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been done of a third homologous or heterologous vaccine dose with mRNA or Ad26.COV2.S (Janssen) vaccine in recipients of solid organ transplants who responded poorly to the two-dose vaccine series.[9] The third vaccine dose was administered a median of 67 days (IQR 54–81) after the second dose, and was safe but produced a boost in antibody titres in only 25% of patients without an initial response—a single case of post-vaccine antibody-mediated organ rejection occurred in a patient who had received a heart transplant. No studies on third doses of the same or different vaccine have been reported in patients with haematological malignancies.

Until further data become available, the study by Maneikis and colleagues will help inform crucial clinical decisions. In places where community SARS-CoV-2 prevalence is declining, the primary SARS-CoV-2 immunisation should be timed to treatment to ensure the best possible immune protection. In addition, the study provides the evidence base for counselling patients on the importance of adherence to non-pharmacological interventions against SARS-CoV-2 until better vaccination or prophylactic immune therapeutics are available; this is especially important as less restrictive public health measures are adopted. Finally, the study underscores the crucial need for research to improve SARS-CoV-2 immunisation strategies in individuals who are less protected by current approaches.

I declare no competing interests.

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# Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma

Published **Online**
July 2, 2021
https://doi.org/10.1016/S2352-3026(21)00199-X

Individuals with lymphoid malignancies are at risk of developing severe COVID-19 and are less likely to develop protective immune responses to SARS-CoV-2 vaccination than the general population because of disease-related or treatment-related immunosuppression. Data on vaccine responses in chronic lymphocytic leukaemia have shown antibody responses in 52–75% of individuals after the second dose.[1,2] Vaccine responses after two doses in people with other lymphoid malignancies remain undefined.

In this interim analysis of the UK PROSECO study (a multicentre, prospective, observational study assessing COVID-19 vaccine immune responses in lymphoid malignancies [NCT04858568]), we report antibody levels before vaccination and 2 weeks after the first dose or 2–4 weeks after the second dose, or both, in participants with lymphoma recruited from general hospitals in Southampton, Nottingham, Leicester, Portsmouth and Oxford, UK. Participants were given either ChAdOx1 (AstraZeneca, Oxford, UK) or BNT162b2 (Pfizer-BioNTech, Puurs, Belgium) vaccines, with two doses given 10–12 weeks apart.[3,4] IgG antibodies against SARS-CoV-2 spike (S), receptor binding domain (RBD), and nucleocapsid (N) antigens were measured using a qualified electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA)[5] and responses were reported in binding antibody units per mL (BAU/mL), and calibrated against the WHO COVID-19 international

reference serum (National Institute for Biological Standards and Control number 20/136). Anti-S IgG concentrations of 0·55 BAU/mL or lower, anti-RBD IgG concentrations of 0·73 BAU/mL or lower, and anti-N IgG concentrations of 0·64 BAU/mL or lower were below the lower limit of detection. Participants with an anti-N IgG concentration of more than 6·60 BAU/mL were considered to have had previous contact with SARS-CoV-2 and were excluded from the primary analysis. Antibody titres were compared with those in healthy volunteers recruited from the UK and Latvia who had received the vaccine as part of the government vaccine roll-out. Associations were calculated using the Mann-Whitney *U* test, with p values of 0·05 or lower being considered to be statistically significant.

Between Jan 11 and May 7, 2021, 129 participants with lymphoma were recruited, of whom 48 (37%) were female, with a median age of 69 years (IQR 57–74). 12 (9%) of 129 participants had Hodgkin lymphoma, 34 (26%) had aggressive B-cell non-Hodgkin lymphoma (with 26 [76%] of 34 having diffuse large B-cell lymphoma), 79 (61%) had indolent B-cell non-Hodgkin lymphoma (with 34 [43%] of 79 having follicular lymphoma and 17 [22%] having chronic lymphocytic leukaemia), and four (3%) had peripheral NK/T cell lymphoma (appendix p 1). 150 healthy volunteers were recruited, of whom 100 (67%) were female, with a median age of 45 years (IQR 34–47).

