The XBB.1.5 mRNA booster vaccine does not significantly increase the percentage of XBB.1.5 monoreactive T cells

476

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Background

- SARS-CoV-2 variant evolution has driven vaccine updates, including the XBB.1.5 monovalent booster vaccine.
- Prior studies indicate bivalent vaccines mainly elicit cross-reactive T cell responses rather than variant-specific responses.
- Understanding the ability of the XBB.1.5 booster to elicit mono-reactive T cell responses is crucial for optimizing future vaccine strategies.

Objectives

- Assess the proportion of cross-reactive vs mono-reactive T cell responses to XBB.1.5 spike protein.
- Determine whether the XBB.1.5 booster increases mono-reactive T cell responses.
- Evaluate cytokine secretion profiles before and after XBB.1.5 booster administration.
- Investigate the percentages of epitopes with XBB.1.5 mutations targeted by T cells changes post –booster.

Spike-specific T cells secrete higher levels of TNF-α after the XBB.1.5 booster

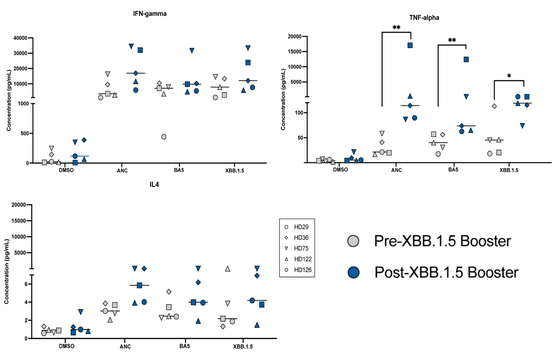


Figure 1: Cytokine Responses to Ancestral, BA.5, and XBB.1.5 Spike Peptides Pre and Post XBB.1.5. Booster Administration. Cytokine levels of IFN-gamma, TNF-alpha, and IL4 were measured in pg/mL using an MSD ELISA assay following stimulation with different spike peptides before and after XBB.1.5 booster administration. This figure displays the cytokine responses elicited by stimulation with the three spike proteins both pre and post booster administration. Symbols in grey represent measurements before the booster, and symbols in blue represent measurements after the booster. The median value for each group is indicated by the horizontal line within each set of data points. Statistical significance between pre- and post-vaccine measurements was assessed using the paired t-test . **p < 0.01.

Summary

- The XBB.1.5 booster vaccine did not increase the percentage of XBB.1.5 mono-reactive T cell responses
- The percent of epitopes targeted by T cells that would have an XBB.1.5 mutation did not significantly change after the vaccine
- Spike-specific T cells secrete higher levels of TNF-α after the vaccine suggesting qualitative changes in the immune response.

Results

The XBB.1.5 booster does not increase the percentage of T cell clonotypes that are mono-reactive to the XBB.1.5 spike protein

