Three-month follow-up of durability of response to the third dose of the SARS-CoV-2 BNT162b2 vaccine in adults aged 60 years and older: a prospective cohort study

Noa Eliakim-Raz,1,2 Amos Stemmer3, Yaara Leibovici-Weisman,4 Asaf Ness,4 Muhammad Awwad,4 Nassem Ghantous,4 Noam Erez,5 Avital Bareket-Samish,6 Adva Levy-Barda,7 Haim Ben-Zvi,8,9 Neta Moskovits,10 Erez Bar-Haim11, Salomon M Stemmer2,12

ABSTRACT

Objective To evaluate the durability of response 3 months after the third BNT162b2 vaccine in adults aged 60 years and older.

Design Prospective cohort study.

Setting Single tertiary centre.

Participants Healthcare workers/family members aged ≥60 years old who received the third BNT162b2 dose.

Interventions Blood samples were drawn immediately before (T0), 10–19 days (T1) and 74–103 days (T2) after the third dose.

Primary and secondary outcome measures Anti-spike IgG titres were determined using a commercial assay and seropositivity was defined as ≥50 arbitrary units (AU)/mL. Neutralising antibody titres were determined at T2. Adverse events, COVID-19 infections and Clinical Frailty Scale (CFS) levels were documented.

Results The analysis included 97 participants (median age, 70 years (IQR, 66–74), 58% CFS level 2). IgG titres, which increased significantly from T0 to T1 (median, 440 AU/mL (IQR, 294–923) and median, 25 429 AU/mL (IQR, 14 203–36 114), respectively; p<0.001), decreased significantly by T2, but all remained seropositive (median, 8306 AU/mL (IQR, 4595–14 701), p<0.001 vs T1). In a multivariable analysis, only time from the second vaccine was significantly associated with lower IgG levels at T2 (p=0.017). At T2, 60 patients were evaluated for neutralising antibodies; all were seropositive (median, 440 AU/mL (IQR, 294–923)). Neutralising antibody and anti-spike IgG levels were correlated (r=0.6, p<0.001). No major adverse events or COVID-19 infections were reported.

Conclusions Anti-spike IgG and neutralising antibody levels remain adequate 3 months after the third BNT162b2 vaccine in healthy adults aged ≥60 years, although the decline in IgG is concerning. A third dose of vaccine in this population should be top priority.

INTRODUCTION

The COVID-19 pandemic, which has been affecting global health for the past 2 years, is caused by SARS-CoV-2. Age and frailty are among the strongest predictors of COVID-19 mortality.1,2 Due to immunosenescence, the primary vaccine response in those aged 65 years and older is associated with lower rates of protection compared with younger individuals.3 The BNT162b2 messenger RNA (mRNA) vaccine (Pfizer/BioNTech) induces generally lower antigen-binding IgG and virus-neutralising responses in individuals aged 65–85 years compared with those aged 18–55 years, when monitored 2 weeks post vaccination,4 and immunity wanes in all age groups.5,6 In Israel, COVID-19 was first diagnosed at the end of February 2020, and since then and up to our study period three waves of the pandemic have been clearly defined in the country. In July 2021, the Israel Ministry of Health has approved mRNA-based vaccines (Pfizer/BioNTech, mRNA-BNT162b2, which requires two doses, 21 days apart) and a national immunisation programme started vigorously on 19 December 2020. The national immunisation programme prioritised elderly adults and other populations at higher risk of severe COVID-19, followed by...
the general population. The first wave in Israel resulted in 4000 hospitalisations and 329 deaths, whereas the second and third waves were severe and ended with 40000 hospitalisations and 6099 more deaths.7

We recently reported the initial findings of a prospective cohort study that evaluated the anti-spike (anti-S) IgG antibody response before and after the third dose of the BNT162b2 vaccine in adults aged 60 years and older.8 We showed that the third dose of vaccine was associated with significantly increased IgG titres, 10–19 days after that dose, with no major adverse events. The difference in median IgG titres before and after the third dose was >50-fold.8

The durability of response to the vaccine in adults aged 60 years and older is yet to be determined. Understanding the extent of waning immunity is critical to policy making, especially surrounding vaccination strategies. In this study, we evaluated the anti-S IgG antibody titres and neutralising antibodies 3 months after the third BNT162b2 dose in adults aged 60 years and older.

