**Online Methods**

Study participants

504 adult individuals from Sri Lanka, were recruited at the time they received the first dose of the vaccine following informed written consent. Blood samples were obtained at baseline (at the time of recruitment) to determine SARS-CoV2 seropositivity, and at 4 weeks from receiving the first dose of the vaccine. The presence of comorbid illness such as diabetes, hypertension was recorded. The SARS-CoV-2 specific antibody assays were carried out in all the individuals, while certain assays were done in a sub cohort (see below). We also compared the ACE2 receptor blocking antibodies, antibodies to the RBD of different variants detected by HAT and ex vivo IFNγ ELISpot responses in individuals 4 weeks after a single dose of AZD1222 (Covishield) vaccine (n=69) 1, and with those who were naturally infected (n=36) as previously reported by us2. Overall seroconversion rates for Gam-COVID-Vac first dose was also compared with AZ first dose at 4 weeks, using our previously published data3.

Ethics approval was obtained from the Ethics Review Committee of University of Sri Jayewardenepura (COVID 01/21).

SARS-CoV-2 specific total antibodies, ACE-2 receptor blocking antibodies and antibodies to the RBD of SARS-CoV2 variants

Antibodies to SARS-CoV-2 were detected by Wantai SARS-CoV-2 antibody ELISA (Beijing Wantai Biological Pharmacy Enterprise, China), which detects IgM, IgG and IgA antibodies. Surrogate virus neutralization test (sVNT)4 was used to detect ACE2 receptor blocking antibodies as previously described5. Inhibition percentage ≥ 25% in a sample was considered as positive for ACE2 blocking antibodies. This assay was found to be 100% specific for measuring ACE2 blocking antibodies in the Sri Lankan population 5.

Haemagglutination tests for detection of antibodies to the RBD in WT and SARS-CoV-2 variants

For the HATs, sera were doubling-diluted in 50ul PBS in V bottomed 96 well plates, 50ul of ~1% v/v O-ve red cells were added, followed by 50ul of the relevant IH4-RBD reagent diluted to 2ug/ml (100ng/well). Plates were incubated for 1 hour at RT, tilted for ~20 seconds to allow a red cell “teardrop” to form, photographed and read by eye. The RBD-specific antibody titre for the serum sample was defined by the last well in which the complete absence of “teardrop” formation was observed. The HAT titration was performed using 7 doubling dilutions of serum from 1:20 to 1:1280, to determine presence of RBD-specific antibodies. A titre of 1:20 was considered as a positive response, as previously determined by us6. The IH4-RBD reagents for each VOC were standardized by titration with the monoclonal antibody EY-6A7,8 that binds to a conserved epitope common to all variants. A 20ug/ml solution of EY-6A titrated equally with a standard (2ug/ml) solution of each of the new IH4-RBD reagents. All were therefore added as 50ul from a 2ug/ml stock solution (100ng/well) as described8.

Ex vivo ELISpot assays

Ex vivo IFNγ ELISpot assays were carried out using freshly isolated peripheral blood mononuclear cells (PBMC). Two pools of overlapping peptides named S1 (peptide 1 to 130) and S2 (peptide 131 to 253) covering the whole spike protein (253 overlapping peptides) were added at a finalconcentration of 10 µM and incubated overnight as previously described 9,10. 100,000 cells/well were added, PHA was included as a positive control of cytokine stimulation and media alone was applied to the PBMCs as a negative control. All peptide sequences were derived from the wild-type consensus and were tested in duplicate.

Briefly, ELISpot plates (Millipore Corp., Bedford, USA) were coated with anti-human IFNγ antibody overnight(Mabtech, Sweden). The plates were incubated overnight at 37°C and 5%CO2. The cells were removed, and the plates developed with asecond biotinylated Ab to human IFNγ and washed a furthersix times. The plates were developed with streptavidin-alkalinephosphatase (Mabtech AB) and colorimetric substrate. Thespots were enumerated using an automated ELISpot reader (AID Germany). Background (PBMCs plus media alone) was subtracted and data expressed as number of spot-forming units (SFU) per 106 PBMCs. A positive response was defined as mean±2 SD of the background responses. An example of a ex vivo ELISpot assay for S1, S2, is shown in online methods figure 1.



