

Update 10/3/2021  
Gamma and Delta Variants, C.1.2, Mu

Bette Korber and James Theiler

# Summary

Bette Korber and James Theiler

- 1. Delta variants:** We have been inclusive of Delta variants, capturing not only those that are increasing in frequency relative to other forms of Delta, but those that are simple common with an emphasis on those that carry mutations in the RBD, NTDs, and furin cleavage site. There are notes in column T regarding the reason for inclusion of each Delta variant. Almost all distinct Delta variants have 2 forms, one that carry the G142D mutation and one that has the ancestral G in this position, 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 include the version of each variant that carries G142D, and we disregard this position when counting Delta variants of Spike.
- 2. C.1.2:** This variant was increasingly sampled in South Africa in July, but has not been sampled through September, and seems to be in decline there. It currently not be expanding in other countries where it has been found.
- 3. Mu:** In the most recent sampling in GISAID, Delta variants have been increasing relative to Mu even in Chile and Columbia, where a strong Mu presence had been maintained through the summer. In the USA and Mexico Mu continues to decline.
- 4. Gamma:** Gamma variants with positive charge in the furin cleavage site gain in frequency relative to baseline Gamma in parts of S. America, in particular the added mutation P681H. There was a transient increase in frequency of Gamma relative to Delta in S. America in the late summer, based on the early September GISAID sample; we noted this 9/11/2021, with the caveat that it might be a sampling artifact due to small size. Indeed, continuing sampling through September suggests Delta has been increasing relative to Gamma in S. America, particularly in Brazil; Peru and Chili are still in flux, and we are continuing to monitor these.

# Delta Variants and G142D

Analysis of the ARTIC version 3 and version 4 SARS-CoV-2 primers and their impact on the detection of the G142D amino acid substitution in the spike protein

Davis et al. bioRxiv <https://doi.org/10.1101/2021.09.27.461949>;

“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
  - Causes undercounting for new mutant forms, 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 when there is choice, and ignore this position when counting variants.

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

```

11111111
11111111222223444555666677788901112222
2225667799134455582455580145047178801957570261356
51791670757282567812801398762172370829109044429724
Global cseqs= 246849
LRATTHAVKTKSDGYEYFRGAYTPDVKVGLNTTQQAETIADNVGPGMSV

```

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.

	Global	UK	Eu-UK	NAmer	Asia	Africa	SAmer	Ocean	Local	Exact	Pct	[Context]
001	246849	98889	78696	53631	9404	441	4724	1064	201341	82988	69985	84% [T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
002	83021	69888	8841	3093	727	1	59	412	6964	5747	82%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
003	6973	706	4275	1298	183	0	10	501	1102	825	74%	[T19R,T95I,D138H,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N] *
004	96	1	82	5	6	0	0	2	73	57	78%	[T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R]
005	435	41	248	129	6	0	2	9	423	344	81%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R]
006	1077	19	1034	15	1	0	8	0	1075	1002	93%	[T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,T719I,D950N]
007	627	12	610	5	0	0	0	0	627	591	94%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,T719I,D950N]
008	771	758	9	1	3	0	0	0	771	719	93%	[T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,P1162S]
009	14	7	6	0	1	0	0	0	14	14	100%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,P1162S]
010	618	609	9	0	0	0	0	0	618	574	92%	[T19R,T51I,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
011	7	6	1	0	0	0	0	0	7	7	100%	[T19R,T51I,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
012	544	536	7	0	1	0	0	0	544	492	90%	[T19R,V70F,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
013	9	3	5	0	1	0	0	0	9	9	100%	[T19R,V70F,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
014	474	399	74	0	1	0	0	0	474	421	88%	[T19R,T95I,G142D,E156-,F157-,R158G,Y248H,L452R,T478K,D614G,P681R,D950N]
015	14	4	10	0	0	0	0	0	14	10	71%	[T19R,T95I,E156-,F157-,R158G,Y248H,L452R,T478K,D614G,P681R,D950N]
016	458	397	38	20	3	0	0	0	458	395	86%	[L5F,T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
017	27	1	16	8	2	0	0	0	27	18	66%	[L5F,T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
018	457	86	76	274	19	0	2	0	457	366	80%	[T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,V1104L]
019	386	19	102	261	3	0	0	1	386	265	68%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,V1104L]
020	342	7	323	1	0	11	0	0	342	302	88%	[T19R,H66Y,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
021	68	11	57	0	0	0	0	0	68	58	85%	[T19R,H66Y,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
022	339	0	318	16	5	0	0	0	339	276	81%	[T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,I850L,D950N]
023	188	0	180	6	2	0	0	0	188	93	49%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,P681R,I850L,D950N]
024	301	62	199	31	7	0	2	0	284	208	73%	[T19R,T95I,G142D,E156-,F157-,R158G,L452R,T478K,D614G,Q677H,P681R,D950N]
025	231	4	218	4	0	0	5	0	231	173	74%	[T19R,T95I,E156-,F157-,R158G,L452R,T478K,D614G,Q677H,P681R,D950N]
026	63	0	20	6	37	0	0	0	61	50	81%	[T19R,G142D,L452R,T478K,D614G,P681R,D950N] **
027	365	1	196	32	136	0	0	0	296	219	73%	[T19R,L452R,T478K,D614G,P681R,D950N]

How to read this

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 lineage 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

This example was from  
 An XSpike run in mid-August

\*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.

11111111  
 11111111222222344455566677788901112222  
 2225667799134455582455580145047178801957570261356  
 51791670757282567812801398762172370829109044429724  
 Global cseqs= 246849

	Global	UK	Eu-UK	NAmer	Asia	Africa	SAmer	Ocean	Local	Exact	Pct	[Context]
LRATTHAVKTKSDGYEFRGAYTPDVVKGLNLTQQAETIADNVGPGMSV	246849	98889	78696	53631	9404	441	4724	1064	201341	<-----	Total	
028	42256	13595	12670	15432	383	64	82	30	42194	35980	85%	[T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
029	14574	320	8054	5311	595	19	275	0	14552	12327	84%	[T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
030	2215	9	124	54	2017	0	0	11	2215	1995	90%	[T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,V1264L]
031	213	0	44	13	156	0	0	0	213	182	85%	[T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N,V1264L]
032	1761	1	8	1748	1	0	2	1	1761	1445	82%	[T19R,S112L,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
033	587	0	6	581	0	0	0	0	587	496	84%	[T19R,S112L,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
034	1378	616	738	11	8	0	5	0	1376	904	65%	[T19R,G142D,E156-,F157-,R158G,P251L,L452R,T478K,D614G,P681R,D950N]
035	784	25	748	7	3	0	1	0	784	685	87%	[T19R,E156-,F157-,R158G,P251L,L452R,T478K,D614G,P681R,D950N]
036	160	0	112	39	4	0	5	0	134	101	75%	[T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R]
037	1370	3	826	461	16	6	58	0	1342	990	73%	[T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R]
038	1173	39	277	824	18	13	2	0	1172	935	79%	[T19R,K77T,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
039	450	2	133	315	0	0	0	0	450	357	79%	[T19R,K77T,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
040	761	19	738	4	0	0	0	0	761	740	97%	[T19R,G142D,E156-,F157-,R158G,V308L,L452R,T478K,D614G,P681R,D950N]
041	56	13	43	0	0	0	0	0	56	53	94%	[T19R,E156-,F157-,R158G,V308L,L452R,T478K,D614G,P681R,D950N]
042	362	65	122	167	5	1	2	0	361	305	84%	[LSF,T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
043	122	1	40	79	2	0	0	0	122	107	87%	[LSF,T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
044	453	17	429	7	0	0	0	0	453	427	94%	[T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,A688V,D950N]
045	18	1	10	7	0	0	0	0	18	5	27%	[T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,A688V,A701V,D950N]
046	86	3	33	12	38	0	0	0	86	79	91%	[T19R,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,T791I,D950N]
047	366	1	20	4	341	0	0	0	366	317	86%	[T19R,E156-,F157-,R158G,L452R,T478K,D614G,P681R,T791I,D950N]
048	63	0	41	22	0	0	0	0	63	49	77%	[T19R,G142D,E156-,F157-,R158G,T478K,D614G,P681R,D950N]
049	361	0	338	21	2	0	0	0	308	270	87%	[T19R,E156-,F157-,R158G,T478K,D614G,P681R,D950N]
050	311	18	277	10	2	0	4	0	305	286	93%	[T19R,A27S,G142D,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]
051	183	11	168	3	0	0	1	0	183	155	84%	[T19R,A27S,E156-,F157-,R158G,L452R,T478K,D614G,P681R,D950N]

