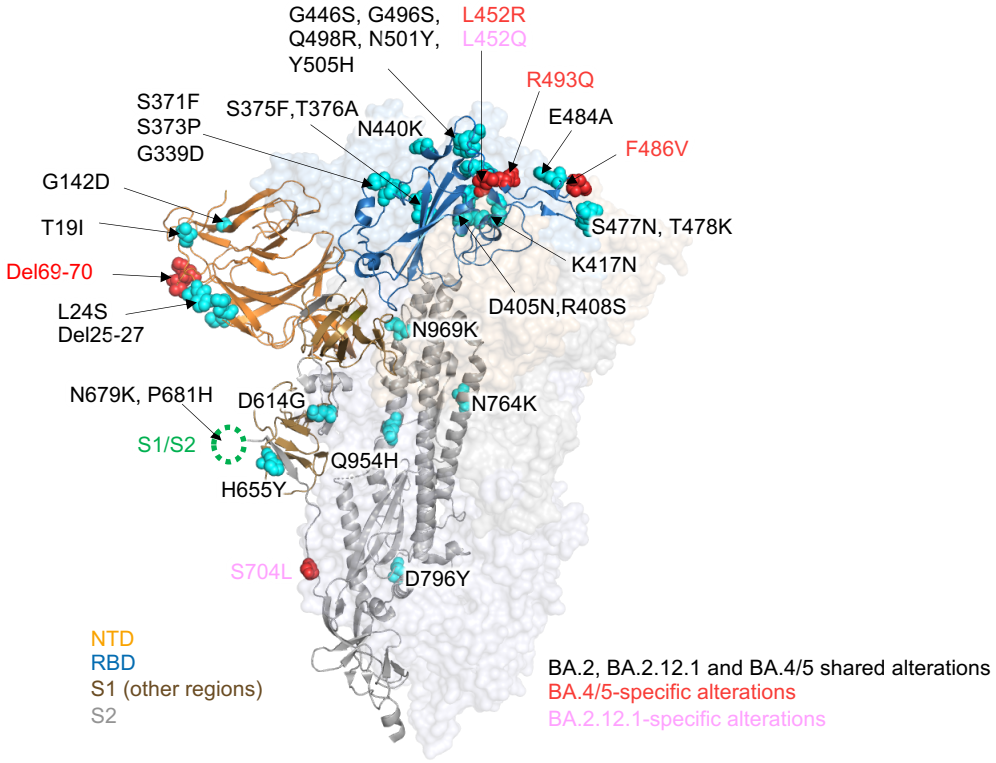
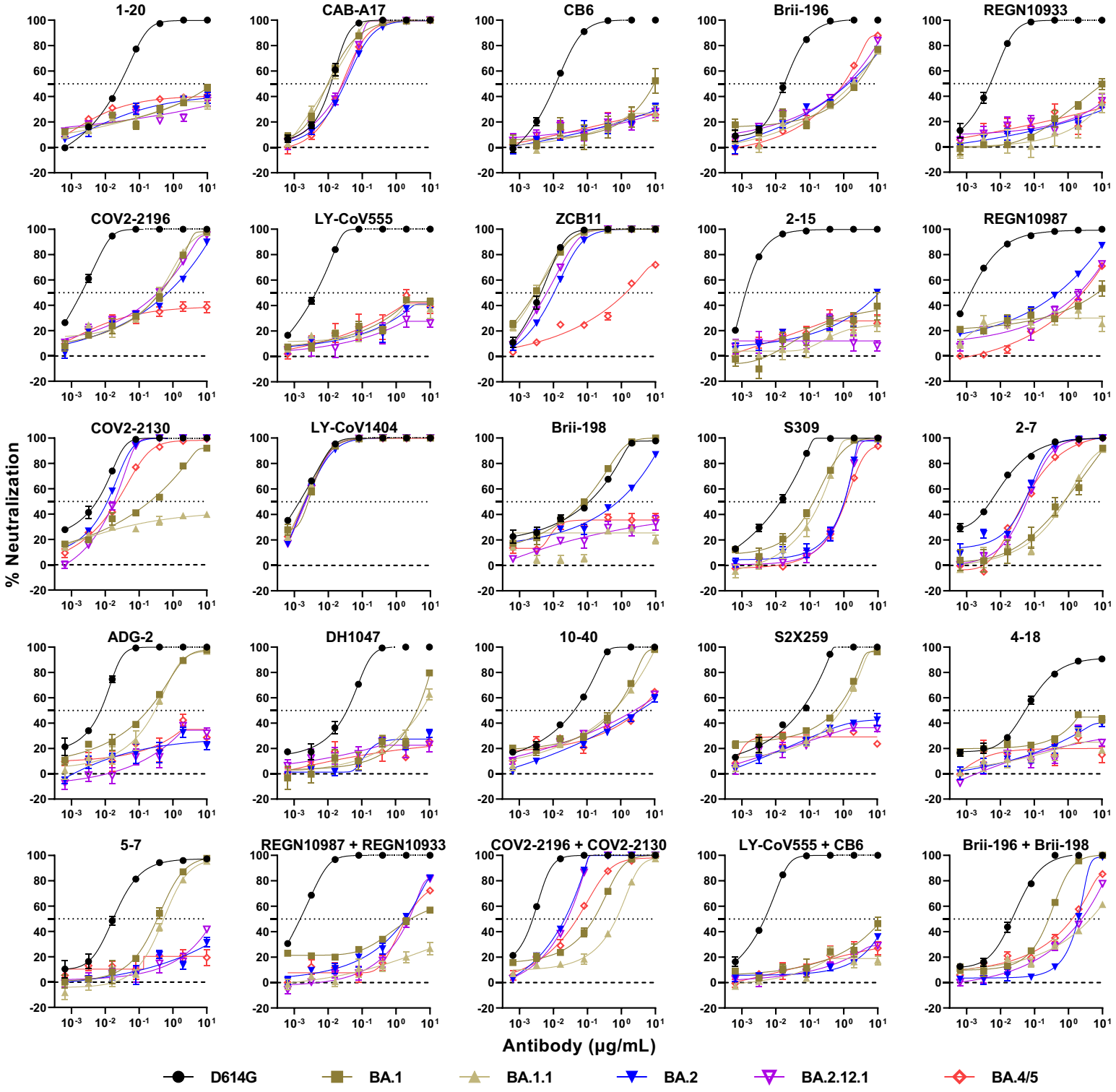


