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.

large, representative ongoing survey of the US population—by modelling the hypothesised non-linear relationships. The analysis included premenopausal, non-pregnant women (aged 15–49 years) and children (12–59 months). Individuals with biochemical evidence of inflammation or liver disease were excluded to obtain an apparently healthy population.

Using this analysis, Mei and colleagues[1] found that within each subpopulation, associations between ferritin and haemoglobin and ferritin and sTfR became evident below very similar ferritin thresholds: ferritin concentration of less than 25 µg/L in women and less than 20 µg/L in children. Above and at these thresholds, the association between ferritin and haemoglobin plateaued and the association between ferritin and sTfR reached its minimum. These data suggest that, at least in a US population, haemoglobin concentrations begin to fall and sTfR concentrations rise below a ferritin concentration of less than 25 µg/L in women and 20 µg/L children.

These thresholds have important population-health implications: applying them would raise the prevalence of iron deficiency in the US population from 16·6% to 31·3% in women and from 9·7% to 32·4% in children. However, these thresholds imply a different meaning to previous definitions: rather than thresholds at which bone marrow iron is exhausted, they reflect points where responses to iron depletion can be detected. Although higher than WHO thresholds, the reported ferritin thresholds are not dissimilar to concentrations previously shown to have high sensitivity and acceptable specificity for detecting absent bone marrow iron stores in several other studies.[9] Previous conceptualisations of progressive iron deficiency have proposed that ferritin falls early as storage iron is depleted.[10] The similarity of thresholds linking ferritin with increasing sTfR and decreasing haemoglobin suggests these consequences of iron deficiency occur at a similar point during body iron depletion: once storage iron is depleted during early stages of iron deficient erythropoiesis.[10]

This analysis still requires validation. External validation is essential before adapting the results into policy. However, the approaches used by the authors can be adapted by others to develop corroborating evidence using independent data. Ultimately, linking proposed thresholds to clinical and functional outcomes will be essential to guide clinical management.

S-RP reports grants from the National Health and Medical Research Council Australia and The Bill & Melinda Gates Foundation; and consulted for WHO, Keros Therapeutics, and Vifor Pharma. SB declares no competing interests.

*Sabine Braat, *Sant-Rayn Pasricha*
pasricha.s@wehi.edu.au

Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health (SB), Department of Medical Biology, Parkville, VIC 3052, Australia (S-RP); Population Health and Immunity Division, Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia (SB, S-RP); Diagnostic Haematology, The Royal Melbourne Hospital, Melbourne, VIC, Australia (S-RP); Clinical Haematology, The Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Parkville VIC 3050 Australia (S-RP)

1 Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. *Lancet* 2021; **397:** 233–48.
2 Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. *Cell* 2017; **168:** 344–61.
3 Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta* 2003; **329:** 9–22.
4 WHO. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020.
5 Garcia-Casal MN, Pasricha SR, Martinez RX, Lopez-Perez L, Pena-Rosas JP. Serum or plasma ferritin concentration as an index of iron deficiency and overload. *Cochrane Database Syst Rev* 2021; **5:** CD011817.
6 Hallberg L, Bengtsson C, Lapidus L, Lindstedt G, Lundberg PA, Hulten L. Screening for iron deficiency: an analysis based on bone-marrow examinations and serum ferritin determinations in a population sample of women. *Br J Haematol* 1993; **85:** 787–98.
7 Daru J, Colman K, Stanworth SJ, De La Salle B, Wood EM, Pasricha SR. Serum ferritin as an indicator of iron status: what do we need to know? *Am J Clin Nutr* 2017; **106** (suppl 6)**:** 1634s–39.
8 Mei Z, Yaw Addo OY, Jefferds ME, Sharma AJ, Flores-Ayala RC, Brittenham GM. Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study. *Lancet Haematol* 2021; **8:** e572–82.
9 Jonker FA, Calis JC, van Hensbroek MB, et al. Iron status predicts malaria risk in Malawian preschool children. *PLoS One* 2012; **7:** e42670.
10 Suominen P, Punnonen K, Rajamaki A, Irjala K. Serum transferrin receptor and transferrin receptor-ferritin index identify healthy subjects with subclinical iron deficits. *Blood* 1998; **92:** 2934–39.

Blunted humoral response after mRNA vaccine in patients with haematological malignancies

Published **Online** July 2, 2021 https://doi.org/10.1016/S2352-3026(21)00197-6

See **Articles** page e583

Patients with haematological malignancies are at a higher risk for severe COVID-19 outcomes than healthy individuals.[1] These patients can also have long-term direct and indirect clinical consequences of SARS-CoV-2 infection, including stalled cancer care. Therefore, to reduce the impact of COVID-19 on this clinically vulnerable population, optimal vaccine protection is paramount. The COVID-19 mRNA vaccines produce a

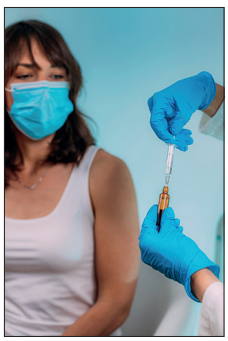
robust adaptive immune response in healthy individuals and have been a tremendous success in real-world conditions. However, the pivotal mRNA vaccine trials excluded patients with cancer who were on active treatment.[2] As such, little information is available about vaccine efficacy in patients with haematological malignancies.

