SARS-CoV-2 and HIV variant evolution

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April 8, 2024
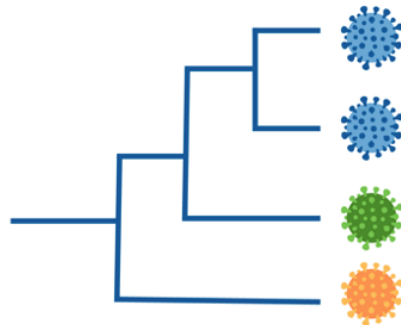
Major Lineage Shifts the Pandemic: 2020-02-15 to 2024-04-01
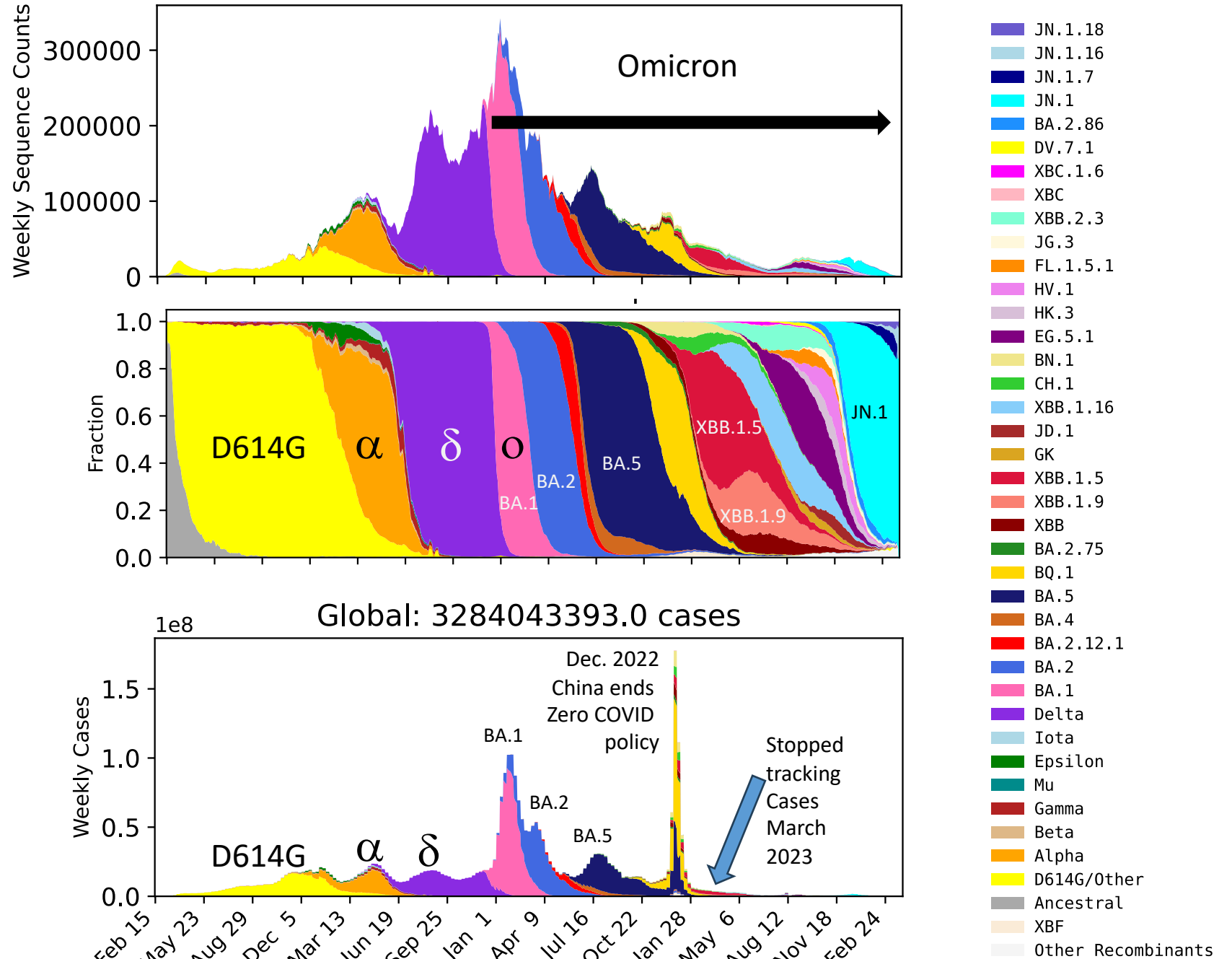
Major Lineage Shifts the Pandemic: 2020-02-15 to 2024-04-01
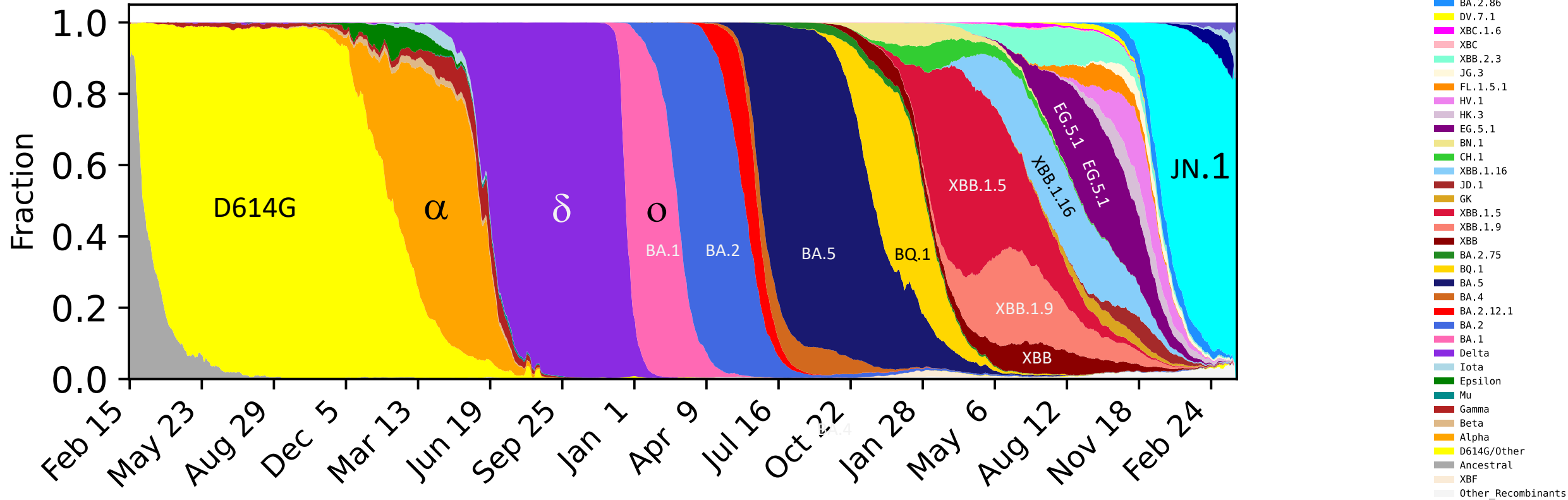
Three evolutionary mechanisms that give rise to variants that have resulted in transitions on a global scale:

   i. **Gradual accumulation** of mutations with a selective advantage:

    BQ.1: BA.5 + K444T + N460K, then **BQ.1.1** adds R346T, all confer NAb resistance

   ii. **Recombination** bringing together multiple advantageous mutations, followed by additions:

    XBB: x BJ.1 x BM.1.1.1, then **XBB.1** adds G252V and, **XBB.1.5/9** adds F486P

T19I,L24S,P25-,P26-,A27-,**V83A**,G142D,**Y144**-,**H146Q,Q183E,V213E**,G339H,R346T,**L368I**,S371F,S373P,S375F,T376A,D405N,R408S,K417N,N440K,**V445P**,G446S,**N460K**,S477N,T478K,E484A,F486S,F490S,Q498R,N501Y,Y505H,D614G,H655Y,N679K,P681H,N764K,D796Y,Q954H,N969K

   iii. **Radically different new form(s) appear**, likely introduced from within-host evolution from long-term infection

    First Alpha, BA.1 and BA.2, BA.2.86, and J.1 adds L455S

SARS-CoV-2 Phylogeny

Full Length genome, ML tree, 100 randomly sampled
sequences from the global GISAID collection per month.

XBC.1.6 <- BA.2 x B.1.617.2 (Delta)

XDD <- EG.5.1.1 x JN.1

JN.1

Big jump to JN.1

XBB.1.5

BQ.1   Gradual Accumulation to BQ.1

BA.5

Recombination

XBB <- BJ.1 (BA.2) x BM.1.1.1 (BA.2.75)

EG.5.1

BA.2

Big jump to BA.1/2

BA.1

Delta

Will Fischer

shortname

Ancestral		CH.1	
D614G/Other		XBB.1.5	
Alpha		XBB.1.9	
Unassigned		XBB.2.3	
Gamma		XBB.1.16	
Beta		XBC.1.6	
Epsilon		EG.5.1	
Delta		XBB.1.16.6	
Iota		GK	
Mu		FL.1.5.1	
BA.1		DV.7.1	
BA.2		JD.1	
BA.4		HV.1	
Other_Recombinants		JF.1	
BA.2.12.1		HK.3	
BA.5		BA.2.86	
BA.2.75		JN.1	
BQ.1		JG.3	
XBB		FL.1.5.2	
BN.1		NA	
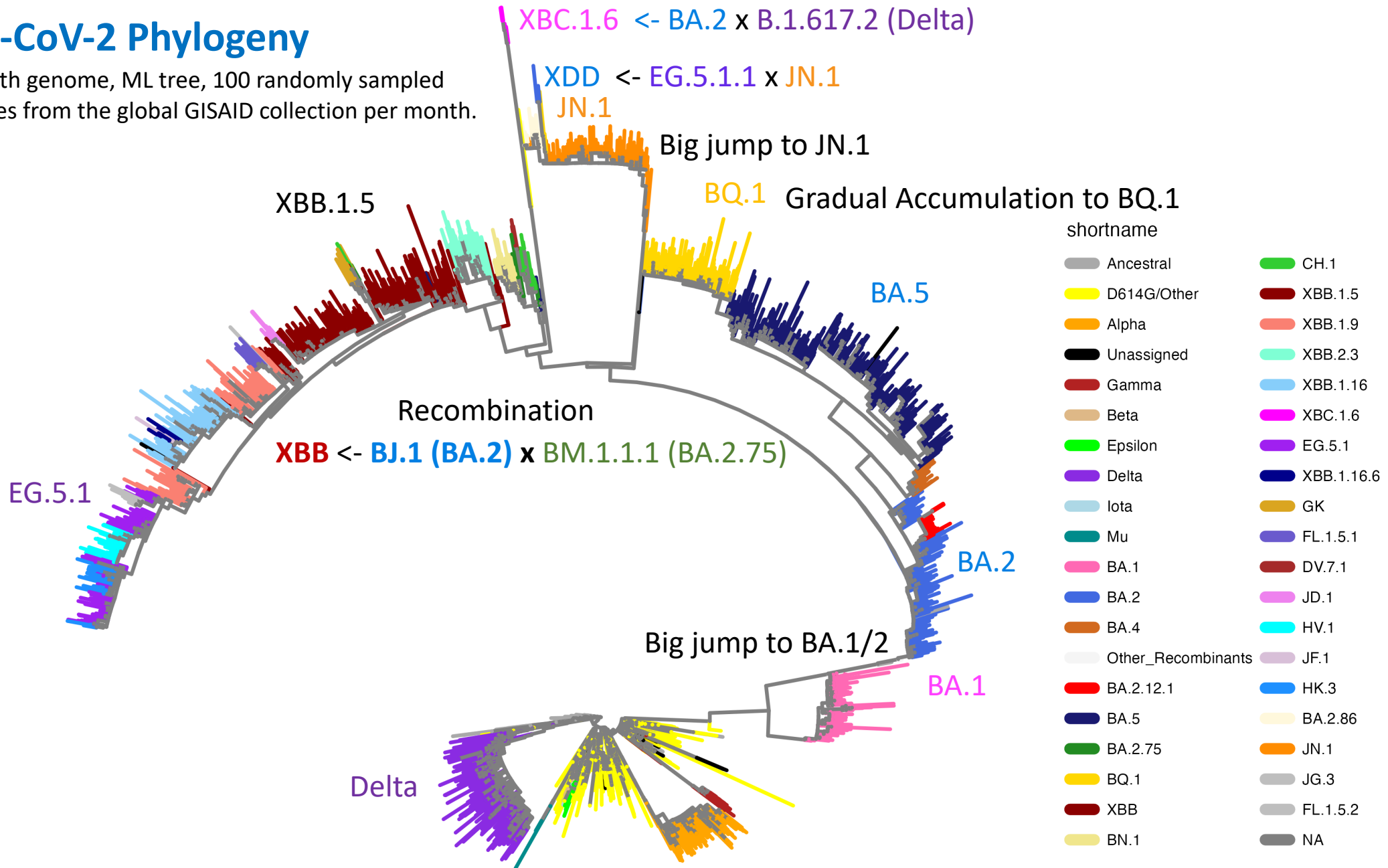
Pango *lineage* nomenclature

https://www.pango.network
Rambaut et al. *Nature Microbiology* **volume 5**, pages 1403–1407 (2020)

- Phylogenetically based and signify groups or clusters of infections with shared ancestry.
- Pango lineages highlight epidemiologically-relevant events
  - appearance of the virus in a new locations
  - rapid increase in cases

Pango designation listings are kept up to date by Cornelius Roemer (3820 currently):

https://github.com/cov-lineages/pango-designation/blob/master/lineage_notes.txt

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Example 1: the first Omicrons

B.1.1.529   South Africa and Botswana lineage
BA.1   Alias of B.1.1.529.1
BA.1.1   Alias of B.1.1.529.1.1
BA.1.1.1   Alias of B.1.1.529.1.1.1
BC.1   Alias of B.1.1.529.1.1.1.1
BA.2   Alias of B.1.1.529.2
BA.2.1   Alias of B.1.1.529.2.1

Example 2: XBB, a recombinant lineage that become globally dominant

XBB   Recombinant of BJ.1 x BM.1.1.1, USA and Singapore
XBB.1   defined by S:G252V
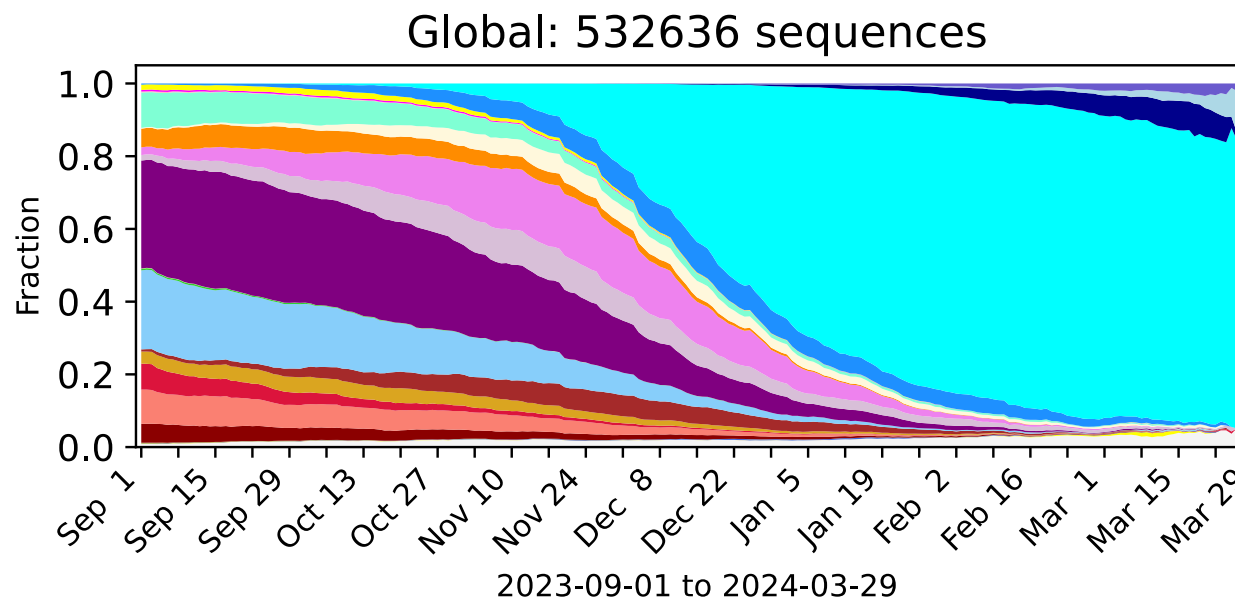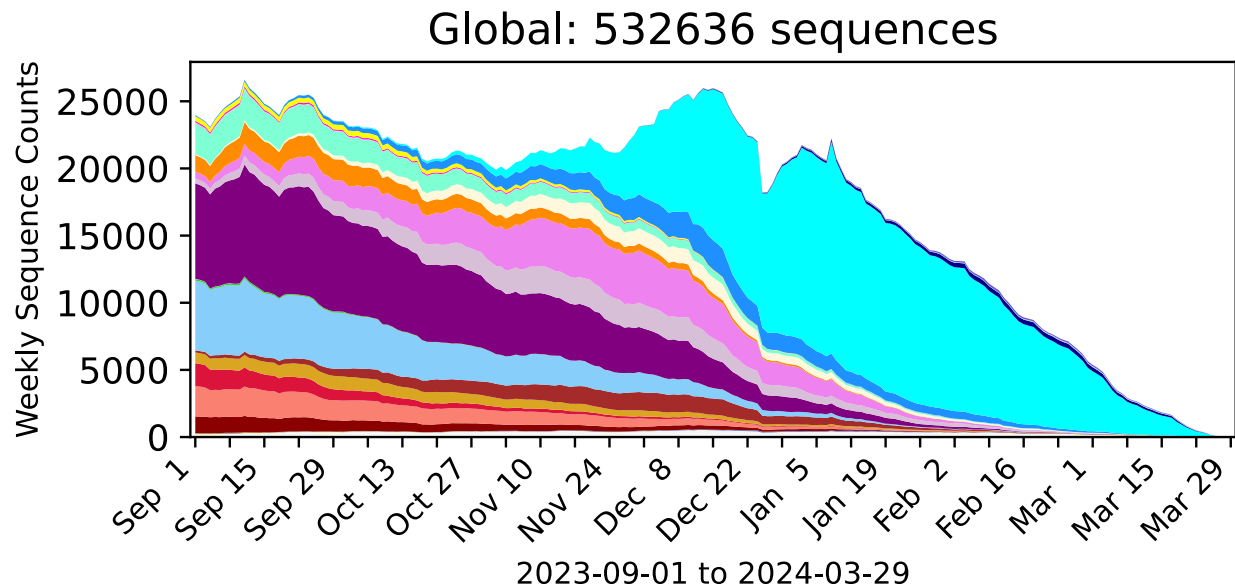XBB.1.5 defined by S:F486P
XBB.1.5.1 defined by S:T573I
HJ.1   Alias of XBB.1.5.1.1, defined by S:E324K, C4543T
XBB.1.9 defined by ORF1a:G1819S, ORF1a:T4175I
XBB.1.9.1 S:F486P (after C11956T)

Each designation represents not one thing but represents a complex evolving lineage!

