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.

Long-term immunogenicity of BNT162b2 vaccination in older people and younger health-care workers

The COVID-19 mRNA vaccine BNT162b2 (Comirnaty) is highly immunogenic and effective in preventing severe illness.[1] Studies have indicated decreasing anti-SARS-CoV-2 antibody concentrations, but largely stable vaccine efficacy and effectiveness 6 months after vaccination.[2,3] The emergence of variants of concern (VOCs), such as the delta (B.1.617.2) VOC, has raised concerns about waning protection, particularly in high-risk populations such as older people, who display lower immune responses to BNT162b2 vaccination than younger adults.[4] Increasing infection rates have led several countries, including the USA, Israel, and Germany, to initiate booster campaigns for vulnerable populations, including for older people. Epidemiological data suggest a reduction in protection against symptomatic infection with SARS-CoV-2 as a function of time since vaccination;[5,6] however, the durability of vaccine-induced immunity in older people is currently unknown. Following up on a previous study,[7] we describe interim results of a prospective cohort study comparing immune responses in a cohort of fully vaccinated older people with those in younger health-care workers,[4,7] measured 6 months after the first dose (ie, 5 months after the completion of two-dose immunisation with BNT162b2).

6-month follow-up visits were completed by 82 older people (median age 82·5 [IQR 78–87] years; 74·4% female) and 107 health-care workers (median age 35 [IQR 30–48] years; 60·7% female; (appendix p 3). We excluded 12 participants (two older people and ten health-care workers) with serologically confirmed or PCR-confirmed SARS-CoV-2 infection at baseline or before the second vaccination from the analysis. The seropositivity rate for anti-SARS-CoV-2 S1-IgG and the median anti-SARS-CoV-2 S1-IgG concentrations at 6 months were lower in the older people than in the health-care workers (48 [60%] of 80 [95% CI 48%–71%] *vs* 95 [98%] of 97 [93%–100%], p<0·0001; and 1·2 signal-to-cutoff ratio [IQR 0·5–2·2] *vs* 3·2 signal-to-cutoff ratio [2·4–4·1], p<0·0001; figure A, appendix p 4). Similar results were obtained for serum anti-receptor binding domain (RBD) and anti-full spike-IgG concentrations (appendix p 1 and p 4), and surrogate virus neutralisation test (appendix p 1 and p 4). The recent rise in viral variants carrying immune escape mutations in the spike protein might further reduce vaccine-induced immunity in older people. A significant decline in serum neutralising activity against pseudovirus carrying the delta VOC spike was observed in both groups from 4 weeks after completion of two-dose immunisation to the 6-month follow-up (figure B; appendix p 6). At 6 months, only 43 (61%) of 71 older people (95% CI 48%–72%; geometric mean 50% inhibition dilution (ID_{50}) 14·5,

