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.

Omicron neutralising antibodies after third COVID-19 vaccine dose in patients with cancer

Patients with cancer are at greater risk of severe COVID-19 and have been prioritised for COVID-19 vaccination globally. We previously showed that following two doses of COVID-19 vaccines, neutralising antibody (nAb) responses against the B.1.1.7 (alpha), B.1.351 (beta), and B.1.617.2 (delta) variants of concern (VOCs) are decreased compared to the wild type (WT) SARS-CoV-2, particularly in patients with blood cancer.[1] More recently, we reported that following a third vaccine dose, nAb responses to these VOCs increase in most patients with cancer, including those with no or waning response following two vaccine doses.[2] Since November, 2021, the B.1.1.529 (omicron) VOC has rapidly become the dominant SARS-CoV-2 VOC globally. Omicron partially evades vaccine-induced immunity,[3] but a third vaccine dose increases omicron nAb responses in the general population.[4–6] Comparable data in patients with cancer are lacking, leaving patients and cancer physicians without the means to calibrate infection risk[7] while maintaining necessary cancer treatments. We used live-virus micro-neutralisation assays to evaluate response to omicron following three doses of COVID-19 vaccine in participants of the CAPTURE study (NCT03226886), a prospective, longitudinal cohort of patients with cancer.

We evaluated 199 patients with cancer, 115 (58%) of whom had solid cancer and 84 (42%) blood cancer, all of whom received a third dose of BNT162b2 (appendix p 1) after two doses of either BNT162b2 (33%) or ChAdOx1 (67%). A matched sample obtained before the third dose was also evaluated in 179 of 199 patients (100 of 115 patients with solid cancer; 79 of 84 with blood cancer). The median time between the second and third doses was 176 days (IQR 166–188). 23 of 199 patients had a history of SARS-CoV-2 infection, all before the second vaccine dose, and none with omicron. nAb titres (nAbT) against delta and omicron were measured at a median of 11 days (IQR 0–78) before and 23 days (19–29) after the third vaccine dose. As described previously for this assay, nAbT was categorised as undetectable (<40, the lower limit of detection) or detectable (>40).[1,8,9]

Among the 100 patients with solid cancer, after two vaccine doses, nAbT against omicron was detectable in 37 (37%) patients (appendix p 4), whereas nAbT against delta was detectable in 56 (56%) patients (McNemar test, p=0·0002) and nAbT against WT SARS-CoV-2 was detectable in 97 (97%) patients (p<0·0001).[2] Among the 115 patients with solid cancer who had a third vaccine dose, nAbT against omicron was detectable in 104 (90%) patients, whereas nAbT against delta was detectable in 112 (97%) patients (p=0·013), and nAbT against WT SARS-CoV-2 was detectable in 114 (99%) patients (p=0·0044).[2]

Among 79 patients with blood cancer, after two vaccine doses, nAbT against omicron was detectable in 15 (19%) patients (appendix p 4), whereas nAbT against delta was detectable in 31 (39%) patients (McNemar test, p=0·0002) and nAbT against WT SARS-CoV-2 was detectable in 31 (89%) patients (p<0.0001).[2] Among the 84 patients who received a third vaccine dose, nAbs against omicron was detectable in 47 (56%) patients, whereas nAbT against delta was detectable in 60 (71%) patients (p=0.0009), and nAbT against WT SARS-CoV-2 was detectable in 72 (86%) patients (p<0·0001).[2] Considering the 64 of 79 patients with blood cancer who had undetectable nAbT against omicron after two vaccine doses, 29 (45%) developed nAbs against omicron after the third dose, indicating effective boosting in many patients. The nAbT against omicron correlated with nAbT against WT SARS-CoV-2 and delta (appendix p 4) but were consistently lower.

Overall, our data from patients with cancer highlight the higher immune evasive capacity of omicron than delta, which is consistent with the observations in the general population. We found that a third vaccine dose boosted the neutralising response against omicron in patients with cancer, but the effect was blunted in patients with blood cancer compared to those with solid cancer.

Multivariable logistic regression analysis (appendix p 3) confirmed that after three doses, detectable nAbT against omicron was significantly associated with cancer type (solid *vs* blood cancer odds ratio [OR] 7·51 [95% CI 4·05–14·63], p<0·001) but not age, sex, or the vaccine type administered as first and second dose (BNT162b2 *vs* ChAdOx1).