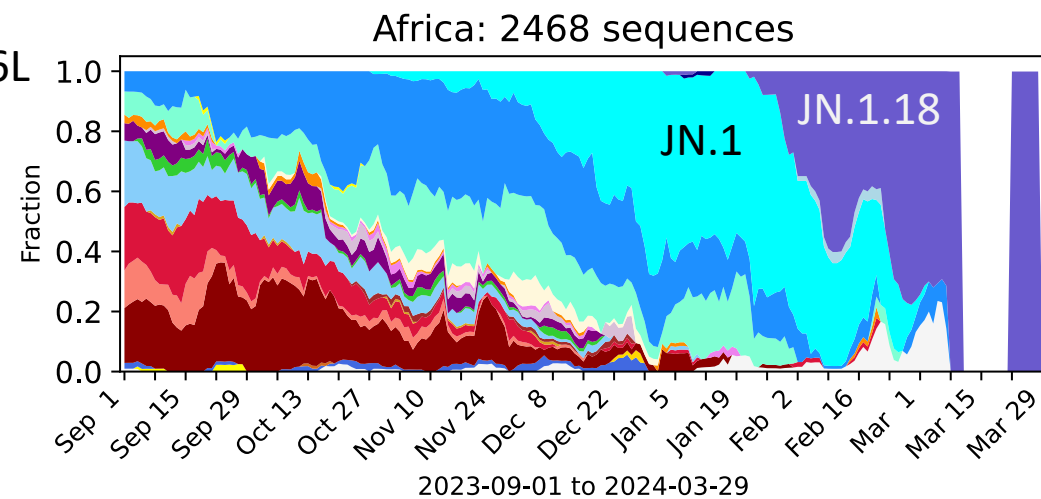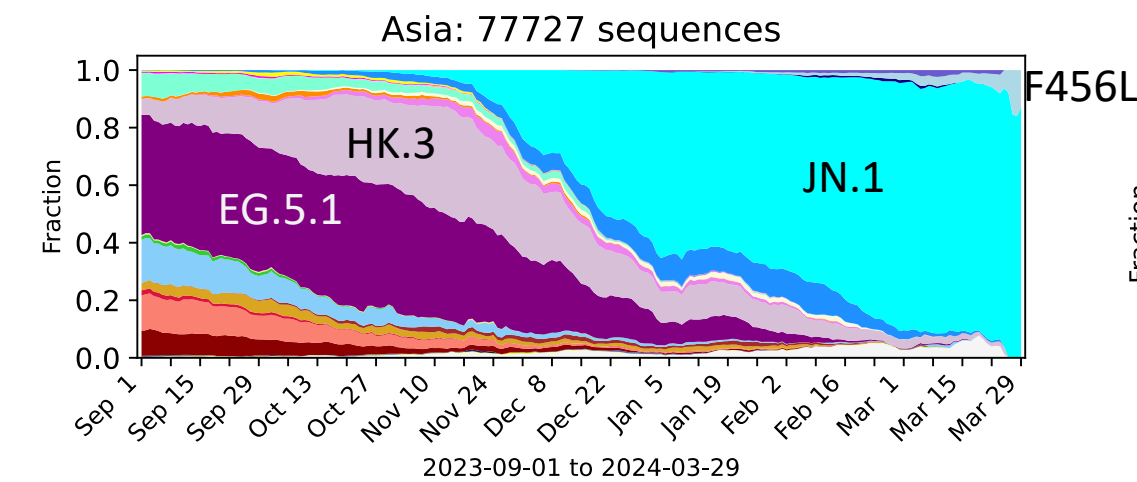# Global SARS-CoV-2 lineages in the last 7 months

Global: 532636 sequences

Weekly Sequence Counts vs 2023-09-01 to 2024-03-29

Global: 532636 sequences
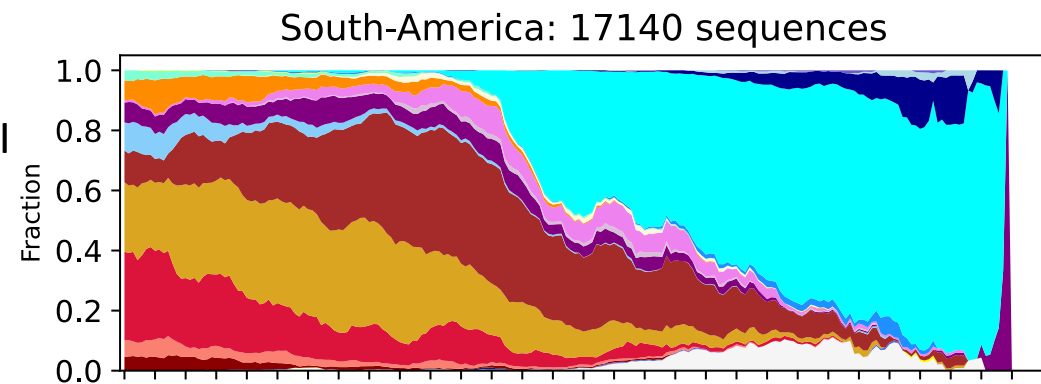
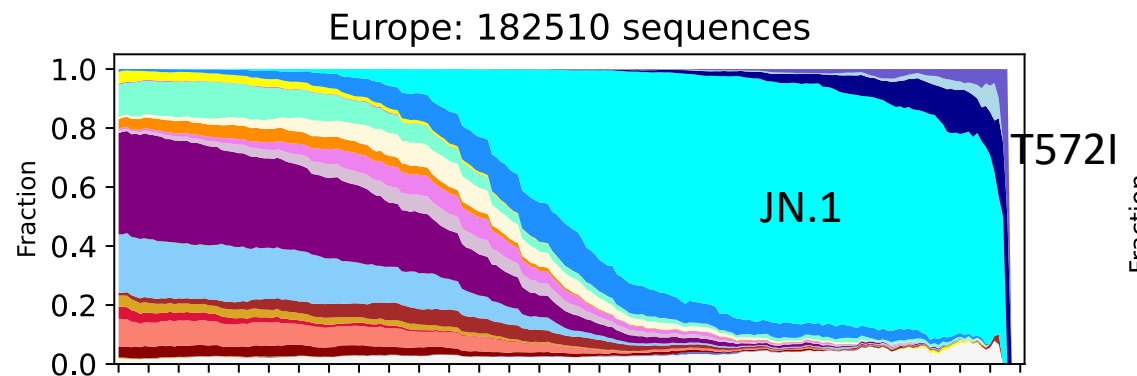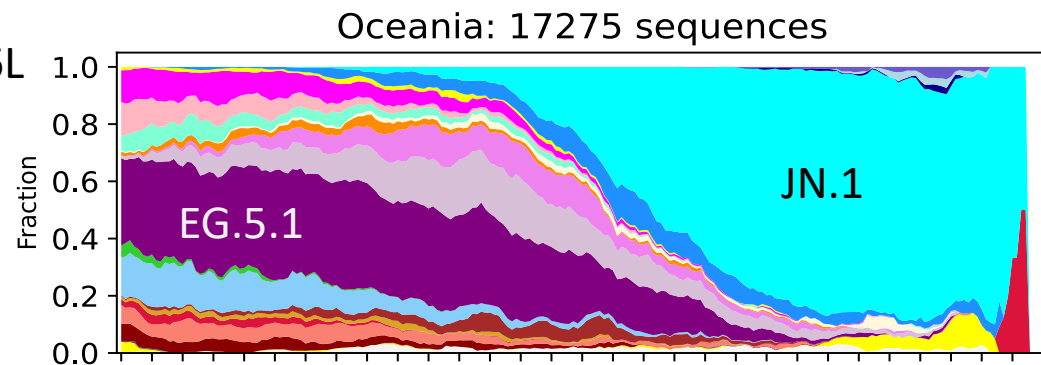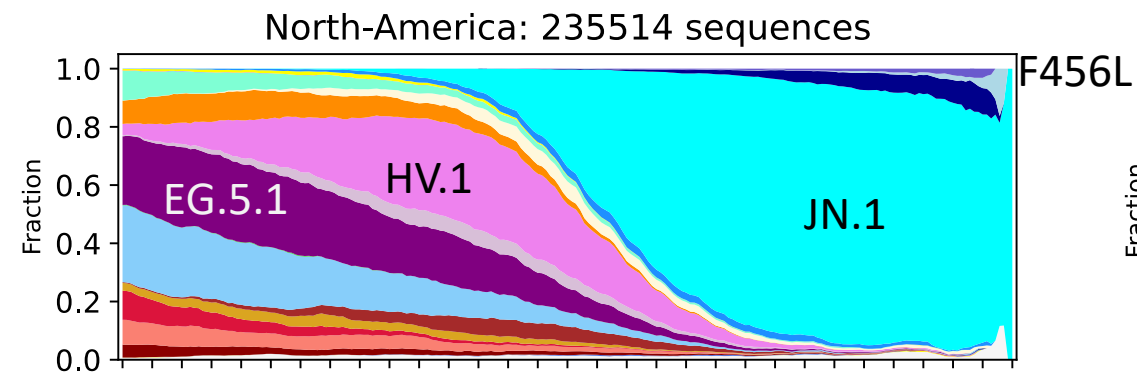Fraction vs 2023-09-01 to 2024-03-29

Legend:
- JN.1.18 R346T
- JN.1.16 F456L
- JN.1.7   T572I
- JN.1
- BA.2.86
- DV.7.1
- XBC.1.6
- XBC
- XBB.2.3
- JG.3
- FL.1.5.1
- HV.1
- HK.3
- EG.5.1
- BN.1
- CH.1
- XBB.1.16
- JD.1
- GK
- XBB.1.5
- XBB.1.9
- XBB
- BA.2.75
- BQ.1
- BA.5
- BA.4
- BA.2.12.1
- BA.2
- BA.1
- Delta
- Iota
- Epsilon
- Mu
- Gamma
- Beta
- Alpha
- D614G/Other
- Ancestral
- XBF
- Other_Recombinants

BA.2.86/BA.2.86.1: origins: Late July, a few cases in Denmark and South Africa, then Thailand, USA

The distinguishing mutations in JN.1 vs BA.2.86.1 are:

Spike:	**L455S**
ORF1a:	**R3821K**
ORF7b:	**F19L**

Frequency by Continent: Distinct variant histories, but JN.1 is a global sweep

Remember, the last few weeks always have a lag and so very small numbers, see next slide

JN.1 lineages with Pango designations, highlighting repeated mutations

Pango designations from Cornelius Roemer: https://github.com/cov-lineages/pango-designation/blob/master/lineage_notes.txt

