Supplemental information

Omicron BQ.1.1 and XBB.1 unprecedentedly escape

broadly neutralizing antibodies

elicited by prototype vaccination

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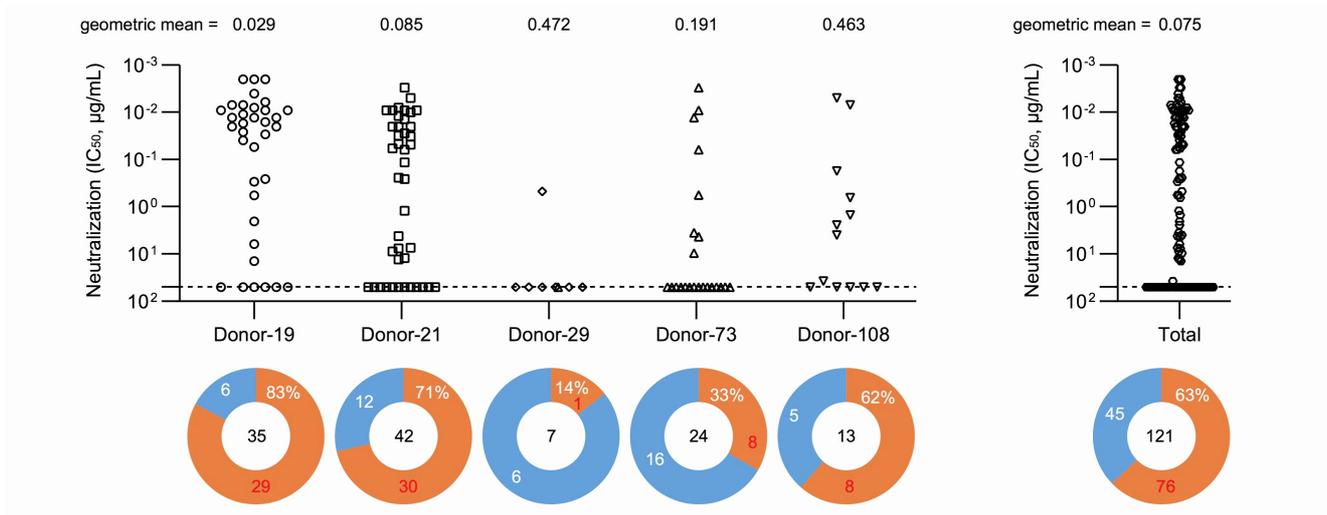
Figure S1. Isolation of 121 SARS-CoV-2 WT RBD-specific mAbs, Related to Figure 1. Neutralization (IC_{50}) of 121 mAbs against WT SARS-CoV-2, whose cut-off value was set as 50 μg/mL. Geometric mean potency was calculated