

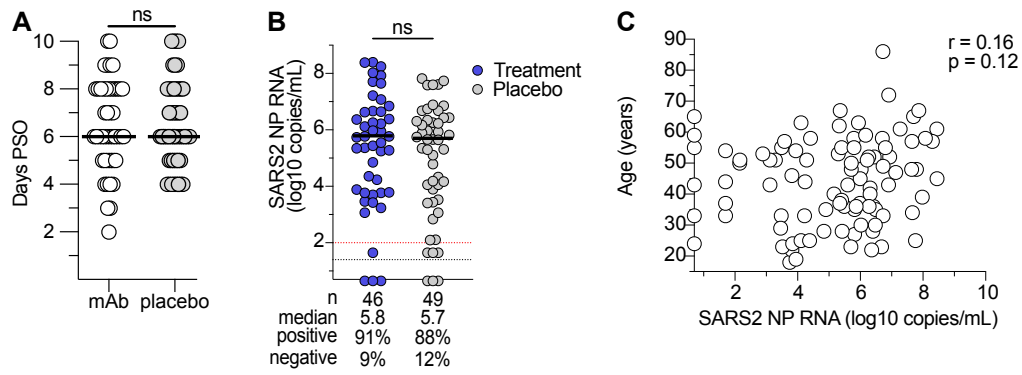


Figure S1. Days from symptom onset to study entry and SARS2 NP RNA at study entry by clinical trial group.

A. Days PSO at study day 0 for bamlanivimab (mAb; $n = 46$) and placebo group participants ($n = 49$); line = median (day 6). **B.** SARS2 NP RNA at day 0 by treatment group (Treatment = bamlanivimab). **C.** Relationship between day 0 SARS2 NP RNA and participant age. Lines and bars as in **Fig. 1B-C**. ns = not significant by Mann-Whitney test. **Related to Figure 1.**

