Update 10/29/2021
Delta Variants

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Los Alamos
NATIONAL LABORATORY

Update Summary

1. **Delta variants: there were well over 10,000 distinct Spikes that were found more than 4 times among current Delta variants. In our current summaries we include 65 of these variants of particular interest.**

2. **We define Delta variants to be of interest that have one or more of the following characteristics:**
   1. The are increasing in frequency relative to other forms of the Delta lineage in multiple geographic locations
   2. They are very common among Delta variants, although may not be consistently increasing in frequency, so the high sampling frequency associated with the variant may just be the result of founder effects or random events.
   3. They carry are recurrently sampled and reflect the addition of a mutation that is the RBD, NTDss or near the furin cleavage sites in addition to the P681R

3. **This summary contains Highlights of regional sampling of interesting Delta variants:**
   Y145H, V1264L, (Y145H + V1264L), Q677H, Q675H, S112L and E484Q

4. **Sequencing issues with position 142 in Delta:** Almost all distinct Delta variants have 2 forms, one that carry the G142D mutation and one that carries the ancestral G, but the G142 calls are often likely to a sequencing artifact that can arise from using ARTIC 3 primers; the problem is resolved with ARTIC 4 primers. Because of this we generally include the version of each variant form that carries G142D, and we disregard position 142 when counting Delta variants of Spike.

Delta Variants

- Y145H
  - 10% in the UK, up to 20 in Scotland
  - Found mid-march in the US

- V1264L
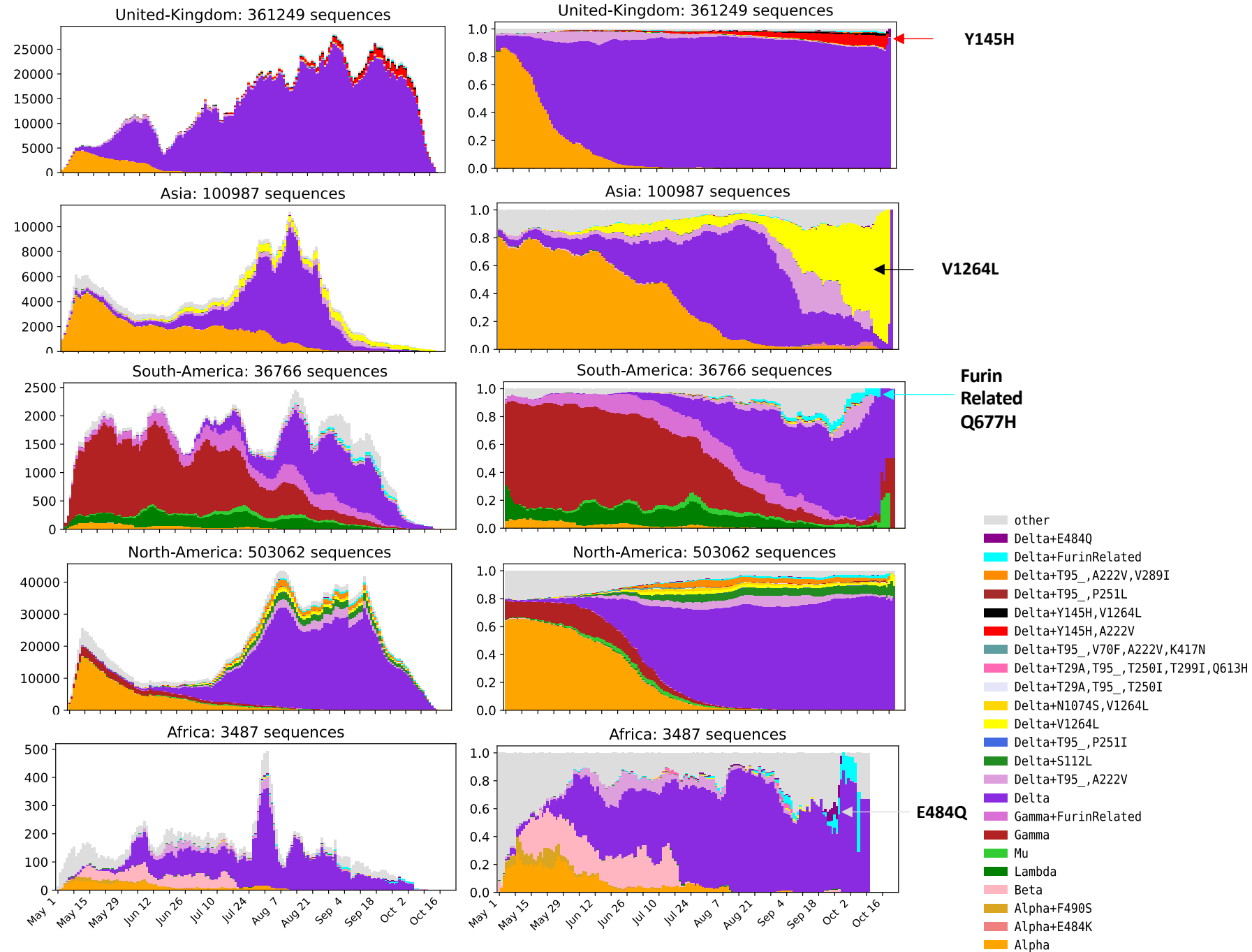 - Very common, but no consistent pattern of increase

- 484Q
  - Still very rare globally, tends to increase when introduced.
  - Recent sampling from Africa is very sparse, but when the full data with out excluing

- Q677H
  - Still very rare globally
 - Q677H enhances infectivity, syncytia formation and couple with N501Y relative NAb resistance

United-Kingdom: 361249 sequences

United-Kingdom: 361249 sequences — Y145H

Asia: 100987 sequences

Asia: 100987 sequences — V1264L

South-America: 36766 sequences

South-America: 36766 sequences — Furin Related Q677H

North-America: 503062

Africa: 3487 sequences

E484Q

other
Delta+E484Q
Delta+FurinRelated
Delta+T95_,A222V,V289I
Delta+T95_,P251L
Delta+Y145H,V1264L
Delta+Y145H,A222V
Delta+T95_,V70F,A222V,K417N
Delta+T29A,T95_,T250I,T299I,Q613H
Delta+T29A,T95_,T250I
Delta+N1074S,V1264L
Delta+V1264L
Delta+T95_,P251I
Delta+S112L
Delta+T95_,A222V
Delta
Gamma+FurinRelated
Gamma
Mu
Lambda
Beta
Alpha+F490S
Alpha+E484K
Alpha

Y145H

AY.4.2

See: Isotonic Regression, cov.lanl.gov
Found in 12 countries more than 10 times, 07/27/21 – 10/25/21.
Rare outside of the UK, but significantly increasing in all 12.

