Robust heterologous immune responses in older adult survivors of COVID-19

Older adults from long-term care facilities who had been infected with COVID-19 during the first wave of the pandemic were found to have robust cellular and humoral responses to SARS-CoV-2 spike protein. Importantly, serostatus did not affect humoral immunity to influenza or other respiratory syncytial viruses.

This is a summary of:
Tut, G. et al. Robust SARS-CoV-2-specific and heterologous immune responses in vaccine-naive residents of long-term care facilities who survive natural infection . *Nat. Aging* https://doi.org/10.1038/s43587-022-00224-w (2022).

Published online:
30 May 2022

The problem

The COVID-19 pandemic has resulted in high rates of mortality in older adults, although why this population is particularly susceptible remains unknown. Possible reasons include an aging-related impairment of innate immune or adaptive responses, as well as increased prevalence of comorbidities. In an attempt to identify the underlying causes of heightened susceptibility, previous studies have investigated rates of SARS-CoV-2 infection within long-term care facilities (LTCFs) and identified several factors that may affect susceptibility to severe infection[1]. For example, cognitive impairment and extreme aging[2–4] have been found to be significant risk factors for mortality amongst older residents, which is estimated to be as high as 30% (ref. [2]). Another potentially important factor is whether SARS-CoV-2 infection supresses immunity against other pathogens (that is, whether it causes heterologous immune responses). Indeed, seasonal respiratory viruses such as influenza and respiratory syncytial virus remain a cause of considerable morbidity and mortality in older adults, and it is currently unclear whether primary SARS-CoV-2 infection affects the response against these pathogens. We therefore set out to determine virus-specific and general inflammatory profiles in both staff and residents in the LTCF setting over a four-month period, and related these findings to SARS-CoV-2 serostatus.

The observation

Blood samples were collected from 276 staff and residents (age interquartile range of 76–90 years old for residents, and 42–62 years old for staff) at LTCFs in England between June and November 2020, prior to the introduction of the UK COVID-19 vaccination programme on 8 December 2020. Baseline samples were collected between June and July with follow-up samples at two and four months later from the same participants. On the basis of nucleocapsid-antibody status, 163 donors were found to be SARS-CoV-2-seropositive, whereas 113 were seronegative. Given that the peak of primary SARS-CoV-2 infections within LTCFs occurred in April 2020 in the UK, these time points probably represent up to seven months after primary infection.

Our initial experiments focused on humoral immunity to the original Wuhan-Hu-1 strain and the B.1.1.7 (Alpha), B.351 (Beta) and P.1 (Gamma) variants of concern. Further analyses involved measurement of cross-reactivity to other coronaviruses, the quality of immune response to other respiratory viruses, and the quantity and quality of cellular responses to SARS-CoV-2 in older adults.

We found that SARS-CoV-2-specific antibody responses were higher in residents than in staff (and thus, in older than younger adults) (Fig. 1a, b) and that specific antibody responses are comparable in the assayed variants of concern. In addition, we observed that those with previous SARS-CoV-2 infection exhibited a boosted response against other betacoronaviruses. Importantly, we found that SARS-CoV-2 serostatus did not impair antibody responses against other common respiratory viruses such as influenza and respiratory syncytial virus. Finally, we show that SARS-CoV-2-specific cellular responses are similar across all ages investigated (Fig. 1c) and that this is mostly driven by $CD4^+$ T cells (Fig. 1d).

The implications

We investigated SARS-CoV-2-specific immune responses in staff and residents of LTCFs and found robust responses against the spike protein across all age groups and no negative effect on immunity to other respiratory viruses. These findings are broadly reassuring for future LTCF management decisions. Antibody responses against the SARS-CoV-2 spike protein and receptor-binding domain are thought to be critical in preventing reinfection. As such, we were encouraged to find that antibody responses against spike and receptor-binding domain were robust in older people. The importance of cellular immunity is coming to the forefront in trying to understand reinfections and vaccine responses in the Omicron era, and it was therefore encouraging that spike-specific cellular responses were of similar magnitude within both staff and residents.

Potential limitations of our study include the fact that all seropositive donors clearly represent survivors of acute SARS-CoV-2 infection and, as mortality rates were high within the LTCF-resident age group, there may have been potential selection bias for donors with the most effective underlying immune function.

It will now be important to assess how infection status acts to support the longevity of vaccine-induced immune responses and if this should be used as a determinant of the need for multiple vaccine boosters.

Gokhan Tut and Paul Moss
University of Birmingham, Birmingham, UK.

