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**Supplementary information**

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**Rapid evaluation of COVID-19 vaccine effectiveness against symptomatic infection with SARS-CoV-2 variants by analysis of genetic distance**

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**Rapid evaluation of COVID-19 vaccine effectiveness against symptomatic infection with SARS-CoV-2 variants by analysis of genetic distance**

**Table 1: The source of COVID-19 vaccine efficacy or effectiveness (VE) data by December 24, 2021**

No.	Developers	Vaccine platforms	Vaccine products	Countries	Epidemiological studies	VE source	Data derived from
1	Bharat Biotech	Inactivated virus	COVAXIN	India	Phase 3 clinical trial	<sup>1</sup>	Table 2
2	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV	United Arab Emirates, Bahrain	Phase 3 clinical trial	<sup>2</sup>	Table 2
3	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	United Arab Emirates, Bahrain	Phase 3 clinical trial	<sup>2</sup>	Table 2
4	Sinovac Research and Development Co. Ltd	Inactivated virus	SARS-CoV-2 vaccine (Inactivated)	Brazil	Phase 3 clinical trial	<sup>3</sup>	Table 2
5				Indonesia	Phase 3 clinical trial	<sup>4</sup>	Table 3
6	BioNTech / Pfizer + Fosun Pharma	RNA based vaccine	BNT162b2 (3 LNP-mRNAs)	Argentina	Phase 3 clinical trial	<sup>5</sup>	Table 3
7				Brazil	Phase 3 clinical trial	<sup>5</sup>	Table 3
8				United States of America	Phase 3 clinical trial	<sup>5</sup>	Table 3
9				Argentina	Phase 3 clinical trial	<sup>6</sup>	Table 3
10				Brazil	Phase 3 clinical trial	<sup>6</sup>	Table 3
11				United States of America	Phase 3 clinical trial	<sup>6</sup>	Table 3
12	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	RNA based vaccine	mRNA-1273	United States of America	Phase 3 clinical trial	<sup>7</sup>	Figure 4
13				United States of America	Phase 3 clinical trial	<sup>8</sup>	Figure 3
14	Novavax	Protein Subunit	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M)	Mexico	Phase 3 clinical trial	<sup>9</sup>	Figure 3
15				United States of America	Phase 3 clinical trial	<sup>9</sup>	Figure 3
16				South Africa (B.1.351)	Phase 3 clinical trial	<sup>10</sup>	Text
17				United Kingdom (B.1.1.7)	Phase 3 clinical trial	<sup>11</sup>	Figure 4
18				United Kingdom (Non-B.1.1.7)	Phase 3 clinical trial	<sup>11</sup>	Figure 4
19	CanSino Biological Inc./Beijing Institute of Biotechnology	Viral vector (Non-replicating)	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	Argentina	Phase 3 clinical trial	<sup>12</sup>	Table 2
20	Gamaleya Research Institute; Health Ministry of the Russian Federation	Viral vector (Non-replicating)	Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)	Russia	Phase 3 clinical trial	<sup>13</sup>	Table 2
21	Janssen Pharmaceutical	Viral vector (Ad26)	Ad26.COVS.2S	Argentina, Chile, Colombia, Mexico, Peru	Phase 3 clinical trial	<sup>14</sup>	Table 3
22				Brazil	Phase 3 clinical trial	<sup>14</sup>	Table 3
23				South Africa (B.1.351)	Phase 3 clinical trial	<sup>14</sup>	Table 3
24				United States of America	Phase 3 clinical trial	<sup>14</sup>	Table 3
25					Viral vector (Non-replicating)	AZD1222 (ChAdOx1-S)	Brazil (B.1.1.28)