Among patients with haematological malignancies, vaccine-induced immunity is generally subdued and depends on the type of cancer and its treatment, as well as the immunogenicity of the specific vaccine. Responses to traditional influenza and pneumococcal immunisation are inadequate, especially in haematopoietic stem-cell transplantation (HSCT) recipients or after B-cell depleting therapies such as Bruton's tyrosine kinase inhibitors (BTKIs) or anti-CD20 antibodies.[3]

Nevertheless, advancements in vaccine technologies hold immense promise. Newer recombinant, adjuvanted vaccines have improved clinical protection in immunocompromised patients. For example, randomised controlled trials of the recombinant zoster vaccine early after autologous HSCT show a 68% (95% CI 55·6–77·5) vaccine efficacy[4] compared with an efficacy of 91% (86·8–94·5) in adults aged 70 years or older. Additionally, the recombinant zoster vaccine elicits humoral and cellular immune responses in the majority of patients with haematological malignancies, with an estimated 87% effectiveness in preventing herpes zoster.[5]

Vaccine responses with newer B-cell depleting therapies also have been studied. A report comparing antibody response to recombinant hepatitis vaccine (CpG-adjuvanted hepatitis B vaccine) and shingles vaccine (recombinant zoster vaccine) among recipients of BTKIs showed an overall low response rate to the hepatitis B vaccine. However, for the recombinant herpes zoster vaccine, humoral immune responses were slightly lower, but not significantly different, than those in treatment-naive individuals, suggesting that BTKIs might not impair recall responses as much as a response to novel viral antigens.[6]

In *The Lancet Haematology*, Kazimieras Maneikis and colleagues[7] present findings from their prospective national study in Lithuania in which they measured post-vaccination SARS-CoV-2 antibody responses in 857 SARS-CoV-2 seronegative patients with haematological malignancies. The authors measured anti-S1 IgG antibody concentrations before first immunisation with BNT162b2 (Comirnaty; Pfizer-BioNTech), on the day of the second immunisation, and 7–21 days after the second immunisation. Compared with 68 healthy 18–60-year-olds, patients with haematological malignancies also aged 18–60 years had significantly lower antibody concentrations after the second vaccine dose (median 6961 AU/mL [IQR 1292–20 672] *vs* 21 395 AU/mL [14 831–33 553]; p<0·0001). The comparison of untreated and treated patients with haematological malignancies showed lower antibody concentrations in treated individuals, especially in those treated with BTKIs (n=44) and anti-CD20 therapies (n=87) within the past 12 months. A small number of evaluated patients on venetoclax (n=10) and ruxolitinib (n=16) also responded poorly. As expected, responses improved if the vaccines were administered 6 months after HSCT or the last therapy, except for rituximab, where humoral responses were largely absent for the first 12 months after treatment. Additionally, the finding that the second BNT162b2 dose did not augment antibody concentrations in most patients who responded poorly to the first dose might provide practical insight to the commonly posed question of whether a third homologous vaccine dose might boost clinical protection. Overall, nine vaccine breakthrough infections occurred in patients who had received both doses of the vaccine.


Microgen Images/Science Photo Library

The main limitation of the study is that the authors did not evaluate T-cell response to the BNT162b2 vaccine. SARS-CoV-2 infected patients with haematological malignancies without demonstrable seroconversion (humoral response) might have preserved T-cell responses that corelate with improved survival, suggesting that cellular immunity will have an essential role in vaccine-mediated protection.[8] Additionally, study participants represented a diverse group of patients with haematological malignancies with a small sample size to measure the effect of specific treatments. Despite the limitations, the study results further our understanding of vaccine elicited humoral immunity in a highly heterogeneous population in which many factors can influence vaccine response (eg, age, cancer, current and past treatments, comorbidities, duration of cancer).

Enhancing SARS-CoV-2 vaccine responses to reach better clinical protection in immunocompromised patients is an area of active research—an early analysis has

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.

Mini Kamboj
kambojm@mskcc.org

Infectious Disease Service, Department of Medicine and Division of Quality and Safety, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Department of Medicine, Weill Cornell Medical College, New York, NY, USA

1 Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 2020; **136:** 2881–92.
2 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.
3 Kamboj M, Shah MK. Vaccination of the stem cell transplant recipient and the hematologic malignancy patient. *Infect Dis Clin North Am* 2019; **33:** 593–609.
4 Bastidas A, de la Serna J, El Idrissi M, et al. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. *JAMA* 2019; **322:** 123–33.
5 Dagnew AF, Ilhan O, Lee WS, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infect Dis* 2019; **19:** 988–1000.
6 Pleyer C, Ali MA, Cohen JI, et al. Effect of Bruton tyrosine kinase inhibitor on efficacy of adjuvanted recombinant hepatitis B and zoster vaccines. *Blood* 2021; **137:** 185–89.
7 Maneikis K, Šablauskas K, Ringelevičiūtė U, et al. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. *Lancet Haematol* 2021; published online July 2. https://doi.org/10.1016/S2352-3026(21)00169-1.
8 Bange EM, Han NA, Wileyto P, et al. CD8$^+$ T cells contribute to survival in patients with COVID-19 and hematologic cancer. *Nat Med* 2021; published online May 20. https://doi.org/10.1038/s41591-021-01386-7.
9 Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med* 2021; published online June 15. https://doi.org/10.7326/L21-0282.

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