Predicting COVID-19 infection risk in people who are immunocompromised by antibody testing

People with blood cancers have an increased risk of severe COVID-19 disease despite booster vaccine doses.[1] This group, like other disease groups at increased risk of severe COVID-19, includes individuals with highly heterogeneous immune responses to vaccination.[2] Although vaccine response studies and population studies identify similar diseases and treatments associated with increased risk of severe COVID-19, a direct correlation between antibody levels after vaccination and infection risk has been difficult to define. Identification of a laboratory correlate of infection risk would allow doctors and policy makers to target additional COVID-19 treatment or prophylactic efforts to people who are most in need.

The PROSECO study (NCT04858568) enrolled 592 participants with lymphoma from nine hospitals in England between March 11, 2021, and Sept 9, 2022, for longitudinal peripheral blood sampling before and after one to four COVID-19 vaccine doses (appendix p 1).[2] 524 (89%) participants were eligible for analysis after vaccination and were contacted to participate in a follow-up questionnaire to measure infections and preceding social behaviours. 396 (76%) of those 524 participants responded. 334 (84%) of 396 participants were eligible for analysis after two vaccine doses, 315 (80%) were eligible for analysis after three vaccine doses, and 266 (67%) were eligible for analysis after four vaccine doses. Demographic and clinical information of participants was also collected (appendix pp 2–3).

A breakthrough infection was defined as a SARS-CoV-2 infection occurring 2 weeks or more after vaccine administration, confirmed by antigen or PCR testing. 20 (6%) of 334 participants developed a breakthrough infection after two vaccine doses, 40 (13%) of 315 developed a breakthrough infection after three vaccine doses, and 36 (14%) of 266 developed a breakthrough infection after four vaccine doses (appendix p 4). Median interval between the second vaccine dose and a breakthrough infection was 22·2 weeks (IQR 17·3–30·7), between the third vaccine dose and a breakthrough infection was 12·5 weeks (8·2–19·7), and between the fourth vaccine dose and a breakthrough infection was 11·0 weeks (5·2–13·7). Breakthrough infection after the second vaccine dose occurred during the alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529, BA.1 and BA.2) variant waves, whereas infections after third and fourth vaccine doses occurred primarily during the omicron wave (appendix p 5). The symptoms manifested during a breakthrough infection are described in the appendix (p 6). All 12 admissions to hospital (12 [13%] of 96 participants with breakthrough infections) due to COVID-19 occurred after receipt of either three or four vaccine doses. Five (5%) of 96 participants with breakthrough infections required oxygen supplementation, but no participants were admitted to intensive care and no deaths occurred due to COVID-19 disease (appendix p 6). Median duration of inpatient stay in hospital was 2 days (IQR 1–6). The treatments administered to participants with breakthrough infection are listed in the appendix (p 6).

Social behaviour before breakthrough infection was ascertained via questionnaires (appendix p 7). Participants who reported they were worried about COVID-19 experienced significantly fewer breakthrough infections than those who reported they were not (61 [25%] of 241 *vs* 35 [38%] of 93; p=0·031). No significant differences were observed between type and duration of contact with people infected with SARS-CoV-2 or practice of COVID-19 prevention measures between participants with breakthrough infection and participants without breakthrough infection.

Peripheral blood was sampled from participants at median 3·0 weeks (IQR 3·0–4·0) after two vaccine doses, 5·0 weeks (5·0–7·0) after three vaccine doses, and 6·0 weeks (5·0–9·5) after four vaccine doses. Antibody and cellular responses to the vaccines were assessed by anti-spike IgG quantification, pseudovirus neutralisation, and T-cell IFNγ response to spike peptides from the wild-type Wuhan strain. Plasma was available for analysis in 273 (82%) of 334 participants after the second vaccine dose, 237 (75%) of 315 participants after the third vaccine dose, and 177 (67%) of 266 participants after the fourth vaccine dose at the time of data cutoff. Anti-spike IgG levels were not significantly different in participants who had a breakthrough infection compared with participants who did not have a breakthrough infection after two vaccine doses (geomean 80·4 binding antibody units (BAU)/mL [95% CI 21·1–306·3] *vs* 38·1 BAU/mL [26·13–55·46]; appendix p 8). However, lower anti-spike IgG levels were observed in participants who had a breakthrough infection compared with those who did not after three vaccine doses (50·2 BAU/mL [15·0–167·7] *vs* 141·0 BAU/mL [88·4–225·0]; p=0·045) and four vaccine doses (30·9 BAU/mL [4·3–224·5] *vs* 305·7 BAU/mL [179·2–521·4]; p=0·0090). No differences were observed in cellular responses between participants with breakthrough infection and participants without breakthrough infection (appendix p 9).

