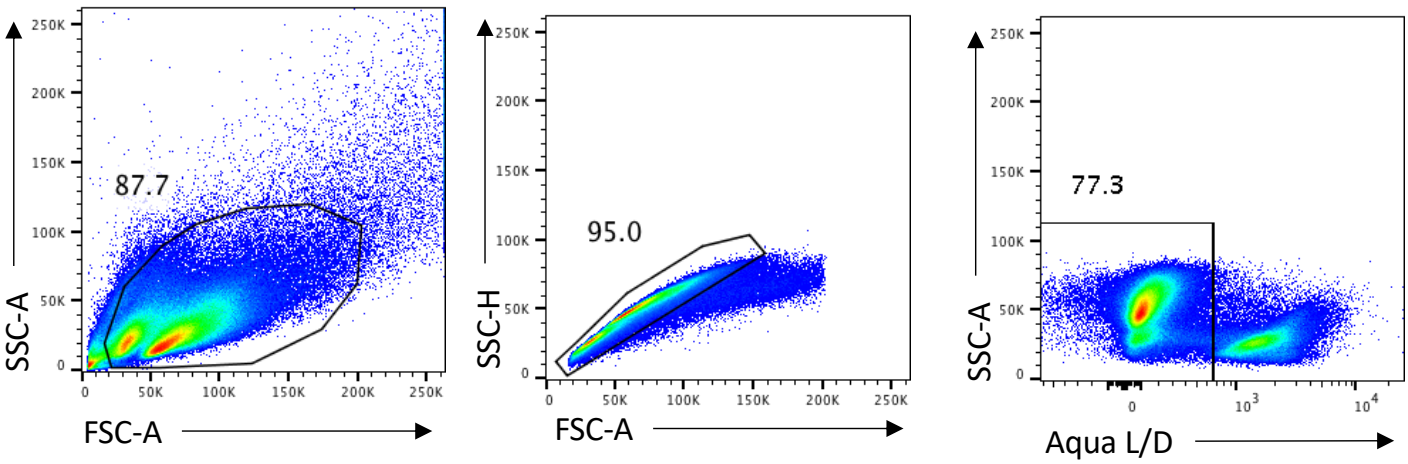
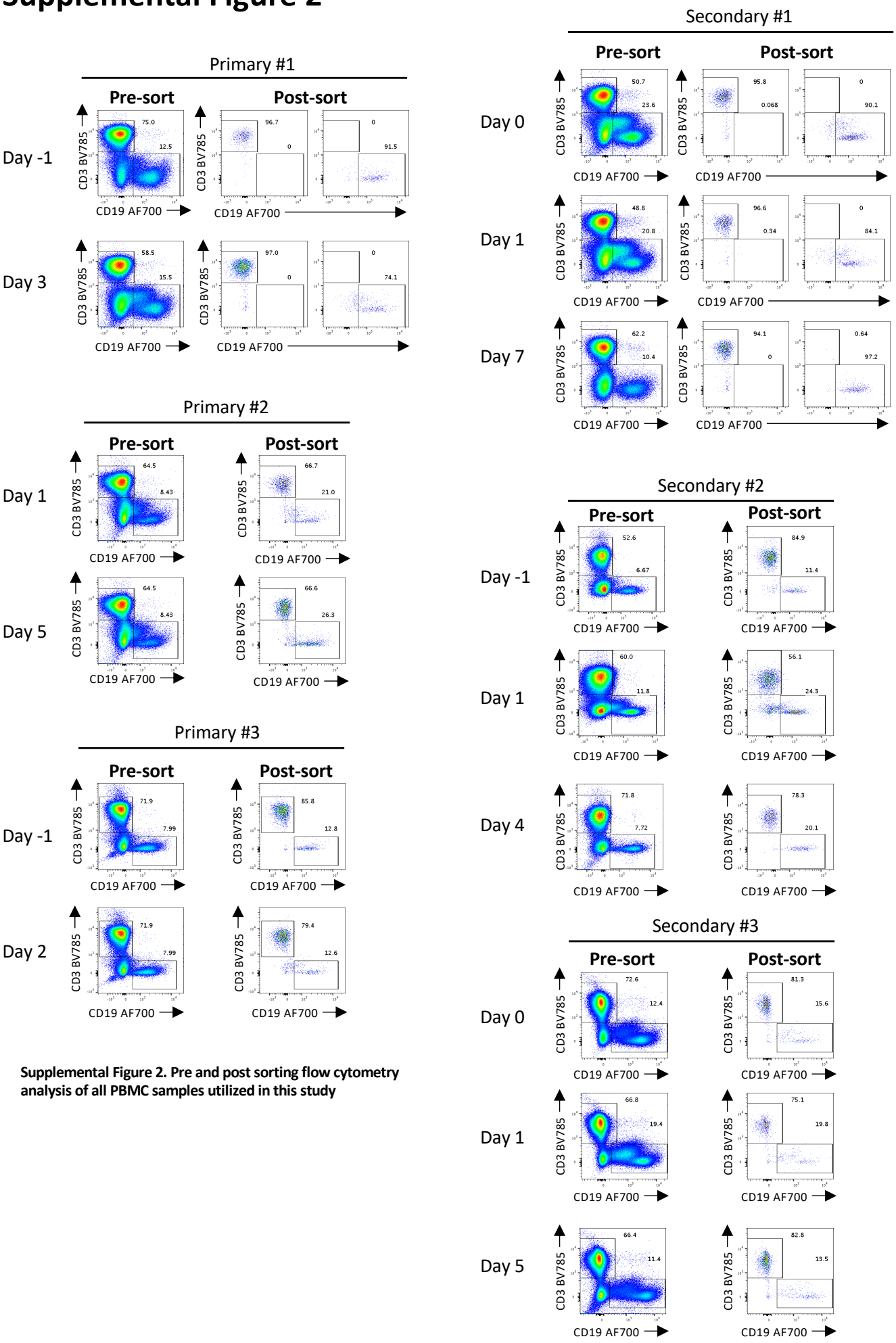
Supplemental Figure 1