Extended Data Fig. 1 | Mutations within BA.2, BA.2.12.1 and BA.4/5 denoted on the full SARS-CoV-2 spike trimer. The green circle shows the S1/S2 cleavage site. The SARS-CoV-2 spike structure was downloaded from PDB 6ZGE.

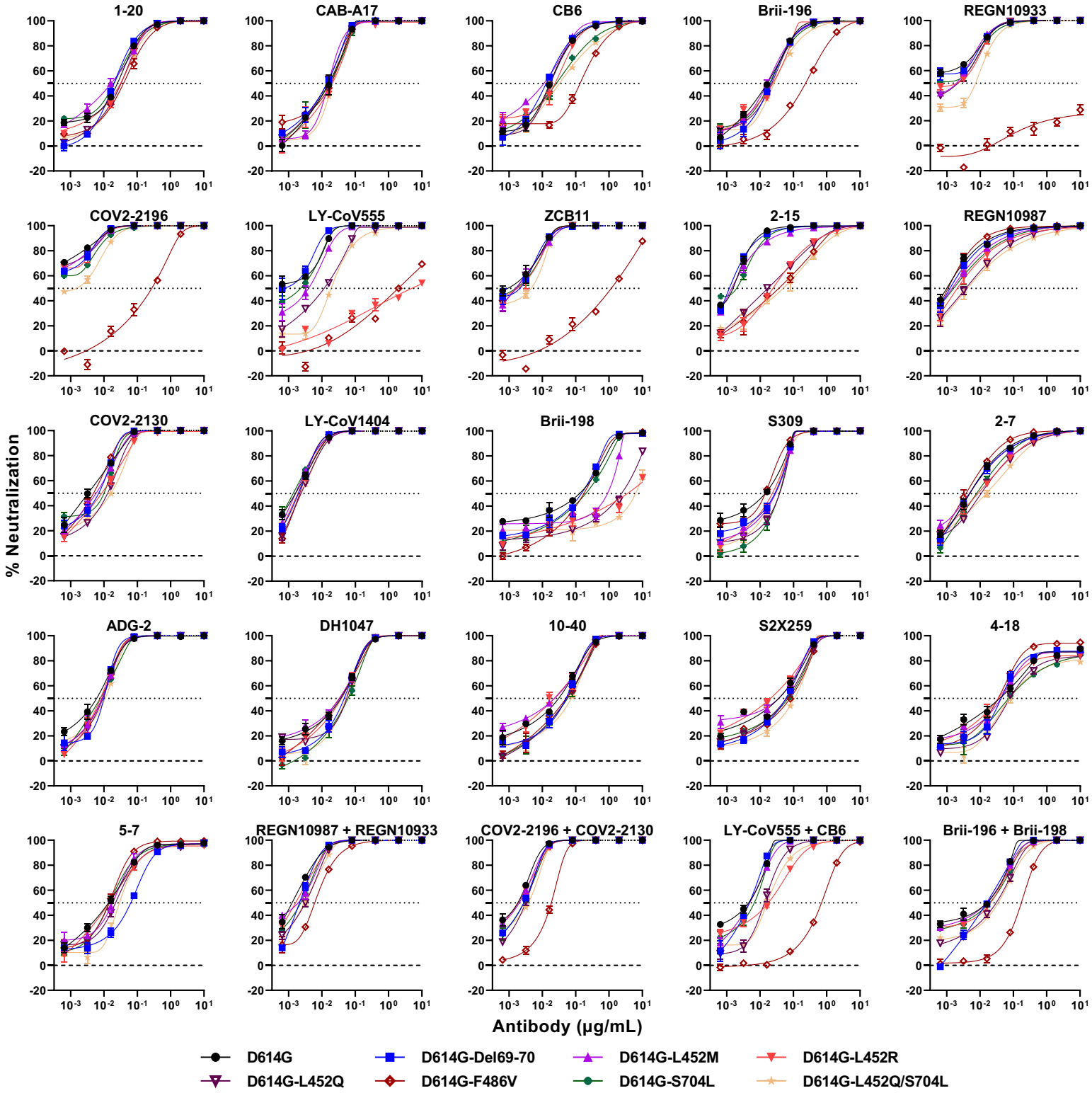


Extended Data Fig. 2 | Pseudovirus neutralization curves of D614G and Omicron subvariants by monoclonal antibodies. Data are shown as mean ± standard error of mean (SEM) from three technical replicates.

