Supplementary Table 1: SARS-CoV-2 Spike Variants with a Global Prevalence Above 0.1% (February 2021)

S1 NTD				S1 RBD				S1 CTD				S2			
Pos	Ref	Mut	Pcnt	Pos	Ref	Mut	Pcnt	Pos	Ref	Mut	Pcnt	Pos	Ref	Mut	Pcnt
222	A	V	23	501	N	Y	11	614	D	G	95	716	T	I	11
69	H	-	13	477	S	N	5.30	570	A	D	11	982	S	A	11
144	Y	-	11	439	N	K	2.40	681	P	H	11	1118	D	H	11
18	L	F	10	452	L	R	0.50	677	Q	H	0.78	1163	D	Y	0.53
5	L	F	1.60	484	E	K	0.37	583	E	D	0.65	1167	G	V	0.45
98	S	F	1.50	453	Y	F	0.31	675	Q	H	0.54	701	A	V	0.34
262	A	S	1.10	417	K	N	0.21	655	H	Y	0.32	1176	V	F	0.34
272	P	L	0.81	520	A	S	0.18	626	A	S	0.24	688	A	V	0.33
153	M	T	0.76	494	S	P	0.16	622	V	F	0.19	936	D	Y	0.32
80	D	Y	0.50	501	N	T	0.11	613	Q	H	0.18	1073	K	N	0.26
13	S	I	0.40					673	S	T	0.15	939	S	F	0.25
21	R	I	0.39					572	T	I	0.13	769	G	V	0.23
152	W	C	0.37					640	S	F	0.13	1078	A	S	0.23
54	L	F	0.36					677	Q	P	0.12	1263	P	L	0.23
176	L	F	0.32					679	N	K	0.12	1219	G	C	0.22
143	V	F	0.27					574	D	Y	0.10	723	T	I	0.21
215	D	H	0.27					675	Q	R	0.10	1020	A	S	0.21
49	H	Y	0.26					681	P	R	0.10	732	T	A	0.20
253	D	G	0.26									1228	V	L	0.17
256	S	L	0.25									859	T	I	0.16
95	T	I	0.24									1252	S	F	0.15
26	P	S	0.23									772	V	I	0.14
138	D	Y	0.23									812	P	S	0.14
80	D	A	0.21									812	P	L	0.14
241	L	-	0.21									845	A	S	0.14
181	G	V	0.20									879	A	S	0.13
215	D	G	0.20									1073	K	T	0.12
255	S	F	0.20									1084	D	Y	0.12
164	N	T	0.19									780	E	Q	0.11
23	Q	H	0.18									929	S	T	0.11
12	S	F	0.15									957	Q	L	0.11
29	T	I	0.15									1122	V	L	0.11
153	M	I	0.15									1191	K	N	0.11
20	T	I	0.14									1219	G	V	0.11

189	L	F	0.14			839	D	Y	0.10
146	H	Y	0.13			1104	V	L	0.10
210	I	-	0.13			1117	T	I	0.10
254	S	F	0.13			1162	P	S	0.10
75	G	R	0.12			1229	M	I	0.10
138	D	H	0.12						
26	P	L	0.11						
245	H	Y	0.11						
22	T	I	0.10						
27	A	S	0.10						
67	A	V	0.10						
233	I	V	0.10						
261	G	V	0.10						

Footnote: NTD – N-terminal domain; RBD – receptor binding domain; CTD – C terminal domain; Mutation prevalences obtained February 2021 from COVID CG

Supplementary Table 2. Neutralizing Monoclonal Antibodies (mAbs) with Published High-Resolution Structures[1]

Name (Synonyms)	PDB Code	Epitope – Class[3]	IC_{50} (ng/ml) (wildtype)[4]	Reference
mAbs in phase 3 trials[2]				
Casirivimab (CAS; REGN-10933)	6XDG	RBM-1	8	1,2
Regdanvimab (CT-P59)	7CM4	RBM-1	8	3
Tixagevimab (TIX; COV2-2196/AZD8895)	7L7D	RBM-1	15	4,5
Etesevimab (ETE; CB6; JS016; LY-CoV16)	7C01	RBM-1	835	6
Bamlanivimab (BAM; LY-CoV555)	7KMG	RBM-2	10	7
Cilgavimab (CIL; COV2-2130; AZD1061)	7L7E	RBM-2	105	4,5
Imdevimab (IMD; REGN10987)	6XDG	RBD-core-1	6	1,2
Sotrovimab (S309; VIR-7831; GSK4182136)	6WPS	RBD-core-1	80	8
mAbs tested against ≥1 mutant pseudovirus				
BD-629	7CH5	RBM-1	4	9,10
CC12.1	6XC2	RBM-1	46	11,12
B38	7BZ5	RBM-1	180	13
P2C-1F11	7CDI	RBM-1	280	14
CV30	6XE1	RBM-1	118	15,16
COVA2-39	7JMP	RBM-1	54	17,18
BD-368-2	7CHH	RBM-2	15	9,10
P2B-2F6	7BWJ	RBM-2	410	14
C121	7K8X	RBM-2	2_{PV}	19,20
C119	7K8W	RBM-2	-	19,20
C144	7K90	RBM-3	3_{PV}	19,20
2-4	6XEY	RBM-3	-	21
S2M11	7K43	RBM-3	1	22
C110	7K85	RBD-core-1	-	19,20
C135	7K8Z	RBD-core-1	3_{PV}	19,20
COVA1-16	7JMW	RBD-core-2	745	17,18
H014	7CAH	RBD-core-2	570	23
4A8	7C2L	NTD	610	24
4-8	-	NTD	-	21
COVA2-04	7JMO	RBM-1	2500	17,18
DH1047	7LD1	RBD-core-2	-	25
S2E12	7K4N	RBM-1	4.2	22