**Online methods figure 1**: An example of an ex vivo ELISpot response at 4 weeks following the Gam-COVID-Vac

Intracellular cytokine staining

Intracellular cytokine staining was carried out in freshly isolated PBMCs. PBMCs were incubated with CD107a FITC (Biolegend, USA) for 30 minutes in RPMI 1640 and 10% heat inactivated human serum (Sigma Andrich). Cells were stimulated with overlapping peptides pool of SARS-CoV-2 spike protein for 2 hours at 1mM concertation before adding monensin (Biolegend, USA). The PBMC were incubated for a further 14 hours before staining with with anti‐CD3 APC Cy7 (clone OKT3), anti‐CD8 BV650 (clone SK1) and anti-CD4 PB (clone OKT4). Then the cells were fixed with fixation buffer and permeabilized with perm wash buffer (Biolegend, USA) and stained for IFN-γ APC (clone 4S. B3).  Live/Dead fixable aqua dead cell stain (Thermo Fisher Scientific, USA) was used according to the manufacturer's protocol to exclude dead cells. Cells were acquired on a BD FACSAria III Cell Sorter using DIVA v8 software (BD Biosciences, USA). For each donor, unstimulated cells were included as a negative control. Flow cytometry data were analyzed using FlowJo v.10.7.1 software (FlowJo). Fluoresces Minus One (FMO) controls were used to draw the gates for both CD107a and IFN-γ (online methods figure 2). The proportion of cells expressing S pool of peptide specific CD107a or producing IFNγ, was determined by subtracting the expression levels/production levels in the unstimulated wells, from the peptide stimulated wells.



**Online methods figure 2:** Gating strategy used to identify CD107a expressing CD4+ and CD8+ T cells and IFNγ producing CD4+ and CD8+ T cells. The cells were initially gates on FSC-H and FSC-A to gate the singlets. The lymphocytes from these cells were then identified by gating them on the FSC and SSC. From these cells, the live cells were then gates and then CD3+ T cells were gated. From these CD3+ T cells, CD107a expressing CD4+ and CD8+ T cells were identified and IFNγ producing CD4+ T cells and CD8+ T cells were identified.

B cell ELISpot assays

Briefly, freshly isolated PBMCs were stimulated in a 24 well plate using IL-2 and R848 (a TLR 7/8 agonist) in RPMI supplemented with 10% fetal bovine serum, 1% penicillin streptomycin and 1% glutamine at 4 million cells/well and incubated at 37 °C with 5% CO2 for 3 days. They were then washed and rested overnight and 100,000 cells/well were added. 50,000 cells/well were added to the positive control wells. A Human IgG ELISpot kit (Mabtech 3850-2A) was used according to the manufacturer’s instructions to quantify IgG-secreting cells specific to SARS-COV2 S1, S2 and N recombinant proteins, which were coated at 2µg/ml in phosphate buffered saline (PBS). All experiments were carried out in duplicate and anti-human IgG monoclonal capture antibodies, was used as a positive control, and media alone as a negative control. Thespots were enumerated using an automated ELISpot reader (AID Germany). A positive response was defined as mean±2 SD of the background responses. An example of a B cell ELISpot assay for S1, S2 and N recombinant proteins is shown in online methods figure 3.



**Online methods figure 3:** An example of a B cell ELISpot assay at 4 weeks following the Gam-COVID-Vac for S1, S2 and N recombinant protein.

Statistical analysis

95% confidence intervals for each category were calculated using the R software (version 4.0.3) and R-studio (version 1.4.1106). Pearson Chi Square Association tests were performed at a confidence level of 95% using the R software in order to identify the statistically significant associations of the age categories and the sex of study participants with antibody responses at 4 weeks. GraphPad Prism version 6 was used for other statistical analysis. In instances when the data were not paired, the Mann-Whitney U test (two tailed) was used and the Wilcoxon matched-pairs signed rank test was used when comparing paired data. The Kruskal-Wallis test was used to compare the differences of the antibody levels in different age groups. Spearman rank order correlation coefficient was used to evaluate the correlation between variables including the association between RBD antibodies, SARS-CoV-2 antibodies, SARS-CoV-2-specific T cell responses and age.

**References**

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