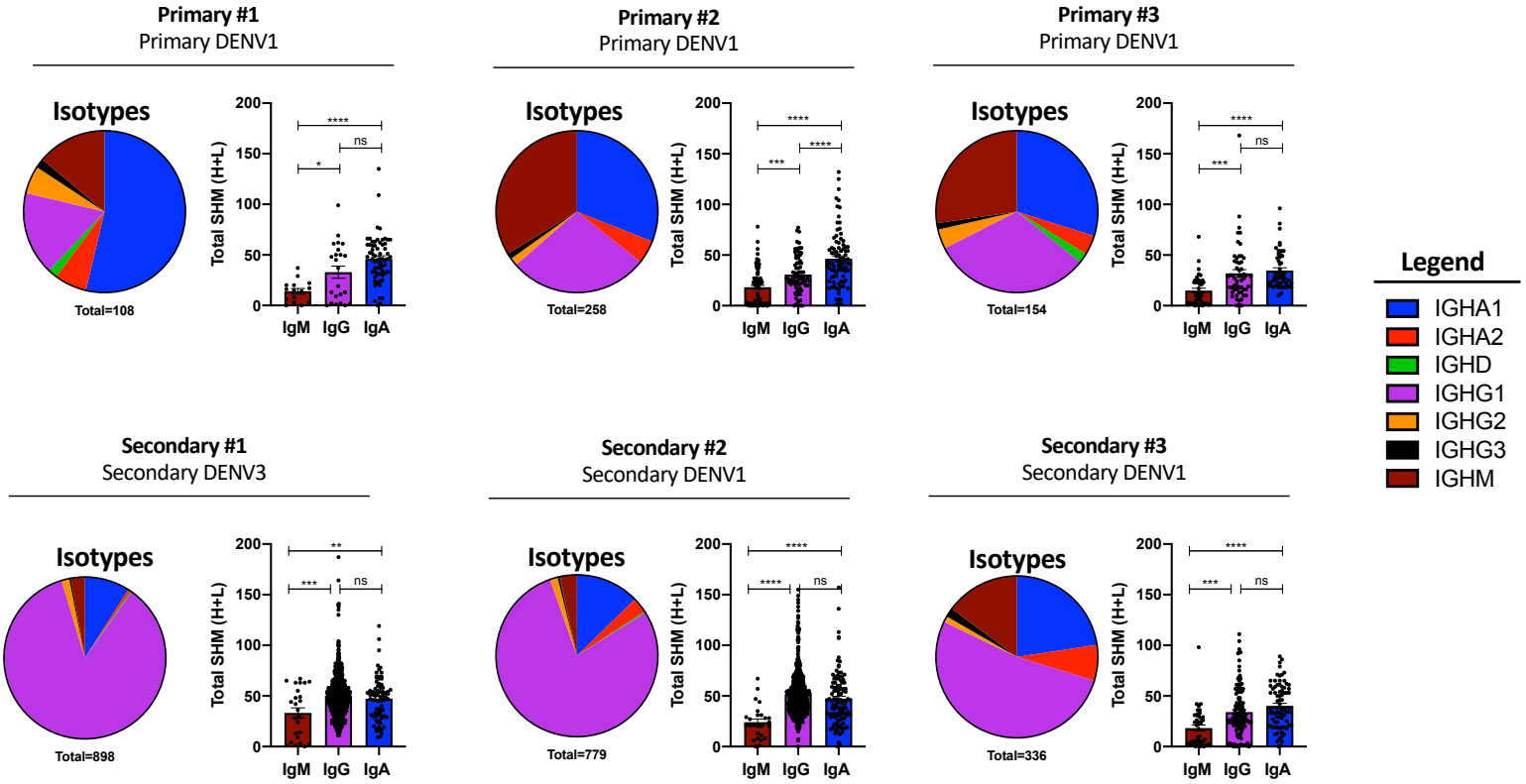
Supplemental Figure 1. Gating strategy for Figure 1B and Supplemental Figure 2