by neutralization of less than 50 μg/mL. The data are means of at least two independent experiments. A total of 76 mAbs (63%) could effectively neutralize WT SARS-CoV-2 pseudovirus.
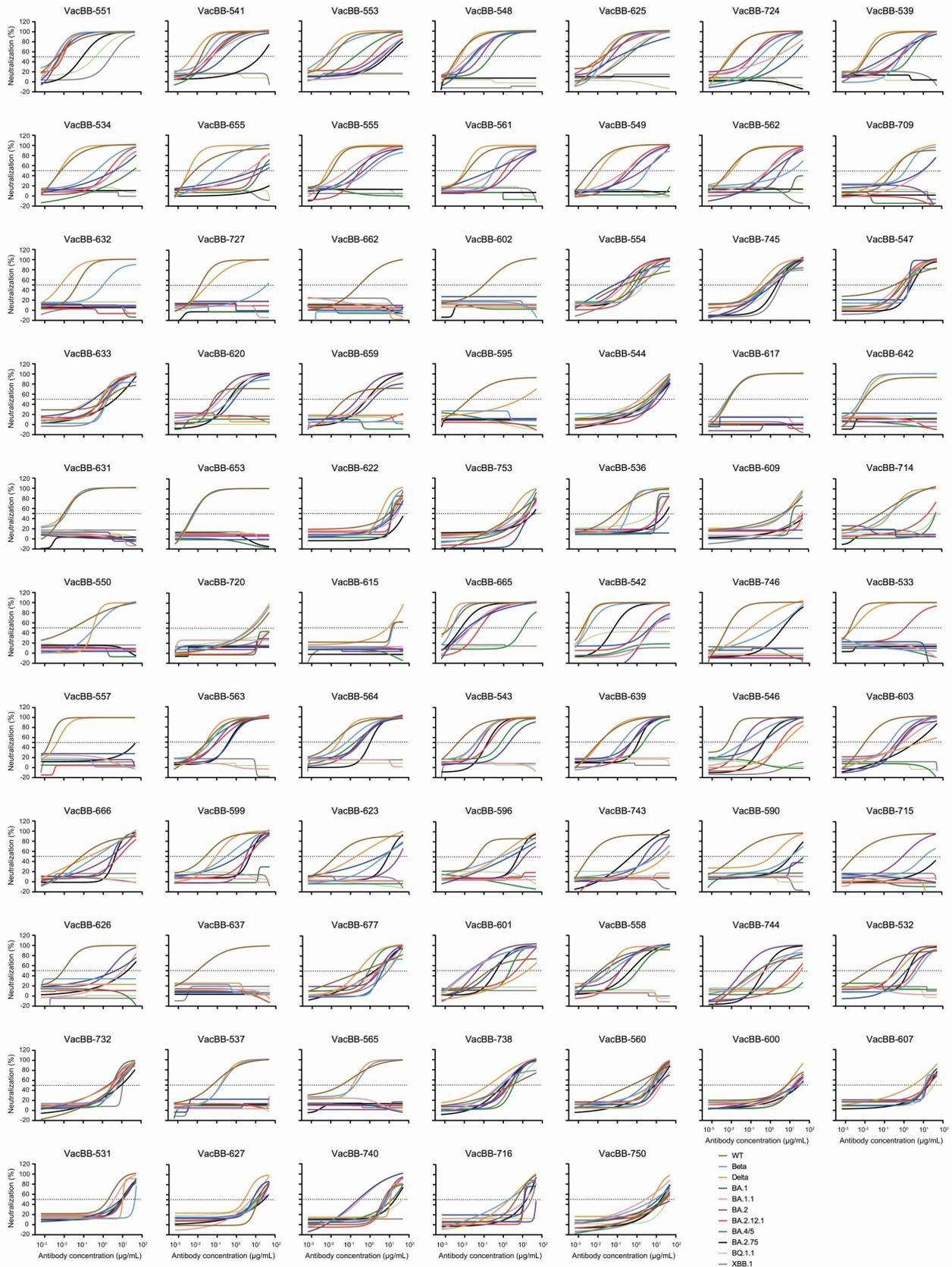
Figure S2. Neutralization curves of 75 distinct nAbs against WT SARS-CoV-2, Beta, Delta, and various Omicron subvariants including BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BQ.1.1, and XBB.1, Related to Figure 1.