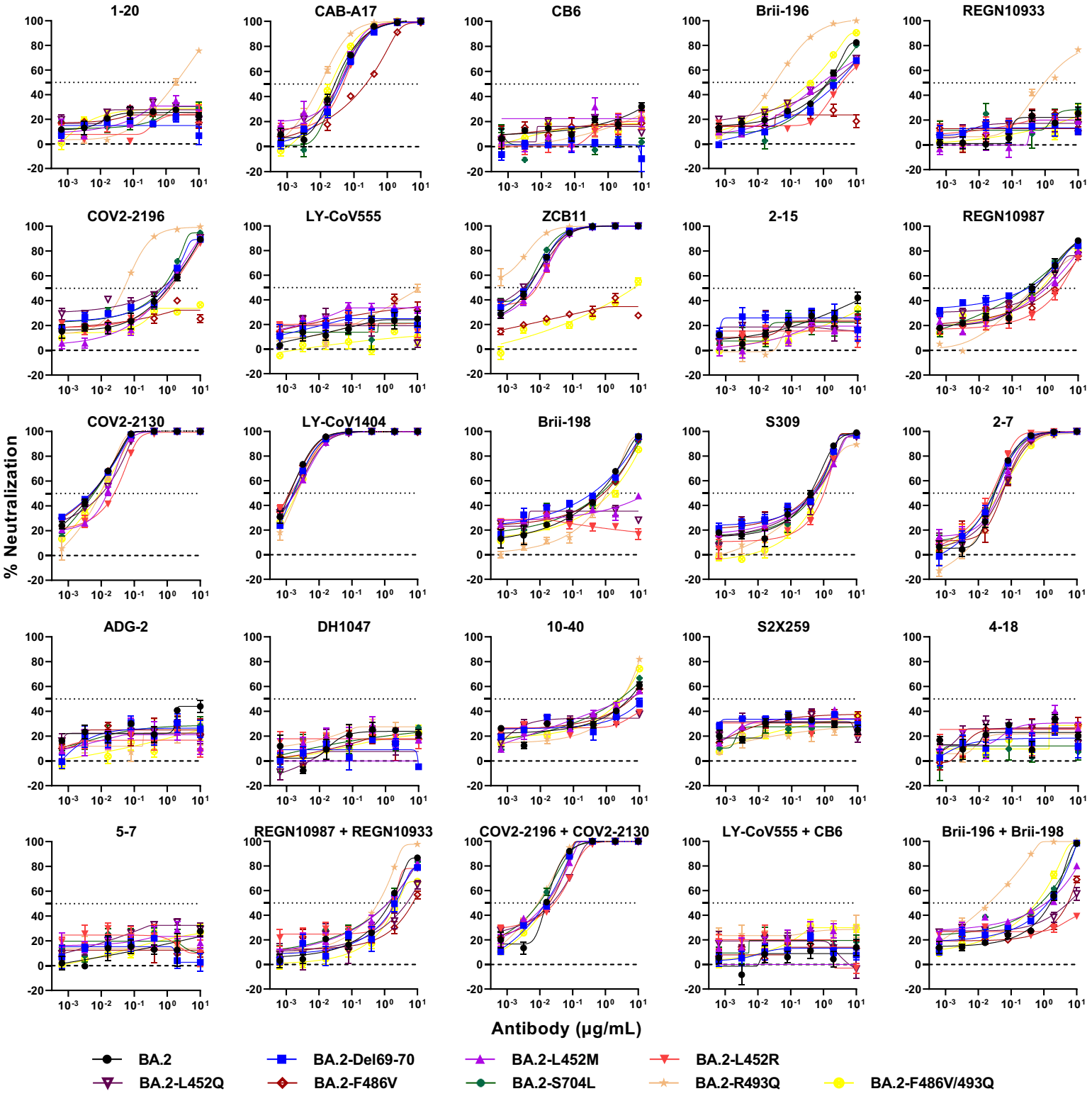
IC_{50} (μg/mL)	RBD mAbs																			NTD mAbs		Combination			
	Class 1				Class 2					Class 3						Class 4									
	1-20	CAB-A17	CB6	Brii-196	REGN 10933	COV2-2196	LY-CoV555	ZCB11	2-15	REGN 10987	COV2-2130	LY-CoV1404	Brii-198	S309	2-7	ADG-2	DH1047	10-40	S2X259	4-18	5-7	REGN 10987 + REGN 10933	COV2-2196 + COV2-2130	LY-CoV555 + CB6	Brii-196 + Brii-198
D614G	0.027	0.012	0.012	0.018	0.005	0.002	0.004	0.004	0.001	0.001	0.006	0.001	0.110	0.014	0.005	0.007	0.037	0.042	0.055	0.054	0.017	0.001	0.002	0.005	0.022
BA.1	>10	0.010	9.253	2.385	>10	0.432	>10	0.003	>10	7.586	0.209	0.003	0.078	0.127	0.716	0.181	4.322	0.644	0.590	>10	0.347	2.951	0.154	>10	0.260
BA.1.1	>10	0.010	>10	1.792	>10	0.385	>10	0.003	>10	>10	>10	0.002	>10	0.200	0.763	0.295	5.723	0.600	0.859	>10	0.534	>10	0.708	>10	4.394
BA.2	>10	0.031	>10	1.346	>10	0.704	>10	0.010	>10	0.505	0.012	0.002	0.782	1.019	0.050	>10	>10	3.642	>10	>10	>10	1.882	0.021	>10	1.907
BA.2.12.1	>10	0.027	>10	1.171	>10	0.361	>10	0.006	>10	2.125	0.018	0.002	>10	1.035	0.059	>10	>10	2.519	>10	>10	>10	2.400	0.026	>10	1.936
BA.4/5	>10	0.025	>10	0.978	>10	>10	>10	1.351	>10	2.682	0.022	0.002	>10	1.120	0.049	>10	>10	3.404	>10	>10	>10	1.998	0.049	>10	2.445

<0.01	<0.1	<1	<10	>10

Extended Data Fig. 3 | Neutralization IC_{50} values for indicated pseudoviruses by monoclonal antibodies.