To evaluate the risk factors associated with breakthrough infection, we conducted a multivariable logistic regression analysis. Previous or no anticancer treatment, increased number of vaccine doses, anti-spike IgG levels, and pseudoneutralisation titres were associated with reduced risk of breakthrough infection regardless of the timing of infection (appendix pp 10–11). To assess whether these risks changed with the number of vaccine doses administered, the same analysis was repeated, considering the timing of the breakthrough infection (appendix p 11). In this analysis, the only significant

Published Online
June 29, 2023
https://doi.org/10.1016/S0140-6736(23)01180-7

See Online for appendix

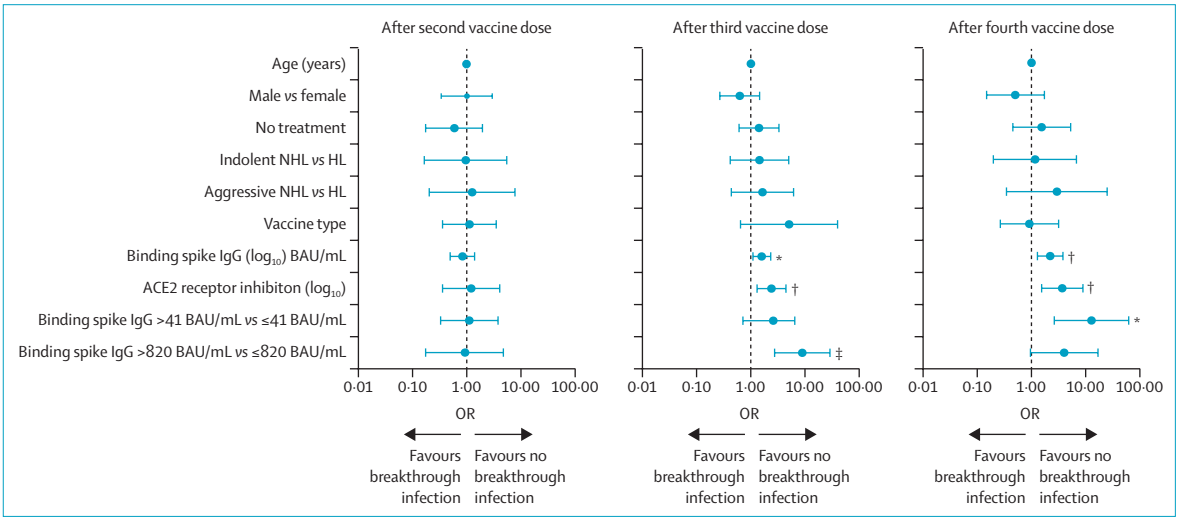

Figure: **Factors associated with COVID-19 breakthrough infection after second, third, and fourth vaccine doses**
Forest plots show the adjusted odds ratio with 95% CI of factors associated with breakthrough infection after vaccination. Statistical analysis was conducted with multivariable logistic regression analysis adjusted for age and treatment group. ACE2=angiotensin-converting enzyme-2. BAU=binding antibody units. HL=Hodgkin lymphoma. NHL=non-Hodgkin lymphoma. OR=odds ratio. *p value <0·05. †p value <0·01. ‡p value <0·001.