A 50% reduction in viral infectivity was indicated by a horizontal dashed line. One out of at least two independent experiments with similar results.
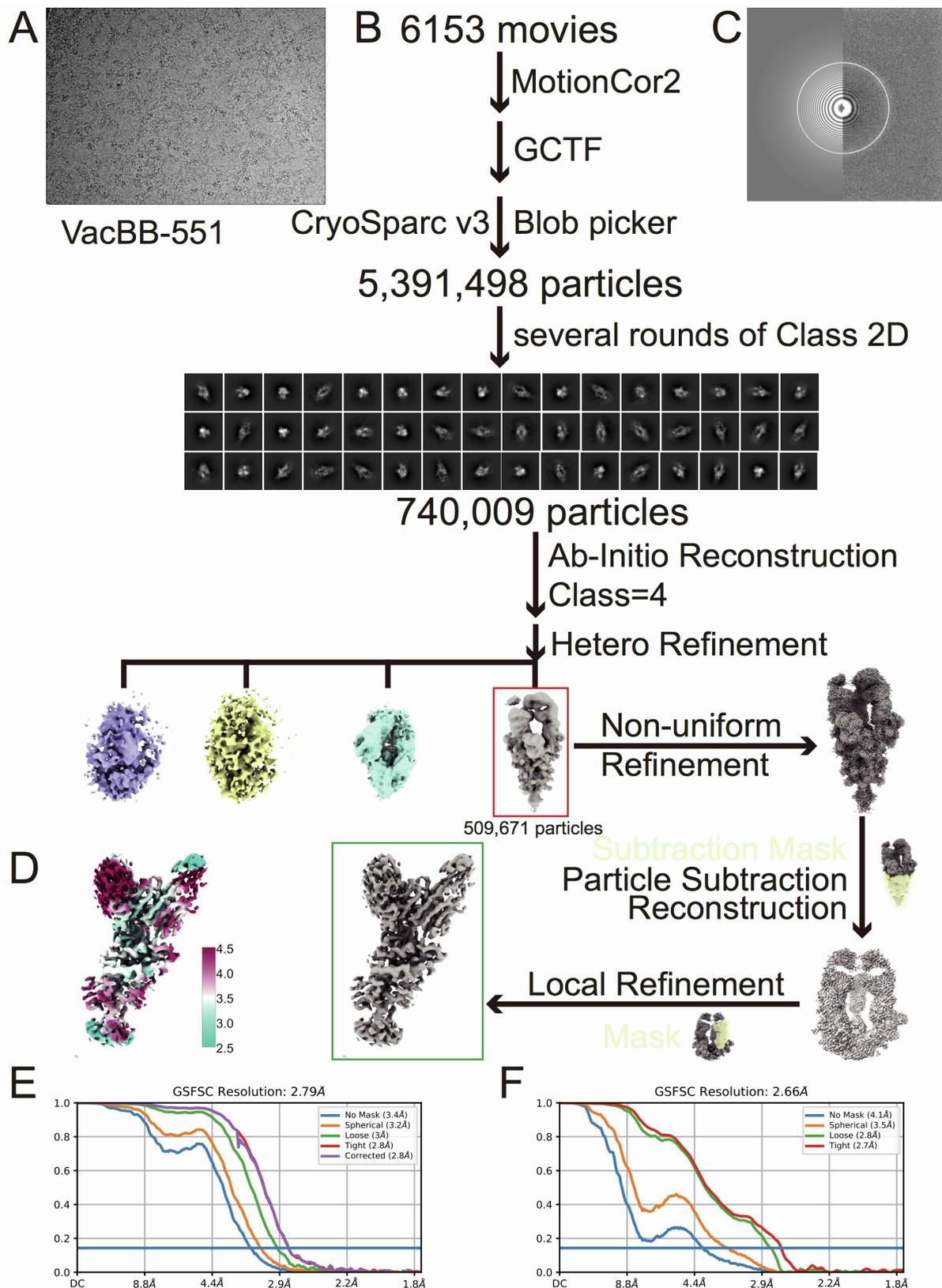
Figure S3. Cryo-EM image-processing workflow for BA.2 spike: VacBB-551, Related to Figure 2.