2024-04-01

	GISAID counts	Alias, defining mutations
JN.1	**68,676**	**Alias of B.1.1.529.2.86.1.1, S:L455S, ORF1a:R3821K, ORF7b:F19L, Europe**
JN.1.1	**17,535**	Alias of B.1.1.529.2.86.1.1.1, ORF1a:F499L, C11747T, France
JN.1.1.1	517	Alias of B.1.1.529.2.86.1.1.1.1, S:T572I after C9142T, France/Sweden
JN.1.1.2	106	Alias of B.1.1.529.2.86.1.1.1.2, S:G181E, France
JN.1.1.3		Alias of B.1.1.529.2.86.1.1.1.3, S:R346T, ORF1b:H2388Y, France/Sweden
JN.1.1.4	140	Alias of B.1.1.529.2.86.1.1.1.4, S:V1264L,
JN.1.1.5	362	Alias of B.1.1.529.2.86.1.1.1.5, S:R346T on C9142T branch
KR.1	46	Alias of B.1.1.529.2.86.1.1.1.5.1, S:F456L, after C28498T
JN.1.1.6	64	Alias of B.1.1.529.2.86.1.1.1.6, S:F456L
JN.1.1.7	75	Alias of B.1.1.529.2.86.1.1.1.7, S:S31F
JN.1.2	**2,216**	Alias of B.1.1.529.2.86.1.1.2, S:M1229I, USA/Canada
JN.1.2.1	58	Alias of B.1.1.529.2.86.1.1.2.1, S:H1101Y, Ireland
JN.1.3	380	Alias of B.1.1.529.2.86.1.1.3, ORF8:Q18*, Netherlands
JN.1.4	**24,970**	Alias of B.1.1.529.2.86.1.1.4, ORF1a:T170I, Denmark/Singapore
JN.1.4.1	172	Alias of B.1.1.529.2.86.1.1.4.1, S:E654V, Ireland
JN.1.4.2	757	Alias of B.1.1.529.2.86.1.1.4.2, S:N185D, USA
JN.1.4.3	152	Alias of B.1.1.529.2.86.1.1.4.3, S:T572I, USA
KQ.1	148	Alias of B.1.1.529.2.86.1.1.4.3.1, S:R346T, USA
JN.1.4.4	368	Alias of B.1.1.529.2.86.1.1.4.4, S:R346T
JN.1.4.5	**7,911**	Alias of B.1.1.529.2.86.1.1.4.5, ORF8:S103L, after T18453C
KV.1	45	Alias of B.1.1.529.2.86.1.1.4.5, S:S680F
JN.1.4.6	411	Alias of B.1.1.529.2.86.1.1.4.6, S:T572I, after T18453C
JN.1.5	**2,216**	Alias of B.1.1.529.2.86.1.1.5, ORF1b:V1271T, Asia
JN.1.6	960	Alias of B.1.1.529.2.86.1.1.6, G22627A
JN.1.6.1	232	Alias of B.1.1.529.2.86.1.1.6.1, S:R346T, Sweden
JN.1.7	**2,855**	Alias of B.1.1.529.2.86.1.1.7, S:T572I, S:E1150D
JN.1.7.1	39	Alias of B.1.1.529.2.86.1.1.7.1, S:R346K, England
JN.1.7.2	271	Alias of B.1.1.529.2.86.1.1.7.2, ORF1b:C1563F, Americas
JN.1.8	**1,452**	Alias of B.1.1.529.2.86.1.1.8, ORF7a:T28I
JN.1.8.1	**2,164**	Alias of B.1.1.529.2.86.1.1.8.1, S:T572I, USA/Denmark
JN.1.8.2	48	Alias of B.1.1.529.2.86.1.1.8.2, S:R346T
KY.1		Alias of B.1.1.529.2.86.1.1.8.2.1, ORF1a:N3774D, Nigeria
JN.1.8.3		Alias of B.1.1.529.2.86.1.1.8.3, C13821T, C14925T
JN.1.9	**1,725**	Alias of B.1.1.529.2.86.1.1.9, S:Q183H, USA/UK/Canada
JN.1.9.1	124	Alias of B.1.1.529.2.86.1.1.9.1, S:T572I, ORF1a:A3143V
JN.1.10	111	Alias of B.1.1.529.2.86.1.1.10, S:T95I, USA/Canada
JN.1.11	192	Alias of B.1.1.529.2.86.1.1.11, S:V1104L, G17334T, India
JN.1.11.1	240	Alias of B.1.1.529.2.86.1.1.11.1, S:F456L, India
KP.1	96	Alias of B.1.1.529.2.86.1.1.11.1.1, S:K1086R
KP.1.1	71	Alias of B.1.1.529.2.86.1.1.11.1.1.1, S:R346T
KP.2	225	Alias of B.1.1.529.2.86.1.1.11.1.2, S:R346T, JN.1.11.1 polytomy
KP.2.1	7	Alias of B.1.1.529.2.86.1.1.11.1.2.1, S:Q1201K
KP.2.2	1	Alias of B.1.1.529.2.86.1.1.11.1.2.2, S:F59L, S:K1266R
KP.3	41	Alias of B.1.1.529.2.86.1.1.11.1.3, S:Q493E
JN.1.12	32	Alias of B.1.1.529.2.86.1.1.12, S:F456V, ORF7a:A8T
JN.1.13	69	Alias of B.1.1.529.2.86.1.1.13, S:A1087S, USA
JN.1.13.1	541	Alias of B.1.1.529.2.86.1.1.13.1, S:R346T, S:F59S, USA
KS.1	23	Alias of B.1.1.529.2.86.1.1.13.1.1, S:F456L
JN.1.14	96	Alias of B.1.1.529.2.86.1.1.14, S:R346S, USA
JN.1.15	229	Alias of B.1.1.529.2.86.1.1.15, S:A688V
JN.1.16	**612**	Alias of B.1.1.529.2.86.1.1.16, S:F456L
JN.1.16.1	124	Alias of B.1.1.529.2.86.1.1.16.1, S:R346T
JN.1.17	238	Alias of B.1.1.529.2.86.1.1.17, S:A222V, USA
JN.1.18	**1,246**	Alias of B.1.1.529.2.86.1.1.18, S:R346T, directly on JN.1 polytomy
JN.1.18.1	40	Alias of B.1.1.529.2.86.1.1.18.1, S:T250N
JN.1.18.2	27	Alias of B.1.1.529.2.86.1.1.18.2, S:F59S, after C4331T, T22321C
JN.1.19	**1,327**	Alias of B.1.1.529.2.86.1.1.19, ORF8:I71V
JN.1.20	756	Alias of B.1.1.529.2.86.1.1.20, S:S31F, directly on JN.1 polytomy
JN.1.21	376	Alias of B.1.1.529.2.86.1.1.21, S:H1058Y
JN.1.22	**2,642**	Alias of B.1.1.529.2.86.1.1.22, ORF1a:S505F, C13019T
JN.1.23	47	Alias of B.1.1.529.2.86.1.1.23, S:K444R,S:Y453F,ORF1a:A307V,ORF1a:P2144L, Brazil
JN.1.24	162	Alias of B.1.1.529.2.86.1.1.24, S:C1243F, USA
JN.1.25	36	Alias of B.1.1.529.2.86.1.1.25, C706T, A7708T, India
JN.1.25.1	21	Alias of B.1.1.529.2.86.1.1.25.1, S:R346T, India
JN.1.26	46	Alias of B.1.1.529.2.86.1.1.26, S:R346T, after C26894T, USA
JN.1.27	69	Alias of B.1.1.529.2.86.1.1.27, S:M153I, after C26894T, C25680T, USA
JN.1.28	245	Alias of B.1.1.529.2.86.1.1.28, C24034T, A29700G, East Asia/Oceania
JN.1.28.1	125	Alias of B.1.1.529.2.86.1.1.28.1, ORF1a:P1640L, C19545T, C24370T
KW.1	161	Alias of B.1.1.529.2.86.1.1.28.1.1, S:T572I, Australia
JN.1.29	888	Alias of B.1.1.529.2.86.1.1.29, ORF1a:T3224A, after C2644T, Brazil
JN.1.30	275	Alias of B.1.1.529.2.86.1.1.30, G21255T
JN.1.30.1	31	Alias of B.1.1.529.2.86.1.1.30.1, S:R346T, after T7789C, India
KU.1	9	Alias of B.1.1.529.2.86.1.1.30.1.1, S:K182Q
KU.2	10	Alias of B.1.1.529.2.86.1.1.30.1.2, S:F456L
JN.1.31	**1,363**	Alias of B.1.1.529.2.86.1.1.31, ORF3a:V13L, C19186T
JN.1.32	**1,444**	Alias of B.1.1.529.2.86.1.1.32, S:T572I, directly on JN.1 polytomy
JN.1.33	139	Alias of B.1.1.529.2.86.1.1.33, S:A67V, G2782T, C5512T, China
JN.1.34	223	Alias of B.1.1.529.2.86.1.1.34, S:S704L
JN.1.35	68	Alias of B.1.1.529.2.86.1.1.35, S:S680Y, after T18471C, Australia/New Zealand
JN.1.36	97	Alias of B.1.1.529.2.86.1.1.36, S:Q677H, after A29086T
JN.1.36.1	70	Alias of B.1.1.529.2.86.1.1.36.1, S:S680F, South Korea
JN.1.37	234	Alias of B.1.1.529.2.86.1.1.37, S:S680F
JN.1.38	594	Alias of B.1.1.529.2.86.1.1.38, ORF1b:R1736K, USA
JN.1.39	**3,037**	Alias of B.1.1.529.2.86.1.1.39, G2782T
JN.1.40	32	Alias of B.1.1.529.2.86.1.1.40, S:S31P, Mexico
JN.1.41	219	Alias of B.1.1.529.2.86.1.1.41, S:S1252F, on A29086T, USA
JN.1.42	**2,236**	Alias of B.1.1.529.2.86.1.1.42, C5581A, South America
JN.1.43	**1,168**	Alias of B.1.1.529.2.86.1.1.43, A25237G
JN.1.43.1	775	Alias of B.1.1.529.2.86.1.1.43.1, C19488T, C29218T, Brazil
JN.1.44	347	Alias of B.1.1.529.2.86.1.1.44, ORF6:P57L
JN.1.45		Alias of B.1.1.529.2.86.1.1.45, G18756T

On the next (very full) slide I highlight variants found >50 times in the last 60 days that are increasing sampled, and also capture related forms of Spike

Yellow indicates the form of Spike was observed over 200 times in the last 60 days, or that the relative increase is >50% and the form is not really rare.

Red is a rare related form of a more common Spike that was sampled >10x's but is decreasing. These are just small numbers, and so don't mean too much, they are just there to included as a rare variants of a more common increasing form to show overall counts.

Grey are rare forms, and the letter "v" in a Pago lineage means a non-consensus variant sequence

Footnotes:

[1]JN.1, JN.1.1, JN.1.3, JN.1.4, JN.1.4.5, JN.1.5, JN.1.6, JN.1.8, JN.1.19, JN.1.22, JN.1.23, JN.1.28, JN.1.29, JN.1.30, JN.1.31, and the recombinants XDP, XDD all share the same consensus/founder form of Spike.

[2]The loss of the 4 aa insertion at 16 is likely just a sequencing error, grey letters as not of interest other than for counts.

[3]JN.1+T572I is the consensus form of: JN.1.8.1, JN.1.32, JN.1.4.6, JN.1.4.3, JN.1.1.1, KW.1 and the recombinant XDK share the form of Spike: JN.1+T572I

[4]JN.1+R346T is the consensus form of: JN.1.18, JN.1.4.4, JN.1.1.5, JN.1.6.1, JN.1.26, JN.1.30, JN.1.8.2, JQ.2, and JN.1.25.1

[5]JN.1+F456L is the consensus form of: JN.1.16 and JN.1.1.6

[6]JN.1+R346T+F456L: JN.1.16.1 and KR.1

Pango Lineage	Global Count	Form Count	Form Pct	Counts Early/Later	Fractions Early/Later	Differences Abs	Relative	pval	Mutations relative to JN.1 consensus
JN.1[1]	25828	10689	41.4%	5324/5365	0.44456/0.38731	-5.72%	-12.9%	<1e-10	[ ] Baseline form of JN.1
JN.1v	25828	2036	7.9%	828/1208	0.06914/0.08721	+1.81%	+20.7%	8e-8	-[+16MPLF][2]
JN.1.1.1[3]	25828	1085	4.2%	441/644	0.03682/0.04649	+0.97%	+20.8%	1e-4	+[**T572I**]
JN.1.8.1v	25828	153	0.6%	53/100	0.00443/0.00722	+0.28%	+38.7%	3e-3	+[**T572I**]-[+16MPLF][2]
JN.1.8.1v	25828	53	0.2%	18/35	0.00150/0.00253	+0.10%	+40.5%	7e-2	+[H146Q,**T572I**]
JN.1.7	25828	863	3.3%	328/535	0.02739/0.03862	+1.12%	+29.1%	5e-7	+[**T572I**,E1150D]
JN.1.7v	25828	86	0.3%	21/65	0.00175/0.00469	+0.29%	+62.6%	3e-5	+[**T572I**,E1150D]-[+16MPLF][2] Rare similar variants
JN.1.7v	25828	10	0.0%	1/9	0.00008/0.00065	+0.06%	+87.1%	2e-2	+[**T572I**,E1150D]-[R408S]
JN.1.9.1	25828	14	0.1%	6/8	0.00050/0.00058	+0.01%	+13.3%	1e+0	+[Q183H,**T572I**]
KQ.1	25828	62	0.2%	13/49	0.00109/0.00354	+0.25%	+69.3%	5e-5	+[**R346T**,**T572I**]
KQ.1v	25828	10	0.0%	2/8	0.00017/0.00058	+0.04%	+71.1%	1e-1	+[**R346T**,**T572I**]-[+16MPLF][2] Rare similar variants
JN.1.4.3	25828	18	0.1%	9/9	0.00075/0.00065	-0.01%	-13.5%	8e-1	+[**R346T**,**T572I**]-[K417N]
XDK.1	25828	11	0.0%	2/9	0.00017/0.00065	+0.05%	+74.3%	7e-2	+[V213E,**R346T**,**T572I**]-[V213G]
JN.1.6.1[4]	25828	276	1.1%	115/161	0.00960/0.01162	+0.20%	+17.4%	1e-1	+[**R346T**]
JN.1.6.1v	25828	52	0.2%	10/42	0.00084/0.00303	+0.22%	+72.5%	7e-5	+[**R346T**]-[+16MPLF][2] Rare similar variants
JN.1.4.4	25828	22	0.1%	0/22	0.00000/0.00159	+0.16%	+100.0%	1e-6	+[**R346T**]-[+16MPLF,R403K][2]
JN.1.13.1	25828	237	0.9%	76/161	0.00635/0.01162	+0.53%	+45.4%	8e-6	+[F59S,**R346T**,A1087S]
JN.1.13.1v	25828	15	0.1%	4/11	0.00033/0.00079	+0.05%	+57.9%	2e-1	+[F59S,**R346T**,A1087S]-[N679K] Rare similar variants
JN.1.13.1v	25828	14	0.1%	1/13	0.00008/0.00094	+0.09%	+91.1%	2e-3	+[F59S,**R346T**,A1087S]-[+16MPLF][2]
JN.1.16	25828	179	0.7%	45/134	0.00376/0.00967	+0.59%	+61.2%	6e-9	+[**F456L**]
JN.1.16v	25828	39	0.2%	18/21	0.00150/0.00152	+0.00%	+0.9%	1e+0	+[**F456L**]-[+16MPLF][2]
JN.1.11.1	25828	61	0.2%	9/52	0.00075/0.00375	+0.30%	+80.0%	2e-7	+[**F456L**,V1104L]
KP.1	25828	35	0.1%	19/16	0.00159/0.00116	-0.04%	-27.2%	4e-1	+[**F456L**,K1086R,V1104L]
KP.2	25828	32	0.1%	1/31	0.00008/0.00224	+0.22%	+96.3%	8e-8	+[**R346T**,**F456L**,V1104L]
KP.3	25828	16	0.1%	0/16	0.00000/0.00116	+0.12%	+100.0%	5e-5	+[**F456L**,Q493E,V1104L,V1228A] Rare similar variants
KP.1.1	25828	14	0.1%	2/12	0.00017/0.00087	+0.07%	+80.7%	2e-2	+[**R346T**,**F456L**,K1086R,V1104L]
KR.1	25828	21	0.1%	6/15	0.00050/0.00108	+0.06%	+53.7%	1e-1	+[**R346T**,**F456L**]
JN.1.20	25828	71	0.3%	27/44	0.00225/0.00318	+0.09%	+29.0%	2e-1	+[S31F]
XDD.1.1	25828	13	0.1%	4/9	0.00033/0.00065	+0.03%	+48.6%	3e-1	+[I584V,S704L]
XDD.1.1v	25828	16	0.1%	2/14	0.00017/0.00101	+0.08%	+83.5%	1e-2	+[I584V,S704L]-[+16MPLF][2]
JN.1.23	25828	11	0.0%	3/8	0.00025/0.00058	+0.03%	+56.6%	2e-1	+[K444R,Y453F] Rare, but with interesting mutations
JN.1.23	25828v	9	0.0%	2/7	0.00017/0.00051	+0.03%	+67.0%	2e-1	+[K444R]

Summary of recurrent mutations in JN.1 including in recombinant lineages.

Single recurrent mutations:

S:R346T recurs 15 times + 1 time S:R346K + 1 time S:R346S

S:T572I recurs 9 times

S:F456L recurs 6 times + 2 times S:F456V

S:S680F recurs 3 times + 1 time S680Y

Double recurrent mutations:

S:R346T adds S:F456L 3 times

S:T572I adds S:R346T 3 times, adds S346K 1 time

S:F456L adds S:R346T 3 times

To count a recurrent mutation it must be sampled at least 10 times.

Recurrent Spike mutations within JN.1

R346T: - Enhanced RBD stability while maintaining the intraprotomer down state.

Zhang… Acharya, Cryo-EM structures of SARS-CoV-2 Omicron XBB.1.5, XBB.1.16 and EG.5 spike ectodomains, submitted.

- Enhanced entry and neutralization resistance in an XBB.1.5 backbone

Dadonaite … Bloom,   bioRxiv . 2023 Nov 14:2023.11.13.566961.

- R346T confers resistance to Class 3 antibodies

Wang… Ho et al. Volume 186, Issue 2, 19 January 2023, Pages 279-286.e8

T572I: - Increased ACE2 binding and cell entry in XBB.1.5 and BA.2, enhanced antibody sensitivity in XBB.1.5

Dadonaite … Bloom,   bioRxiv . 2023 Nov 14:2023.11.13.566961

F456L: Note: L455F/**F456L** were the FLip mutations that were highly selected in XBB.1.5 lineages
and in later BA.2 sub lineages prior to JN.1's expansion

- F456L alone decreases RBD stability, but in JN.1 lineages it comes up in the context of L455S

Zhang… Acharya, Cryo-EM structures of SARS-CoV-2 Omicron XBB.1.5, XBB.1.16 and EG.5 spike ectodomains, submitted.

- In XBB.1.5, both L455S and F456L increase immune evasion, and decrease ACE2 binding
In BA.2, L455S and F456L both decreased ACE2 binding, but while F456L decreased entry, L455S did not.

Dadonaite … Bloom,   bioRxiv . 2023 Nov 14:2023.11.13.566961.
Kosugi… Ito The Lancet Microbe 11 January 2024

S680F: Proximal to furin cleavage site
Increased ACE2 binding and decreased cell entry in a BA.2 backbone, little impact in XBB.1.5

Dadonaite … Bloom,   bioRxiv . 2023 Nov 14:2023.11.13.566961

Summary of recurrent mutations within the JN.1 lineage and their global rate of increase between 2023-10-01 - 2024-03-31

SPIKE T572I

SPIKE R346T

SPIKE F456L

Established in 35 countries and significantly increasing in 30/35

Established in 32 countries and significantly increasing in 25/32.

Established in 19 countries and increasing in 18/19 rapidly in Singapore (30%) and China (8%).

