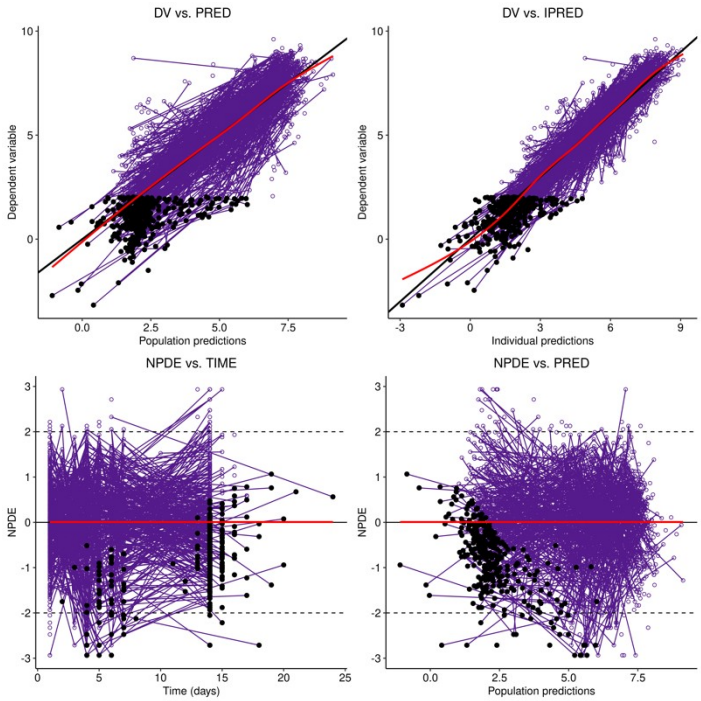
Supplementary Material: Randomized controlled trial of molnupiravir SARS-CoV-2 viral and antibody response in at-risk adult outpatients

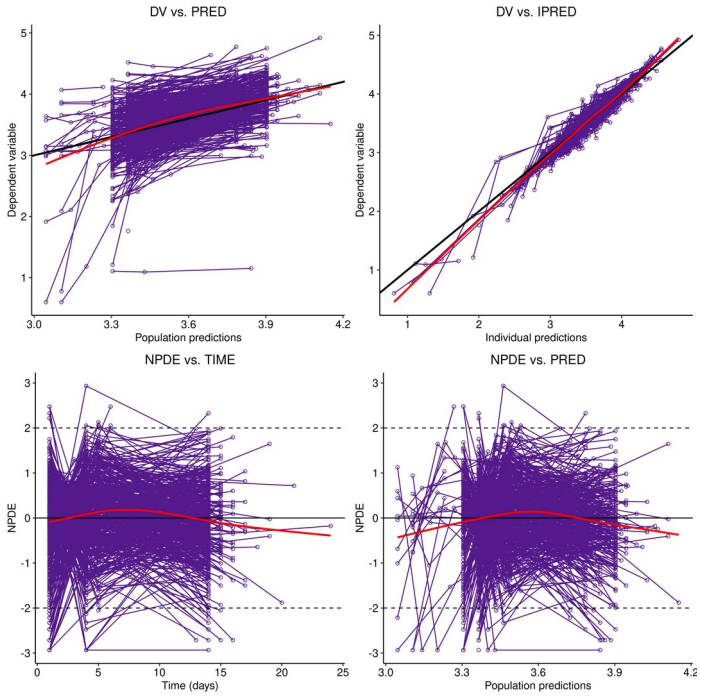
Supplementary Figure 1a | Basic goodness of fit for the viral dynamic model. DV, dependent variable (viral load). Population predictions are the typical predicted for each DV. Individual predictions use the empirical Bayes estimates of the parameters. NPDE: Normalised Prediction Distribution Errors, which are a type of weighted residual and should follow N(0,1). Purple points represent samples above the LLOQ, black dots below. Samples from individual participants are joined and a red smooth is added to compare with either the line of unity (top row) or zero line (bottom row).

a



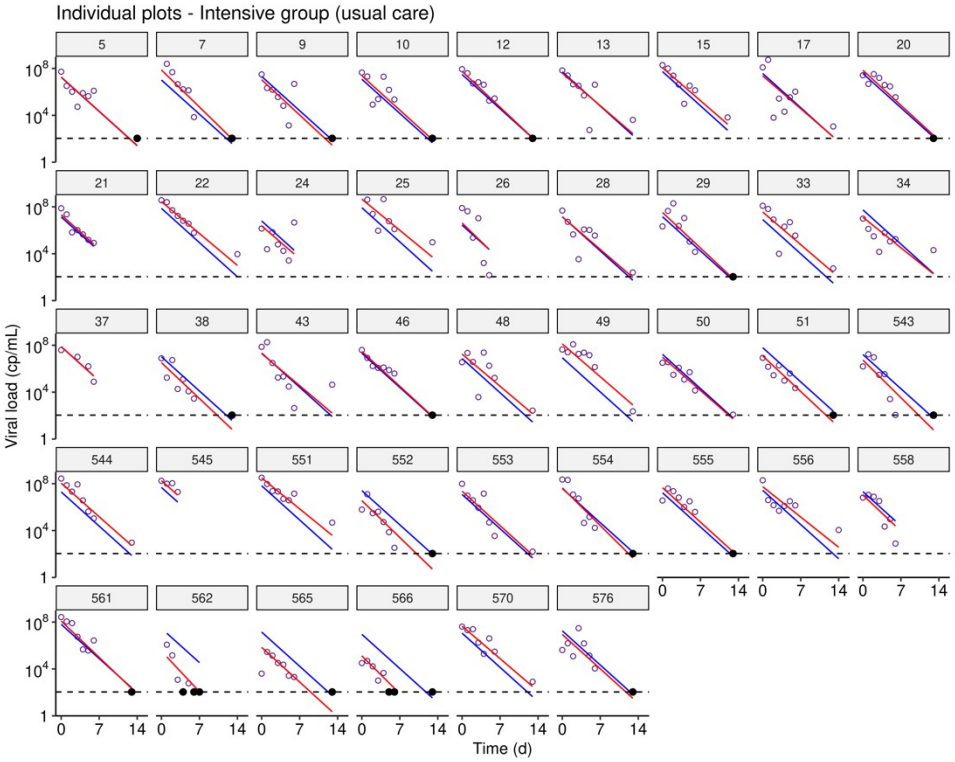
Supplementary Figure 1b | Basic goodness of fit for the antibody dynamic model. DV, dependent variable (spike antibody). Population predictions are the typical predicted for each DV. Individual predictions use the empirical Bayes estimates of the parameters. NPDE: Normalised Prediction Distribution Errors, which are a type of weighted residual and should follow N(0,1). Purple points represent samples from each participant. Samples from individual participants are joined and a red smooth is added to compare with either the line of unity (top row) or zero line (bottom row).

b



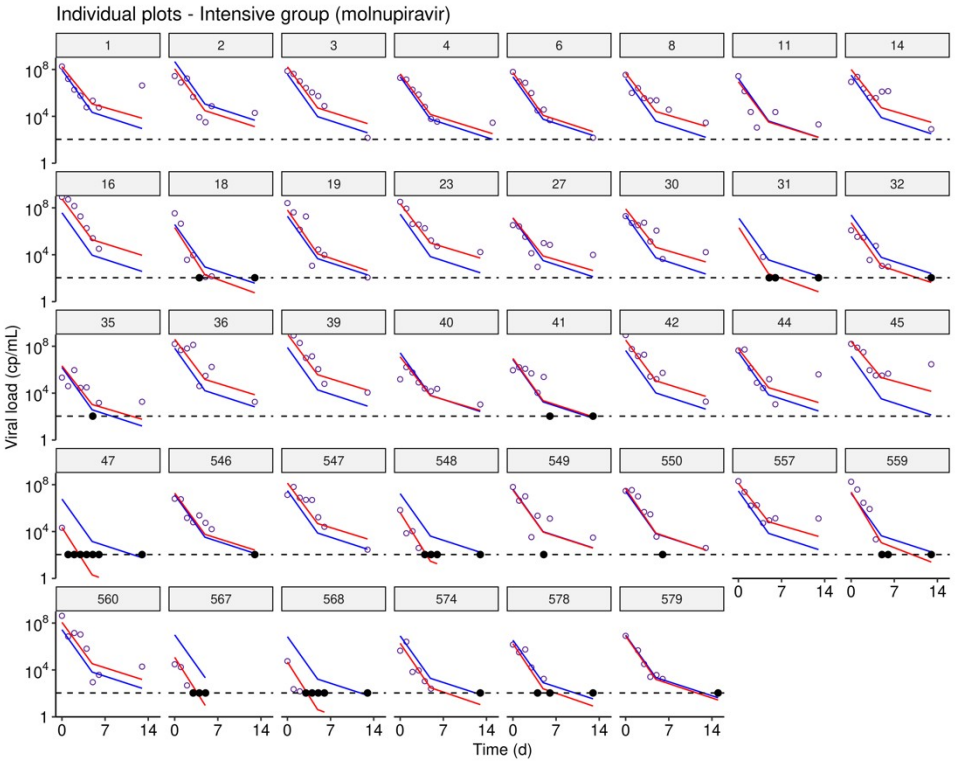
Supplementary Figure 2a | Individual viral load trajectories (open circles) for Usual Care Participants in the intensive sampling arm. Blue line represents population model prediction, red line represents the individual model prediction. black points are observations below the LLOQ

