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## **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.

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WT	319	RVQPTES1VRFPN1TNLCPF <mark>G</mark> EV	'FNAT <mark>R</mark> FASVY/	AWNRKRISN	NCVADYSV.	LYNSASFS	TFKCYGVS	SPTKLNDL	CFTNVYA	.DSFV1RG <mark>D</mark>	EV <mark>R</mark> QIAPGQTG <mark>K</mark> I	418
Beta		RVQPTESIVRFPNITNLCPF <mark>G</mark> EV	'FNAT <mark>R</mark> FASVY/	AWNRKRISN	ICVADYSV	LYN <mark>S</mark> ASFS	TFKCYGVS	SPTKLNDL	CFTNVYA	.DSFVIRG <mark>D</mark>	EV <mark>R</mark> QIAPGQTG <mark>N</mark> I	
Delta		RVQPTESIVRFPNITNLCPF <mark>G</mark> EV	FNAT <mark>R</mark> FASVY	AWNRKRISN	<b>ICVADYSV</b>	LYN <mark>S</mark> ASFS	TFKCYGVS	SPTKLNDL	CFTNVYA	.DSFVIRG <mark>D</mark>	EV <mark>R</mark> QIAPGQTG <mark>K</mark> I	
BA. 1		RVQPTESIVRFPNITNLCPF <mark>D</mark> EV	'FNAT <mark>R</mark> FASVY/	AWNRKRISN	<b>ICVADYSV</b>	LYNLAPFF	TFKCYGVS	SPTKLNDL	CFTNVYA	.DSFVIRG <mark>D</mark>	EV <mark>R</mark> QIAPGQTG <mark>N</mark> I	
BA 1 1		RVQPTESIVREPNITNLCPEDEN	TENAT <mark>K</mark> EASVY	AWNRKRISN	JCVADYSV	I YNLAPFF	TEKCYGVS	SPTKLNDI	CETNVYA	DSEVIRG <mark>D</mark>	EV <mark>R</mark> QIAPGQTGNI	
BA 2		RVOPTES IVREPNITNI CPEDEI	FNATREASVV.	AWNRKRISN	JCVADVSV		AFKCVCV	SPTKI NDI	CETNVVA	DSEVIRCN	EVSOLAPCOTCNI	
DA. 2 10 1		RVQI TESTVRT NTINECI PDEV	TNAT NEASVII	AWNDEDTCN	ICVADVCV		AFREVENCE	DI TALADI	CETNWY	DEEVIDEN		
BA. Z. 1Z. 1		RVQPTESTVRPPNTTNLCPFDEV	FNAIRFASVY	AWNKKKISN	VCVAD15V		AFKUIGV	SP I KLNDL	OFINVYA	DSFVIKGN	EVSQIAPGQIGNI	
BA. 4/5		RVQPTESIVRFPNITNLCPF <mark>D</mark> EV	FNAT <mark>R</mark> FASVY/	AWNRKRISN	CVADYSV	LYNFAPFF	AFKCYGVS	SPTKLNDL	CFTNVYA	IDSFV1RG <mark>N</mark>	EV <mark>SQIAPGQTGN</mark> I	
BA. 2. 75		RVQPTESIVRFPNITNLCPF <mark>H</mark> EV	'FNAT <mark>R</mark> FASVY/	AWNRKRISN	ICVADYSV	LYNFAPFF	AFKCYGVS	SPTKLNDL	CFTNVYA	.DSFVIRG <mark>N</mark>	EV <mark>S</mark> QIAPGQTG <mark>N</mark> I	
BQ. 1. 1		RVQPTESIVRFPNITNLCPF <mark>D</mark> EV	FNAT <mark>T</mark> FASVY	AWNRKRISN	ICVADYSV	LYN <mark>F</mark> APFF	AFKCYGVS	SPTKLNDL	CFTNVYA	.DSFVIRG <mark>N</mark>	EV <mark>S</mark> QIAPGQTG <mark>N</mark> I	
XBB. 1		RVQPTESIVRFPNITNLCPF <mark>H</mark> EV	FNAT <mark>T</mark> FASVY	AWNRKRISN	<b>ICVADYSV</b>	I YN <mark>F</mark> APFF	AFKCYGVS	SPTKLNDL	CFTNVYA	.DSFVIRG <mark>N</mark>	EV <mark>S</mark> QIAPGQTG <mark>N</mark> I	
					3		**		<b>*</b> • •			
WT	/10	ADVNVKI PDDETCCV I AWNSN <mark>N</mark> I	DSKVCCNVNV	VDI EDKS	I KDEEDD	ISTEIVOA	CSTDCNC			OPTNCVCV	ODVDVVVI SEELI	518
WI Data	415	ADVNVKI DDDETCCV I AWNSNNI		VDL EDVCN		ISTELIQA					QI INVVLOPELL	510
beta D 1		ADYNYKLPDDFIGCVIAWNSNNI	DSKVGGNINI	I KLFKKS	LKPFERD	ISTELIQA	GSTPUNG	VINGENCIE	PLQSIGF		QPYRVVLSFELL	
Delta		ADYNYKLPDDF1GCV1AWNSN <mark>N</mark> I	DS <mark>KVG</mark> GNYNYI	RY RLFRKSN	LKPFERD	ISTELYQA	G <mark>SK</mark> PCNG	EGFNCYF	PLQSYGF	QPINGVGY	QPYRVVVLSFELL	