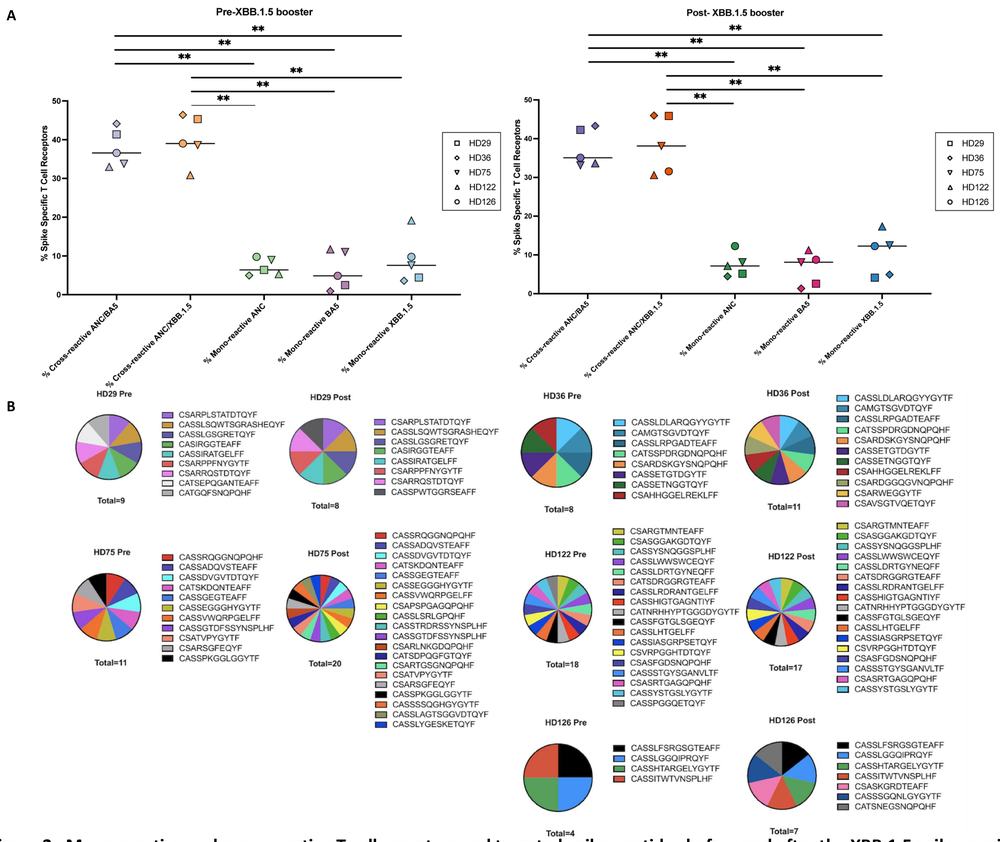


Figure 2: Mono-reactive and cross-reactive T cell receptors and targeted spike peptides before and after the XBB.1.5 spike vaccine. (A)After culture, TCR Vβ CDR3 sequencing was performed to identify antigen-specific memory T cells that expanded in response to spike peptide pools (FEST assay). Cross-reactivity was defined by the functional expansion of the same CD4+ TCR clonotypes in response to pooled ancestral (ANC), Omicron BA.5 (BA.5), and XBB.1.5 peptides. Mono-reactivity was defined as expansion to just 1 of the 3 spike peptide pools. Three technical replicates were run for each peptide culture for each of 5 participants before and after booster administration. (B)Pie charts depicting the distribution of individual T cell receptor (TCR) clonotypes specific to the XBB.1.5 spike protein among study participants before (Pre-Booster) and after (Post-Booster) XBB.1.5 booster administration. Each pie chart represents the proportion of mono-reactive TCRs targeting the XBB.1.5 spike protein within the total spike-specific T cell population for each participant

The percentage of T cell-targeted epitopes containing XBB.1.5 mutations did not significantly change after XBB booster administration.

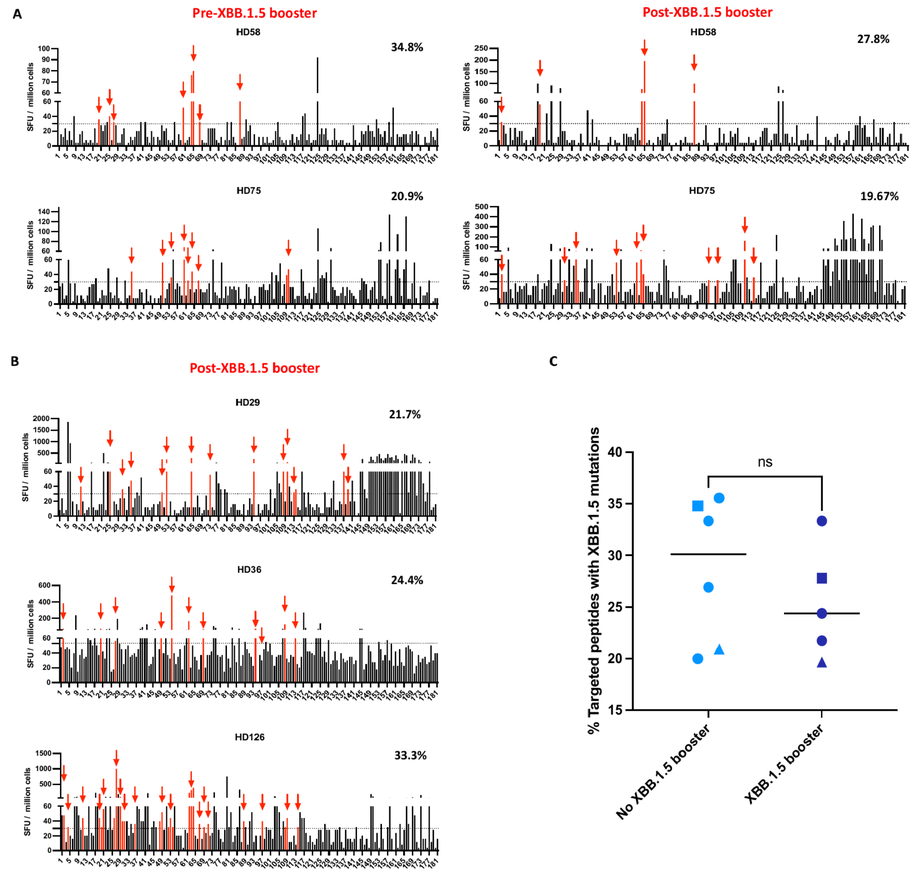


Figure 3: The percentage of ancestral spike peptides targeted by T cells that contain XBB.1.5 mutations pre and post the XBB.1.5 booster. (A) The IFN-γ ELISpot assay was performed on samples obtained from 2 participants before and after XBB.1.5 booster administration. The SFU of PBMCs in response to each of the 181 overlapping peptides are shown. Each data point represents the mean of 2 technical replicate values. The dotted horizontal line represents the threshold for positive responses (SFU ≥30). The red vertical bars represent targeted peptides that would contain an XBB.1.5 mutation. The percentages on the right represent the percentage of targeted peptides that would contain an XBB.1.5 mutation. (B) ELISpot assay performed on samples from 3 participants after XBB.1.5 booster administration. (C) Comparison of percentage of peptides targeted by T cells that contain XBB.1.5 mutations in participants who either received or did not receive the XBB.1.5 booster.

Acknowledgments

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