as younger adults. This follows with our own research on varicella-zoster[9] and influenza[10] vaccination, and challenges the commonly perceived notion that all aspects of adaptive immunity are equally affected by ageing. Second, their results implicate a possible role for central memory CD4 T cells and IFN-γ producing CD8 memory T cells (although not directly measured) in the beneficial effects of previous infection. Both cell types would support mucosal defences against viral infection

by activating local innate cells while stimulating the recruitment of additional effectors through chemokines, such as CXCL10. Central memory T cells can also act as a reservoir for follicular helper T cells in the lymph node, which support the generation of memory B cells and antibody-producing plasma cells.[11] Although it is not yet clear the degree to which previous infection protects our oldest old against future variants of SARS-CoV-2 and more evidence from animal models are needed to confirm the mechanism of protection, the study by Tut and colleagues[8] nonetheless provides additional evidence that policy makers can use when determining priority targets of preventative strategies.

We declare no competing interests.

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1 Auladell M, Phuong HVM, Mai LTQ, et al. Influenza virus infection history shapes antibody responses to influenza vaccination. *Nat Med* 2022; **28:** 363–72.

2 Kelsen SG, Braverman AS, Aksoy MO, et al. SARS-CoV-2 BNT162b2 vaccine-induced humoral response and reactogenicity in individuals with prior COVID-19 disease. *JCI Insight* 2022; **7:** e155889.

3 Hall V, Foulkes S, Insalata F, et al. Protection against SARS-CoV-2 after COVID-19 vaccination and previous infection. *N Engl J Med* 2022; **386**: 1207–20.

4 Stirrup O, Krutikov M, Tut G, et al. SARS-CoV-2 anti-spike antibody levels following second dose of ChAdOx1 nCov-19 or BNT162b2 in residents of long-term care facilities in England (VIVALDI). *J Infect Dis* 2022; published online April 16. https://doi.org/10.1093/infdis/jiac146.

5 Björk J, Bonander C, Moghaddassi M, et al. COVID-19 vaccine effectiveness against severe disease from SARS-CoV-2 Omicron BA.1 and BA.2 subvariants—surveillance results from southern Sweden, December 2021 to March 2022. *Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull* 2022; published online May 5. https://doi.org/10.2807/1560-7917.ES.2022.27.18.2200322

6 McDonald I, Murray SM, Reynolds CJ, Altmann DM, Boyton RJ. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. *NPJ Vaccines* 2021; **6**: 74.

7 Canadian Institute for Health Information. COVID-19's impact on long-term care. 2021. https://www.cihi.ca/en/covid-19-resources/impact-of-covid-19-on-canadas-health-care-systems/long-term-care (accessed May 10, 2022).

8 Tut G, Lancaster T, Sylla P, et al. Antibody and cellular immune responses following dual COVID-19 vaccination within infection-naive residents of long-term care facilities: an observational cohort study. *Lancet Healthy Longev* 2022; **3:** e461–469.

9 Lelic A, Verschoor CP, Lau VWC, et al. Immunogenicity of varicella vaccine and immunologic predictors of response in a cohort of elderly nursing home residents. *J Infect Dis* 2016; **214:** 1905–10.

10 Loeb N, Andrew MK, Loeb M, et al. Frailty is associated with increased hemagglutination-inhibition titers in a 4-year randomized trial comparing standard- and high-dose influenza vaccination. *Open Forum Infect Dis* 2020; **7:** ofaa148.

11 Pepper M, Pagán AJ, Igyártó BZ, Taylor JJ, Jenkins MK. Opposing signals from the Bcl6 transcription factor and the interleukin-2 receptor generate T helper 1 central and effector memory cells. *Immunity* 2011; **35:** 583–95.