factors associated with breakthrough infection after third and fourth doses of vaccines were anti-spike IgG levels (after third dose: odds ratio 1·59 [95% CI 1·09–2·34]; p=0·017; after fourth dose: 2·26 [1·31–3·88]; p=0·0030) and pseudoneutralisation titres (after third dose: 2·41 [1·31–4·46]; p=0·0050; after fourth dose: 3·77 [1·57–9·08]; p=0·0030). Thus, after three vaccine doses the risk of breakthrough infection was 1·6 times less and after four vaccine doses the risk of breakthrough infection was 2·3 times less for every 10-fold increase in anti-spike IgG titre. To establish the optimal antibody threshold that best discriminated between participants with breakthrough infection and participants without breakthrough infection, receiver operating curve analyses were conducted (appendix p 12).[3] The antibody cutoff value after three vaccine doses was 820 BAU/mL (area under the curve [AUC] 0·61; sensitivity 46·6%; specificity 22·6%) and after four vaccine doses was 41 BAU/mL (AUC 0·70; 73·5%; 46·7%). Using these thresholds in the multivariable analysis, anti-spike IgG levels more than 820 BAU/mL after receipt of three vaccine doses were associated with an 8·9-fold (95% CI 2·75–28·85) lower risk of developing a breakthrough infection. After four vaccine doses, anti-spike IgG levels more than 41 BAU/mL were associated with a 13·1-fold (2·69–63·83) lower risk of developing a breakthrough infection (figure; appendix p 11).

Then, we examined the association between admission to hospital due to COVID-19 and antibody and cellular responses. Similarly, lower anti-spike IgG levels were observed in participants who were admitted to hospital after breakthrough infection compared with those who did not require admission to hospital after breakthrough infection (geomean 5·5 BAU/mL [95% CI 0·37–82·1] *vs* 58·9 BAU/mL [18·0–193·1]; p=0·043; appendix p 13). Furthermore, we observed that a higher proportion of participants who were hospitalised had undetectable antibody and cellular response (four [44%] of nine) compared with participants who were not hospitalised (two [4%] of 45).

To our knowledge, this study is the first to successfully establish an association between antibody and T-cell responses and clinical outcomes from COVID-19 disease in people who are immunocompromised. The strengths of the analyses are a detailed clinical dataset, a large and relatively homogeneous group of individuals with lymphoid malignancies, and longitudinal sampling after multiple COVID-19 vaccine doses with paired antibody and cellular data. Limitations of our study are its reliance on self-report of COVID-19 infections by participants, which might underestimate the true incidence of breakthrough infection. Whilst detection of viral nucleocapsid antibodies is an alternate method to assess previous viral exposure, this method is unreliable in people who are immunocompromised as we have observed that the antibodies might not develop or might reduce rapidly after infection. Another limitation of our study is that we did not analyse antibody and cellular reactivity to SARS-CoV-2 variants. However, the aim of our study was to establish a clinically meaningful correlate of infection risk and we have shown that this is feasible without variant analysis. Moreover, our study did not evaluate mucosal antibody responses, which have also been associated with protection against SARS-CoV-2 infection.[4] Finally, the small number of breakthrough infections and admissions to hospital in our study means the sensitivity and specificity of the antibody thresholds defined are relatively low. These thresholds need to be validated in different disease populations and might change depending on the circulating variant or with successive vaccinations.

A range of values might also be used as an alternative to specific cutoffs as the risk of breakthrough infection reduces as antibody level increases. Nonetheless, the antibody thresholds provided by our study are a valuable guide in the use of anti-spike IgG levels for COVID-19 risk quantification in people who are immunocompromised and in identification of those most at risk.

In participants with lymphoma, we observed 6% of breakthrough infections occurring after two vaccine doses, 13% of breakthrough infections occurring after three vaccine doses, and 14% of breakthrough infections occurring after four vaccine doses. We observed that participants who were worried about COVID-19 developed fewer breakthrough infections than participants who were not worried about COVID-19, possibly due to continued shielding or increased care in social mixing. We hypothesise that the lower infection rate after two vaccine doses might be due to reduced virus exposure during the national lockdown period in England and differences in infectivity of the circulating variants. Most breakthrough infections occurred after administration of the third and fourth vaccine doses, coinciding with the omicron variant wave (which has been shown to have increased transmissibility, possibly due to a shorter incubation period).[5] 13% of participants with breakthrough infections were admitted to hospital, primarily after three and four vaccine doses. We also observed that five (56%) of nine participants treated in hospital had absent T-cell responses compared with 7 (16%) of 45 participants who were not, highlighting the additional value of risk stratification by cellular testing.

