Supplemental Online Content

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eMethods

Polymutants. GISAID is continuously receiving and archiving viral sequences globally, along with sample-specific metadata. Besides date and location of collecting viruses, the pertinent data to this project are extracted substituting amino acids (known as "AA.substitutions"), from aligning nucleotide sequence and translating nucleotides to amino acids by GISAID. Upon obtaining the text string on all substituting amino acids, we process all individual samples, and align all substitutions in a matrix form. In comparison with amino acids in the reference sequence, we convert the amino acid substitution matrix into a matrix of binary indicators (0, 1) for wildtype and mutant type, respectively. Note that most amino acids are monomorphic, some take one mutant type, and very few amino acids may have more than two substituting mutants. We call an amino acid a polymutant if it includes three or more mutating amino acids in the study population. While being conceptually straightforward, converting text strings of AA.substitutions into polymutant matrix and a matrix of binary polymutant indicators enables computations required by Statistical Learning Strategy (SLS).

Modeling Temporal Trends. Each polymutant has a specific temporal expansion pattern. Let binary indicator $y_{jt}(=1 \text{ or } 0)$ denote the presence or absence the of mutant type, respectively, observed at time *t* for the *j*th polymutant. To model the non-linear temporal expansion, we applied a generalized additive model (GAM) to regress the mutant indicator over sample collection time via the following probability model,

$$\Pr(y_{jt}=1\,|\,t)=\frac{1}{1+\exp[-\alpha-s_j(t)]}, \tag{1}$$

where α is a constant coefficient and $s_j(t)$ is a non-linear function of time *t*, and both are estimated by the restricted maximum likelihood method[1]. Upon completing the estimation, the above function is used with the estimated coefficient and non-linear function to compute the probability of observing mutating amino acid at the time *t*, yielding a *p*-value that measures if the function $s_j(t)$ deviates from zero. Also produced is the maximum proportion as $P_{\max}=\max[\Pr(y_{jt}=1\,|\,t)]$. The function "gam" was used to fit the GAM (R packages MGCV [2]). The smoothing parameter $k = 7$ was chosen.

Upon fitting the GAM, SLS can use the fitted values to compute locally averaged mutation percentage (LAMP) daily from the first to the last reporting day. The temporal pattern of LAMP can be used to describe the temporal expansion of the *j*th polymutant. By using *p*-value, SLS calls a polymutant with a significant trend, if *p*-value < 0.05, and with a substantial presence if the maximum proportion (Pmax) is greater than 10%.

Haplotype Analysis. SARS-COV-2 is an RNA virus, i.e., a single strand, and thus multiple polymutants from the same virus share the same haplotype. Once two or more polymutants are identified, SLS converts polymutant matrix to a vector of polymutant haplotypes and computes their haplotype frequencies as part of the haplotype analysis. When confining the analysis to viruses of a specific variant, SLS can generate variant specific haplotype frequencies, denoted as $f(h\,|\,\text{variant})$.

Bayes' Prediction Probability. When predicting variant type based on viral sequences or polymutant haplotype (*H*), the haplotype-based artificial intelligence (HAI) relies on the following posterior probability:

$$\Pr(V\,|\,H=h)=\frac{f(H=h\,|\,\text{Variant}=V)p(\text{Variant}=V)}{\sum_V f(H=h\,|\,\text{Variant}=V)p(\text{Variant}=V)}, \tag{2}$$

in which the summation is over all possible variants, $f(H=h\,|\,\text{Variant}=V)$ is an empirically estimated haplotype frequency of a specific viral variant, and $p(\text{Variant}=V)$ is the proportion of the variant. Note that HAI treats variant-unassigned viruses as a separate class. On each virus, HAI computes an array of variant-specific prediction probabilities. If a prediction probability exceeds 0.99, HAI predicts the corresponding variant. If the prediction probability for the variant-unassigned viruses exceeds 0.99, HAI predicts that the corresponding viruses do not have any known variant assignment, i.e., unpredictable (**UP**). Otherwise, HAI predicts that viruses include a mixture variant (**MV**) of two or more variant-specific haplotypes. Note that the posterior probability above (2) is strictly derived under the assumption that all variants are exclusive of each other, but, when dealing with recombinants, the quantity on the right hand side (2) is preferably interpreted as a risk score, in which the summation in the denominator serves as a normalizing factor so that the summation of all risk scores equals one.

Post-prediction modification. Among those MV predictions, their polymutant haplotypes include polymutants of two or more variants, some of which are recombinants. To tease out which MVs are recombinants, HAI utilizes a post-prediction modification. It extracts variant-specific polymutants. We call a MV recombinant if the polymutant includes mutating amino acids from two variants. For all other MVs, they will be re-assigned to be of specific variants.

Statistical Software. The statistical package R (version: R 4.2.1) and RStudio (Release 782775e, 2022-07-22) are used to implement all computational procedures in the HAI.

eTable 1. A List of Known Variants Assigned by GISAID
Fourteen variants established at GISAID and their basic annotations: WHO nomeclaure, clade/lineages assigned by phylogenic analysis, location(s) where the variant is first reported, and current designation by CDC

ID	WHO	Clade/Lineages	First Detect in	Variant
1	Alpha	B.1.1.7+Q.*	United Kingdom	VOC
2	Beta	GH/501Y.V2 (B.1.351+B.1.351.2+B.1.351.3)	South Africa	VOC
3	Delta	GK (B.1.617.2+AY.*)	India	VOC
4	Epsilon	GH/452R.V1 (B.1.429+B.1.427)	USA/California	VOI
5	Eta	G/484K.V3 (B.1.525)	UK/Nigeria	VOI
6	Gamma	GR/501Y.V3 (P.1+P.1.*)	Brazil/Japan	VOC
7	GH/490R	(B.1.640+B.1.640.*)	Congo/France	VUM
8	Iota	GH/253G.V1 (B.1.526)	USA/New York	VOI
9	Kappa	G/452R.V3 (B.1.617.1)	India	VOI
10	Lambda	GR/452Q.V1 (C.37+C.37.1)	Peru	VOI
11	Mu	GH (B.1.621+B.1.621.1)	Colombia	VOI
12	Omicron	GRA (B.1.1.529+BA.*)	Botswana/South Africa/Hong Kong	VOC
13	Theta	GR/1092K.V1 (P.3)	Philippines	VOI
14	Zeta	GR/484K.V2 (P.2)	Brazil	VOI

eTable 2. Haplotype Frequencies Among Alpha Viruses

alpha. Haplotype frequencies of core haplotypes associated with alpha-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Count	Freq	Mut	NSP3	NSP3	NSP3	NSP12	NSP12	NSP13	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS8	NS8	N	N	N	N
				T183	A890	I1412	P227	P323	K460	N501	A570	D614	P681	T716	S982	D1118	R52	Y73	D3	R203	G204	S235
1	293153	51.06%	17	**I**	**D**	**T**	**P**	**L**	**K**	**Y**	**D**	**G**	**H**	**I**	**A**	**H**	**I**	**C**	**L**	**K**	**R**	**F**
2	105858	18.44%	18	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.
3	67800	11.81%	18	.	.	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4	36990	6.44%	17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.
5	4410	0.77%	16	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	4203	0.73%	16	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.
7	3217	0.56%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.
8	2174	0.38%	15	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	G	.
9	2081	0.36%	17	.	.	I	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.
10	1904	0.33%	17	.	.	.	.	.	R	N	.	.	.	.	.	.	.	.	.	.	.	.
11	1777	0.31%	17	.	.	.	L	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.
12	1524	0.27%	17	.	.	I	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
13	1361	0.24%	17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	P	.
14	1226	0.21%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.
15	1086	0.19%	16	.	.	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.
16	1013	0.18%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	G	S
17	947	0.16%	17	.	.	.	L	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.
18	942	0.16%	17	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	D	.	.	.
19	847	0.15%	16	.	.	.	L	.	.	.	.	.	.	T	S	.	.	.	.	.	.	.
20	810	0.14%	17	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.
21	786	0.14%	18	.	.	.	.	.	R	.	.	.	R	.	.	.	.	.	.	.	.	.
22	719	0.13%	16	.	.	.	.	.	R	.	.	.	.	.	.	.	R	Y	.	.	.	.
23	710	0.12%	15	.	.	.	.	.	.	.	.	.	.	.	.	.	R	Y	.	.	.	.
24	677	0.12%	16	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
25	677	0.12%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
26	647	0.11%	16	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
27	631	0.11%	18	.	.	.	L	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.
28	617	0.11%	15	.	.	.	.	.	.	.	.	.	.	T	S	.	.	.	.	.	.	.
29	592	0.10%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	R	G	.
30	587	0.10%	16	.	.	.	.	.	R	.	.	.	.	T	S	.	.	.	.	.	.	.

eTable 3. Haplotype Frequencies Among Beta Viruses

Beta. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	**Count**	**Freq**	**Mut**	NSP2	NSP3	NSP3	NSP3	NSP5	NSP12	NSP13	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	NS3	E	NS8	N
				T85	S794	K837	N1778	K90	P323	T588	L18	D80	D215	K417	E484	N501	D614	A701	Q57	S171	P71	I121	T205
1	3323	15.78%	15	**I**	**S**	**N**	**N**	**R**	**L**	**T**	**L**	**A**	**G**	**N**	**K**	**Y**	**G**	**V**	**H**	**L**	**L**	**I**	**I**
2	2770	13.16%	16	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.
3	1733	8.23%	16	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4	1703	8.09%	17	.	.	.	S	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.
5	1411	6.70%	17	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	L	.
6	982	4.66%	17	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	L	.
7	933	4.43%	16	.	.	.	.	.	H	.	F	.	.	.	.	.	.	.	.	.	.	.	.
8	385	1.83%	13	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.
9	372	1.77%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.
10	276	1.31%	18	.	.	.	S	.	.	.	F	.	.	.	.	.	.	.	.	.	.	L	.
11	270	1.28%	16	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.
12	241	1.14%	14	.	.	.	.	.	.	.	F	.	.	.	E	N	.	.	.	.	.	.	.
13	220	1.04%	13	.	.	.	.	.	.	.	.	D	D	.	.	.	.	.	.	.	.	.	.
14	209	0.99%	17	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.
15	195	0.93%	14	.	.	K	.	.	.	I	.	.	.	K	.	.	.	.	.	S	.	L	.
16	187	0.89%	15	.	.	.	.	.	.	I	.	.	.	K	.	.	.	.	.	S	.	L	.
17	118	0.56%	15	.	.	.	S	.	.	.	F	.	.	.	E	N	.	.	.	.	.	.	.
18	115	0.55%	14	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.
19	106	0.50%	14	.	L	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.
20	98	0.47%	15	.	.	.	.	.	.	I	.	.	.	.	E	N	.	.	.	.	.	L	.
21	96	0.46%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.
22	95	0.45%	15	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	S	.	.	.
23	93	0.44%	17	.	.	.	.	.	H	.	F	.	.	.	.	.	.	.	.	.	.	L	.
24	83	0.39%	14	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.
25	77	0.37%	14	.	.	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.
26	72	0.34%	14	.	.	.	.	.	H	.	F	.	.	.	E	N	.	.	.	.	.	.	.
27	71	0.34%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T
28	70	0.33%	15	.	.	.	.	.	.	.	F	.	.	K	.	.	.	.	.	.	.	.	.
29	65	0.31%	10	.	.	K	.	.	.	.	.	D	D	.	.	.	.	A	.	S	.	.	.
30	61	0.29%	15	.	.	K	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.
31	60	0.28%	12	.	.	K	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.
32	56	0.27%	15	.	.	.	.	.	.	.	F	.	.	.	E	N	.	.	.	.	.	L	.
33	54	0.26%	14	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	L	.
34	54	0.26%	10	.	.	.	.	.	.	.	.	D	D	K	E	N	.	.	.	.	.	.	.
35	52	0.25%	14	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
36	49	0.23%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	.	.	.	.
37	48	0.23%	14	.	.	K	.	.	.	I	.	.	.	.	E	N	.	.	.	.	.	L	.
38	42	0.20%	16	.	.	K	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	L	.
39	42	0.20%	12	.	.	.	.	.	.	.	.	D	D	.	.	.	.	.	.	.	P	.	.

eTable 4. Haplotype Frequencies Among Delta Viruses

Delta. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Count	Freq	Mut	NSP3	NSP3	NSP3	NSP3	NSP3	NSP4	NSP4	NSP4	NSP6	NSP6	NSP12	NSP12	NSP13	NSP14	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	M	NS7a	NS7a	NS7b	N	N	N	N
				A488	P822	P1228	P1469	A1711	V167	A446	T492	T77	V149	P323	G671	P77	A394	T19	T95	G142	E156	A222	L452	T478	D614	P681	D950	S26	I82	V82	T120	T40	D63	R203	G215	D377
1	482881	22.55%	27	S	P	L	S	A	L	A	I	A	V	L	S	L	V	R	T	D	G	A	R	K	G	R	N	L	T	A	I	I	G	M	C	Y
2	276071	12.89%	29	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
3	233724	10.92%	26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4	205786	9.61%	28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	74239	3.47%	22	A	L	P	P	.	V	V	T	T	A	.	.	.	A	.	.	.	.	V	.	.	.	.	.	.	.	.	.	T	.	.	G	.
6	64840	3.03%	27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
7	50506	2.36%	30	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	I	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.
8	37778	1.76%	28	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	I	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
9	37472	1.75%	27	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	33301	1.56%	21	A	L	P	P	.	V	V	T	T	A	.	.	.	A	.	.	G	.	V	.	.	.	.	.	.	.	.	.	T	.	.	G	.
11	30783	1.44%	25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
12	15479	0.72%	21	A	L	P	P	.	V	V	T	T	A	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	G	.
13	11681	0.55%	26	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
14	10633	0.50%	25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.
15	10548	0.49%	20	A	L	P	P	.	V	V	T	T	A	.	.	.	A	.	.	G	.	.	.	.	.	.	.	.	.	.	.	T	.	.	G	.
16	10494	0.49%	26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	8398	0.39%	24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	V	T	.	.	.	.	.
18	7751	0.36%	24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	D	.	.	.	.	.	D	.	.	.
19	6618	0.31%	28	.	.	.	.	V	.	.	.	.	.	.	G	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
20	6330	0.30%	25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	T	.	.	.	.	.
21	6227	0.29%	28	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
22	6076	0.28%	27	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	V	T	.	.	.	.	.
23	5657	0.26%	26	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	G	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
24	5648	0.26%	23	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	E	.	.	.	.	.	.	.	.	V	T	.	.	.	.	.
25	5640	0.26%	27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
26	5437	0.25%	27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
27	4911	0.23%	26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
28	4782	0.22%	28	.	.	P	.	V	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
29	4736	0.22%	26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	G	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
30	4657	0.22%	26	.	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
31	4533	0.21%	26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.
32	4517	0.21%	25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.
33	4437	0.21%	26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	G	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.
34	4261	0.20%	28	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	I	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
35	4184	0.20%	17	A	L	P	P	.	V	.	T	T	.	.	G	P	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	G	.
36	4060	0.19%	27	.	.	P	.	V	.	.	.	.	.	.	G	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
37	3911	0.18%	26	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	V	T	T	.	.	.	.
38	3793	0.18%	19	A	L	P	P	.	V	V	T	T	A	.	.	.	A	.	.	G	E	.	.	.	.	.	.	.	.	.	.	T	.	.	G	.
39	3778	0.18%	24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	L	T	.	.	.	.	.	.	.	.	.	.	.	.

