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Supplemental information

Evasion of neutralizing antibody responses by the SARS-CoV-2 BA.2.75 variant

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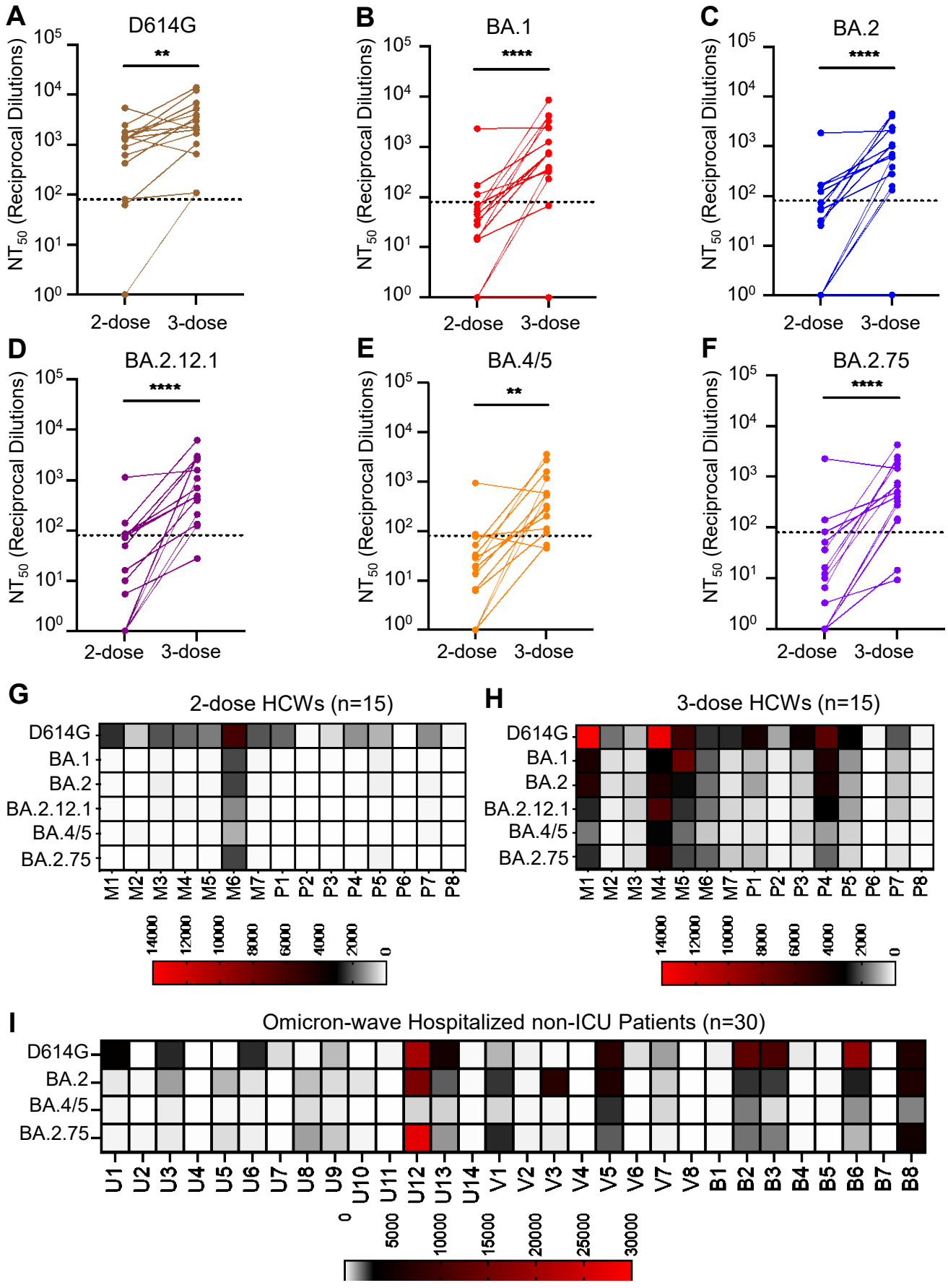

Figure S1: Neutralization of Omicron subvariants by vaccinee and COVID-19 patient sera, related to Figure 1. (**A-F**) Comparison of the neutralizing antibody titers in HCWs between 2-dose and 3-dose booster mRNA vaccination against the D614G (A), BA.1 (B), BA.2 (C), BA.2.12.1 (D), BA.4/5 (E), and BA.2.75 (F) variants. Lines connect samples from the same HCW, the dotted lines represent the limit of quantification (NT_{50} = 80), and significance was determined by paired, two-tailed Student's t

test with Welch's correction. (**G-I**) Heatmaps display the nAb titers for HCWs 3-4 weeks after second mRNA vaccine dose (G), 1-12 weeks after mRNA vaccine booster dose (H), and for hospitalized Omicron wave COVID-19 patients (I). HCWs are indicated as 'M' for Moderna mRNA-1273 vaccinated or 'P' for Pfizer/BioNTech BNT162b2 vaccinated, and Omicron wave patients are indicated as 'U' for unvaccinated, 'V' for 2-dose vaccinated, and 'B' for vaccinated and boosted. P-values are represented as **$p < 0.01$ and ****$p < 0.0001$.