(A) Representative cryo-EM micrographs and CTF estimation result **(C)** of BA.2-S: VacBB-551. **(B)** Single-particle cryo-EM images processing workflow, local resolution estimation **(D)** and FSC curve for global **(E)** and local **(F)** resolution for the immune complex of SARS-CoV-2 Omicron BA.2 spike: VacBB-551.
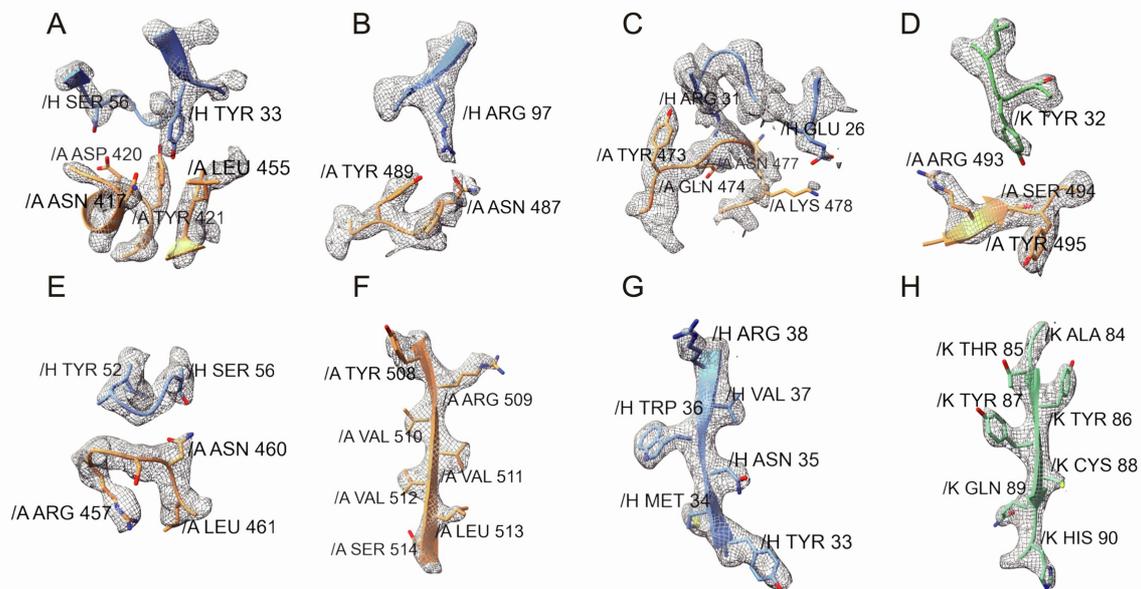
Figure S4. Cryo-EM density maps for BA.2 spike: VacBB-551 complex, Related to Figure 2.