Extended Data Fig. 4 | Neutralization curves for monoclonal antibodies against individual SARS-CoV-2 mutations in the background of D614G. Data are shown as mean ± SEM from three technical replicates.



Extended Data Fig. 5 | Neutralization curves for monoclonal antibodies against individual SARS-CoV-2 mutations in the background of BA.2. Data are shown as mean ± SEM from three technical replicates.

a

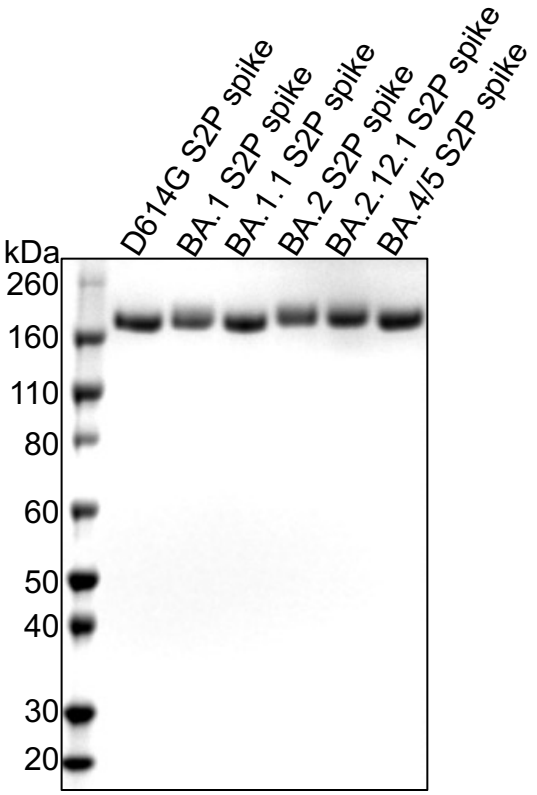
IC50 (μg/mL)	RBD mAbs																			NTD mAbs		Combination			
	Class 1				Class 2					Class 3						Class 4									
	1-20	CAB-A17	CB6	Brii-196	REGN 10933	COV2-2196	LY-CoV555	ZCB11	2-15	REGN 10987	COV2-2130	LY-CoV1404	Brii-198	S309	2-7	ADG-2	DH1047	10-40	S2X259	4-18	5-7	REGN 10987 + REGN 10933	COV2-2196 + COV2-2130	LY-CoV555 + CB6	Brii-196 + Brii-198
D614G	0.026	0.016	0.017	0.016	<0.001	<0.001	0.002	0.002	0.002	0.001	0.003	0.002	0.129	0.014	0.005	0.006	0.037	0.031	0.036	0.038	0.014	0.001	0.002	0.005	0.016
D614G-Del69-70	0.020	0.014	0.013	0.021	<0.001	<0.001	0.001	0.002	0.001	0.001	0.007	0.002	0.148	0.028	0.005	0.010	0.047	0.051	0.059	0.042	0.064	0.002	0.003	0.005	0.016
D614G-L452M	0.017	0.016	0.011	0.016	0.002	<0.001	0.004	0.002	0.001	0.001	0.006	0.002	0.892	0.029	0.005	0.009	0.034	0.023	0.036	0.042	0.018	0.002	0.002	0.005	0.016
D614G-L452R	0.032	0.020	0.024	0.024	0.002	<0.001	5.018	0.002	0.024	0.002	0.009	0.002	3.526	0.023	0.009	0.008	0.039	0.023	0.020	0.035	0.014	0.002	0.002	0.018	0.021
D614G-L452Q	0.033	0.014	0.018	0.023	0.002	<0.001	0.012	0.002	0.017	0.004	0.013	0.002	2.346	0.038	0.011	0.009	0.056	0.055	0.061	0.078	0.022	0.003	0.003	0.013	0.031
D614G-F486V	0.039	0.019	0.135	0.231	>10	0.272	1.961	1.174	0.036	0.001	0.005	0.002	0.175	0.014	0.004	0.009	0.033	0.051	0.079	0.034	0.014	0.006	0.019	0.701	0.174
D614G-S704L	0.020	0.017	0.026	0.019	<0.001	<0.001	0.002	0.002	0.002	0.002	0.010	0.001	0.199	0.038	0.008	0.008	0.061	0.057	0.069	0.071	0.015	0.002	0.003	0.007	0.019
D614G-L452Q/S704L	0.033	0.020	0.032	0.026	0.007	0.001	0.019	0.005	0.049	0.004	0.016	0.002	6.166	0.028	0.015	0.011	0.052	0.074	0.106	0.076	0.029	0.003	0.004	0.016	0.035