S2H14	7JX3	RBM-1	900_{PV}	[26]
S2X35	7JXE	RBD-core-2	NA	[26]

Footnote: [1]mAbs in phase 3 clinical trials and mAbs that have undergone high-resolution structural studies (XR crystallography or cryo-EM) and been studied for their neutralizing activity against variants with one or more spike mutations. [2]Some of the mAbs in clinical trials have undergone Fc modifications such as changes to result in prolonged half-lives. The following mAbs are being studied only in combination – casirivimab/imdevimab and cilgavimab/tixagevimab. Bamlanivimab has been studied alone and in combination with etesevimab. The FDA has granted emergency use authorization (EUA) for the use bamlanivimab, bamlanivimab/etesevimab, and casirivimab/imdevimab. [3]The classification is derived from Finkelstein [27] which is slightly more granular than Barnes [28]; RBD – receptor binding domain, RBM – receptor binding motif, NTD – N-terminal domain. [4]IC_{50}s were obtained using infectious wildtype viruses (WT) defined as the Wuhan-Hu-1 reference sequence (GenBank accession: NC_945512.2). Results obtained using just pseudotyped viruses (PV) are indicated with a subscript. A dash indicates that susceptibility data was not available.

Supplementary Table 3. Experimentally confirmed cytotoxic T cell epitopes identified in more than one study

Peptide	Positions	Region	HLA	Notes	Mutations (≥0.1%)	Reference
YLQPRTFLL	269-277	NTD	A*02:01	Multiple patients	P272L (0.8%)	[30]
YLQPRTFLL	269-277	NTD	A*02:01	Multiple patients		[31]
YLQPRTFLL	269-277	NTD	A*02:01	NA		[32]
YLQPRTFLL	269-277	NTD	A*02:01	Multiple patients		[33]
YLQPRTFLL	269-277	NTD	A*02:01	Vaccinated persons		[34]
NYNYLYRLF	448-456	RBD	A*24:02	Multiple patients	L452R (0.5%); Y453F (0.3%)	[33]
NYNYLYRLF	448-456	RBD	A*24:02	Vaccinated persons		[34]
RLQSLQTYV	1000-1008	S2	A*02:01	Vaccinated persons	None	[34]
RLQSLQTYV	1000-1008	S2	A*02:01	NA		[32]
VVFLHVTYV	1060-1068	S2	A*02:01	NA	None	[35]
VVFLHVTYV	1060-1068	S2	A*02:01	NA		[32]
QYIKWPWYI	1208-1216	S2	A*24:02	Multiple patients	None	[30]
QYIKWPWYI	1208-1216	S2	A*24:02	Vaccinated persons		[34]
QYIKWPWYI	1208-1216	S2	A*24:02	Multiple patients		[33]
FIAGLIAIV	1220-1229	S2	A*02:01	NA	V1228L (0.2%)	[35]
FIAGLIAIV	1220-1228	S2	A*02:01	NA		[32]

Footnote: FVFLVLLPL (Positions 2-10) was found in one study [35] to be an HLA*02 CTL epitope: L5F is a recurrent mutation that has been hypothesized to possibly represent a CTL escape mutation [36].

References

1. Hansen, J. *et al.* Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science* (2020) doi:10.1126/science.abd0827.
2. Baum, A. *et al.* REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. *Science* **370**, 1110–1115 (2020).
3. Kim, C. *et al.* A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. *Nature Communications* **12**, 288 (2021).
4. Zost, S. J. *et al.* Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature* 1–7 (2020) doi:10.1038/s41586-020-2548-6.
5. Dong, J. *et al.* Genetic and structural basis for recognition of SARS-CoV-2 spike protein by a two-antibody cocktail. *bioRxiv* https://doi.org/10.1101/2021.01.27.428529 (2021).
6. Shi, R. *et al.* A human neutralizing antibody targets the receptor binding site of SARS-CoV-2. *Nature* (2020) doi:10.1038/s41586-020-2381-y.
7. Jones, B. E. *et al.* LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. *bioRxiv* https://doi.org/10.1101/2020.09.30.318972 (2020).
8. Pinto, D. *et al.* Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature* (2020) doi:10.1038/s41586-020-2349-y.
9. Cao, Y. *et al.* Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells. *Cell* (2020) doi:10.1016/j.cell.2020.05.025.
10. Du, S. *et al.* Structurally Resolved SARS-CoV-2 Antibody Shows High Efficacy in Severely Infected Hamsters and Provides a Potent Cocktail Pairing Strategy. *Cell* **183**, 1013-1023.e13 (2020).
11. Rogers, T. F. *et al.* Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. *Science* **369**, 956–963 (2020).
12. Yuan, M. *et al.* Structural basis of a shared antibody response to SARS-CoV-2. *Science* (2020) doi:10.1126/science.abd2321.
13. Wu, Y. *et al.* A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. *Science* **368**, 1274–1278 (2020).