26	AstraZeneca + University of Oxford			Brazil (P.1)	Phase 3 clinical trial	15	Table 2
27				Brazil (P.2)	Phase 3 clinical trial	15	Table 2
28				United States of America	Phase 3 clinical trial	16	Figure 3
29				Chile, Peru	Phase 3 clinical trial	16	Figure 3
30				Brazil	Phase 3 clinical trial	17	Table 2
31				United Kingdom	Phase 3 clinical trial	17	Table 2
32				United Kingdom, Brazil, South Africa	Phase 3 clinical trial	18	Table 1
33				United Kingdom (B.1.1.7)	Phase 3 clinical trial	19	Table 1
34				Bharat Biotech	Inactivated virus	COVAXIN	India
35	India (Vellore)	Cohort	21				Text
36	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products Sinovac Research and Development Co. Ltd	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV  SARS-CoV-2 vaccine (Inactivated)	China (Guangzhou) (B.1.617.2)	Cohort	22	Table 2
37	Sinovac Research and Development Co. Ltd	Inactivated virus	SARS-CoV-2 vaccine (Inactivated)	Brazil (Manaus)	Case-control	23	Text
38				Brazil (São Paulo State)	Case-control	24	Table 2
39	BioNTech / Pfizer + Fosun Pharma	RNA based vaccine	BNT162b2 (3 LNP-mRNAs)	Italy	Cohort	25	Table 3
40				Israel	Cohort	26	Table 2
41				US (Kentucky)	Cohort	27	Table 1
42				Italy	Cohort	28	Table 2
43				Israel	Cohort	29	Table 2b
44				Israel	Cohort	30	Table
45				United Kingdom (B.1.1.7)	Case-control	31	Table 1
46				United Kingdom (B.1.617.2)	Case-control	31	Table 1
47				United Kingdom (B.1.1.7)	Case-control	32	Table 2
48				United Kingdom (B.1.617.2)	Case-control	32	Table 2
49				United States of America (North Carolina)	Cohort	33	Text
50				United States of America	Case-control	34	Table 3
51				Italy (Treviso)	Cohort	35	Table 2
52				United Kingdom	Case-control	36	Text
53				Israel	Cohort	37	Table 2
54				United Kingdom (Scotland) (B.1.1.7)	Test-negative case-control	38	Table S5

55				United Kingdom (Scotland) (B.1.617.2)	Test-negative case-control	38	Table S5
56				Canada	Case-control	39	Table 2
57				Israel	Cohort	40	Table 4
58				Israel	Cohort	41	Text
59	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	RNA based vaccine	mRNA-1273	United States of America	Case-control	34	Table 3
60				United States of America (North Carolina)	Cohort	33	Text
61				United States of America (Southern California)	Cohort	42	Table 3
62	BioNTech / Pfizer + Fosun Pharma	RNA based vaccine	BNT162b2 (3 LNP-mRNAs)  mRNA-1273	Canada (Ontario) (Earlier variant)	Test-negative case-control	43	eTable 6
63	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)			Canada (Ontario) (B.1.1.7)	Test-negative case-control	43	eTable 6
64				Canada (Ontario) (B.1.351/P.1)	Test-negative case-control	43	eTable 6
65				France (Earlier variant)	Case-control	44	Text
66				France (B.1.1.7)	Case-control	44	Text
67				France (B.1.351/P.1)	Case-control	44	Text
68				United States of America (33 U.S. sites)	Test-negative case-control	45	Table 2
69				United States of America (Michigan, Pennsylvania, Texas, Washington, and Wisconsin)	Test-negative case-control	46	Table 2
70	Janssen Pharmaceutical	Viral vector (Ad26)	Ad26.COV2.S	United States of America (North Carolina)	Cohort	33	Text
71				Brazil (Mato-Grosso do Sul)	Test-negative case-control	47	Table 2
72	AstraZeneca + University of Oxford	Viral vector (Non-replicating)	AZD1222 (ChAdOx1-S)	United Kingdom (B.1.617.2)	Case-control	31	Table 1
73				India	Case-control	48	Table 2
74				United Kingdom (B.1.1.7)	Case-control	32	Table 2
75				United Kingdom (B.1.617.2)	Case-control	32	Table 2
76				India (Puducherry)	Test-negative case-control	49	Table 2
77				United Kingdom (Scotland) (B.1.1.7)	Test-negative case-control	38	Table S5
78				United Kingdom (Scotland) (B.1.617.2)	Test-negative case-control	38	Table S5

**Table 2: COVID-19 VE prediction models for different vaccine platforms based on the genetic distance on the RBD**

<b>Vaccine platforms</b>		<b>Slope (95% CI)</b>	
mRNA		-5.2 (-8.0, -2.4)	
Viral-vector		-6.8 (-9.4, -4.2)	
Protein subunit		-14.3 (-19.2, -9.4)	
Inactivated		-15.8 (-19.3, -12.4)	
<b>Random effects variance</b>	146.0	<b>Two-sided <i>p</i>-value for RBD mismatch</b>	0.038
<b>Error variance</b>	38.8	<b><i>R</i><sup>2</sup></b>	86.3%