a

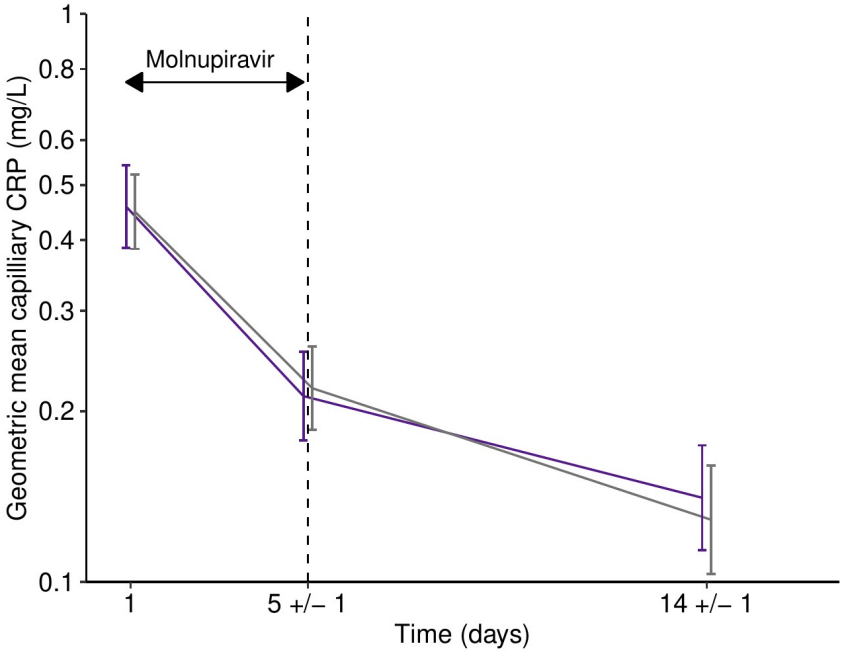


Supplementary Figure 2b | Individual viral load trajectories (open circles) for molnupiravir-treated participants in the intensive sampling arm. Blue line represents population model prediction, red line represents the individual model prediction. Black points are observations below the LLOQ

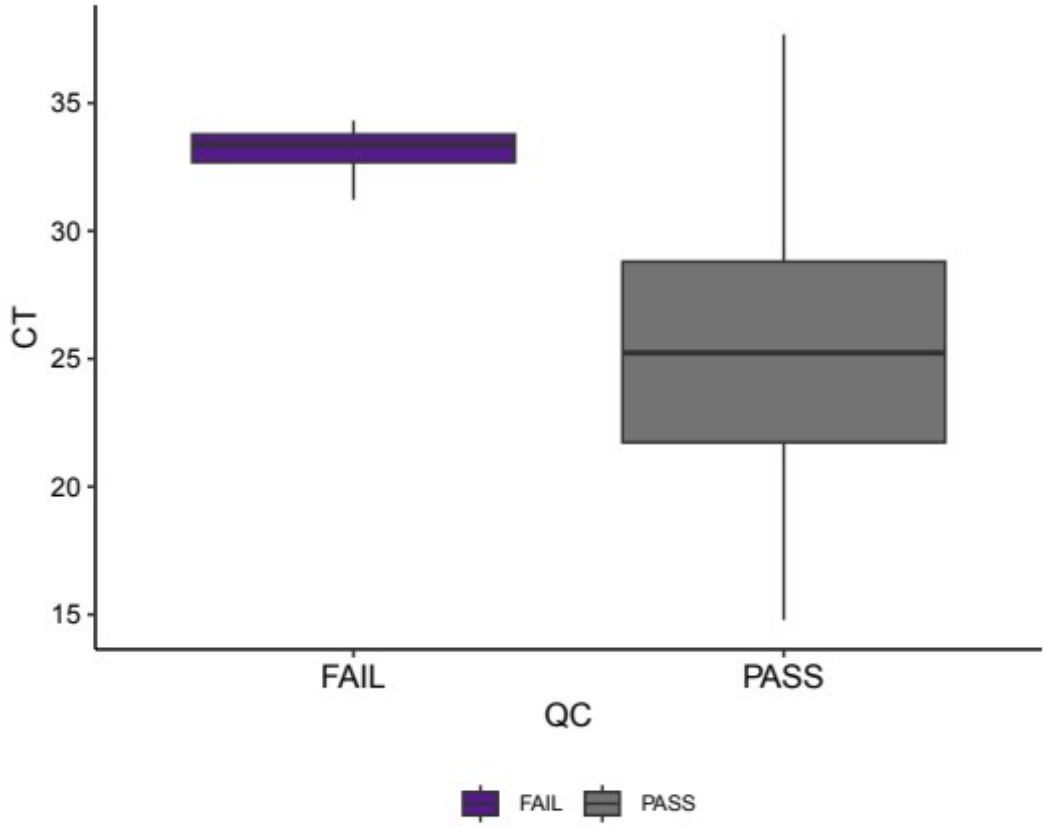
b



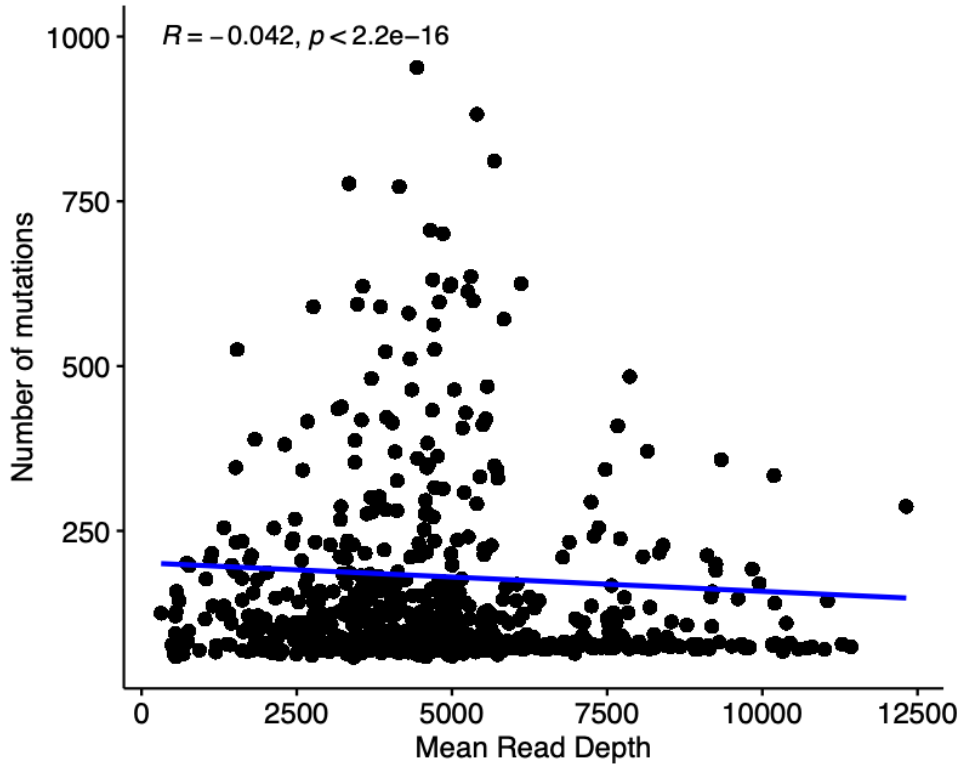
Supplementary Figure 3 | Capillary CRP dynamics with time in molnupiravir treated (purple) and Usual Care (grey). Lines are geometric means, error bars represent 95% CI of the geometric mean.