The combination of R346T and F456L is increasing fast in countries where it is present
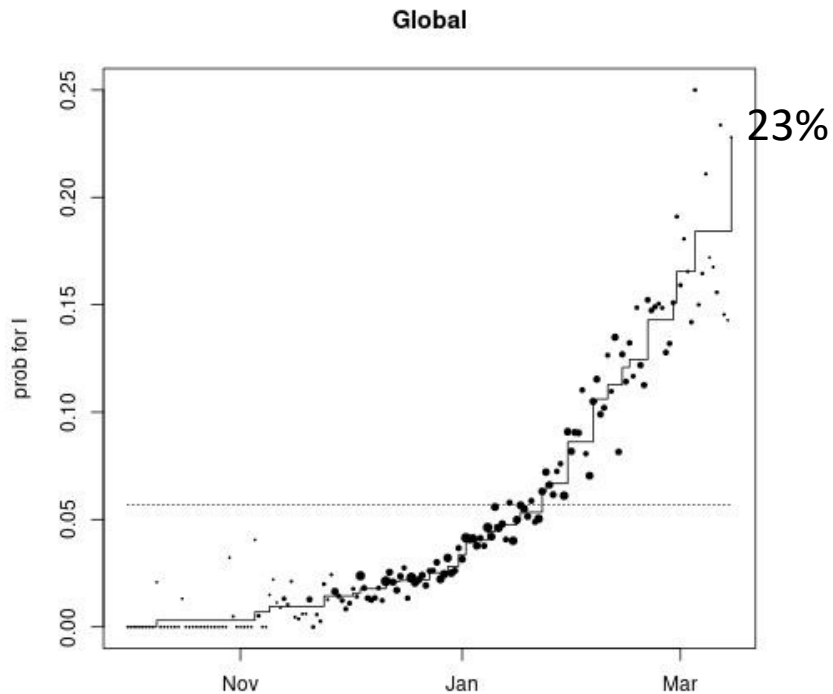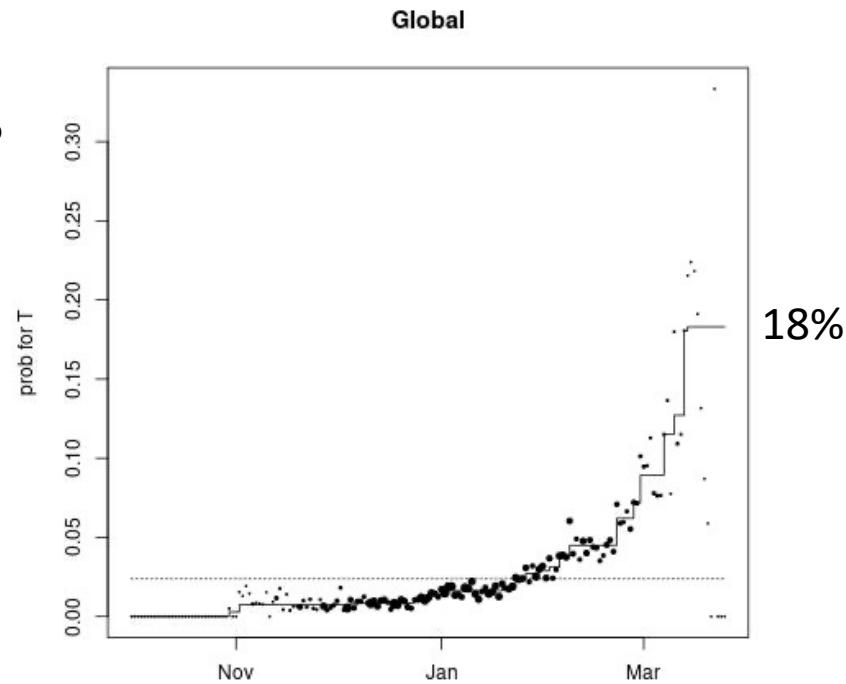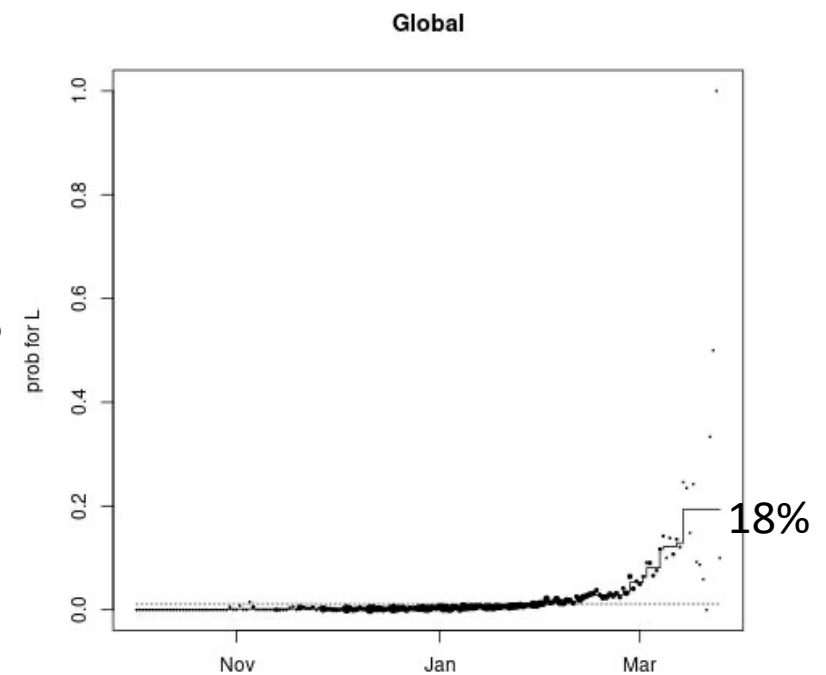
	# LT	# Others	Total	LT/Total (%)	# days	Time window	p-val
Canada	31	14019	14050	0.22	152	158	0.00249
Japan	22	2746	2768	0.79	139	156	0.00249
Nigeria	11	134	145	7.59	20	30	0.14925
Singapore	30	3244	3274	0.92	131	153	0.00249
USA	227	51228	51455	0.44	163	165	0.00249
United-Kingdom	72	12764	12836	0.56	155	164	0.00249

Position: SPIKE 456 L, SPIKE 346 T
Assumption: Test amino acid form is increasing over time
Correlated variant: Do not consider. Include all sequences
Range of dates: 2023-10-01 - 2024-03-15
Pango lineage designation in GISAID : all JN.1 sublineages
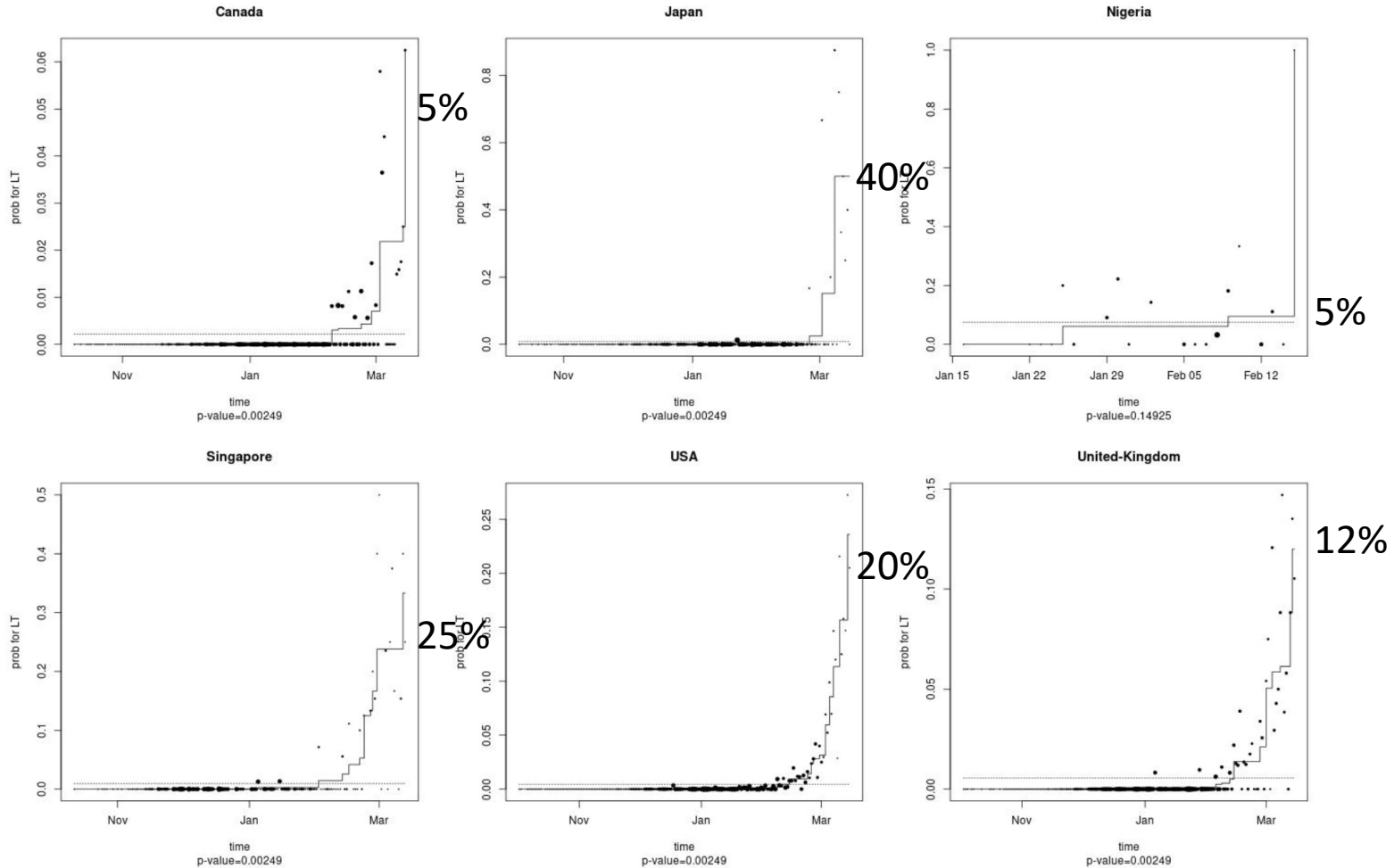
The plots to the relative frequency of R346T and F456L in combination per day

Tracking convergence

i) Based on our full GISAID alignments and the UShER-based Pango nomenclature (used to recapitulate the tree), we define all Spike mutations that give rise to lineages that are sampled:

>100x, beginning to be established and spread
> 10x, suggesting at least transmission in a local outbreak (viable)

We then track their number of recurrences, and their total numbers.

ii) Candidates for positive selection:

- Highly recurrent mutations
- Mutations that happen just once but then give rise to a dominant sublineage
- Sites that take on multiple amino acid changes

XBB.1.5 and BA.2 lineages have additional phenotypic data for mutations

Full-spike deep mutational scanning helps predict the evolutionary success of SARS-CoV-2 clades

Sera escape (XBB.1.5 only):

- The mutations that escape neutralization by sera from humans who were multiply vaccinated and recently infected by XBB or one its descendant lineages (XBB*)
- Escape at each site was averaged across sera collected from 10 individuals
- Escape mutations can have very different effects across sera

Entry (XBB.1.5 and BA.2):

- They measured the effects of all library mutations on spike-mediated cell entry in 293T-ACE2 cells
- Library design favors functionally tolerated mutations in spike, so most just slightly impaired cell entry

ACE2 binding (XBB.1.5 and BA.2):

There are several distinct mechanisms that could affect what they define as ACE2 binding:
- direct changes in RBD-ACE2 binding affinity,
- changes in spike that modulate the conformation of the RBDs, e.g. up/down movements,
- ACE2-induced shedding of the S1 subunit.

XBB.1.5
Candidate sites for positive selection among the 190,933 lineage sequences

A. Convergence: Repeated mutations initiating a clade of >100 sequences,
B. Expansion: A single sublineage of >950 sequences (0.5%)

Number of repeated Mutations   Counts   Dadonaite… Bloom*

	site	mutation	c100 parent lineages	c100 child lineages	c10 parent lineages	c10 child lineages	lineage sequences	total sequences	wuhan ancestral	clade founder	mutant	human sera escape	spike mediated entry	ACE2 binding	region
A	456	**F456L**	**5**	**8**	**8**	**23**	**4815**	**37184**	F	F	L	0.2001	-0.02328	-0.3013	**RBD**
	478	T478R	6	7	**16**	**33**	1104	6671	T	K	R	0.02994	0.03784	-0.09573	**RBD**
	475	**A475V**	**3**	**3**	**7**	**10**	**4430**	**15192**	A	A	V	0.1601	0.02726	-0.7293	**RBD**
	621	P621S	1	3	1	4	730	1997	P	P	S	-0.1209	0.01162	-0.1898	other
	883	T883I	2	3	5	12	1075	3594	T	T	I	0.07632	-0.1008	-0.1625	S2
	455	**L455F**	**2**	**2**	**3**	**3**	246	**15837**	L	L	**F**	0.1516	0.1212	-0.9594	**RBD**
	511	V511I	2	2	2	2	604	2032	V	V	I		-0.05504	-0.09951	RBD
	573	**T573I**	**2**	**2**	**2**	**4**	**3990**	**10743**	T	T	I	-0.02976	0.07914	-0.07144	other
B	704	**S704L**	**1**	**1**	**2**	**4**	**278**	**10377**	S	S	**L**	-0.05457	0.07445	0.2691	S2
	1045	K1045R	1	1	1	1	1170	3448	K	K	R	0.05959	-0.06603	-0.1069	S2
	146	H146K	1	1	16	62	1156	3322	H	Q	K	-0.06804	0.05065	-0.02033	NTD
	323	T323I	1	1	4	6	635	2546	T	T	I	-0.137	-0.257	-0.1482	other
	248	Y248H	1	1	2	2	1071	2272	Y	Y	H	-0.02197	-0.1426	0.036	NTD
	410	I410V	1	1	1	1	850	1880	I	I	V	-0.08488	-0.07955	0.2584	**RBD**
	978	N978S	1	1	1	1	618	1736	N	N	S	-0.1159	-0.1005	-0.1391	S2
	554	E554K	1	1	8	10	271	1345	E	E	K	0.08039	-0.0152	-0.1947	other
	748	E748V	1	1	1	1	774	1322	E	E	V	0.07404	0.06399	-0.4767	S2
	1181	K1181I	1	1	1	1	492	1249	K	K	I	-0.003512	-0.1511	0.04976	S2
	675	Q675H	1	1	2	3	229	1209	Q	Q	H	-0.001338	-0.3333	-0.1003	other
	147	K147I	1	1	1	1	579	1142	K	K	I	-0.06132	0.03518	0.1232	NTD

**Full-spike deep mutational scanning helps predict the evolutionary success of SARS-CoV-2 clades

Parent versus child lineages

The number of recurrent F456L mutations that gave rise to established lineages sampled >100s would be between 5 and 8

site mutation

	parent lineages	child lineages
455 L455F	2	2
456 F456L	5	8

5 is a minimum number of recurrences within XBB.1.5, as 5 different lineages are involved that have at least one F456L emerge in a distinct virus.

XBB.1.5->XBB.1.5.59
XBB.1.5->XBB.1.5.70
XBB.1.5->XBB.1.5.10
XBB.1.5->XBB.1.5.72

XBB.1.5.102->JD.1

XBB.1.5.73->GN.1

FD.1->FD.1.1

FD.5 ->FD.5.1

		Counts in GISAID as of 2024/02/25
XBB	Recombinant of BJ.1 and BM.1.1.1 with breakpoint in S1, USA and Singapore	
XBB.1	Mostly Bangladesh and Singapore, defined by S:G252V	
XBB.1.5	USA, S:F486P	
XBB.1.5.59	add S:F456L (T22928C), ORF1a:S2822P, England	1704
XBB.1.5.70	add S:F456L (T22928C), S:L455F (G22927T), ORF1a:A4068S, Brazil,	1210
XBB.1.5.10	add S:F456L (T22928C), USA-NC	2998
XBB.1.5.72	add S:F456L (T22928C), ORF1a:G445S, T9823C, T10204C, South America	2390
XBB.1.5.102	C6896T, C14085T, C19488T, Brazil-Amazonas	29
JD.1 +	Alias of XBB.1.5.102.1, S:L455F (G22927T), S:F456L (T22928C), A14634G, T28282C, Brazil,	14681
XBB.1.5.73	T28271C, USA/Peru	91
GN.1+	Alias of XBB.1.5.73.1, S:F456L (T22928C), Peru/Costa Rica	1939
FD.5*	Alias of XBB.1.5.15.5, ORF10:A8V, Peru	166
FD.5.1	Alias of XBB.1.5.15.5.1, S:F456L (T22928C), S:N185D, Peru	357
FD.1	Alias of XBB.1.5.15.1, ORF7b:E3*, England/Canada	207
FD.1.1	Alias of XBB.1.5.15.1.1, S:F456L (T22928C), Canada-QC	2149