Spike T19R,T95I,G142D,**Y145H**,E156-,F157-,R158G,**A222V**,L452R,T478K,D614G,P681R,D950N

p-val, resampling statistic
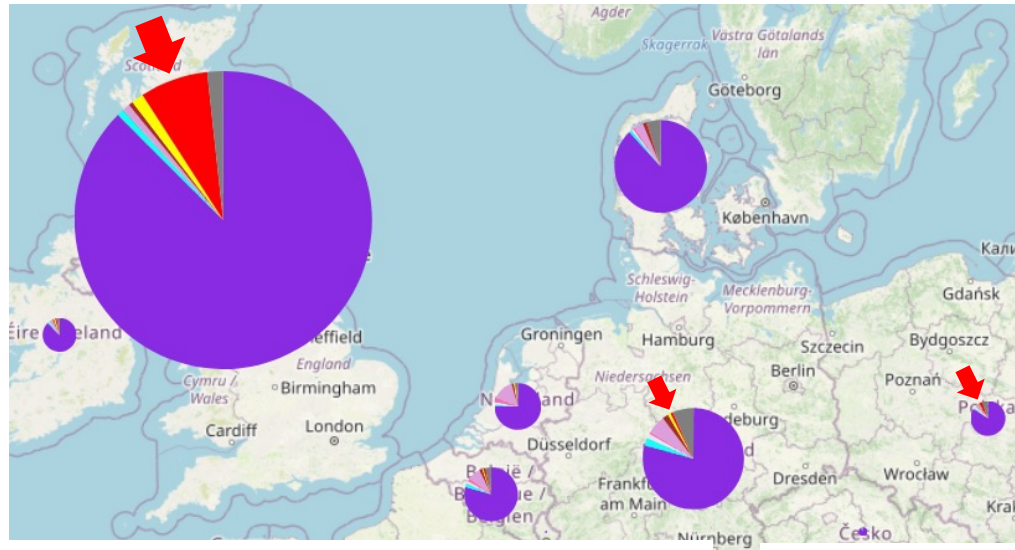
Country level	# H	# Others	total	# days	time window	p-val
Belgium	37	9709	9746	81	85	0.00249
Denmark	193	35786	35979	81	80	0.00249
France	11	10230	10241	76	76	0.00249
Germany	197	46468	46665	78	77	0.00249
Ireland	67	10474	10541	73	76	0.00249
Italy	38	8772	8810	79	80	0.00249
Netherlands	18	11746	11764	76	75	0.00249
Poland	46	2316	2362	81	81	0.00249
Romania	31	1907	1938	69	76	0.00498
Switzerland	22	16496	16518	83	82	0.00498
USA	57	358308	358365	84	84	0.01244
United-Kingdom	14238	265939	280177	81	80	0.00249

The # Others refers to other Deltas in the time window
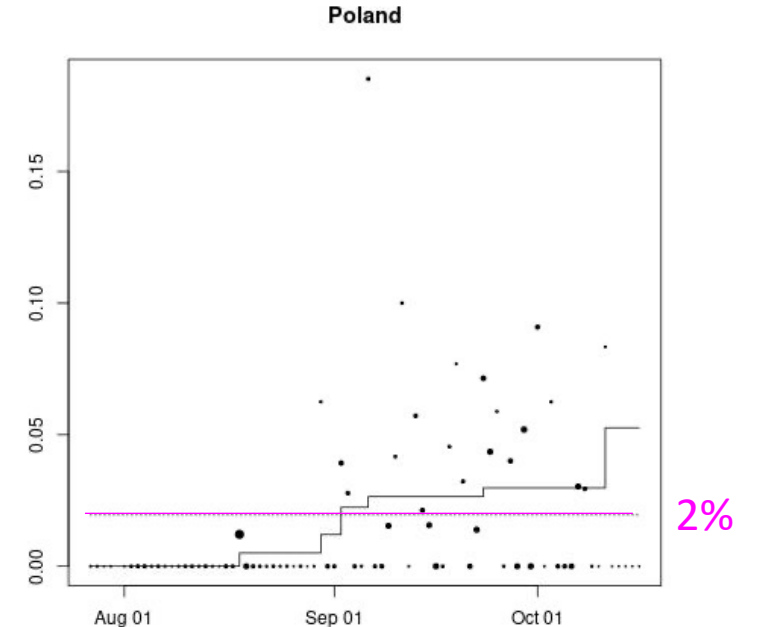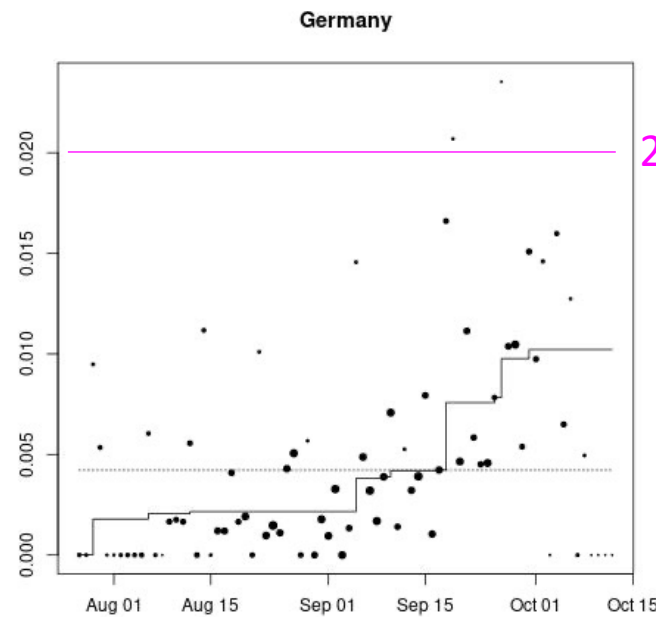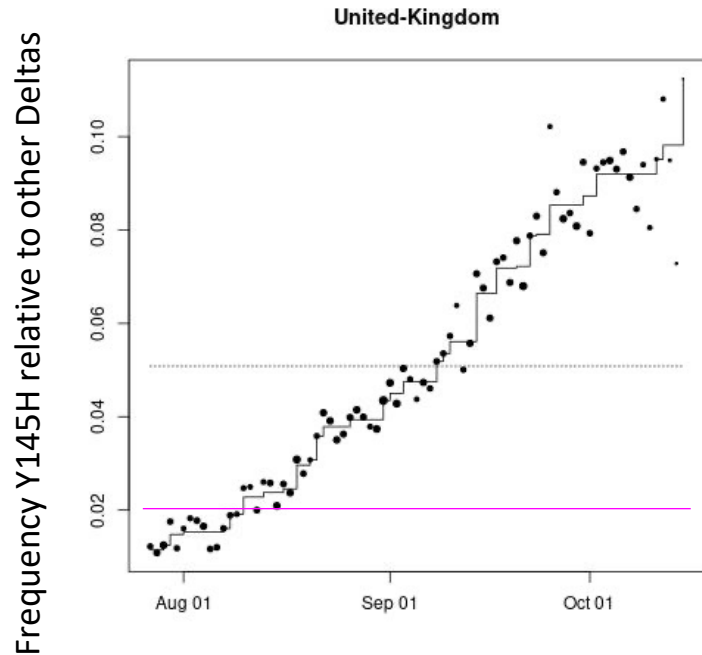
Date: 07/27/21 – 10/25/21

V1264L

	N exact	N included
T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,**V1264L**	6034	30172
T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,**L1234I**,**V1264L**	1006	1179
T19R,G142D,E156-,F157-,R158G,**A222V**,L452R,T478K,D614G,P681R,D950N,**V1264L**	5863	19575
T19R,G142D,E156-,F157-,R158G,**A222V**,L452R,T478K,D614G,P681R,D950N,**N1074S**,**V1264L**	4692	7296
T19R,T95I,G142D,**Y145H**,E156-,F157-,R158G,**A222V**,L452R,T478K,D614G,P681R,D950N,**V1264L**	867	1622