eTable 5. Haplotype Frequencies Among Epsilon Viruses

Epsilon. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Count	Freq	Mut	NSP2	NSP9	NSP12	NSP13	NSP13	Spike	Spike	Spike	Spike	NS3	NS8	NS8	N	N
				T85	I65	P323	P53	D260	S13	W152	L452	D614	Q57	A65	V100	T205	M234
1	11106	30.92%	10	**I**	**V**	**L**	**P**	**Y**	**I**	**C**	**R**	**G**	**H**	**A**	**V**	**I**	**M**
2	7653	21.30%	12	.	.	.	.	.	.	.	.	.	.	.	L	.	I
3	6205	17.27%	10	.	I	.	L	.	.	.	.	.	.	.	.	.	.
4	2642	7.35%	11	.	I	.	L	.	.	.	.	.	.	V	.	.	.
5	716	1.99%	11	.	.	.	.	.	.	.	.	.	.	.	.	.	I
6	605	1.68%	9	.	.	P	.	.	.	.	.	.	.	.	.	.	.
7	497	1.38%	9	.	.	.	.	.	S	.	.	.	.	.	.	.	.
8	443	1.23%	10	.	I	.	L	.	.	W	.	.	.	V	.	.	.
9	321	0.89%	9	.	I	.	L	.	S	.	.	.	.	.	.	.	.
10	304	0.85%	11	.	.	P	.	.	.	.	.	.	.	.	L	.	I
11	272	0.76%	11	.	.	.	.	.	S	.	.	.	.	.	L	.	I
12	262	0.73%	9	.	I	.	.	.	.	.	.	.	.	.	.	.	.
13	256	0.71%	9	.	I	P	L	.	.	.	.	.	.	.	.	.	.
14	236	0.66%	9	.	.	.	.	.	.	W	.	.	.	.	.	.	.
15	169	0.47%	9	.	.	.	.	.	.	.	L	.	.	.	.	.	.
16	158	0.44%	11	.	.	.	.	.	.	W	.	.	.	.	L	.	I
17	148	0.41%	10	.	I	P	L	.	.	.	.	.	.	V	.	.	.
18	148	0.41%	8	.	I	P	.	.	.	.	.	.	.	.	.	.	.
19	141	0.39%	11	.	.	.	.	.	.	.	L	.	.	.	L	.	I
20	117	0.33%	11	.	.	.	.	.	.	.	.	.	.	V	.	.	.
21	108	0.30%	9	.	I	.	L	.	S	W	.	.	.	V	.	.	.
22	107	0.30%	9	.	.	.	.	.	.	.	.	.	.	.	.	T	.
23	98	0.27%	9	.	I	.	L	.	.	W	.	.	.	.	.	.	.
24	98	0.27%	8	.	.	.	.	.	S	W	.	.	.	.	.	.	.
25	82	0.23%	10	.	I	.	L	.	.	.	L	.	.	V	.	.	.
26	79	0.22%	11	.	I	.	.	.	.	.	.	.	.	.	L	.	I
27	78	0.22%	8	.	I	.	L	.	S	W	.	.	.	.	.	.	.
28	74	0.21%	8	.	.	.	.	D	S	.	.	.	.	.	.	.	.
29	71	0.20%	10	.	I	P	.	.	.	.	.	.	.	.	L	.	I
30	70	0.19%	10	.	I	.	L	.	S	.	.	.	.	V	.	.	.
31	64	0.18%	9	.	I	.	L	.	.	.	L	.	.	.	.	.	.
32	54	0.15%	9	.	I	.	L	.	.	W	L	.	.	V	.	.	.
33	52	0.14%	10	.	.	.	.	.	S	W	.	.	.	.	L	.	I
34	51	0.14%	9	.	.	.	.	D	.	.	.	.	.	.	.	.	.
35	46	0.13%	8	.	.	.	.	.	.	W	L	.	.	.	.	.	.
36	44	0.12%	8	.	I	.	.	.	S	.	.	.	.	.	.	.	.
37	41	0.11%	8	.	I	.	.	.	.	.	.	.	Q	.	.	.	.

eTable 6. Haplotype Frequencies Among Eta Viruses

Eta. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Core Haplotypes	Coun	Freq	Mut	T1189 NSP3	K1771 NSP3	P323 NSP12	K160 NSP16	Q52 Spike	A67 Spike	E484 Spike	D614 Spike	Q677 Spike	F888 Spike	L21 E	I82 M	A12 N	I205 N
1	IKFKRVKGHLFTGI	2188	46.41%	12	I	K	F	K	R	V	K	G	H	L	F	T	G	I
2	IKFRRVKGHLFTGI	536	11.37%	13	.	.	.	R	.	.	.	.	.	.	.	.	.	.
3	IRFKRVKGHLFTGI	425	9.02%	13	.	R	.	.	.	.	.	.	.	.	.	.	.	.
4	IKFKQVKGHLLTGI	338	7.17%	10	.	.	.	.	Q	.	.	.	.	.	L	.	.	.
5	IKFKRVKGHLLTGI	204	4.33%	11	.	.	.	.	.	.	.	.	.	.	L	.	.	.
6	IKFRRVKGHLFTAT	149	3.16%	11	.	.	.	R	.	.	.	.	.	.	.	.	A	T
7	IKFKQVKGHLFTGI	90	1.91%	11	.	.	.	.	Q	.	.	.	.	.	.	.	.	.
8	IKFKRAKGHLFTGI	61	1.29%	11	.	.	.	.	.	A	.	.	.	.	.	.	.	.
9	IKFKRVKGHLFTGT	50	1.06%	11	.	.	.	.	.	.	.	.	.	.	.	.	.	T
10	IKFKRVKGHLFTAI	49	1.04%	11	.	.	.	.	.	.	.	.	.	.	.	.	A	.
11	IKFKRVEGHLFTGI	35	0.74%	11	.	.	.	.	.	.	E	.	.	.	.	.	.	.
12	IKFKQAKGHLFTGI	25	0.53%	10	.	.	.	.	Q	A	.	.	.	.	.	.	.	.
13	IKFKRVKGHLFTVI	21	0.45%	12	.	.	.	.	.	.	.	.	.	.	.	.	V	.
14	IKFKRVKGHFFTGI	20	0.42%	11	.	.	.	.	.	.	.	.	.	F	.	.	.	.
15	TKFKRVKGHLFTGI	19	0.40%	11	T	.	.	.	.	.	.	.	.	.	.	.	.	.
16	IKFRRVKGHLFTGT	17	0.36%	12	.	.	.	R	.	.	.	.	.	.	.	.	.	T
17	IRFKQVKGHLLTGI	17	0.36%	11	.	R	.	.	Q	.	.	.	.	.	L	.	.	.
18	IRFKRVKGHLLTGI	15	0.32%	12	.	R	.	.	.	.	.	.	.	.	L	.	.	.
19	IKFKRVKGHLLTGT	14	0.30%	10	.	.	.	.	.	.	.	.	.	.	L	.	.	T
20	IRFKRAKGHLFTGI	11	0.23%	12	.	R	.	.	.	A	.	.	.	.	.	.	.	.
21	IRFKRVKGHLFTGT	11	0.23%	12	.	R	.	.	.	.	.	.	.	.	.	.	.	T
22	IKFKQAEGHLFTGI	10	0.21%	9	.	.	.	.	Q	A	E	.	.	.	.	.	.	.
23	IRFKQVKGHLFTGI	10	0.21%	12	.	R	.	.	Q	.	.	.	.	.	.	.	.	.
24	IKFKQVKGHLLTGT	9	0.19%	9	.	.	.	.	Q	.	.	.	.	.	L	.	.	T
25	IKFKQVKGHLLTVI	9	0.19%	10	.	.	.	.	Q	.	.	.	.	.	L	.	V	.
26	IKFKRAKGHLLTGI	9	0.19%	10	.	.	.	.	.	A	.	.	.	.	L	.	.	.
27	IKFKRVEGHLFTGT	8	0.17%	10	.	.	.	.	.	.	E	.	.	.	.	.	.	T
28	TKFKRVKGHFFTAI	8	0.17%	9	T	.	.	.	.	.	.	.	.	F	.	.	A	.
29	TKFKRVKGHLFTAI	8	0.17%	10	T	.	.	.	.	.	.	.	.	.	.	.	A	.
30	IKFKQVKGHFFIGI	7	0.15%	9	.	.	.	.	Q	.	.	.	.	F	.	I	.	.
31	IKFKRVEGHFFTGT	7	0.15%	9	.	.	.	.	.	.	E	.	.	F	.	.	.	T
32	IRFKRVEGHLFTGI	7	0.15%	12	.	R	.	.	.	.	E	.	.	.	.	.	.	.
33	TKFKRVKGHLLTAT	7	0.15%	8	T	.	.	.	.	.	.	.	.	.	L	.	A	T
34	IKFKRVKGHLLTVI	6	0.13%	11	.	.	.	.	.	.	.	.	.	.	L	.	V	.
35	IKFKRAKGHLFTAI	5	0.11%	10	.	.	.	.	.	A	.	.	.	.	.	.	A	.
36	IKFKRVEGHLLTGI	5	0.11%	10	.	.	.	.	.	.	E	.	.	.	L	.	.	.
37	IKFKRVKGHFFTAI	5	0.11%	10	.	.	.	.	.	.	.	.	.	F	.	.	A	.
38	IKFKRVKGHFFTGT	5	0.11%	10	.	.	.	.	.	.	.	.	.	F	.	.	.	T
39	IKFKRVKGHLFTGV	5	0.11%	12	.	.	.	.	.	.	.	.	.	.	.	.	.	V

eTable 7.Haplotype Frequencies Among Gamma Viruses

Gamma. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	**Freq**	%	#	NSP3	NSP3	NSP4	NSP12	NSP13	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	NS8	N	N	N
				S370	K977	S184	P323	E341	L18	T20	P26	D138	R190	K417	E484	N501	D614	H655	T1027	V1176	S253	E92	P80	R203	G204
1	36853	61.22%	21	**L**	**Q**	**S**	**L**	**D**	**F**	**N**	**S**	**Y**	**S**	**T**	**K**	**Y**	**G**	**Y**	**I**	**F**	**P**	**K**	**R**	**K**	**R**
2	7567	12.57%	22	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
3	1626	2.70%	20	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.
4	1400	2.33%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	G
5	1375	2.28%	20	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.	.	.	.
6	1365	2.27%	20	.	.	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.
7	1005	1.67%	19	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	.	.
8	324	0.54%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.
9	263	0.44%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.
10	259	0.43%	20	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	T	V	.	.	.	.	.
11	246	0.41%	18	.	.	.	.	E	.	T	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.
12	230	0.38%	21	.	.	N	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.	.	.	.
13	220	0.37%	21	.	.	N	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.
14	205	0.34%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.
15	203	0.34%	21	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.
16	181	0.30%	20	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	173	0.29%	17	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	R	G
18	166	0.28%	18	.	.	.	.	.	.	.	.	.	R	.	E	N	.	.	.	.	.	.	.	.	.
19	157	0.26%	20	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.
20	137	0.23%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	V	.	.	.	.	.
21	135	0.22%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.
22	133	0.22%	21	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.
23	124	0.21%	20	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.
24	122	0.20%	19	.	.	.	.	.	.	.	.	.	R	K	.	.	.	.	.	.	.	.	.	.	.
25	100	0.17%	16	.	.	.	.	.	L	T	P	D	R	.	.	.	.	.	.	.	.	.	.	.	.
26	91	0.15%	18	.	.	.	.	.	L	T	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.
27	90	0.15%	20	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
28	90	0.15%	17	.	.	.	.	.	L	T	P	.	R	.	.	.	.	.	.	.	.	.	.	.	.
29	83	0.14%	18	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	R	G
30	72	0.12%	19	.	.	.	.	.	.	.	.	D	.	K	.	.	.	.	.	.	.	.	.	.	.
31	72	0.12%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	H	.	.	.	.	.	.	.
32	68	0.11%	20	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
33	67	0.11%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.
34	66	0.11%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.
35	64	0.11%	20	.	.	N	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	.	.
36	62	0.10%	19	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	E	.	.	.