In a separate multivariable logistic regression analysis, we considered only patients with blood cancer. Treatment with anti-CD20 monoclonal antibodies within 12 months, and Bruton's tyrosine kinase inhibitors (BTKi) within 28 days of the third vaccine dose was significantly associated with undetectable nAbT against omicron (OR 0·04 [95% CI 0·003–0·21], p=0·0074. None of ten patients who received anti-CD20 and one of five patients who received BTKi had detectable nAbT against omicron following three vaccine doses. The presence of progressive disease versus complete response following the most recent anticancer treatment was also significantly associated with undetectable nAbT against omicron (OR 0·08 [95% CI 0·01–0·46], p=0·027). Blood cancer subtype, vaccine type administered as first and second dose, and age were not significantly associated with detectable nAbT against omicron.

Published Online January 25, 2022 https://doi.org/10.1016/S0140-6736(22)00147-7

See Online for appendix

Finally, we evaluated omicron nAbT in four patients with a history of breakthrough delta infection after two vaccine doses. The time from the second vaccine dose to infection ranged from 112 to 176 days. COVID-19 symptoms were mild (n=3 patients, WHO COVID-19 severity index 2–3, including fever [n=2], coryza [n=2], cough [n=2]), and one patient was asymptomatic. None of the patients had detectable nAbT against omicron or delta[2]) before infection. Following infection, all patients developed detectable nAbT against omicron (as well as delta[2]; appendix p 5), suggesting that two vaccine doses and a third antigenic challenge via delta infection can lead to a functional immune response against omicron.[6]

There are limitations to our study. Additional subgroup analyses were limited by the heterogeneity and size of the blood cancer cohort and will require more patients. The exact correlates of immune protection against VOC remain undefined; however, multiple studies have shown that higher nAbT correlate with reduced risk of symptomatic infection.[10,11] Finally, we did not evaluate vaccine-induced cellular responses to omicron as we had for other VOCs.[2] We note that emerging reports suggest T-cell responses against omicron remain comparable to ancestral variants in the general population without cancer.[12,13]

In conclusion, we show that most of the patients with cancer in the CAPTURE cohort lacked detectable nAbT against omicron following two vaccine doses, independent of the vaccine type. A third dose of BNT162b2 resulted in a significant increase in patients with nAbT against omicron. Whereas only a few patients with solid cancer lacked nAbT against omicron after three vaccine doses, a substantial proportion of patients with blood cancer, especially those on B-cell-depleting therapies or with progressive cancer, did not mount a detectable response. We previously showed that T-cell responses against delta are detected in patients with cancer even in the absence of humoral response.[1] T cells probably continue to offer a degree of protection against severe COVID-19, and we note that ancestral SARS-CoV-2-specific T cells cross-recognise omicron.[12] Given the high transmissibility and current prevalence of omicron, continued mask-wearing, physical distancing, and vaccination of close contacts will be crucial to protecting patients with blood cancer. Further, early treatment with neutralising monoclonal antibodies[6] or antivirals might be beneficial and are being deployed to vulnerable patient groups in the UK.[14] The incremental benefit of a third vaccine dose in boosting nAb responses in patients with blood cancer lends support for a fourth dose in this population, as per UK guidance at the time of writing.

For **UK guidance on booster vaccine** see https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-booster-vaccine/

DC has received institutional grant funding from MedImmune/AstraZeneca, Clovis, Eli Lilly, 4SC, Bayer, Celgene, Leap, and Roche. DLVB has received grant funding from AstraZeneca. CS is funded by CRUK (TRACERx, PEACE and CRUK Cancer Immunotherapy Catalyst Network), the CRUK Lung Cancer Centre of Excellence (C11496/A30025), the Rosetrees Trust, Butterfield and Stoneygate Trusts, the Novo Nordisk Foundation (ID16584), a Royal Society Professorship Enhancement award (RP/EA/180007), the National Institute of Health Research (NIHR) Biomedical Research Centre at University College London Hospitals, the CRUK University College London Centre, the Experimental Cancer Medicine Centre, and the Breast Cancer Research Foundation (BCRF 20-157). This work was supported by a Stand Up To Cancer-LUNGevity-American Lung Association Lung Cancer Interception Dream Team Translational research grant. Stand Up To Cancer is a division of the Entertainment Industry Foundation. Research grants are administered by the American Association for Cancer Research, the scientific partner of SU2C. CS received an ERC Advanced Grant (PROTEUS) from the European Research Council under the European Union's Horizon 2020 research and innovation programme (835297). CS is a Royal Society Napier Research Professor (RP150154). ST is funded by Cancer Research UK (A29911); the Francis Crick Institute, which receives its core funding from Cancer Research UK (FC10988), the UK Medical Research Council (FC10988), and the Wellcome Trust (FC10988); the NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research (grant reference number A109), the Royal Marsden Cancer Charity, The Rosetrees Trust (A2204), Ventana Medical Systems (grant reference numbers 10467 and 10530), the National Institute of Health (U01 CA247439) and Melanoma Research Alliance (686061). ST has received speaking fees from Roche, AstraZeneca, Novartis, and Ipsen.
ST has the following patents filed: Indel mutations as a therapeutic target and predictive biomarker PCTGB2018/051892 PCTGB2018/051893 and Clear Cell Renal Cell Carcinoma Biomarkers P113326GB. All other authors declare no competing interests. AF, STCS, LA, MW, and RH contributed equally.