We defined the antibody level associated with increased risk of infection after three and four COVID-19 vaccine doses in a population of people with lymphoid malignancies. The optimal antibody titre predicting breakthrough infection and no breakthrough infection is 20-fold lower after four vaccine doses than after three vaccine doses, implying that lower antibody titres are required to protect against breakthrough infection with increasing vaccine doses. This finding is consistent with the current understanding of antibody affinity maturation, in which antibody avidity increases over time and with repeated vaccinations to produce higher quality antibodies.[6] These data support the need to promote booster-vaccine uptake, particularly among people who are immunocompromised. We also advocate for the standardisation and commencement of routine antibody testing in people who are immunocompromised to enable precise risk delineation for individuals and focusing of efforts to protect the most vulnerable groups.

RW curated, analysed, and validated the data and edited this Correspondence. MJ investigated and analysed the data. NC, AK, and NT contributed to data acquisition, administered the study, and curated the data. BS analysed and validated the data and edited this Correspondence. TM, VW, and ABA-N contributed to data acquisition. AO'C, MJA, GPC, and CPF contributed to data aquisition and edited the manuscript. AJD contributed to data acquisition, acquired funding, and edited the manuscript. DG supervised data analysis and edited the manuscript. SHL conceptualised, supervised, and administered the study; acquired, curated, analysed, and validated the data; wrote the original draft; and acquired funding. All authors reviewed the manuscript, had full access to the data, and were responsible for the decision to submit for publication. SHL has received speaker honoraria from AstraZeneca. MJA receives research funding from Pfizer. GPC receives research funding from Pfizer and participates in advisory boards for AstraZeneca and Pfizer. AJD receives research funding and honoraria from AstraZeneca and Janssen. CPF has received speaker and consultancy honoraria from Janssen and AstraZeneca. All other authors declare no competing interests. The databases with individual-level information used for this work are not publicly available due to personal data protection. Individual participant data that underlie the results reported in this Correspondence, after de-identification (ie, text, tables, figures, and appendices), and the study protocol will be shared on request to the corresponding author for individual participant data meta-analysis. De-identified participant data supporting the findings will be available on completion of the study on reasonable request to the corresponding author after approval by an independent review committee. Proposals can be submitted up to 12 months after completion of the study (ie, Jan 31, 2025). The study design and statistical analysis plan are included in the appendix (pp 14–15). The PROSECO study is funded by the Blood Cancer UK Vaccine Research Collaborative, which is led by Blood Cancer UK in partnership with Myeloma UK, Anthony Nolan, and the British Society for Haematology (21009), awarded to SHL and supported by a Cancer Research UK Advanced Clinician Scientist Fellowship to SHL (A27179), Cancer Research UK and National Institute for Health Research (NIHR) Southampton Experimental Cancer Medicine Centre awarded to AJD (A25141), NIHR Southampton Clinical Research Facility Southampton Research Biorepository, and NIHR Southampton Biomedical Research Centre. DG receives support from the NIHR Great Ormond Street Biomedical Research Centre. GPC receives support from the NIHR Oxford Biomedical Research Centre and Cancer Research UK Experimental Cancer Medicines Centre. MJA receives support from NIHR Leicester Biomedical Research Centre. The funding sources had no role in the writing of this Correspondence or decision to submit for publication. No pharmaceutical company or other agency has paid us to write this Correspondence. We acknowledge the contribution of other members listed within the appendix (p 16).