# Mu

Mu $\mu$	<b>B.1.621</b>	T95I,+143T,Y144S,Y145N,R346K,E484K,N501Y,D614G,P681H,D950N
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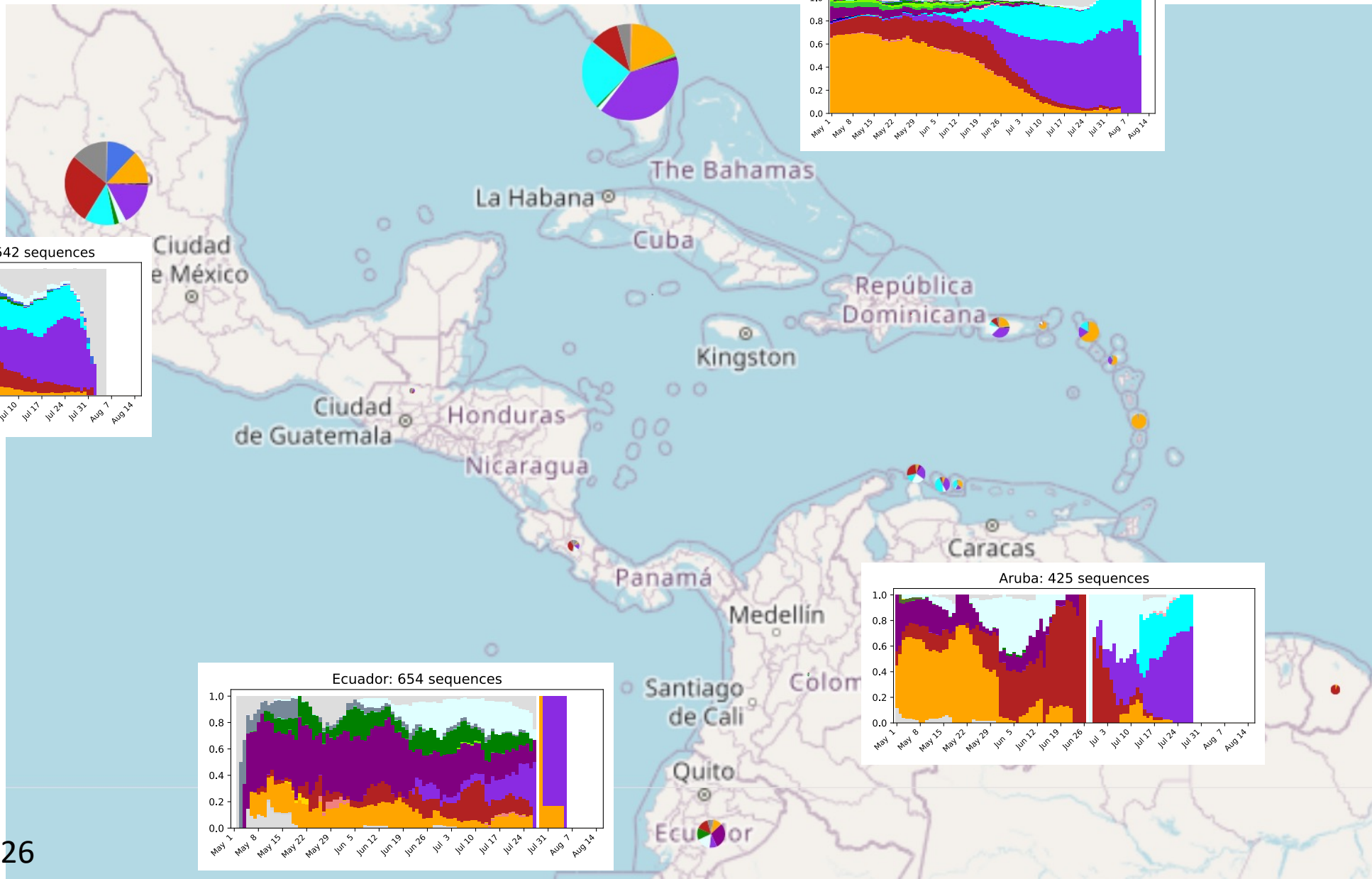
Mu was first sampled in Columbia, and seems to have a particularly high level of relative resistance to sera. It was gaining prevalence in some regions in North America over the summer, peaking in July but currently declining relative to Delta in the Americas and the Caribbean.

It has recently be named a WHO variant of interest.

# B.1.621, Mu T95I,+143T,Y144S,Y145N,R346K,E484K,N501Y,D614G,P681H,D950N

Ice blue band at the top

- other
- B.1.621**
- B.1.619
- B.1.1.318
- B.1.623
- B.1.620
- B.1.1.523
- C.36
- B.1.214.2
- A.2.5.2
- B.1.258.17
- B.1.575
- R.1
- B.1.1.519
- A23.1
- A.27
- C.37=Lambda
- B.1.617.1=Kappa
- B.1.526.1
- B.1.526.2
- B.1.526=Iota
- B.1.525=Eta
- P.2=Zeta
- B.1.429/7=Epsilon
- Delta-AY.1
- Delta-AY.2
- Delta+A222V
- B.1.617.2=Delta
- P.1=Gamma
- B.1.351=Beta
- Alpha+T20I
- Alpha+F490S
- Alpha+E484K
- Alpha+W152R
- B.1.1.7=Alpha
- Near-Furin
- GV-clade
- G-clade
- Ancestral

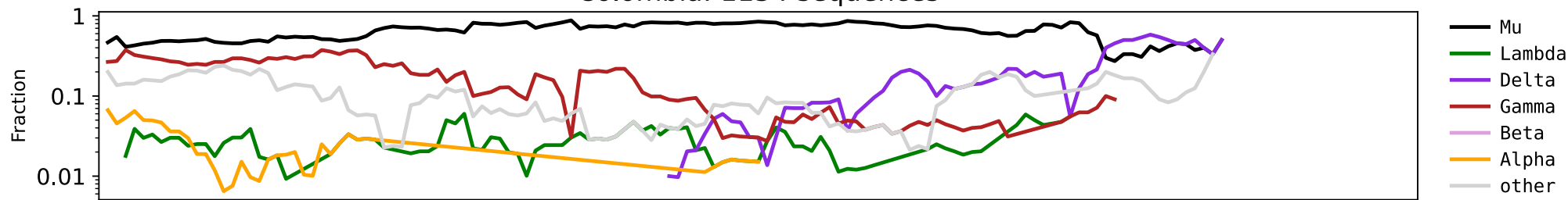


Map, June 1 though August 26  
 Indicated further monitoring was warranted.

