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.

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Dynamics of humoral and T-cell immunity after three BNT162b2 vaccinations in adults older than 80 years

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See **Online** for appendix

A third mRNA-based booster vaccination is the currently favoured strategy to maintain protection against SARS-CoV-2 infection. Yet, significant waning of specific immunity within 6 months after two doses,[1] along with a higher incidence of breakthrough infections associated with the time elapsed since the second dose,[2,3] raise concerns regarding the durability of immunity also after the booster vaccination.

We compared the specific humoral and cellular responses (figure; appendix pp 10–13) after three versus two BNT162b2 (Pfizer-BioNTech) doses in a cohort of adults older than 80 years (median age 83 years [IQR 81–86]; appendix pp 3–4) at risk for severe COVID-19 and immune senescence. Our data demonstrate the induction of marginally higher spike S1-specific blood IgG concentrations 2 weeks after three than after two doses (appendix p 5). By contrast, functionally relevant receptor binding domain-specific IgG (figure A) and SARS-CoV-2-neutralising antibody (appendix p 5) titres were substantially increased after three compared with two doses, reflecting enhanced antibody production or affinity maturation.

By contrast, spike-specific CD4 T-cell frequencies reached similar levels after two and three doses (figure B; appendix p 5). After the respective acute response, frequencies returned to approximately pre-third vaccination levels, with no significant differences in the rate of decline after the second and third vaccinations (figure B; appendix p 6). Quantified cytoplasmic expression of the effector cytokine interferon γ (IFNγ) indicated functional enhancement of spike-specific T cells upon second but not further upon third vaccination, while more cytoplasmic IFNγ was found in spike-specific CD4 T cells from adults older than 80 years who had recovered from COVID-19 (appendix p 5). Thus, even a third BNT162b2 dose failed to induce durably enhanced quantities of spike-specific T cells and a functional quality reached after natural infection. Neither age nor comorbidities were significantly correlated with the observed immune response, perhaps due to the limited size of our cohort (appendix pp 7–9).

Concentrations of S1-specific IgG and neutralising antibodies also declined from the acute responses at weeks 5 and weeks 26, but at a lower rate and with an extended half-life after the third (week 40) compared with the second (week 24) dose (figure A; appendix pp 5–6), yielding more persistent, enhanced IgG quantity or quality after the third than after the second vaccination.

We conclude that a third dose of BNT162b2 in older adults, while establishing immunity in primary non-responders,[4] induces a durably escalated humoral response in the bulk of vaccinees for at least 3 months, indicating longer lasting humoral immunity. In a younger cohort, this boost also led to a strong increase of neutralising antibodies against the omicron (B.1.1.529) variant and protection from infection with the omicron variant.[5,6] Although neutralising antibody data for omicron are not yet available for our cohort, the strong rise in titres of neutralising antibodies against the BavPat1/2020 isolate used in our neutralisation assay (appendix p 5) suggests better neutralisation against omicron by the booster dose than for the second dose, as also demonstrated by others,[7] at least