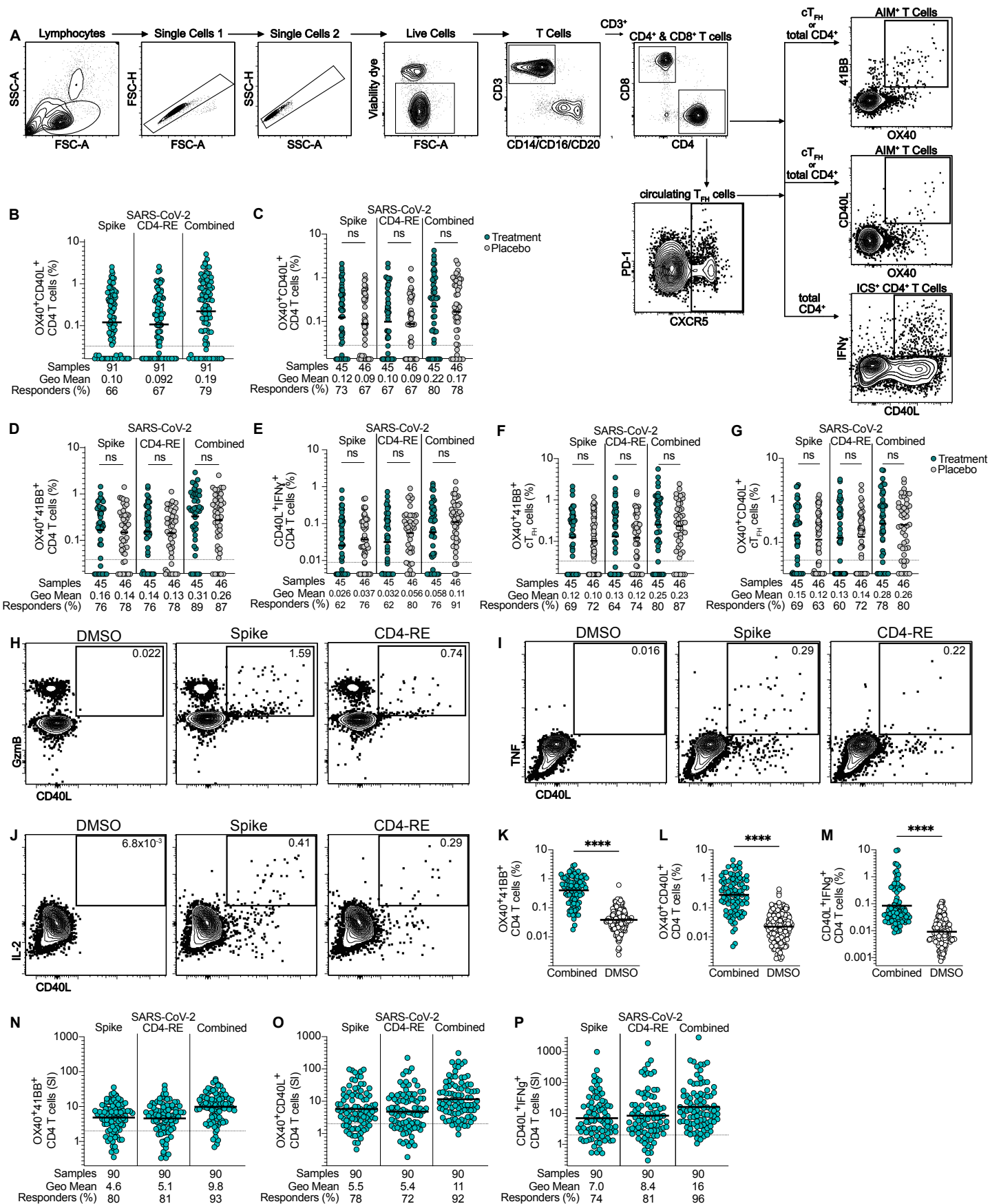


Figure S2. Antigen-specific CD4 T cell responses to primary SARS2 infection and acute COVID-19.

A. Gating strategy and representative flow cytometry gating for CD4 AIM and AIM+ICS assay readouts using IFN γ as the example cytokine shown. **B.** Study day 0 Spike, CD4-RE, or Combined (Spike + CD4-RE) AIM $^{+}$ CD4 T cells by surface OX40 $^{+}$ CD40L $^{+}$. **C-E** Study day 0 Spike, CD4-RE, and combined total CD4 T cells by clinical trial assignment (bamlanivimab = "Treatment", saline = "Placebo") by **(C)** surface OX40 $^{+}$ CD40L $^{+}$, **(D)** OX40 $^{+}$ 41BB $^{+}$, or **(E)** surface CD40L and intracellular IFN γ . **F-G.** Study day 0 Spike, CD4-RE, and combined circulating TFH cells by surface **(F)** OX40 $^{+}$ 41BB $^{+}$ or **(G)** OX40 $^{+}$ CD40L $^{+}$. **H-J.** Example flow cytometry gating and frequencies for total CD4 T cells based on surface CD40L $^{+}$ and intracellular production of **(H)** GzmB, **(I)** TNF, **(J)** IL-2. **K-M.** % SARS2-specific of total CD4 T cells for MP versus DMSO stimulated by **(K)** OX40 $^{+}$ 41BB $^{+}$ **(L)** OX40 $^{+}$ CD40L $^{+}$, and **(M)** CD40L $^{+}$ IFN γ $^{+}$. **N-P.** Spike, non-Spike (CD4-RE) and total (Spike + CD4-RE = Combined) SARS2-specific CD4 T cells by **(N)** OX40 $^{+}$ 41BB $^{+}$, **(O)** OX40 $^{+}$ CD40L $^{+}$, and **(P)** CD40L $^{+}$ IFN γ $^{+}$ by stimulation index (SI, fold-change relative to DMSO control; see Methods for details). Bars, dotted lines, and flow cytometry gate labels as in **Fig. 2**. ns = not significant between Treatment and Placebo group by Mann-Whitney for comparison of the same stimulation condition. **** = $p \leq 0.0001$ by Mann-Whitney. **Related to Figure 2.**