METHODS

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Study setting and participants

Rabin Medical Center (RMC) is a tertiary hospital staffed by 7500 healthcare workers, including employees, students and volunteers. Following the authorisation of a third dose in Israel on 1 August 2021, RMC offered this dose to healthcare workers and their family members. Between 4 and 12 August, study participants were recruited from those aged 60 years and older at the RMC vaccination centre. Exclusion criteria included prior SARS-CoV-2 infection (confirmed by PCR); steroidal treatment equivalent to 15 mg prednisone for the past 21 days or longer; active chemotherapy, immunotherapy or biological treatments; active solid, haematological malignancy or both; and conditions affecting immunocompetence, including liver cirrhosis, haemodialysis, solid organ transplant, bone marrow transplant, AIDS, inherent immune deficits such as congenital/acquired deficiencies of the complement system, and asplenia or functional asplenia (eg, sickle cell disease).

Sample collection

Blood samples were drawn from the study participants before they received their third dose of the BNT162b2 vaccine (T0; 4–12 August 2021). Blood samples were also drawn 10–19 days (T1; 16–24 August 2021) and 74–103 days after the third vaccination (T2; 3–15 November 2021; except for two patients who came to their follow-up appointment on the wrong date and for whom the blood sample was drawn on 17 October 2021).

At T2, a second blood sample was drawn from 60 participants who were randomly selected for neutralisation antibody analysis and was sent to the Israel Institute for Biological Research (Ness Ziona, Israel), where SARS-CoV-2 pseudovirus neutralisation assay was performed. The serum samples were stored in −80°C until the day of analysis.

Assessments

Titres of anti-S IgG antibodies in the serum from the blood samples were determined at the RMC microbiological laboratory, using a chemiluminescent microparticle immunoassay, performed on the Abbott architect i2000sr platform, in accordance with the manufacturer’s package insert for SARS-CoV-2 IgG II Quant assay (Abbott Laboratories, Abbott Park, Illinois, USA; reference 6S60-22).9 The strength of the response (in relative light units (RLU)) was determined relative to IgG II calibrator/standard and reflects the quantity of IgG antibodies present. Seropositivity was defined as 50 arbitrary units (AU)/mL and higher. The assay is 98.1% sensitive 15 days or longer after the onset of COVID-19 symptoms or positive PCR test result and 99.6% specific.10

Pseudovirus-neutralising assay was performed using pseudoviruses expressing SARS-CoV-2 spike protein. Plasmids encoding a luciferase reporter (pGreenFire1, System Biosciences), lentivirus backbone (psPAX, Addgene) and S genes (19 S-covid-pCMV3, a kind gift from Professor Yossef Shaul, Weizmann Institute of Science, Rehovot, Israel) were cotransfected into HEK293T cells (ATCC CRL-3216). Forty-eight hours later, the medium was collected and virus aliquots were stored at −80°C for future use. One day before the pseudovirus neutralisation assay, hACE2-expressing HEK293T cells were plated in a white-well 96-well plate (2×104 cells per well). On the day of the assay, heat-inactivated sera were twofold serially diluted and mixed with pseudovirus, incubated for 1 hour at 37°C, and added to hACE2-expressing HEK293T cells. Twenty-four hours later, cells were lysed and luciferase activity (in RLU) was measured.11 12 Per cent neutralisation was normalised using uninfected cells as 100% neutralisation and cells infected with only pseudovirus as 0% neutralisation. IC50 titres were determined using a log (agonist) versus normalised-response (variable slope) non-linear function using Prism software (GraphPad). Seropositivity was defined as a titre of 20 and higher.