(A-E) Local density maps and models for the interaction regions between VacBB-551 and BA.2 RBD. **(F)** Typical local density maps and models for BA.2 spike RBD. **(G, H)** Typical local density maps and models for heavy chain (G) and light chain (H) of VacBB-551. RBDs were colored by sand brown, heavy chain of VacBB-551 was colored by cornflower blue and light chain was colored by medium sea green.
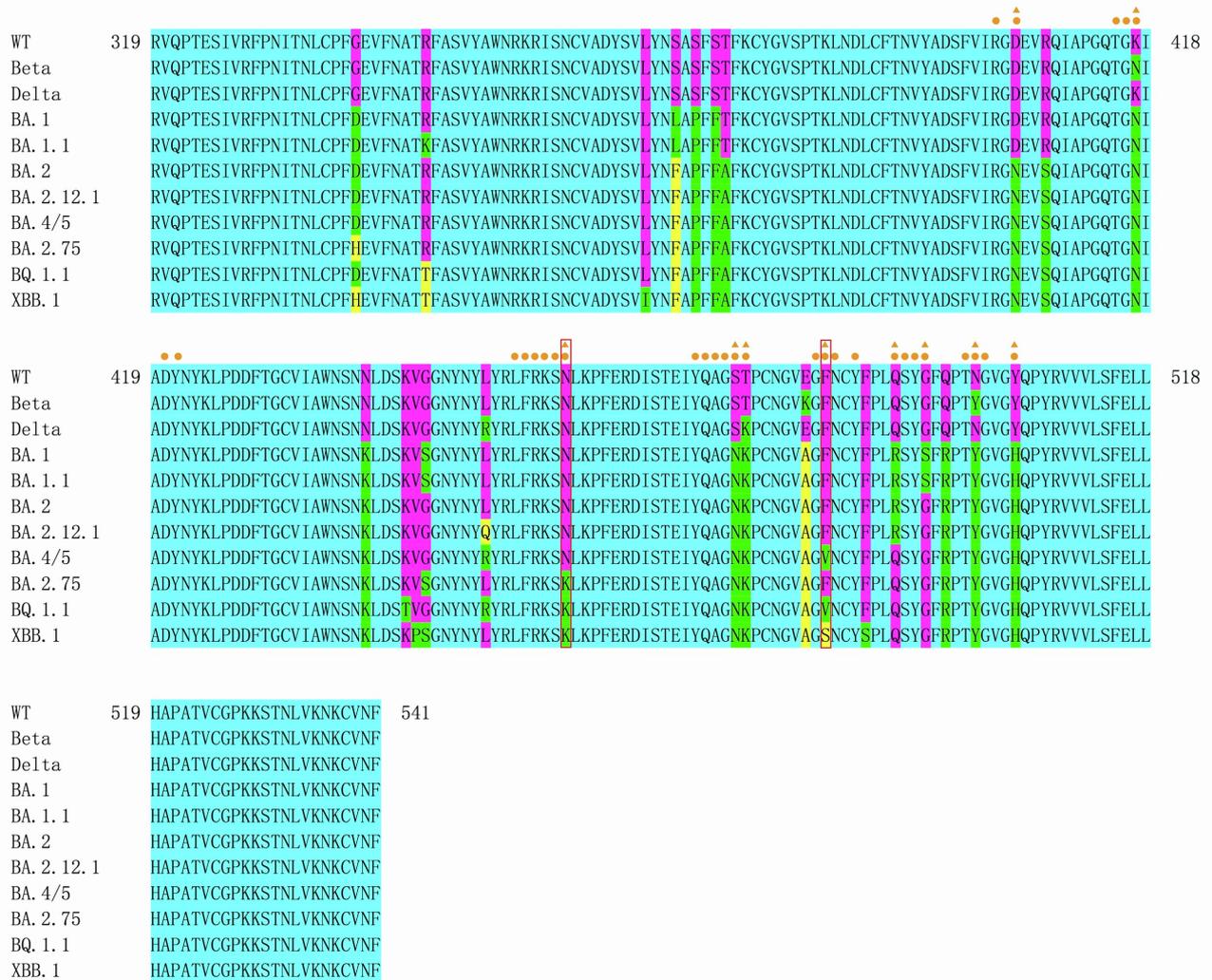
Figure S5. Sequence alignment of RBD proteins among WT SARS-CoV-2, Beta, Delta, and Omicron subvariants including BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BQ.1.1, and XBB.1, Related to Figure 3.