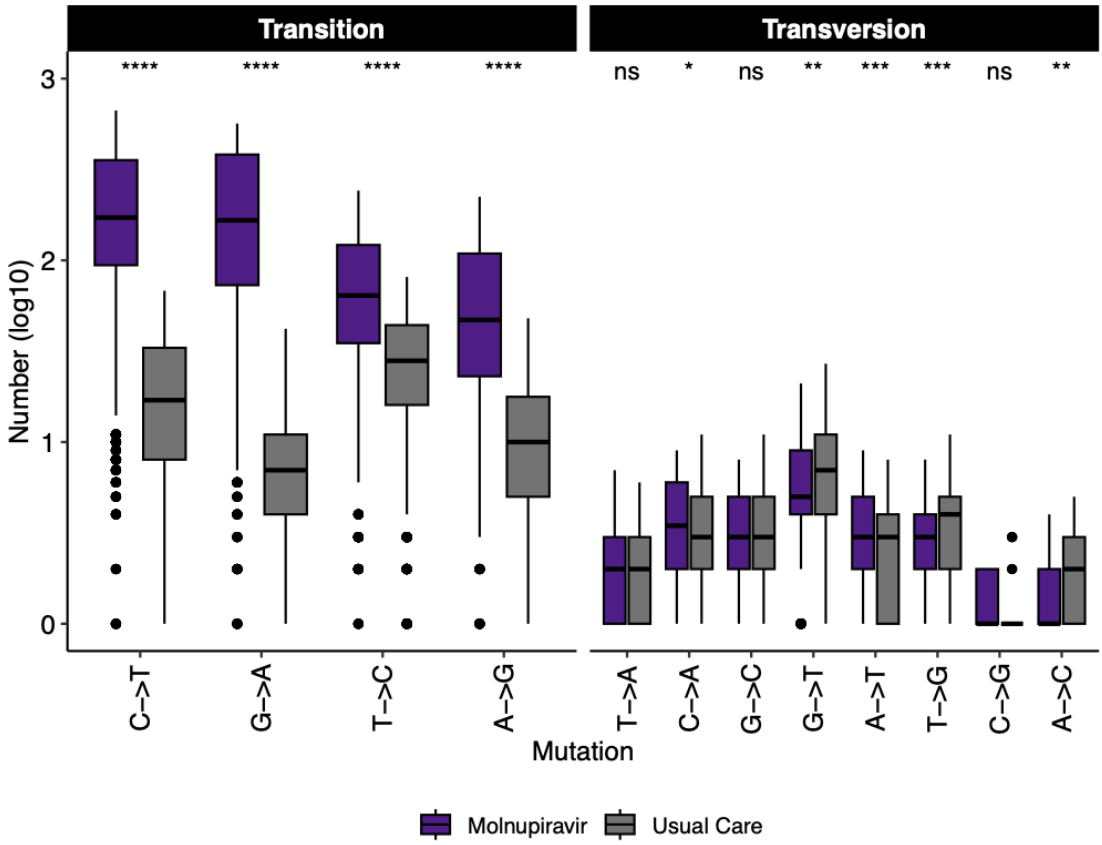
Supplementary Figure 4 | Relationship between SARS-CoV-2 sequencing success and viral load. Box- plot showing the quantitative PCR cycle threshold (CT) values for viral sequences with 90% coverage and mean read depth (MRD) of x10 (n=1437) in grey (PASS) and those (n=137) that failed to reach this threshold in purple (FAIL). Means and standard deviations (boxed area) are shown. All samples failing sequencing had CT values >31. Sequencing of a further 19 samples with CT values of >38 was not attempted. CT values for PASS samples were significantly lower than those for FAIL samples ($p<0.001$ Mann-Whitney U test).



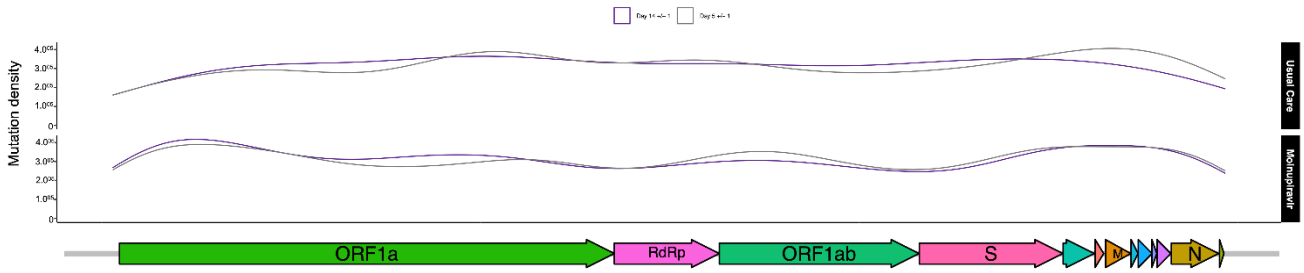
Supplementary Figure 5 | Relationship between number of mutations above 1% single nucleotide allele frequencies detected per sample and the mean read depth of the sample.



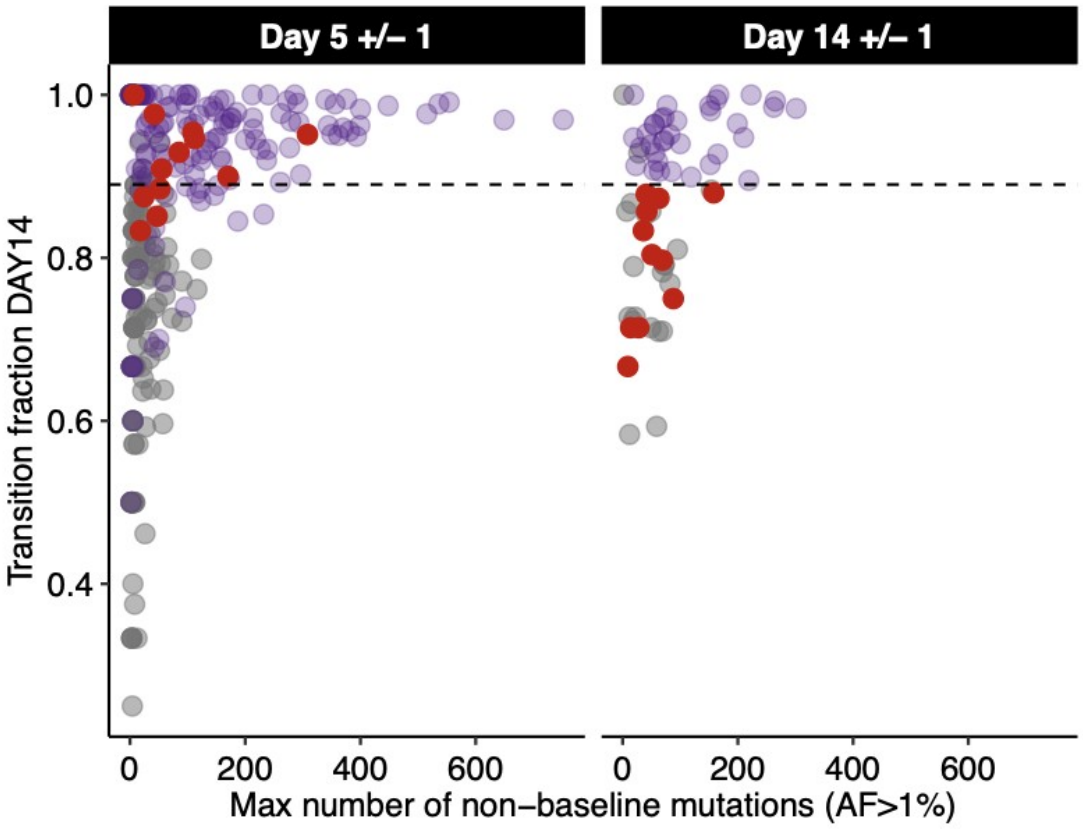
Supplementary Figure 6 | Total transition and transversion mutations over time in viral sequences from molnupiravir and Usual Care participants. Boxplots represent the total number of new single nucleotide polymorphisms (SNPs) above 1% allele frequency detected in samples collected from participants after baseline, divided by treatment group and type of nucleotide substitution. Samples from the molnupiravir treated group are shown in purple, while those from the Usual Care treatment group are shown in grey. Each data point aggregates all post-baseline timepoints for one participant, counting SNPs only once per individual. A total of 831 samples (excluding baseline) were analysed. A Mann-Whitney U test was used (* p<0.05, ** p<0.01, ****p<0.001, **** p<0.0001).



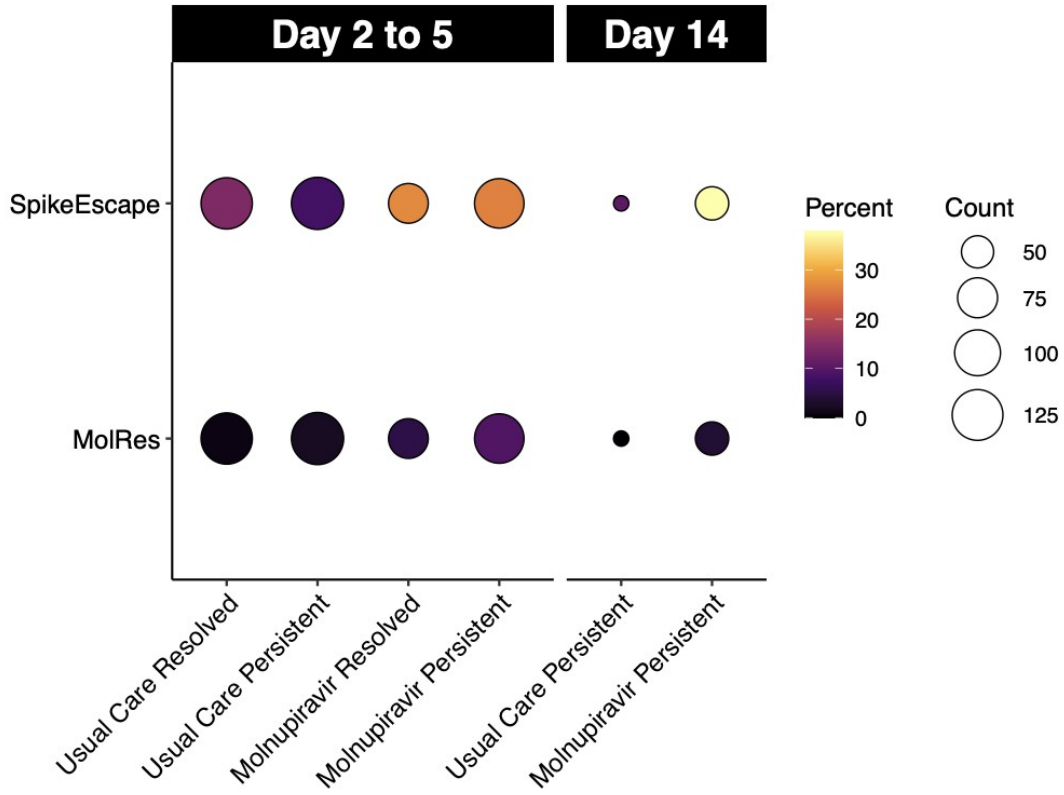
Supplementary Figure 7 | Distribution along the SARS-CoV-2 genome of new post-baseline synonymous and non-synonymous mutations (allele frequency > 5%) at Day 5 (grey) and Day 14 (purple) in molnupiravir and Usual Care participants. The x-axis shows the position along the SARS-CoV-2 genome. The y-axes show the mutation density (mutations at each position/total mutations) for each participant group.