The frailty of all participants was assessed at recruitment and confirmed at each timepoint thereafter via an interview using the 9-point Clinical Frailty Scale (CFS).13 In addition, data were derived from the electronic medical records of all participants, including age, sex, vaccine doses and vaccination dates, and comorbidities.

Before the third vaccination and during both postvaccination follow-up appointments, the study participants completed a questionnaire on adverse reactions post vaccination and whether they had a confirmed COVID-19 infection since the third dose/dose following up, and if so their symptoms were documented.
Participant characteristics were analysed using descriptive statistics. The difference in anti-S IgG values from T0 to T1 and from T1 to T2 was evaluated using a linear mixed effects model. Spearman correlation was used to assess the correlation between the anti-S IgG antibody values and neutralising antibodies titres. Univariate and multivariable analyses were performed by fitting a linear model on the log of anti-S IgG antibody values at T2 and included age and days from the second vaccination as continuous variables, and sex, comorbidities (dyslipidaemia, hypertension, obesity, diabetes and ischaemic heart disease) and CFS as categorical variables.

For all analyses, IgG values above 80 000 AU/mL were considered as 80 000 AU/mL. A p value of less than 0.05 was considered significant. All tests were two-sided. Statistical analysis was performed using R V.4.0.2.14

RESULTS
Overall, 130 consecutive individuals aged 60 years and older were approached at the RMC vaccination centre, of whom 1 did not meet the eligibility criteria due to active malignancy and 28 refused participation. IgG levels at T0 were determined for 101 participants (78%). A total of four participants (3%) were lost to follow-up. Thus, the final cohort included 97 participants (figure 1). The median age was 70 years (IQR, 66–74) and 61% were women. The most common comorbidity was dyslipidaemia (61%), followed by hypertension (49%). The frailty of majority of the participants (58%) was characterised as ‘well’ (CFS level 2) (table 1).

IgG titres, which increased significantly from before the third dose (T0) to a median of 14 days (IQR, 14–17) after the third dose (T1) (median of 440 AU/mL (IQR, 294–923) vs 25 429 AU/mL (IQR, 14 203–36 114); p<0.001), decreased significantly approximately 3 months after the third dose (T2; median of 94 days (IQR, 92–97) after the third dose), but all participants remained seropositive. At the T2 timepoint, the median IgG titre was 8306 AU/mL (IQR, 4595–14 701) (p<0.001 vs T1) (table 1, figure 2).

In univariate and multivariable analyses, the only variable significantly associated with lower IgG levels at T2 was the number of days from the second dose of vaccine (table 2).

All participants for whom neutralising antibody levels were assessed (n=60) were positive for these antibodies. The median value of neutralising antibody titre was 1294

Table 1  Baseline demographics and cohort characteristics before and up to 3 months after the third BNT162b2 dose

| Characteristics | N=97 |
|-----------------|------|
| Age             | Median (IQR), years | 70.0 (66–74) |
| Sex, male, n (%)| 38 (39) |
| Comorbidities, n (%) | | |
| Dyslipidaemia   | 59 (61) |
| Hypertension    | 48 (49) |
| Obesity         | 26 (27) |
| Diabetes        | 19 (20) |
| Ischaemic heart disease | 17 (18) |
| Congestive heart failure | 1 (1) |
| Clinical Frailty Scale, n (%) | | |
| Very fit (level 1) | 28 (29) |
| Well (level 2)   | 56 (58) |
| Managing well (level 3) | 8 (8) |
| Vulnerable (level 4) | 4 (4) |
| Mildly frail (level 5) | 1 (1) |
| Analysis before the third dose (T0) | | |
| Median (IQR) IgG titres, AU/mL | 440 (294–923) |
| Analysis 10–19 days after the third dose (T1) | | |
| Median (IQR) days after the first dose | 236 (232–240) |
| Median (IQR) days after the third dose | 14 (14–17) |
| Median (IQR) IgG titres, AU/mL | 25 429 (14 203–36 114) |
| Analysis 74–103 days after the third dose (T2) | | |
| Median (IQR) days after the first dose | 316 (312–320) |
| Median (IQR) days after the third dose | 94 (92–97) |
| Median (IQR) IgG titres, AU/mL | 8306 (4595–14 701) |
| Median (IQR) neutralising antibody titre | 1294 (848–2072) |