**Table 3: COVID-19 VE prediction models for six vaccine products based on the genetic distance on the RBD**

<b>Vaccine products</b>		<b>Slope (95% CI)</b>	
Moderna: mRNA-1273		-4.8 (-7.8, -1.9)	
Pfizer–BioNTech: BNT162b2		-7.5 (-10.9, -4.1)	
Oxford–AstraZeneca: AZD1222		-5.0 (-7.8, -2.2)	
Janssen: Ad26.COVS.2		-8.5 (-12.1, -4.9)	
Sinovac: CoronaVac		-13.6 (-17.1, -10.1)	
Novavax: NVX-CoV2373		-14.1 (-18.2, -10.0)	
<b>Random effects variance</b>			
	145.0	<b>Two-sided <i>p</i>-value for RBD mismatch</b>	0.006
<b>Error variance</b>			
	26.9	<b><i>R</i><sup>2</sup></b>	87.9%

**Table 4: COVID-19 VE prediction models for different vaccine platforms based on the genetic distance on the NTD and S protein**

<b>By genetic distance on the NTD:</b>			
<b>Vaccine platforms</b>		<b>Slope (95% CI)</b>	
mRNA		-2.5 (-4.6, -0.5)	
Viral-vector		-4.0 (-6.1, -1.8)	
Protein subunit		-5.6 (-9.5, -1.7)	
Inactivated		-7.8 (-10.2, -5.5)	
<b>Random effects variance</b>	105.9	<b>Two-sided <i>p</i>-value for NTD mismatch</b>	0.086
<b>Error variance</b>	62.4	<b><i>R</i><sup>2</sup></b>	75.8%

<b>By genetic distance on the S protein:</b>			
<b>Vaccine platforms</b>		<b>Slope (95% CI)</b>	
mRNA		-0.8 (-1.7, 0.2)	
Viral-vector		-1.6 (-2.6, -0.6)	
Protein subunit		-2.2 (-4.0, -0.5)	
Inactivated		-4.1 (-5.2, -2.9)	
<b>Random effects variance</b>	79.6	<b>Two-sided <i>p</i>-value for S protein mismatch</b>	0.082
<b>Error variance</b>	64.3	<b><i>R</i><sup>2</sup></b>	78.4%



**Table 5: The source of COVID-19 vaccine efficacy or effectiveness (VE) for validation**

No.	Vaccine products	Vaccine Platforms	Observed VE	(95%CI)	References
Alpha (B.1.1.7)					
[1]	BNT162b2	mRNA	97	(96, 98)	<sup>31</sup>
[2]	BNT162b2	mRNA	93.7	(91.6, 95.3)	<sup>32</sup>
[3]	BNT162b2	mRNA	92	(88, 94)	<sup>38</sup>
[4]	BNT162b2	mRNA	90	(85, 94)	<sup>43</sup>
[5]	BNT162b2	mRNA	86	(81, 90)	<sup>44</sup>
[6]	AZD1222	Viral vector	81	(72, 87)	<sup>38</sup>
[7]	AZD1222	Viral vector	74.5	(68.4, 79.4)	<sup>32</sup>
[8]	AZD1222	Viral vector	70.4	(43.6, 84.5)	<sup>19</sup>
Beta (B.1.351)					
[9]	BNT162b2	mRNA	77	(63, 86)	<sup>44</sup>
[10]	Ad26.COV2.S	Viral vector	52	(30.3, 67.4)	<sup>14</sup>
Gamma (P.1)					
[11]	BNT162b2	mRNA	88	(61, 96)	<sup>43</sup>
[12]	AZD1222	Viral vector	63.6	(-2.1, 87)	<sup>15</sup>
Delta (B.1.617.2)					
[13]	BNT162b2	mRNA	88	(85.3, 90.1)	<sup>32</sup>
[14]	BNT162b2	mRNA	84	(82, 86)	<sup>31</sup>
[15]	BNT162b2	mRNA	83	(78, 87)	<sup>38</sup>
[16]	AZD1222	Viral vector	71	(66, 74)	<sup>31</sup>
[17]	AZD1222	Viral vector	67	(61.3, 71.8)	<sup>32</sup>
[18]	AZD1222	Viral vector	61	(51, 70)	<sup>38</sup>
[19]	Covaxin	Inactivated	65.2	(33.1, 83)	<sup>1</sup>
[20]	CoronaVac	Inactivated	60.4	(31.8, 88.9)	<sup>22</sup>
B.1.1.28					
[21]	AZD1222	Viral vector	72.6	(46.4, 86)	<sup>15</sup>
Zeta (P.2)					
[22]	AZD1222	Viral vector	68.7	(54.9, 78.3)	<sup>15</sup>
Omicron (B.1.1.529)					
[23]	mRNA-1273	mRNA	13.9	(10.5, 17.1)	<sup>50</sup>