*Ratna Wijaya, Marina Johnson, Nicola Campbell, Beth Stuart, Adam Kelly, Nicole Tipler, Tobias Menne, Matthew J Ahearne, Victoria Willimott, Anna Bowzyk Al-Naeeb, Christopher P Fox, Graham P Collins, Ann O'Callaghan, Andrew J Davies, David Goldblatt, *Sean H Lim, on behalf of the PROSECO investigators*

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Published **Online**
June 28, 2023
https://doi.org/10.1016/S0140-6736(23)01171-6

Addressing disparities and challenges in global health from an LMIC perspective

Researchers from low-income and middle-income countries (LMICs) who have experience of submitting their manuscripts to internationally acclaimed high-impact journals would reverberate unanimously with Richard Horton's Offline piece, published on May 20, on the case for global health.[1] Horton's critique highlights crucial issues surrounding power dynamics, resource allocation, and colonial practices in the field of global health.[1] While acknowledging the importance of these discussions, we wish to underscore the disparities and challenges faced by LMIC researchers in global health and suggest feasible alternatives to address them.

The roots of the term global health can be traced back to the old-fashioned and outdated term tropical medicine. The term tropical medicine emphasised diseases predominantly found in the countries that were ruled by the colonial nations.[2] From Indian cholera in the 19th century to the more recent SARS-CoV-2, often called the Wuhan virus, western nomenclature has linked diseases with people and nations predominantly from LMICs. The asymmetries in the power dynamics between the high-income countries (HICs) and LMICs lie at the core of the present-day structure of global health. Large concentrations of resources, expertise, universities, and high-impact journals in the HICs have substantially distanced LMICs from having a better visibility and greater impact.[3] The word decolonisation is quaint in the sense that the researchers in the LMICs have to depend on the initiatives of HICs to get included and recognised.

Global health journals' policy to waive off article processing charges for researchers from low-income countries has an altruistic connotation. However, this creates an issue for the researchers from middle-income and upper-middle-income countries including India, where the article processing charges are decided on a case-by-case basis. "Your manuscript does not fit the scope of the journal" is another humiliating statement that researchers from LMICs have to bear that subtly questions their ability to judge if the contents of their own manuscript were fit for submission to a particular journal or not. The authors have faced both of these issues while submitting manuscripts on endometriosis and snakebite envenomation to high-impact journals that only publish public health articles. Lack of publications in high-impact journals later jeopardises the individual's chances of acquiring funds, grants, and awards. Journals also often have strict requirements regarding study design, statistical analysis, and reporting formats that can be more aligned with HIC research contexts. These requirements can create a perceived hierarchy in which research from LMICs is undervalued or overlooked if it does not meet certain predetermined criteria. Consequently, LMIC researchers can feel pressured to conform to these standards, potentially compromising the contextual relevance and applicability of their work.[4]

The best global health education courses and universities lie entirely in HICs. This disparity puts a great deal of additional economic pressure on aspiring LMIC researchers. Such barriers perpetuate the culture of grooming future global health professionals who can afford these courses. Under-representation of LMICs in global health leadership roles further skews the dynamic in favour of HICs. Organisations such as The Consortium of Universities for Global Health, which originated in the USA, were established to support global health academic institutions around the world, but it has only 8·7% and 2·7% of member institutions belonging to LMICs and low-income countries, respectively—about 83% of the institutions belong to HICs.[3] An unexceptionable aspect of global health education is direct exposure to health issues in LMICs and the affecting factors via facilitated field visits. However, such opportunities are replaced by so-called parachute visits whereby researchers from HICs only conduct small research projects by utilising local resources but miss out on potential future collaborations.[5]

The onus of improving the global health situation lies on LMICs as much as it lies on HICs. Decolonisation starts only when the colonised revolt. Providing research opportunities, supporting data even if they go against the established political narrative, increasing research funding, and promoting evidence-based decision making are the first steps of this rebellion. Global funders and philanthropists should be encouraged only when they support the actual LMIC cause and not when they push for their own agenda. Imposition of HIC norms and solutions should be replaced by priority setting based on people's demands and research needs. Respecting local culture, promoting diversity, investing more, and including LMICs to have a greater say in global health can ensure that decolonisation does not just remain a buzzword.[6]