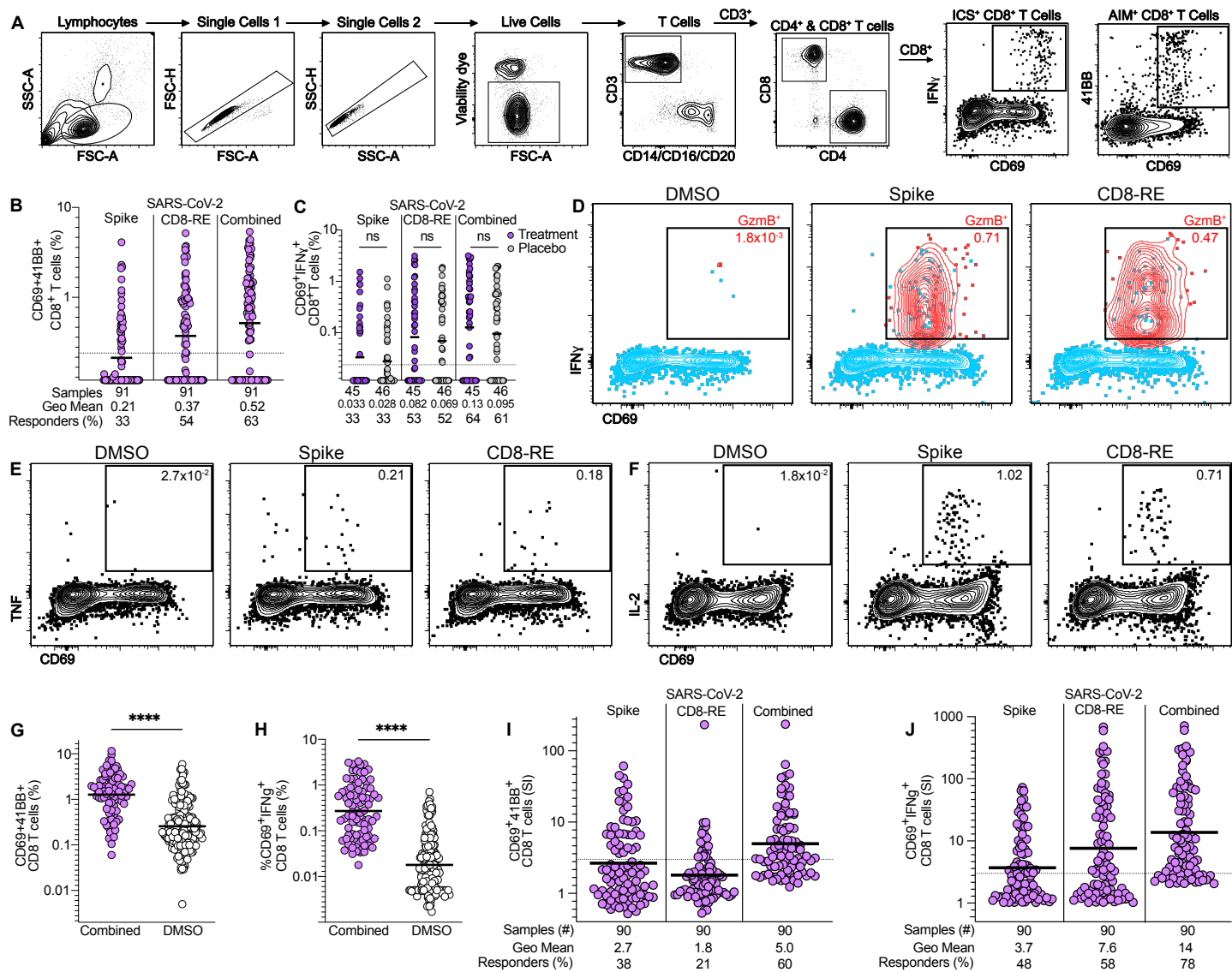


Figure S3. Antigen-specific CD8 T cell responses to primary SARS2 infection and acute COVID-19.

A. Gating strategy and representative flow cytometry gating for CD8 AIM and main ICS assay readouts. **B-C.** Study day 0 Spike, CD8-RE, or Combined CD8 responses by (B) AIM (CD69⁺41BB⁺) for all participants or (C) main ICS readout (CD69⁺IFN γ ⁺) by clinical trial assignment (bamlanivimab = "Treatment", saline = "Placebo"). Bars and lines as in Fig. 3. ns = not significant between Treatment and Placebo group by Mann-Whitney for comparison of the same stimulation condition. **D-F.** Representative flow cytometry gating and frequencies for other intracellular cytokine production by SARS2-specific surface CD69⁺ CD8 T cells for (D) GzmB (frequency of triple positive red cells out of total CD69⁺IFN γ ⁺; other cells shown in light blue), (E) TNF, (F) IL-2. **G-H.** % SARS2-specific of total CD8 T cells for MP stimulated conditions versus DMSO control conditions by (G) CD69⁺41BB⁺ and (H) CD69⁺IFN γ ⁺. **I-J.** Spike, non-Spike (CD8-RE) and total (Spike + CD8-RE = Combined) SARS2-specific CD8 T cells by (I) CD69⁺41BB⁺ and (J) CD69⁺IFN γ ⁺ by stimulation index (SI, fold-change relative to DMSO control; see Methods). ns = not significant, **** = $p \leq 0.0001$ by Mann-Whitney. **Related to Figure 3.**