Common!
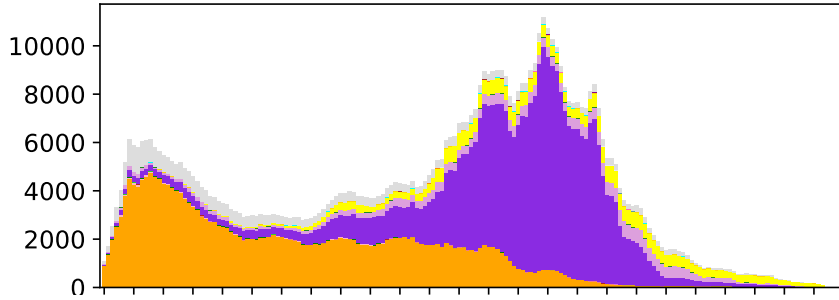
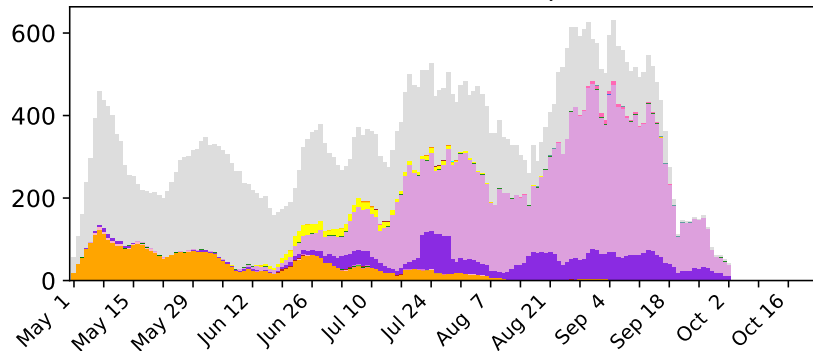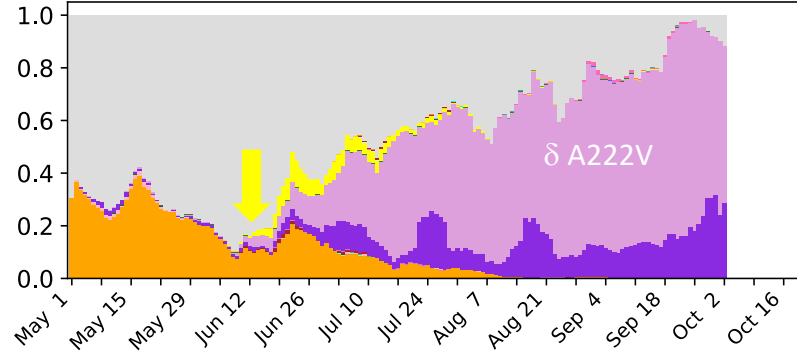Asia: 100987 sequences
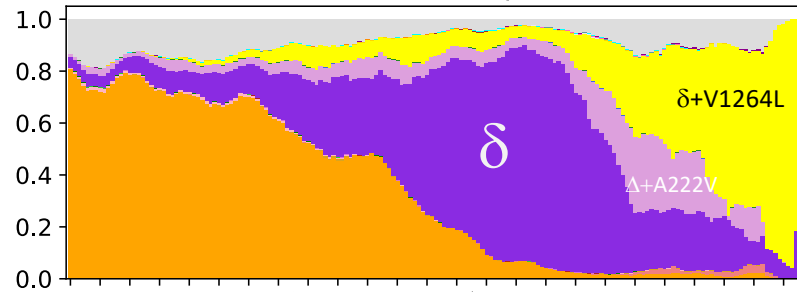
Singapore: 5387 sequences
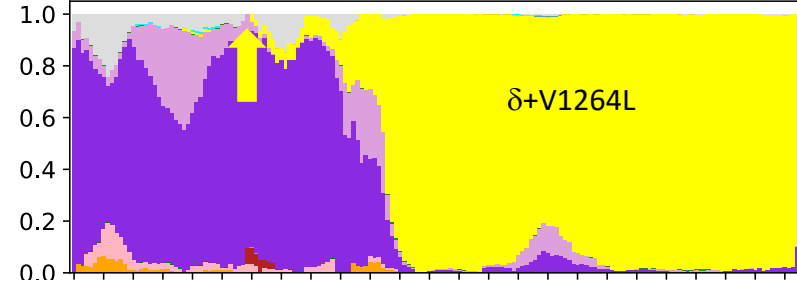
South-Korea: 7555 sequences

Singapore is enriched in the most recent samples from Asia, and had a unique early expansion of Delta+N1074S

However regional sampling differences dictate the frequency of δ+V1264L sampled in Asia, and the apparent shift towards δ+V1264L might result

Still, V1264L is interesting: common in α, γ, and δ

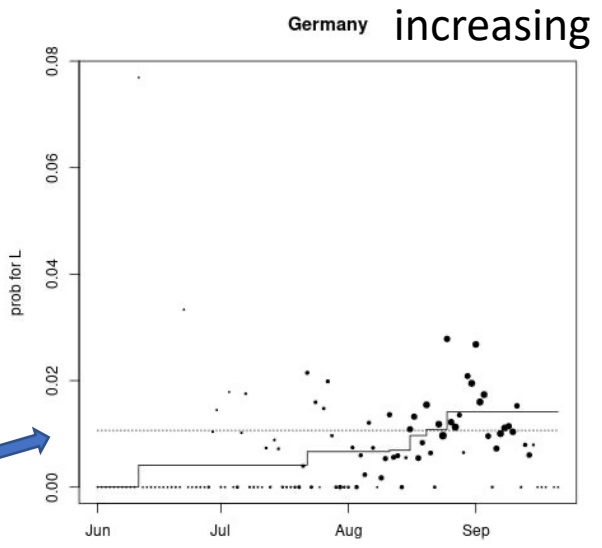# Delta variant with 1264L in common but may be with possible sampling/founder effects:

Position: SPIKE 1264 L
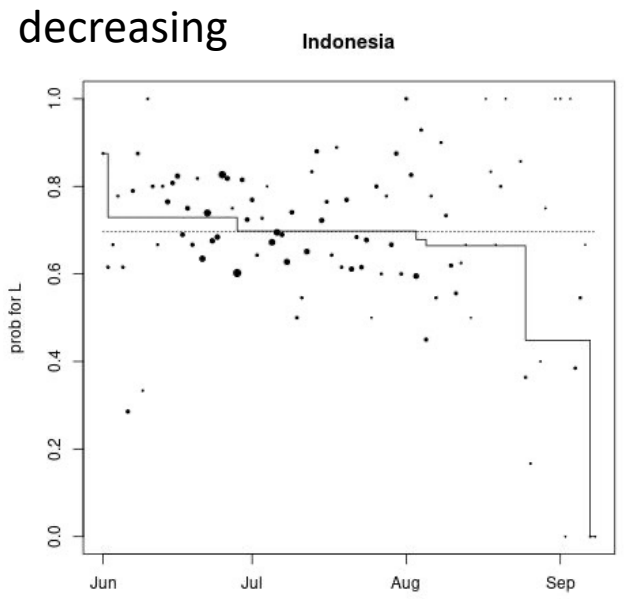
Range of dates: 2021-06-01 - 2021-10-03

p-val, resampling statistic

|	# L	# Others	total	# days with	time window	p-val increasing 16/33	p-val decreasing 16/33
Australia	37	2447	2484	110	114	0.17662	0.03483
Bahrain	178	227	405	36	89	0.99751	0.00249
Belgium	66	8823	8889	113	113	0.03731	0.77114
Brazil	38	4948	4986	102	114	0.02488	0.92289
Canada	59	17925	17984	98	97	0.17413	0.00249
Costa-Rica	17	195	212	59	72	0.86816	0.08209
Denmark	136	38153	38289	97	107	0.02488	0.00746
Finland	13	5026	5039	94	95	0.8209	0.00249
France	143	18031	18174	108	107	0.65174	0.00249
Germany	369	34271	34640	112	112	0.00249	0.48507
Hong-Kong	29	148	177	71	99	0.94776	0.00249
India	27	4339	4366	103	103	0.62687	0.59204
Indonesia	1269	554	1823	94	99	0.4403	0.00249
Ireland	26	11666	11692	104	106	0.00249	0.95522
Israel	35	1781	1816	58	86	0.22637	0.44279
Italy	48	10744	10792	114	115	0.00249	0.98259
Japan	165	11645	11810	108	107	0.00746	0.00249
Malaysia	446	661	1107	95	97	0.00249	0.00995
Mexico	1694	4196	5890	107	107	0.99502	0.00249
Netherlands	120	15350	15470	111	110	0.79602	0.21393
Norway	30	5553	5583	111	110	0.06716	0.23632
Peru	14	205	219	55	78	0.81095	0.08458
Puerto-Rico	17	594	611	69	90	0.99751	0.00249
Singapore	3933	548	4481	112	114	0.00249	0.99751
Slovakia	31	1511	1542	85	96	0.00249	0.94279
South-Africa	18	2456	2474	92	100	0.0398	0.84328
South-Korea	105	2512	2617	89	90	0.99254	0.00249
Spain	40	8568	8608	112	112	0.00249	0.71642
Sweden	166	17578	17744	111	110	0.04478	0.0199
Switzerland	198	13748	13946	113	112	0.00249	0.16915
Turkey	89	41176	41265	63	98	0.79602	0.00249
USA	11190	272638	283828	116	115	0.0398	0.97264
United-Kingc	1580	303531	305111	116	116	0.00249	0.00249