b

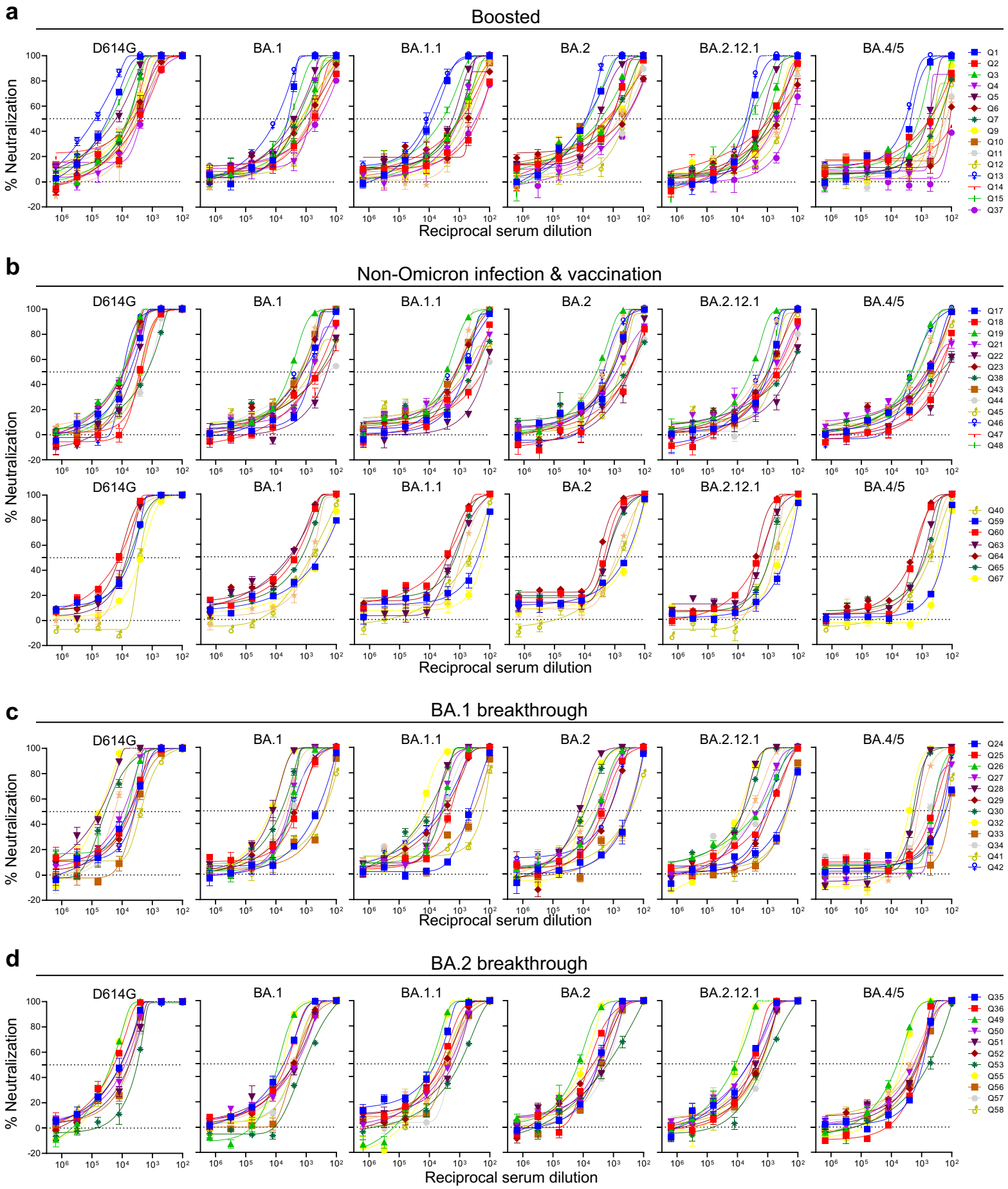
IC50 (μg/mL)	RBD mAbs																			NTD mAbs		Combination			
	Class 1				Class 2					Class 3						Class 4									
	1-20	CAB-A17	CB6	Brii-196	REGN 10933	COV2-2196	LY-CoV555	ZCB11	2-15	REGN 10987	COV2-2130	LY-CoV1404	Brii-198	S309	2-7	ADG-2	DH1047	10-40	S2X259	4-18	5-7	REGN 10987 + REGN 10933	COV2-2196 + COV2-2130	LY-CoV555 + CB6	Brii-196 + Brii-198
BA.2	>10	0.027	>10	1.329	>10	1.060	>10	0.005	>10	0.495	0.005	0.001	0.642	0.393	0.032	>10	>10	4.824	>10	>10	>10	1.475	0.016	>10	1.592
BA.2-Del69-70	>10	0.040	>10	2.726	>10	0.835	>10	0.004	>10	0.298	0.005	0.002	0.394	0.469	0.031	>10	>10	>10	>10	>10	>10	2.178	0.015	>10	1.320
BA.2-L452M	>10	0.036	>10	0.907	>10	0.970	>10	0.007	>10	1.081	0.015	0.002	>10	0.557	0.042	>10	>10	4.246	>10	>10	>10	1.276	0.015	>10	1.163
BA.2-L452R	>10	0.047	>10	6.815	>10	1.228	>10	0.008	>10	2.832	0.025	0.001	>10	1.022	0.026	>10	>10	>10	>10	>10	>10	1.864	0.028	>10	>10
BA.2-L452Q	>10	0.036	>10	1.717	>10	0.655	>10	0.003	>10	0.872	0.010	0.002	>10	0.535	0.051	>10	>10	>10	>10	>10	>10	4.793	0.024	>10	5.525
BA.2-F486V	>10	0.229	>10	>10	>10	>10	>10	>10	>10	1.681	0.005	0.001	0.887	0.412	0.054	>10	>10	5.759	>10	>10	>10	7.366	0.020	>10	5.377
BA.2-R493Q	2.020	0.010	>10	0.033	0.960	0.049	>10	<0.001	>10	0.454	0.009	0.002	1.089	0.485	0.049	>10	>10	3.008	>10	>10	>10	0.641	0.009	>10	0.021
BA.2-S704L	>10	0.033	>10	1.464	>10	0.686	>10	0.004	>10	0.262	0.006	0.002	0.735	0.539	0.029	>10	>10	2.537	>10	>10	>10	1.262	0.010	>10	0.800
BA.2-F486V/R493Q	>10	0.020	>10	0.394	>10	>10	>10	7.766	>10	0.757	0.009	0.002	1.414	0.754	0.044	>10	>10	2.751	>10	>10	>10	2.498	0.017	>10	0.586