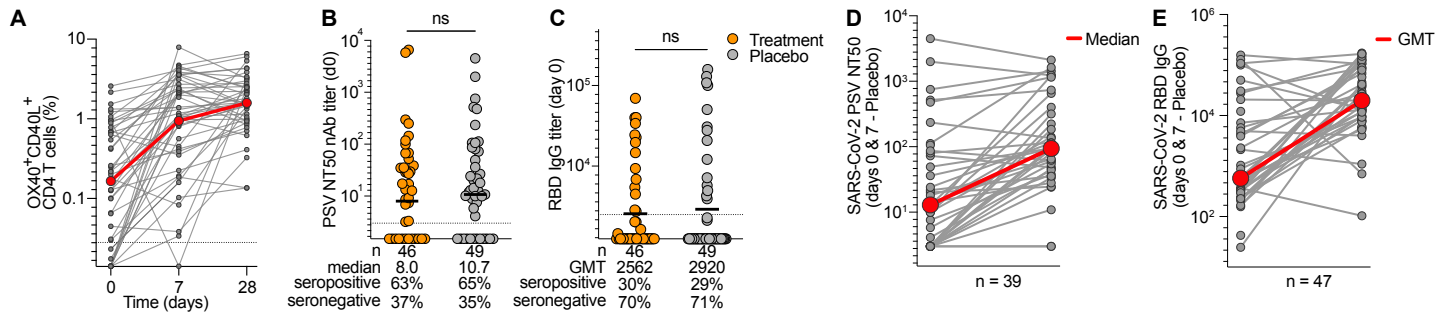


Figure S4. Humoral responses to primary SARS2 infection and acute COVID-19.

A. Longitudinal AIM⁺ CD4 T cell responses by surface OX40⁺CD40L⁺ in the placebo group (n = 49) at study days 0, 7, and 28. Red line is median for each time point. **B-C.** Day 0 (**B**) nAb titers and (**C**) RBD IgG titers by clinical trial assignment (bamlanivimab = "Treatment", saline = "Placebo"). **D-E.** Day 0 and 7 (**D**) nAb titers and (**E**) RBD IgG titers for the placebo group (n = 49) participants. Bars and lines as in **Fig. 4** unless labeled differently. **Related to Figure 4.**