AU, arbitrary units.
(IQR, 848–2072). Evaluating the correlation between anti-S IgG titres and neutralising antibody titres in these participants at T2 demonstrated a positive linear correlation (r=0.6, p<0.001) (figure 3).

During the study period (median follow-up of 94 days; IQR, 92–97), no major adverse events were reported and no participant had a COVID-19 infection. No change in frailty levels was observed in any of the participants throughout the study period.

**DISCUSSION**
This prospective cohort study demonstrated that anti-S IgG antibody levels increased significantly from before the third BNT162b2 dose to approximately 2 weeks after (median of 440 AU/mL vs 25,429 AU/mL). However, approximately 3 months after that dose, a significant decrease in anti-S IgG levels was observed (median of 8306 AU/mL), although all participants remained seropositive.

In patients after natural COVID-19 infection, anti-S IgG levels were shown to be sustained, or progressively but moderately declined, whereas the anti-receptor-binding domain of the spike protein (anti-RBD) IgG levels declined more commonly. One study showed that...

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**Table 2**  Univariate and multivariable analyses of log IgG values

| Characteristics          | Univariate analysis | Multivariable analysis |
|-------------------------|---------------------|------------------------|
|                         | β (95% CI)          | P value                | β (95% CI)          | P value                |
| Age                     | −0.01 (−0.05 to 0.02) | 0.53                   | 0.00 (−0.04 to 0.04) | 0.91                   |
| Sex                     |                     |                        |                       |                        |
| Female                  | NA                  |                        | NA                    |                        |
| Male                    | −0.19               | 0.31                   | −0.24 (−0.07 to 0.23) | 0.23                   |
| Days from second vaccination | −0.03 (−0.06 to −0.00) | 0.031                  | −0.04 (−0.07 to −0.01) | 0.017                  |
| Comorbidities           |                     |                        |                       |                        |
| Diabetes                | −0.16 (−0.62 to 0.30) | 0.48                   | −0.02 (−0.52 to 0.49) | 0.95                   |
| Dyslipidaemia           | −0.12 (−0.49 to 0.26) | 0.54                   | −0.06 (−0.48 to 0.35) | 0.76                   |
| Ischaemic heart disease | −0.12 (−0.60 to 0.36) | 0.63                   | 0.12 (−0.47 to 0.71) | 0.69                   |
| Hypertension            | −0.24 (−0.61 to 0.12) | 0.19                   | −0.20 (−0.65 to 0.25) | 0.39                   |
| Obesity                 | 0.05 (−0.36 to 0.46) | 0.81                   | 0.24 (−0.19 to 0.67) | 0.28                   |
| Clinical Frailty Scale  |                     |                        |                       |                        |
| Very fit                | NA                  |                        | NA                    |                        |
| Well                    | −0.19 (−0.60 to 0.22) | 0.40                   | −0.08 (−0.56 to 0.40) | 0.74                   |
| Managing well           | −0.45 (−1.2 to 0.27) | 0.20                   | −0.34 (−1.1 to 0.42) | 0.40                   |
| Vulnerable              | −1.0 (−1.9 to −0.04) | 0.045                  | −1.0 (−2.0 to −0.03) | 0.047                  |
| Mildly frail            | 0.43 (−1.4 to 2.2)  | 0.6                    | 0.75 (−1.2 to 2.7)  | 0.45                   |

NA, not applicable.
within 1.3 and 6.2 months of SARS-CoV-2 infection, titres of IgM and IgG antibodies against RBD decreased significantly while neutralising activity in the plasma decreased fivefold in pseudotype virus assays. Neutralisation antibody dynamics were similar to that of anti-RBD antibodies in other studies as well. Overall, seropositivity rates remain high (88%–90%) 6–8 months after natural infection.