Countries where the variant was sampled 10 times or more since June 1

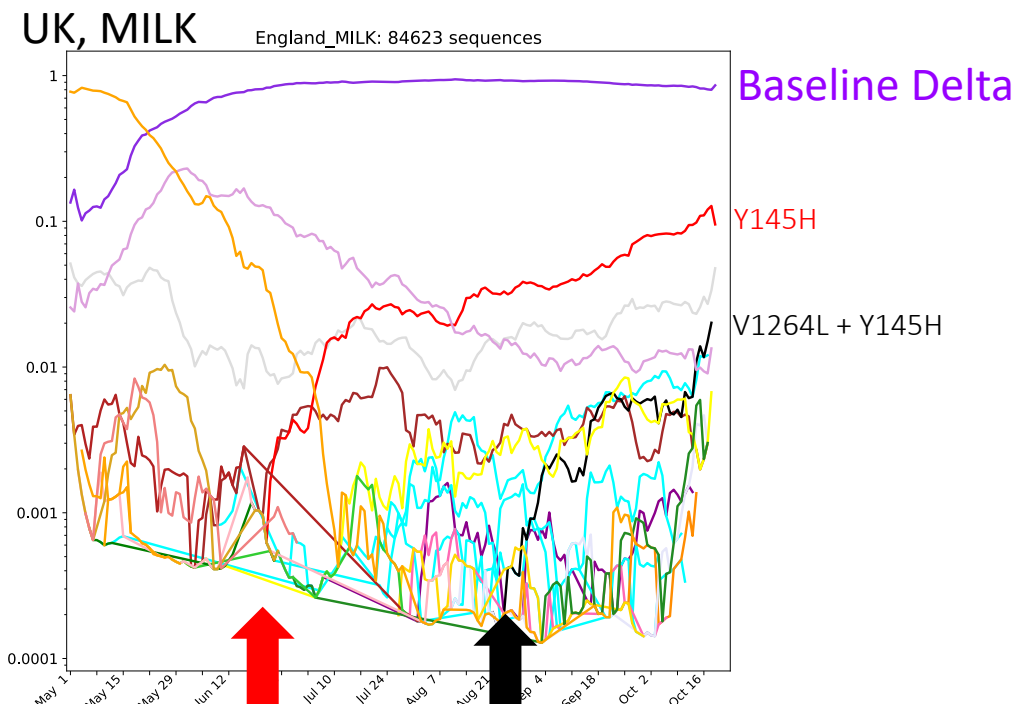**Isotonic Regression**
cov.lanl.gov

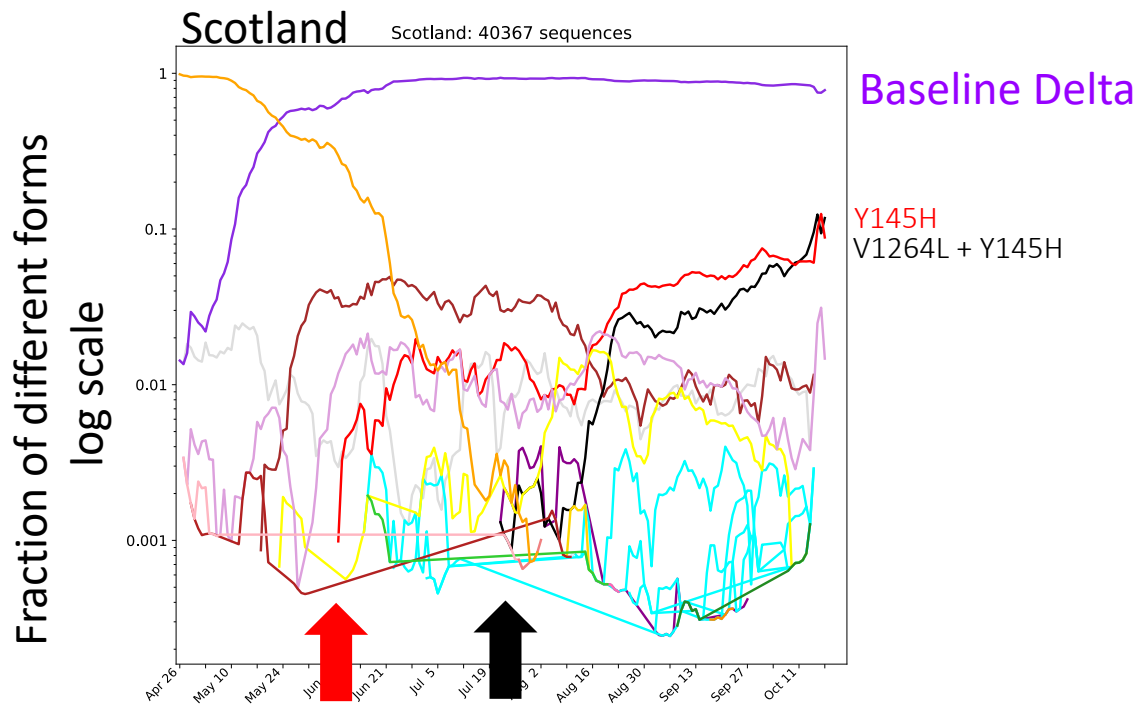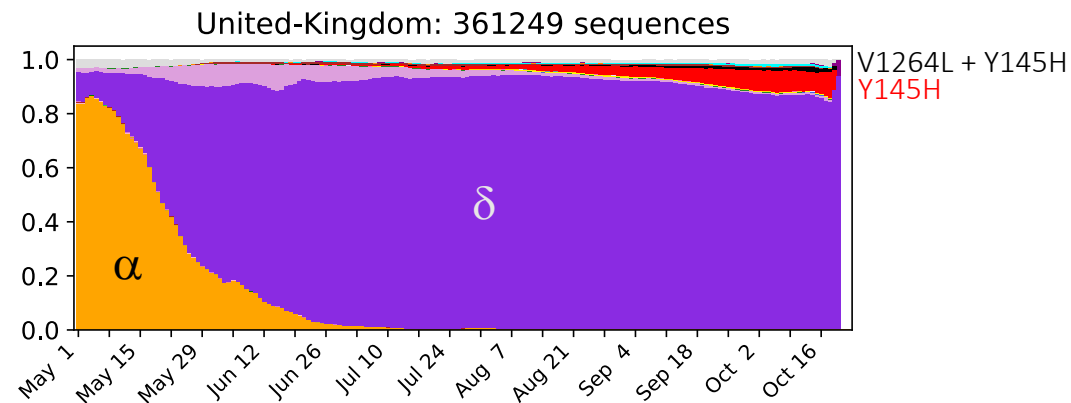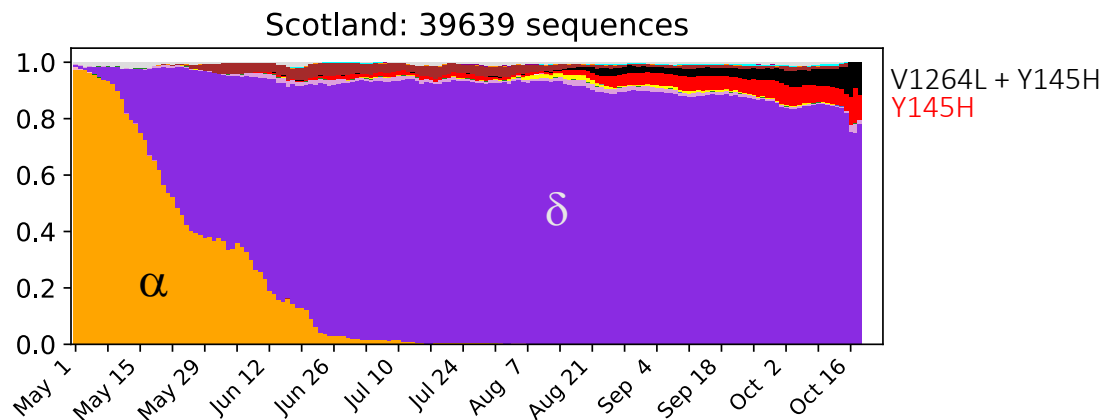increasing — Germany