EXPERT OPINION

"The paper by Tut et al. is a useful advance to the literature with its novel comparison across the age range in care home residents and staff. This is a setting which all would agree is of the utmost importance, yet the logistics of doing strong immunology in this context have meant it has been an under-populated dataset." **Danny Altmann, Imperial College London, London, UK.**

FIGURE

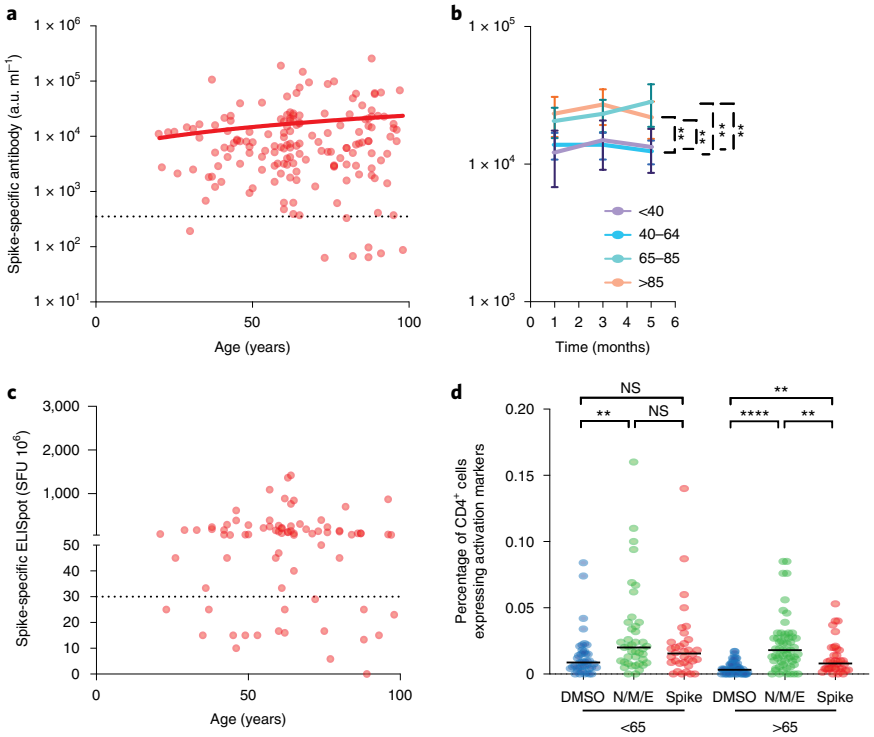

Fig. 1 | Robust humoral and cellular responses in COVID-19-infected older adults. a, SARS-CoV-2 spike-specific IgG titre in relation to age within seropositive donors ($n = 163$). Dashed line represents cut-off for positive response. a.u., arbitrary units. **b**, Mean spike-specific antibody responses at baseline, and at two- and four-month follow up, within four age groups (<40 (purple, $n = 19$), 40–64 (blue, $n = 67$), 65–85, (green, $n = 42$) and >85 years old (orange, $n = 35$)). **c**, Spike-specific cellular peripheral blood mononuclear cell response in relation to age in seropositive donors ($n = 80$). Dashed line indicates cut-off for positive response. SFU, spot-forming unit. **d**, Quantification of SARS-CoV-2-specific T cells based on percentage expression of both CD137⁺ and CD154⁺ on CD4⁺ cells after stimulation with spike or a combination of nucleocapsid, membrane and envelope (N/M/E) peptides.

BEHIND THE PAPER

At the start of the pandemic, we knew very little about the virus, although it was clear that the older population was particularly susceptible, as evidenced by the unusually high rates of mortality in care homes during the first four months of the pandemic. The VIVALDI study was set up by Laura Shallcross at University College London (UCL) to qualitatively assess the effect of the pandemic in care homes, although it became clear that an understanding of the immune responses to SARS-CoV-2 in this vulnerable population was also needed. This is where the collaboration between UCL and University of Birmingham was established, in which we draw upon our expertise in cellular immune responses. Our work very much followed the development of the pandemic and had to be updated with the emergence of variants of concern. A particularly exciting highlight was establishing that older adults also made a significant antibody response to variants of concern after surviving the initial Wuhan-Hu-1 strain. **G.T.**

REFERENCES

1. Hollinghurst, J. et al. The impact of COVID-19 on adjusted mortality risk in care homes for older adults in Wales, UK: a retrospective population-based cohort study for mortality in 2016–2020. *Age Ageing* **50**, 25–31 (2021).
This paper compares mortality rates between 2016–2019 and 2020 from care home residents.

2. Dutey-Magni, P. F. et al. COVID-19 infection and attributable mortality in UK care homes: cohort study using active surveillance and electronic records (March–June 2020). *Age Ageing* **50**, 1019–1028 (2021).
This paper reports the morality rates in care home residents who tested positive for SARS-CoV-2.

3. Atkins, J. L. et al. Preexisting comorbidities predicting severe COVID-19 in older adults in the UK Biobank community cohort. *J. Gerontol. Series A* **75**, 2224–2230 (2020).
This paper looks at pre-existing comorbidities and risk factors for predicting severe COVID-19 in older adults.

4. Morciano, M., Stokes, J., Kontopantelis, E., Hall, I. & Turner, A. J. Excess mortality for care home residents during the first 23 weeks of the COVID-19 pandemic in England: a national cohort study. *BMC Med.* **19**, 71 (2021).
This paper looks at excess mortality amongst care home residents during the COVID-19 pandemic in England.

FROM THE EDITOR

"By all accounts, COVID-19 is an age-related disease that is often severe and fatal in older individuals and yet there is a paucity of studies on how the immune system responds to SARS-CoV-2 in older adults. This study contributes to addressing this important knowledge gap by focusing on residents in long-term care facilities, a particularly vulnerable and frail population in which multiple diseases often co-exist." **Sebastien Thuault, Chief Editor, *Nature Aging*.**