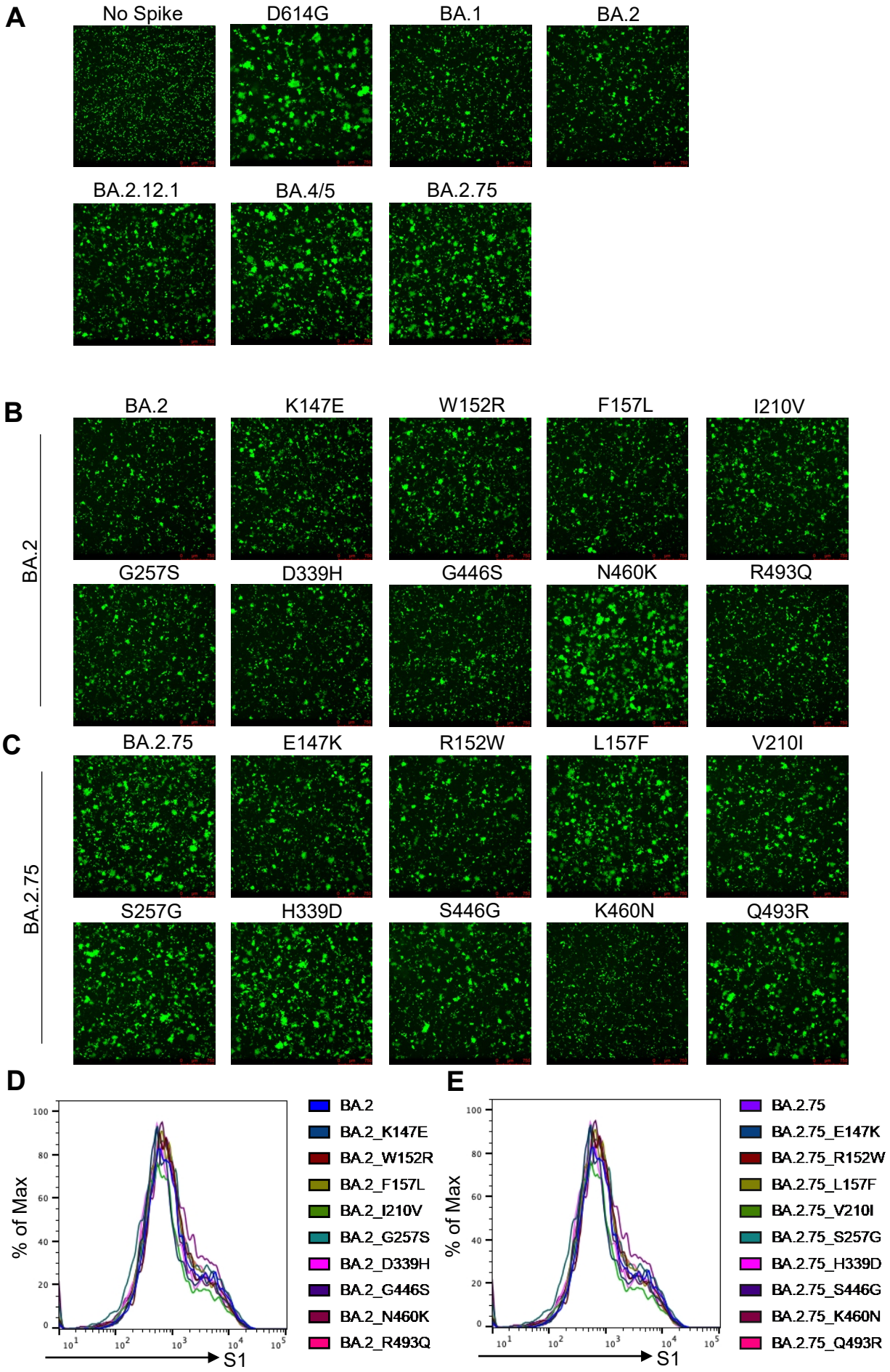

Figure S2: Syncytia formation and cell surface expression of Omicron subvariants, as well as BA.2- and BA.2.75-derived single mutants, related to Figures 3 and 4. (**A-C**) Fluorescence images

displaying syncytia formation are presented for HEK293T-ACE2 cells 24 hr after co-transfection with a GFP expression construct and SARS-CoV-2 variant S proteins (A), BA.2 single mutants S proteins (B), or BA.2.75 single reversion mutant S proteins (C). Scale bars represent 150 μm. (**D-E**) Histograms of surface staining with anti-S1 antibody of HEK293T cells expressing S proteins from BA.2 with single mutations from BA.2.75 lineage defining mutations (D) and from BA.2.75 with single reversion mutations from BA.2.75 lineage defining mutations (E).