*FD.5 is noted in UShER Pango designations, but not yet in GISAID

XBB.1.5, continued

We also track all of the lineages where the mutations are found

site	mutation	c100 parent lineages	c100 child lineages	c10 parent lineages	c10 child lineages	lineage sequences	total sequences	wuhan ancestral	clade founder	mutant	human sera escape	spike mediated entry	ACE2 binding	region	Codon	Transition Transversion	AA change	lineage_transitions
456	F456L	5	8	8	23	4815	37184	F	F	L	0.2001	-0.02328	-0.3013	RBD	TTT->CTT	TC	F->L	XBB.1.5.102->JD.1, XBB.1.5->XBB.1.5.70, XBB.1.5->XBB.1.5.10, XBB.1.5.73->GN.1, XBB.1.5->XBB.1.5.72, FD.1->FD.1.1, FD.5->FD.5.1, XBB.1.5->XBB.1.5.59
478	T478R	6	7	16	33	1104	6671	T	K	R	0.02994	0.03784	-0.09573	RBD	AAA->AGA	AG	K->R	XBB.1.5->XBB.1.5.27, XBB.1.5.48->GV.1, XBB.1.5.95->HS.1, XBB.1.5.68->HZ.1, FK.2->FK.2.1, XBB.1.5->XBB.1.5.49,
475	A475V	3	3	7	10	4430	15192	A	A	V	0.1601	0.02726	-0.7293	RBD	GCC-> GTC	CT	A->V	GK.3->GK.3.1, JD.1->JD.1.1, GK.1->GK.1.8
621	P621S	1	3	1	4	730	1997	P	P	S	-0.1209	0.01162	-0.1898	other	CCT-> TCT	CT	P->S	XBB.1.5->XBB.1.5.91, XBB.1.5->XBB.1.5.50, XBB.1.5->XBB.1.5.90
883	T883I	2	3	5	12	1075	3594	T	T	I	0.07632	-0.1008	-0.1625	S2	ACT-> ATT	CT	T->I	XBB.1.5->XBB.1.5.32, XBB.1.5.17->FH.1, XBB.1.5->XBB.1.5.4
455	L455F	2	2	3	3	246	15837	L	L	F	0.1516	0.1212	-0.9594	RBD	TTG -> TTT	GT	L->F	XBB.1.5.102->JD.1, XBB.1.5->XBB.1.5.70
511	V511I	2	2	2	2	604	2032	V	V	I		-0.05504	-0.09951	RBD	GTA -> ATA	GA	V->I	XBB.1.5.70->GK.2, XBB.1.5->XBB.1.5.71
573	T573I	2	2	2	4	3990	10743	T	T	I	-0.02976	0.07914	-0.07144	other	ACT _> ATT	CT	T->I	XBB.1.5->XBB.1.5.1, GK.1->GK.1.1
704	S704L	1	1	2	4	278	10377	S	S	L	-0.05457	0.07445	0.2691	S2	TCA -> TTA	CT	S -> L	XBB.1.5.70->GK.1
1045	K1045R	1	1	1	1	1170	3448	K	K	R	0.05959	-0.06603	-0.1069	S2	AAG -> AGG	AG	K -> R	XBB.1.5->XBB.1.5.37
146	H146K	1	1	16	62	1156	3322	H	Q	K	-0.06804	0.05065	-0.02033	NTD	CAA -> AAA	CA	H -> K	XBB.1.5.15->FD.2
323	T323I	1	1	4	6	635	2546	T	T	I	-0.137	-0.257	-0.1482	other	ACA -> ATA	CT	T -> I	XBB.1.5->XBB.1.5.12
248	Y248H	1	1	2	2	1071	2272	Y	Y	H	-0.02197	-0.1426	0.036	NTD	TAT -> CAT	TC	Y -> H	JD.1.1->JD.1.1.1
410	I410V	1	1	1	1	850	1880	I	I	V	-0.08488	-0.07955	0.2584	RBD	ATC -> GTC	AG	I -> V	EU.1->EU.1.1
978	N978S	1	1	1	1	618	1736	N	N	S	-0.1159	-0.1005	-0.1391	S2	AAT -> AGT	AG	N -> S	XBB.1.5->XBB.1.5.35
554	E554K	1	1	8	10	271	1345	E	E	K	0.08039	-0.0152	-0.1947	other	GAG -> AAG	GA	E -> K	GK.1->GK.1.8
748	E748V	1	1	1	1	774	1322	E	E	V	0.07404	0.06399	-0.4767	S2	GAA -> GTA	AT	E -> V	XBB.1.5.24->GF.1
1181	K1181I	1	1	1	1	492	1249	K	K	I	-0.003512	-0.1511	0.04976	S2	AAA -> ATA	AT	K -> I	XBB.1.5->XBB.1.5.5
675	Q675H	1	1	2	3	229	1209	Q	Q	H	-0.001338	-0.3333	-0.1003	other	CAG -> CAT	GT	Q -> H	XBB.1.5.14->EL.1
147	K147I	1	1	1	1	579	1142	K	K	I	-0.06132	0.03518	0.1232	NTD	AAA -> ATA	AT	K -> I	XBB.1.5->XBB.1.5.2

A475V: GK.3 -> GK.3.1, JD.1 -> JD.1.1, and GK.1 -> GK.1.8

Three separate lineages that each independently acquired A475V in a sublineage that sampled >100 times and came to be the dominant form

GK.3 GK.1 and JD.1 all only carry ancestral A475 when sampled in May-June.
All three lineages pick up A475V, and the A475V-carrying sublineages begin to expand in July

GK.3 -> GK.3.1

GK.1 -> GK.1.8
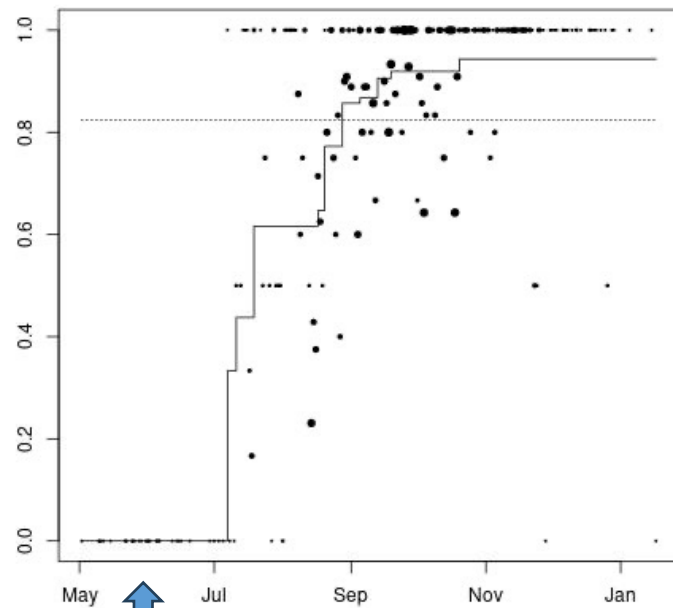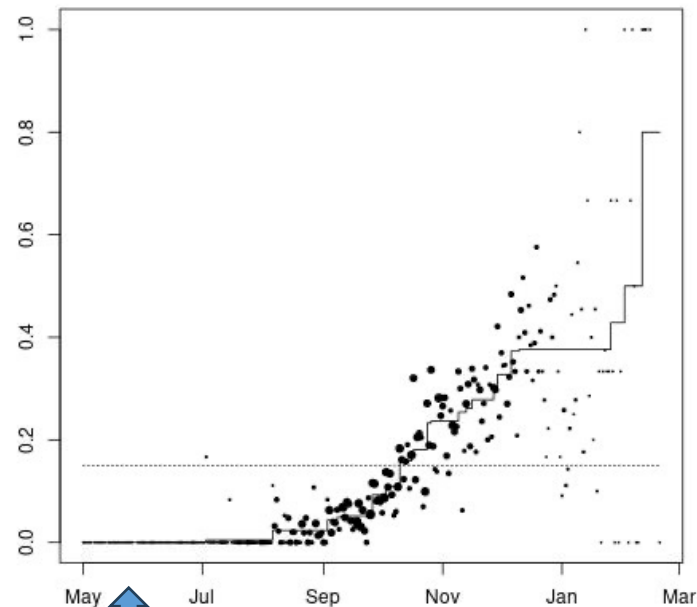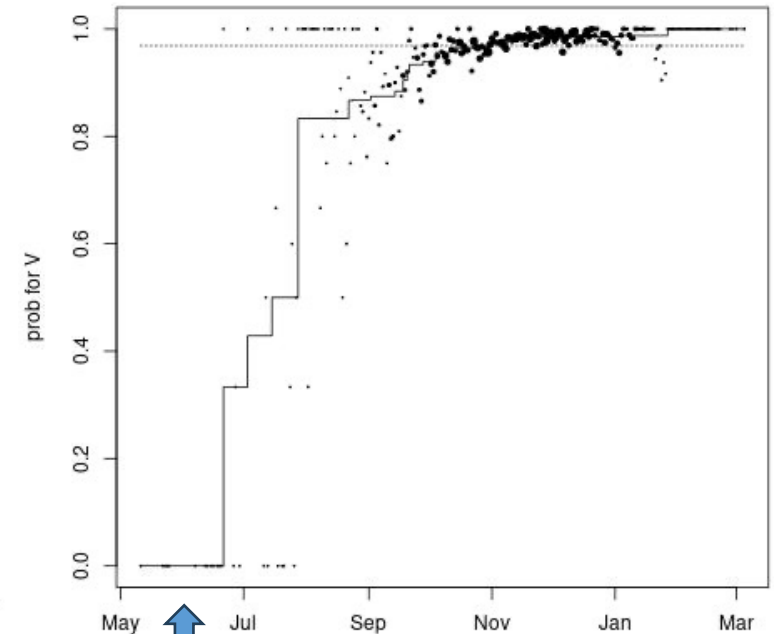
JD.1 -> JD.1.1

14987 JD.1, JD.1.1, JD.1.1.1, JD.1.1.2, JD.1.1.3 sequences

Range of dates: 2023-05-01 - 2024-03-20
These forms are no longer or rarely sampled after Jan because of being replaced the JN.1 global sweep

RBD XBB.1.5 C100 vs escape

C100 child
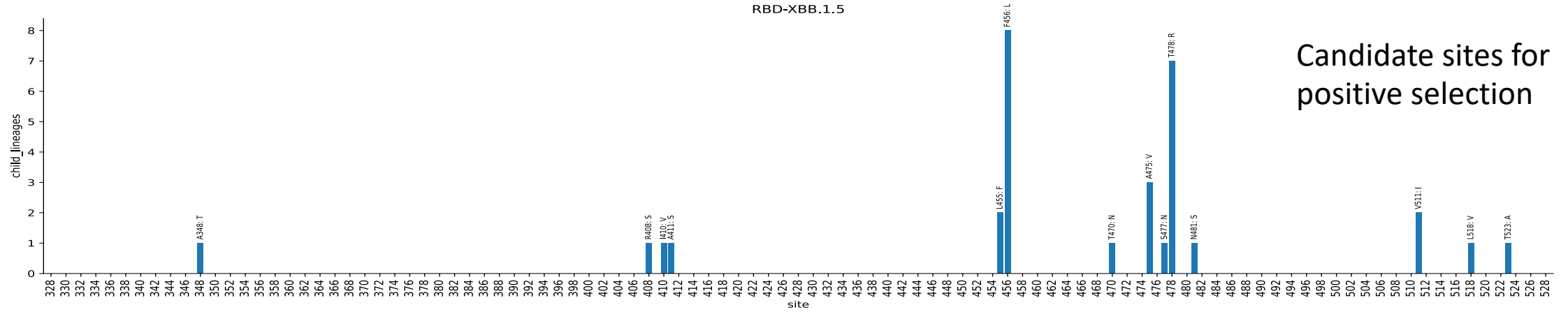
Candidate sites for positive selection

Positive escape
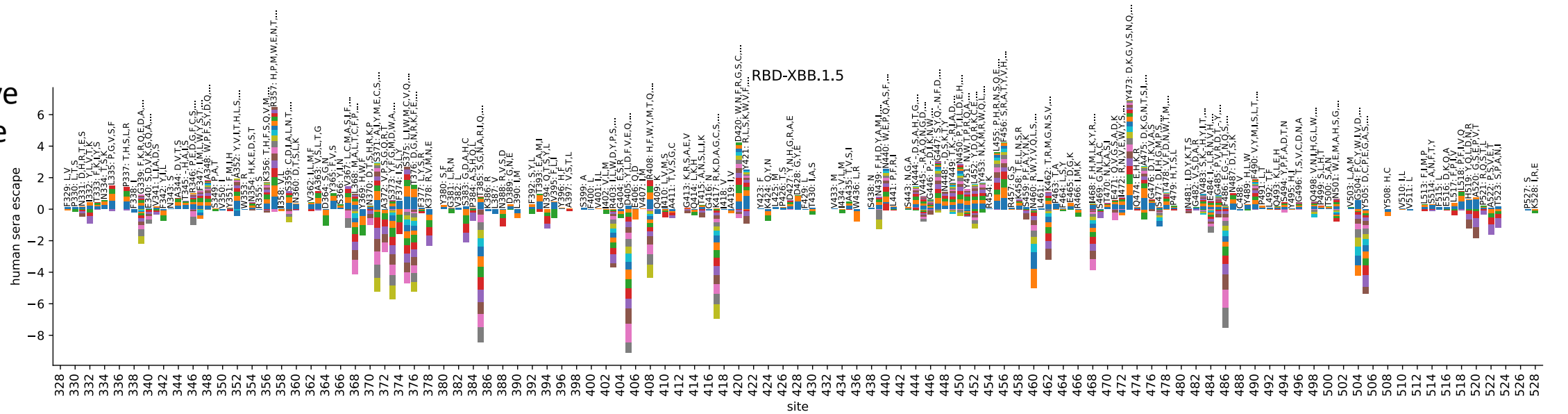
357   420   440   455,456   473   Dadonaite, strongest escape

RBD XBB.1.5 C100 vs escape
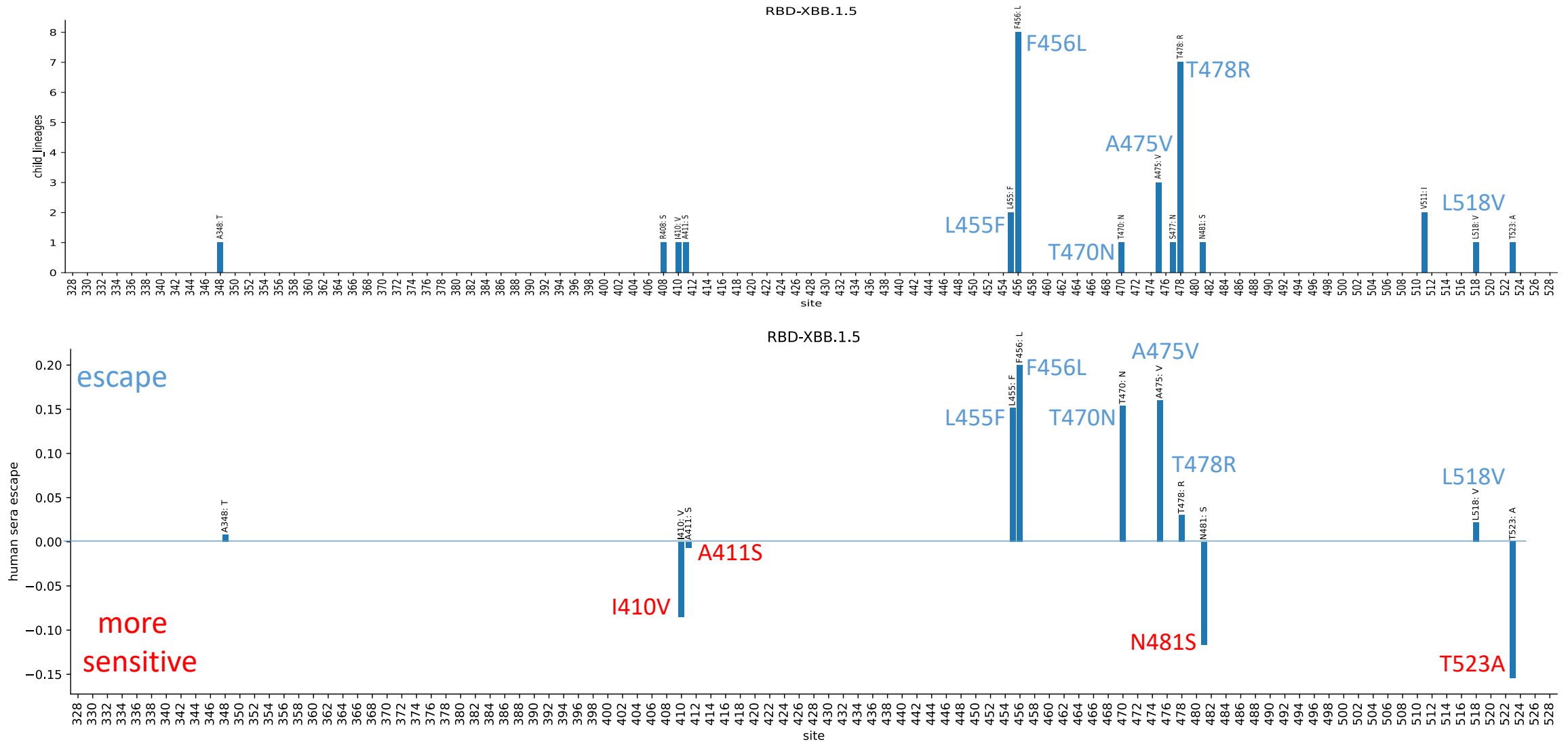
Dadonaite et al. found the most resistance conferring sites in the RBD included 357, 371, 420, the 440-447 loop, 455-456, and 473. Of these, only 455-456 were repeatedly selected, however T470N, A475V, T478R, L518V conferred some resistance.