**Table 6: SARS-CoV-2 variants tracked by WHO, including variants of concern (VOCs), variants of interest (VOIs), variants under monitoring (VUMs) and formerly monitored variants (March 16, 2022)**

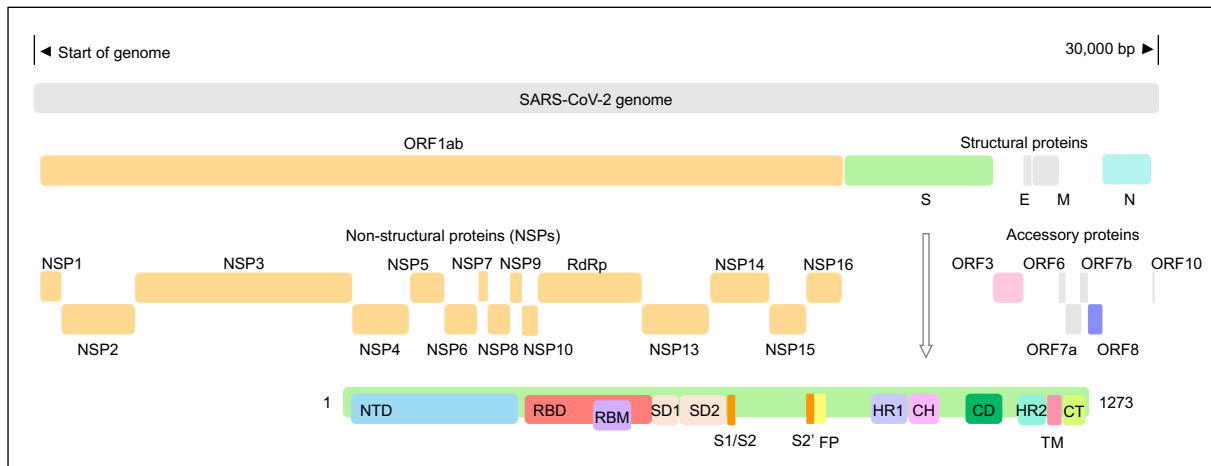
Pango lineages	WHO label	Nextstrain clade	GISAIID clade	VOI or VOC	Earliest documented samples	Mutations in S protein
B.1.1.7	Alpha	20I (V1)	GRY	VOC	United Kingdom	69-70del, 144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
B.1.351	Beta	20H (V2)	GH/501Y.V2	VOC	South Africa	D80A, D215G, Δ242-244, K417N, E484K, N501Y, D614G, A701V
P.1	Gamma	20J (V3)	GR/501Y.V3	VOC	Brazil	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F
B.1.617.2	Delta	21A, 21I, 21J	G/478K.V1	VOC	India	T19R, 157del, L452R, T478K, D614G, P681R, D950N
B.1.1.529	Omicron	21K, 21L, 21M	GRA	VOC	Multiple countries	T19I, L24del, P25del, P26del, A27S, A67V, H69del, V70del, T95I, G142D, V143del, Y144del, Y145del, N211I, L212V, V213R, V213G, ins214EP, R214del, R216E, G339D, R346K, S371F, S371L, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, N856K and L981F,
C.37	Lambda	21G	GR/452Q.V1	VOI	Peru	G75V, T76I, 249del, 251del, 252del, L452Q, F490S, D614G, T859N
B.1.621	Mu	21H	GH	VOI	Colombia	T95I, Y144S, Y145N, R346K, E484K, N501Y, D614G, P681H, D950N
B.1.1.318	-	-	GR	VUM	Multiple countries	T95I, E484K, D614G, P681H, D796H
C.1.2	-	-	GR	VUM	South Africa	P9L, P25L, C136F, R190S, D215G, Y449H, T478K, E484K, N501Y, D614G, H655Y, N679K, T716I
B.1.640	-	-	GH/490R	VUM	Multiple countries	P9L, E96Q, R190S, I210T, D215H, R346S, N394S, Y449N, E484K, F490R, N501Y, D614G, P681H, T859N, D936H, D1139H
AV.1	-	-	GR	Formerly monitored variants	United Kingdom	D80G, T95I, G142D, N439K, E484K, D614G, P681H, I1130V, D1139H
AT.1	-	-	GR	Formerly monitored variants	Russian Federation	P9L, H245P, E484K, D614G, E780K
P.2	Zeta	20B/S.484K	GR/484K.V2	Formerly monitored variants	Brazil	E484K, D614G, V1176F
P.3	Theta	21E	GR/1092K.V1	Formerly monitored variants	Philippines	141-143del, E484K, N501Y, D614G, P681H, E1092K, H1101Y, V1176F
R.1	-	20B	GR	Formerly monitored variants	Multiple countries	W152L, E484K, D614G, G769V
B.1.466.2	-	-	GH	Formerly monitored variants	Indonesia	N439K, D614G, P681R
B.1.1.519	-	20B/S.732A	GR	Formerly monitored variants	Multiple countries	T478K, D614G, P681H, T732A
C.36.3	-	-	GR	Formerly monitored variants	Multiple countries	S12F, W152R, R346S, L452R, D614G, Q677H, A899S
B.1.214.2	-	-	G	Formerly monitored variants	Multiple countries	Q414K, N450K, D614G, T716I
B.1.427/B.1.429	Epsilon	21C	GH/452R.V1	Formerly monitored variants	California, United States of America	S13I, W152C, L452R, D614G