decreasing — Indonesia

neutral — Netherlands
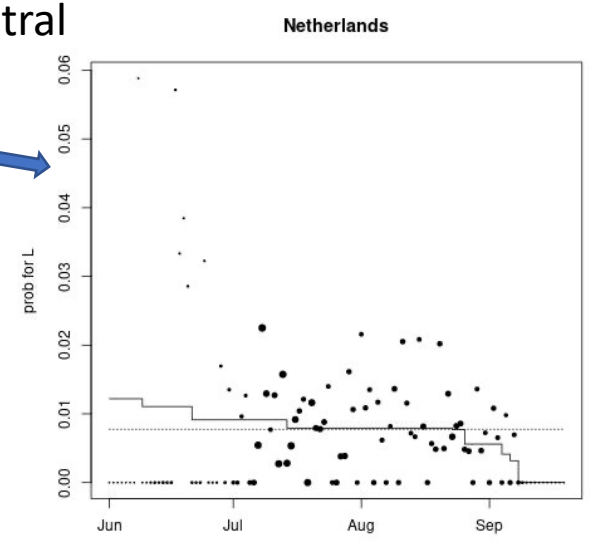
V1264L + **Y145H**   So far, it is found mostly in Scotland, split between Pango lineages AY.4, AY.4.2, found 1622 times
In the UK, is is most common in the MILK (shown) and ALDP subsets

Delta Spike form   T19R,T95I,G142D,**Y145H**,E156-,F157-,R158G,**A222V**,L452R,T478K,D614G,P681R,D950N,**V1264L**

Scotland: 39639 sequences

United-Kingdom: 361249 sequences

V1264L + Y145H
Y145H

δ

α

Scotland

Scotland: 40367 sequences

UK, MILK

England_MILK: 84623 sequences

Baseline Delta

Baseline Delta

Fraction of different forms
log scale

Y145H
V1264L + Y145H

Y145H

V1264L + Y145H

Sampling a month delayed

Example of a Delta variant 677H that is generally increasing in frequency relative to other Deltas

Position: SPIKE 677 H
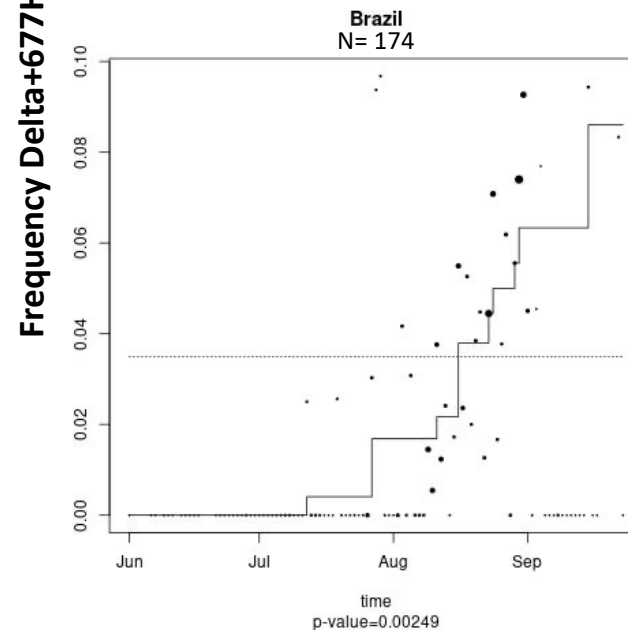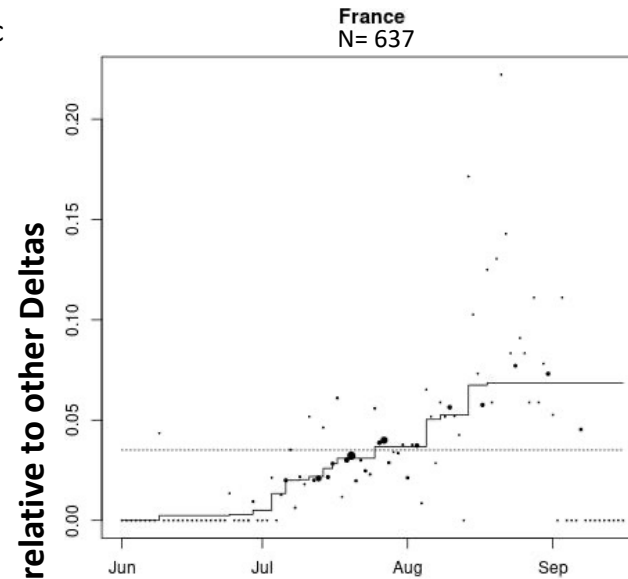**Range of dates**: 2021-06-01 - 2021-10-03

