Double-dose mRNA vaccination to SARS-CoV-2 progressively increases recognition of Spike RBD-specific memory B cells to variants-of-concern

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Background: SARS-CoV-2 vaccination coverage is increasing worldwide, however emerging variants of concern (VoC) challenge its protection. Booster vaccinations improve protection against severe disease from VoC, but the underlying mechanism is currently unknown. We here addressed recognition of Spike receptor binding domain (RBD) from SARS-CoV-2 Wuhan and VoC by serum IgG and circulating memory B-cells (Bmem) after 1st and 2nd dose of vaccination.

Methods: Recombinant Nucleocapsid protein (NCP) and Spike RBD from Wuhan, Beta, Gamma and Delta variants were produced for ELISA-based serology, and biotinylated for fluorescent tetramer formation to identify RBD-specific Bmem by flow cytometry. Samples were collected from healthy adults before and 1 month after 1st and 2nd dose immunisation with the Pfizer mRNA (n=30) SARS-CoV-2 vaccine.

Results: None of the participants carried IgG to NCP or RBD before \vaccination. IgG to RBD progressively increased after 1st and 2nd dose of vaccination. No participants formed anti-NCP antibodies indicating absence of infection for the duration of the study. Relative recognition of RBD from VoC was significantly reduced for Beta and Gamma. All participants formed RBD-specific Bmem, which were predominantly IgM^+ or $IgG1^+$, and only $IgG1^+$ cell numbers increased after the second dose. Approximately 50% of RBD-specific Bmem showed reactivity to either Gamma or Delta. This proportion significantly increased after the 2nd dose to approximately 70% of RBD-specific cells recognizing either variant.

Conclusion: Pfizer mRNA vaccination generates a robust serological response with some loss in recognition to VoC, particularly Beta and Gamma. RBD-specific Bmem show evidence of class switching with an increase in only $IgG1^+$ not IgM^+ cells post-dose 2. The 2nd dose of vaccination increases the recognition of RBD-specific Bmem to Gamma and Delta variants. This would fit with a model of additional affinity maturation enabling the antibody reactivity to overcome the mismatches in variants and bind with sufficient affinity.

Disclosure of Interest Statement: GEH is supported by an RTP PhD scholarship, MCvZ and REO'H are supported by an NHMRC Ideas grant (2000773). This work is supported by an unrestricted grant from BD Biosciences.