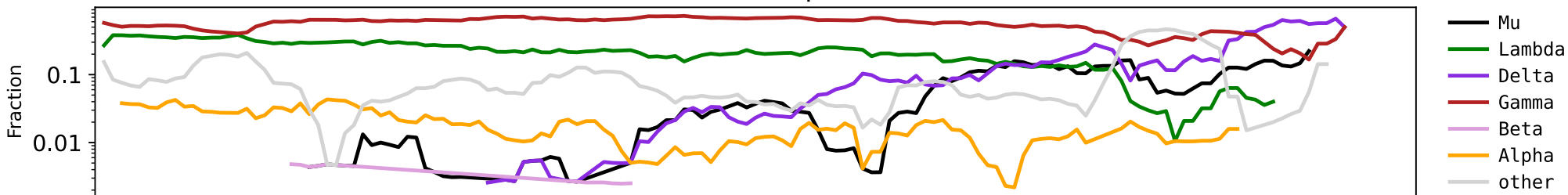


# Countries that had high frequency of Mu (Columbia and Chile) are transitioning towards Delta, Mu is rare in USA and Mexico

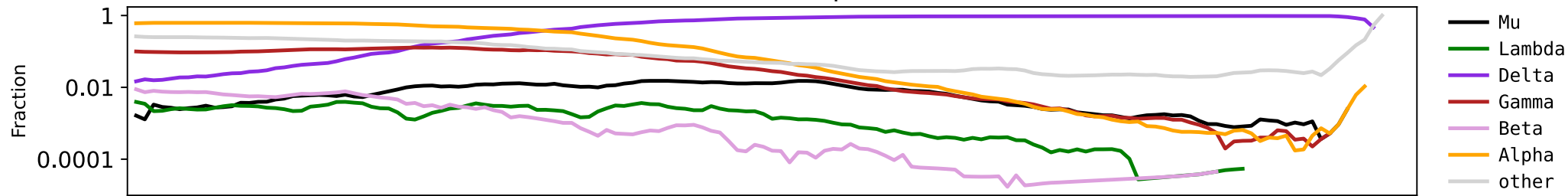
## Colombia: 1134 sequences



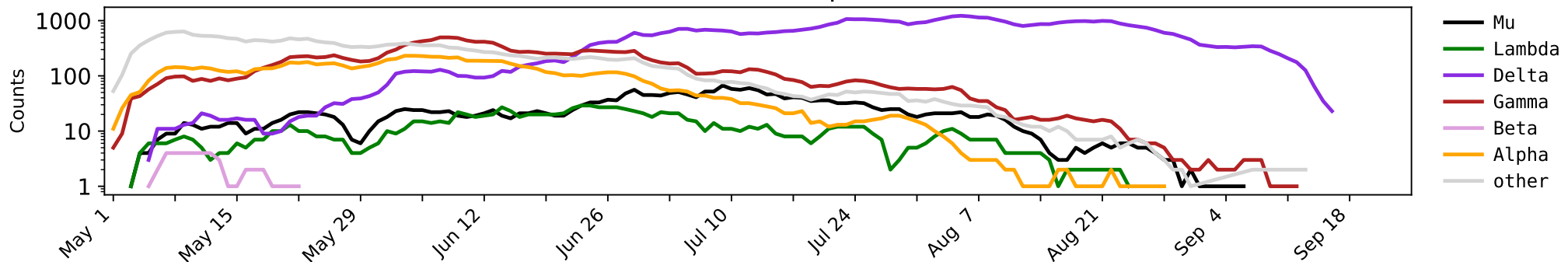
## Chile: 5392 sequences



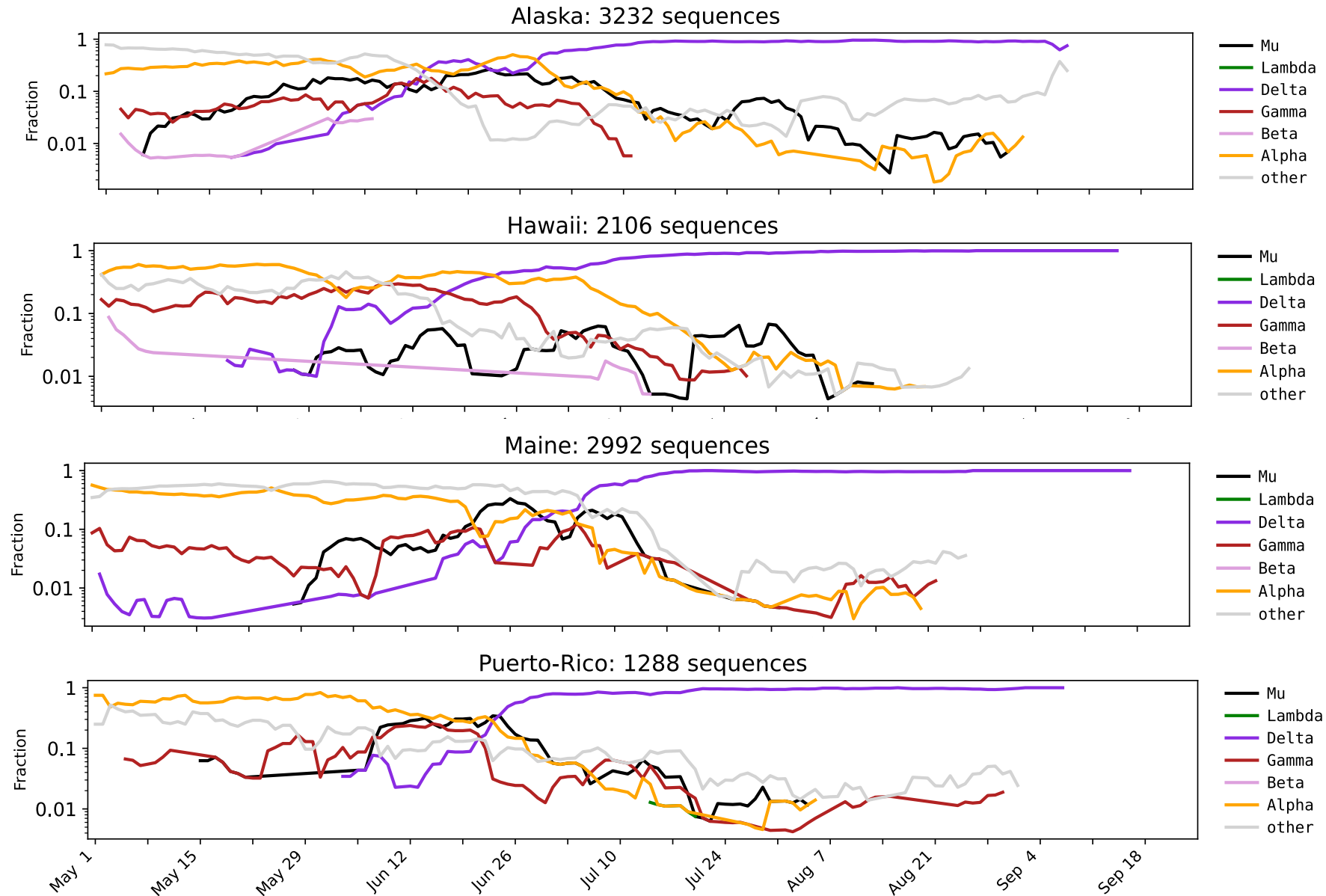
## USA: 464296 sequences



## Mexico: 16818 sequences



# Within the US, some states that had particularly high frequencies of Mu in June and July transitioned to Delta



 Mu peak