*Annika Fendler, Scott T C Shepherd, Lewis Au, Mary Wu, Ruth Harvey, Andreas M Schmitt, Zayd Tippu, Benjamin Shum, Sheima Farag, Aljosja Rogiers, Eleanor Carlyle, Kim Edmonds, Lyra Del Rosario, Karla Lingard, Mary Mangwende, Lucy Holt, Hamid Ahmod, Justine Korteweg, Tara Foley, Taja Barber, Andrea Emslie-Henry, Niamh Caulfield-Lynch, Fiona Byrne, Daqi Deng, Svend Kjaer, Ok-Ryul Song, Christophe Queval, Caitlin Kavanagh, Emma C Wall, Edward J Carr, Simon Caidan, Mike Gavrielides, James I MacRae, Gavin Kelly, Kema Peat, Denise Kelly, Aida Murra, Kayleigh Kelly, Molly O'Flaherty, Robyn L Shea, Gail Gardner, Darren Murray, Nadia Yousaf, Shaman Jhanji, Kate Tatham, David Cunningham, Nicholas Van As, Kate Young, Andrew J S Furness, Lisa Pickering, Rupert Beale, Charles Swanton, Sonia Gandhi, Steve Gamblin, David L V Bauer, George Kassiotis, Michael Howell, Emma Nicholson, Susanna Walker, James Larkin, *Samra Turajlic, on behalf of the CAPTURE consortium*
samra.turajlic@crick.ac.uk

Cancer Dynamics Laboratory (AF, STCS, LA, ZT, BS, TB, AE-H, NC-L, FB, DD, ST), High Throughput Screening Laboratory (MW, O-RS, CQ, CK, ECW, MH), Worldwide Influenza Centre (RH), Structural Biology Scientific Technology Platform (SK), Cell Biology of Infection Laboratory (EJC, RB), Safety, Health & Sustainability (SC), Scientific Computing Scientific Technology Platform (MG), Metabolomics Scientific Technology Platform (JIM), Department of Bioinformatics and Biostatistics (GKe), Cancer Evolution and Genome Instability Laboratory (CS), Neurodegeneration Biology Laboratory (SGan), Structural Biology of Disease Processes Laboratory (SGam), RNA Virus Replication Laboratory (DLVB), and Retroviral Immunology Laboratory (GKa), The Francis Crick Institute, London NW1 1AT, UK; Skin and Renal Units (STCS, LA, AMS, ZT, BS, SF, AR, EC, KE, LDR, KL, MM, LH, HA, JK, TF, KP, DK, AM, KK, MO'F, KY, AJSF, LP, JL, ST); Department of Pathology

(RLS, GG, DM), Lung Unit (NY), Acute Oncology Service (NY), Anaesthetics, Perioperative Medicine and Pain Department (SJ, KT, SW), Gastrointestinal Unit (DC), Clincal Oncology Unit (NVA), and Haemato-oncology Unit (EN), The Royal Marsden NHS Foundation Trust, London, UK; University College London Hospitals NHS Foundation Trust Biomedical Research Centre, London, UK (ECW); Translational Cancer Biochemistry Laboratory (RLS) and Melanoma and Kidney Cancer Team (ST), Institute of Cancer Research, London, UK; Division of Medicine, University College London, London, UK (RB); University College London Cancer Institute, London, UK (CS); UCL Queen Square Institute of Neurology, London, UK (SGan)

1 Fendler A, Shepherd STC, Au L, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. *Nature Cancer* 2021; published online Oct 27. https://doi.org/10.1038/s43018-021-00274-w.

2 Fendler A, Shepherd STC, Au L, et al. Immune responses following third COVID-19 vaccination are reduced in patients with hematologic malignancies compared to patients with solid cancer. *Cancer Cell* 2022; published online Dec 29. https://doi.org/10.1016/j.ccell.2021.12.013.

