

Different risks, different responses: COVID-19 vaccination in immunocompromised patients

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Immunocompromised individuals, including those with haematological malignancies, autoimmune diseases, or solid organ dysfunction, as well as those receiving long-term immunosuppressive therapy, bear a disproportionate burden from COVID-19, with markedly higher risks of severe disease and death than the general population.^{1,2} Yet the magnitude and durability of vaccine-induced protection in these groups remain highly variable, shaped not merely by the underlying diagnosis but by the specific immunosuppressive agents in use. Importantly, protection against SARS-CoV-2 is mediated by both humoral and cellular immunity, and these 2 arms can be affected differentially by specific immunosuppressive regimens. A complete appraisal of vaccine-induced protection therefore requires more than measurement of neutralising antibody titres alone. Understanding this heterogeneity is now essential for translating vaccine research into individualised clinical practice.

The study in this issue examines this question in a focused and clinically relevant population: patients with chronic myeloid leukaemia (CML) receiving tyrosine kinase inhibitors (TKIs).¹ In this longitudinal cohort, CML patients on TKIs developed robust initial antibody responses after primary vaccination that were broadly similar to those of healthy controls, and T-cell responses remained comparable throughout follow-up. However, the proportion with positive neutralising activity against Omicron BA.1 declined significantly at 6 months after booster vaccination (50.0% versus [vs] 88.9% in controls, $P=0.003$), before recovering by 12 months. These findings were not materially influenced by TKI class (imatinib vs nilotinib) or duration of treatment. The spontaneous recovery in Omicron-neutralising activity between 6 and 12 months, in the absence of further intervention, is of particular biological interest and is consistent with progressive affinity maturation of memory B cells, through which continued germinal-centre selection yields antibodies of higher avidity and broader variant coverage over time. Equally important, T-cell responses in this cohort were preserved throughout follow-up, and because SARS-CoV-2-specific T-cell

epitopes were distributed across the entire viral proteome rather than being concentrated within the spike receptor-binding domain, cellular immunity was comparatively resistant to escape by variants of concern. Taken together, these observations suggest that the transient 6-month reduction in Omicron-neutralising positivity is unlikely to translate into a clinically meaningful window of vulnerability in a cohort in which T-cell immunity remains intact.

The study's longitudinal design, use of World Health Organization-standardised assays, and assessment of both humoral and T-cell immunity are notable strengths. Its limitations include the small single-centre sample, substantial attrition among controls that necessitated recruitment of a replacement cohort, delayed anti-nucleocapsid testing in the CML group, restriction to BNT162b2 vaccination, and, most importantly, the lack of clinical outcome data.

The importance of these findings becomes clearer when viewed alongside earlier studies of vaccine responses in immunocompromised patients. In a prospective Singapore cohort of 519 individuals, including patients with autoimmune diseases, chronic comorbidities, and healthy controls, not all immunocompromised groups were equally vulnerable.² Patients with neuromyelitis optica and those receiving mycophenolate or rituximab were most likely to have subprotective vaccine responses, with mycophenolate use emerging as the strongest independent predictor of poor response (odds ratio 13.7). By contrast, patients with chronic comorbidities such as hypertension, diabetes, and hyperlipidaemia had antibody levels comparable to healthy controls, suggesting that their higher COVID-19 mortality is unlikely to be due to vaccine failure alone. These findings argue against broad, diagnosis-based booster policies and favour instead targeted serological monitoring and additional vaccine doses for the narrower subset of patients whose humoral responses are genuinely impaired, especially those on B-cell-depleting or -suppressing agents. The same cohort also highlighted the value of hybrid immunity.² Vaccinated individuals with breakthrough infection had neutralising antibody

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Accepted 23 April 2026

Published: 24 April 2026

levels that were 28.7% higher (95% confidence interval 24.7–32.7) than vaccinated individuals without prior infection at 6 months after boosting, across all disease groups. Infection during the Delta wave also conferred cross-protective Omicron neutralisation comparable to Omicron infection itself, whereas natural infection alone in unvaccinated individuals produced markedly weaker responses. Together, these findings reinforce that vaccination remains essential even after prior infection, and that hybrid immunity provides the broadest and most durable cross-variant protection.