eTable 8. Haplotype Frequencies Among GH/490R Viruses

GH/490R. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	**Freq**	%	#	NSP2	NSP2	NSP2	NSP3	NSP3	NSP4	NSP4	NSP4	NSP6	NSP13	NSP16	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	NS3	N	N
				P129	G221	E272	L1301	A1537	S386	R401	T492	V149	Q586	R216	P9	E96	R190	I210	Y449	F490	N501	D936	T32	A54	D22	E378
1	78	18.10%	20	**L**	**G**	**G**	**F**	**S**	**F**	**H**	**I**	**A**	**Q**	**R**	**L**	**Q**	**S**	**T**	**N**	**R**	**Y**	**H**	**I**	**S**	**Y**	**Q**
2	69	16.01%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.	.
3	37	8.58%	21	.	S	.	.	.	.	.	.	.	H	H	.	.	.	.	Y	.	.	.	.	A	.	.
4	35	8.12%	22	.	S	.	.	.	.	.	.	.	H	H	.	.	.	.	.	.	.	.	.	A	.	.
5	22	5.10%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	D	.
6	17	3.94%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	A	.	.
7	13	3.02%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.
8	12	2.78%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	R	I	.	.	.	.	.	.	.	.
9	10	2.32%	9	.	.	E	L	A	S	R	T	V	.	.	.	.	.	I	.	S	.	D	.	A	.	E
10	9	2.09%	15	.	.	.	.	.	.	.	.	.	.	.	.	E	R	I	.	.	.	.	.	A	D	.
11	7	1.62%	17	.	.	.	.	.	.	.	.	.	.	.	.	.	R	I	.	.	.	.	.	A	.	.
12	6	1.39%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.
13	5	1.16%	8	.	.	E	L	A	S	R	T	V	.	.	.	.	.	I	Y	S	.	D	.	A	.	E
14	5	1.16%	16	.	.	.	.	A	.	.	.	.	.	.	.	.	R	I	.	.	.	.	.	A	.	.
15	5	1.16%	19	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.
16	4	0.93%	8	.	.	E	L	A	S	R	T	V	.	.	.	.	R	I	.	S	.	D	.	A	.	E
17	4	0.93%	10	.	.	E	L	A	S	R	T	V	.	.	.	.	.	I	.	S	.	D	.	.	.	E
18	4	0.93%	18	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.	.
19	4	0.93%	19	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
20	4	0.93%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	A	.	.
21	4	0.93%	21	.	S	.	.	.	.	.	.	.	H	H	.	.	R	.	.	.	.	.	.	A	.	.
22	3	0.70%	9	.	.	E	L	A	S	R	T	V	.	.	.	.	R	I	.	S	.	D	.	.	.	E
23	3	0.70%	16	.	.	.	.	.	.	.	.	.	.	.	.	E	R	I	.	.	.	.	.	.	D	.
24	3	0.70%	19	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
25	3	0.70%	18	.	.	.	L	A	.	.	.	.	H	H	.	.	.	.	Y	.	.	.	.	A	.	.
26	3	0.70%	20	.	S	.	.	.	.	.	.	.	H	H	.	.	R	I	.	.	.	.	.	A	.	.
27	2	0.46%	5	.	.	E	L	A	S	R	T	V	.	.	.	E	R	I	.	S	.	D	T	A	D	E
28	2	0.46%	17	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	A	D	.
29	2	0.46%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.
30	2	0.46%	17	.	.	.	L	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.	.
31	2	0.46%	17	.	S	.	.	.	.	.	.	.	H	H	.	.	R	I	Y	F	N	.	.	A	.	.
32	2	0.46%	17	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	D	.
33	1	0.23%	7	.	.	E	L	A	S	R	T	V	.	.	P	.	R	I	.	S	.	D	.	A	.	E
34	1	0.23%	15	.	.	E	L	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	A	.	E
35	1	0.23%	14	.	.	.	.	A	.	.	.	.	.	.	.	E	R	I	.	.	.	.	.	A	D	.
36	1	0.23%	14	.	.	.	.	A	.	.	.	.	.	.	.	.	R	I	.	.	.	.	.	A	D	E
37	1	0.23%	17	.	.	.	.	A	.	.	.	.	.	.	.	.	R	I	.	.	.	.	.	.	.	.
38	1	0.23%	17	.	.	.	.	A	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	A	.	.
39	1	0.23%	18	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E
40	1	0.23%	17	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	A	.	.

eTable 9. Haplotype Frequencies Among Iota Viruses

Iota. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Freq	%	#	NSP2	NSP4	NSP12	NSP13	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	NS3	NS7a	NS8	N	N	N	N
				T85	L438	P323	Q88	L5	T95	D253	S477	E484	D614	A701	Q957	P42	Q57	L116	T11	P13	P199	S202	M234
1	10264	47.21%	15	**I**	**P**	**L**	**H**	**F**	**I**	**G**	**S**	**K**	**G**	**V**	**Q**	**L**	**H**	**L**	**I**	**P**	**L**	**S**	**I**
2	5329	24.51%	16	.	.	.	.	.	.	.	N	E	.	A	R	.	.	F	.	L	P	R	M
3	1395	6.42%	15	.	.	.	.	.	.	.	N	E	.	.	.	.	.	.	.	.	.	.	.
4	902	4.15%	14	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.
5	296	1.36%	15	.	.	.	.	.	.	.	N	E	.	A	R	.	.	.	.	L	P	R	M
6	279	1.28%	14	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.
7	178	0.82%	14	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
8	152	0.70%	15	.	.	.	.	.	.	.	N	E	.	A	.	.	.	F	.	L	P	R	M
9	105	0.48%	14	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.	.	.	.	.
10	101	0.46%	14	.	.	.	Q	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
11	87	0.40%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.
12	84	0.39%	14	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.	.	.	.
13	83	0.38%	14	.	.	.	.	.	.	.	N	E	.	A	.	.	.	.	.	.	.	.	.
14	77	0.35%	13	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	T	.	.	.	.
15	74	0.34%	15	.	.	.	.	.	.	.	.	E	.	A	R	.	.	F	.	L	P	R	M
16	72	0.33%	15	.	.	.	.	L	.	.	N	E	.	A	R	.	.	F	.	L	P	R	M
17	55	0.25%	13	.	.	.	.	.	.	.	N	E	.	A	.	.	.	F	T	.	P	R	M
18	53	0.24%	13	.	.	P	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.
19	49	0.23%	13	.	.	.	.	L	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.
20	46	0.21%	15	.	.	.	Q	.	.	.	N	E	.	A	R	.	.	F	.	L	P	R	M
21	43	0.20%	15	.	.	.	.	.	.	.	N	E	.	A	R	P	.	F	.	L	P	R	M
22	43	0.20%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.
23	41	0.19%	14	.	.	.	.	L	.	.	N	E	.	A	R	.	.	.	.	L	P	R	M
24	38	0.17%	14	.	.	.	.	.	.	.	.	E	.	A	R	.	.	.	.	L	P	R	M
25	37	0.17%	13	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	M
26	36	0.17%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.
27	33	0.15%	15	.	.	.	.	.	.	D	N	E	.	A	R	.	.	F	.	L	P	R	M
28	29	0.13%	14	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
29	29	0.13%	14	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
30	28	0.13%	15	.	.	.	.	.	.	.	N	E	.	A	R	.	.	F	T	L	P	R	M
31	26	0.12%	13	.	.	.	.	.	.	.	.	E	.	A	.	.	.	.	.	.	.	.	.
32	26	0.12%	13	.	.	.	Q	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
33	24	0.11%	13	.	.	.	.	.	.	D	.	E	.	.	.	.	.	.	.	.	.	.	.
34	24	0.11%	13	.	.	.	.	.	.	.	N	E	.	A	.	.	.	.	T	.	.	.	.
35	24	0.11%	13	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.

eTable 10. Haplotype Frequencies Among Kappa Viruses

Kappa. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Freq	%	#	NSP3	NSP6	NSP12	NSP13	NSP13	NSP15	NSP15	NSP15	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	M	NS7a	NS8	N	N	N
				T749	T77	P323	G206	M429	P65	K259	S261	T95	G142	E154	L452	E484	D614	P681	Q1071	H1101	S26	I82	V82	S69	D3	R203	D377
1	679	17.36%	20	I	A	L	C	I	P	R	A	I	D	K	R	Q	G	R	H	H	L	S	A	S	D	M	Y
2	228	5.83%	21	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
3	165	4.22%	19	.	.	.	G	.	.	.	S	T	.	.	.	.	.	.	.	D	.	I	.	L	Y	.	.
4	145	3.71%	18	.	.	.	G	.	.	.	S	T	.	.	.	.	.	.	.	D	.	I	.	L	.	.	.
5	126	3.22%	18	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	Q	.	.	.	.	.	.	.	.
6	96	2.45%	15	.	.	.	G	.	.	.	S	T	G	.	.	.	.	.	Q	D	.	I	.	.	.	.	.
7	89	2.28%	19	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.
8	78	1.99%	18	.	.	.	.	.	.	.	.	.	G	E	.	.	.	.	.	.	.	.	.	.	.	.	.
9	65	1.66%	19	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	65	1.66%	17	.	.	.	G	.	.	.	S	T	.	.	.	.	.	.	.	D	.	I	.	.	.	.	.
11	57	1.46%	17	.	.	.	.	.	.	.	.	T	G	E	.	.	.	.	.	.	.	.	.	.	.	.	.
12	57	1.46%	17	.	.	.	G	.	.	.	.	T	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.
13	49	1.25%	16	.	.	.	G	.	.	.	S	T	G	.	.	.	.	.	Q	D	.	I	.	.	Y	.	.
14	40	1.02%	15	.	.	.	G	.	.	.	.	T	G	E	.	.	.	.	.	.	.	I	.	.	.	.	.
15	38	0.97%	14	.	.	.	G	.	.	.	S	T	G	E	.	.	.	.	Q	D	.	I	.	.	.	.	.
16	37	0.95%	18	.	.	.	.	.	.	.	.	T	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	34	0.87%	18	.	.	.	G	.	.	.	S	T	.	.	.	.	.	.	.	Y	.	I	.	L	.	.	.
18	34	0.87%	16	.	.	.	G	.	.	.	S	T	G	E	.	.	.	.	.	D	.	I	.	L	.	.	.
19	34	0.87%	18	.	.	.	G	.	.	.	S	T	G	.	.	.	.	.	.	D	.	I	.	L	Y	.	.
20	33	0.84%	15	.	.	.	G	.	.	.	.	T	G	.	.	.	.	.	Q	.	.	I	.	.	.	.	.
21	32	0.82%	16	.	.	.	G	.	.	.	S	T	G	.	.	.	.	.	.	D	.	I	.	.	.	.	.
22	29	0.74%	18	.	.	.	G	.	.	.	S	T	.	E	.	.	.	.	.	D	.	I	.	L	Y	.	.
23	26	0.66%	15	.	.	.	G	.	.	.	S	T	G	E	.	.	.	.	.	D	.	I	.	.	.	.	.
24	23	0.59%	17	.	.	.	G	.	.	.	S	T	G	.	.	.	.	.	.	D	.	I	.	L	.	.	.
25	23	0.59%	19	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
26	22	0.56%	17	.	.	.	.	.	.	.	.	.	G	E	.	.	.	.	Q	.	.	.	.	.	.	.	.
27	22	0.56%	20	.	.	.	.	.	S	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.
28	21	0.54%	14	.	.	.	G	.	.	.	.	T	G	E	.	.	.	.	Q	.	.	I	.	.	.	.	.
29	21	0.54%	16	.	.	.	G	.	.	.	.	T	G	.	.	.	.	.	.	.	.	I	.	.	.	.	.
30	21	0.54%	17	.	.	.	G	.	.	.	S	T	G	E	.	.	.	.	.	D	.	I	.	L	Y	.	.
31	20	0.51%	16	.	.	.	G	.	.	.	S	T	G	E	.	.	.	.	.	D	.	I	.	.	Y	.	.
32	18	0.46%	19	.	.	.	.	.	.	.	.	.	V	S	.	.	.	.	Q	.	.	.	.	.	.	.	.
33	18	0.46%	19	.	.	.	.	.	S	.	.	.	G	E	.	.	.	.	.	.	.	.	.	.	.	.	.
34	18	0.46%	20	.	.	.	.	.	S	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.
35	18	0.46%	20	T	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
36	17	0.43%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.
37	17	0.43%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	.	.	.	.	.	.	.	.
38	16	0.41%	17	.	.	.	G	.	.	.	S	T	.	E	.	.	.	.	.	D	.	I	.	L	.	.	.
39	15	0.38%	16	.	.	.	.	.	.	.	.	T	G	E	.	.	.	.	Q	.	.	.	.	.	.	.	.
40	15	0.38%	17	.	.	.	G	.	.	.	S	T	G	.	.	.	.	.	.	D	.	I	.	.	Y	.	.

eTable 11. Haplotype Frequencies Among Lambda Viruses Lambda

Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Freq	%	#	NSP3	NSP3	NSP3	NSP4	NSP4	NSP5	NSP12	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	N	N	N	N	N
				T428	P1469	F1569	L438	T492	G15	P323	G75	T76	D253	L452	F490	D614	T859	A110	P13	A119	R203	G204	G214
1	2885	56.57%	18	**I**	**S**	**V**	**P**	**I**	**S**	**L**	**V**	**I**	**N**	**Q**	**S**	**G**	**N**	**A**	**L**	**A**	**K**	**R**	**C**
2	472	9.25%	17	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.
3	401	7.86%	17	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4	323	6.33%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	P	.	.	.
5	137	2.69%	16	.	.	.	.	.	.	.	G	T	.	.	.	.	.	.	.	.	.	.	.
6	104	2.04%	19	.	.	.	.	.	.	.	.	.	D	.	.	.	.	S	.	P	.	.	.
7	54	1.06%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.
8	40	0.78%	16	.	.	.	.	.	G	.	.	.	D	.	.	.	.	.	.	.	.	.	.
9	36	0.71%	15	.	.	.	.	.	.	.	G	T	D	.	.	.	.	.	.	.	.	.	.
10	30	0.59%	17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.	.
11	27	0.53%	15	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	R	G	.
12	23	0.45%	16	.	P	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.
13	23	0.45%	18	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	P	.	.	.
14	23	0.45%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	G	.
15	20	0.39%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
16	18	0.35%	15	.	.	.	.	.	G	.	G	T	.	.	.	.	.	.	.	.	.	.	.
17	17	0.33%	17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.
18	17	0.33%	17	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.
19	12	0.24%	17	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
20	11	0.22%	17	.	.	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.
21	11	0.22%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	.	.	.	.
22	10	0.20%	14	.	.	.	.	.	G	.	G	T	D	.	.	.	.	.	.	.	.	.	.
23	9	0.18%	16	.	.	.	.	.	.	.	.	.	.	L	F	.	.	.	.	.	.	.	.
24	7	0.14%	14	.	P	.	.	.	.	.	.	.	D	L	F	.	.	.	.	.	.	.	.
25	7	0.14%	19	.	.	.	.	.	G	.	.	.	.	.	.	.	.	S	.	P	.	.	.
26	7	0.14%	17	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.
27	6	0.12%	15	.	P	.	.	.	.	.	.	.	.	L	F	.	.	.	.	.	.	.	.
28	6	0.12%	17	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	S
29	6	0.12%	14	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	R	G	G
30	6	0.12%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.
31	6	0.12%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.

