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Bivalent COVID-19 mRNA vaccine against omicron subvariants in immunocompromised patients

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Despite the end of the global COVID-19 public health emergency, SARS-CoV-2 infection continues to result in moderate to severe disease in immunocompromised patients.[1] Omicron variants (eg, BQ.1.1 and XBB.1.5) seem to escape immunity conferred by vaccination and previous infection.[2] The US Food and Drug Administration proposed booster doses of bivalent mRNA vaccine specifically for immunocompromised patients in an effort to enhance protection for this vulnerable population. Data in small sets of immunocompetent persons demonstrate higher neutralisation against these variants after receiving a bivalent vaccine as well as protection against symptomatic infection.[3,4] However, there is little data regarding humoral and cellular immune responses to new bivalent vaccine formulations in immunocompromised people specifically in relation to the

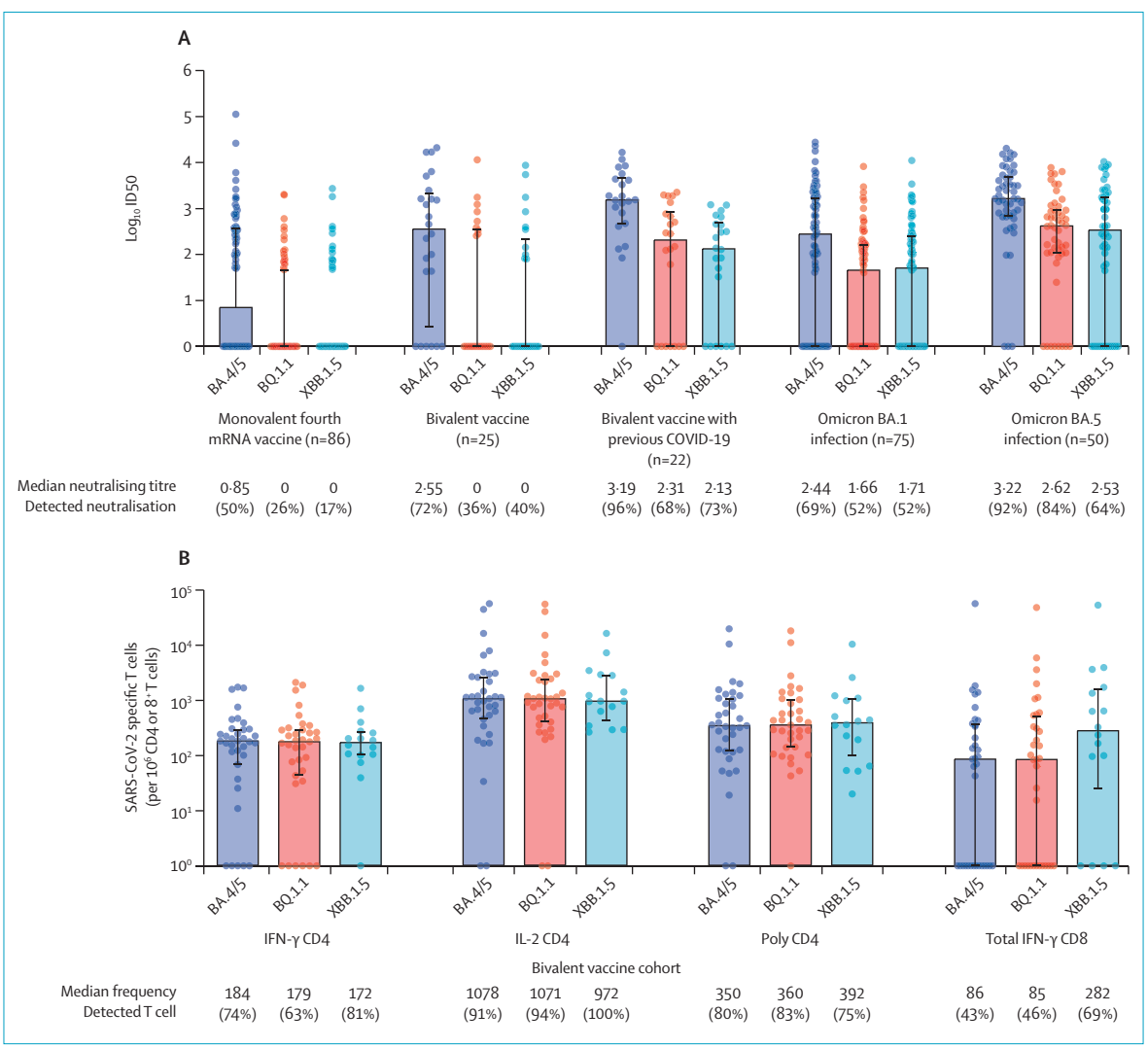

***Figure*: Humoral and cellular immune responses to Omicron subvariants in organ transplant recipients**
(A) Neutralising antibody activity (log_{10} ID50) against Omicron BA.4/5, BQ.1.1, and XBB.1.5 in transplant recipients after fourth dose of mRNA monovalent vaccine, bivalent booster vaccine without previous COVID-19, bivalent vaccine with previous COVID-19, previous BA.1 infection, or previous BA.4/5 infection. Each dot represents a patient and the heights of the bars represent the median value of the neutralisation titre against each subvariant. The top horizontal line represents the 75th percentile, and the bottom line the 25th percentile. The top row of numbers displays the median neutralisation titre against each subvariant in each group. The second row of numbers represents the proportion of individuals in each group that have detectable neutralisation against each subvariant. (B) Comparison of BA.4/5-, BQ.1.1- and XBB.1.5- directed T-cell responses in transplant recipients after receiving bivalent mRNA vaccination. Patients with and without a history of COVID-19 are included. Variant-specific T-cell frequencies per 10^6 cells are shown for: IFN-γ monofunctional, IL-2 monofunctional, and polyfunctional (IFN-γ$^+$ and IL-2$^+$) CD4$^+$ T-cells, and total IFN-γ expressing CD8$^+$ T cells. Poly=polyfunctional.

currently circulating variants. We evaluated immunogenicity of the BA.4/5-bivalent vaccine to induce neutralising antibody and T-cell responses in immunosuppressed solid organ transplant recipients. Responses to BA.4/5, BQ.1.1, and XBB.1.5 were measured after bivalent vaccine and compared with cohorts either after monovalent vaccination or after SARS-CoV-2 infection.