<0.01	<0.1	<1	<10	>10

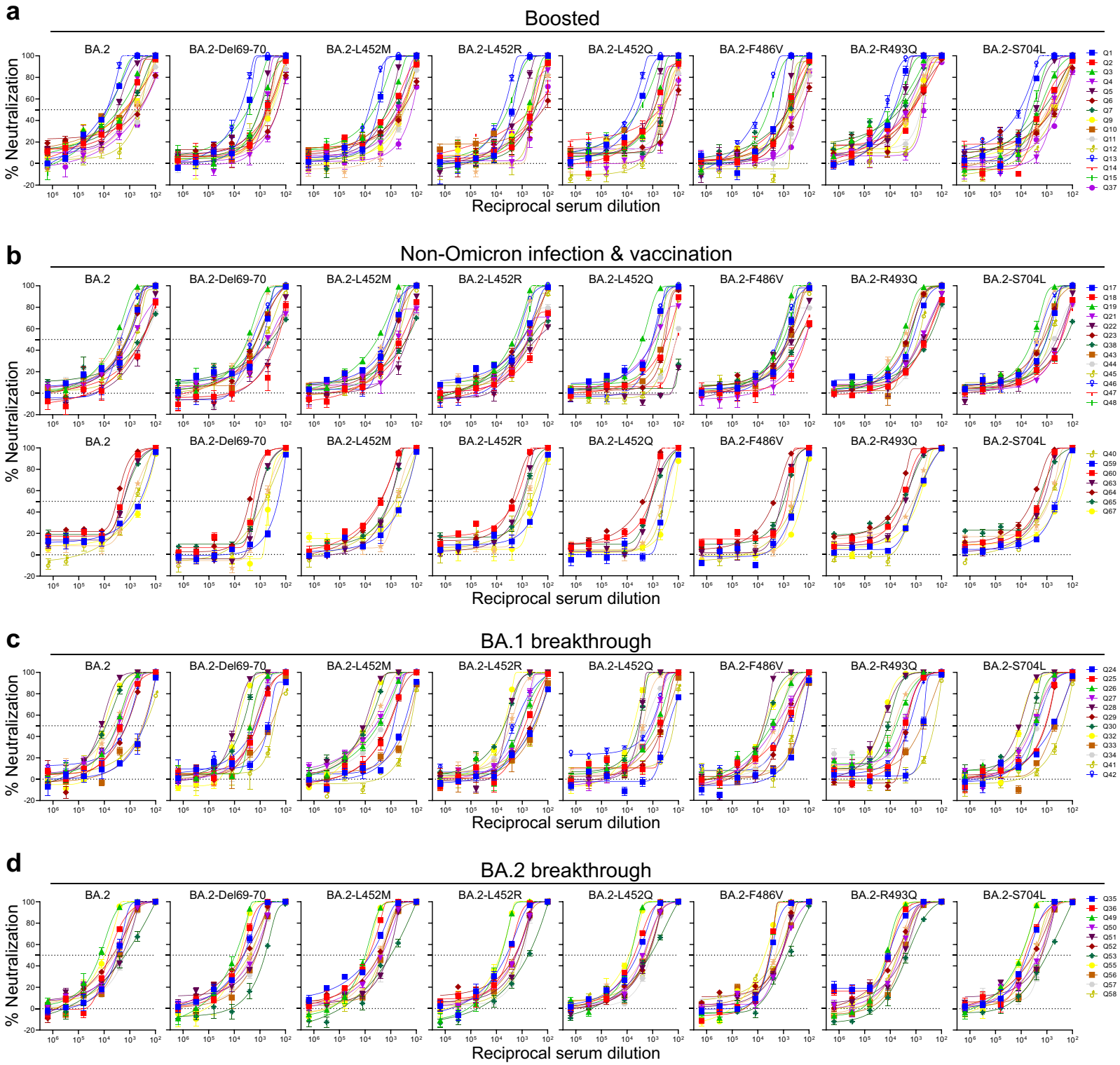
Extended Data Fig. 6 | Neutralization IC_{50} values for monoclonal antibodies. IC_{50} values of **a**, D614G carrying individual mutations; **b**, BA.2 carrying individual mutations.



Extended Data Fig. 7 | SDS-polyacrylamide gel of purified spike trimers of D614G and Omicron subvariants.