eTable 12. Haplotype Frequencies Among Mu Viruses Mu

Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Freq	%	#	NSP3	NSP3	NSP3	NSP4	NSP4	NSP6	NSP12	NSP12	NSP13	NSP13	NSP13	NSP15	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	NS3	NS3	NS3	NS3	NS3	NS8	NS8	NS8	N
				T237	T720	N1329	T189	T492	Q160	P323	Y521	E261	P419	P491	S261	T95	Y144	Y145	R346	E484	N501	D614	P681	D950	I20	Q57	L106	V256	N257	V259	T11	P38	S67	T205
1	1406	17.96%	21	**A**	**I**	**N**	**T**	**I**	**R**	**L**	**Y**	**E**	**S**	**P**	**S**	**I**	**S**	**N**	**K**	**K**	**Y**	**G**	**H**	**N**	**I**	**H**	**L**	**I**	**N**	**V**	**K**	**S**	**F**	**I**
2	667	8.52%	27	.	.	D	I	.	.	.	.	.	.	S	L	.	.	.	.	.	.	.	.	.	.	.	.	.	H	L	.	.	.	.
3	561	7.16%	24	.	.	.	.	.	.	.	C	D	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.	.	.	.	.	.	.	.
4	482	6.16%	22	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.
5	405	5.17%	22	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	238	3.04%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
7	224	2.86%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
8	210	2.68%	22	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
9	140	1.79%	26	.	.	D	I	.	.	.	.	.	.	S	L	.	.	.	.	.	.	.	.	.	.	.	.	.	H	L	.	.	S	.
10	125	1.60%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	B	.	.	.	.	.	.	.	.	S	.
11	110	1.40%	21	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	B	.	.	.	.	.	.	.	.	S	.
12	96	1.23%	25	.	.	.	.	.	.	.	C	D	.	.	L	.	.	.	.	.	.	.	.	.	M	.	.	.	.	.	.	.	.	.
13	92	1.17%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.
14	81	1.03%	21	.	.	.	.	.	.	.	.	.	.	S	.	.	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
15	75	0.96%	21	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.
16	64	0.82%	21	.	.	.	.	.	.	.	.	.	.	S	.	.	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	62	0.79%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	T	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
18	59	0.75%	21	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	B	.	.	.	.	.	.	.	.	S	.
19	57	0.73%	23	.	.	.	.	.	.	.	C	D	.	.	.	.	.	.	.	.	.	.	.	B	M	.	.	.	.	.	.	.	S	.
20	49	0.63%	21	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	B	.	.	F	.	.	.	.	.	S	.
21	44	0.56%	23	.	.	.	.	.	.	.	C	D	.	.	.	.	Y	.	.	.	.	.	.	.	M	.	.	.	.	.	.	.	.	.
22	42	0.54%	23	.	.	.	.	.	.	.	C	D	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.	.	.	.	.	.	S	.
23	42	0.54%	18	.	.	.	.	.	.	.	.	.	.	.	.	T	Y	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
24	37	0.47%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	.	.	.	.	.	.
25	37	0.47%	21	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	S	.
26	36	0.46%	21	.	.	.	.	.	.	.	C	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
27	31	0.40%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	S	.
28	26	0.33%	22	.	.	.	.	.	.	.	C	D	.	.	.	.	Y	Y	.	.	.	.	.	.	M	.	.	.	.	.	.	.	.	.
29	26	0.33%	19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	T
30	25	0.32%	21	.	.	.	.	.	.	.	.	.	.	S	.	.	T	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
31	24	0.31%	18	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	Y	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
32	24	0.31%	21	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.
33	22	0.28%	26	.	.	D	I	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	H	L	.	.	.	.
34	21	0.27%	23	.	.	.	.	.	.	.	C	D	.	.	.	.	T	Y	.	.	.	.	.	.	M	.	.	.	.	.	.	.	.	.
35	21	0.27%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.	.	.	.	.
36	20	0.26%	23	.	.	.	.	.	.	.	C	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
37	20	0.26%	20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
38	20	0.26%	20	.	.	.	.	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
39	19	0.24%	25	.	.	D	I	.	.	.	.	.	.	S	L	.	.	Y	.	.	.	.	.	.	.	.	.	.	H	.	.	.	.	.

eTable 13. Haplotype Frequencies Among Omicron Viruses

Omicron. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Freq	%	#	NSP1	NSP3	NSP3	NSP3	NSP3	NSP3	NSP4	NSP4	NSP4	NSP4	NSP5	NSP6	NSP12	NSP13	NSP14	NSP15	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	E	M	M	M	N	N	N	N
				S135	T24	K38	G489	L1266	A1892	L264	T327	L438	T492	P132	I189	P323	R392	I42	T112	T19	A27	A67	T95	G142	L212	V213	G339	R346	S371	S373	S375	T376	D405	R408	K417	N440	G446	S477	T478	E484	Q493	G496	Q498	N501	Y505	T547	D614	H655	N679	P681	N764	D796	N856	Q954	N969	L981	T223	T9	D3	Q19	A63	P13	R203	G204	S413
1	269527	16.85%	46	S	T	R	G	I	T	L	T	L	I	H	V	L	R	V	T	T	A	V	I	D	I	V	D	K	L	P	F	T	D	R	N	K	S	N	K	A	R	S	R	Y	H	K	G	Y	K	H	K	Y	K	H	K	F	T	I	G	E	T	L	K	R	S
2	262537	16.41%	48	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
3	189880	11.87%	45	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4	59561	3.72%	42	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	41552	2.60%	43	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	33570	2.10%	41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	R	S	S	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
7	28398	1.77%	41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.
8	20799	1.30%	47	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	.	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
9	14333	0.90%	42	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	14131	0.88%	48	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	Z	.	.	.	.	R
11	13166	0.82%	47	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	.	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
12	11981	0.75%	40	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.
13	10932	0.68%	44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
14	10375	0.65%	40	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	N	G	S	T	E	Q	G	Q	N	Y	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
15	9726	0.61%	30	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	R	S	S	S	.	.	.	K	N	G	S	T	E	Q	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
16	9372	0.59%	47	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	N	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
17	8908	0.56%	45	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
18	7726	0.48%	44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.
19	7324	0.46%	40	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
20	6598	0.41%	41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
21	6484	0.41%	31	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	S	S	S	.	.	.	K	N	G	S	T	E	Q	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
22	6296	0.39%	39	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	G	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
23	5886	0.37%	40	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
24	5224	0.33%	45	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	Q	N	Y	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
25	5081	0.32%	29	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	G	R	S	S	S	.	.	.	K	N	G	S	T	E	Q	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
26	4705	0.29%	45	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.
27	4598	0.29%	41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
28	4446	0.28%	47	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	.	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
29	4275	0.27%	42	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	.	I	S	A	T	.	L	G	G	R	S	S	S	.	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
30	4047	0.25%	40	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	.	A	T	.	L	G	.	R	F	.	.	.	.	.	.	.	G	.	.	.	Q	G	Q	N	Y	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
31	4018	0.25%	47	R	I	K	S	L	A	F	I	.	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
32	3955	0.25%	47	.	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	.	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	.	.	.	.	.	R
33	3628	0.23%	41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	N	G	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.
34	3602	0.23%	44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.
35	3455	0.22%	45	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
36	3438	0.21%	44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
37	3326	0.21%	42	.	.	K	.	.	.	.	.	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.	.	.	.
38	3277	0.20%	47	R	I	K	S	L	A	F	I	F	.	.	I	.	C	.	I	I	S	A	T	G	L	G	.	R	F	.	.	A	N	S	.	.	G	.	.	.	.	G	.	.	.	T	.	.	.	.	.	.	N	.	.	L	I	.	D	Z	.	.	.	.	R
39	3264	0.20%	35	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	N	G	S	T	E	Q	G	Q	N	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

eTable 14. Haplotype Frequencies Among Theta Viruses

Theta. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	Freq	%	#	NSP2	NSP2	NSP2	NSP3	NSP3	NSP4	NSP4	NSP4	NSP6	NSP7	NSP12	NSP13	NSP13	NSP14	Spike	Spike	Spike	Spike	Spike	NS3	NS8	NS8	N	N	N
				Y316	G339	A419	D736	S1807	T204	D217	L438	D112	L71	P323	L280	A368	K155	P9	E484	N501	T573	V1176	A23	K2	K68	R203	G204	T391
1	123	37.27%	15	**Y**	**G**	**A**	**G**	**F**	**T**	**N**	**P**	**E**	**F**	**L**	**F**	**V**	**K**	**P**	**K**	**Y**	**T**	**F**	**A**	**Q**	**K**	**K**	**R**	**T**
2	53	16.06%	20	C	.	V	.	.	.	.	.	.	.	.	.	.	R	L	.	.	.	.	.	.	.	.	.	I
3	19	5.76%	14	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.
4	14	4.24%	19	C	.	V	.	.	.	.	.	.	.	.	L	.	R	L	.	.	.	.	.	.	.	.	.	I
5	11	3.33%	18	.	S	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	I	.	S	.	E	.	.	.
6	9	2.73%	13	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	.
7	7	2.12%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.
8	6	1.82%	19	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	S	.	E	.	.	.
9	5	1.52%	16	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	5	1.52%	13	.	.	.	.	S	.	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
11	3	0.91%	11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	R	G	.
12	2	0.61%	13	.	.	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
13	2	0.61%	14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.	.
14	2	0.61%	13	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	G	.
15	2	0.61%	16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.
16	2	0.61%	15	.	.	.	.	.	.	.	.	.	.	.	L	.	.	L	.	.	.	.	.	.	.	.	.	.
17	2	0.61%	10	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	E	N	.	.	.	.	.	R	G	.
18	2	0.61%	16	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
19	2	0.61%	16	.	S	.	.	.	.	.	.	.	.	.	L	.	.	.	E	N	I	.	S	.	E	.	.	.
20	1	0.30%	10	C	.	.	D	.	.	.	L	.	.	.	L	.	R	.	E	N	.	.	.	.	.	R	G	.
21	1	0.30%	16	C	.	V	D	.	.	.	.	D	.	P	L	.	R	L	.	.	.	.	.	.	.	.	.	I
22	1	0.30%	12	C	.	V	.	.	.	D	L	D	.	P	L	A	R	L	E	N	.	.	.	.	.	.	.	I
23	1	0.30%	16	C	.	V	.	.	.	D	.	.	.	P	L	A	R	L	.	.	.	.	.	.	.	.	.	I
24	1	0.30%	13	C	.	V	.	.	.	.	L	.	.	.	.	A	R	.	E	N	.	V	.	.	.	.	.	.
25	1	0.30%	19	C	.	V	.	.	.	.	L	.	.	.	.	.	R	L	.	.	.	.	.	.	.	.	.	I
26	1	0.30%	18	C	.	V	.	.	.	.	.	.	.	.	.	.	R	L	E	N	.	.	.	.	.	.	.	I
27	1	0.30%	19	C	.	V	.	.	.	.	.	.	.	.	.	.	R	L	E	.	.	.	.	.	.	.	.	I
28	1	0.30%	19	C	.	V	.	.	.	.	.	.	.	.	.	.	R	L	.	N	.	.	.	.	.	.	.	I
29	1	0.30%	18	C	.	V	.	.	.	.	.	.	.	.	.	.	R	L	.	.	.	.	.	.	.	R	G	I
30	1	0.30%	18	C	.	V	.	.	.	.	.	.	.	.	L	A	R	L	.	.	.	.	.	.	.	.	.	I
31	1	0.30%	17	C	.	V	.	.	.	.	.	.	.	.	L	.	R	L	E	N	.	.	.	.	.	.	.	I
32	1	0.30%	18	C	.	V	.	.	.	.	.	.	L	.	.	.	R	.	.	.	.	.	.	.	.	.	.	I
33	1	0.30%	17	C	.	V	.	.	.	.	.	.	L	.	L	A	R	L	.	.	.	.	.	.	.	.	.	I
34	1	0.30%	11	.	.	.	D	.	.	.	L	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	.
35	1	0.30%	9	.	.	.	D	.	.	.	L	.	.	.	.	.	.	.	E	N	.	.	.	.	.	R	G	.
36	1	0.30%	8	.	.	.	D	.	.	.	L	.	.	.	L	.	.	.	E	N	.	.	.	.	.	R	G	.
37	1	0.30%	9	.	.	.	D	.	.	.	.	D	.	P	L	.	.	.	E	N	.	.	.	.	.	.	.	.
38	1	0.30%	12	.	.	.	D	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	.	.	.
39	1	0.30%	11	.	.	.	D	.	.	.	.	.	.	.	.	.	.	.	E	N	.	.	.	.	.	R	.	.

eTable 15. Haplotype Frequencies Among Zeta Viruses

Zeta. Haplotype frequencies of core haplotypes associated with variant-specific polymutants, for those haplotypes with 0.1% haplotype frequency.

ID	**Freq**	**%**	**#**	NSP5	NSP7	NSP12	Spike	Spike	Spike	N	N	N	N
				L205	L71	P323	E484	D614	V1176	A119	R203	G204	M234
1	2550	0.8736	10	**V**	**F**	**L**	**K**	**G**	**F**	**S**	**K**	**R**	**I**
2	85	0.0291	9	L	.	.	.	.	.	.	.	.	.
3	80	0.0274	9	.	.	.	E	.	.	.	.	.	.
4	21	0.0072	9	.	.	.	.	.	V	.	.	.	.
5	18	0.0062	9	.	.	.	.	.	.	A	.	.	.
6	17	0.0058	8	.	.	P	E	.	.	.	.	.	.
7	17	0.0058	9	.	.	P	.	.	.	.	.	.	.
8	14	0.0048	8	.	.	P	.	.	V	.	.	.	.
9	12	0.0041	7	.	.	.	.	.	.	.	R	G	M
10	10	0.0034	8	.	.	.	.	.	.	.	R	G	.
11	10	0.0034	9	.	.	.	.	.	.	.	R	.	.
12	9	0.0031	9	.	.	.	.	.	.	.	.	.	M
13	8	0.0027	8	.	.	.	E	.	.	.	.	.	M
14	8	0.0027	10	.	.	.	.	.	.	.	.	L	.
15	4	0.0014	8	.	.	.	.	.	.	A	.	.	M
16	4	0.0014	8	.	.	.	.	.	V	.	.	.	M
17	3	0.001	6	L	.	.	E	D	V	.	.	.	.
18	3	0.001	8	.	.	.	.	.	.	A	R	.	.

eTable 16. Concordance Analysis in the Training Set

Result from the concordance analysis of GISAID assigned variant (columns) with haplotype-based variant assigment (rows) in the training data set with 4,393,998 viruses (50% of all viruses at GISAID, downloaded on March 14, 2022).

Predction[1]	Alpha	Beta	Delta	Epsilon	Eta	Gamma	GH/490R	Iota	Kappa	Lambda	Mu	Omicron	Theta	Zeta	UA[4]	Sub-total
Alpha	573,599		4			3									2,497	576,103
Beta		8,021													90	8,111
Delta	1	1	2,120,806						6			2			1,486	2,122,302
Epsilon	1		9	35,883				1			3	1			145,822	181,720
Eta	1		2		4,695										33	4,731
Gamma			1			59,471									95	59,567
GH/490R							422									422
Iota	1	1						18,589							68	18,659
Kappa	1		2						3,796						48	3,847
Lambda						1				5,077					6	5,084
Mu				1							5,634				38	5,673
Omicron			2									1,487,867			704	1,488,573
Theta													148		1	149
Zeta						4				1			1	2,918	24,546	27,470
MV[2]	385	12,940	19,917	11	16	658	8	3,140	43	9	2,193	112,137	181	1	7,633	159,272
UP[3]	446	97	1,702	53	3	63	1	12	66	13	2	1,333		1	360,335	364,127
Sub-total	574,435	21,060	2,142,445	35,948	4,714	60,200	431	21,742	3,911	5,100	7,832	1,601,340	330	2,920	543,402	5,025,810

[1] Posterial probability threshold=0.99; [2] MV for mixture of variants; [3] UP for unpredictable variant; [4] UC for unclassified variant

eTable 17. Concordance Analysis in the Validation Set

Result from the concordance analysis of GISAID assigned variant (columns) with haplotype-based variant assigment (rows) in the training data set with 4,393,998 viruses (50% of all viruses at GISAID, downloaded on March 14, 2022).