## C.1.2

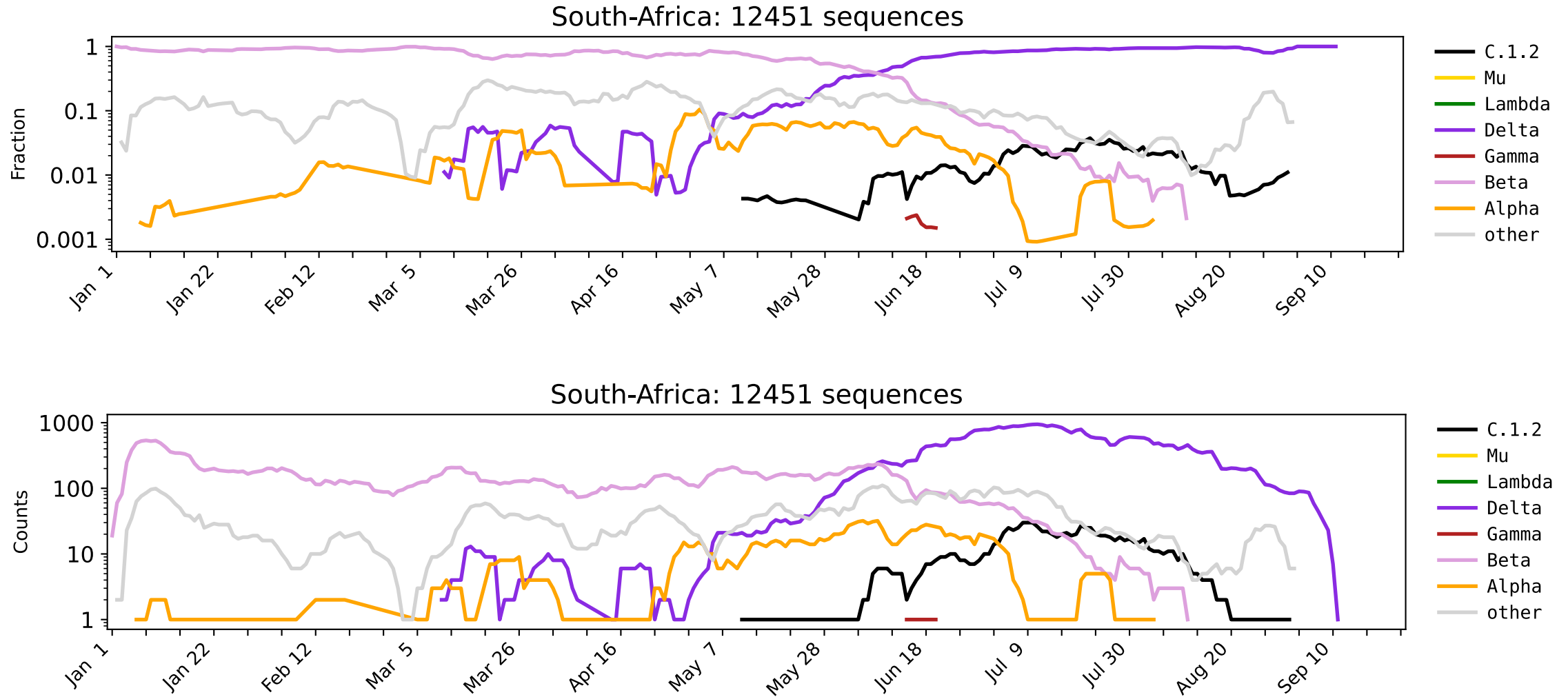
C.1.2

P9L,C136F,Y144-,R190S,D215G,A243-,L244-,Y449H,E484K,N501Y,D614G,H655Y,N679K,T716I,T859N

See: Scheepers et al. The continuous evolution of SARS-CoV-2 in South Africa: a new lineage with rapid accumulation of mutations of concern and global detection.

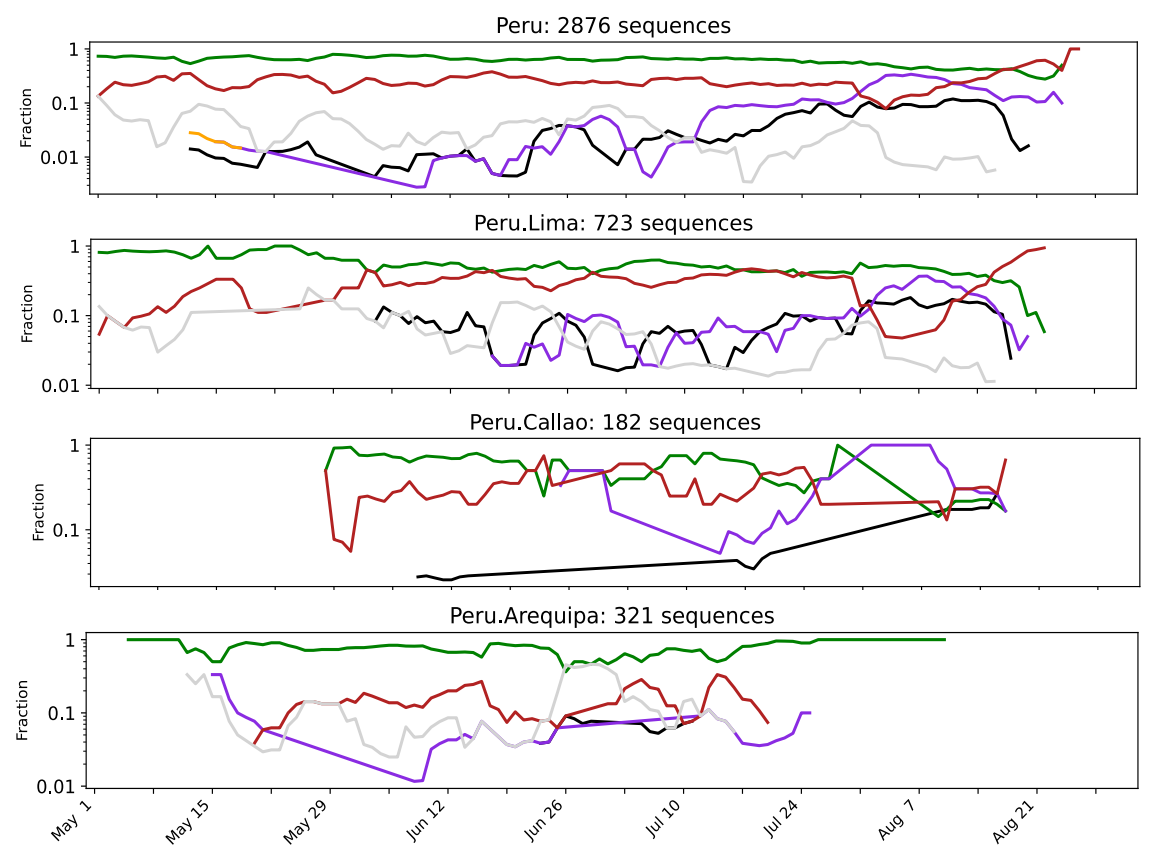
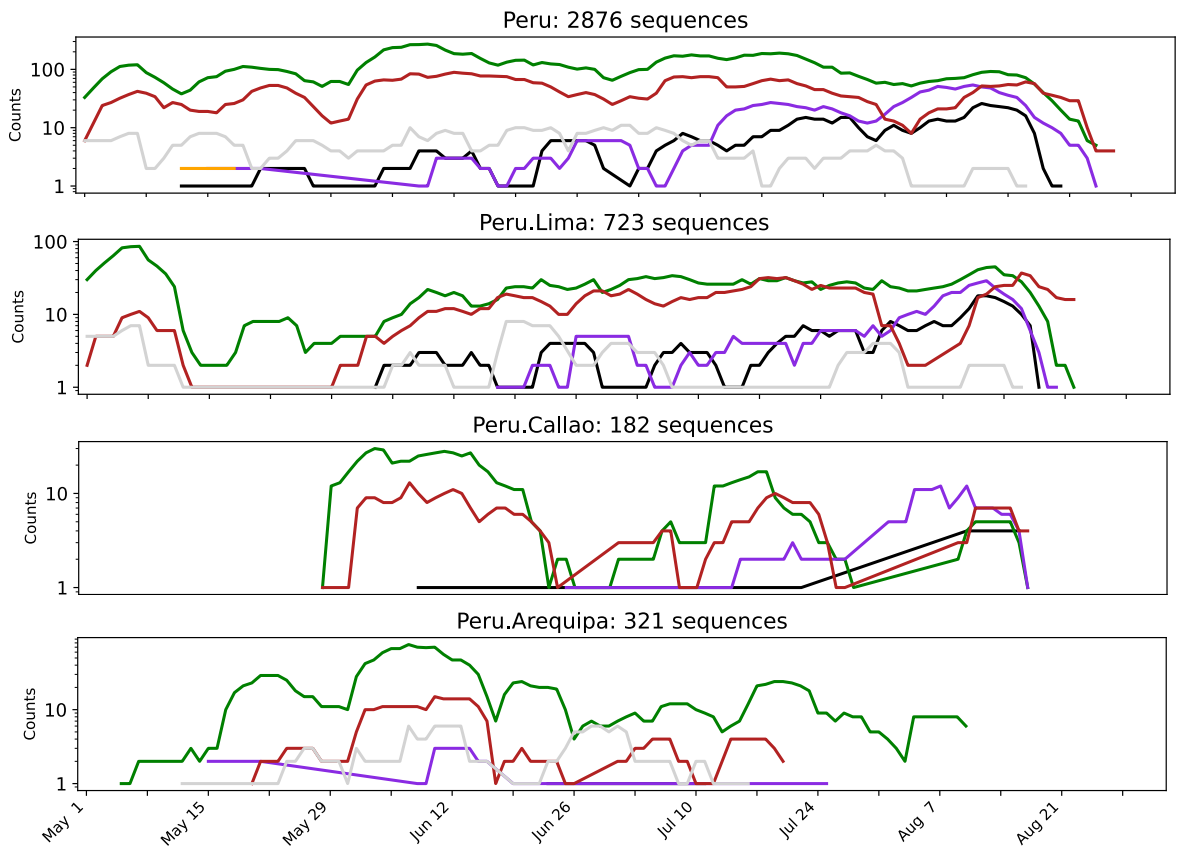
<https://www.medrxiv.org/content/10.1101/2021.08.20.21262342v2>