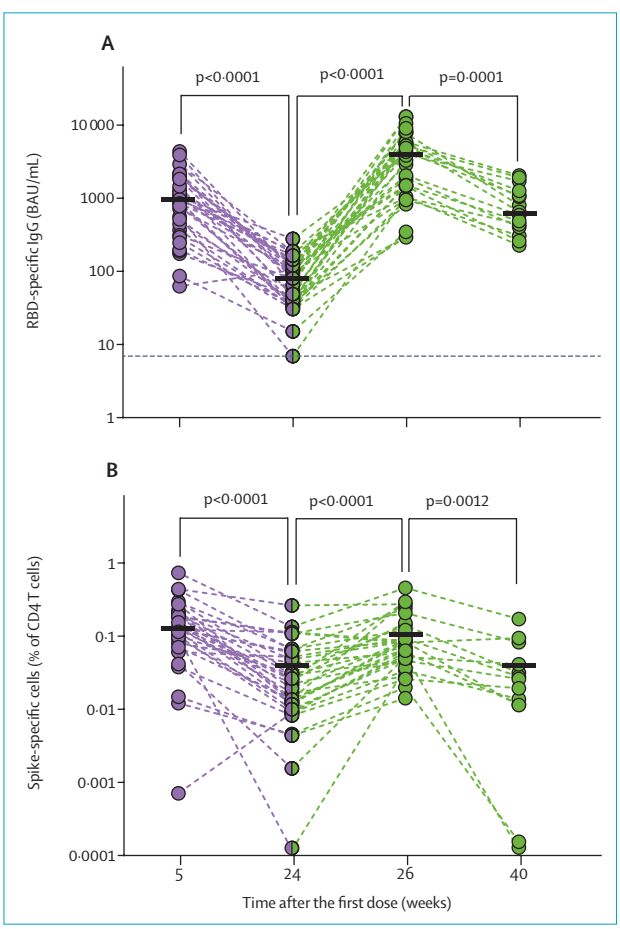

Figure: **Humoral and cellular SARS-CoV-2 immunity in donors older than 80 years after two and three doses of BNT162b2**
Immune response kinetics were followed in older adults in the course of vaccinations with BNT162b2 (second vaccination occurred 3 weeks and third vaccination occurred a median of 24 weeks [IQR 23–25] after first vaccination). Green indicates data related to the third dose of BNT162b2. Each symbol represents data of one donor at one timepoint. Horizontal lines indicate median values of datapoints in each column. p values were determined by two-tailed Wilcoxon matched-pairs signed rank test. (A) SARS-CoV-2 RBD-specific serum IgG levels; for weeks 5, 24, 26, and 40, number of participants was 35, 36, 34, and 15, respectively. The dotted horizontal line indicates the cutoff for antibody positivity at 7·1 BAU/mL. (B) Frequencies of SARS-CoV-2 spike-specific CD4 T cells identified as CD40 ligand-positive, interferon γ-positive CD4 T cells after overnight stimulation of peripheral blood mononuclear cells with SARS-CoV-2 spike peptides; for weeks 5, 24, 26, and 40, number of participants was 34, 35, 33, and 13, respectively. RBD=receptor-binding domain. BAU=binding antibody units.

in the short term. The level of T-cell immunity to SARS-CoV-2 in peripheral blood required for protection is still not established, although peripheral T cells induced by BNT162b2 apparently react well against the omicron variant.[8] As for our cohort, our data show two important aspects of a third compared with a second dose—namely, peak virus-specific T-cell frequencies were not further increased by a third dose, and average per-cell production of IFNγ remained unaltered and was still remarkably lower than in recovered donors of a similar age. Thus, at least in older adults, the durability and quality of vaccine-induced immunity should be considered in the recommendation of booster vaccinations, in addition to the severity of breakthrough SARS-CoV-2 infections caused by current and future viral mutants.

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*Addi J Romero-Olmedo, Axel Ronald Schulz, Svenja Hochstätter, Dennis Das Gupta, Heike Hirseland, Daniel Staudenraus, Bärbel Camara, Kirsten Volland, Véronique Hefter, Siddhesh Sapre, Verena Krähling, Helena Müller-Kräuter, Ho-Ryun Chung, Henrik E Mei, Christian Keller, *Michael Lohoff*

lohoff@med.uni-marburg.de

Institute of Medical Microbiology and Hospital Hygiene (AJR-O, DDG, DS, BC, ML), Institute of Virology (SH, KV, VH, SS, VK, HM-K, CK), and Institute of Medical Bioinformatics and Biostatistics (H-RC), Philipps-University Marburg, Marburg 35043, Germany; Deutsches Rheumaforschungszentrum Berlin, a Leibniz Institute, Berlin, Germany (ARS, HH, HEM); German Center for Infection Research, partner site Gießen–Marburg–Langen, Marburg, Germany (VK, HM-K)

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Antibody durability at 1 year after Sputnik V vaccination

Antibody waning against SARS-CoV-2 over time after vaccination, together with the emergence of new viral variants, pose great challenges for ending the pandemic. To our knowledge, no previous work has assessed the long-term prevalence of anti-SARS-CoV-2 antibodies in individuals vaccinated with Sputnik V (Gam-COVID-Vac).[1] We assessed the persistence of anti-spike IgG antibodies and their neutralising capacity against the original SARS-CoV-2 lineage (B.1) and a local isolate of the BA.1 lineage of the omicron (B.1.1.529) variant in a longitudinal cohort during 1 year after Sputnik V vaccination in Argentina.

We used 400 paired serum samples (100 samples at each timepoint, including at baseline before vaccination) from 100 volunteers who received two doses of Sputnik V that were obtained between Jan 1, 2021, and Jan 15, 2022. Participants with current or previous SARS-CoV-2 infection, determined by assessing seropositivity to nucleocapsid protein, were excluded from the analysis. The geometric mean (GM) of international units of IgG anti-spike antibodies[2] per mL (IU/mL) were 994 (95% CI 769–1285) at 42 days, 80 (60–106) at 180 days, and 36 (27–47) at 360 days after completion of the two-dose vaccination scheme (figure A; appendix p 2). Overall, a 27-fold reduction in IgG was observed 1 year after Sputnik V vaccination.

We assessed the GM half-maximal neutralising titre (GMT, IC_{50}) using a pseudotyped vescicular stomatitis virus carrying the spike of a viral isolate from Wuhan at the early stage of the pandemic (appendix p 4). The GMT at 42 days after vaccination was 133 (95% CI 92–193), at 180 days was 28 (19–39), and at 360 days was 11 (8–16; figure B).

Considering previous studies indicating that antibody responses undergo a maturation process,[3,4] we analysed the serum neutralising activity over time against the omicron variant. To this aim, we assessed the neutralising activity elicited by the Sputnik V vaccine[5] using the original B.1 isolate and a local isolate of BA.1 omicron. For this analysis, we used 60 samples (20 samples per timepoint) with the highest neutralising GMT for the original B.1 virus. For all timepoints analysed, we found a substantial decrease in the serum neutralising capacity against the omicron variant compared with the B.1 lineage (64-fold reduction at 42 days, 32-fold reduction at 180 days, and 28-fold reduction at 360 days after vaccination; appendix p 2). Six (30%) of the 20 immunised individuals remained positive for neutralising antibodies against omicron at 42 days after vaccination. This proportion increased to 45% (nine of 20) at 360 days. Similar results have been obtained using other vaccines

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