B.1.1.523	-	-	GR	Formerly monitored variants	Multiple countries	F306L, E484K, S494P, D614G, E780A, D839V, T1027I
B.1.619	-	20A/S.126A	G	Formerly monitored variants		I210T, N440K, E484K, D614G, D936N, S939F, T1027I
B.1.620	-	-	G	Formerly monitored variants	Multiple countries	P26S, V126A, H245Y, S477N, E484K, D614G, P681H, T1027I, D1118H
B.1.526	Iota	21F	GH/253G.V1	Formerly monitored variants	New York, United States of America	L5F, T95I, D253G, D614G, A701V
B.1.525	Eta	21D	G/484K.V3	Formerly monitored variants	Multiple countries	Q52R, A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L
B.1.617.1	Kappa	21B	G/452R.V3	Formerly monitored variants	India	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H
B.1.630	-	-	GH	Formerly monitored variants	Dominican Republic	P9L, C136F, A222V, A243del, L244del, L452R, T478R, E484Q, H655Y, D614G, D950N

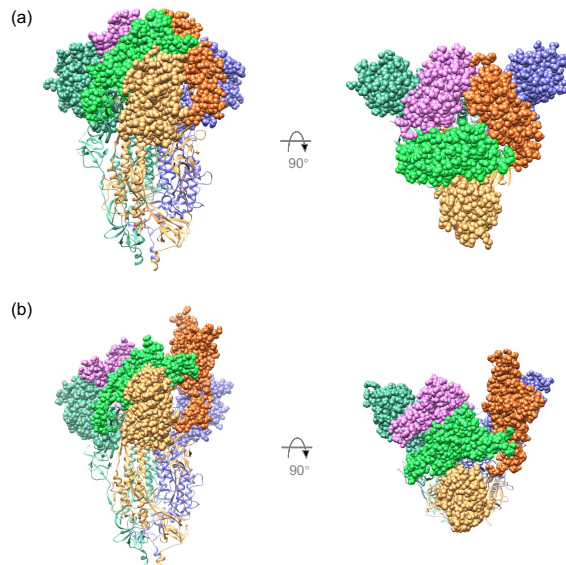
**Table 7: Randomly selected strains from the variants tracked by WHO to investigate the best candidate vaccine antigens**