Published Online
October 20, 2021
https://doi.org/10.1016/S2213-2600(21)00456-2

See Online for appendix

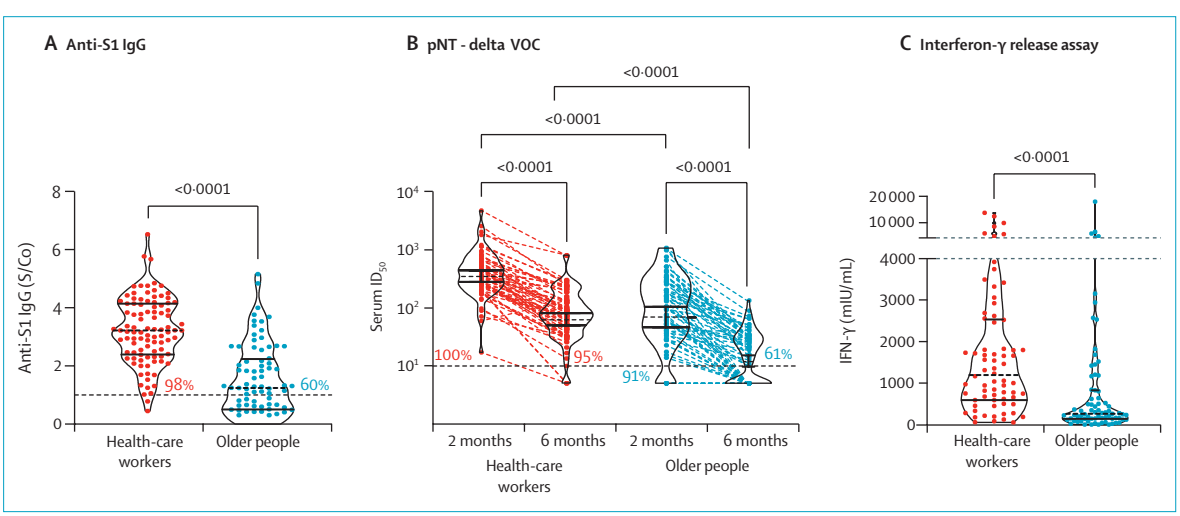

***Figure*: BNT162b2-induced SARS-CoV-2 antibody and T-cell response at 6-month follow-up in health-care workers and older people**
Health-care workers were enrolled at Charité - Universitätsmedizin Berlin (n=107) and older people were enrolled at an assisted living facility in Berlin, Germany (n=82). (A) Anti-S1 IgG in serum measured by a microarray-based immunoassay. (B) Serum neutralisation titres (serum ID_{50}) against the delta (B.1.617.2) VOC were measured 4 weeks after completion of the two-dose vaccine regimen with BNT162b2, and at the 6-month follow-up using a pseudovirus neutralisation assay. (C) SARS-CoV-2 S1-specific T-cell response detected by inteferon-γ release assay. Dotted horizontal lines indicate the manufacturer's threshold such as that for anti-S1 IgG ≥1 S/Co (A) and the lower limit of detection (1:10 dilution) for pNT (B). Horizontal lines within plotted data regions indicate the median and IQR, except for pNT, for which the geometric mean and 95% CI is shown. P values (all less than 0·0001) were calculated by the non-parametric Mann Whitney *U* test. ID_{50}=50% inhibition dilution. IU=international units. pNT=pseudovirus neutralisation test. S/Co=signal-to-cutoff ratio. VOC=variant of concern.

[95% CI 11·5–18·2]) compared with 79 (95%) of 83 health-care workers (95% CI 88%–99%; geometric mean ID_{50} 72·7 [95% CI 58·7–89·9]) showed neutralising capacity against the delta VOC (figure B). Similarly, neutralisation of the alpha (B.1.1.7) VOC was observed in 49 (69%) of 71 older people (95% CI 57%–80%; geometric mean ID_{50} 20·2 [95% CI 15·3–26·5]) compared with 79 (95%) of 83 health-care workers (95% CI 88%–99%; geometric mean ID_{50} 134·4 [95% CI 104·2–173·4]) at the 6-month follow-up (appendix p 1). Binding capacity of serum antibodies to distinct RBD mutations present in VOCs (K417N/T, L452R, T478K, E484K/Q, N501Y, and E484Q) were significantly lower in older people than in health-care workers (p<0·0001 for all RBDs, appendix p 1). Consistent with the lower antibody response, SARS-CoV-2 S1 T-cell reactivity was lower in older people than in health-care workers (261·6 milli-international units [mIU]/mL [IQR 141·5–828·6] *vs* 1198·0 mIU/mL [593·9–2533·6], p<0·0001; figure C).

The study provides evidence of significantly reduced markers of immunity following a regular two-dose regimen of BNT162b2 in older people versus younger adults, with 39% of older participants lacking detectable serum neutralising activity against the currently dominant delta VOC at 6-month follow-up. By contrast, neutralising activity was still detectable in nearly all young adults after 6 months. Decline in antibody concentrations within the first 6 months after vaccination is generally expected and has also been observed for COVID-19 vaccines.[3] In our study, all investigated markers of immunity were markedly reduced in older people at 6-month follow-up, suggesting that the established two-dose vaccination regimen elicits less durable immune responses than those in young adults. Of note, vaccine-specific memory B cells might be present despite reduced antibody concentrations,[8] but remain to be investigated in detail in older people (appendix p 7). Yet, in light of the recent surge in hospitalisations (even in countries with high vaccination rates such as Israel), along with strong epidemiological evidence of waning protection[6] and the increased risk of severe disease and death from COVID-19 in older people, the current data might further support booster vaccinations for this population. Further studies are needed that investigate long-term immunity from COVID-19 vaccines in high-risk populations and the safety and effectiveness of additional boosters.

VMC is named together with Euroimmun on a patent application filed recently regarding the diagnosis of SARS-CoV-2 by antibody testing (application number EP20158626.0). HG and FKl are named on a patent application regarding neutralising antibodies against SARS-related coronaviruses (application number EP20177354). All other authors declare no competing interests. We thank all study participants at Charité – Universitätsmedizin Berlin for their participation. We also thank the entire staff of the Department for Occupational Medicine, the Charité Clinical Study Center at Charité – Universitätsmedizin Berlin, and the Berlin Institute of Health (BIH) for their support during the study. SARS-CoV-2 RBD variant antigens were kindly provided by InVivo BioTech Services (Hennigsdorf, Germany) to the Seramun Diagnostica (Heidesee, Germany). Parts of this work were supported by grants from the BIH and Berlin University Alliance. This study was further supported by the German Ministry of Education and Research through Forschungsnetzwerk der Universitätsmedizin zu COVID-19, (COVIM, FKZ: 01KX2021) to LES, FKu, FKI, CD, and VMC; through VARIPath projects (01KI2021) to VMC; and through Deutsche Forschungsgemeinschaft (SFB-TR84) to NS and LES. The study was supported by a donation from Zalando to Charité – Universitätsmedizin Berlin.

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