Epitope residues of VacBB-551 were indicated by orange solid circles. Non-conservative residues among epitope residues were indicated by orange solid triangles. Conserved residues were highlighted in cyan among different RBD proteins. The N460K in BA.2.75, BQ.1.1, and XBB.1, and F486V/S in BA.4/5, BQ.1.1, and XBB.1 were boxed out by the red line.

Table S2. Cryo-EM data collection and processing, model building and refinement statistics, Related to Figure 2.

Data Collection & Processing	
	BA.2-S: VacBB-551
Microscope	FEI Titan Krios
Camera	Gatan K3
Magnification	105K
Voltage(kV)	300
Automation software	EPU
Total dose (e–/Å2)	50
Frames	32
Defocus range (μm)	-1.5-2.5
Pixel size (Å/pixel)	0.855
Symmetry imposed	C1
Micrographs used (no.)	6153
Initial particles images	5,391,498
Final particles images	509,671
Overall resolution($\mathring{A}$)	2.79
Local resolution($\mathring{A}$)	2.66
Model Building & Refinement (Phenix 1.20 real-space-refine)	
Composition	
Nonhydrogen atoms	3116
Protein residues	396
Ligands	0
Bonds (RMSD)	
Length ($\mathring{A}$) (# > 4σ)	0.0003(0)
Angles (°) (# > 4σ)	0.544(0)
MolProbity score	1.52
Clashscore	3.27
Rotamer outliers (%)	0.6
Ramachandran plot	
Favored (%)	94.10
Allowed(%)	5.38
Outliers(%)	0.51

Table S3. Contacts between VacBB-551 and BA.2 RBD (distance cutoff 5 Å), Related to Figure 2.

VacBB-551			
RBD	Heavy Chain	RBD	Light Chain
T415	S56, F58	R403	Y32, E91
G416	F58	F486	Q55, N56
N417	Y33, Y52	S494	Y32
D420	Y52, S56	Y495	Y32
Y421	Y33, Y52, A53, G54	Y501	P30
L455	Y33, G100	G502	G28
F456	Y33	H505	P30, H90, E91
R457	A53, G54		
K458	S30, R31, A53		
S459	G54		
N460	G54, S56		
Y473	R31, A53		
Q474	R31		
A475	I28, R31, N32, R97		
G476	I28		
N477	I28, R31		
K478	G26		
F486	R97, F105		
N487	G26, R97		
Y489	R97, L99, D104		
R493	G100, R102		

Table S4. The list of primers used in this study, Related to STAR Methods.

Primer name	Sequence (5'-3')
WT_N460K-F	CAGGAAGAGCAAACTGAAACCATTTGAGAGGGACAT
WT_N460K-R	TCAGTTTGCTCTTCCTGAACAGTCTGTAGAGG
WT_F486V-F	GGAGGGCGTAAACTGTTACTTTCCACTCCAATCCT
WT_F486V-R	AACAGTTTACGCCCTCCACTCCATTACATGGT
WT_F486S-F	GAGGGCTCCAACTGTTACTTTCCACTCCAATCCT
WT_F486S-R	TAACAGTTGGAGCCCTCCACTCCATTACATGG
BA.2_N460K-F	AAGTCCAAGCTGAAACCTTTCGAGAGGGACAT
BA.2_N460K-R	GGTTTCAGCTTGGACTTTCTGAACAGTCTATACAGGTAGT
BA.2_F486V-F	CGGCGTTAACTGCTACTTTCCTCTGAGAAGCTA
BA.2_F486V-R	AGTAGCAGTTAACGCCGGCCACGCCGTTGCAG
BA.2_F486S-F	CGGCTCTAACTGCTACTTTCCTCTGAGAAGCTA
BA.2_F486S-R	AGTAGCAGTTAGAGCCGGCCACGCCGTTGCAG
BA.2.75_K460N-F	GAAGAGCAACCTCAAGCCTTTCGAGAGAGACATC
BA.2.75_K460N-R	GCTTGAGGTTGCTCTTCCGAAACAGTCTGTACAG
BQ.1.1_K460N-F	AAAGTCCAACCTGAAGCCCTTCGAGAGAGATATC
BQ.1.1_K460N-R	GCTTCAGGTTGGACTTTCTGAACAGTCTGTAGCG
BQ.1.1_V486F-F	GCCGGCTTCAACTGTTACTTCCCTCTGCAGAGC
BQ.1.1_V486F-R	TAACAGTTGAAGCCGGCCACGCCGTTACAAGG
XBB.1_K460N-F	GAAGAGCAACCTGAAGCCTTTCGAGAGGGATA
XBB.1_K460N-R	GCTTCAGGTTGCTCTTCCGGAACAGTCTATACAGG
XBB.1_S486F-F	CGGGTTCAACTGCTACAGCCCCCTGCAGAGCT
XBB.1_S486F-R	TGTAGCAGTTGAACCCGGCGACGCCATTACAA