Pango lineages	Accession number	Strain names	Source
B.1.1.7	EPI_ISL_1718637	hCoV-19/England/ALDP-15182AD/2021	GISAID
B.1.351	EPI_ISL_1534311	hCoV-19/South Africa/NHLS-UCT-GS-B188/2021	GISAID
P.1	EPI_ISL_1495024	hCoV-19/Brazil/MG-LBI246/2021	GISAID
B.1.617.2	EPI_ISL_1704630	hCoV-19/India/MH-ICMR-NIV-INSACOG-GSEQ-1304/2021	GISAID
BA.1	EPI_ISL_9215151	hCoV-19/USA/CA-Curative-120628/2021	GISAID
BA.1.1	EPI_ISL_7877115	hCoV-19/India/un-LNHD6/2021	GISAID
BA.2	EPI_ISL_7971635	hCoV-19/South Africa/NICD-N23195/2021	GISAID
BA.3	EPI_ISL_7747499	hCoV-19/South Africa/CERI-KRISP-K033318/2021	GISAID
C.37	EPI_ISL_1629764	hCoV-19/Peru/LIM-UPCH-0372/2021	GISAID
B.1.621	EPI_ISL_2828025	hCoV-19/Colombia/BOL-INS-VG-2019/2021	GISAID
B.1.1.318	EPI_ISL_7335871	hCoV-19/USA/CA-CDPH-3000035642/2021	GISAID
C.1.2	EPI_ISL_7456442	hCoV-19/South Africa/NICD-N21411/2021	GISAID
B.1.640.1	EPI_ISL_7267558	hCoV-19/France/CVL-CERBAHC-11681217/2021	GISAID
B.1.640.2	EPI_ISL_7412265	hCoV-19/USA/TX-CDC-ASC210487089/2021	GISAID
AT.1	EPI_ISL_3454818	hCoV-19/Russia/OMS-RII-MH22451S/2021	GISAID
AV.1	EPI_ISL_3291235	hCoV-19/England/PHEC-Q303Q1F8/2021	GISAID
P.2	EPI_ISL_1240642	hCoV-19/Brazil/MG-FUNED-49391-21/2021	GISAID
P.3	EPI_ISL_1122458	hCoV-19/Philippines/PH-PGC-02772/2021	GISAID
R.1	EPI_ISL_1793651	hCoV-19/Japan/YCH0165/2021	GISAID
B.1.466.2	EPI_ISL_7472531	hCoV-19/Indonesia/JB-GS-WJHL-ITB-GS-184/2021	GISAID
B.1.1.519	EPI_ISL_7703862	hCoV-19/USA/CA-CDPH-3000109212/2021	GISAID
C.36.3	EPI_ISL_8215718	hCoV-19/Egypt/NRC-627/2021	GISAID
B.1.214.2	EPI_ISL_4370585	hCoV-19/USA/CO-CDC-FG-014845/2021	GISAID
B.1.429	EPI_ISL_1525760	hCoV-19/USA/CA-CDC-FG-015454/2021	GISAID
B.1.1.523	EPI_ISL_8189540	hCoV-19/Russia/MAG-CRIE-L188T0024u/2021	GISAID
B.1.619	EPI_ISL_7667718	hCoV-19/Canada/QC-1nQUP-9969036211/2021	GISAID
B.1.620	EPI_ISL_7120450	hCoV-19/Congo/RC-116/2021	GISAID
B.1.525	EPI_ISL_1729603	hCoV-19/Germany/BY-RKI-I-095380/2021	GISAID
B.1.526	EPI_ISL_1200537	hCoV-19/USA/NY-NYCPHL-003648/2021	GISAID
B.1.617.1	EPI_ISL_1818634	hCoV-19/India/KA-NIMH-SEQ-374/2021	GISAID
B.1.630	EPI_ISL_2828025	hCoV-19/Colombia/BOL-INS-VG-2019/2021	GISAID
B.1	EPI_ISL_1473493	hCoV-19/England/CAMC-145D216/2021	GISAID
B.1.2	EPI_ISL_1553218	hCoV-19/USA/IL-S21WGS344/2021	GISAID
B.1.617.3	EPI_ISL_1704623	hCoV-19/India/MH-ICMR-NIV-INSACOG-GSEQ-1294/2021	GISAID

**Fig. 1: Schematic representation of the SARS-CoV-2 genome**



**Fig. 2: Structure of the SARS-CoV-2 Spike protein**



Legend: The location of receptor-binding domain (RBD) and N-terminal domain (NTD) are displayed on the 3D structure of SARS-CoV-2 Spike protein. Panel (a): the conformation of the prefusion trimer; all RBDs in the closed position. Panel (b): the active conformation; one RBD in the open position. The structures are shown from the side view and the top view, respectively. The RBD codons are highlighted in orchid, green and orange spheres. The NTD codons are marked in purple, dark green and yellow. Chimera<sup>51</sup> was used to generate the stereo view of S protein structure with 6VXX<sup>52</sup> and 7DWZ<sup>53</sup> of Protein Data Bank.

## References

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