Ten participants with previous COVID-19 infection, as determined by increased anti-N IgG antibodies (appendix p 2), were excluded, leaving 119 participants to be included in analyses. 52 (44%) of 119 participants with lymphoma were on treatment, defined as receiving systemic anti-lymphoma therapy at the time of administration of the first dose of vaccine, having completed treatment 6 months or fewer before the first vaccine dose, or treatment commenced less than 1 month after the first dose of vaccination. 22 (72%) of 31 participants after one dose of vaccine and 20 (61%) of 33 participants after two doses of vaccine did not have detectable anti-S IgG antibodies (figure). Antibody titres were also significantly reduced in participants on treatment compared with those not on treatment (defined as treatment naive or completed therapy >6 months before the first vaccine dose; figure). After the second dose, geometric mean titres (GMT) for both vaccines were 2·5 BAU/mL (95% CI 1·1–5·8) for participants on treatment and 141·8 BAU/mL (75·6–266·0) for participants not on treatment. Antibody levels were also compared in participants on the basis of their disease remission status at the time of the first vaccination but no correlation was observed (appendix p 3).

All 150 healthy volunteers had detectable antibodies (figure). Individuals vaccinated with BNT162b2 developed higher antibody levels after both the first and second doses (GMT after dose 1: 172 BAU/mL [95% CI 109–272]; after dose 2: 2339 BAU/mL [1923–2844]) than

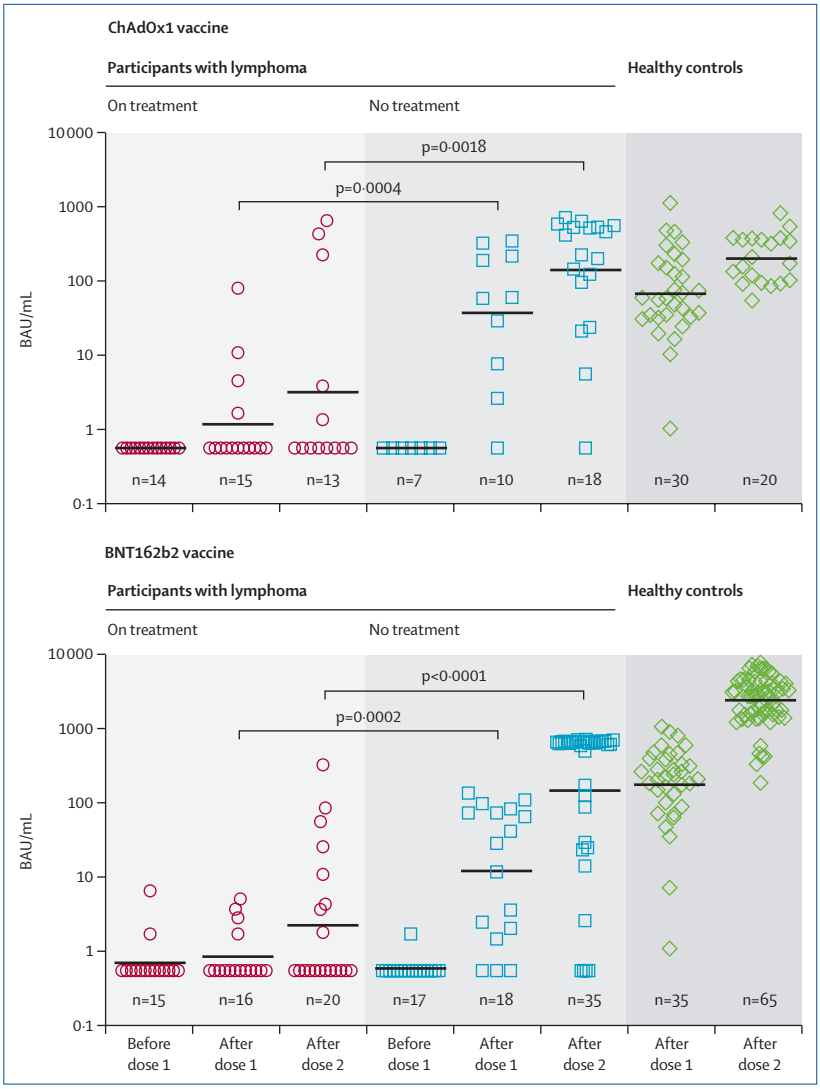


***Figure:*** **Anti-spike IgG response to first and second doses of SARS-CoV-2 vaccination**
Each datapoint represents an individual's response. Anti-spike IgG before vaccine, after dose 1 was 4 weeks after the first dose, and after dose 2 was 2–4 weeks after the second dose with ChAdOx1 or BNT162b2 in patients with lymphoma and healthy controls are shown. Bold horizontal lines show the geometric mean titres. BAU=binding antibody units.