Supplemental Figure 2



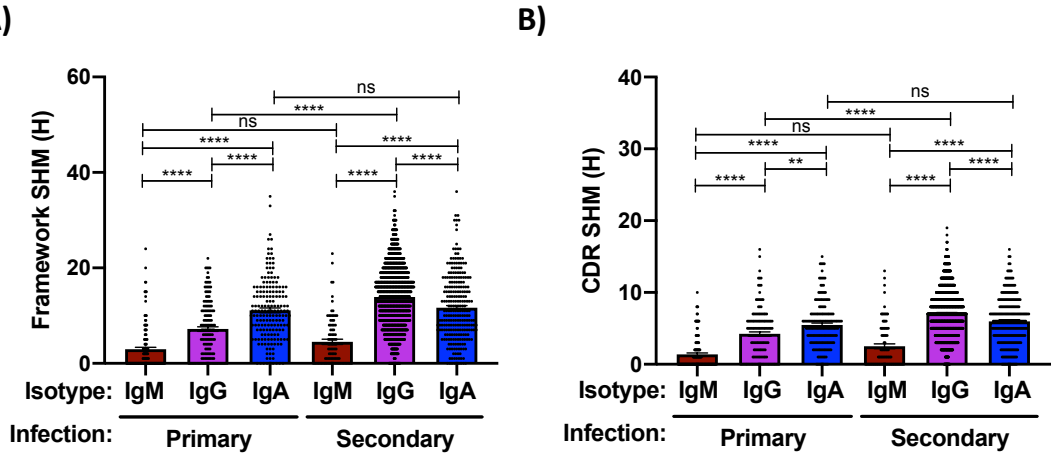
Supplemental Figure 2. Pre and post sorting flow cytometry analysis of all PBMC samples utilized in this study