# C.1.2: not recently sampled in South Africa – by Pango lineage name



9/24/2021: Current count: 21 times outside of S. Africa, no increase in rare samples in other countries.  
Found 162 times inside South Africa

# Peru is transitioning from Lambda to Gamma/Delta



- Mu
- Lambda
- Delta
- Gamma
- Beta
- Alpha
- other

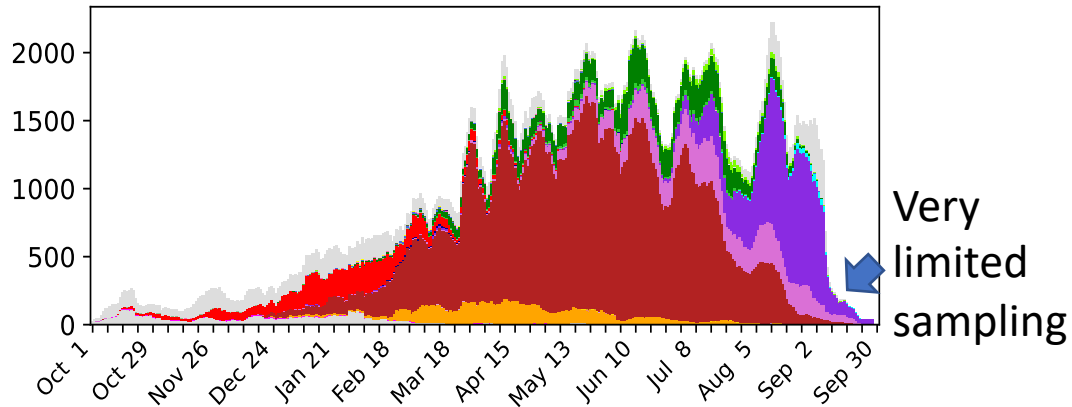
The last few slides show Gamma variants with positive charge near the furin cleavage site and prevalence relative to baseline Gamma and Delta

Different forms of positive charge near furin were regionally sampled.

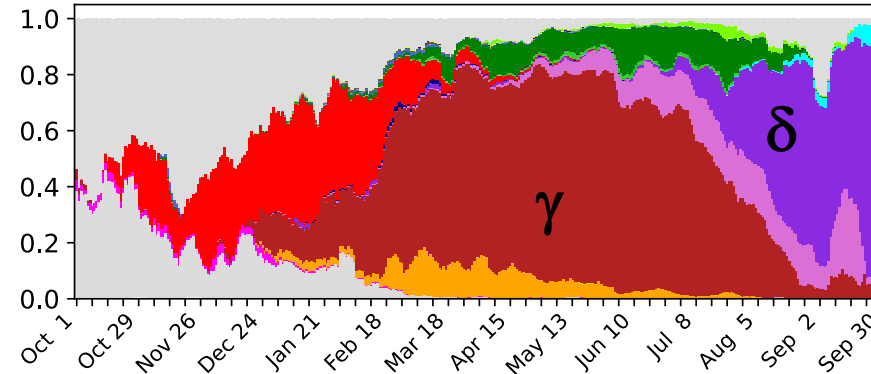
Positive charge

# South America is still in transition towards high Delta prevalence, and a set of P.1 variants have increased that carry positive charge near the furin cleavage site have competitive edge

South-America: 49736 sequences



South-America: 49736 sequences



- other
- B.1.621=Mu
- B.1.619
- B.1.1.318
- B.1.623
- B.1.620
- C.36.3
- B.1.214.2
- A.2.5.2
- B.1.258.17
- B.1.575
- R.1
- B.1.1.519
- C.37=Lambda
- B.1.617.1=Kappa
- B.1.637
- B.1.526=Iota
- B.1.525=Eta
- P.2=Zeta
- B.1.429/7=Epsilon
- Delta-AY.2
- Delta+FurinRelated
- B.1.617.2=Delta
- Gamma+FurinRelated
- P.1=Gamma
- B.1.351=Beta
- Alpha+T20I
- Alpha+F490S
- Alpha+E484K
- Alpha+W152R
- B.1.1.7=Alpha
- FurinRelated
- GV-clade
- G-clade
- Ancestral

$\gamma$ +furin related, defined in the next few slides.

P.1, Gamma:

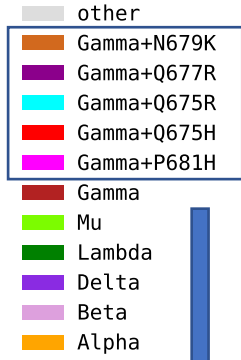
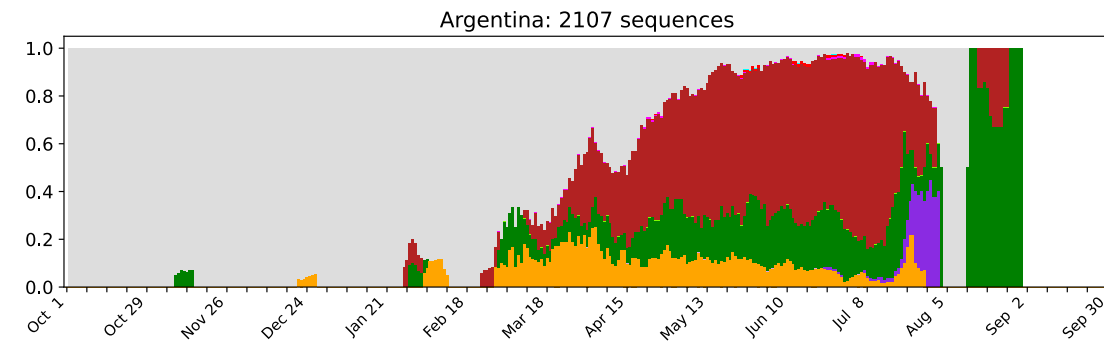
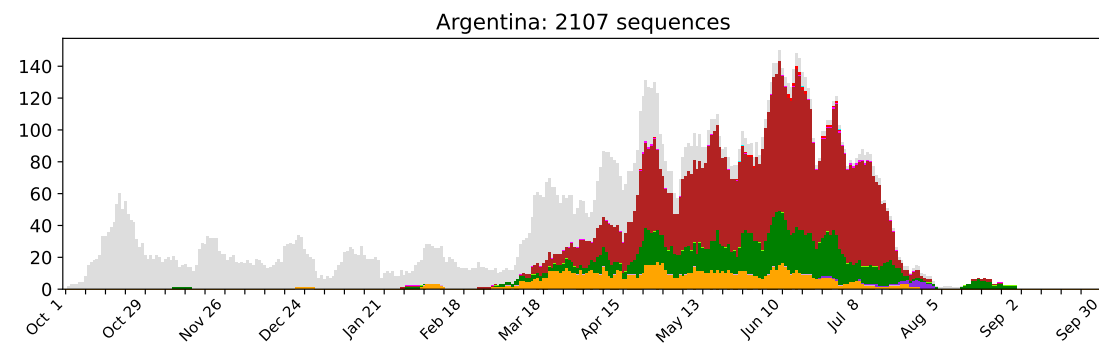
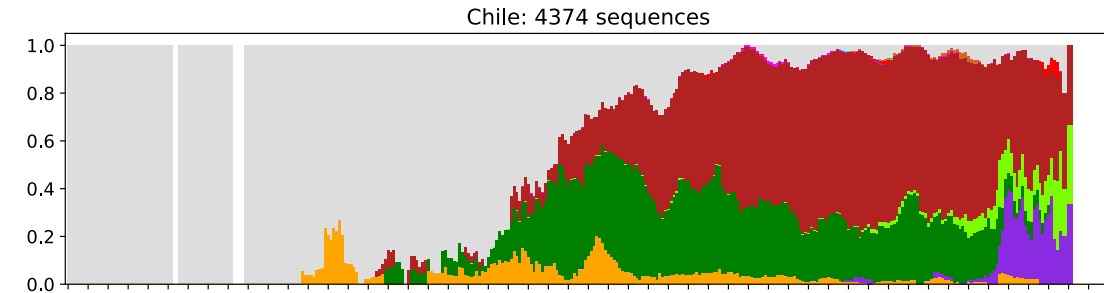
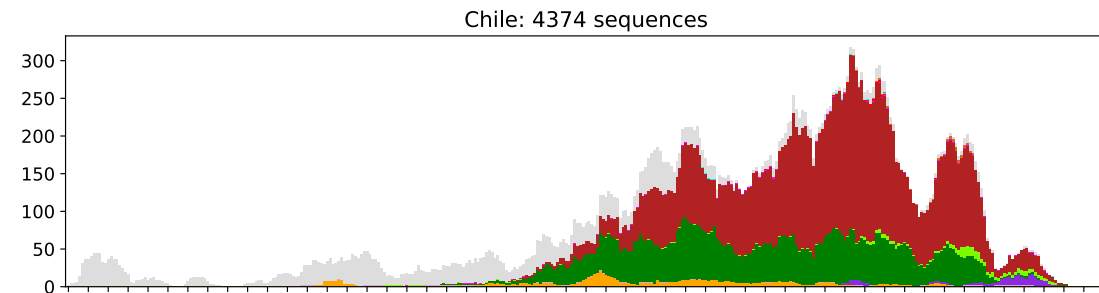
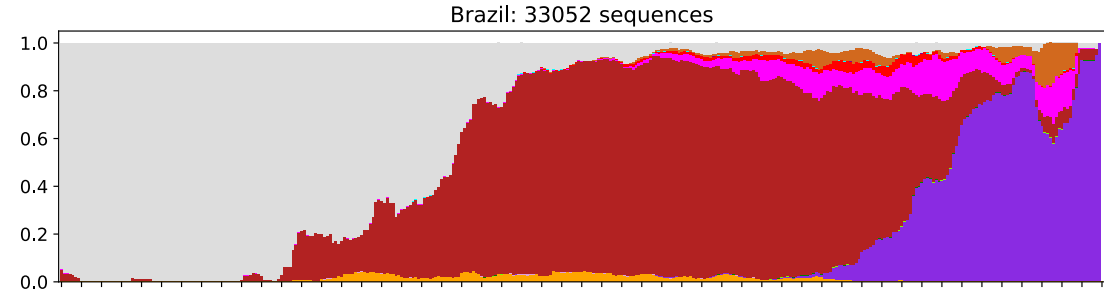
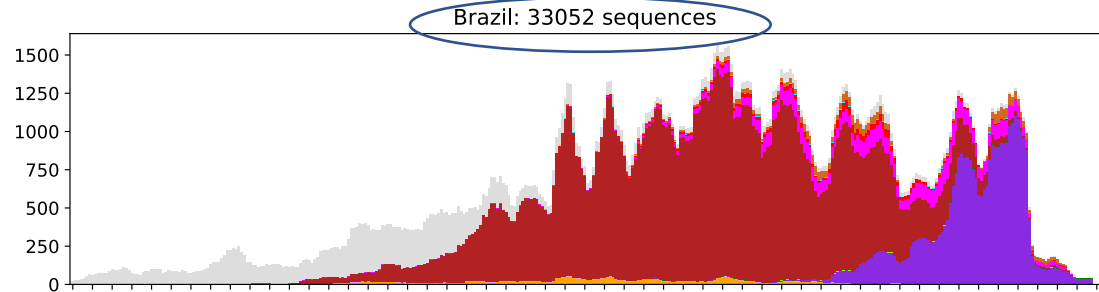
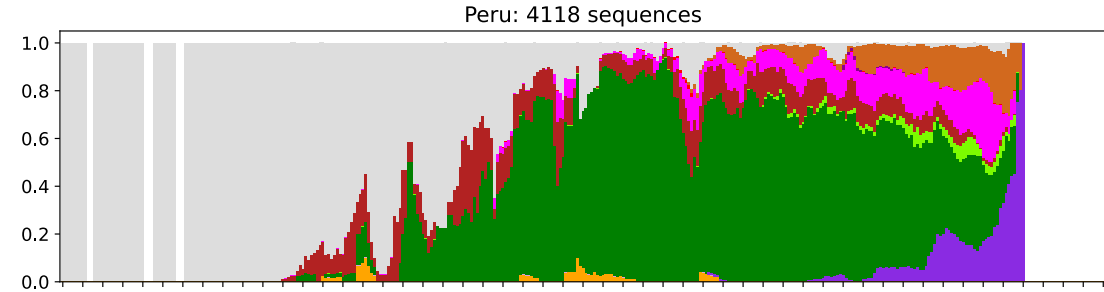
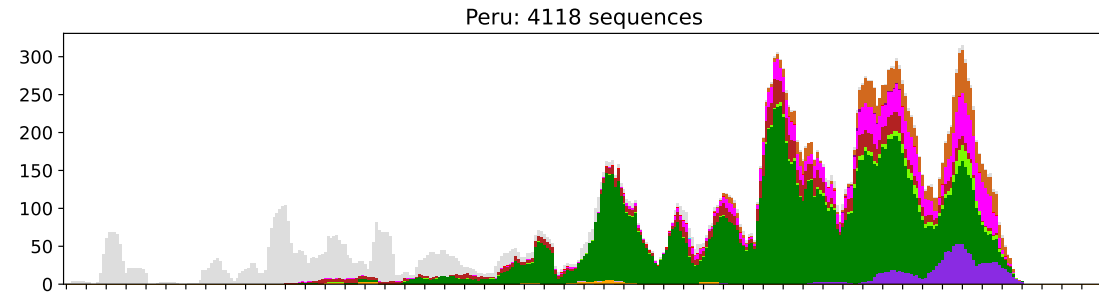
L18F,T20N,P26S,D138Y,R190S,K417T,E484K,N501Y,D614G,H655Y,T1027I,V1176

Gamma basic backbone carries H655Y\*, but is accruing additional positive charge near the furin cleavage site

\*H655Y: Escalera et al. SARS-CoV-2 variants of concern have acquired mutations associated with an increased spike cleavage  
 bioRxiv doi: 10.1101/2021.08.05.45529

**We need to be CAUTIOUS with recent data, it is always very limited.  
 There is generally a ~2 week lag between sampling and GISAID.**