Extended Data Fig. 8 | Neutralization curves of serum against D614G and Omicron sublineages. Neutralization by **a**, boosted vaccinee sera. **b**, non-Omicron infection & vaccination sera. **c**, BA.1 breakthrough sera. **d**, BA.2 breakthrough sera. Error bars denote mean ± SEM for three technical replicates.



Extended Data Fig. 9 | Neutralization curves of serum against BA.2 and BA.2 carrying individual mutations. Neutralization by **a**, boosted vaccinee sera. **b**, non-Omicron infection & vaccination sera. **c**, BA.1 breakthrough sera. **d**, BA.2 breakthrough sera. Error bars denote mean ± SEM for three technical replicates.

Extended Data Table 1 | Mutation frequencies at position F486 within different SARS-CoV-2 variants.

Mutation	Count in BA.1	Frequency in BA.1	Count in BA.2	Frequency in BA.2	Count in other variants	Frequency in other variants
F486V	23	2.17E-06	134	1.26E-05	898	8.48E-05
Del486	193	1.82E-05	549	5.18E-05	760	7.17E-05
F486L	37	3.49E-06	10	9.44E-07	155	1.46E-05
F486S	61	5.76E-06	10	9.44E-07	142	1.34E-05
F486I	5	4.72E-07	2	1.89E-07	34	3.21E-06
F486Y	12	1.13E-06	2	1.89E-07	20	1.89E-06
F486W	8	7.55E-07	1	9.44E-08	10	9.44E-07
F486T	5	4.72E-07	0	0	5	4.72E-07
F486E	2	1.89E-07	0	0	3	2.83E-07
F486N	2	1.89E-07	0	0	3	2.83E-07
F486H	2	1.89E-07	0	0	2	1.89E-07
F486P	2	1.89E-07	0	0	2	1.89E-07
F486R	1	9.44E-08	0	0	2	1.89E-07
F486C	0	0	0	0	1	9.44E-08
F486G	1	9.44E-08	0	0	1	9.44E-08
F486M	0	0	0	0	1	9.44E-08
F486Q	0	0	1	9.44E-08	1	9.44E-08

Extended Data Table 2 | Demographics on the clinical cohorts.

Sample ID	Vaccine type and infected strain	Days post-vaccination or *infection (after last exposure)	Documented COVID-19	Age	Gender
Boosted					
Q1	mRNA-1273/mRNA-1273/mRNA-1273	29	No	66	Female
Q2	BNT162b2/BNT162b2/BNT162b2	30	No	68	Male
Q3	BNT162b2/BNT162b2/BNT162b2	14	No	64	Female
Q4	BNT162b2/BNT162b2/BNT162b2	34	No	55	Male
Q5	BNT162b2/BNT162b2/BNT162b2	34	No	45	Male
Q6	BNT162b2/BNT162b2/BNT162b2	15	No	50	Female
Q7	BNT162b2/BNT162b2/BNT162b2	15	No	48	Female
Q8	BNT162b2/BNT162b2/BNT162b2	29	No	71	Male
Q9	BNT162b2/BNT162b2/BNT162b2	90	No	59	Male
Q10	BNT162b2/BNT162b2/BNT162b2	33	No	45	Male
Q11	BNT162b2/BNT162b2/BNT162b2	87	No	66	Female
Q12	BNT162b2/BNT162b2/BNT162b2	84	No	26	Male
Q13	mRNA-1273/mRNA-1273/mRNA-1273	23	No	28	Female
Q14	BNT162b2/BNT162b2/BNT162b2	14	No	78	Male
Q15	BNT162b2/BNT162b2/mRNA-1273	32	No	39	Male
Q37	BNT162b2/BNT162b2/BNT162b2	20	No	Unknown	Female
Non-Omicron infection & vaccination					
Q16	R.1/mRNA-1273/mRNA-1273	7	Yes	64	Female
Q17	R.1/mRNA-1273/mRNA-1273	7	Yes	34	Female
Q18	R.1/mRNA-1273/mRNA-1273	28	Yes	52	Male
Q19	R.1/mRNA-1273/mRNA-1273	21	Yes	67	Female
Q20	R.1/mRNA-1273/mRNA-1273	>28	Yes	69	Male
Q21	R.1/mRNA-1273/mRNA-1273	>28	Yes	57	Female
Q22	BNT162b2/B.1.526	*89	Yes	42	Male
Q23	BNT162b2/B.1.526	*82	Yes	32	Male
Q38	BNT162b2/B.1.1.7	*59	Yes	22	Female
Q39	BNT162b2/B.1.1.7	*213	Yes	66	Male
Q40	BNT162b2/B.1.617.2	*31	Yes	50	Female
Q43	BNT162b2/BNT162b2/B.1.526	*62	Yes	3	Male
Q44	WA1/mRNA-1273/mRNA-1273	114	Yes	49	Female
Q45	WA1/BNT162b2/BNT162b2	57	Yes	35	Female
Q46	WA1/BNT162b2/BNT162b2	46	Yes	30	Female
Q47	WA1/BNT162b2/BNT162b2	57	Yes	32	Female
Q48	WA1/BNT162b2/BNT162b2	50	Yes	64	Female
Q59	BNT162b2/BNT162b2/B.1.617.2	*35	Yes	58	Female
Q60	B.1.617.2/BNT162b2/BNT162b2	40	Yes	61	Male
Q63	BNT162b2/BNT162b2/B.1.617.2	*30	Yes	40	Female
Q64	mRNA-1273/mRNA-1273/B.1.617.2	*66	Yes	29	Male
Q65	BNT162b2/BNT162b2/B.1.617.2	*62	Yes	33	Female
Q66	BNT162b2/BNT162b2/B.1.617.2	*60	Yes	42	Female
Q67	BNT162b2/BNT162b2/B.1.617.2	*73	Yes	37	Male
BA.1 breakthrough					
Q24	BNT162b2/BNT162b2/BA.1	*14	Yes	Unknown	Unknown
Q25	BNT162b2/BNT162b2/BA.1	*14	Yes	Unknown	Unknown
Q26	mRNA-1273/mRNA-1273/BA.1	*35	Yes	Unknown	Unknown
Q27	BNT162b2/BNT162b2/BNT162b2/BA.1	*135	Yes	78	Male
Q28	BNT162b2/BNT162b2/BNT162b2/BA.1	*14	Yes	Unknown	Unknown
Q29	BNT162b2/BNT162b2/BNT162b2/BA.1	*14	Yes	Unknown	Unknown
Q30	BNT162b2/BNT162b2/BNT162b2/BA.1	*14	Yes	Unknown	Unknown
Q31	BNT162b2/BNT162b2/BNT162b2/BA.1	*41	Yes	48	Male
Q32	BNT162b2/BNT162b2/BNT162b2/BA.1	*26	Yes	38	Female
Q33	BNT162b2/BNT162b2/B.1.617.2/BNT162b2/BA.1	*19	Yes	35	Female
Q34	BNT162b2/BNT162b2/mRNA-1273/mRNA-1273/BA.1	*67	Yes	40	Male
Q41	WA1/BNT162b2/BA.1	*21	Yes	52	Male
Q42	WA1/BNT162b2/BA.1	*44	Yes	37	Intersex
BA.2 breakthrough					
Q35	BNT162b2/BNT162b2/BA.2	*14	Yes	50	Female
Q36	BNT162b2/BNT162b2/BNT162b2/Ad26.COV2.S/BA.2	*22	Yes	69	Male
Q49	BNT162b2/BNT162b2/mRNA-1273/BA.2	*16	Yes	32	Male
Q50	mRNA-1273/mRNA-1273/mRNA-1273/BA.2	*14	Yes	34	Male
Q51	BNT162b2/BNT162b2/mRNA-1273/BA.2	*19	Yes	33	Female
Q52	BNT162b2/BNT162b2/mRNA-1273/BA.2	*18	Yes	29	Female
Q53	BNT162b2/BNT162b2/BNT162b2/BA.2	*25	Yes	34	Male
Q54	BNT162b2/BNT162b2/BNT162b2/BA.2	*36	Yes	37	Female
Q55	BNT162b2/BNT162b2/mRNA-1273/BA.2	*18	Yes	41	Female
Q56	mRNA-1273/mRNA-1273/mRNA-1273/BA.2	*21	Yes	36	Female
Q57	BNT162b2/BNT162b2/mRNA-1273/BA.2	*32	Yes	28	Male
Q58	BNT162b2/BNT162b2/mRNA-1273/BA.2	*23	Yes	33	Female

