**Supplemental Methods:**

Human Subjects: Blood was collected in EDTA tubes, processed by density gradient separation at UCSD or LJI, and cryopreserved in 10% DMSO in heat inactivated fetal bovine serum and stored in liquid nitrogen until ready to use.

ELISAs: Recombinant proteins for Spike and the RBD were provided by the Saphire laboratory as previously described (1–3). Recombinant nucleocapsid protein was purchased from Genscript. Corning 96-well half area plates were coated with 1g/mL of recombinant protein in phosphate buffered saline (PBS) overnight at 4C. The next day, plates were blocked with PBS containing 3% milk ad 0.05% Tween-20 for 1.5 hours at room temperature (RT). All plasma was heat inactivated at 56C for 30-60 minutes prior to addition to the plates. Plasma was diluted in PBS containing 1% milk and 0.05% Tween-20 and incubated at RT for 1.5 hours. Plates were washed 5x with 0.05% PBS-Tween. Anti-human IgG peroxidase antibody produced in goat (Sigma A6029) was used at 1:5000 dilution in PBS containing 1% milk and 0.05% Tween-20. Plates were washed 5x with 0.05% PBS-Tween and developed using TMB Substrate kit (ThermoScientific) at room temperature. The reaction was stopped with 2M sulfuric acid. Plates were read on a Spectramax Plate Reader at 450nm using SoftMax Pro. A positive control standard was used by pooling plasma from 6 convalescent subjects to normalize between experiments. Endpoint titers were plotted for each sample using background subtracted data and calculated at the dilution which gives a reading above the limit of detection of 0.1. The limit of detection was set at 3 based on the lowest dilution of plasma used.

Neutralizing Antibody Titers: Vero cells were seeded in 96-well plate to produce a monolayer at time of infection, as previously described (2,3). Pre-titrated rVSV-SARS-CoV-2 (Spike pseudotyped VSV-G-GFP) were incubated with serially diluted human plasma at 37C for 60 minutes prior to addition to confluent Vero cell monolayers. Cells were incubated for 12-16 hours at 37C I 5% CO2, fixed with 4% paraformaldehyde, stained with 1g/mL of Hoescht, and imaged using a Cellnsight CX5 imager to quantify total number of cells expressing GFP. The limit of detection was set at 19 based on lowest dilution of plasma. Neutralization IC50 titers were calculated using One-Site Fit Log IC50 regression in GraphPad Prism 8.0.

Antigen-specific memory B cells: As previously described (3), biotinylation of full-length Spike and RBD recombinant proteins was performed using biotin-protein ligase standard reaction kit (Avidity, Cat # Bir500A) and dialyzed overnight against PBS. Biotinylated Spike was mixed with Streptavidin BV421 (Biolegend 405225) and Streptavidin Alexa Fluor 647 (ThermoFisher S21374) at 20:1 ratio (~ 6:1 molar ratio). Biotinylated RBD was mixed with streptavidin PE/Cyanine 7 (Biolegend 405225) at 2.2:1 ratio (~ 4:1 molar ratio). The antigen probes were mixed in Brilliant Buffer (BD Bioscience 566349) containing 5 M free d-Biotin to ensure minimal cross-reactivity of antigen probes. PBMCs were stained with the antigen probe cocktail at 4C for 60 minutes prior to surface staining. Dead cells were stained using LIVE/DEAD Fixable Blue Stain kit (ThermoScientific L34962) at 4C for 30 minutes.