p-val, resampling statistic

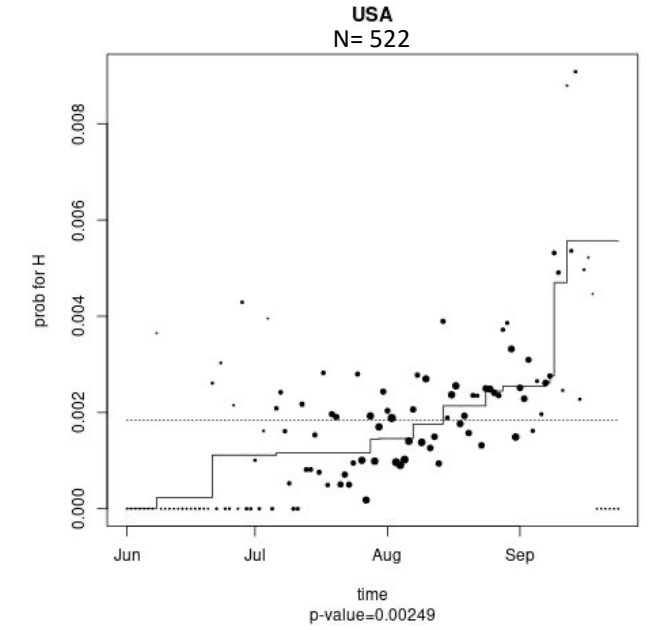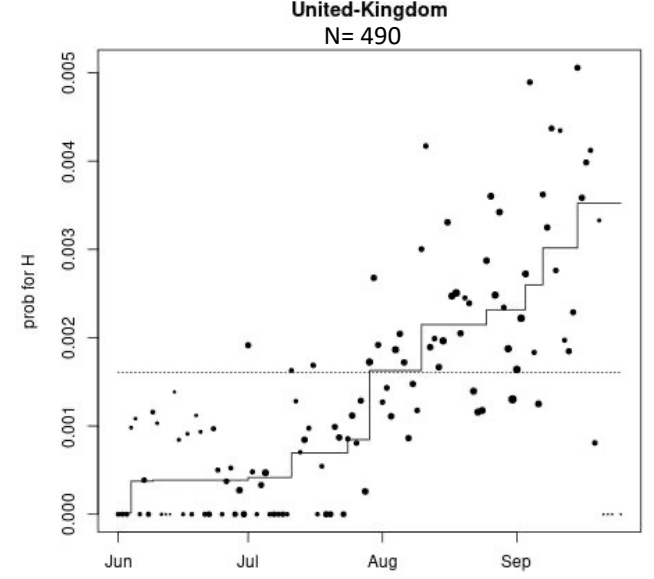|	# H	# Others	total	# days	time window	p-val increasing 19/23	p-val decreasing 5/23
Belgium	191	8698	8889	113	113	0.00249	0.80348
Brazil	174	4812	4986	102	114	0.00249	0.99502
Canada	25	17959	17984	98	97	0.74378	0.00249
Czech-Repub	11	853	864	96	108	0.03483	0.04478
Denmark	216	38073	38289	97	107	0.00249	0.99502
Finland	12	5027	5039	94	95	0.00249	0.98259
France	637	17537	18174	108	107	0.00249	0.83831
Germany	345	34295	34640	112	112	0.00249	0.3408
India	50	4316	4366	103	103	0.00746	0.5
Ireland	38	11654	11692	104	106	0.00249	0.99751
Italy	346	10446	10792	114	115	0.00249	0.04975
Japan	18	11792	11810	108	107	0.78856	0.27861
Lithuania	13	723	736	76	99	0.75373	0.00995
Netherlands	64	15406	15470	111	110	0.00249	0.78607
Norway	41	5542	5583	111	110	0.00746	0.04229
Portugal	29	5102	5131	104	105	0.00249	0.99005
Slovenia	20	4049	4069	81	88	0.02239	0.96269
Spain	86	8522	8608	112	112	0.00249	0.95025
Sweden	108	17636	17744	111	110	0.00249	0.65672
Switzerland	206	13740	13946	113	112	0.03731	0.00249
Turkey	20	41245	41265	63	98	0.98507	0.00249
USA	522	283306	283828	116	115	0.00249	0.94527
United-Kingd	490	304621	305111	116	116	0.00249	0.91294

23 Countries where the variant was sampled 10 times or more since June 1

Watch for: increased sampling, increasing frequencies within sample, geographic spread, consistency of the pattern: going up!

Higher frequencies

France
N= 637

Brazil
N= 174

time
p-value=0.00249

Steady, but still low frequencies

United-Kingdom
N= 490

USA
N= 522

time
p-value=0.00249
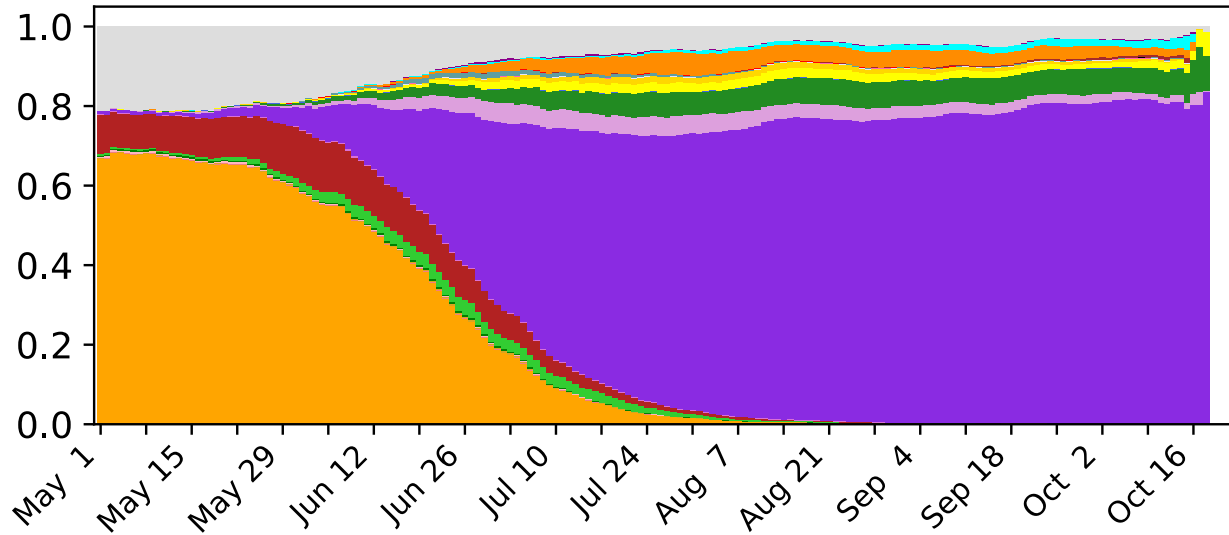
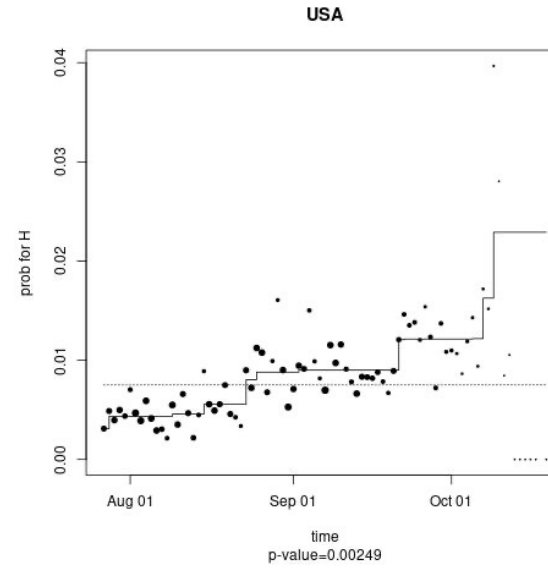**Frequency Delta+677H relative to other Deltas**

Delta variants in the US

675H is present ~2,700 times in the US, may be slowly increasing

112L is common ~24,000 time in the US, but not obviously increasing
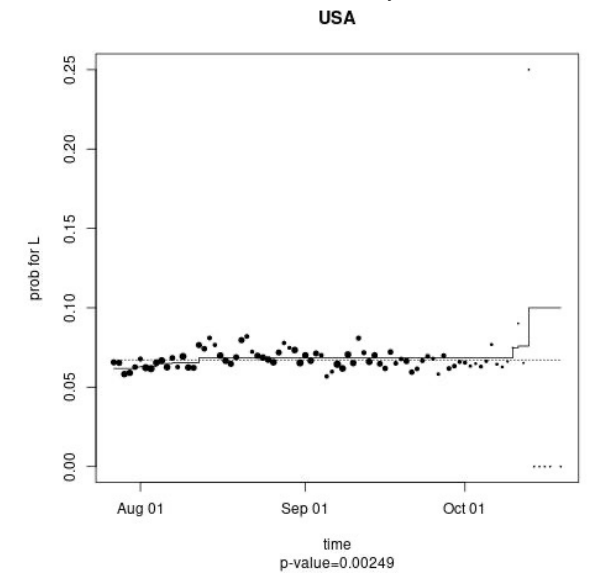
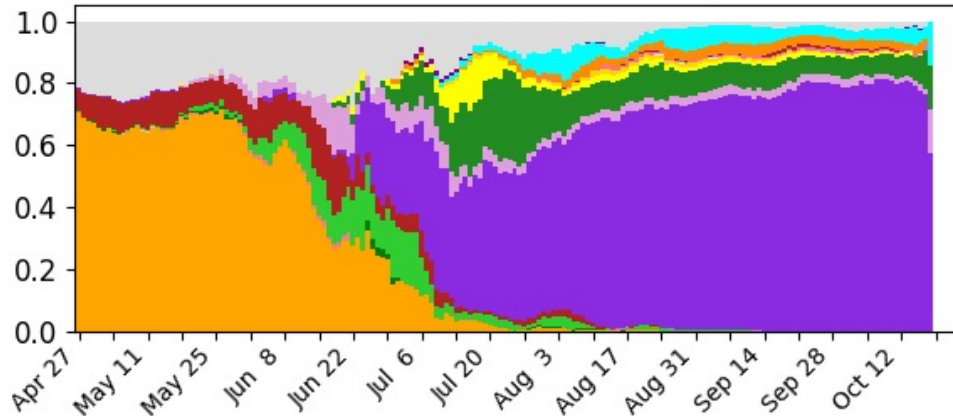USA: 436480 sequences