Supplemental Figure 3



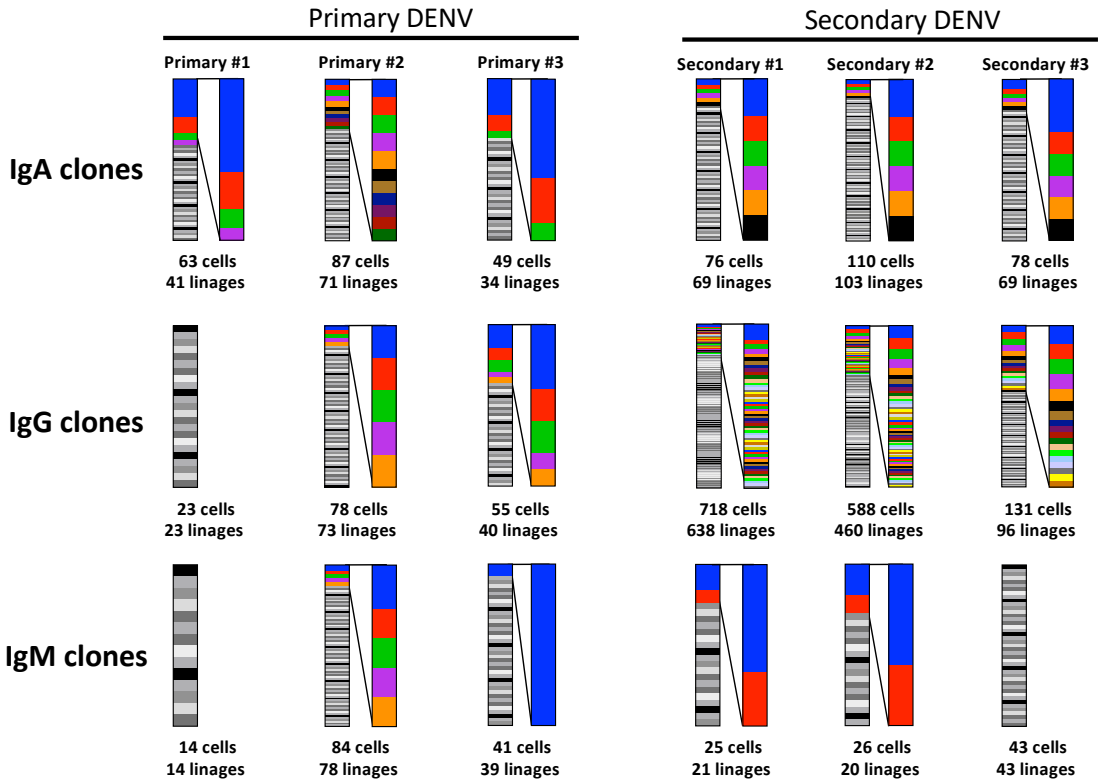
<u>Supplemental Figure 3.</u> Isotype distribution and somatic hypermutation burden of immunoglobulins expressed by circulating B cell plasmablasts during primary and secondary natural DENV infection. Immunoglobulin sequence analysis was restricted to cells from which both a full-length heavy/light chain was successfully isolated and annotated by scRNAseq. Isotype distribution and hypermutation burden of immunoglobulins expressed by transcriptionally defined plasmablasts phenotype B cells within all subjects in all time points captured in the dataset. Plasmablasts and pre-plasmablasts are merged for this analysis. Analysis split by subject, and hypermutation burden split by isotype. Error bars +/- SEM. * p <0.05, ** p <0.01, *** p <0.001, **** p <0.0001, one-way ANOVA