See Online for appendix

did those vaccinated with ChAdOx1 (GMT after dose 1: 67 BAU/mL [40–111]; after dose 2: 199 BAU/mL [140–282]; p<0·0001). The median ages for the healthy volunteers were 57 years (IQR 47–61) for ChAdOx1 and 44 years (33–54) for BNT162b2. No correlation was observed between anti-S IgG concentrations and age for BNT162b2 (data not shown), indicating that the superior response with BNT162b2 was not due to the difference in age between the vaccinees. No difference was observed in antibody concentrations between the two vaccines within the lymphoma cohort, but this might be because of the small sample size.

Among the participants with lymphoma who were not on treatment, six (100%) of six participants with Hodgkin lymphoma and 13 (81%) of 16 with aggressive B-cell non-Hodgkin lymphoma developed robust antibody levels (ie, comparable to responses among in healthy volunteers after the first and second doses; GMT after dose 2 of 652·2 BAU/mL [95% CI 604·7–703·4] among those with Hodgkin lymphoma and 244·6 BAU/mL [31·12–1923] among those with aggressive B-cell non-Hodgkin lymphoma; appendix p 4). The exceptions among the participants with aggressive B-cell non-Hodgkin lymphoma were recipients of chimeric antigen receptor (CAR) T cells. Among these participants, three (100%) of three had no detectable antibodies after the first dose. One of these patients developed antibodies after the second dose, but the other two have yet to be tested. A fourth patient was tested after the second vaccine dose only, for whom antibodies were undetectable. These results were observed despite these participants having completed CAR T cell treatment 11–23 months before vaccination. 32 (89%) of 36 participants with indolent B-cell non-Hodgkin lymphoma who were not being treated had detectable antibodies after two doses of vaccine but their GMTs were reduced compared with the levels seen in participants with Hodgkin lymphoma and aggressive B-cell non-Hodgkin lymphoma treatment naivety or completion of treatment more than 3 years previously. In participants who completed treatment before vaccination, those vaccinated 6 months or more after chemotherapy with or without anti-CD20 or anti-CD20 monotherapy, and 2 months or fewer of Bruton Tyrosine Kinase inhibitor monotherapy had no detectable antibodies (appendix p 5).

In summary, individuals with Hodgkin lymphoma and aggressive B-cell non-Hodgkin lymphoma can develop robust serological responses as early as 6 months after treatment. Individuals vaccinated while receiving systemic anti-lymphoma therapy are unlikely to develop antibody responses and should be revaccinated after treatment completion. We recommend revaccination 6 months after completion of anti-CD20 containing therapy. For patients on non-anti-CD20 containing chemotherapy, earlier revaccination might also be effective but more data are required to support this. Patients with indolent lymphomas might have impaired serological responses irrespective of their treatment history and might benefit from further measures to protect them against COVID-19, such as boosting with alternative vaccines or prophylactic monoclonal antibodies against SARS-CoV-2

Details of contributions of authors and acknowledgments are in the appendix (p 6). CPF receives consultancy fees from AstraZeneca (not related to vaccines) and participates in an advisory board for AstraZeneca (not related to vaccines). MA receives research funding from Pfizer (not related to vaccines), GPC receives research funding from Pfizer (not related to vaccines) and participates in advisory boards for AstraZeneca and Pfizer (not related to vaccines). AJD reports receiving research funding and honoraria from AstraZeneca and Janssen (not related to vaccines). DG receives support from the NIHR Great Ormond Street Biomedical Research Centre All other authors declare no competing interests.

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