Predction[1]	Alpha	Beta	Delta	Epsilon	Eta	Gamma	GH/490R	Iota	Kappa	Lambda	Mu	Omicron	Theta	Zeta	UA[4]	Sub-total
Alpha	1,148,060	1	4			6			1						5,218	1,153,290
Beta		15,492													145	15,637
Delta	4		4,246,693			1			11			5			3,184	4,249,898
Epsilon	2	8	24	71,899		1		3			7	3			298,020	369,967
Eta	1	1	5		9,398										92	9,497
Gamma			1			118,898									193	119,092
GH/490R							8									8
Iota		2						37,951							143	38,096
Kappa			40						7,558						113	7,711
Lambda						2				10,058					16	10,076
Mu				1							7,348				60	7,409
Omicron			2							1		3,003,288			1,600	3,004,891
Theta													414		1	415
Zeta	3	5	3			12		4				2		5,886	53,014	58,929
MV[2]	732	26,350	35,585	56	54	1,399	879	5,315	90	12	8,518	194,988	211	1	18,028	292,218
UP[3]	825	122	3,248	84	3	86		14	98	24	5	3,232		1	706,744	714,486
Sub-total	1,149,627	41,981	4,285,605	72,040	9,455	120,405	887	43,287	7,758	10,095	15,878	3,201,518	625	5,888	1,086,571	10,051,620

[1]Posterial probability threshold=0.99; [2]MV for mixture of variants; [3]UP for unpredictable variant; [4]UA for unassigned variant

eTable 18. Concordance Analysis in the Prospective Set

Result from the concordance analysis of GISAID assigned variant (columns) with haplotype-based variant assigment (rows) in the prospective data set with 343,431 viruses, collected after March 14, 2022 and downloaded on May 18, 2022.

Predction[1]	Alpha	Delta	Epsilon	Eta	Lambda	Omicron	Zeta	**UA[4]**	Sub-total
Alpha	2					4			6
Delta		171				3			174
Epsilon			0			2		3	5
Eta				0				1	1
Lambda					1				1
Omicron						319,812		567	320,379
Zeta							0	1	1
MV[2]		5				22,072		30	22,107
UP[3]		4				1,699		524	2,227
Sub-total	2	180			1	343,592		1,126	344,901

eTable 19. Four Mixture Variants with Omicron-Delta

Four recombinants of Omicron with A) Delta, B) Alpha, C) Zeta and D) Epsilon variants, in which all observed recombinants include polymutants in their respective variant-specific core haplotypes and indicator of 1 and 2 corresponded to the variant (1) recombinaned with Omicron (2)

Delta-Omicron	Freq	NSP1	NSP3	NSP3	NSP3	NSP3	NSP3	NSP4	NSP5	NSP6	NSP13	NSP14	NSP15	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	E	M	M	M	M	N	N	N
		S135	T24	K38	G489	L1266	A1892	L264	P132	I189	R392	I42	T112	G339	R346	S371	S373	S375	T376	D405	R408	K417	N440	L452	S477	E484	Q498	N501	Y505	T547	H655	N679	D796	N856	Q954	N969	L981	T223	T9	D3	Q19	A63	I82	P13	G204	S413
Indicator		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2
1	1	R	I	.	S	.	.	F	H	.	C	V	I	D	.	F	P	F	A	N	S	N	K	R	N	A	R	Y	H	.	Y	.	.	.	.	.	.	I	I	.	E	T	.	L	R	R
2	1	.	I	.	S	.	.	F	H	.	C	V	I	D	.	F	P	F	A	N	S	N	K	R	N	A	R	Y	H	.	Y	.	.	.	.	.	.	I	I	.	E	T	.	L	R	R
3	1	.	.	R	.	I	T	.	H	V	.	V	.	D	K	L	P	F	.	.	.	.	.	R	N	.	R	Y	H	K	Y	K	Y	K	H	K	F	.	I	G	E	.	T	L	R	.

eTable 20. Four Mixture Variants with Omicron-Alpha

Four recombinants of Omicron with A) Delta, B) Alpha, C) Zeta and D) Epsilon variants, in which all observed recombinants include polymutants in their respective variant-specific core haplotypes and indicator of 1 and 2 corresponded to the variant (1) recombinaned with Omicron (2)

Alpha-Omicron	Freq	NSP1	NSP3	NSP3	NSP3	NSP3	NSP3	NSP3	NSP3	NSP4	NSP4	NSP4	NSP4	NSP5	NSP6	NSP13	NSP14	NSP15	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	E	M	M	M	NS8	N	N	N	N
		S135	T24	K38	T183	G489	L1266	I1412	A1892	L264	T327	L438	T492	P132	I189	R392	I42	T112	T19	A27	A67	T95	G142	L212	V213	G339	R346	S371	S373	S375	T376	D405	R408	K417	N440	G446	S477	T478	E484	Q493	G496	Q498	Y505	T547	H655	N679	T716	N764	D796	N856	Q954	N969	L981	S982	T223	T9	D3	Q19	A63	R52	D3	P13	S235	S413
Indicator		2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	1	1	2	1	2
1	2	R	I	.	I	S	.	.	.	F	I	F	I	H	V	C	V	I	I	S	.	.	D	S	G	D	.	F	P	F	A	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	.	.	E	T	.	.	L	.	R
2	1	R	I	.	I	N	.	.	.	F	I	F	I	H	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	N	K	S	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	.	R
3	1	R	I	.	I	S	.	.	.	F	I	F	I	H	.	C	.	.	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	K	.	K	.	.	.	K	.	.	I	I	.	E	T	.	.	L	.	R
4	1	R	I	.	I	S	.	.	.	F	I	F	I	H	.	C	V	I	I	S	.	.	D	.	G	D	.	Y	P	F	A	N	S	N	.	.	N	K	.	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	.	R
5	1	R	I	.	I	S	.	.	.	F	I	.	I	H	.	C	V	I	I	S	.	.	D	S	G	D	.	.	.	.	.	.	.	.	.	.	N	K	A	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	.	R
6	1	R	I	.	I	S	.	.	.	.	I	F	I	H	.	C	.	I	I	S	.	.	D	.	G	D	.	F	P	F	A	.	.	.	.	.	.	.	A	R	.	R	H	.	Y	K	.	.	Y	.	H	K	.	.	I	I	.	E	.	.	.	L	.	R
7	1	R	I	.	.	.	.	.	.	F	I	F	I	H	.	C	V	I	I	d	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	K	I	K	Y	K	H	K	F	.	I	I	.	E	T	.	.	L	.	R
8	1	R	I	.	.	S	.	.	.	F	I	F	I	H	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	.	.	N	.	.	N	K	A	R	.	R	H	.	Y	K	I	K	Y	.	H	K	.	.	I	I	.	.	.	.	.	L	.	R
9	1	R	I	.	.	S	.	.	.	F	I	F	I	H	.	C	V	I	.	.	.	.	D	.	G	D	.	F	P	F	A	.	.	.	K	.	N	K	A	R	.	R	.	.	Y	K	.	.	.	.	H	K	.	.	I	I	.	.	T	I	.	L	.	R
10	1	R	I	.	.	S	.	.	.	F	I	F	I	H	.	C	V	.	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	N	K	A	R	S	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	I	.	L	.	R
11	1	R	I	.	.	S	.	.	.	F	I	F	I	.	.	.	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	.	.	.	.	.	.	.	.	.	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	F	R
12	1	R	I	.	.	S	.	.	.	F	I	.	I	H	.	C	V	I	I	S	.	.	D	.	G	.	.	.	.	.	.	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	.	.	K	Y	.	H	K	.	A	I	I	.	E	T	.	.	L	.	R
13	1	R	I	.	.	S	.	.	.	F	I	.	I	H	.	C	V	I	I	S	.	.	.	.	G	.	.	.	.	.	.	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	A	I	I	.	E	T	.	.	L	.	R
14	1	R	I	.	.	S	.	.	.	F	I	.	I	H	.	C	V	.	I	S	.	.	D	.	G	.	.	F	P	F	A	N	S	N	K	.	.	K	A	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	A	I	I	.	E	T	.	.	L	.	R
15	1	R	I	.	.	S	.	.	.	F	.	.	.	H	.	C	V	I	I	.	.	.	.	.	.	D	.	F	P	F	A	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	F	R
16	1	R	I	.	.	S	.	T	.	.	I	F	I	H	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	.	.	N	K	.	.	.	.	.	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	.	R
17	1	R	I	.	.	S	.	T	.	.	I	F	I	H	.	C	V	.	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	.	.	.	.	.	.	.	.	.	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	L	.	.
18	1	R	.	.	.	S	.	.	.	.	I	F	I	H	.	C	.	I	I	S	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	K	.	K	Y	.	H	K	.	A	I	I	.	E	T	.	.	L	.	R
19	1	.	I	.	I	S	.	.	.	F	I	F	I	H	.	C	V	I	I	S	.	.	D	S	G	D	.	F	P	F	A	N	S	N	K	.	N	K	A	R	.	R	H	.	Y	K	.	K	Y	.	H	K	.	.	I	I	.	E	T	.	.	.	.	R
20	1	.	.	.	.	.	I	.	T	.	.	.	I	H	V	.	V	.	.	.	V	I	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	K	Y	K	.	K	Y	K	H	K	F	A	.	I	G	E	T	.	.	L	.	.
21	1	.	.	R	I	.	I	.	T	.	.	.	I	H	V	.	V	.	.	.	V	I	D	I	.	D	T	F	P	.	.	.	.	N	K	S	N	K	A	R	S	R	H	K	Y	K	.	K	Y	K	H	K	F	.	.	I	G	E	T	.	.	L	.	.
22	1	.	.	R	I	.	I	.	T	.	.	.	I	.	V	.	V	.	.	.	V	I	D	I	.	D	K	L	P	F	.	.	.	.	K	.	N	K	A	R	S	R	H	K	Y	K	.	K	Y	K	H	K	F	.	.	I	.	E	T	.	.	L	.	.
23	1	.	.	R	I	.	.	.	T	.	.	.	I	H	V	.	.	.	.	.	V	I	D	I	.	D	.	L	P	F	.	.	.	N	K	S	N	K	A	R	S	R	H	K	Y	K	.	.	Y	K	.	K	F	.	.	I	G	E	T	.	.	L	.	.
24	1	.	.	R	.	.	.	.	T	.	.	.	I	H	V	.	.	.	.	.	V	I	D	I	.	D	.	L	P	F	.	.	.	N	K	S	N	K	A	.	S	R	H	K	Y	K	.	K	Y	K	H	K	F	.	.	I	G	E	T	.	L	L	.	.

eTable 21. Four Mixture Variants with Omicron-Zeta

Four recombinants of Omicron with A) Delta, B) Alpha, C) Zeta and D) Epsilon variants, in which all observed recombinants include polymutants in their respective variant-specific core haplotypes and indicator of 1 and 2 corresponded to the variant (1) recombinaned with Omicron (2)

Epsilon-Omicron	Freq	NSP1	NSP2	NSP3	NSP3	NSP3	NSP3	NSP3	NSP4	NSP4	NSP4	NSP4	NSP5	NSP6	NSP9	NSP13	NSP14	NSP15	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	Spike	NS3	NS3	E	M	M	M	N	N	N	N	N
		S135	T85	T24	K38	G489	L1266	A1892	L264	T327	L438	T492	P132	I189	I65	R392	I42	T112	T19	A27	A67	T95	G142	L212	V213	G339	R346	S371	S373	S375	T376	D405	R408	K417	N440	G446	L452	S477	T478	E484	Q493	G496	Q498	N501	Y505	T547	H655	N679	P681	N764	D796	N856	Q954	N969	L981	Q57	T223	T9	D3	Q19	A63	P13	R203	G204	T205	S413
Indicator		2	1	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	2
1	96	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	E	T	L	K	R	.	R
2	94	R	I	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	.	R
3	88	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	I	R
4	8	R	I	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	.	.	.	R
5	8	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	.	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	E	T	L	K	R	.	R
6	7	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	.	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	I	R
7	6	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	.	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	E	T	L	K	R	.	R
8	6	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	.	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	I	R
9	6	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	.	.	.	.	.	.	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	E	T	L	K	R	.	R
10	6	R	.	I	.	S	.	.	F	I	F	I	H	.	V	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	.	R
11	5	R	I	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	.	.	.	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	.	R
12	5	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	.	.	.	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	I	R
13	4	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	Z	T	L	K	R	.	R
14	4	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	.	K	R	I	R
15	4	.	I	.	R	.	I	T	.	.	.	I	H	V	.	.	V	.	.	.	V	I	D	I	.	D	K	L	P	F	.	.	.	N	K	S	.	N	K	A	R	S	R	Y	H	K	Y	K	H	K	Y	K	H	K	F	.	.	I	G	E	T	L	K	R	.	.
16	3	R	I	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	.	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	.	R
17	3	R	I	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	.	.	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	.	R
18	3	R	I	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	N	.	.	.	.	.	.	.	.	.	.	.	.	Y	K	H	K	Y	.	H	K	.	.	I	I	.	E	T	L	K	R	.	R
19	3	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	.	.	.	D	.	G	D	.	F	P	F	A	N	S	N	K	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	E	T	L	K	R	.	R
20	3	R	.	I	.	S	.	.	F	I	F	I	H	.	.	C	V	I	I	S	.	.	D	.	G	D	.	F	P	F	A	N	S	.	.	.	.	N	K	A	R	.	R	Y	H	.	Y	K	H	K	Y	.	H	K	.	H	I	I	.	E	T	L	K	R	.	R

eTable 22. Four Mixture Variants with Omicron-Epsilon
Geo- and temporal distribution of Epsilon-Omicron recombinants in the world.