Supplemental Figure 4



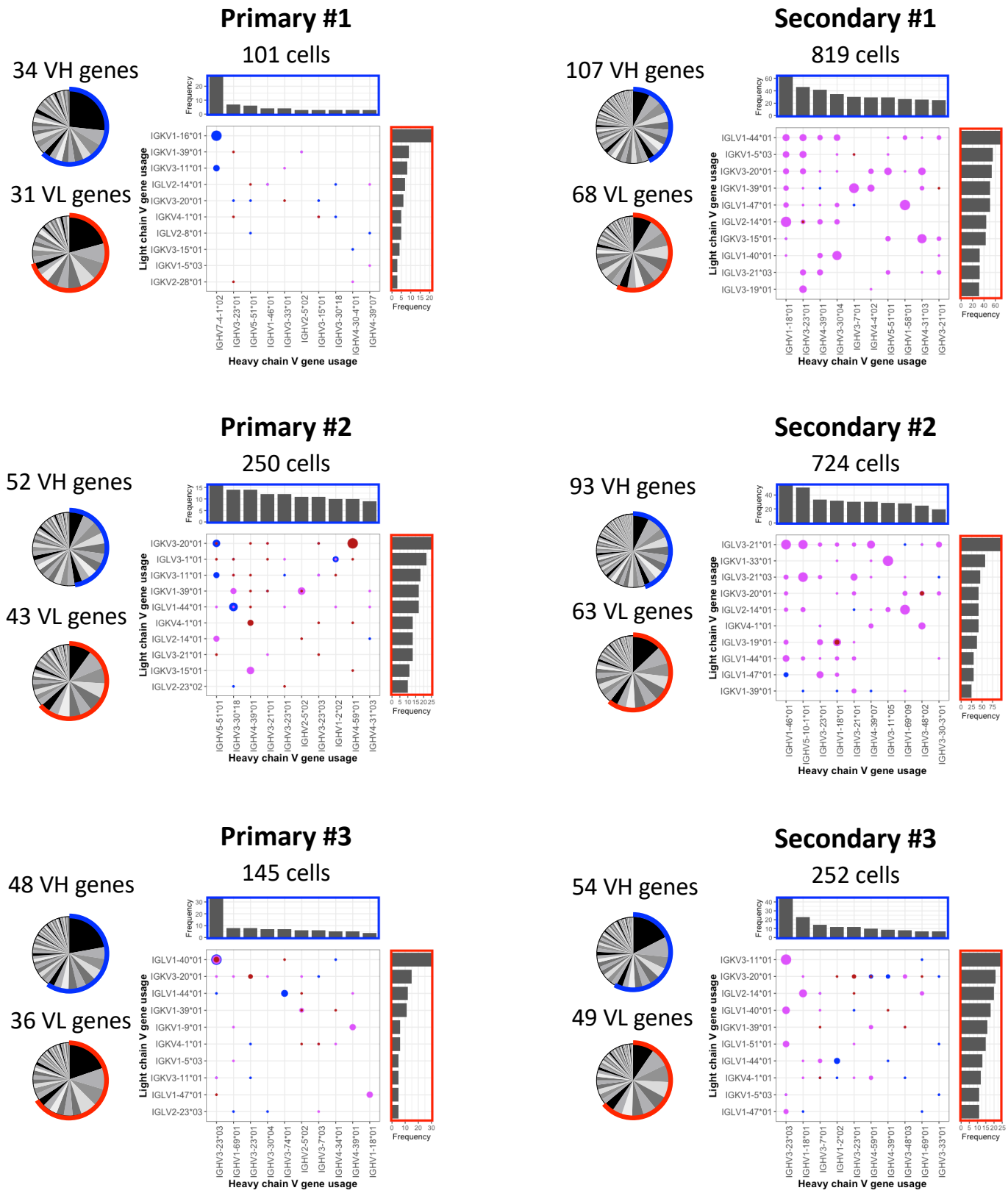
Supplemental Figure 4. Somatic hypermutation burden of the framework and CDR regions of immunoglobulin heavy chains expressed by circulating plasmablasts during primary and secondary natural DENV infections Immunoglobulin sequence analysis was restricted to cells from which a full-length heavy/light chain pair was successfully isolated and annotated by scRNAseq. **A)** Immunoglobulin heavy chain framework region somatic hypermutation (SHM) burden of immunoglobulins expressed by plasmablasts from all subjects at all time points captured in this analysis. Analysis split by isotype. **B)** Immunoglobulin heavy chain CDR region somatic hypermutation (SHM) burden of immunoglobulins expressed by plasmablasts from all subjects at all time points captured in this analysis. Analysis split by isotype. Error bars +/- SEM. ** p <0.01, **** p <0.0001, one-way ANOVA.

Supplemental Figure 5



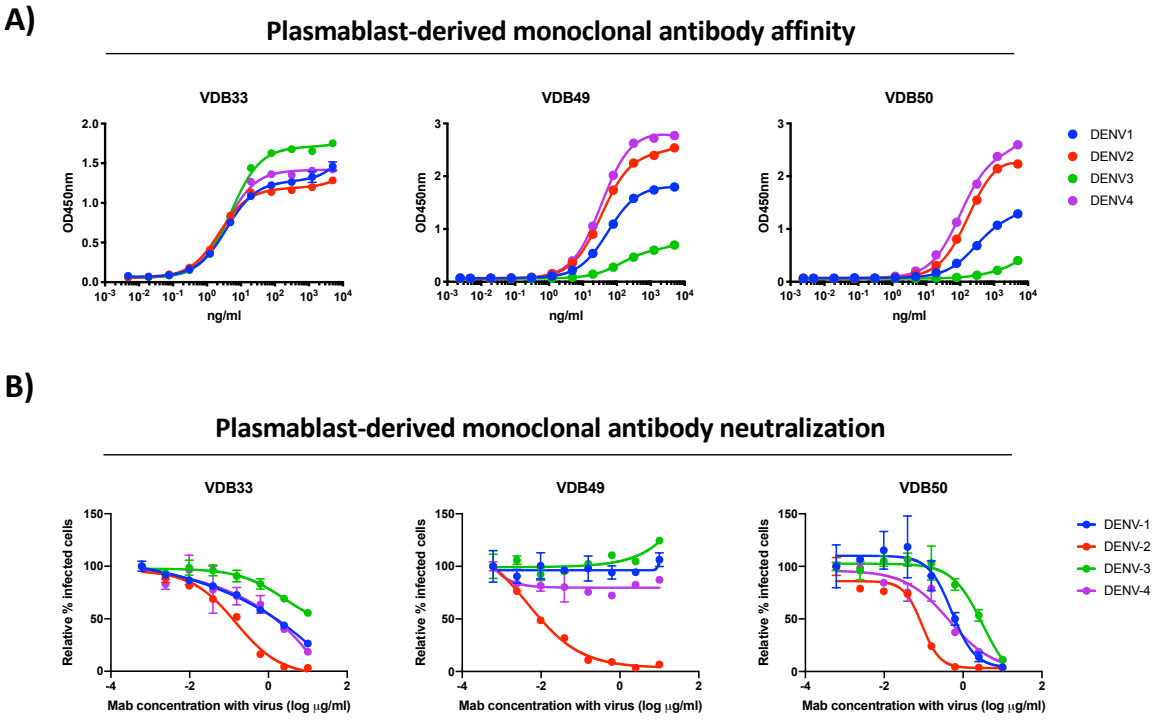
<u>Supplemental Figure 5.</u> Clonal diversity of DENV-elicited plasmablasts from primary or secondary DENV infection. Each line segment indicates a unique clonal linage from the indicated individual. Colored segments indicate expanded clones. Clones binned and analyzed by the indicated isotype.