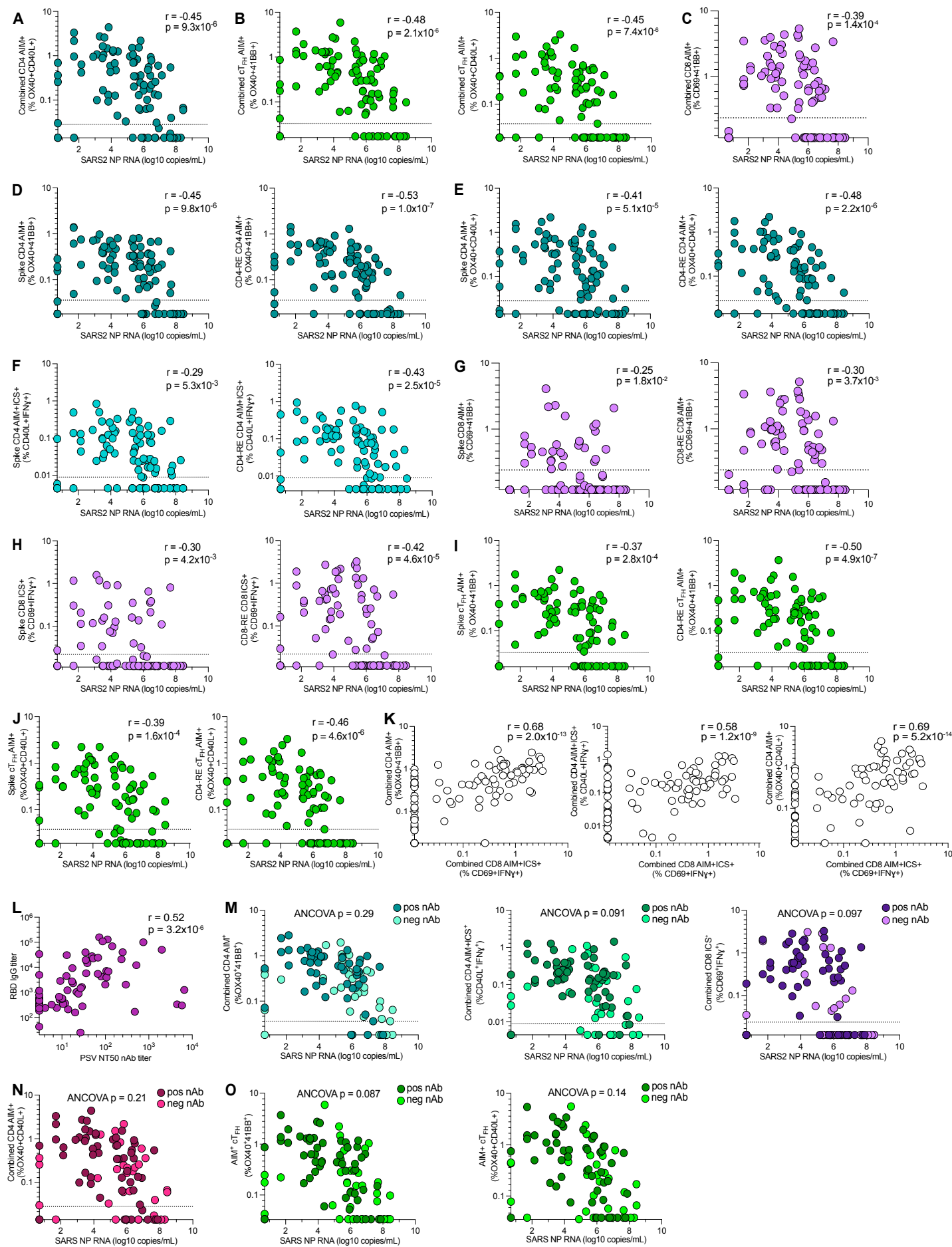


Figure S5. Unadjusted correlative relationships between virus-specific immune responses and upper airway SARS2 RNA levels. A-D. Correlation analyses similar to **Fig. 5A-C** but for study day 0 SARS2 NP RNA and SARS2-specific T cell responses by (A) CD4 T cell OX40⁺CD40L⁺ AIM; (B) circulating T_{FH} by OX40⁺41BB⁺ AIM or OX40⁺CD40L⁺ AIM; (C) CD8 T cell CD69⁺41BB⁺ AIM. **D-J.** Relationships for study day 0 SARS2 NP RNA and SARS2-specific T cell responses as in **Fig. 5A-C** and **Fig. S5A-C** split by responses to S or non-S MP stimulation for (D) CD4 T cell OX40⁺41BB⁺ AIM (E) CD4 T cell OX40⁺CD40L⁺ AIM, (F) CD4 T cell CD40L⁺IFN γ ⁺, (G) CD8 T cell CD69⁺41BB⁺ AIM, (H) CD8 T cell CD69⁺IFN γ ⁺, (I) circulating T_{FH} by OX40⁺41BB⁺ AIM, (J) circulating T_{FH} by OX40⁺CD40L⁺ AIM. **K.** Relationships between study day 0 SARS2-specific combined CD4 and CD8 responses by AIM and/or ICS. **L.** Relationship between day 0 nAb and RBD IgG titers. **M-O.** Impact of study day 0 nAb serostatus on relationships between study day 0 T cell responses and SARS2 NP RNA shown in **Fig. S5B** (O for circulating T_{FH}), **Figs. 5A-C** and **Fig. S5A** (M and N for total CD4 and CD8) by ANCOVA. All correlations by two-tailed nonparametric testing; r = Spearman's rank correlation coefficient. **Related to Figure 5.**