14. Ju, B. *et al.* Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 1–8 (2020) doi:10.1038/s41586-020-2380-z.

15. Seydoux, E. *et al.* Analysis of a SARS-CoV-2-Infected Individual Reveals Development of Potent Neutralizing Antibodies with Limited Somatic Mutation. *Immunity* **53**, 98-105.e5 (2020).

16. Hurlburt, N. K. *et al.* Structural basis for potent neutralization of SARS-CoV-2 and role of antibody affinity maturation. *Nat Commun* **11**, 5413 (2020).

17. Brouwer, P. J. M. *et al.* Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. *Science* (2020) doi:10.1126/science.abc5902.

18. Liu, H. *et al.* Cross-Neutralization of a SARS-CoV-2 Antibody to a Functionally Conserved Site Is Mediated by Avidity. *Immunity* (2020) doi:10.1016/j.immuni.2020.10.023.

19. Robbiani, D. F. *et al.* Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature* **584**, 437–442 (2020).

20. Barnes, C. O. *et al.* Structures of Human Antibodies Bound to SARS-CoV-2 Spike Reveal Common Epitopes and Recurrent Features of Antibodies. *Cell* (2020) doi:10.1016/j.cell.2020.06.025.

21. Liu, X. *et al.* Neutralizing Antibodies Isolated by a site-directed Screening have Potent Protection on SARS-CoV-2 Infection. *bioRxiv* https://doi.org/10.1101/2020.05.03.074914 (2020).

22. Tortorici, M. A. *et al.* Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms. *Science* **370**, (2020).

23. Lv, Z. *et al.* Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. *Science* (2020) doi:10.1126/science.abc5881.

24. Chi, X. *et al.* A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. *Science* **369**, 650–655 (2020).

25. Li, D. *et al.* The functions of SARS-CoV-2 neutralizing and infection-enhancing antibodies in vitro and in mice and nonhuman primates. *bioRxiv* https://doi.org/10.1101/2020.12.31.424729 (2021).

26. Piccoli, L. *et al.* Mapping Neutralizing and Immunodominant Sites on the SARS-CoV-2 Spike Receptor-Binding Domain by Structure-Guided High-Resolution Serology. *Cell* **183**, 1024-1042.e21 (2020).

27. Finkelstein, M. T. *et al.* Structural Analysis of Neutralizing Epitopes of the SARS-CoV-2 Spike to Guide Therapy and Vaccine Design Strategies. *Viruses* **13**, https://doi.org/10.3390/v13010134 (2021).

28. Barnes, C. O. *et al.* SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. *Nature* 1–6 (2020) doi:10.1038/s41586-020-2852-1.

29. Starr, T. N. *et al.* Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. *Cell* (2020) doi:10.1016/j.cell.2020.08.012.

30. Ferretti, A. P. *et al.* Unbiased Screens Show CD8+ T Cells of COVID-19 Patients Recognize Shared Epitopes in SARS-CoV-2 that Largely Reside outside the Spike Protein. *Immunity* **53**, 1095-1107.e3 (2020).

31. Shomuradova, A. S. *et al.* SARS-CoV-2 Epitopes Are Recognized by a Public and Diverse Repertoire of Human T Cell Receptors. *Immunity* **53**, 1245-1257.e5 (2020).

32. Sekine, T. *et al.* Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. *Cell* **183**, 158-168.e14 (2020).

33. Kared, H. *et al.* SARS-CoV-2-specific CD8+ T cell responses in convalescent COVID-19 individuals. *J Clin Invest* (2021) doi:10.1172/JCI145476.

34. Sahin, U. *et al.* BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. *medRxiv* https://doi.org/10.1101/2020.12.09.20245175 (2020).

35. Qiu, C. *et al.* CD8+ T cell epitope variations suggest a potential antigen presentation deficiency for spike protein of SARS-CoV-2. *bioRxiv* https://doi.org/10.1101/2021.01.22.427863 (2021).

36. Martin, D. The emergence and ongoing convergent evolution of the N501Y lineages coincided with a major global shift in the SARS-Cov-2 selective landscape - SARS-CoV-2 coronavirus / SARS-CoV-2 Molecular Evolution. *Virological* https://virological.org/t/the-emergence-and-ongoing-convergent-evolution-of-the-n501y-lineages-coincided-with-a-major-global-shift-in-the-sars-cov-2-selective-landscape/618 (2021).