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.

Durability of omicron-neutralising serum activity after mRNA booster immunisation in older adults

Advanced age is a key risk factor for morbidity and mortality associated with SARS-CoV-2 infection. Therefore, older adults have generally been prioritised for COVID-19 vaccination. Moreover, lower vaccine immunogenicity and more pronounced waning of humoral immunity in older individuals than in younger individuals have prompted early booster campaigns.[1] The omicron variant (B.1.1.529) of SARS-CoV-2 shows substantial resistance to vaccine-induced serum neutralising activity and hence is of particular concern.[2] Although booster immunisations can elicit omicron-neutralising activity,[3] their immediate and long-term effects in older individuals are not known, which limits informed guidance on vaccination strategies in this susceptible population.

We longitudinally determined SARS-CoV-2-neutralising serum activity in a prospective cohort of 37 individuals with a median age of 82 years (range 76–96; appendix p 2).[4] Individuals were recruited at a general practitioner surgery in Berlin, Germany, with the support of the Charité-Universitätsmedizin Berlin, and received their first COVID-19 vaccination on Jan 15, 2021. Participants were followed-up for 10 months after their second dose of BNT162b2 (Pfizer-BioNTech) and up to 4·5 months after a booster dose of BNT162b2. We determined geometric mean 50% inhibitory serum dilutions (ID_{50}) against the Wu01 vaccine strain as well as the delta (B.1.617.2) and omicron variants (BA.1) using an in-house pseudovirus assay.

After their second dose of BNT162b2, serum samples were collected at 1 month (median 26 days [IQR 25–27]; visit 1) and 5 months (median 153 days [151–154]; visit 2) of follow-up. Two BNT162b2 doses induced detectable Wu01-neutralising and delta-neutralising activity in most individuals (35 [95%] of 37 for Wu01 and 31 [84%] for delta), while activity against omicron was not or only minimally detectable (figure; appendix p 3). Over the next 4 months, Wu01-neutralising titres decreased 6-fold (from a geometric mean ID_{50} of 260 on visit 1 to 42 on visit 2) and delta-neutralising titres decreased 7-fold (from a geometric mean ID_{50} of 89 to 13).

All individuals received a booster dose of BNT162b2 at 7 months (median 209 days [IQR 189–228]) and early post-boost serum samples were obtained 1 month later (median 23 days [IQR 21–29]; visit 3). Booster immunisation resulted in an over 50-fold increase in Wu01-neutralising and delta-neutralising titres (to a geometric mean serum ID_{50} of 2912 for Wu01 and 750 for delta). The BNT162b2 booster elicited robust omicron-neutralising activity (to a geometric mean ID_{50} of 256) in 33 (89%) of 37 participants (figure; appendix p 3).

To determine post-boost durability of SARS-CoV-2-neutralising activity in older adults, we obtained samples 3·5 months (median 106 days [IQR 86–125]) after booster vaccination (visit 4). Neutralising titres decreased by 2·7-fold (to geometric mean ID_{50} of 1077) against the Wu01 variant, 2·3-fold (to 345) against the delta variant, and 3·0-fold (to 85) against the omicron variant. However, most individuals maintained detectable serum neutralisation against Wu01 (36 [97%] of 37), delta (34 [92%]), and omicron (30 [81%]; corresponding to 30 [91%] of 34 individuals with activity at the early post-boost visit [ie, visit 3]). To assess the rate of decrease in neutralising activity, we separately analysed the pre-booster (visit 1–2) and post-booster (visit 3–4) periods using linear mixed-effect models (appendix p 4). Neutralising activity against the variants showed similar changes, with estimated post-booster half-lives of 52 days (95% CI 46–59) for the Wu01 variant, 64 days (52–83) for the delta variant, and 41 days (34–52) for the omicron variant (appendix p 4).

In the absence of omicron variant-specific vaccines, booster immunisations are crucial to restore vaccine effectiveness against severe outcomes.[5] We found that booster immunisations can effectively elicit omicron variant-neutralising activity in the majority of older individuals. Although our analyses were limited to four sampling timepoints and different pre-boost and post-boost observational periods, our results suggest that neutralising activity