675H slow increase
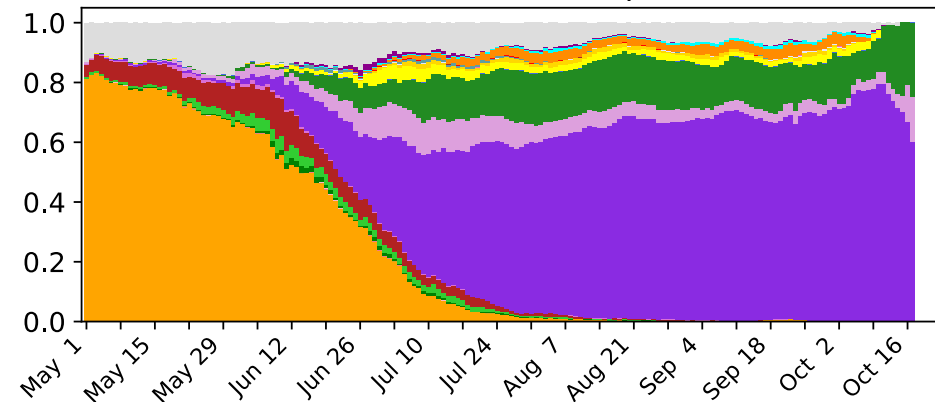
112L common, stable

675H most common
USA.Massachusetts: 22724 sequences

112L most common
USA.Texas: 24388 sequences

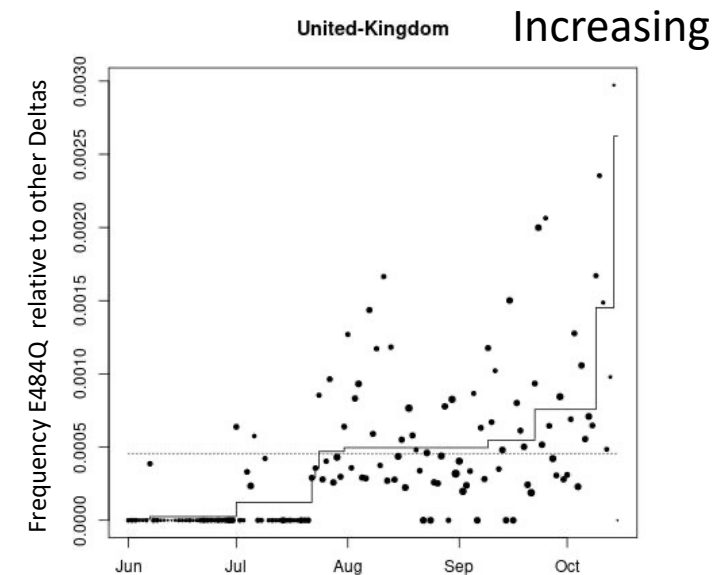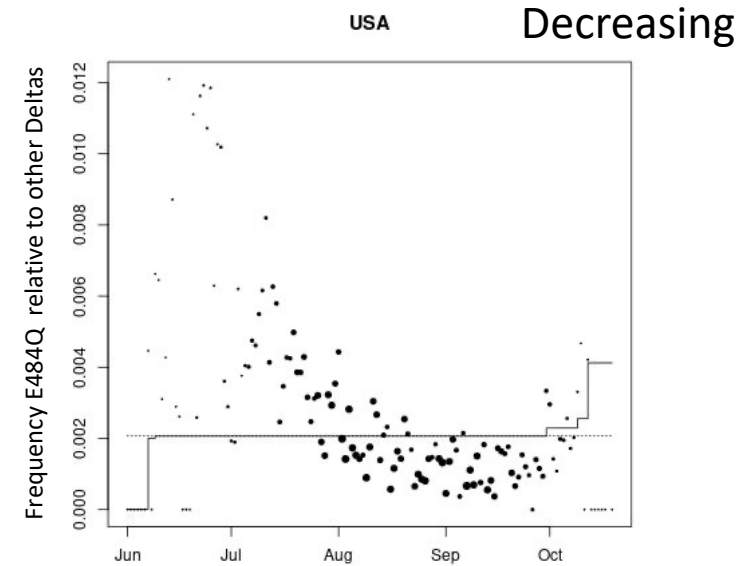# Delta and E484Q mutation in the US, UK, and in Africa

Delta with an additional E484Q additional mutation is most often sampled in the US, 907 times since June, but declining in the US overall. It is found 180 times in the UK where it tends to be very slightly increasing.

Nations where E484Q in a Delta backgound is found more then 10 times

Country level

	# Q	# Others	total	# days	time window	p-val
Belgium	12	12616	12628	137	141	0.39303
Denmark	17	47026	47043	120	130	0.00249
France	47	20875	20922	132	132	0.00249
Germany	66	51244	51310	134	133	0.03234
India	72	6339	6411	122	129	0.00249
Ireland	15	15013	15028	128	132	0.00249
Japan	11	38485	38496	133	135	0.00249
Mexico	11	8319	8330	133	134	0.00249
Netherlands	14	19083	19097	132	131	0.00249
Nigeria	27	705	732	60	85	0.00249
Peru	29	709	738	79	107	0.00249
Sweden	51	22246	22297	132	131	0.00249
Switzerland	13	19519	19532	139	138	0.00746
USA	907	437631	438538	140	140	0.61692
United-Kingdom	180	393733	393913	137	136	0.00249

June 1 – Oct 24

USA — Decreasing


United-Kingdom — Increasing

Delta and E484Q mutation in the US, UK, and in Africa

We can undercount African sequences at cov.lanl.gov due filtering out sequences with a high fraction of unresolved bases (Ns). But E484Q in a Delta background is present in Africa, particularly in Nigeria and South Africa, and so we went back to the unfiltered set to determine The frequency of E484Q in a Delta background. It E484Q had been sampled roughly in 65 among allAfrican sequences, 34 times in Nigeria, 22 times South Africa, and in a few other African nations as well. It is often associated with the PANGO sublineage AY.36. The plot below shots the frequency and sampling of E484Q and E484K in a Delta backgound in Nigeria.