3 Cele S, Jackson L, Khoury D, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature* 2021; published online Dec 23. https://doi.org/10.1038/s41586-021-04387-1.

4 Gruell H, Vanshylla K, Tober-Lau P, et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 omicron variant. *Research Square* 2021; published online Dec 27. https://doi.org/10.21203/rs.3.rs-1168453/v1 (preprint).

5 Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. *N Engl J Med* 2021; published online Dec 29. https://doi.org/10.1056/NEJMc2119358.

6 Wu M, Wall EC, Carr EJ, et al. Three-dose vaccination elicits neutralising antibodies against omicron. *Lancet* 2022; published online Jan 19. https://doi.org/10.1016/S0140-6736(22)00092-7.

7 Schmidt AL, Labaki C, Hsu CY, et al. COVID-19 vaccination and breakthrough infections in patients with cancer. *Ann Oncol* 2021; published online Dec 24. https://doi.org/10.1016/j.annonc.2021.12.006

8 Wall EC, Wu M, Harvey R, et al. AZD1222-induced neutralising antibody activity against SARS-CoV-2 delta VOC. *Lancet* 2021; **398:** 207–09.

9 Wall EC, Wu M, Harvey R, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* 2021; **397:** 2331–33.

10 Cromer D, Steain M, Reynaldi A, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. *Lancet Microbe* 2022; **3:** e52–61.

11 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature Med* 2021; **27:** 1205–11.

12 Gao Y, Cai, C, Grifoni A, et al. Ancestral SARS-CoV-2-specific T cells cross-recognize Omicron. *Nature Med* 2022; published online Jan 14. https://doi.org/10.1038/s41591-022-01700-x.

13 GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS CoV-2 omicron-specific T- and B-cell responses in COVID-19 vaccine recipients. *medRxiv* 2021; published online Dec 29. https://doi.org/10.1101/2021.12.27.21268416 (preprint).

14 UK Department of Health and Social Care. Press release: UK's most vulnerable people to receive life-saving COVID-19 treatments in the community. Dec 8, 2021. https://www.gov.uk/government/news/uks-most-vulnerable-people-to-receive-life-saving-covid-19-treatments-in-the-community (accessed Dec 14, 2021).

COVID-19 booster doses in pregnancy and global vaccine equity

Immunisation against SARS-CoV-2 with mRNA vaccines remains the most effective way of preventing COVID-19-related morbidity and mortality. Medium-term data show that the efficacy of mRNA vaccination (two doses) is robust for up to 5–6 months, as supported by immunogenicity studies.[1,2] Thereafter, the effectiveness of mRNA vaccines diminishes, and booster doses have been recommended for various high-risk groups. In 2021, the American College of Obstetricians and Gynecologists recommended booster doses for pregnant and postpartum women on the basis of their increased risk of COVID-19-related complications.[3] However, data on the durability of immune response in pregnant women are scarce.

Barda and colleagues reported the effectiveness of booster mRNA vaccines in a large population study from Israel.[4] A booster dose administered at least 5 months after the second dose significantly reduced the rate of new COVID-19 infections, hospital admissions, and severe infections in a cohort of 1 158 269 individuals with a median follow-up time of 2 weeks. Based on these results, the number-needed-to-boost (NNB) to prevent one excess case of hospital admission was lower than the NNB to prevent severe COVID-19 (table). However, for each of these outcomes, NNBs were about 20 times higher in those younger than 40 years, and 10–25 times higher in those without comorbidities, reflecting much lower absolute complication rates. Although these NNB estimates to prevent severe COVID-19 might be an overestimate for pregnant women, who have a two to three times increased risk of severe COVID-19 (compared with other women of reproductive age), even halving these NNBs based on age would mean that more than 10 000 booster doses would be required to prevent one case of hospitalisation or severe COVID-19 in pregnancy when administered 5 months after the second dose. The actual NNB to prevent hospitalisation

Published **Online** February 18, 2022 https://doi.org/10.1016/S0140-6736(22)00166-0

	Hospital admissions		Severe COVID-19	
	Excess cases without boosters (per 100 000)	Number-needed-to-boost to prevent one case	Excess cases without boosters (per 100 000)	Number-needed-to-boost to prevent one case
By age, years				
16–39	4·9	20 408	2·5	40 000
40–69	96·7	1034	54·4	1838
By comorbidity				
Without existing comorbidities	11·9	8403	3·1	32 258
One to two comorbidities	101·9	981	78·8	1269

Table: **Rate of breakthrough cases without boosters and number-needed-to-boost to prevent one case, by age and comorbidity[4]**