Extended Data Table 3 | Oligos used to construct spike expression plasmids.

Oligo name	Targeted mutation	Oligo sequence
WQ-1	L452Q	TCTTCCTGAACAGTCTGTACTGGTAGTTGTAGTTGCCTCC
WQ-2		GGAGGCAACTACAACTACCAGTACAGACTGTTCAGGAAGA
WQ-3	L452M	TCTTCCTGAACAGTCTGTACATGTAGTTGTAGTTGCCTCCC
WQ-4		GGGAGGCAACTACAACTACATGTACAGACTGTTCAGGAAGA
WQ-5	L452R	TCCTGAACAGTCTGTAGCGGTAGTTGTAGTTGCCT
WQ-6		AGGCAACTACAACTACCGCTACAGACTGTTCAGGA
WQ-7	S704L	GTTGTTGCTGTAAGCCACTAAGTTCTCTGCTCCCAGAC
WQ-8		GTCTGGGAGCAGAGAACTTAGTGGCTTACAGCAACAAC
WQ-9	2P_K986P/V987P	TCTGGACCTCAGCCTCCGGCGGGTCCAGTCTGCTCAGGA
WQ-10		TCCTGAGCAGACTGGACCCGCCGGAGGCTGAGGTCCAGA
WQ-11	Furin-mut	GCTTGCCACAGAGCTTGCGCTCCCGTGGCTCTTGGT
WQ-12		ACCAAGAGCCACGGGAGCGCAAGCTCTGTGGCAAGC
WQ-13	F486V	GTGGAAAGTAACAGTTGACGCCCTCCACTCCATTAC
WQ-14		GTAATGGAGTGGAGGGCGTCAACTGTTACTTTCCAC
WQ-15		TGGAAAGTAACAGTTGACGCCGGCCACTCCATTA
WQ-16		TAATGGAGTGGCCGGCGTCAACTGTTACTTTCCA
WQ-17	Del69-70	TGGTTCCATGCCATCTCTGGCACCAATGGC
WQ-18		GCCATTGGTGCCAGAGATGGCATGGAACCA
WQ-19	R493Q	GGTTGGTCTGAAGCCATAGGACTGGAGTGGAAAGTAACAGTTGAC
WQ-20		GTCAACTGTTACTTTCCACTCCAGTCCTATGGCTTCAGACCAACC