# South American P.1 is acquiring +charge near furin site, but Delta has arrived.



Furin  
Related:  
Positive  
charge  
near the  
furin  
cleavage  
site

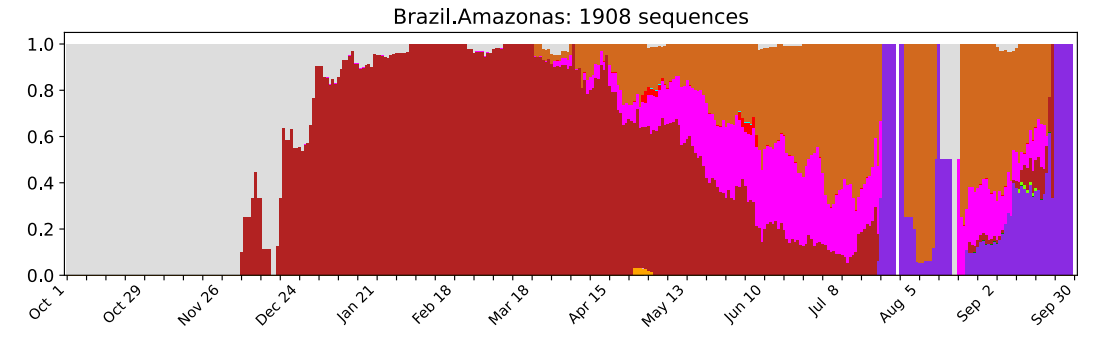
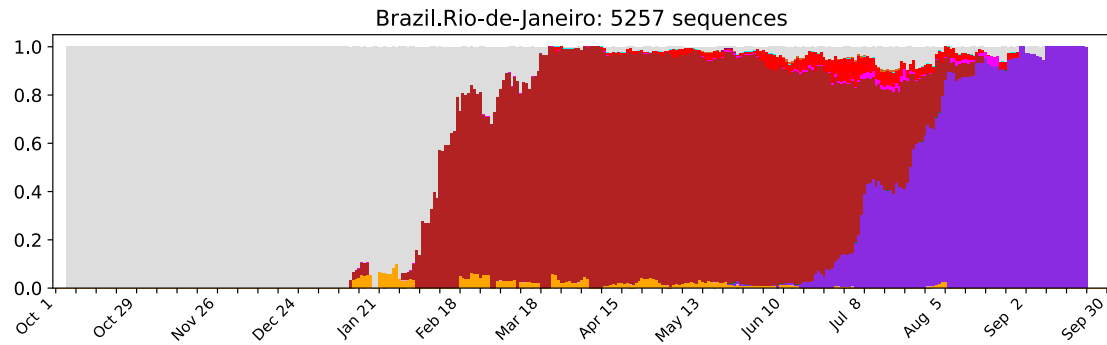
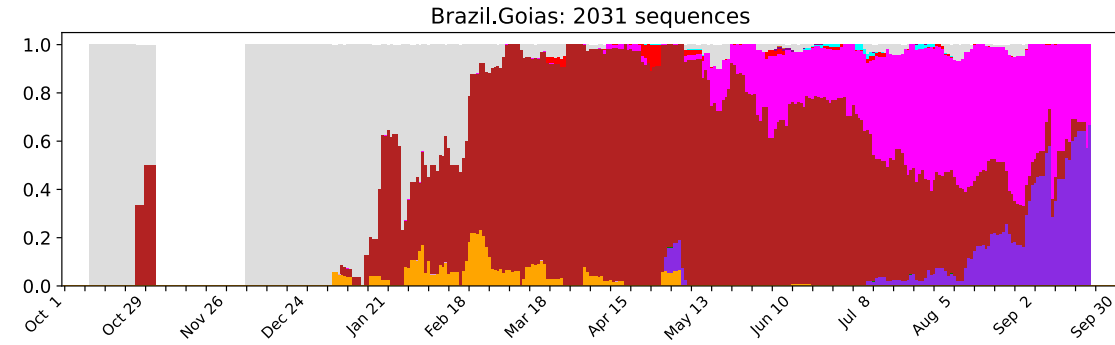
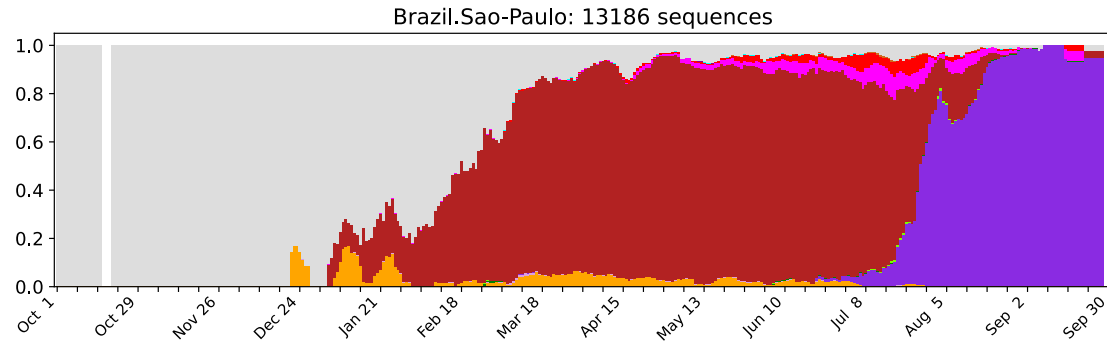
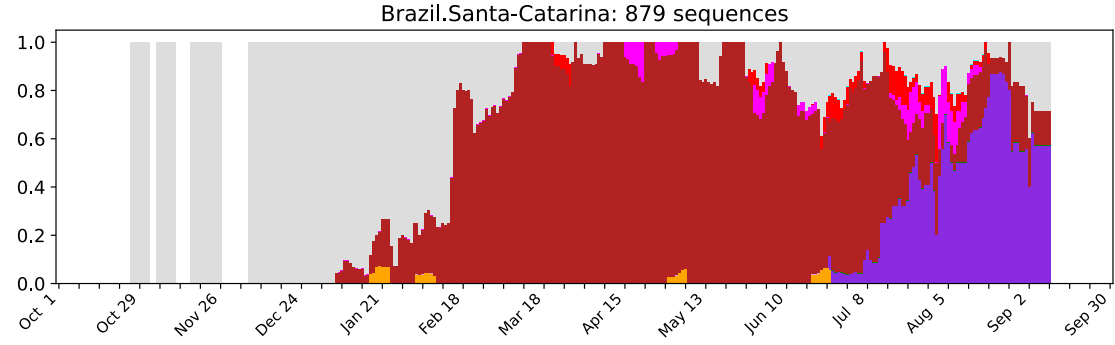
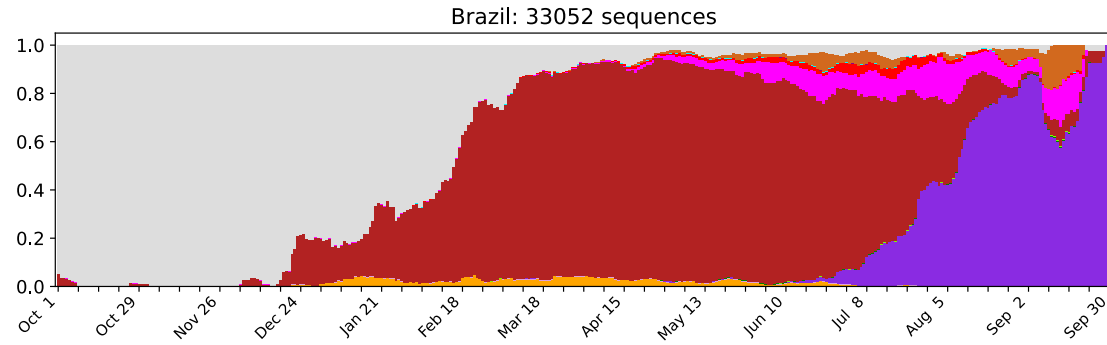