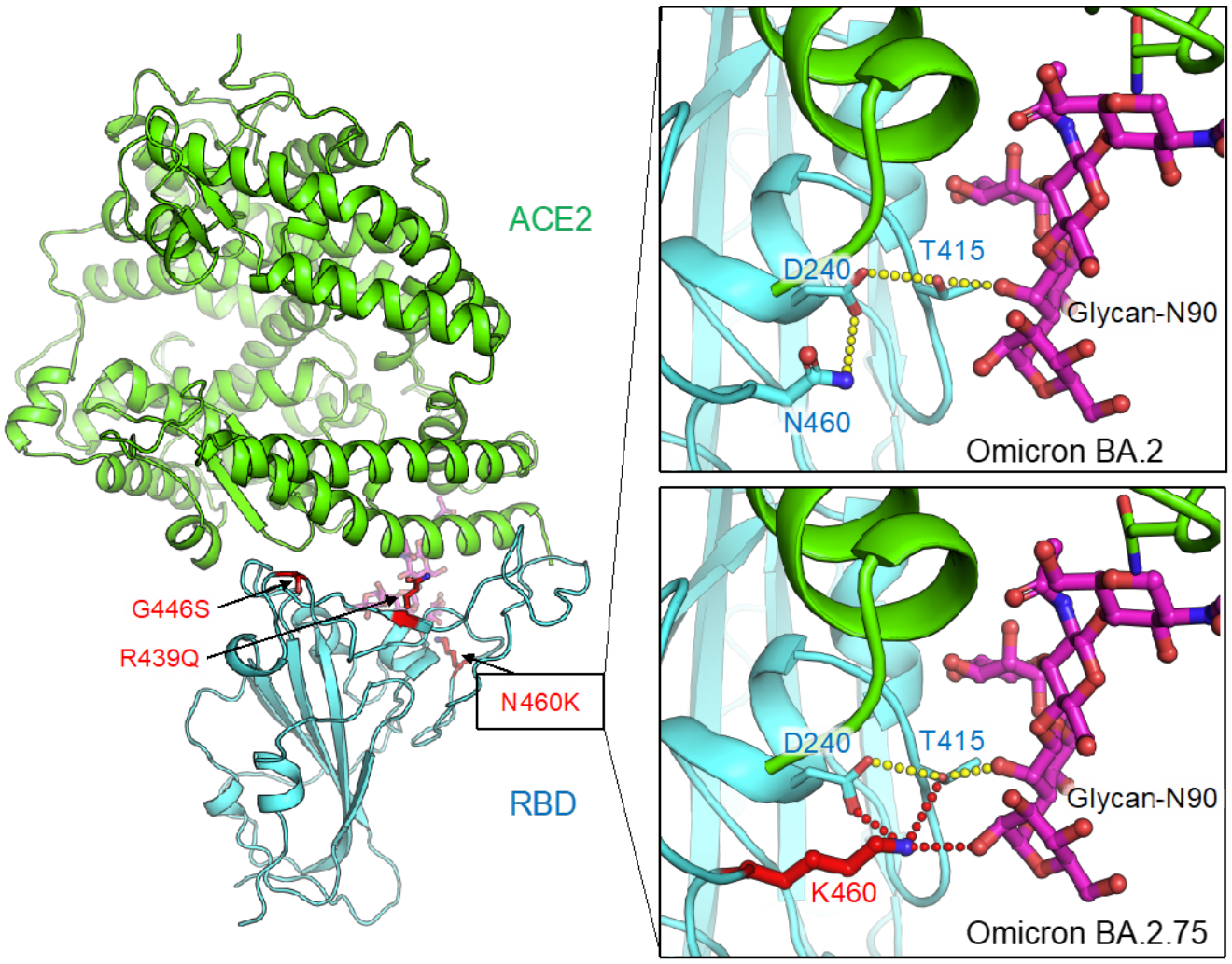

Figure S3: Structural modeling of SARS-CoV2 Omicron BA.2.75 RBD-ACE2 complex, related to Figure 4. Structural homology model of Omicron BA.2.75 RBD-ACE2 complex viewed as ribbon. Upper inset: The RBD residues N460-D240-T415 and hACE2 glycan N-90 form hydrogen bond network. Lower inset: the mutation N460K enhances this hydrophilic interaction network by forming salt-bridge with D240 and two additional hydrogen bonds with T415 and glycan-N90 on hACE2. Hydrogen bonds and salt bridges were shown as dashes and colored in yellow (present in BA.2) and red (present only in BA.2.75).