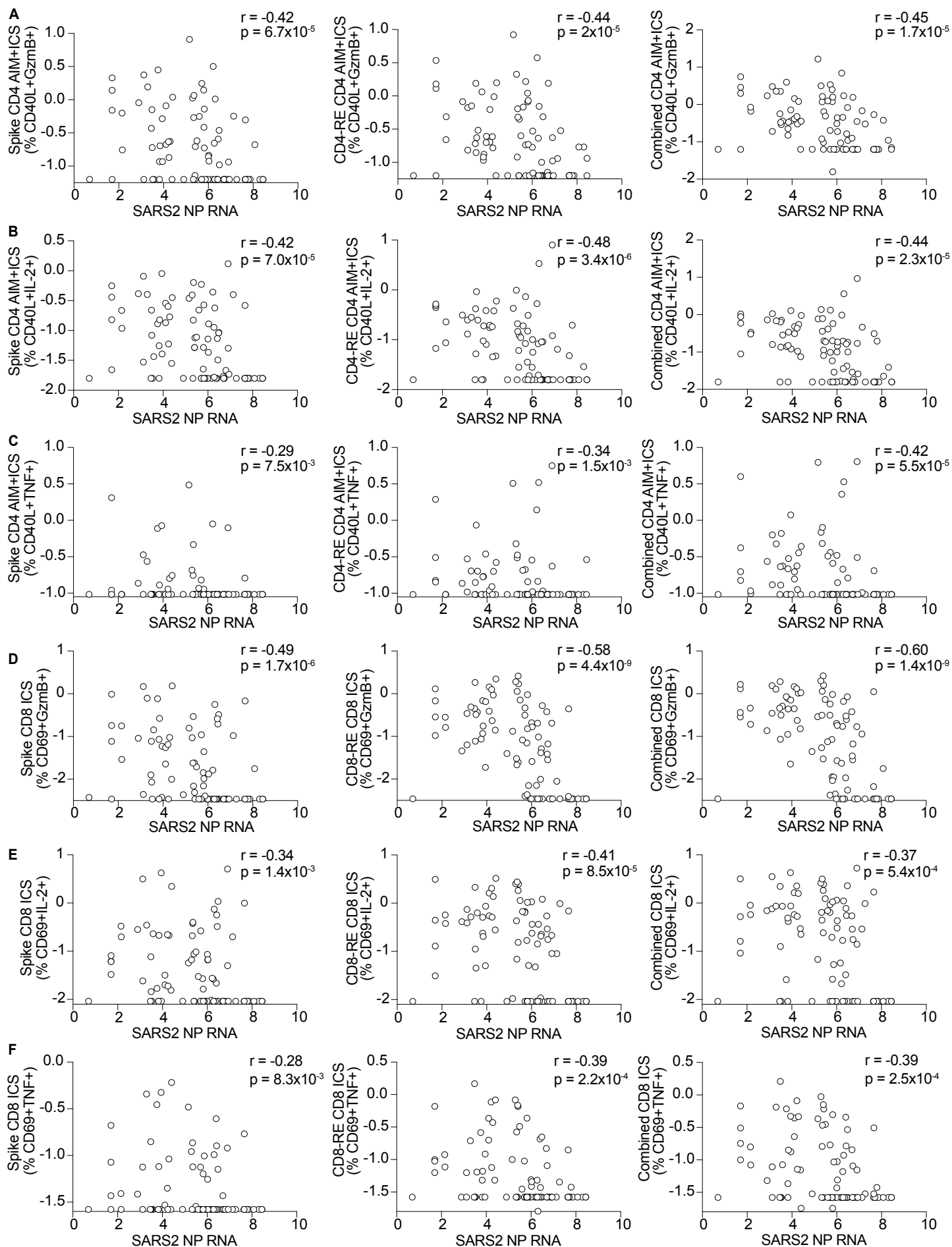


Figure S6. Additional unadjusted correlative relationships between SARS2-specific T cell cytokine production and SARS2 NP RNA levels. A-C. Correlation analyses for study day 0 SARS2 NP RNA and SARS2 Spike (left), non-Spike (CD4-RE; middle), and combined (right) CD4 T cell cytokine production by CD4 T cell AIM+ICS: **(A)** CD40L⁺GzmB⁺ **(B)** CD40L⁺IL-2⁺ **(C)** CD40L⁺TNF⁺. **D-F.** Correlation analyses for study day 0 SARS2 NP RNA and SARS2 Spike (left), non-Spike (CD8-RE; middle), and combined (right) CD8 T cell cytokine production by CD8 T cell ICS: **(D)** CD69⁺IFN γ ⁺GzmB⁺, **(E)** CD69⁺IL-2⁺, **(F)** CD69⁺TNF⁺. All correlations by two-tailed nonparametric testing; r = Spearman's rank correlation coefficient. **Related to Figure 5.**