# Gamma + furin related, Brazil

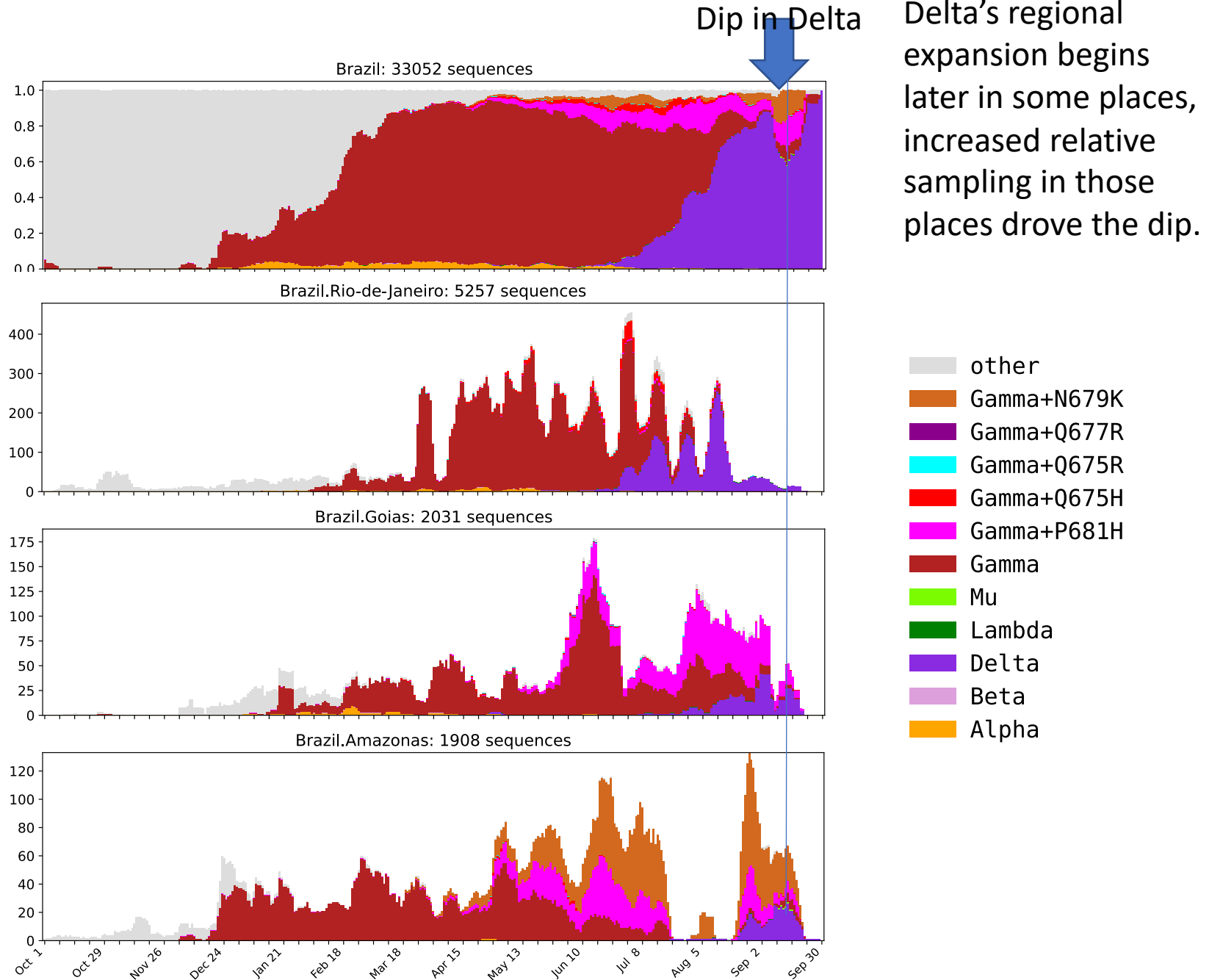
P.1 -> P.1 Plus Furin, both -> Delta

Particular furin-related mutations were regional

- other
- Gamma+N679K
- Gamma+Q677R
- Gamma+Q675R
- Gamma+Q675H
- Gamma+P681H
- Gamma
- Mu
- Lambda
- Delta
- Beta
- Alpha

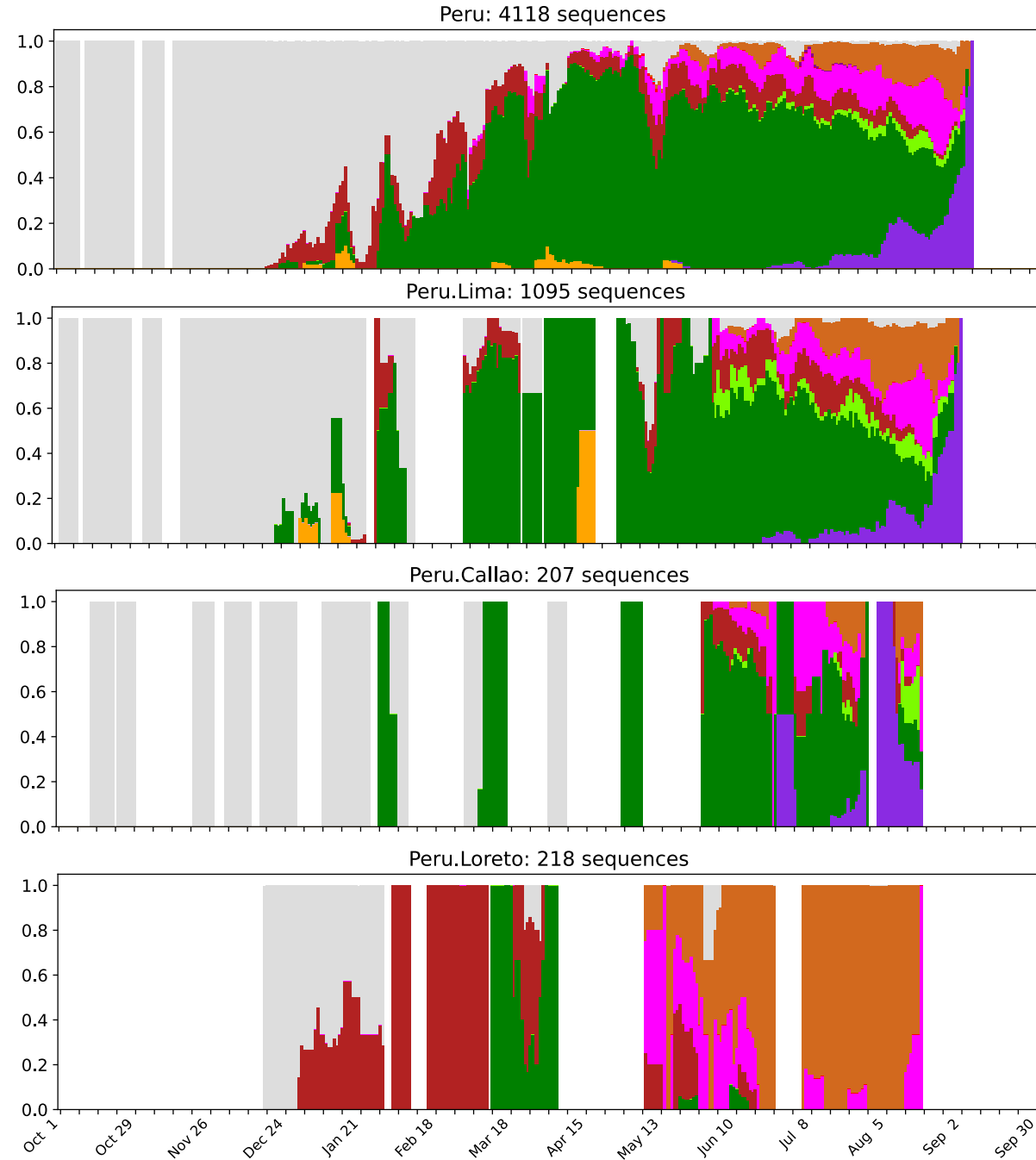


Regional sampling biases altered the apparent trajectory of Delta's increasing prevalence in Brazil



# Peru is behind Brazil, adds Lambda and Mu into the Mix

Lambda -> Gamma  
 Lambda & Gamma -> Gamma+furin  
 Increasing Mu  
 Delta is newly arrived.



- other
- Gamma+N679K
- Gamma+Q677R
- Gamma+Q675R
- Gamma+Q675H
- Gamma+P681H
- Gamma
- Mu
- Lambda
- Delta
- Beta
- Alpha