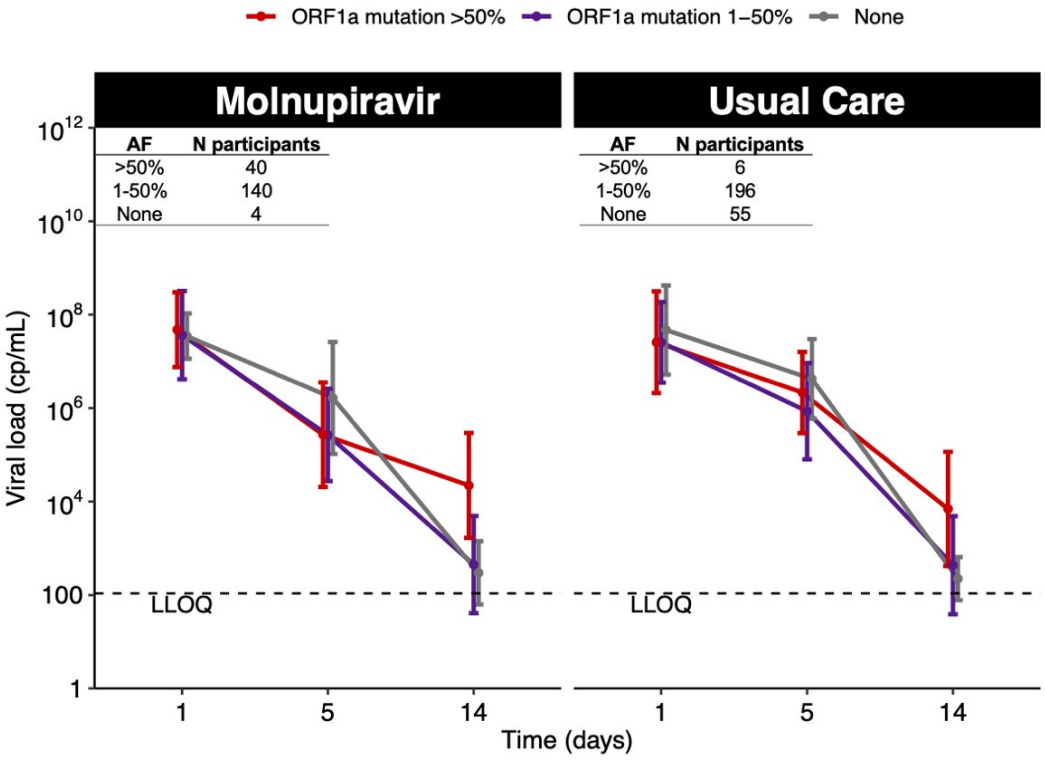
Supplementary Figure 8 | Scatter plot showing the number of new post-baseline mutations above 1% allele frequency (y axis) compared to the transition fraction (number of transitions/total transitions plus transversions) per sample for Days 5 and 14 (x axis). Samples are colour-coded by the treatment received: molnupiravir: purple, and Usual Care: grey. The black dotted line represents the transition fraction threshold below which all Usual Care samples cluster. Day 14 molnupiravir-treated samples which cluster with Day 14 Usual Care samples are shown in red.



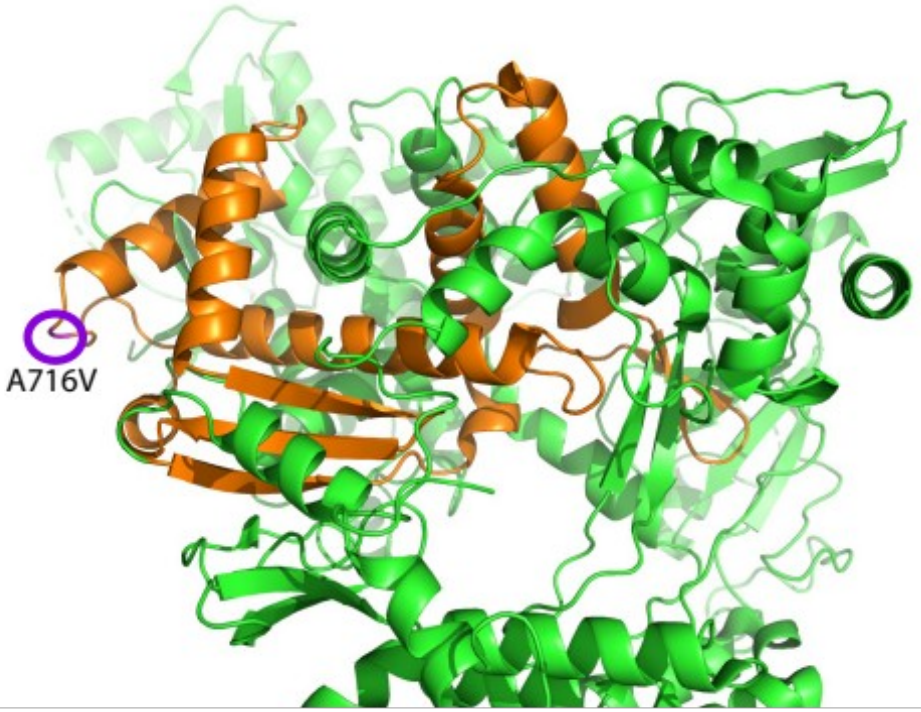
Supplementary Figure 9 | Numbers and frequency of participants with new post-baseline spike escape or molnupiravir resistance mutations at >1% frequency during treatment (Days 2-5) or at Day 14. Participants are divided by treatment (molnupiravir or Usual Care). 'Resolved' participants are those that do not have detectable viral load at Day 14, and 'persistent' participants are those with detectable viral load above LLOQ at ≥ Day 14. Where a participant has more than one sample taken between Days 2-5, the mean number of relevant SNPs detected/participant is included. The size of the circle indicates the number of participants in that group with one or more relevant new mutations by mutation-category and time point. The heat map shows the proportion of participants in each group with a new relevant mutation by mutation-category and time point.



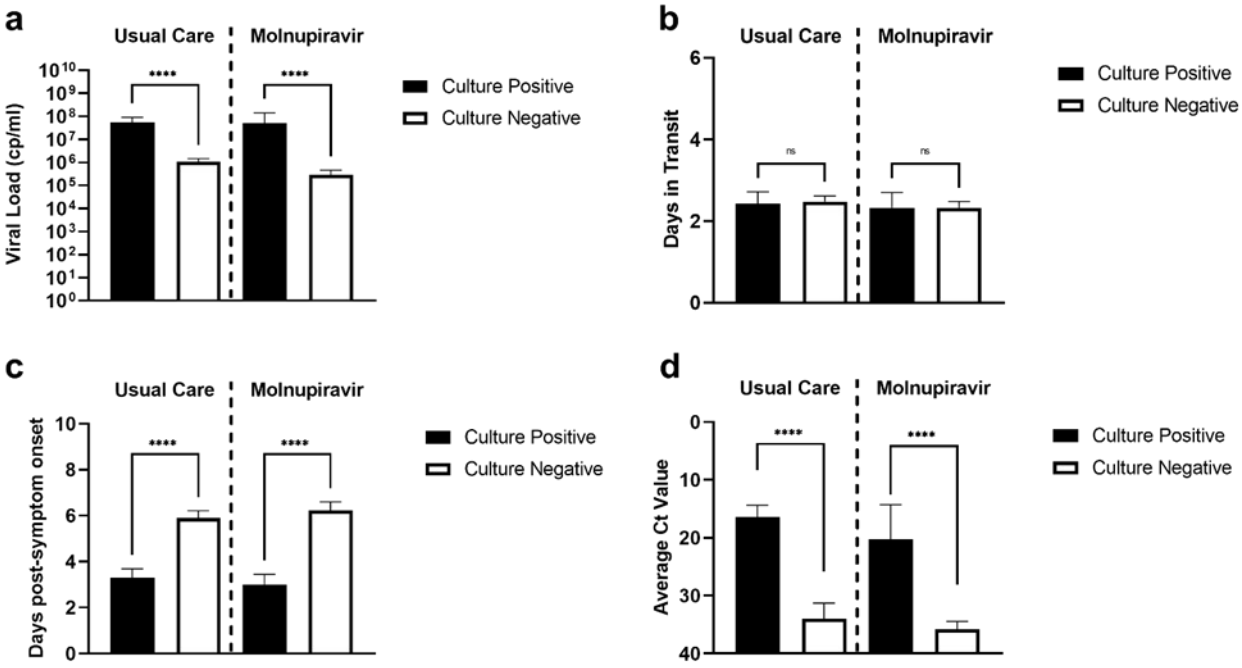
Supplementary Figure 10 | Viral load trajectories (mean and std deviation) for participants with any ORF1a post-baseline missense mutation at any time point which was above the consensus level (allele frequency (AF) >50%) in red, below the consensus level (1-50%) in purple or with no mutations (grey), for molnupiravir-treated and Usual Care groups. Participants included (441) were required to have viral load data for baseline, Day 5 and Day 14 and sequence data for all positive viral loads.