RBD XBB.1.5 Escape vs ACE2 and entry

More neutralization resistant
  - reduced ACE2 binding
  - enhanced cell entry

More neutralization sensitive
  - bound ACE2 more tightly
  - but had reduced Spike mediated entry
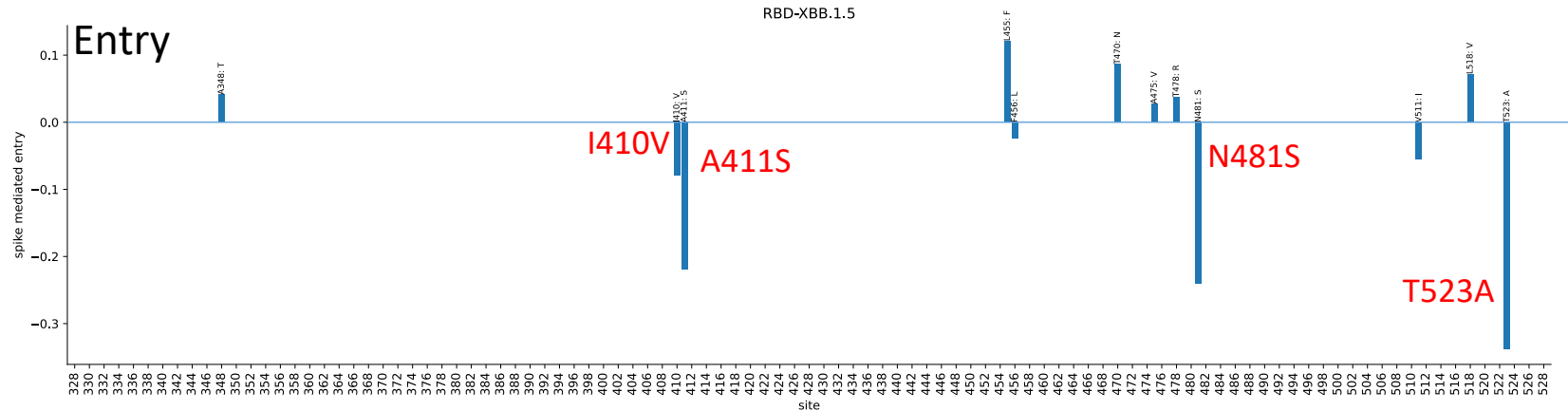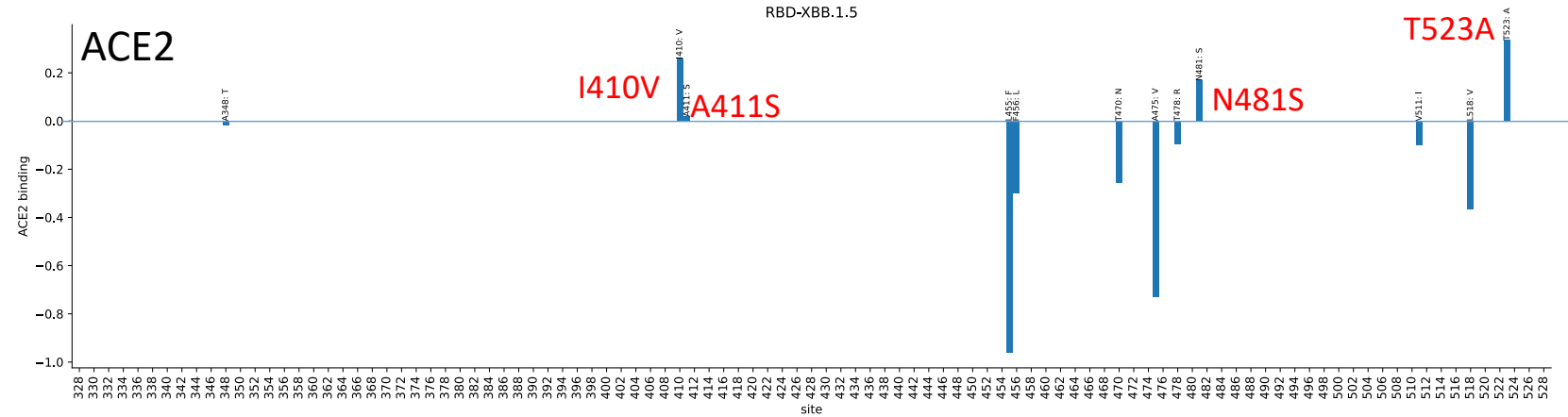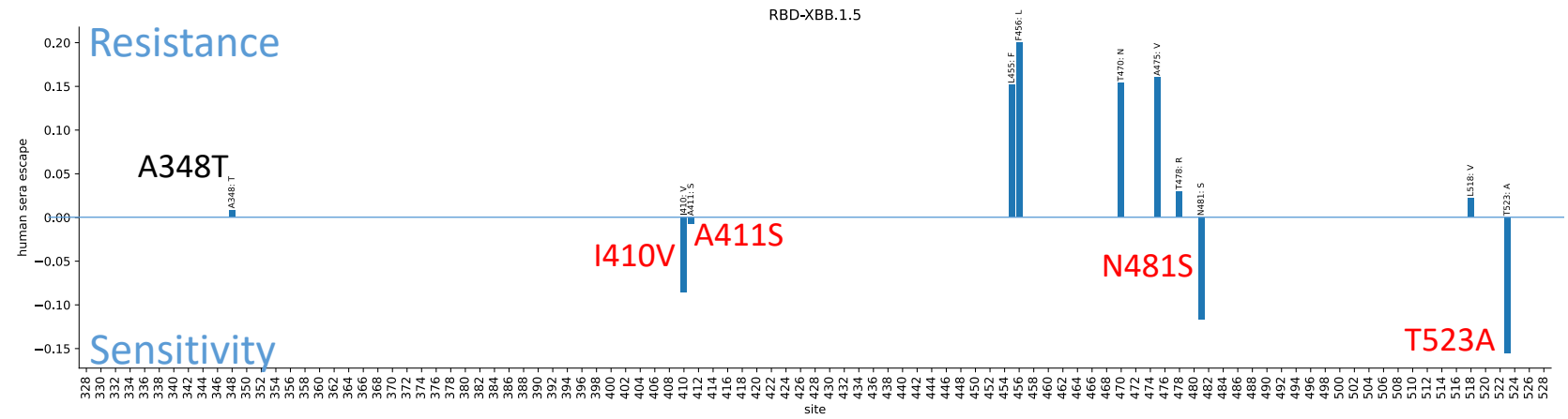
Foreshadowing

A variant capable of a global selective sweep is generally highly enriched for recurrent mutations evident *prior* to its emergence
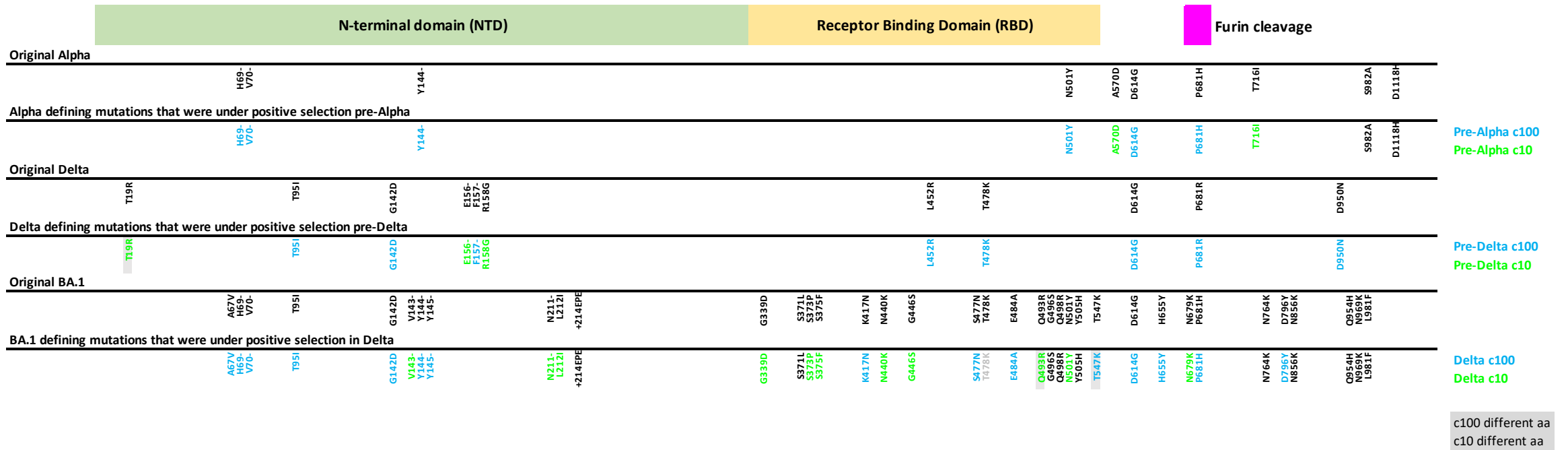
BA.2.86 carried 19 sites that were found to have repeat mutations that arose independently in BA.2
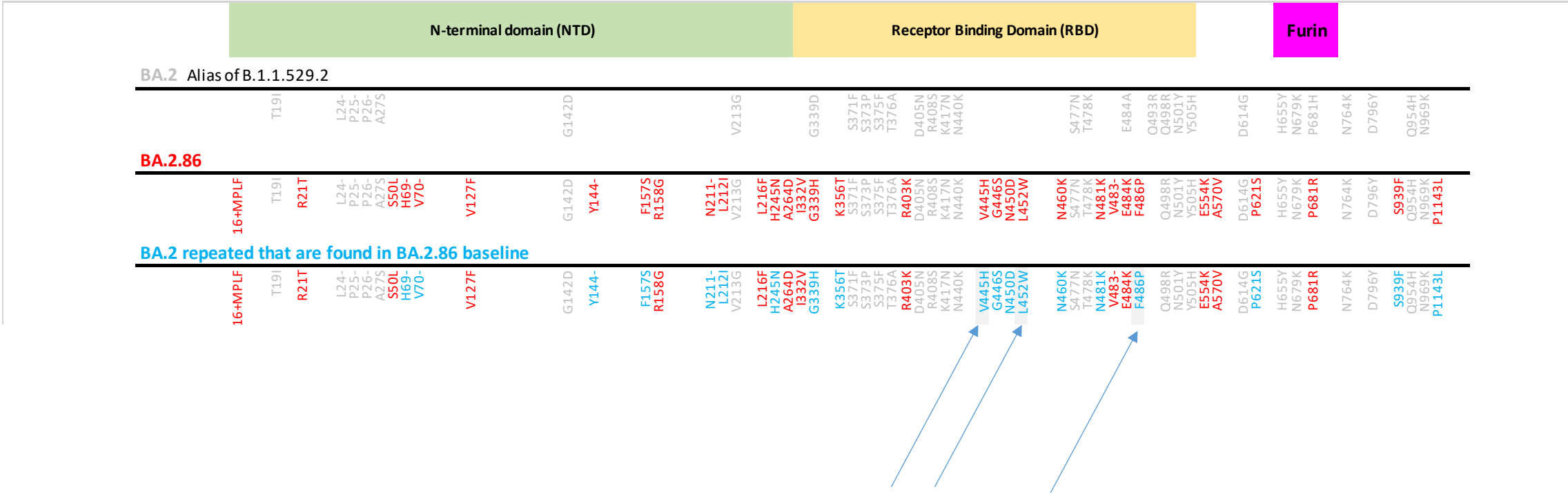
Sometime the sites had multiple or distinct mutations in BA.2.86 relative to those in BA.2. These are denoted with gray fill.

BA.2.86 lineage repeat mutations all also arose independently in other BA.2 lineages

N-terminal domain (NTD)	Receptor Binding Domain (RBD)	Furin

BA.2 Alias of B.1.1.529.2

T19I • L24- P25- P26- A27S • G142D • V213G • G339D • S371F S373P S375F T376A • D405N R408S K417N N440K • S477N T478K • E484A • Q493R Q498R N501Y Y505H • D614G • H655Y N679K P681H • N764K • D796Y • Q954H N969K

BA.2.86

16+MPLF • T19I R21T • L24- P25- P26- A27S S50L H69- V70- • V127F • G142D Y144- • F157S R158G • N211- L212I V213G • L216F H245N A264D I332V G339H • K356T S371F S373P S375F T376A R403K D405N R408S K417N N440K • V445H G446S N450D L452W • N460K S477N T478K N481K V483- E484K F486P • Q498R N501Y Y505H E554K A570V • D614G P621S • H655Y N679K P681R • N764K • D796Y • S939F Q954H N969K P1143L

BA.2 repeated that are found in BA.2.86 baseline

16+MPLF • T19I R21T • L24- P25- P26- A27S S50L H69- V70- • V127F • G142D Y144- • F157S R158G • N211- L212I V213G • L216F H245N A264D I332V G339H • K356T S371F S373P S375F T376A R403K D405N R408S K417N N440K • V445H G446S N450D L452W • N460K S477N T478K N481K V483- E484K F486P • Q498R N501Y Y505H E554K A570V • D614G P621S • H655Y N679K P681R • N764K • D796Y • S939F Q954H N969K P1143L

BA.2.86 repeated mutations were also all found repeated in BA.2

16+MPLF • T19I R21T • L24- P25- P26- A27S S50L H69- V70- • V127F • G142D Y144- • F157S R158G • N211- L212I V213G • L216F H245N A264D I332V G339H R346T K356T S371F S373P S375F T376A R403K D405N R408S K417N N440K • V445H G446S N450D L452W L455S F456L N460K S477N T478K N481K V483- E484K F486P • Q498R N501Y Y505H E554K A570V T572I • D614G P621S • H655Y N679K P681R • N764K • D796Y • S939F Q954H N969K P1143L M1229I

Another clade, BA.2.87.1 was detected in South Africa last fall that hasn't expanded beyond 9 initial samples.

It only carried 10 BA.2 commonly repeated mutations, while JN.1 carried 20.

JN.1, 20 BA.2 Convergent sites

BA.87.1, 10 BA.2 Convergent sites
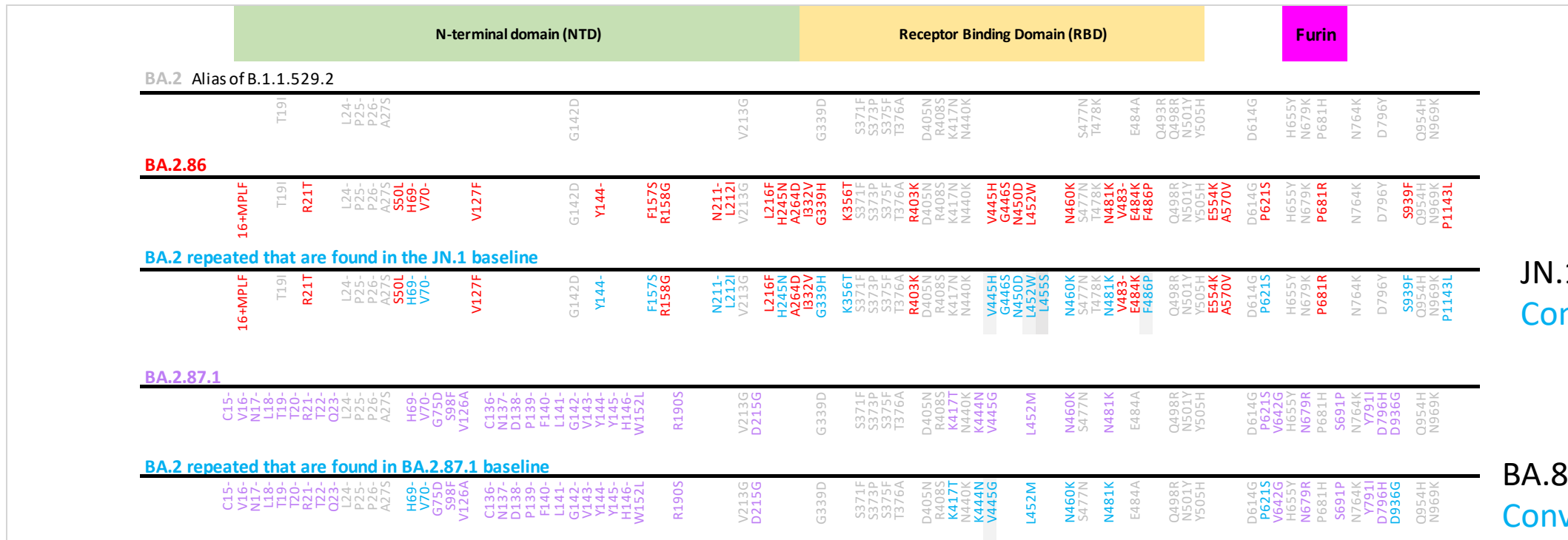
Tracking a the most highly recurrent mutation site in lineages Omicron: R346 K/T/S/I

BA.1 starts out with ancestral Spike R346

Here are all the lineages which had a mutation that changed the amino acid at R346
BA.1 is the only Omicron lineage that favors variants with **R346K**

BA.1 lineages and Spike 346

Grey R346 Ancestral

BA.1, BA.1.15, BA.1.17.2, BA.1.17, BA.1.20, BA.1.15.1, BA.1.16, BA.1.14, BA.1.21, BA.1.13.1, BA.1.14.1, BA.1.1.10, BA.1.13, BA.1.18, BA.1.19, BA.1.15.2, BA.1.10, BA.1.12, BA.1.1.9, BA.1.17.1, BA.1.9, BA.1.8, BA.1.5, BA.1.14.2, BA.1.3, BA.1.1.8, BA.1.1.7, BA.1.6, BA.1.1.17, BA.1.4, BA.1.7, BA.1.21.1, BA.1.1.3, BA.1.16.1, BA.1.15.3, BA.1.22, BA.1.16.2, BA.1.2, BD.1