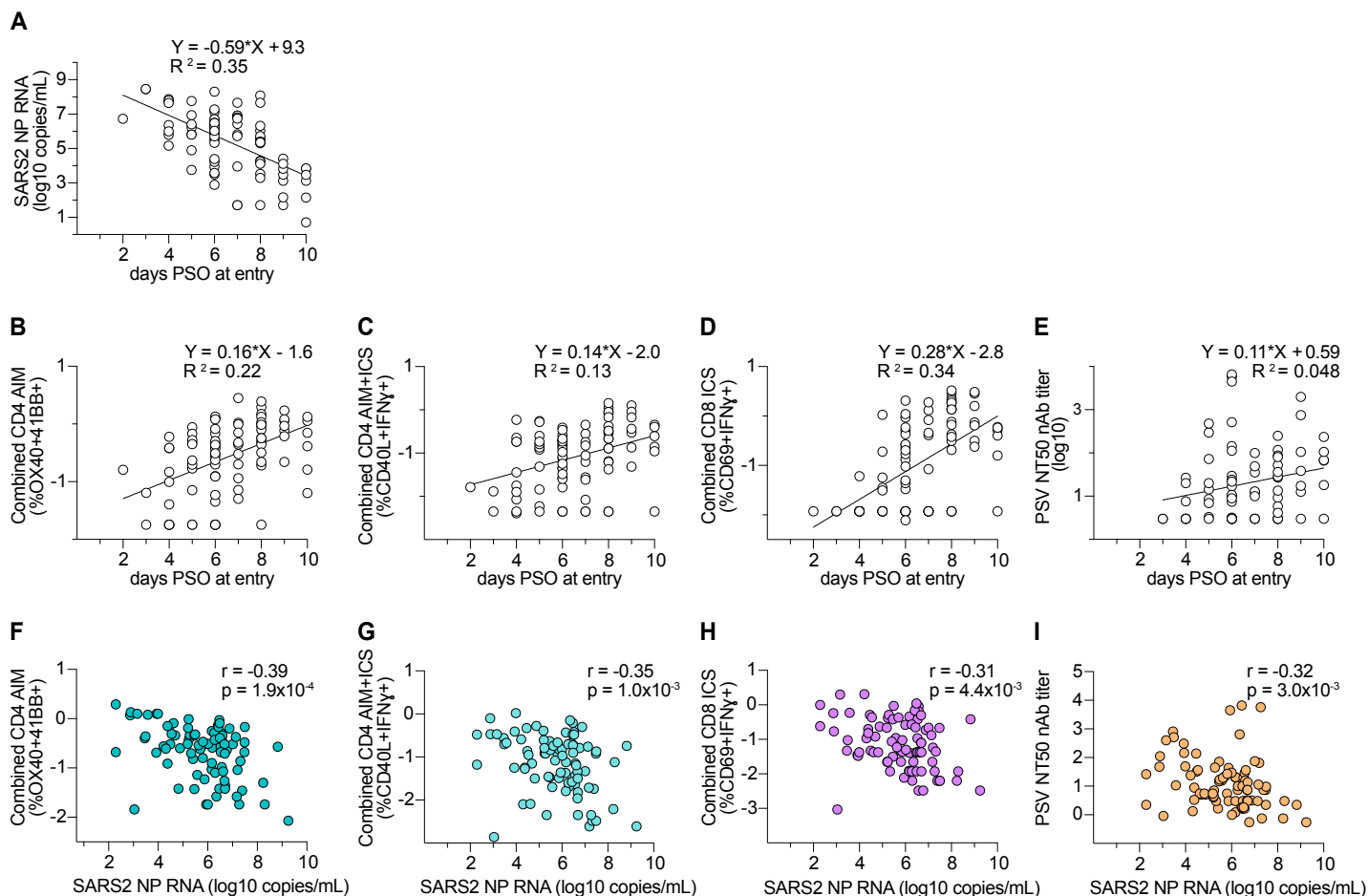


Figure S7. Adjusted correlative relationships between virus-specific immune responses and upper airway SARS2 RNA levels.