We used a pseudovirus variant-specific neutralisation assay to measure neutralising antibody in sera of 47 transplant recipients 4–6 weeks after receiving mRNA bivalent vaccine (divided into 25 patients with no history of COVID-19 and 22 patients with history of COVID-19). We compared the neutralising antibody response to those who received a fourth dose of monovalent vaccine (n=86), and to transplant cohorts after natural infection with either BA.1 (n=75) or BA.4/5 (n=50). Baseline characteristics across groups are shown in the appendix (pp 7–8). Results are shown in figure A. Although patients who received a bivalent booster had good neutralising titres against BA.4/5, the response to BQ.1.1 and XBB.1.5 was only marginally higher than the cohort that had previously received 4-doses of monovalent vaccine, and inferior to any cohort with previous infection (figure A; appendix p 13). For example, median titre against XBB.1.5 after bivalent vaccine in previously uninfected patients was 0 log_{10} ID50 (IQR 0–2·2) and ten (40·0%) of 25 patients had any detectable level of neutralisation. By contrast, previous Omicron infection with BA.5 resulted in significantly better neutralisation against both BQ.1.1 and XBB.1.5 ($p<0·001$ and $p=0·003$ respectively *vs* bivalent vaccine; figure A, appendix p 9).

See **Online** for appendix

In the cohort that received bivalent vaccine, variant-specific SARS-CoV-2 $CD4^+$ and $CD8^+$ T-cell responses were measured using an intracellular cytokine staining flow cytometry assay (figure B) for BA.4/5 (n=35), BQ.1.1 (n=35) and XBB.1.5 (n=16). Both $CD4^+$ and $CD8^+$ T-cell responses were preserved across all three variants and were quite strong. For example, polyfunctional XBB.1.5-specific $CD4^+$ T-cells were detected at a median frequency of 392 per 10^6 cells (IQR 97–1072) and were similar to that seen for BA.4/5 and BQ.1.1 after bivalent vaccine. The $CD8^+$ T-cell response rate was lower than the $CD4^+$ T-cell response but still preserved across variants. Previous infection with COVID-19 did not influence T-cells responses in this cohort (appendix p 7). Additionally, in a subset comparison of BA.4/5 and BQ.1.1 T-cell response before and after bivalent vaccine (n=9), no significant improvement was observed (appendix p 9). Similar results were observed comparing BA.4/5 T-cell responses after 4-dose monovalent and after bivalent vaccine (appendix p 14).

Overall, our study suggests that, while bivalent vaccination increases BA.4/5-directed neutralising antibody in immunocompromised people, it only modestly impacts BQ.1.1 and XBB.1.5 neutralization. By contrast, substantial cross-protective neutralising antibody is observed following previous Omicron infection. T-cell responses are more readily detectable and conserved across BA.4/5, BQ.1.1, and XBB.1.5 variants, thereby possibly providing some cross-variant protection. However, no additional boosting of T-cell response was evident following bivalent vaccine. Our results suggest that, although vaccination is important, additional strategies such as the ongoing development of prophylactic monoclonal antibodies and use of early COVID-19 therapies are crucial for immunocompromised patients.

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