R346T
BA.1.23, BA.1.24

R346K
BA.1.1, BA.1.1.2, BA.1.1.18, BA.1.1.1, BA.1.1.14, BA.1.1.15, BA.1.1.13, BA.1.1.12, BA.1.1.16, BA.1.1.11, BA.1.1.4, BA.1.1.6, BA.1.1.9, BA.1.1.8, BA.1.1.7, BA.1.1.17, BA.1.1.5, BA.1.1.3, BC.1, BC.2

BA.1 is essentially replaced by BA.2

Global: 2504340 sequences

BA.1
R346K

BA.1
R346

Weekly Sequence Counts

Fraction

Weekly Cases

1e8

2021-12-01 to 2022-05-01

BA.2
R346K
R346T A very rare BA.1 lineage form
R346

BA.1
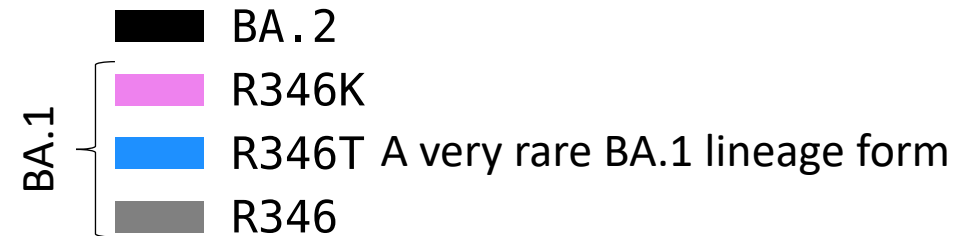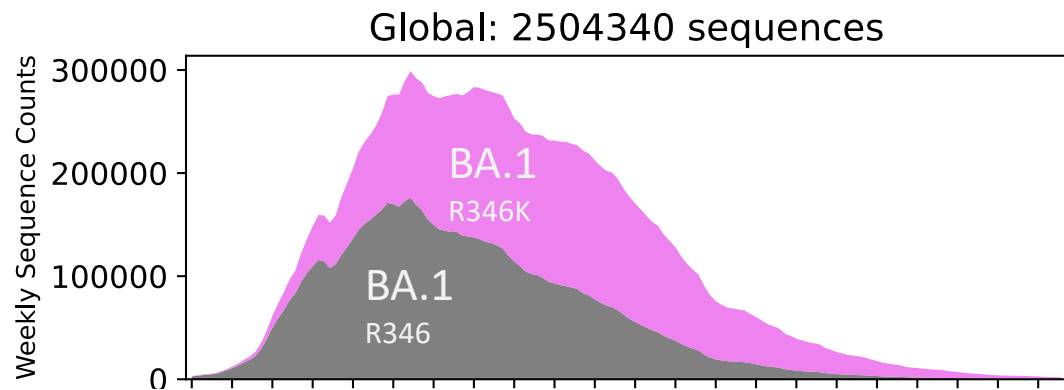
BA.1 starts with ancestral R346

R346 transitions to R346K

As BA.2 globally replaces BA.1, most BA.1 variants that persist into the Spring of 2022 carry R346K.

Fraction

2021-12-01 to 2022-05-01
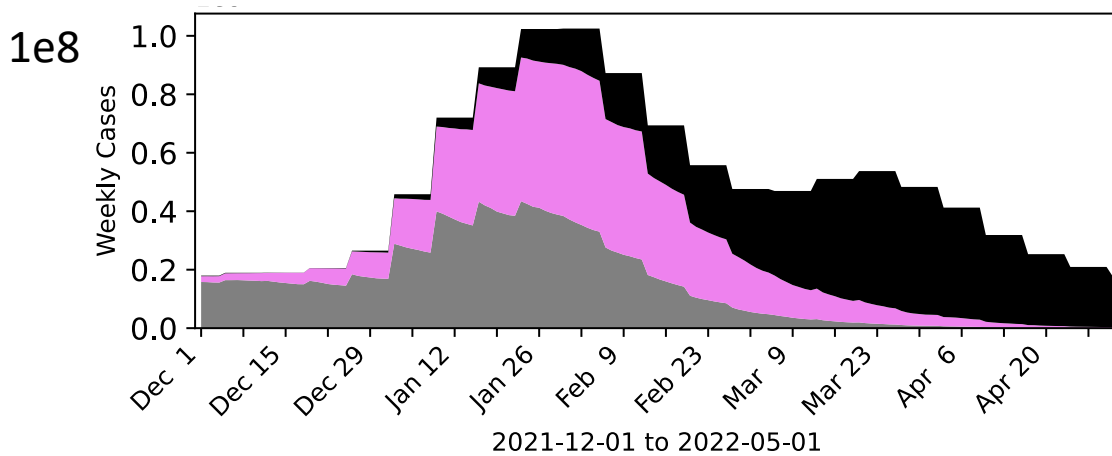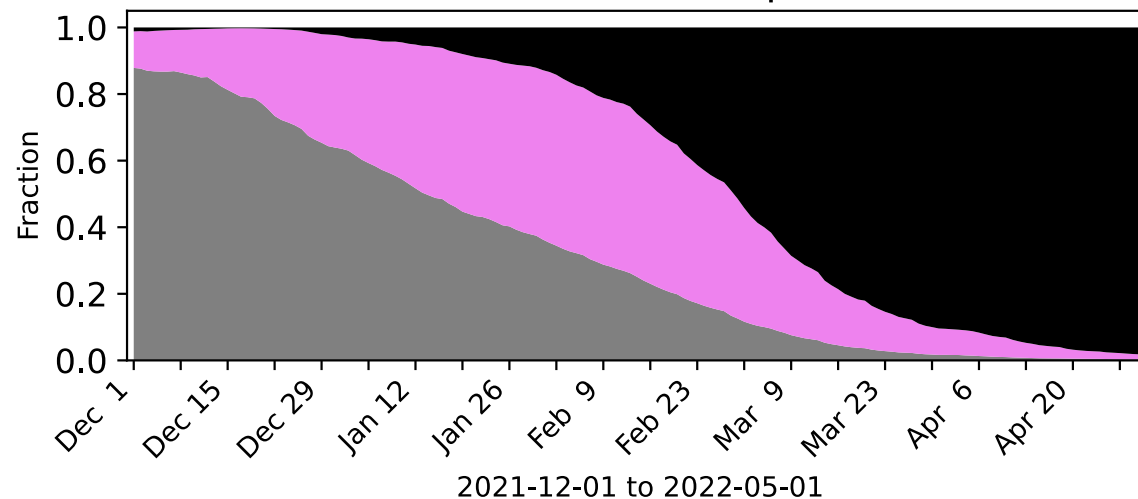
The peak of the Omicron pandemic in early 2022 is dominated by BA.1 enriched for R346K.

BA.2 starts out with ancestral R346

Here are all the lineages which had a mutation changed the amino acid at R346

BA.2 R346

BA.2, BA.2.1, BA.2.10, BA.2.10.1, BA.2.10.2, BA.2.10.3, BA.2.10.4, BA.2.11, BA.2.12, BA.2.12.1, BA.2.12.2, BA.2.13, BA.2.13.1, BA.2.14, BA.2.15, BA.2.16, BA.2.17, BA.2.18, BA.2.19, BA.2.2, BA.2.20, BA.2.21, BA.2.22, BA.2.23, BA.2.23.1, BA.2.24, BA.2.25, BA.2.25.1, BA.2.26, BA.2.27, BA.2.28, BA.2.29, BA.2.3, BA.2.3.1, BA.2.3.10, BA.2.3.11, BA.2.3.12, BA.2.3.13, BA.2.3.14, BA.2.3.15, BA.2.3.16, BA.2.3.17, BA.2.3.18, BA.2.3.19, BA.2.3.2, BA.2.3.20, BA.2.3.21, BA.2.3.4, BA.2.3.5, BA.2.3.6, BA.2.3.7, BA.2.3.8, BA.2.3.9, BA.2.30, BA.2.31, BA.2.31.1, BA.2.32, BA.2.33, BA.2.34, BA.2.35, BA.2.36, BA.2.37, BA.2.38, BA.2.38.1, BA.2.38.2, BA.2.38.3, BA.2.38.4, BA.2.39, BA.2.4, BA.2.40, BA.2.40.1, BA.2.41, BA.2.42, BA.2.43, BA.2.44, BA.2.45, BA.2.46, BA.2.47, BA.2.48, BA.2.49, BA.2.5, BA.2.50, BA.2.51, BA.2.52, BA.2.53, BA.2.54, BA.2.55, BA.2.56, BA.2.56.1, BA.2.57, BA.2.58, BA.2.59, BA.2.6, BA.2.60, BA.2.61, BA.2.62, BA.2.63, BA.2.64, BA.2.65, BA.2.66, BA.2.67, BA.2.68, BA.2.69, BA.2.7, BA.2.70, BA.2.71, BA.2.72, BA.2.73, BA.2.75, BA.2.75.1, BA.2.75.10, BA.2.75.3, BA.2.75.4, BA.2.75.5, BA.2.75.8, BA.2.77, BA.2.78, BA.2.79, BA.2.79.1, BA.2.8, BA.2.81, BA.2.83, BA.2.85, BA.2.86, BA.2.86.1, BA.2.86.2, BA.2.86.3, BA.2.86.4, BA.2.86.5, BA.2.87.1, BA.2.9, BA.2.9.1, BA.2.9.2, BA.2.9.3, BA.2.9.5, BA.2.9.6, BA.2.9.7, BG.1, BG.2, BG.3, BG.4, BG.5, BG.6, BG.7, BH.1, BL.3, BL.4, BM.1, BM.3, BM.4, BM.4.1, BM.5, BM.6, BN.2, BN.2.1, BN.3, BN.3.1, BN.4, BN.5, BN.6, BP.1, BR.1, BR.1.1, BR.1.2, BR.4, BR.5, BR.5.1, BY.1.1, CM.1, CM.10CM.12, CM.2, CM.2.1, CM.3, CM.4, CM.4.1, CM.5, CM.5.1, CM.5.2, CM.6, CM.6.1, CM.7, CM.7.1, CM.7.1.1, CM.8, CM.8.1, CM.8.1.1, CM.8.1.2, CM.8.1.3, CM.8.1.4, CM.8.1.5, CM.9, DV.1, DV.1.1, DV.2, DV.3, DV.3.1, DV.4, DV.5, DV.6, DV.6.1, DV.6.2, DV.7, DV.7.1

R346K

BA.2.2.1

R346I

BL.5

R346T all others

BA.2.3.22, BA.2.74, BA.2.75.2, BA.2.75.6, BA.2.75.7, BA.2.75.9, BA.2.76, BA.2.76.1, BA.2.76.2, BA.2.80, BA.2.82, BA.2.9.4, <u>BJ.1</u>, BL.1, BL.1.1, BL.1.2, BL.1.3, BL.1.4, BL.1.5, BL.2, BL.2.1, BL.6, BM.1.1, <u>**BM.1.1.1**</u>, BM.1.1.2, BM.1.1.3, BM.1.1.4, BM.1.1.5, BM.2, BM.2.1, BM.2.2, BM.2.3, BM.4.1.1, BN.1, BN.1.1, BN.1.1.1, BN.1.10, BN.1.11, BN.1.2, BN.1.2.1, BN.1.2.2, BN.1.2.3, BN.1.2.4, BN.1.2.5, BN.1.2.6, BN.1.2.7, BN.1.3, BN.1.3.1, BN.1.3.10, BN.1.3.11, BN.1.3.12, BN.1.3.13, BN.1.3.2, BN.1.3.3, BN.1.3.4, BN.1.3.5, BN.1.3.6, BN.1.3.7, BN.1.3.8, BN.1.3.9, BN.1.4, BN.1.4.1, BN.1.4.2, BN.1.4.3, BN.1.4.4, BN.1.4.5, BN.1.5, BN.1.5.1, BN.1.5.2, BN.1.6, BN.1.7, BN.1.8, BN.1.9, BR.2, BR.2.1, BR.3, BS.1, BS.1.1, BS.1.2, BY.1, BY.1.1.1, BY.1.2, BY.1.2.1, CA.1, CA.2, CA.3, CA.3.1, CA.4, CA.5, CA.6, CA.7, CB.1, CJ.1, CJ.1.1, CJ.1.2, CJ.1.3, CJ.1.3.1, CJ.1.3.2, CM.11, CV.1, CV.2, DD.1, DS.1, DS.2, DS.3, DV.7.1.1, DV.7.1.2, DV.7.1.3, DV.7.2, DV.8, EJ.1, EJ.2, EJ.3, EP.1, EP.1.1, EP.1.1.1, EP.2, FJ.1, FK.1, FK.1.1, FK.1.1.1, FK.1.1.2, FK.1.2, FK.1.2.1, FK.1.2.2, FK.1.3, FK.1.3.1, FK.1.3.2, FK.1.4, FK.1.4.1, FK.1.5, FR.1, FR.1.1, FR.1.2, FR.1.3, FR.1.4, FR.1.5, FR.2, FS.1, FV.1, GP.1, GP.2, GP.3, GQ.1, GQ.1.1, JL.1,

R346T CH.1

CH.1, CH.1.1, CH.1.1.1, CH.1.1.10, CH.1.1.11, CH.1.1.12, CH.1.1.13, CH.1.1.14, CH.1.1.15, CH.1.1.16, CH.1.1.17, CH.1.1.18, CH.1.1.19, CH.1.1.2, CH.1.1.20, CH.1.1.21, CH.1.1.22, CH.1.1.23, CH.1.1.24, CH.1.1.25, CH.1.1.26, CH.1.1.27, CH.1.1.28, CH.1.1.29, CH.1.1.3, CH.1.1.30, CH.1.1.31, CH.1.1.32, CH.1.1.4, CH.1.1.5, CH.1.1.6, CH.1.1.7, CH.1.1.8, CH.1.1.9, CH.2, CH.3, CH.3.1

XBB all have R346T

XBB is a BA.2 recombinant: BJ.1 (Alias of B.1.1.529.2.10.1.1) and BM.1.1.1 (Alias of B.1.1.529.2.75.3.1.1.1) with breakpoint in S1
JN.1 clears all XBB and BA.2 lingering lineages with a global sweep, it starts out with ancestral R346
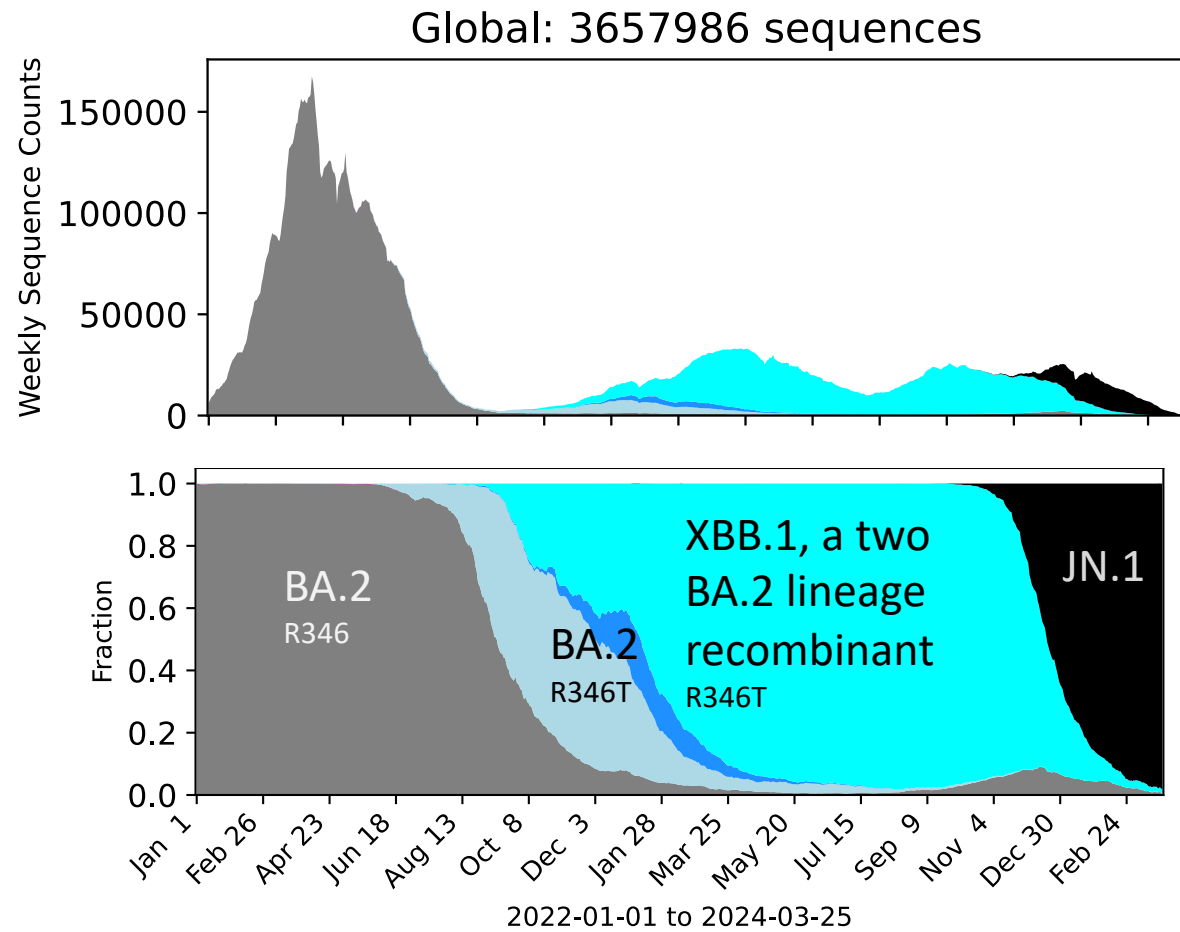
BA.2: still going...