Supplementary Figure 11 | Structure of the SARS-CoV-2 RNA-dependent RNA polymerase based on PDB:6M71 (https://www.rcsb.org/structure/6m71). The catalytic site of the protein is highlighted in orange with the recurrent mutation found in our study at position 716 highlighted in purple.



Supplementary Figure 12 | Viral culture results. Plots demonstrating the difference between swab samples from Usual Care (n=558) or molnupiravir-treated (n=425) samples tested for viable virus culture in Calu-3 cells. Samples were characterised as culture positive (filled bar) requiring both observed cytopathogenic effects and a positive lateral flow immunochromatography test of culture medium, and otherwise were designated culture negative (empty bar). a, The participant's viral load at time of sample as determined by PCR (median ± 95% CI). b, The number of transport days between the swab collection and arrival at laboratory (geometric mean ± 95% CI). c, The number of days-post symptom onset at time of sample collection. d, Supernatant from a subset of Calu-3 cultured samples were tested by qRT-PCR using primers to SARS-CoV-2 N gene (n= 31) (geometric mean ± 95% CI). One-way ANOVA was used to calculate significance between specific groups, where **** = p<0.0001, ns = not significant.



Supplementary Table 1 | Number of participants and collected samples for both less intensive and intensive cohorts for baseline (Day 1), Day 5 and Day 14. The numbers (frequency) successfully sequenced is shown overall and for those with paired baseline and either/both Days 5 and 14 samples.

		Day 1		Day 5		Day 14	
	Treatment	Less intensely sampled	Intensely sampled	Less intensely sampled	Intensely sampled	Less intensely sampled	Intensely sampled
Total participants	Molnupiravir	215	38	207	38	171	34
Total participants sequenced		212 (98.6%)	37 (97.4%)	124 (59.9%)	32 (84.2%)	33 (19.3%)	13 (34.2%)
Participants with Paired baseline + at least one other sequence		130 (60.5%)	31 (81.6%)	124 (59.9%)	31 (81.6%)	33 (19.3%)	13 (34.2%)
Total participants	Usual Care	282	42	246	42	208	35
Total participants sequenced		277 (98.2%)	40 (95.2%)	175 (71.13%)	41 (97.6%)	17 (8.1%)	4 (11.4%)
Participants with Paired baseline + at least one other sequence		174 (61.7%)	40 (95.2%)	171 (69.5%)	40 (95.2%)	17 (8.1%)	4 (11.4%)

Supplementary Table 2 | Lineage assignment of baseline samples (Day 1) from participants for whom viral sequence was available by treatment group.

VOC_VUI	LINEAGE	Number of participants	Percentage	Treatment
Omicron (BA.2-like)	BA.2	161	72.85%	Molnupiravir
Omicron (BA.2-like)	BA.2.9	11	4.98%	Molnupiravir
Omicron (BA.2-like)	BA.2.3	10	4.52%	Molnupiravir
Omicron (BA.2-like)	BA.2.1	8	3.62%	Molnupiravir
Omicron (BA.2-like)	BA.2.23	8	3.62%	Molnupiravir
Omicron (BA.2-like)	BA.2.10	4	1.81%	Molnupiravir
Omicron (BA.2-like)	BA.2.18	3	1.36%	Molnupiravir
Omicron (BA.1-like)	BA.1.1	2	0.90%	Molnupiravir
Omicron (BA.2-like)	BA.2.22	2	0.90%	Molnupiravir
Omicron (BA.2-like)	BA.2.37	2	0.90%	Molnupiravir
Omicron (BA.2-like)	BA.2.3.9	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2.36	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2.39	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2.50	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2.51	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2.52	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2.8	1	0.45%	Molnupiravir
Omicron (BA.2-like)	XN	1	0.45%	Molnupiravir
Omicron (Unassigned)	XL	1	0.45%	Molnupiravir
Omicron (Unassigned)	XQ	1	0.45%	Molnupiravir
Omicron (BA.2-like)	BA.2	203	75.19%	Usual Care
Omicron (BA.2-like)	BA.2.9	16	5.93%	Usual Care
Omicron (BA.2-like)	BA.2.3	10	3.70%	Usual Care
Omicron (BA.2-like)	BA.2.1	6	2.22%	Usual Care
Omicron (BA.2-like)	BA.2.23	6	2.22%	Usual Care
Omicron (BA.2-like)	BA.2.10	5	1.85%	Usual Care
Omicron (BA.2-like)	BA.2.22	3	1.11%	Usual Care
Omicron (BA.2-like)	BA.2.18	2	0.74%	Usual Care
Omicron (BA.2-like)	BA.2.38	2	0.74%	Usual Care
Omicron (XE-like)	XE	2	0.74%	Usual Care
Omicron (BA.1-like)	BA.1.1	1	0.37%	Usual Care
Omicron (BA.1-like)	BA.1.1.15	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.10.1	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.31	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.41	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.45	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.5	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.50	1	0.37%	Usual Care

Omicron (BA.2-like)	BA.2.55	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.6	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.65	1	0.37%	Usual Care
Omicron (BA.2-like)	BA.2.8	1	0.37%	Usual Care
Omicron (BA.5-like)	BF.1	1	0.37%	Usual Care
Omicron (Unassigned)	BA.2	1	0.37%	Usual Care
Omicron (Unassigned)	XQ	1	0.37%	Usual Care

Supplementary Table 3 | Baseline characteristics of the thirteen molnupiravir-treated group samples with viral sequences at day 14 which appeared to have low mutagenesis (≤89%) comparable to the Usual Care group. Asterisks highlight the four participants who also had Day 5 transition fractions similar to the Usual Care group. nMut refers to the number of mutations detected at different allele frequency thresholds.

Participant ID	Time (Days)	Transition Fraction	nMut (>1%)	nMut (>5%)	nMut (>50%)	CRP (mg/L)	Sex	Lung disease	Heart disease	Kidney disease	Liver disease	Neuro disease	Diabetes	Immune disease
2	4	1.000	7	0	0	0.18	M	Yes	No	Yes	No	No	Yes	Yes
80	4	0.909	55	0	0	0.19	F	Yes	Yes	No	No	No	No	No
98	4	1.000	2	0	0	0.65	F	Yes	No	No	No	No	No	Yes
113*	4	0.885	52	38	0	0.15	F	No	No	No	No	No	No	No
181	4	0.951	308	3	2	0.13	M	No	No	No	No	No	No	No
227	4	0.900	170	3	0	1.03	F	No	No	No	No	No	No	No
246*	4	0.833	18	4	2	0.2	M	No	No	No	No	No	No	No
248	4	0.954	109	2	0	0.07	F	No	No	No	No	No	No	No
286	4	0.976	42	0	0	0.13	F	No	No	No	No	No	No	No
308*	4	0.851	47	17	0	0.18	F	No	No	No	No	No	Yes	No
366*	4	0.875	24	17	0	0.29	F	No	Yes	No	No	No	Yes	No
2	5	0.919	135	61	0	0.18	M	Yes	No	Yes	No	No	Yes	Yes
387	5	0.946	112	1	2	0.18	M	No	Yes	No	No	No	No	No
536	5	0.929	85	7	2	0.6	F	Yes	No	No	No	No	Yes	No
2	6	0.973	73	69	0	0.18	M	Yes	No	Yes	No	No	Yes	Yes
2	14	0.750	88	13	8	0.04	M	Yes	No	Yes	No	No	Yes	Yes
80	14	0.797	69	15	4	0.17	F	Yes	Yes	No	No	No	No	No
98	14	0.880	158	33	24	0.31	F	Yes	No	No	No	No	No	Yes
113	14	0.714	28	20	0	0.09	F	No	No	No	No	No	No	No
181	14	0.857	42	20	38	0.08	M	No	No	No	No	No	No	No
246	14	0.804	51	29	44	0.2	M	No	No	No	No	No	No	No
248	14	0.833	36	28	14	0.15	F	No	No	No	No	No	No	No

286	14	0.667	9	6	0	0.09	F	No	No	No	No	No	No	No
366	14	0.878	41	0	34	0.27	F	No	Yes	No	No	No	Yes	No
387	14	0.873	63	40	38	0.58	M	No	Yes	No	No	No	No	No
536	14	0.714	14	12	0	0.24	F	Yes	No	No	No	No	Yes	No
227	15	0.857	77	24	22	0.35	F	No	No	No	No	No	No	No
308	16	0.611	18	15	6	0.21	F	No	No	No	No	No	Yes	No

Supplementary Table 4 | Putative post-baseline resistance mutations identified at Day 14 both at allele frequency above 5% and at consensus level (>50%). Detailed are mutations in NSP12/RdRp that are considered to be associated with drug resistance to molnupiravir based on comparative genomics using the SARS2-ResistanceDB (retrieved from https://github.com/ucl-pathgenomics/SARS2-ResistanceDB), and Spike mutations considered to be relevant for immune system escape retrieved from the Pokay database (https://github.com/nodrogluap/pokay).