A-E. Log-linear regression models to account for variance in days from COVID-19 symptom onset to study entry (study day 0) for (A) SARS2 NP viral RNA, (B-C) SARS2-specific CD4 T cell responses, (D) SARS2-specific CD8 T cell responses, (E) and SARS2 nAb titers. Days post-symptom onset (PSO) at study day 0 values were plotted versus (A) SARS2 NP viral RNA or (B-E) immune responses at study day 0. Linear regression equations used for adjusted correlation analyses in **F-I** are shown. All immune response values in B-E were transformed to log₁₀. **F-I.** Correlation analyses as in **Fig. 5A-D** for SARS2 NP RNA and SARS2-specific T cell responses by (F) CD4 AIM⁺, (G) CD4 IFNγ, (H) CD8 IFNγ, and (I) nAb titers. In **F-I**, adaptive immune response values were adjusted to day 6 PSO using the related log-linear regression lines shown in **B-E** and plotted versus the corresponding adjusted day 6 PSO SARS2 NP RNA values generated from **A**. All correlations by two-tailed nonparametric testing; r = Spearman's rank correlation coefficient. **Related to Figure 5.**

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SUPPLEMENTAL TABLES

Table S1. Antibodies used (from Ref. 21)

Marker-Fluorophore	Clone	Vendor	Catalog #	Assay
Fixable live/dead blue	N/A	Thermo Fisher	L34962	AIM, AIM+ICS
CD3-BUV395	UCHT1	BD	563546	AIM, AIM+ICS
CD4-cFluor B548	SK3	Cytek	SKU R7-20044	AIM, AIM+ICS
CD8a-BUV805	SK1	BD	612889	AIM, AIM+ICS
CD14/CD16/CD20-BV510	63D3/3G8/2H7	BioLegend	367123/302048/302340	AIM, AIM+ICS
CD45RA- BV570	HI100	BioLegend	304132	AIM, AIM+ICS
CCR7-BV711	G043H7	BioLegend	353228	AIM
CCR7-PE-Cy7	G043H7	BioLegend	353226	AIM+ICS
OX40-APC	Ber-Act35	BioLegend	350008	AIM
OX40-APC/Fire750	Ber-Act35	BioLegend	350031	AIM+ICS
CD137-BUV737	4B4-1	BD	568348	AIM
CD137-PE-Cy5	4B4-1	BioLegend	309808	AIM+ICS
CD40L-PE/Dazzle594	24-31	Biolegend	310840	AIM
CD40L-PerCP-eF710	24-31	Thermo	46-1548-42	AIM+ICS
CD25-APC/Fire750	BC96	BioLegend	302642	AIM
CD25-BV650	BC96	BioLegend	302634	AIM+ICS
CD69-FITC	FN50	BioLegend	310904	AIM
CD69-BV605	FN50	BioLegend	310938	AIM+ICS
CCR6-BUV496	11A9	BD	612948	AIM
ICOS-BUV563	DX29	BD	741421	AIM
CXCR5-BV421	J252D4	BioLegend	356920	AIM
CXCR3-BV605	G025H7	BioLegend	353728	AIM
CD38-BV650	HB-7	BioLegend	356620	AIM
PD-1-BV785	EH12.2H7	BioLegend	329930	AIM
CD95	DX2	BD	566542	AIM
PD-L1-PE	29E.2A3	BioLegend	329706	AIM
HLA-DR-APC-R700	Tu39	BD	746979	AIM
CCR4-PE-Cy7	L291H4	BioLegend	359410	AIM+ICS
IFN γ -AF488	4S.B3	BioLegend	502515	AIM+ICS
IL-2-BB700	MQ1-17H12	BD	566405	AIM+ICS
IL-4-BUV737	MP4-25D2	BD	612835	AIM+ICS
IL-10-PE/Dazzle594	JES3-19F1	BioLegend	506812	AIM+ICS
IL-17a-BV785	BL168	BioLegend	512338	AIM+ICS
IL-21-PE	4BG1	BioLegend	516704	AIM+ICS
GzmB-AF647	GB11	Biolegend	515406	AIM+ICS
TNF α -eF450	Mab11	eBioscience	48-7349-42	AIM+ICS