Antibodies included: CD62L (BUV395, Clone SK11), CD19 (BUV563, Clone SJ25C1), CD307 (BU615, Clone 509F6), CD95 (BUV737, Clone DX2), CXCR3 (BUV805, Clone 1 C6/CXCR3), IgD (BV510, Clone IA6-2), IgM (BV570, Clone MHM-88), CD24 (BV605, Clone ML5), CD20 (BV650, Clone 2H7), CXCR5 (BV750, Clone RF8B2), CD71 (BV786, Clone M-A712), CD27 (BB515, Clone M-T271), IgA (VioBright FITC, Clone IS11-8E10), CD3 (PerCP, Clone Sk7), CD14 (PerCp, Clone 63D3), CD16 (PerCp, Clone 3G8), CD56 (PerCp, Clone HCD56), IgG (PerCPCy5.5, Clone M1310G05), CD85 (PE/Dazzle 594, Clone GHI/75), CD11c (PECy-5, Clone 3.9), CD21 (AF700, Clone Bu32), CD38 (APC/Fire 810, Clone HIT2), Streptavidin BV421, Streptavidin 721, Streptavidin PE, Streptavidin PECy5.5, Streptavidin Alexa Fluor 647).

Cells were acquired on Cytek Aurora CS and analyzed using FlowJo 10.7.1.

Immunophenotyping: PBMCs were stained for B cells and T cell subsets.

Antibodies for B cells included: Live/Dead e780, CD3 (APC-eFluor 780, Clone OKT3), CD14 (APC-eFluor 780, Clone 61D3), CD16 (APC-eFluor 780, Clone CB16), CD19 (AF700, Clone H1B19), IgD APC, IgM (BV421, Clone G20-127), CD20 (BV570, Clone 2H7), IgG (BV650, Clone G18-145), IgA (FITC, Clone IS11-8E10), CD27 (PerCPe710, Clone O323), CD38 (Pe-Cyanine7, Clone HIT2).

Antibodies for T cells included: Live/Dead e780, CD19 (APC-eFluor 780, Clone HIB19), CD14 (APC-eFluor 780, Clone 61D3), CD16 (APC-eFluor 780, Clone CB16), CD8 (AF700, Clone RPA-T8), CD4 (APC, Clone OKT4), CXCR5 (BV421, Clone J25D4), CD45RA (BV570, Clone HI100), CXCR3 (BV650, Clone G025H7), PD-1 (BV785, Clone EH12.2H7), CCR7 (FITC, Clone G043H7), CCR4 (PE, Clone 161), ICOS (PerCPe710, Clone ISA-3), CCR6 (Pe-Cyanine7, Clone 11A9).

Cells were acquired on BD FACS Celesta and analyzed using FlowJo 9.6.

Activation Induced Marker T cell Assay: As previously described (4,5), PBMCs (1x106 cells) were cultured in 96 well U-bottom plates containing 5% human AB serum (GemBio) in RPMI supplemented with penicillin/streptomycin and L-Glutamax. Prior to addition of megapools, cells were blocked with anti-CD40 mAb (Miltenyi Biotec) at 37C for 15 minutes. An equimolar amount of DMSO as a negative control, SARS-CoV-2 Spike megapool (1g/mL), CMV megapool (1g/mL), or staphylococcal enterotoxin B (SEB at 1g/mL) was added to the cells. SARS-CoV-2 Spike megapools and CMV megapools were provided by the Sette lab (1,6). Cells were stimulated for 24 hours and then stained. Antigen-specific CD4+ T cells are defined as OX40+CD40L+CD4+ T cells. Antigen-specific CD8+ T cells are defined as CD69+41BB+CD8+ T cells.

Antibodies included: Live/Dead e780, CD19 (APC-eFluor 780, Clone HIB19), CD14 (APC-eFluor 780, Clone 61D3), CD16 (APC-eFluor 780, Clone CB16), CCR7 (AF700, Clone G043H7), 41BB/CD137 (APC, Clone 4B4-1), CXCR5 (BV421, Clone J25D4), CD45RA (BV570, Clone HI100), CD8a (BV650, Clone RPA-T8), CD4 (BV786, Clone OKT4), OX40 (FITC, Clone Ber-ACT35), CD40L/CD154 (PerCP-eFluor 710, Clone 24-21), CD69 (Pe-Cyanine7, Clone FN50).

Cells were acquired on BD FACS Celesta and analyzed using FlowJo 9.6.

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