The fraction of different forms of Spike 484 among Nigerian Delta variants

Nigeria: 1334 sequences

Nigeria: 1334 sequences

Very limited sampling
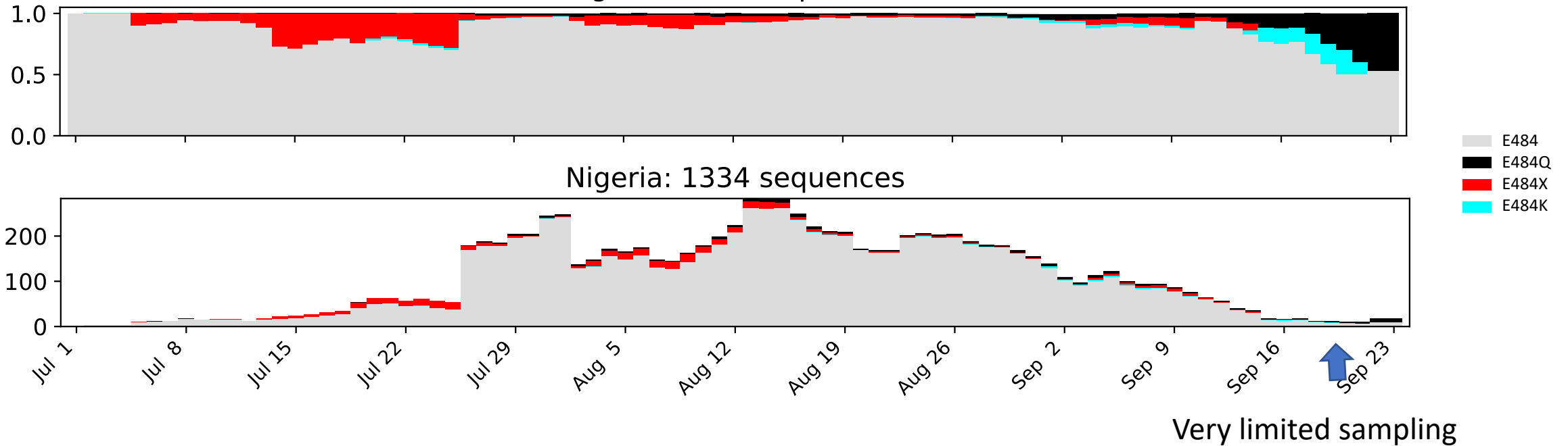
Conclusion: 484Q is currently rare globally, but given that it may confer enhanced to Delta variants resistance, it is worth continued monitoring and phenotypic testing.

Delta Variants and G142D

"Importantly, we also find nearly universal presence of spike protein substitution G142D in Delta-lineage samples. Due to the prior release and widespread use of the ARTIC V3 primers during the initial surge of the Delta variant, it is likely that the G142D amino acid substitution is substantially underrepresented among early Delta variant genomes deposited in public repositories.

- Why might this matter?
  - It will potentially distort phylogenies with limited diversity within Delta
  - It could cause undercounting for new mutant forms of Delta, as new forms are artificially divided between G142 and G142D
    - We allow either form in our counts of Delta variants and for dynamics tracking.
  - G142D is a potent resistance mutation for NTDss antibodies. Spike reagents using the ancestral form G142 may not capture the full resistance profile of the Delta form, and the ancestral form is likely to be much rarer than the data suggests.

The next 2 slides provide examples of
how the G142D toggle recurs in many variants.

We use the G142D option to represent a new
Delta variant when there is choice, and ignore this
position when counting variant forms.

Small alignment of the most variable positions in Spike, position numbers are written vertically.

To represent these variants**, we would choose the version with** G142D **present**

Few NTDss and RBD *common* changes

NTDss RBD

XSpike run on just Deltas: the most common forms with I95T
The most common forms of Spike, those found > 300 time in the past 3 months.
G142D toggles in association with almost all of them… only one exception, D138H.

How to read this

This example was from
An XSPike run in mid-August

Local   Exact   Pct   [Context]
6964   5747   82%   [T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
This mutation list refers to an exact from of Spike that carries this pattern of mutations. It was found exactly 5747 times, and accompanied by additional mutations 6964 times.

Range of dates: 2021-05-26 - 2021-08-24
Pango linage designation in GISAID (version: 2021-07-28): AY.1, AY.10, AY.11, AY.12, AY.2, AY.3, AY.3.1, AY.4, AY.5, AY.6, AY.7, AY.8, AY.9, B.1.617.2

*Only form with > 300 samples to *not* have an ancestral G142 toggle.

XSpike run on just Deltas mutational forms.
G142D toggles in association with all of them.

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                                                        11111111
                      11111111112222223444555666677788901112222
                      2225667799134455582455580145047178801957570261356
                      5179167075728256781280139876217237082910904429724
         Global cseqs= 246849
         LRATTHAVKTKSDGYEFRGAYTPDVVKGLNTTQQSAETTIADNVGPGMSV  Global    UK  Eu-UK  NAmer  Asia Africa SAmer  Ocean  Local  Exact  Pct [Context]
                                                            246849 98889  78696  53631  9404    441  4724   1064 201341 <----------- Total
028 ............D.--G..........R............N.......         42256 13595  12670  15432   383     64    82     30  42194  35980  85% [T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
029 ..............--G..........R............N.......         14574   320   8054   5311   595     19   275      0  14552  12327  84% [T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]

030 ............D.--G..........R............N......L          2215     9    124     54  2017      0     0     11   2215   1995  90% [T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,V1264L]
031 ....L.........--G..........R............N......L           213     0     44     13   156      0     0      0    213    182  85% [T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,V1264L]

032 ...........L.D.--G........R............N.......          1761     1      8   1748     1      0     2      1   1761   1445  82% [T19R,S112L,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
033 ...........L...--G........R............N.......           587     0      6    581     0      0     0      0    587    496  84% [T19R,S112L,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]

034 ............D.--G....L....R............N.......          1378   616    738     11     8      0     5      0   1376    904  65% [T19R,G142D,E156-,F157-,R158G,P251L,L452R,T478K,D614G,P681R,D950N]
035 ..............--G....L....R............N.......           784    25    748      7     3      0     1      0    784    685  87% [T19R,E156-,F157-,R158G,P251L,L452R,T478K,D614G,P681R,D950N]

036 ............D.--G.................R.......N.......         160     0    112     39     4      0     5      0    134    101  75% [T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R]
037 ..............--G.................R.......N.......        1370     3    826    461    16      6    58      0   1342    990  73% [T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R]

038 .......T....D.--G..........R............N.......         1173    39    277    824    18     13     2      0   1172    935  79% [T19R,K77T,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
039 .......T......--G..........R............N.......          450     2    133    315     0      0     0      0    450    357  79% [T19R,K77T,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]

040 ............D.--G.....L.R............N.......            761    19    738      4     0      0     0      0    761    740  97% [T19R,G142D,E156-,F157-,R158G,V308L,L452R,T478K,D614G,P681R,D950N]
041 ..............--G.....L.R............N.......             56    13     43      0     0      0     0      0     56     53  94% [T19R,E156-,F157-,R158G,V308L,L452R,T478K,D614G,P681R,D950N]

042 F...........D.--G..........R............N.......          362    65    122    167     5      1     2      0    361    305  84% [L5F,T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
043 F.............--G..........R............N.......          122     1     40     79     2      0     0      0    122    107  87% [L5F,T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]

044 ..........A.D.--G..........R.....V.....N.......          453    17    429      7     0      0     0      0    453    427  94% [T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,A688V,D950N]
045 ..........A...--G..........R.....V.....N.......           18     1     10      7     0      0     0      0     18      5  27% [T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,A688V,A701V,D950N]

046 ............D.--G..........R...........I.N.......          86     3     33     12    38      0     0      0     86     79  91% [T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,T791I,D950N]
047 ..............--G..........R...........I.N.......         366     1     20      4   341      0     0      0    366    317  86% [T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,T791I,D950N]

048 ............D.--G..........R........N.......             63     0     41     22     0      0     0      0     63     49  77% [T19R,G142D,E156-,F157-,R158G,T478K,D614G,P681R,D950N]
049 ..............--G..........R........N.......            361     0    338     21     2      0     0      0    308    270  87% [T19R,E156-,F157-,R158G,T478K,D614G,P681R,D950N]

050 ..S.........D.--G..........R............N.......          311    18    277     10     2      0     4      0    305    286  93% [T19R,A27S,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
051 ..S...........--G..........R............N.......          183    11    168      3     0      0     1      0    183    155  84% [T19R,A27S,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
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