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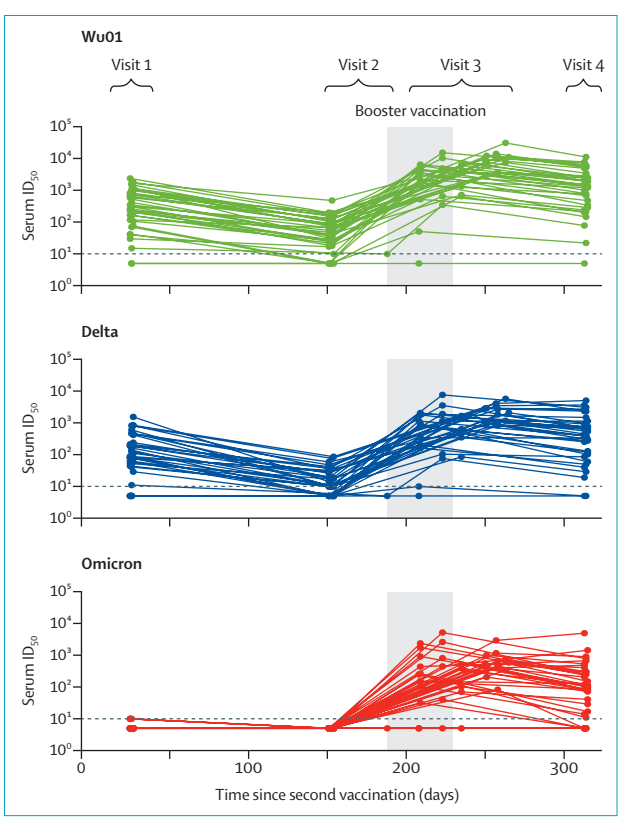

Figure: **Longitudinal assessment of SARS-CoV-2-neutralising serum activity in older adults**
Wu01-neutralising, delta-neutralising, and omicron-neutralising serum 50% geometric mean inhibitory serum dilutions (serum ID_{50}) determined using pseudovirus neutralisation assays for 37 individuals. Lines connect study visits (visit 1 to 4) for each individual. Grey areas indicate booster administration period. Dotted lines show lower limit of quantification.

against different variants decreases at similar decay rates. Although neutralising activity does not equal protection from infection, our findings suggest that previous observations on waning humoral immunity can guide subsequent booster vaccination strategies in the older population.

KV, HG, and FKl are listed as inventors on patent applications regarding SARS-CoV-2-neutralising antibodies filed by the University of Cologne. All other authors declare no competing interests. KV, PT-L, and HG contributed equally. FKu, LES, and FKl contributed equally. Acknowledgments are listed in the appendix (p 7).

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Effectiveness of ChAdOx1 nCoV-19 vaccine during the delta (B.1.617.2) variant surge in India

We read with interest the study by Ramachandran Thiruvengadam and colleagues.[1] However, we feel there are some aspects of the study that require further input from the authors.

The mean age of cases is reported to be 35 years and of controls to be 32 years.[1] In India, vaccination of the general population in the 18–45 years age group began in early May, 2021; in this age group, only frontline workers were vaccinated from mid-January to late April, 2021. Considering the quoted duration of the study (April 1 to May 31, 2021), most fully vaccinated individuals would have been frontline workers, and predominantly health workers. However, the unvaccinated group would be representative of the general population. Therefore, the two groups had different levels of exposure to SARS-CoV-2, making comparison and estimates of vaccine efficacy difficult.

The controls were selected on the basis of RT-PCR negativity in a defined time period. However, some of them might have been affected during the first wave of COVID-19 with mild or asymptomatic disease and might have been partially immune to reinfection during the study period, which would be an unknown variable in the study modifying reinfection rate or severity. Measurement of serum neutralising antibody titres against spike or nucleocapsid proteins at baseline could have been used to eliminate this group from the study.

Compared with the total study population, the number of people analysed for T-cell response was small (48 [1·1%] of 4360). Furthermore, the T-cell responses to spike peptide pools of wild-type SARS-CoV-2 and delta (B.1.617.2) SARS-CoV-2 were only studied in a healthy vaccinated group. An unvaccinated group could have been included to check whether cross-reactive T cells primed by endemic coronaviruses can also respond to wild-type SARS-CoV-2 or the delta variant. The concept of cross-immunity has been expanded in the context of COVID-19, both theoretically and experimentally.[2,3] Additionally, these data would have helped us to understand the intensity of the T-cell immune response in the vaccinated population compared with the unvaccinated population. Even those positive for antibodies against SARS-CoV-2 nucleocapsid at baseline could have been included in this testing to investigate how previous infection affects T-cell responses. Such an investigation becomes more relevant in a real-world study when breakthrough infections are known to be quite common.

Finally, an important prerequisite for test-negative case-control studies is matching of cases and controls for disease severity and confounders.[4] Information on such potential confounders and symptom characterisation (especially disease severity) in the control group should be provided. Furthermore, the test-negative design can control for selection and information bias but is not effective in blocking bias due to health-seeking behaviour, which differs between vaccinated and unvaccinated individuals and is affected by the severity of COVID-19.[4]

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