GENE	Change Observed	Effect	AF	Number of participants
NSP12	V560L	Predicted Resistance Site	>5%	1
NSP12	V234I	Predicted Resistance Site	>50%	1
S	A831V	Immune Modulation/Escape	>5%	1
S	W64R	Immune Modulation/Escape	>5%	1
S	Q1010R	Immune Modulation/Escape	>5%	1
S	P1162S	Immune Modulation/Escape	>5%	2
S	V1128A	Immune Modulation/Escape	>5%	1
S	H146Y	Immune Modulation/Escape	>5%	1
S	C15Y	Immune Modulation/Escape	>5%	1
S	K150R	Immune Modulation/Escape	>50%	1
S	P681R	Immune Modulation/Escape	>50%	1
S	F490L	Immune Modulation/Escape	>50%	1
S	F490S	Immune Modulation/Escape	>50%	2

Supplementary Table 5 | Summary details of viral mutations for four post-molnupiravir treatment (>5 days) samples with culturable virus. Total numbers of post-baseline transitions and transversions at ≥5% allele frequency per sample and details of amino acid changes are shown.

Participant ID	Time (Days)	Number of transitions	Number of transversions	AA change from baseline	Positive Day 14 VL
45	Day 6	9	1	R408S, G295S, G133D, V1931I, A1812T, V699I, E381K, P34L, A143T, K160E	Yes
85	Day 14	79	2	R408S, N507I, A2129T, G251D, S1924N, S2535L, N192S, V2133I, A90V, T2306I, A2123T, H1613Y, S815P, D2544N, V84I, N43S, S201N, N2539D, T247I, V116A, A570T, R476H, A2575V, G120R, P1088L, D3511N, A1670V, N804D, V89I, D543N, C15Y, A217T, P820S, A607V, T49I, P3395H, A41V, D571N, G146D, V808I, T812I, P25S, V45I, L95S, V4I, M3280I, S778N, C1254Y, A2621T, C563Y, G11R, A1070T, V29I, M584V, T602I, P46S, P271L, R2818H, Y449H, A2745V, A656T, A4V, P792S, S461L, T334I, V1177I, S330L, R634H, E132K, K440R, T325I, H373Y, V1290I, A382V, P322S, H69Y, R3802H, G1068R, S173N, F13S, G2927S	Yes
557	Day 7	35	0	V544I, N3168D, S3195N, S34F, T2611I, E2617R, A3620V, K3630R, T3287I, V2816I, T2846I, T2906I, V244I, S50G, V70I, L7S, A64T, H245Y, E102K, V202I, V596M, V841I, M1057I, R173C, P461S, A1060T, D294N, T1322I, D909N, P1921L, F2182L, G2284S, T547I, V1765I, M1448I	Yes
530	Day 6	1	0	A181V	Yes

Supplementary Table 6 | New post-baseline, consensus level (AF >=50%), missense transition (G->A or C->T) mutations at Day 14 for molnupiravir-treated and Usual Care participants. Total molnupiravir: 224 and Usual Care: 6.

AA change	Mutation	Gene	Treatment
D72N	G->A	E	Molnupiravir
L19F	C->T	E	Molnupiravir
A2T	G->A	M	Molnupiravir
R44K	G->A	M	Molnupiravir
D415N	G->A	N	Molnupiravir
G129D	G->A	N	Molnupiravir
H145Y	C->T	N	Molnupiravir
P365L	C->T	N	Molnupiravir
V246I	G->A	N	Molnupiravir
A130T	G->A	NSP12	Molnupiravir
A716V	C->T	NSP12	Molnupiravir
C22Y	G->A	NSP12	Molnupiravir
D303N	G->A	NSP12	Molnupiravir
G228D	G->A	NSP12	Molnupiravir
G228S	G->A	NSP12	Molnupiravir
H725Y	C->T	NSP12	Molnupiravir
H882Y	C->T	NSP12	Molnupiravir
P169S	C->T	NSP12	Molnupiravir
S15N	G->A	NSP12	Molnupiravir
S549N	G->A	NSP12	Molnupiravir
S778N	G->A	NSP12	Molnupiravir
T591I	C->T	NSP12	Molnupiravir
T76I	C->T	NSP12	Molnupiravir
V182I	G->A	NSP12	Molnupiravir
V234I	G->A	NSP12	Molnupiravir
V257I	G->A	NSP12	Molnupiravir
V359I	G->A	NSP12	Molnupiravir
V605I	G->A	NSP12	Molnupiravir
V905I	G->A	NSP12	Molnupiravir
A403T	G->A	NSP13	Molnupiravir
A454T	G->A	NSP13	Molnupiravir
A520T	G->A	NSP13	Molnupiravir
A568V	C->T	NSP13	Molnupiravir
D583N	G->A	NSP13	Molnupiravir
H290Y	C->T	NSP13	Molnupiravir
P491S	C->T	NSP13	Molnupiravir
P82L	C->T	NSP13	Molnupiravir
R339H	G->A	NSP13	Molnupiravir
R502H	G->A	NSP13	Molnupiravir
V340I	G->A	NSP13	Molnupiravir

V479I	G->A	NSP13	Molnupiravir
V521I	G->A	NSP13	Molnupiravir
V98I	G->A	NSP13	Molnupiravir
L56F	C->T	NSP7	Molnupiravir
A150V	C->T	NSP8	Molnupiravir
P178S	C->T	NSP8	Molnupiravir
T148I	C->T	NSP8	Molnupiravir
V115I	G->A	NSP8	Molnupiravir
V34I	G->A	NSP8	Molnupiravir
A8T	G->A	ORF10	Molnupiravir
V32I	G->A	ORF10	Molnupiravir
A1074T	G->A	ORF1a	Molnupiravir
A1397V	C->T	ORF1a	Molnupiravir
A1677T	G->A	ORF1a	Molnupiravir
A1679T	G->A	ORF1a	Molnupiravir
A1739V	C->T	ORF1a	Molnupiravir
A1809V	C->T	ORF1a	Molnupiravir
A1923T	G->A	ORF1a	Molnupiravir
A206T	G->A	ORF1a	Molnupiravir
A208T	G->A	ORF1a	Molnupiravir
A2142V	C->T	ORF1a	Molnupiravir
A2213T	G->A	ORF1a	Molnupiravir
A2279T	G->A	ORF1a	Molnupiravir
A2344T	G->A	ORF1a	Molnupiravir
A239V	C->T	ORF1a	Molnupiravir
A2584V	C->T	ORF1a	Molnupiravir
A2614T	G->A	ORF1a	Molnupiravir
A2614V	C->T	ORF1a	Molnupiravir
A2616T	G->A	ORF1a	Molnupiravir
A2745T	G->A	ORF1a	Molnupiravir
A2785T	G->A	ORF1a	Molnupiravir
A3023T	G->A	ORF1a	Molnupiravir
A3061T	G->A	ORF1a	Molnupiravir
A3220T	G->A	ORF1a	Molnupiravir
A3270T	G->A	ORF1a	Molnupiravir
A3571T	G->A	ORF1a	Molnupiravir
A3610V	C->T	ORF1a	Molnupiravir
A3615T	G->A	ORF1a	Molnupiravir
A3634T	G->A	ORF1a	Molnupiravir
A405T	G->A	ORF1a	Molnupiravir
A482T	G->A	ORF1a	Molnupiravir
A541T	G->A	ORF1a	Molnupiravir
A555T	G->A	ORF1a	Molnupiravir
A566T	G->A	ORF1a	Molnupiravir

A668V	C->T	ORF1a	Molnupiravir
A773V	C->T	ORF1a	Molnupiravir
A819T	G->A	ORF1a	Molnupiravir
A876V	C->T	ORF1a	Molnupiravir
A964T	G->A	ORF1a	Molnupiravir
A967T	G->A	ORF1a	Molnupiravir
C2180Y	G->A	ORF1a	Molnupiravir
C231Y	G->A	ORF1a	Molnupiravir
C3762Y	G->A	ORF1a	Molnupiravir
C506Y	G->A	ORF1a	Molnupiravir
C655Y	G->A	ORF1a	Molnupiravir
C800Y	G->A	ORF1a	Molnupiravir
D1179N	G->A	ORF1a	Molnupiravir
D1893N	G->A	ORF1a	Molnupiravir
D194N	G->A	ORF1a	Molnupiravir
D466N	G->A	ORF1a	Molnupiravir
D582N	G->A	ORF1a	Molnupiravir
E102K	G->A	ORF1a	Molnupiravir
E1086K	G->A	ORF1a	Molnupiravir
E2993K	G->A	ORF1a	Molnupiravir
E36K	G->A	ORF1a	Molnupiravir
E640K	G->A	ORF1a	Molnupiravir
E972K	G->A	ORF1a	Molnupiravir
G1408S	G->A	ORF1a	Molnupiravir
G150D	G->A	ORF1a	Molnupiravir
G2534S	G->A	ORF1a	Molnupiravir
G379E	G->A	ORF1a	Molnupiravir
G49S	G->A	ORF1a	Molnupiravir
G98D	G->A	ORF1a	Molnupiravir
H2799Y	C->T	ORF1a	Molnupiravir
L320F	C->T	ORF1a	Molnupiravir
L3829F	C->T	ORF1a	Molnupiravir
M2347I	G->A	ORF1a	Molnupiravir
M2719I	G->A	ORF1a	Molnupiravir
M3527I	G->A	ORF1a	Molnupiravir
M3621I	G->A	ORF1a	Molnupiravir
M3752I	G->A	ORF1a	Molnupiravir
M731I	G->A	ORF1a	Molnupiravir
M789I	G->A	ORF1a	Molnupiravir
M85I	G->A	ORF1a	Molnupiravir
P1786S	C->T	ORF1a	Molnupiravir
P2018S	C->T	ORF1a	Molnupiravir
P2110L	C->T	ORF1a	Molnupiravir
P2685S	C->T	ORF1a	Molnupiravir