Supplemental Figure 6



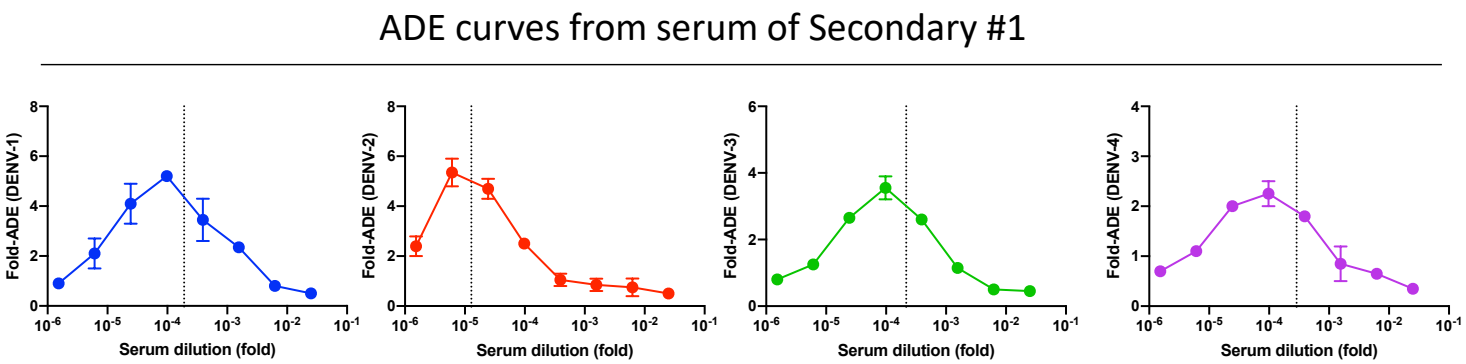
Supplemental Figure 6. Paired heavy/light chain variable region gene segment usage in plasmablasts from primary and secondary DENV infection. Pie charts indicate the relative frequency of VH/VL gene segment usage within the plasmablast population from each subject. Colored arc highlights the 10 most frequently used gene segments within each individual. Histograms and dot plots indicate the 10 most abundant gene segments used within each individual, and the frequency with which the gene segments were used together. Dot plot color indicates antibody isotype. Dot plot color key: Pink = IgG, blue = IgA, red = IgM

Supplemental Figure 7



<u>Supplemental Figure 7.</u> Representative DENV-capture ELISA and FlowNT curves generated from plasmablast-derived monoclonal antibodies. A) Representative ELISA plots demonstrating plasmablast-derived Mab specificity and avidity against DENV1-4. Lines indicates one-site total binding as calculated by non-linear regression curve. Error bars indicate +/- SEM **B)** Representative FlowNT plots demonstrating plasmablast-derived Mab neutralization capacity against DENV1-4. Graphed curves indicate one-site total binding as calculated by non-linear regression curve. Error bars indicate +/- SEM

Supplemental Figure 8



Supplemental Figure 8. ADE potential of early-convalescent serum obtained from subject CHD07-012 against DENV-1, -2, -3, and -4. All values are shown as fold-increased infection above no antibody. Dashed line indicates serum IC_{50} as determined by FlowNT using the same viral preparation as used in the ADE assay. Error bars indicate +/- SEM.