Collection Date	Africa/Mauritius	Africa/South Africa	Asia/Israel	Asia/Japan	Asia/Malaysia	Asia/Singapore	Asia/South Korea	Asia/Thailand	Europe/Austria	Europe/Belgium	Europe/Croatia	Europe/Czech Republic	Europe/Denmark	Europe/Estonia	Europe/Finland	Europe/France	Europe/Germany	Europe/Ireland	Europe/Italy	Europe/Lithuania	Europe/Luxembourg	Europe/Netherlands	Europe/Norway	Europe/Poland	Europe/Portugal	Europe/Slovakia	Europe/Slovenia	Europe/Spain	Europe/Sweden	Europe/Switzerland	Europe/Turkey	Europe/United Kingdom	North America/Canada	North America/Costa Rica	North America/USA	Oceania/Australia	Oceania/New Zealand	South America/Brazil	South America/Chile	South America/Colombia	total
2022-03-15								1																	1				1			1	1		1						6
2022-03-16			1													1												1				1	1		2			1			8
2022-03-17			1													1						1		1					2			1	1								8
2022-03-18																	1	1										1	1			3	1		2						10
2022-03-19													2			1																1			1		1				6
2022-03-20																																			1						1
2022-03-21																2											1					3	1		1						8
2022-03-22									1			1	1			1	1	4										1				2			3						15
2022-03-23					1																			2								3			2						8
2022-03-24								1													1		2									5			3	1					13
2022-03-25																			1													1			1						3
2022-03-26				3	3																																				6
2022-03-27	1											1																				1									3
2022-03-28														1	1	1	1											1	1			1	1			1					9
2022-03-29				2						1							2											1				1	3								10
2022-03-30													1			1												2							1						5
2022-03-31											1	1					3											2				1									8
2022-04-01												1																				3			1				1		6
2022-04-02		1	1														1															3	1								7
2022-04-03																	1										1						2		2						6
2022-04-04				1												2	1																		1				1		6
2022-04-05											1							1					1					1				1			1		1			1	8
2022-04-06		1									3																	1	1			7			2						15
2022-04-07			1														1					1		1	1						1	3		1	1						11
2022-04-08			2												1														1			4									8
2022-04-09																			1													4	2		3						10
2022-04-10							1					1										2	1									3			1						9
2022-04-11								2				1	6			5	3				1				2							7	1		2	1					31
2022-04-12												2	2				3			1			1					1				5	1		1						17
2022-04-13		1	1									2					2						1							1		3	1		1	1					14
2022-04-14																	3					6						1	1			7	1		4						23
2022-04-15																	4															1	1		4						10
2022-04-16			1							1	1					1	4															2	1		3	1					15
2022-04-17							1										1									1						3			2						8
2022-04-18			1														4															9	1		3	2					20
2022-04-19			1										8			1	3				1	1										7	1		3	1			1		28
2022-04-20								1									1					1						2				3	1		1						10
2022-04-21			1										2				3		1			1							1			3	1		5						18
2022-04-22			2				1			1		1	2				4												2			8			5						26
2022-04-23							1					1	1				2		1													5			4						15
2022-04-24										1			1				3															1	1		7						14
2022-04-25										1			2			2	6									1						2	2		7						23
2022-04-26										2			1				3				1	1							1			9			14						32
2022-04-27						1				1			1				1															6	2		4						16
2022-04-28																	5												1			8			5						19
2022-04-29																	1															5	1		8						15
2022-04-30																																1			3		1				5
2022-05-01										1			1																			1	1		2						6
2022-05-02										2			1						1													1			3						8
2022-05-03																	1											3				4			3						11
2022-05-04													1				1		2													2									6
2022-05-05																	1																								1
2022-05-06																		1														2									3
2022-05-08										1																															1
2022-05-09										1																															1
total	1	3	13	6	4	1	4	5	1	13	6	12	33	1	2	19	71	7	7	1	4	14	6	4	4	2	2	18	13	1	1	158	31	1	124	8	3	1	3	1	609

eTable 23. Mixture Variant and Corresponding Lineages

Relationship of mixture variants with their assigned lineages

Lineage	Omicron-Delta	Omicron-Epsilon	Omicron-Alpha	Omicron-Zeta	Alpha-Epsilon	Delta-Kappa	Delta-Zeta	total
AY.25						1		1
AY.38							1	1
AY.4.14						1		1
AY.4.15						1		1
AY.45							1	1
BA.1	1	1	3	1				6
BA.1.1		30	2	2				34
BA.1.1.1		6						6
BA.1.1.14		1						1
BA.1.1.15		1						1
BA.1.1.2		5						5
BA.1.14		3						3
BA.1.15		1						1
BA.1.17		1						1
BA.1.17.2		1						1
BA.1.18		2						2
BA.1.19		1						1
BA.2	2	354	15	5	6			382
BA.2.1		5						5
BA.2.10		5		1	1			7
BA.2.12		4						4
BA.2.15		2						2
BA.2.2		1						1
BA.2.20		3						3
BA.2.21		1						1
BA.2.22		3						3
BA.2.23		4						4
BA.2.24		1						1
BA.2.26		1						1
BA.2.3		88			3			91
BA.2.3.4		9						9
BA.2.4		1						1
BA.2.7		1						1
BA.2.8		1						1
BA.2.9		71	5					76
BA.4		1						1
BA.5				1				1
total	3	609	25	10	10	3	2	662

eTable 24. Unidentifiable Omicron Viruses and Corresponding Lineages

HAI-unpredictable Omicron viruses and their assigned lineages

	O1	**O2**	**O3**	**O4**	total
BA.1	22	5	55	3	85
BA.1.1	3		54	1	58
BA.1.1.1			4		4
BA.1.1.13			1		1
BA.1.1.18			1		1
BA.1.15			2		2
BA.1.15.2			1		1
BA.1.17			5		5
BA.1.20			1		1
BA.1.9			1		1
BA.2	510	253		323	1086
BA.2.10	9	5			14
BA.2.12	23	13			36
BA.2.12.1	18	6			24
BA.2.18	2				2
BA.2.19		1			1
BA.2.23	35	9		3	47
BA.2.3	18	19		1	38
BA.2.3.2		3			3
BA.2.3.3	1				1
BA.2.31	4	2			6
BA.2.32	1				1
BA.2.5	1	1			2
BA.2.6	2				2
BA.2.7	2				2
BA.2.8		2			2
BA.2.9	27	16		9	52
BA.3	1	1			2
BA.3.1	4				4
BA.4	1				1
BA.5	3				3
Unassigned	131	62	9		202
XE	8	1			9
total	826	399	134	340	1699

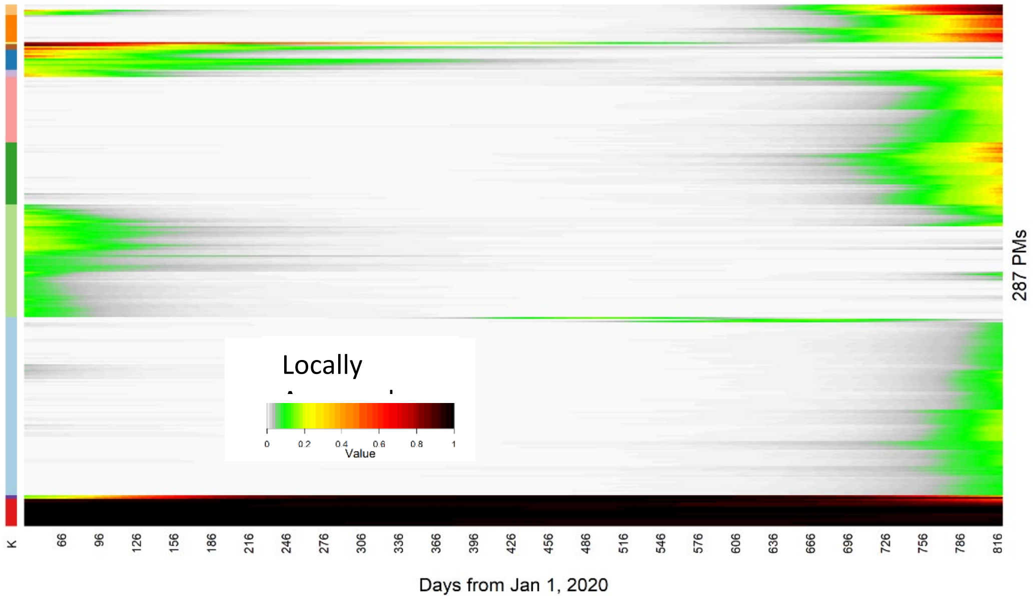
eTable 25. New Mutations Among Variant-Unassigned and Unidentifiable Viruses

Ab initio mutations (excluding all core polymutants of 14 known variants) have been foud to significant temporal trend

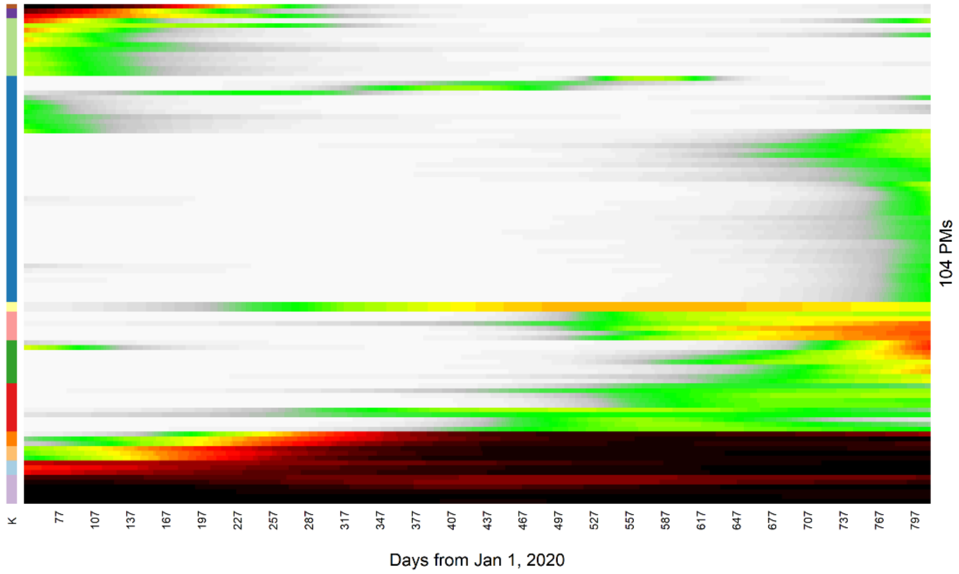
	Polymutant	cluster	p-vlaue	LAMP	LAMP-max
1	NSP1_F143	O1	3.43E-02	2.25E-02	7.62E-02
2	NSP1_K141	O1	3.43E-02	2.25E-02	7.62E-02
3	NSP1_S142	O1	3.43E-02	2.25E-02	7.62E-02
4	Spike_A684	O1	1.94E-02	2.00E-02	9.05E-02
5	Spike_I68	O1	4.10E-02	2.09E-02	1.22E-01
6	NSP2_F356	O2	1.04E-02	2.34E-02	1.09E-01
7	NSP6_L105	O2	2.76E-04	8.18E-02	2.09E-01
8	NS3_H78	O3	3.56E-02	9.53E-02	1.67E-01
9	Spike_L24	O4	3.12E-05	3.30E-01	5.33E-01
10	Spike_P25	O4	1.66E-05	3.32E-01	5.41E-01
11	NSP6_F108	O5	2.09E-06	4.42E-01	6.02E-01
12	NSP6_G107	O5	4.32E-05	5.20E-01	6.70E-01
13	NSP6_S106	O5	6.73E-05	5.14E-01	6.61E-01
14	N_E31	O6	1.99E-02	6.52E-01	7.15E-01
15	N_R32	O6	1.70E-02	6.39E-01	7.00E-01
16	N_S33	O6	1.03E-02	6.49E-01	7.18E-01

eFigure 1. Heatmap-representation of selected polymutant temporal profile from January 1, 2020 to March 14, 2022 within every variant: A) Alpha, B) Beta, C) Delta, D) Epsilon, E) Eta, F) Gamma, G) GH/490R, H) Iota, I) Kappa, J) Lambda, K) Mu L) Omicron, M) Theta, N) Zeta and O) variant-unassigned viruses. In each profile, estimated locally-averaged mutation percentages (LAMP) take value from 0 to 1, and are color-coded (the legend), and each row corresponds to a polymutant while each column corresponds to collection date.

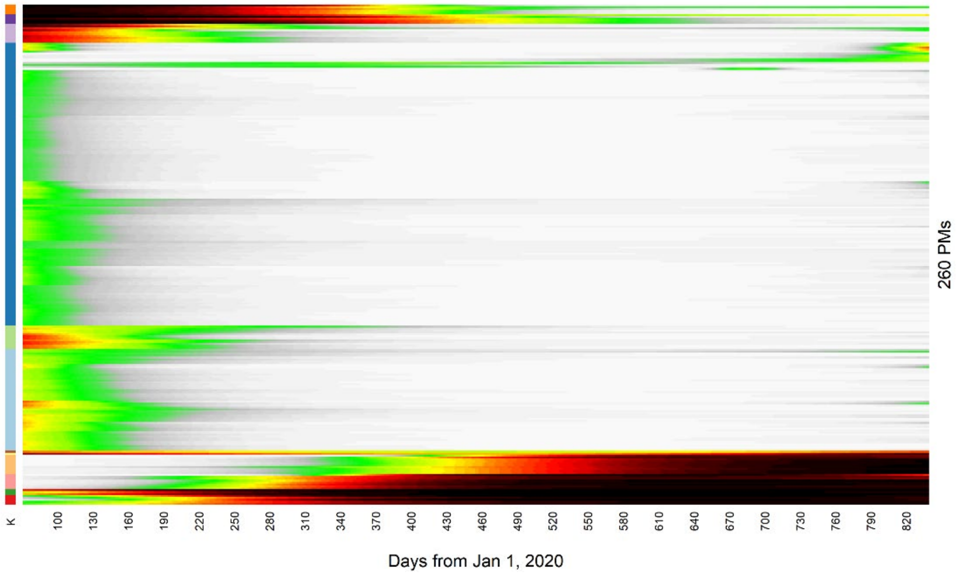
A)