P361S	C->T	ORF1a	Molnupiravir
P67S	C->T	ORF1a	Molnupiravir
P80S	C->T	ORF1a	Molnupiravir
P820L	C->T	ORF1a	Molnupiravir
P959S	C->T	ORF1a	Molnupiravir
R207C	C->T	ORF1a	Molnupiravir
R24H	G->A	ORF1a	Molnupiravir
R3662C	C->T	ORF1a	Molnupiravir
R3821K	G->A	ORF1a	Molnupiravir
R550H	G->A	ORF1a	Molnupiravir
R560H	G->A	ORF1a	Molnupiravir
S1924N	G->A	ORF1a	Molnupiravir
S1952L	C->T	ORF1a	Molnupiravir
S911F	C->T	ORF1a	Molnupiravir
T1004I	C->T	ORF1a	Molnupiravir
T1241I	C->T	ORF1a	Molnupiravir
T1429I	C->T	ORF1a	Molnupiravir
T1437I	C->T	ORF1a	Molnupiravir
T1678I	C->T	ORF1a	Molnupiravir
T1773I	C->T	ORF1a	Molnupiravir
T1890I	C->T	ORF1a	Molnupiravir
T2158I	C->T	ORF1a	Molnupiravir
T2264I	C->T	ORF1a	Molnupiravir
T265I	C->T	ORF1a	Molnupiravir
T2910I	C->T	ORF1a	Molnupiravir
T3032I	C->T	ORF1a	Molnupiravir
T3462I	C->T	ORF1a	Molnupiravir
T3579I	C->T	ORF1a	Molnupiravir
T484I	C->T	ORF1a	Molnupiravir
T568I	C->T	ORF1a	Molnupiravir
T602I	C->T	ORF1a	Molnupiravir
T821I	C->T	ORF1a	Molnupiravir
V1056M	G->A	ORF1a	Molnupiravir
V1063I	G->A	ORF1a	Molnupiravir
V1122I	G->A	ORF1a	Molnupiravir
V1393M	G->A	ORF1a	Molnupiravir
V2238I	G->A	ORF1a	Molnupiravir
V2496M	G->A	ORF1a	Molnupiravir
V2754I	G->A	ORF1a	Molnupiravir
V2955M	G->A	ORF1a	Molnupiravir
V3120I	G->A	ORF1a	Molnupiravir
V3166I	G->A	ORF1a	Molnupiravir
V3593I	G->A	ORF1a	Molnupiravir
V3751I	G->A	ORF1a	Molnupiravir

V3763I	G->A	ORF1a	Molnupiravir
V3847I	G->A	ORF1a	Molnupiravir
A100V	C->T	ORF1ab	Molnupiravir
A319V	C->T	ORF1ab	Molnupiravir
D827N	G->A	ORF1ab	Molnupiravir
E453K	G->A	ORF1ab	Molnupiravir
G416S	G->A	ORF1ab	Molnupiravir
P140S	C->T	ORF1ab	Molnupiravir
T472M	C->T	ORF1ab	Molnupiravir
V1012I	G->A	ORF1ab	Molnupiravir
V269I	G->A	ORF1ab	Molnupiravir
V421I	G->A	ORF1ab	Molnupiravir
V713I	G->A	ORF1ab	Molnupiravir
V841I	G->A	ORF1ab	Molnupiravir
A99T	G->A	ORF3a	Molnupiravir
D238N	G->A	ORF3a	Molnupiravir
E241K	G->A	ORF3a	Molnupiravir
G100D	G->A	ORF3a	Molnupiravir
G49D	G->A	ORF3a	Molnupiravir
H150Y	C->T	ORF3a	Molnupiravir
L147F	C->T	ORF3a	Molnupiravir
L65F	C->T	ORF3a	Molnupiravir
P104S	C->T	ORF3a	Molnupiravir
V168I	G->A	ORF3a	Molnupiravir
V259I	G->A	ORF3a	Molnupiravir
A105T	G->A	ORF7a	Molnupiravir
A79V	C->T	ORF7a	Molnupiravir
D51N	G->A	ORF7a	Molnupiravir
T61I	C->T	ORF7a	Molnupiravir
Q35*	C->T	ORF7b	Molnupiravir
A15V	C->T	ORF8	Molnupiravir
A55T	G->A	ORF8	Molnupiravir
A1226V	C->T	S	Molnupiravir
A263T	G->A	S	Molnupiravir
A570V	C->T	S	Molnupiravir
A653V	C->T	S	Molnupiravir
A672T	G->A	S	Molnupiravir
A67T	G->A	S	Molnupiravir
A684T	G->A	S	Molnupiravir
A829V	C->T	S	Molnupiravir
C1236Y	G->A	S	Molnupiravir
D215N	G->A	S	Molnupiravir
G181E	G->A	S	Molnupiravir
H1088Y	C->T	S	Molnupiravir

Q954*	C->T	S	Molnupiravir
R1185H	G->A	S	Molnupiravir
S1242N	G->A	S	Molnupiravir
S689N	G->A	S	Molnupiravir
T1160I	C->T	S	Molnupiravir
T547I	C->T	S	Molnupiravir
V1061I	G->A	S	Molnupiravir
V622I	G->A	S	Molnupiravir
R146H	G->A	M	Usual Care
P169S	C->T	NSP12	Usual Care
A336V	C->T	NSP13	Usual Care
T1754I	C->T	ORF1a	Usual Care
S1587L	C->T	ORF1a	Usual Care
V1291I	G->A	ORF1a	Usual Care

Supplementary Table 7 | COG-ID for 1436 whole genome sequence uploaded to CLIMB database.

LOND-YYBE13K	LOND-YYBEON5	LOND-YYBEWZC	LOND-YYBEMI3	LOND-YYBEXJQ	LOND-YYBEKBD
LOND-YYBE18X	LOND-YYBEORZ	LOND-YYBEX15	LOND-YYBEMPK	LOND-YYBEXKC	LOND-YYBEKEI
LOND-YYBE1B5	LOND-YYBEOTH	LOND-YYBEX4M	LOND-YYBEMRH	LOND-YYBEXMK	LOND-YYBEKHC
LOND-YYBE1M8	LOND-YYBEP3X	LOND-YYBEX5J	LOND-YYBEO14	LOND-YYBEXPG	LOND-YYBEKI4
LOND-YYBE1N3	LOND-YYBEP5M	LOND-YYBEXD4	LOND-YYBEOGU	LOND-YYBEXRA	LOND-YYBEKSA
LOND-YYBE1RI	LOND-YYBEP6F	LOND-YYBEXNH	LOND-YYBEOWS	LOND-YYBEZ3F	LOND-YYBEMAU
LOND-YYBE1T4	LOND-YYBEP8W	LOND-YYBEXU3	LOND-YYBEP9D	LOND-YYBEZ5B	LOND-YYBEMGA
LOND-YYBE1Y7	LOND-YYBEPAT	LOND-YYBEXWZ	LOND-YYBEPDH	LOND-YYBEZ65	LOND-YYBEMQE
LOND-YYBEI8C	LOND-YYBEPT9	LOND-YYBE15G	LOND-YYBEPJO	LOND-YYBE16Y	LOND-YYBEOC8
LOND-YYBEIFO	LOND-YYBEPYN	LOND-YYBE1CF	LOND-YYBEPKQ	LOND-YYBE1HR	LOND-YYBEOIW
LOND-YYBEIPY	LOND-YYBEQ1H	LOND-YYBE1EP	LOND-YYBEPOB	LOND-YYBE1JM	LOND-YYBEOPF
LOND-YYBEIQ6	LOND-YYBEQ4C	LOND-YYBE1GT	LOND-YYBEPU5	LOND-YYBE1KJ	LOND-YYBEOS1
LOND-YYBEIWT	LOND-YYBEQ5K	LOND-YYBE31T	LOND-YYBEPW3	LOND-YYBE1PD	LOND-YYBEPHJ
LOND-YYBEIZM	LOND-YYBEQFZ	LOND-YYBE363	LOND-YYBEQ7G	LOND-YYBE1QB	LOND-YYBEPIZ
LOND-YYBEJ1B	LOND-YYBEQJX	LOND-YYBE3N1	LOND-YYBEQ8U	LOND-YYBE3C6	LOND-YYBEPMC
LOND-YYBEJ6J	LOND-YYBEQKP	LOND-YYBE3WP	LOND-YYBEQCJ	LOND-YYBE3GK	LOND-YYBEPSI
LOND-YYBEJ8A	LOND-YYBEQR3	LOND-YYBE3YS	LOND-YYBEQHE	LOND-YYBE3H7	LOND-YYBEQB9
LOND-YYBEJ98	LOND-YYBEQWA	LOND-YYBE4DX	LOND-YYBEQSW	LOND-YYBE3JR	LOND-YYBEQIS
LOND-YYBEJES	LOND-YYBESBZ	LOND-YYBE4FM	LOND-YYBESEJ	LOND-YYBE3OI	LOND-YYBEQN7
LOND-YYBEJOF	LOND-YYBETAP	LOND-YYBE4KB	LOND-YYBESIQ	LOND-YYBE3Q4	LOND-YYBEQP8
LOND-YYBEK4O	LOND-YYBETBH	LOND-YYBE4T1	LOND-YYBESMD	LOND-YYBE3RQ	LOND-YYBEQXD
LOND-YYBEK5Q	LOND-YYBETJC	LOND-YYBEAC9	LOND-YYBESOA	LOND-YYBE3SJ	LOND-YYBEQZ1
LOND-YYBEKG3	LOND-YYBETPR	LOND-YYBEAGM	LOND-YYBESP9	LOND-YYBE488	LOND-YYBES1W
LOND-YYBEKR7	LOND-YYBETQN	LOND-YYBEARX	LOND-YYBESWO	LOND-YYBE4BU	LOND-YYBES4R
LOND-YYBEKWH	LOND-YYBETY6	LOND-YYBEATW	LOND-YYBETDA	LOND-YYBE4C7	LOND-YYBES76
LOND-YYBEKYF	LOND-YYBEU1Z	LOND-YYBEAX3	LOND-YYBETHF	LOND-YYBE4XZ	LOND-YYBESAE
LOND-YYBEM9F	LOND-YYBEU5F	LOND-YYBEI95	LOND-YYBETKK	LOND-YYBEA3R	LOND-YYBESKF
LOND-YYBEMBN	LOND-YYBEU69	LOND-YYBEIAJ	LOND-YYBETO7	LOND-YYBEABI	LOND-YYBESRT
LOND-YYBEMHM	LOND-YYBEU7B	LOND-YYBEIEK	LOND-YYBEU97	LOND-YYBEAH6	LOND-YYBET6B
LOND-YYBEMJ1	LOND-YYBEUB4	LOND-YYBEIHB	LOND-YYBEUDS	LOND-YYBEAKD	LOND-YYBET7D
LOND-YYBEMKO	LOND-YYBEUJK	LOND-YYBEIJE	LOND-YYBEUMG	LOND-YYBEASK	LOND-YYBETFW