BA. 1		ADYNYKLPDDFTGCV I AWNSN <mark>K</mark> I	.DS <mark>KVS</mark> GNYNYI	LYRLFRKS	LKPFERD	ISTEIYQA	G <mark>NK</mark> PCNGV	/ <mark>AGF</mark> NCYF	PLRSYSF	°RPTYGVGH	QPYRVVVLSFELL	
BA. 1. 1		ADYNYKLPDDFTGCV I AWNSN <mark>K</mark> I	.DS <mark>KV</mark> SGNYNY	LYRLFRKS <mark>N</mark>	LKPFERD	ISTEIYQA	G <mark>NK</mark> PCNGV	/ <mark>A</mark> G <mark>F</mark> NCYF	PL <mark>R</mark> SY <mark>S</mark> F	° <mark>R</mark> PT <mark>Y</mark> GVG <mark>H</mark>	QPYRVVVLSFELL	
BA. 2		ADYNYKLPDDFTGCVIAWNSN <mark>K</mark> I	.DS <mark>KVG</mark> GNYNYI	LYRLFRKS <mark>N</mark>	LKPFERD	ISTEIYQA	G <mark>NK</mark> PCNGV	/ <mark>A</mark> G <mark>F</mark> NCYF	PL <mark>R</mark> SY <mark>G</mark> F	RPT <mark>Y</mark> GVG <mark>H</mark>	QPYRVVVLSFELL	
BA. 2. 12. 1		ADYNYKLPDDFTGCV I AWNSN <mark>K</mark> I	.DS <mark>KVG</mark> GNYNY <mark>(</mark>	QYRLFRKS <mark>N</mark>	LKPFERD	ISTEIYQA	G <mark>NK</mark> PCNGV	/ <mark>A</mark> G <mark>F</mark> NCYF	PL <mark>R</mark> SY <mark>G</mark> F	RPT <mark>Y</mark> GVG <mark>H</mark>	QPYRVVVLSFELL	
BA. 4/5		ADYNYKLPDDFTGCV I AWNSN <mark>K</mark> I	.DS <mark>KVG</mark> GNYNY	RYRLFRKS	LKPFERD	ISTEIYQA	G <mark>NK</mark> PCNGV	/ <mark>A</mark> GVNCYF	PL <mark>Q</mark> SY <mark>G</mark> F	RPT <mark>Y</mark> GVG <mark>H</mark>	QPYRVVVLSFELL	
BA. 2, 75		ADYNYKLPDDFTGCVIAWNSN <mark>K</mark> I	.DS <mark>KVS</mark> GNYNY	YRLFRKSK	LKPFERD	ISTEIYQA	G <mark>NK</mark> PCNGV	AGENCYE	PLOSYGE	RPT <mark>Y</mark> GVGH	QPYRVVVLSFELL	
BO 1 1		ADYNYKI PDDFTGCV I AWNSNKI	DSTVC GNVNV	RVRLERKSK	I KPFFRD	ISTEIVOA	GNKPCNG		PLOSVGE	RPTYGVGH	OPYRVVVI SFFI I	
VDD 1		ADVNVKI PDDETCCV I AWNSNKI				ICTEIVOA					ODVDVVVI SEELI	
ADD. I		ADINIKLEDDE IGOVIAWNON <mark>A</mark> I	ידעדעוס <mark>פ זע</mark> פטי		LKFFERD	ISTELLØA	G <mark>INIX</mark> E CING	AGDINC 1	L L <mark>A</mark> S I <mark>O</mark> L	INF I I GVGI	QF I KVVVLSPELL	
	1.4.4.2.											
WT	519	HAPATVCGPKKSTNLVKNKCVNF	541									
Beta		HAPATVCGPKKSTNLVKNKCVNF										
Delta		HAPATVCGPKKSTNLVKNKCVNF										
BA. 1		HAPATVCGPKKSTNLVKNKCVNF										
BA. 1. 1		HAPATVCGPKKSTNLVKNKCVNF										
BA. 2		HAPATVCGPKKSTNLVKNKCVNF										
BA. 2. 12 1		HAPATVCGPKKSTNLVKNKCVNF										
RA 4/5		HAPATVCCPKKSTNI VKNKCVNE										
BA 9 75		HADATVCCDKKSTNI VKNCVNI										
DA. 2. 70		HAD ATVCOP KKS INLYKIKCVIN										
RØ. 1. 1		HAPATVCGPKKSINLVKNKCVNF										
XBB. 1		HAPATVCGPKKSTNLVKNKCVNF										

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 refinementstatistics, Related to Figure 2.

Data Collection & Proce	ssing	
	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(Å)	2.79	
Local resolution(Å)	2.66	
Model Building & Refine	ement (Phenix 1.20 real-space-refi	ne)
Composition		
Nonhydrogen atoms	3116	
Protein residues	396	
Ligands	0	
Bonds (RMSD)		
Length (Å) (# > 4σ)	0.0003(0)	
Angles (°) <b>(</b> # > 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	128					
N477	l28, 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				