B) Beta

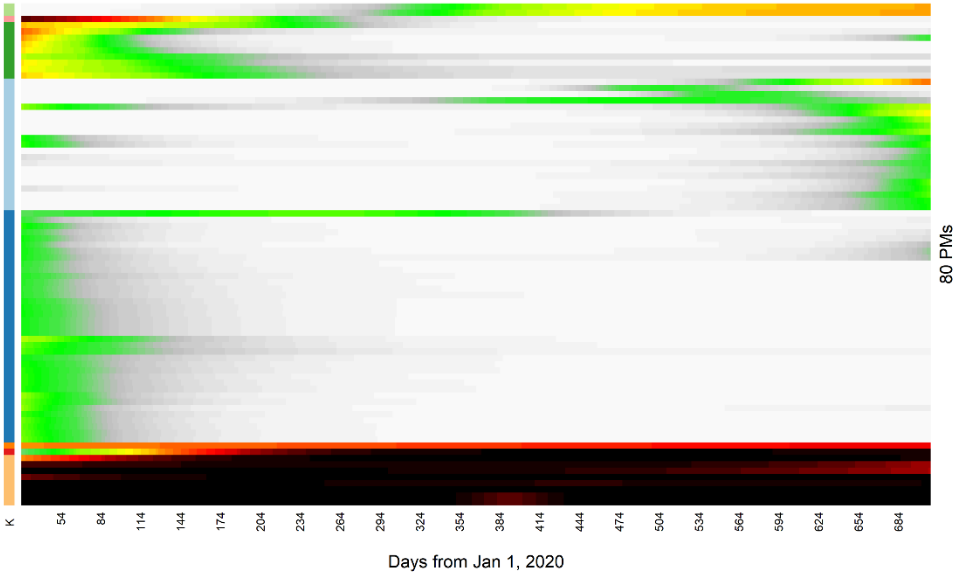

K
77
107
137
167
197
227
257
287
317
347
377
407
437
467
497
527
557
587
617
647
677
707
737
767
797
Days from Jan 1, 2020
104 PMs

C) Delta

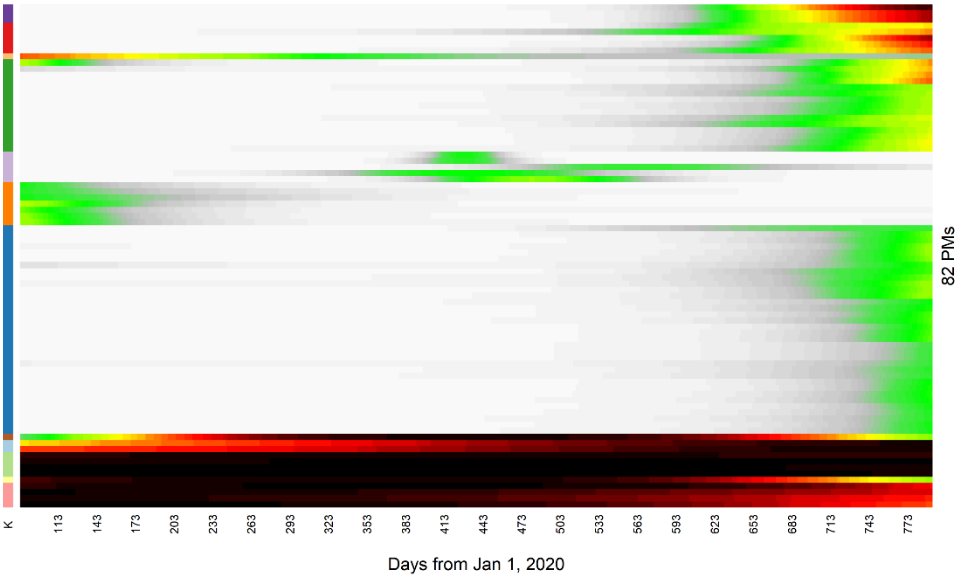


K
100
130
160
190
220
250
280
310
340
370
400
430
460
490
520
550
580
610
640
670
700
730
760
790
820
Days from Jan 1, 2020
260 PMs

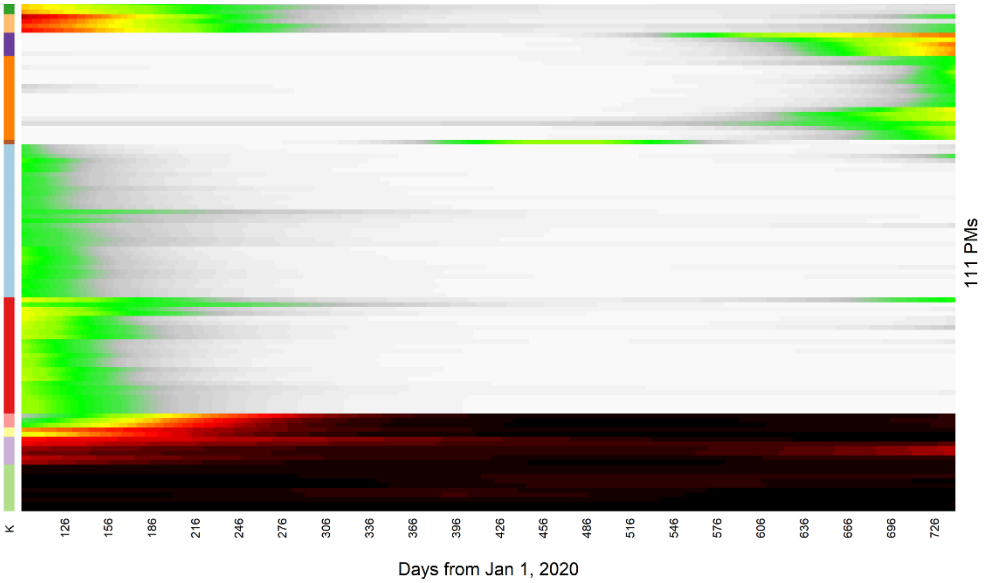
D) Epsilon


K
54
84
114
144
174
204
234
264
294
324
354
384
414
444
474
504
534
564
594
624
654
684
Days from Jan 1, 2020
80 PMs

E) Eta

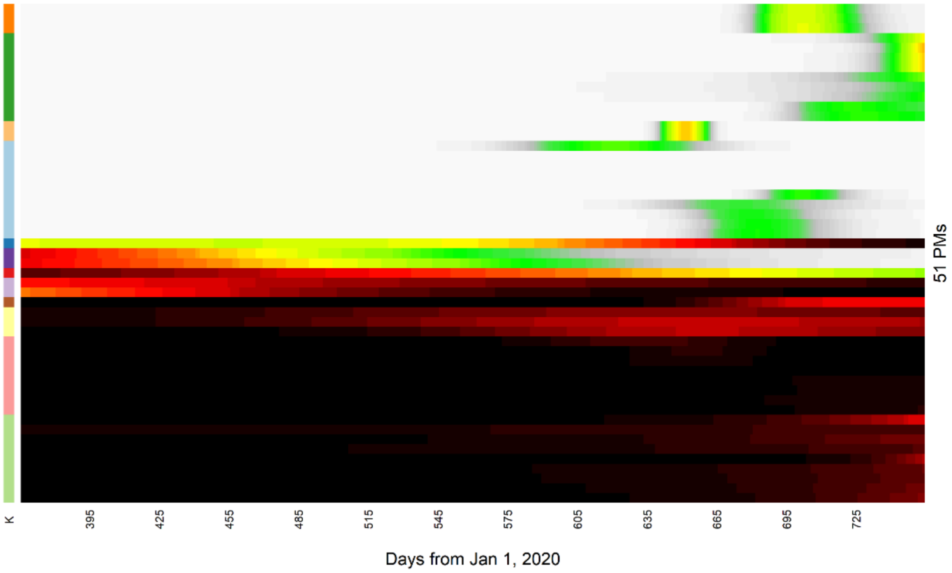

K
113
143
173
203
233
263
293
323
353
383
413
443
473
503
533
563
593
623
653
683
713
743
773
Days from Jan 1, 2020
82 PMs

F) Gamma

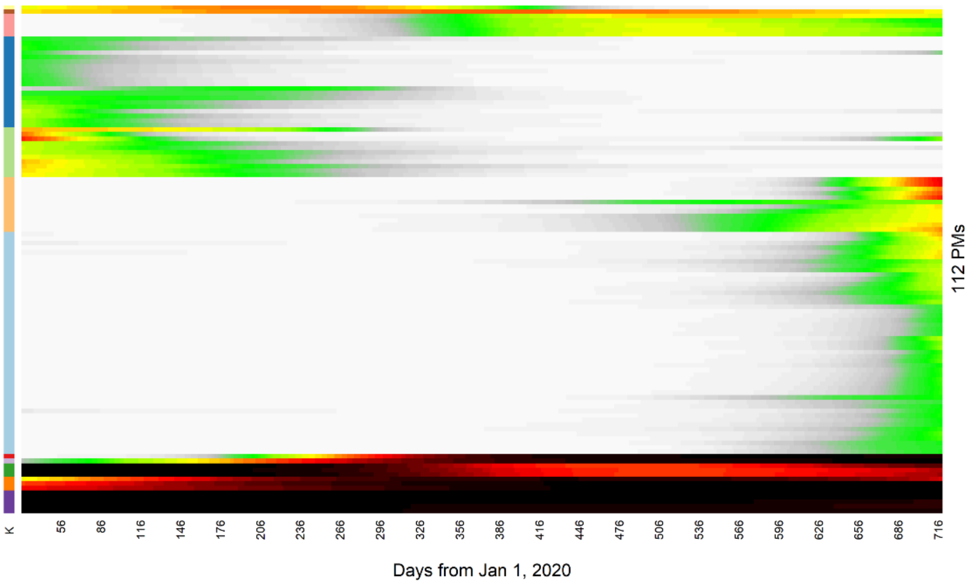


K
126
156
186
216
246
276
306
336
366
396
426
456
486
516
546
576
606
636
666
696
726
Days from Jan 1, 2020
111 PMs

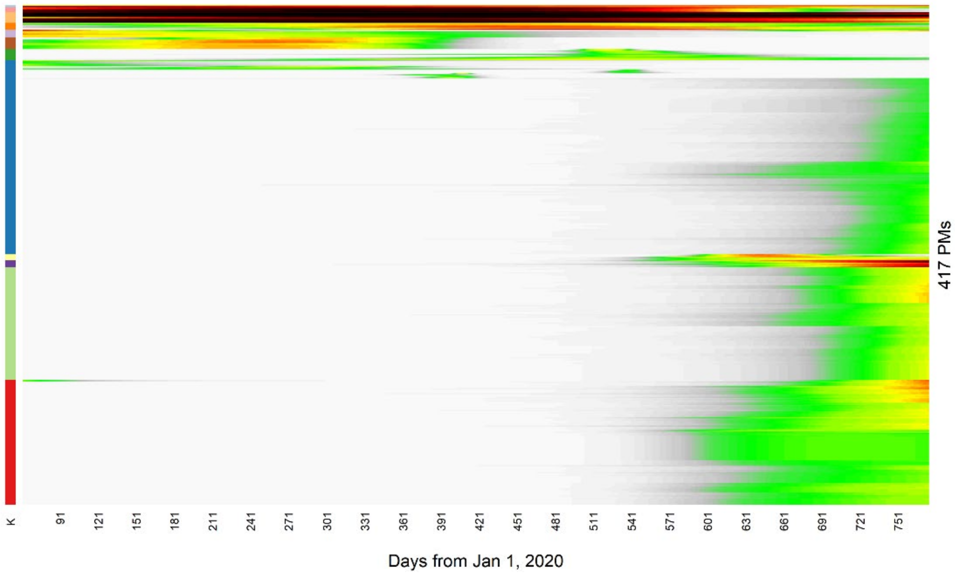
G) GH/450R


K
395
425
455
485
515
545
575
605
635
665
695
725
Days from Jan 1, 2020
51 PMs

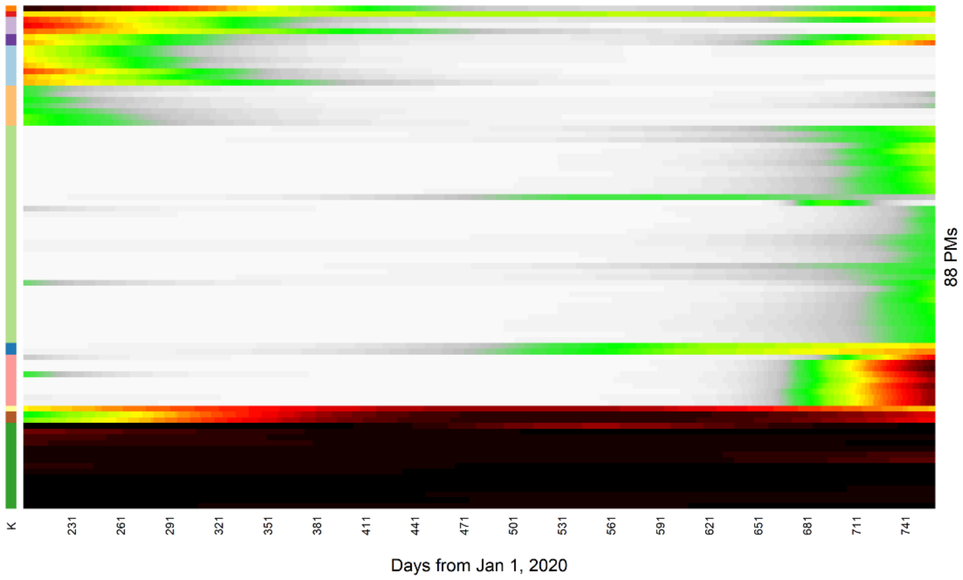
H) Iota


K
56
86
116
146
176
206
236
266
296
326
356
386
416
446
476
506
536
566
596
626
656
686
716
Days from Jan 1, 2020
112 PMs

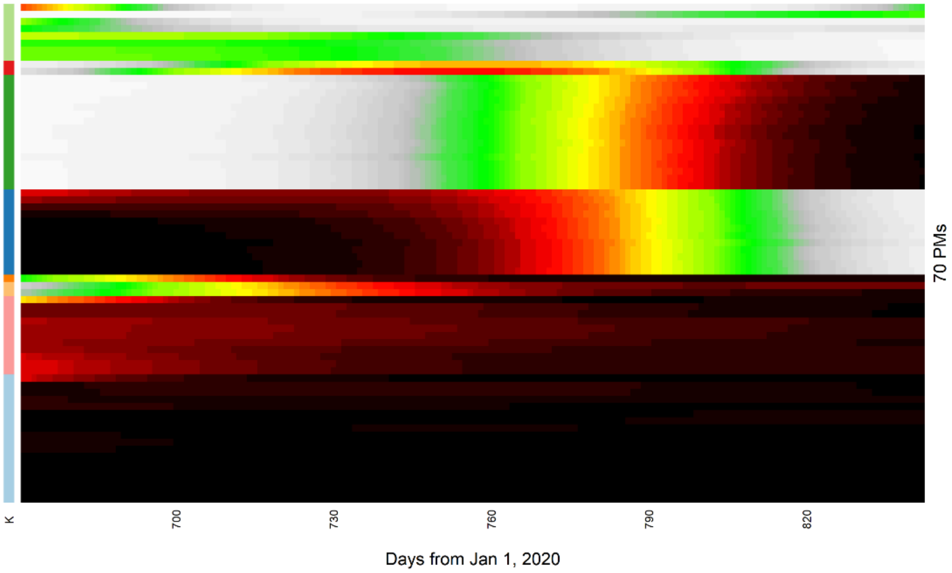
I) Kappa


417 PMs
K
91
121
151
181
211
241
271
301
331
361
391
421
451
481
511
541
571
601
631
661
691
721
751
Days from Jan 1, 2020

