Induction of antibody responses following COVID-19 vaccination and breakthrough infections in naïve and convalescent individuals suggests imprinting to the ancestral strain of SARS-CoV-2

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Background: Binding and neutralising activity of SARS-CoV-2 antibodies (Abs) are important correlates of protection of current COVID-19 vaccines. SARS-CoV-2 exposure status and COVID-19 vaccine types are variables that can have an impact on these responses and cross-protective immunity to variants. We sought to determine antigen (Ag)-specific binding and neutralising antibody (nAb) responses to primary vaccination (two doses) of adenovirus vectored (AZ) and mRNA vaccines and a booster dose of mRNA vaccine in convalescent and infection-naïve individuals.

Methods: SARS-CoV-2-specific Ab (multiplex Luminex assay) and nAb (live virus microneutralization) to ancestral (Wuhan), Alpha, Delta and Omicron (BA1, BA2 and BA5) viruses) were measured in 45 convalescent and 52 infection-naïve individuals post-vaccination and following breakthrough infections in a subgroup of 63 vaccinees.

Results: Levels of anti-SARS-CoV-2 IgG and nAb following primary vaccination (2 doses) with AZ vaccine were significantly lower than following mRNA vaccine, irrespective of SARS-CoV-2 exposure status. However, an mRNA vaccine booster dose resulted in equivalent Ag-specific binding and nAb levels to the ancestral virus in all individuals, irrespective of primary vaccine type. Notably, vaccinated infection-naïve, but not convalescent individuals required the third dose of (mRNA) vaccine to induce nAbs to Omicron subvariants BA1, BA2 and BA5 though titres against the variants were lower than those against the ancestral strain. Importantly, we found that breakthrough infection with an Omicron strain induced greater rises in nAb to ancestral than to Omicron variants.

Conclusion: Three doses of COVID-19 vaccines were required for induction of nAb responses in infection-naïve individuals. Notably, nAb titres following the third dose (mRNA booster) were similar in individuals who received primary vaccination with homologous (mRNA) or heterologous (AZ) platforms. A greater induction of ancestral- than variant-specific nAb titres after breakthrough infection are consistent with immunologic imprinting and recall of pre-existing immunity to the ancestral strain.