LOND-YYBEMSZ
LOND-YYBEUKE
LOND-YYBEISP
LOND-YYBEUQY
LOND-YYBEAWQ
LOND-YYBETRS
LOND-YYBEMU7
LOND-YYBEUNA
LOND-YYBEJ3U
LOND-YYBEURW
LOND-YYBEI1I
LOND-YYBETUZ
LOND-YYBEMZI
LOND-YYBEUYH
LOND-YYBEJ4T
LOND-YYBEUSX
LOND-YYBEIBA
LOND-YYBEUCR
LOND-YYBEO3C
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LOND-YYBEJMO
LOND-YYBEW9H
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LOND-YYBEOAQ
LOND-YYBEW7Y
LOND-YYBEJU9
LOND-YYBEWAK
LOND-YYBEIO3
LOND-YYBEW3E
LOND-YYBEOJP
LOND-YYBEWGX
LOND-YYBEKX8
LOND-YYBEWTA
LOND-YYBEIY4
LOND-YYBEW4G
LOND-YYBEOKM
LOND-YYBEWQ9
LOND-YYBEM19
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LOND-YYBEK7K
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LOND-YYBEWX7
LOND-YYBEMF4
LOND-YYBEXH8
LOND-YYBEK8Z
LOND-YYBEWJJ
LOND-YYBEWNZ
LOND-YYBJE8Z
LOND-YYBJPFS
LOND-YYBJGAS
LOND-YYBJRHO
LOND-YYBJCQF
LOND-YYBEX9B
LOND-YYBJE9G
LOND-YYBJPII
LOND-YYBJGEZ
LOND-YYBJRPX
LOND-YYBJDBE
LOND-YYBEXFS
LOND-YYBJEAW
LOND-YYBJPQR
LOND-YYBJGS4
LOND-YYBJRSH
LOND-YYBJDC1
LOND-YYBEXII
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LOND-YYBJPWZ
LOND-YYBJK3O
LOND-YYBJRTG
LOND-YYBJENB
LOND-YYBEXSU
LOND-YYBJEOR
LOND-YYBJQC8
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LOND-YYBJP5J
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LOND-YYBJM8W
LOND-YYBJDQQ
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LOND-YYBJPAX
LOND-YYBJO8X
LOND-YYBJCB9
LOND-YYBJMBY
LOND-YYBJDRN
LOND-YYBJPU3
LOND-YYBJQ8T
LOND-YYBJOAC
LOND-YYBJCIS
LOND-YYBJMCK
LOND-YYBJDUD
LOND-YYBJPZT
LOND-YYBJQD3
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LOND-YYBJF84
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LOND-YYBJP9B
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LOND-YYBE5DQ	LOND-YYBEI5D	LOND-YYBE7UM	LOND-YYBJD4I	LOND-YYBEHBT	LOND-YYBJPH8
LOND-YYBE5M6	LOND-YYBEINS	LOND-YYBE7XW	LOND-YYBJFBG	LOND-YYBEQ6R	LOND-YYBJPO9
LOND-YYBE5P4	LOND-YYBEMXG	LOND-YYBE7Y1	LOND-YYBJFPQ	LOND-YYBESY3	LOND-YYBJQKM
LOND-YYBE5XS	LOND-YYBEO5E	LOND-YYBE9CA	LOND-YYBJFXK	LOND-YYBET4J	LOND-YYBJS9A
LOND-YYBE5ZF	LOND-YYBEOHG	LOND-YYBE9GR	LOND-YYBJNFB	LOND-YYBETN4	LOND-YYBJWNI
LOND-YYBE67S	LOND-YYBEOY9	LOND-YYBE9NC	LOND-YYBJNOK	LOND-YYBEWMF	LOND-YYBJYD8
LOND-YYBE6DM	LOND-YYBEPR4	LOND-YYBE9UJ	LOND-YYBJNZH	LOND-YYBEWRU	LOND-YYBJZ9Z
LOND-YYBE6J9	LOND-YYBESDU	LOND-YYBE9X1	LOND-YYBJR1R	LOND-YYBEXEO	LOND-YYBE14E
LOND-YYBE6OO	LOND-YYBESZK	LOND-YYBEA8J	LOND-YYBJR51	LOND-YYBEZIP	LOND-YYBE4YI
LOND-YYBE6QI	LOND-YYBEXGW	LOND-YYBEAE8	LOND-YYBJRZ4	LOND-YYBEZKR	LOND-YYBE6C3
LOND-YYBE6XU	LOND-YYBEZ4D	LOND-YYBEAFP	LOND-YYBJY34	LOND-YYBJ898	LOND-YYBE7JY
LOND-YYBE6ZN	LOND-YYBEZFQ	LOND-YYBEAJF	LOND-YYBJY6O	LOND-YYBJ8I5	LOND-YYBEIXH
LOND-YYBE747	LOND-YYBEZP6	LOND-YYBEH8F	LOND-YYBJY89	LOND-YYBJBA5	LOND-YYBEJK1
LOND-YYBE76I	LOND-YYBJBMS	LOND-YYBEHED	LOND-YYBJY9Q	LOND-YYBJBGY	LOND-YYBEKAW

LOND-YYBE78R	LOND-YYBJBQO	LOND-YYBEHG8	LOND-YYBJYAH	LOND-YYBJBTJ	LOND-YYBEOEX
LOND-YYBE7BO	LOND-YYBJY1E	LOND-YYBEHQZ	LOND-YYBJYJ5	LOND-YYBJCYB	LOND-YYBEQYB
LOND-YYBE7H3	LOND-YYBJY4A	LOND-YYBEHTO	LOND-YYBJYK3	LOND-YYBJD1F	LOND-YYBET13
LOND-YYBE7K6	LOND-YYBJYBM	LOND-YYBEHYU	LOND-YYBJYNJ	LOND-YYBJDNG	LOND-YYBETG1
LOND-YYBE7RK	LOND-YYBJYHW	LOND-YYBEO4K	LOND-YYBE34B	LOND-YYBJDZ5	LOND-YYBEWEM
LOND-YYBEWO4	LOND-YYBJC6R	LOND-YYBJCJX	LOND-YYBJCXD	LOND-YYBJG7C	LOND-YYBJKSS
LOND-YYBJ8U9	LOND-YYBJCAO	LOND-YYBJCKP	LOND-YYBJE7K	LOND-YYBJGBF	LOND-YYBJKW4
LOND-YYBJB6X	LOND-YYBJCFZ	LOND-YYBJCN7	LOND-YYBJFAZ	LOND-YYBJKEU	LOND-YYBJM5M
LOND-YYBJBOM	LOND-YYBJCHE	LOND-YYBJCP8	LOND-YYBJG3W	LOND-YYBJKF3	LOND-YYBJMAT
LOND-YYBJRUN	LOND-YYBJRG7	LOND-YYBJR9K	LOND-YYBJQEX	LOND-YYBJPD4	LOND-YYBJNDF
LOND-YYBJTQY	LOND-YYBJYCI				

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