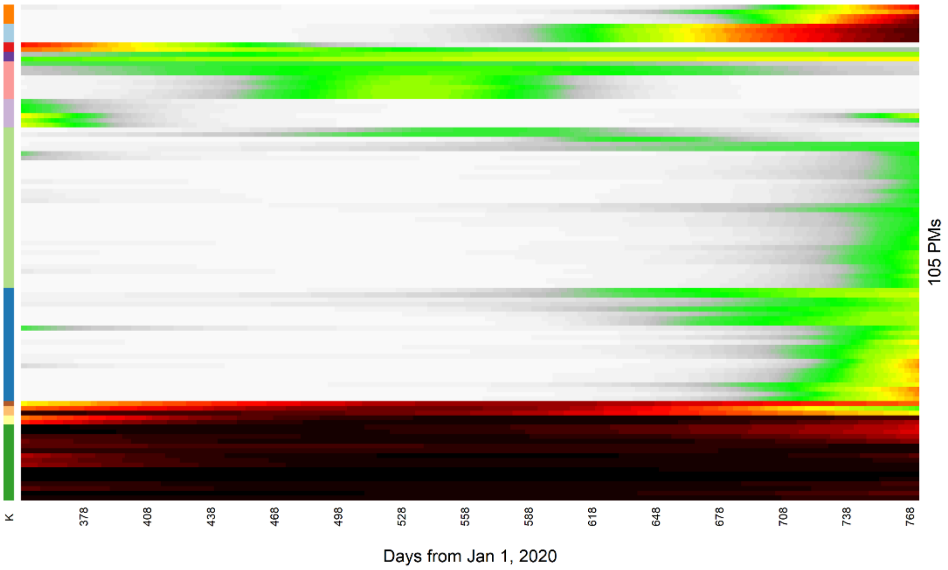
J) Lambda


K
231
261
291
321
351
381
411
441
471
501
531
561
591
621
651
681
711
741
Days from Jan 1, 2020
88 PMs

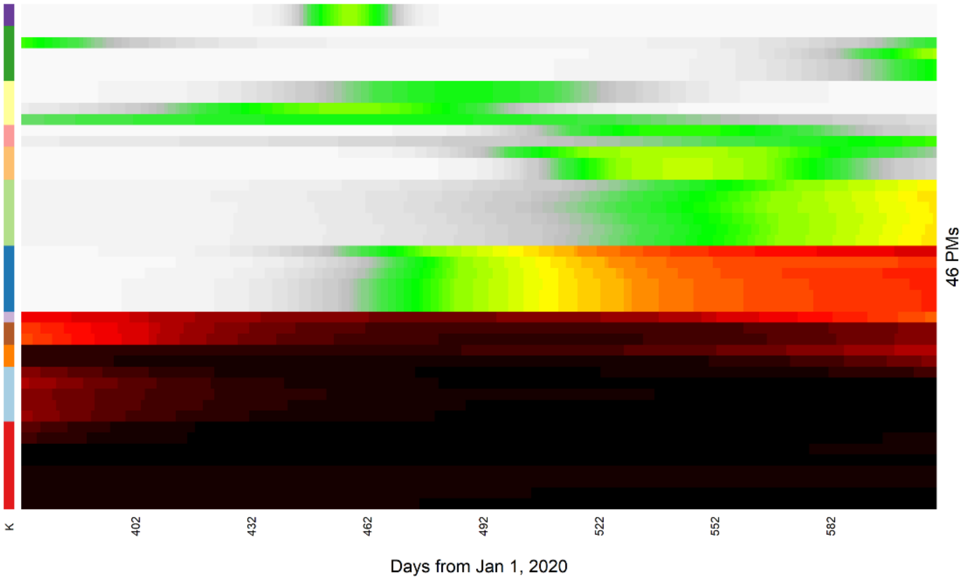
L) Omicron



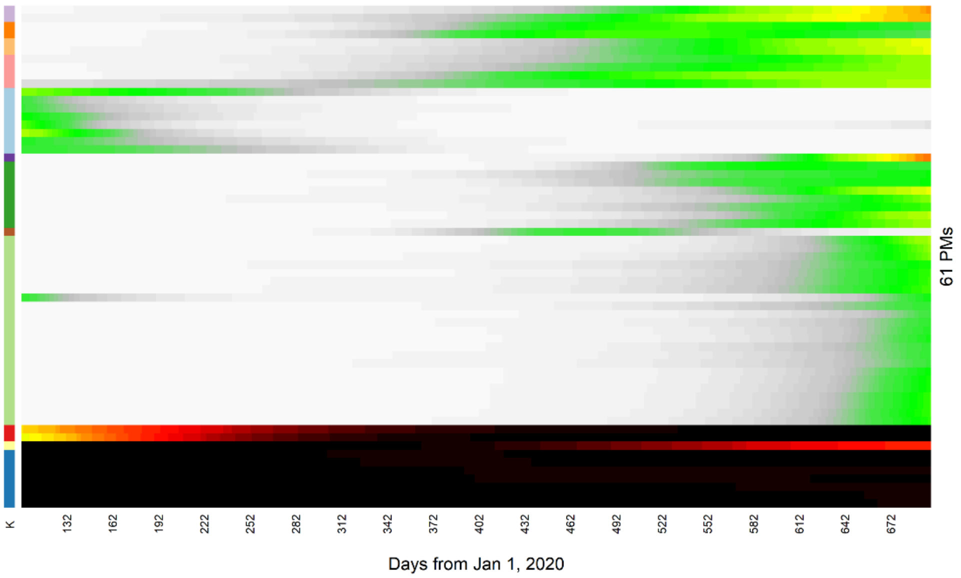
M) Mu


105 PMs
K
378
408
438
468
498
528
558
588
618
648
678
708
738
768
Days from Jan 1, 2020

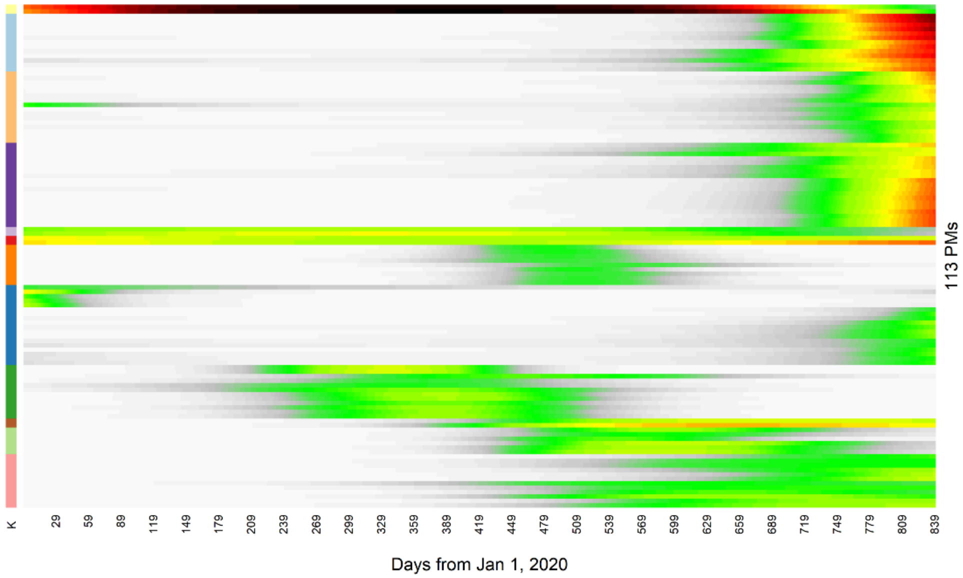
N) Theta



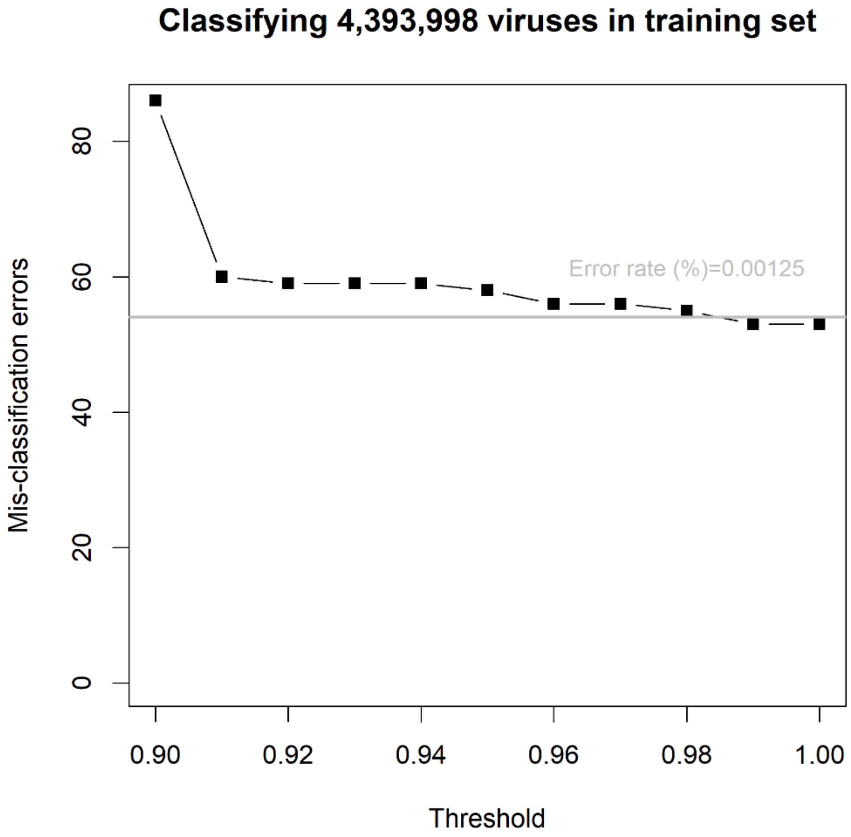
N) Zeta


K
132
162
192
222
252
282
312
342
372
402
432
462
492
522
552
582
612
642
672
Days from Jan 1, 2020
61 PMs

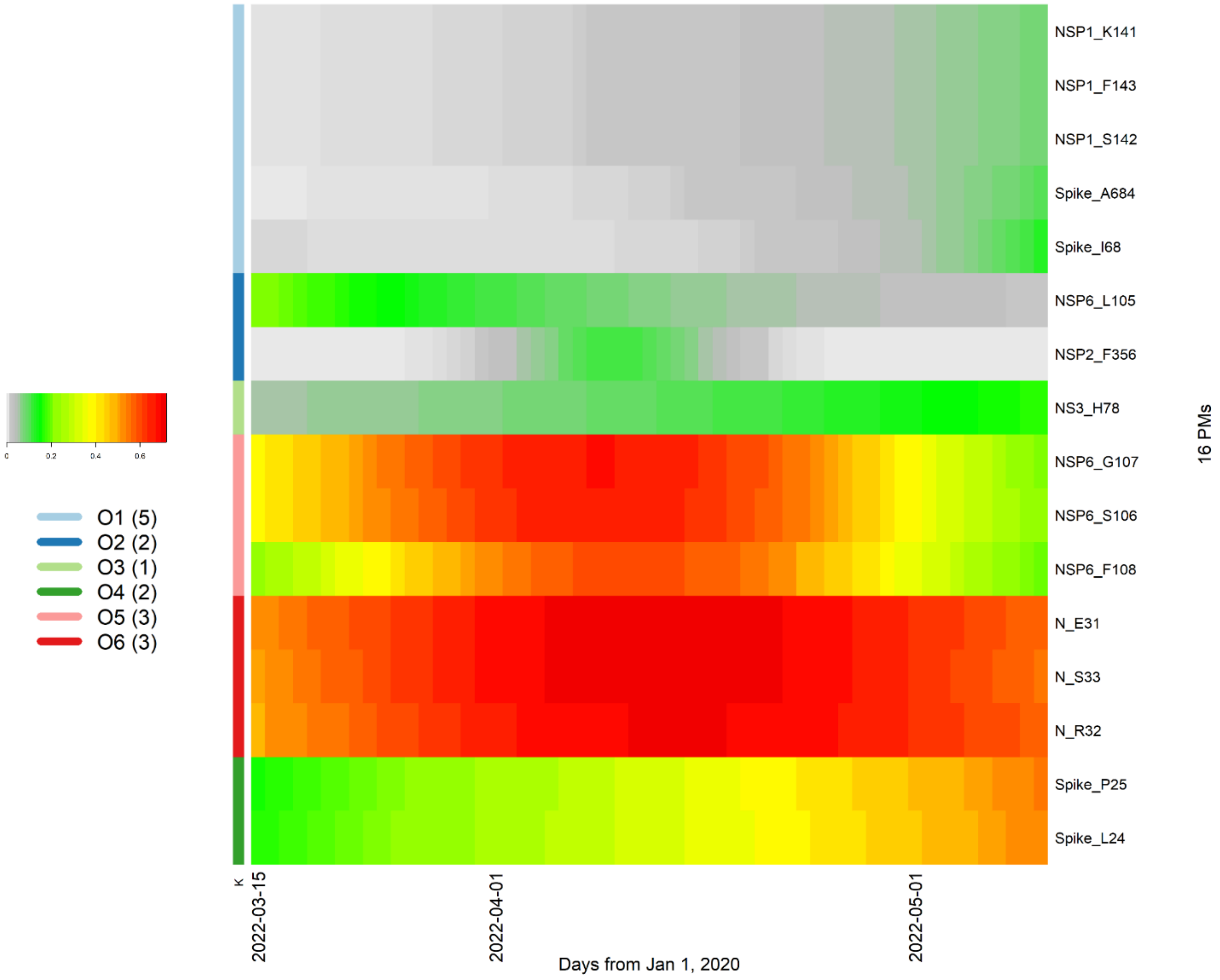
O) Unassigned viruses



eFigure 2. Misclassification errors by haplotype-based variant prediction (HVP), when the prediction probability threshold value is set at 0.9 to 1



eFigure 3. Temporal patterns of sixteen polymutants identified from variant-unassigned 524 viruses that are unpredictable by HAI, excluding those core polymutants of all fourteen variants.


O1 (5)
O2 (2)
O3 (1)
O4 (2)
O5 (3)
O6 (3)
NSP1_K141
NSP1_F143
NSP1_S142
Spike_A684
Spike_I68
NSP6_L105
NSP2_F356
NS3_H78
NSP6_G107
NSP6_S106
NSP6_F108
N_E31
N_S33
N_R32
Spike_P25
Spike_L24
16 PMs
K
Days from Jan 1, 2020