The clinical effectiveness of BNT162b2 against SARS-CoV-2 infection peaks in the first month after the second dose, declines gradually thereafter, and the decline accelerates after the fourth month. A recent study evaluated the long-term effectiveness of the BNT162b2 vaccine in participants of phase II–III randomised trial and found a fourfold decrease in its effectiveness between months 1–2 and 4–7 after the second dose (from 96% to 84%).

The durability of protection after third vaccination in healthy individuals at any age is still unknown. Understanding the extent of waning immunity is critical to public health policy making. To our knowledge, no serological follow-up beyond 1 month after the third dose has been published. The rapid waning of immunity prompted investigation of the durability of the immune response after the third dose in order to assist decision-making regarding additional booster vaccinations.

During the fifth wave, in January 2022, the Israeli Ministry of Health authorised a fourth BNT162b2 dose to individuals aged ≥60 years, assuming waning of immunity. Recent data on 1,252,331 persons who were 60 years of age or older and eligible for the fourth dose demonstrated the rate of severe COVID-19 in the fourth week after receipt of the fourth dose was lower than that in the third week by a factor of 3.5 (95% CI 2.7 to 4.6), and the participants experienced a COVID-19 infection.

In conclusion, in our cohort of 97 adults aged 60 years and older, 3 months after the third BNT162b2 vaccine, high levels of anti-S and neutralising antibodies were found, but with significant waning of the immune response. Although further studies are needed to advance our understanding of waning immunity, the results suggest that a third dose of vaccine for adults aged 60 years and older is effective and should be a top priority worldwide.

Author affiliations
Department of Medicine E and Infectious Diseases Unit, Beilinson Hospital, Petah Tikva, Israel
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
Oncology, Sheba Medical Center at Tel Hashomer, Tel Hashomer, Israel
Department of Medicine E, Beilinson Hospital, Petah Tikva, Israel
Department of Infectious Diseases, Israel Institute for Biological Research, Ness Ziona, Israel
BioInsight, Binyamina, Israel
Biobank, Department of Pathology, Beilinson Hospital, Petah Tikva, Israel
Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel
Clinical Microbiology Laboratory, Beilinson Hospital, Petah Tikva, Israel
Contributors NE-R, AS, YL-W, AN, MA, NG, NE, AB-S, AL-B, HB-Z, NM, EB-H and SMS contributed to this article. NE-R and SMS designed the trial and the study protocol. NE-R, AS, YL-W, AN, MA, NG, NE, AB-S, AL-B, HB-Z, NM, EB-H and SMS contributed to data collection. AS performed the formal analysis. NE-R, AS, YL-W, AN, MA, NG, NE, AB-S, AL-B, HB-Z, NM, EB-H and SMS contributed to data interpretation and revisions. NE-R, AS, YL-W, AN, MA, NG, NE, AB-S, AL-B, HB-Z, NM, EB-H and SMS reviewed the manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Rabin Medical Center (RMC) (reference number 0558-21-RMC). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. This study is ongoing. Individual participant-level data that underlie the results reported in this article (text, tables and figures) will be shared after de-identification, following the publication of the final endpoint of this study (6-month follow-up), upon request from the corresponding author.