Two additional longitudinal studies provide important context. In the 2-year COVAXID follow-up study, Chen and colleagues studied 355 immunocompromised patients across 6 diagnostic groups and showed that initial poor responders, including solid organ transplant recipients and patients with CLL receiving ibrutinib, gradually developed neutralising antibodies after repeated boosters, ultimately reaching levels comparable to healthy controls.³ Notably, no participant was hospitalised with severe COVID-19 between 12 and 24 months, suggesting that even modest serological responses may still confer meaningful protection when T-cell immunity is preserved. This clinical protection, despite ongoing humoral variability, is consistent with a growing body of evidence positioning cellular immunity as an independent, and in some settings the dominant, correlate of protection against SARS-CoV-2. Early functional T-cell responses are associated with rapid viral clearance and milder disease following infection,⁷ and the onset of vaccine-induced protection after mRNA vaccination coincides with the detection of spike-specific T cells before neutralising antibodies are induced.⁸ T cells have also been shown to expand and support abortive clearance of SARS-CoV-2 in exposed seronegative individuals,⁹ and have emerged as the most important predictor of protection against symptomatic breakthrough infection in vaccinated cohorts prior to hybrid immunity.¹⁰ Because T-cell epitopes span the entire SARS-CoV-2 proteome rather than being confined to the spike receptor-binding domain, this arm of immunity is less susceptible to variant escape than neutralising antibodies and provides a biologically coherent explanation for continued protection despite waning Omicron neutralisation.

Ciabattini and colleagues reported similar findings across five immunocompromised groups, showing that the first booster was the most important intervention, restoring both antibody and spike-specific memory B-cell responses in most patients.⁴ They further found that Omicron-adapted vaccines generated variant-specific B-cell responses more effectively than natural infection alone, supporting the use of updated boosters rather than reliance on breakthrough infection.

A smaller subgroup of persistent low responders, mainly solid organ transplant recipients, remained unresponsive despite repeated boosting, underscoring the need for alternative preventive strategies such as pre-exposure monoclonal antibodies in selected patients.

These studies highlight several clear priorities. First, booster strategies should be calibrated to the specific immune deficit created by the underlying disease or treatment, rather than applied uniformly based on diagnosis. For patients whose humoral responses are profoundly impaired, particularly those on B-cell-depleting or -suppressing agents such as rituximab, mycophenolate, or ibrutinib, and recipients of solid organ transplants—repeated updated, variant-adapted boosters and, where appropriate, pre-exposure monoclonal antibodies remain important. For patients such as those with CML on TKIs, in whom T-cell immunity is preserved and humoral responses are only transiently attenuated, the incremental benefit of aggressive variant-specific boosting beyond the standard schedule is less clear, and routine boosting strategies aligned with those used in the general population are likely to be sufficient. Second, future research needs to link immunological findings to clinical outcomes, such as breakthrough infection, hospitalisation, and disease severity, to determine the real-world importance of these serological differences. Incorporating T-cell readouts alongside humoral markers will be particularly valuable, given the current reliance of most clinical monitoring on antibody titres that may underestimate protection in cohorts with preserved cellular immunity. Third, vaccination strategies should be tailored according to treatment class and immune profile, rather than diagnosis alone. Risk-prediction models already validated in other immunocompromised populations show that data-driven tools can be integrated into practice and offer a useful framework for individualising vaccine timing and monitoring.^{5,6} Overall, the evidence points to a consistent message: immunocompromised patients are biologically diverse, and vaccine strategies must reflect that diversity.

The CML data reported here are largely reassuring. The transient reduction in Omicron-neutralising antibody positivity at 6 months after boosting, which resolved spontaneously by 12 months alongside fully preserved T-cell responses, is unlikely to represent a period of meaningful clinical vulnerability. For patients receiving B-cell-depleting or B-cell-suppressing therapies such as rituximab, mycophenolate, or ibrutinib, standard schedules may be inadequate. For many others, including patients with CML on TKIs, hybrid immunity, and preserved T-cell responses together provide meaningful protection. The task ahead

is not simply to generate more data, but to translate existing evidence into more individualised and equitable clinical care.

Ethics statement

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. No funding was received for this work.

Keywords: *chronic myeloid leukaemia, hybrid immunity, immunocompromised patients, SARS-CoV-2 vaccination, tyrosine kinase inhibitors*

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