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ORCID iDs
Amos Stemmer http://orcid.org/0000-0002-2357-3923
Erez Bar-Haim http://orcid.org/0000-0003-3435-8599

REFERENCES
1 Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (cope): a multicentre, European, observational cohort study. Lancet Public Health 2020;5:e44:451–e451.
2 Tehrani S, Killander A, Åstrand P, et al. Risk factors for death in adult COVID-19 patients: frailty predicts fatal outcome in older patients. Int J Infect Dis 2021;102:415–21.
3 Allen JC, Toapanta FR, Chen W, et al. Understanding immunosenescence and its impact on vaccination of older adults. Vaccine 2020;38:8264–72.
4 Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med 2020;383:2439–50.
5 Lumley SF, Wei J, O’Donnell D, et al. The duration, dynamics, and determinants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody responses in individual healthcare workers. Clin Infect Dis 2021;73:e699:709–e709.
6 Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med Overseas Ed 2021;385:e85.
7 NiY, Eliakim-RazN, Bar-LaviY. Comparing Covid-19 pandemic waves in hospitalized patients – a retrospective, multicenter, cohort study. OUP Public Health Emergency Collection.
8 Eliakim-Raz N, Leibovici-Weisman Y, Stemmer A, et al. Antibody titers before and after a third dose of the SARS-CoV-2 BNT162b2 vaccine in adults aged ≥60 years. JAMA 2021;326:2203–4.
9 SARS-CoV-2 Immunassay. Core laboratory at Abbott. Available: https://www.corelaboratory.abbott/en/en/offerings/segments/infectious-disease-sars-cov-2-[Accessed 12 Jan 2022].
10 AdviseDx. SARS-CoV-2 IgG II Instructions for use (architect). Available: www.corelaboratory.abbott [Accessed 12 Jan 2022].
11 Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature 2020;586:567–71.
12 Liu R, Americo JL, Cotter CA, et al. One or two injections of MVA-vectorized vaccine shields hACE2 transgenic mice from SARS-CoV-2 upper and lower respiratory tract infection. Proc Natl Acad Sci U S A 2021;118.
13 Moreno-Aníño R, Torrente Jiménez I, Cartañá Gutiérrez A, et al. Assessing the strengths and weaknesses of the clinical frailty scale through correlation with a frailty index. Aging Clin Exp Res 2020;32:2225–32.
14 R. The R project for statistical computing. Available: https://www.r-project.org/[Accessed 12 Jan 2022].
15 Ward H, Cooke GS, Atchison C, et al. Prevalence of antibody positivity to SARS-CoV-2 following the first peak of infection in England: serial cross-sectional studies of 365,000 adults. Lancet Reg Health Eur 2021;4:100098.
16 Gaebler C, Wang Z, Lorenzi JCC, et al. Evolution of antibody immunity to SARS-CoV-2. Nature 2021;591:839–44.
17 Manisty C, Otter AD, Treibel TA, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet 2021;397:1057–8.
18 Doria-Rose N, Suthar MS, Makowski M, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med 2021;384:2259–61.
19 Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021;371. doi:10.1126/science.abf4063. [Epub ahead of print: 05 02 2021].
20 Gema R, Bañuelos M, Tapias J, et al. Frailty index and late-life mortality in relation to chronological and biological age. J Am Geriatr Soc 2002;50:77–85.
21 Doria-Rose N, Suthar MS, Makowski M, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med 2021;384:2259–61.
22 Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021;371. doi:10.1126/science.abf4063. [Epub ahead of print: 05 02 2021].
23 Gema R, Bañuelos M, Tapias J, et al. Frailty index and late-life mortality in relation to chronological and biological age. J Am Geriatr Soc 2002;50:77–85.
24 Seagle EE, Bednarczyk RA, Hill T, et al. Antibody patterns of persistence and rate of decline following the second dose of the MRNA vaccine. Vaccine 2018;36:818–26.
25 Falsey AR, Frenck RW, Walsh EE, et al. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. N Engl J Med 2021;385:1627–9.
26 Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med 2021;385:1393–400.
27 Mittnacht AB, Graham JE, Mogliner AJ, et al. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMJ Geriatr 2022;1:2–8.
28 Juno JA, Wheatley AK. Boosting immunity to COVID-19 vaccines. Nat Med 2021;27:1874–5.
29 Harvey RA, Rassen JA, Kabelac CA, et al. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med 2021;181:672.
30 Sahin U, Mulk A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and Th1 T cell responses. Nature 2020;586:394–9.