XBB and JN are both BA.2 lineage

Legend:
- JN.1 (black)
- R346Y-All-XBB (cyan)
- R346T-CH.1 (blue)
- R346T-other (light blue)
- R346I-BL.5 (green)
- R346K-BA.2.2.1 (purple)
- BA.2 (gray)

BA.1
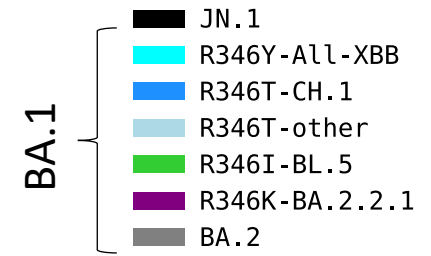
BA.2 starts with ancestral R346

R346 recurrently transitions to within BA.2 R346T,
CH.1 R346T a particularly common BA.2 sublineage
arises but there is a global transition to the BA.2
recombinant XBB.1 lineages are beginning to be favored.

The later lineages had many spike changes relative to BA.2

CH.1.1
+[K147E,W152R,F157L,I210V,G257S,G339H,R346T,K444T,G446S
,L452R,N460K,F486S]-[G339D,Q493R]

XBB.1.5/1.9
+[V83A,Y144del,H146Q,Q183E,V213E,G252V,G339H,R346T,L368I,V445P
,G446S,N460K,F486P,F490S]-[V213G,G339D,Q493R]

JN.1 made a selective sweep to a highly mutated BA.2 form
That did not carry R346T

Global: 3657986 sequences

Weekly Sequence Counts: 150000, 100000, 50000, 0

Fraction: 1.0, 0.8, 0.6, 0.4, 0.2, 0.0

BA.2
R346

BA.2
R346T

XBB.1, a two
BA.2 lineage
recombinant
R346T

JN.1

X-axis: Jan 1, Feb 26, Apr 23, Jun 18, Aug 13, Oct 8, Dec 3, Jan 28, Mar 25, May 20, Jul 15, Sep 9, Nov 4, Dec 30, Feb 24

2022-01-01 to 2024-03-25

JN.1: R346T is just beginning to expand
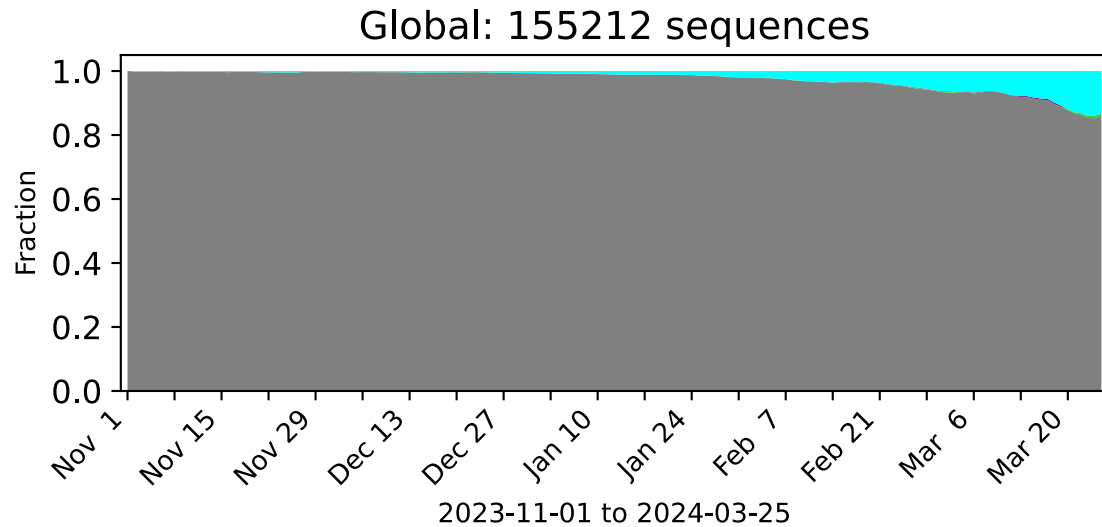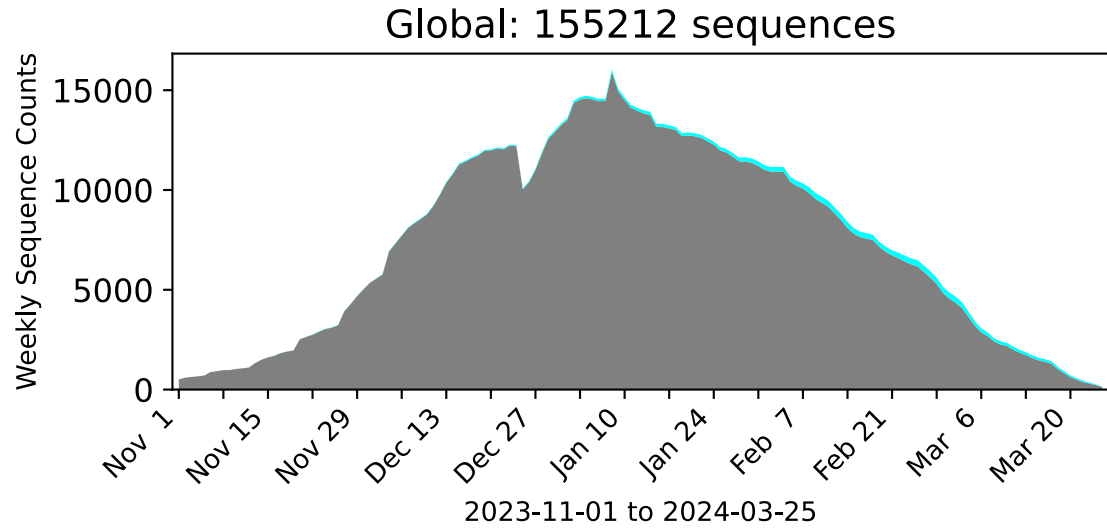
Global: 203846 sequences
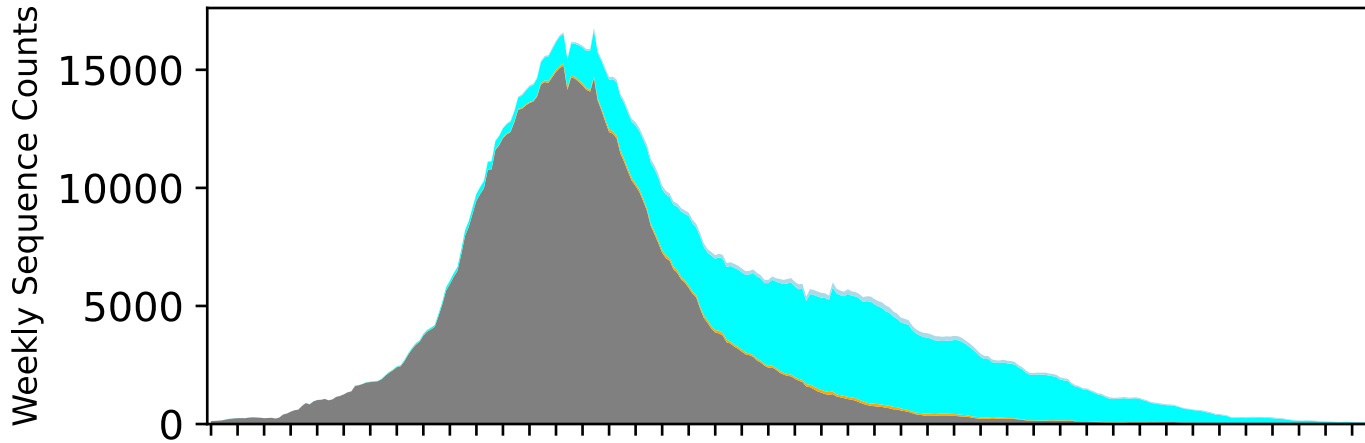
BA.4

- R346T/other-BA.4
- R346T/BA.4.6
- R346S
- R346/BA.4
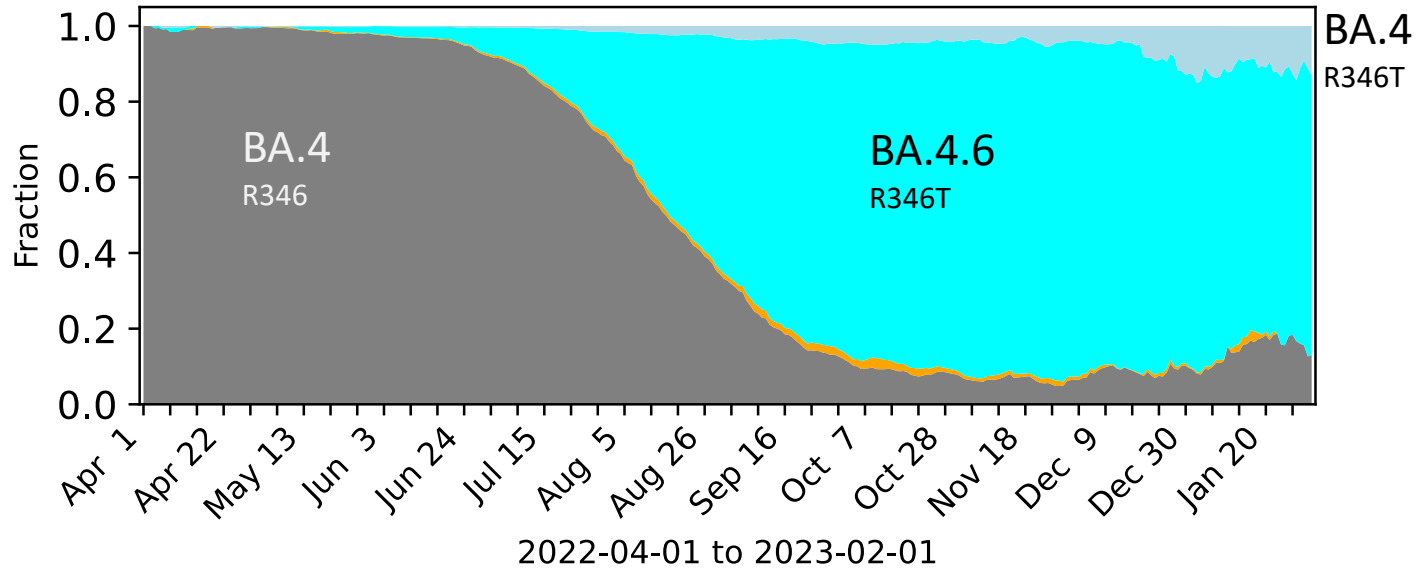
BA.4 and BA.4.6 relative to BA.5:

BA.4 adds N658S
BA.4.6 adds N658S + T346T

BA.5

Global: 2345023 sequences
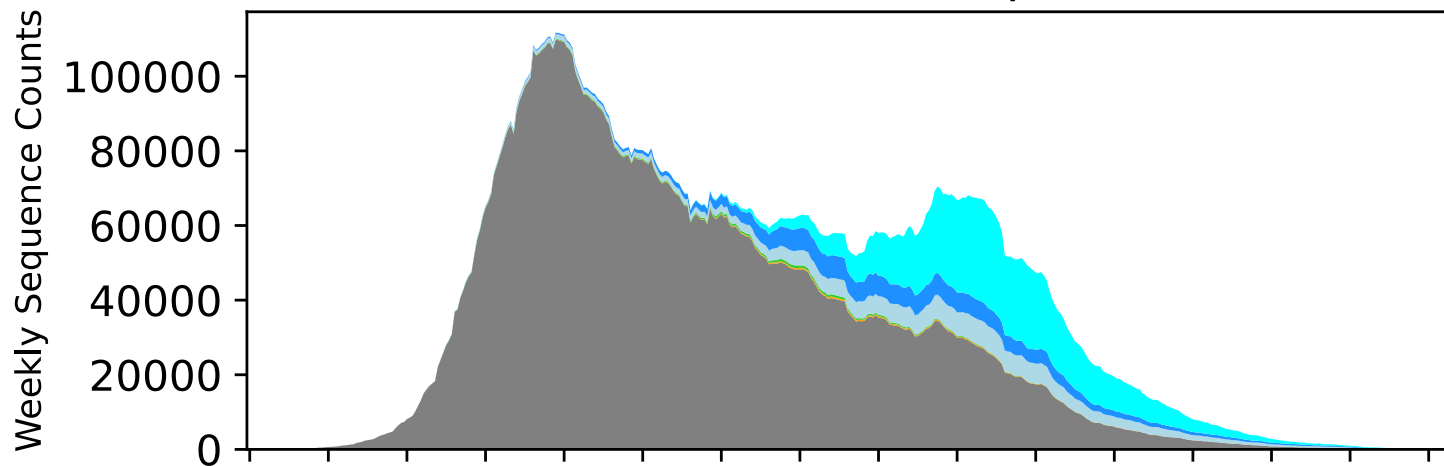
Legend:
- R346T-BQ.1.1
- R346T-BF.7
- R346T-other-BA.5
- R346I
- R346S
- R346/BA.5

Global: 2345023 sequences

BA.5 R346

BQ.1.1 R346T

BF.7

Other BA.5

2022-04-01 to 2023-06-01
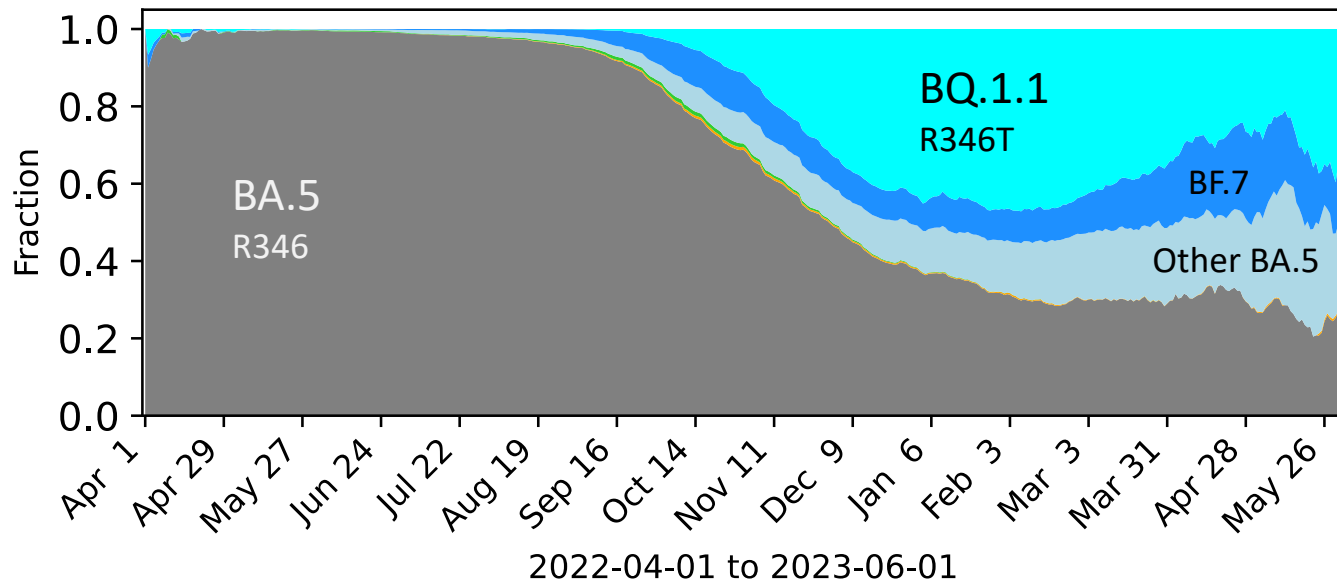
Global: 2862977 sequences

XBB

2022-04-01 to 2023-06-01
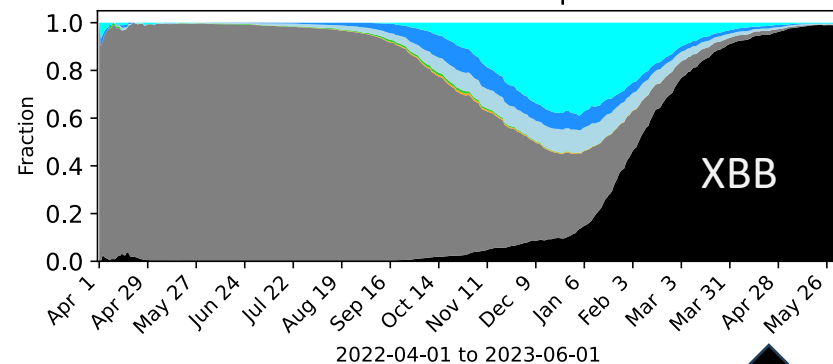
XBB.1 lineage is replacing BA.5

Philippines → Australia
New Zealand

XBC

Global: 6305 sequences
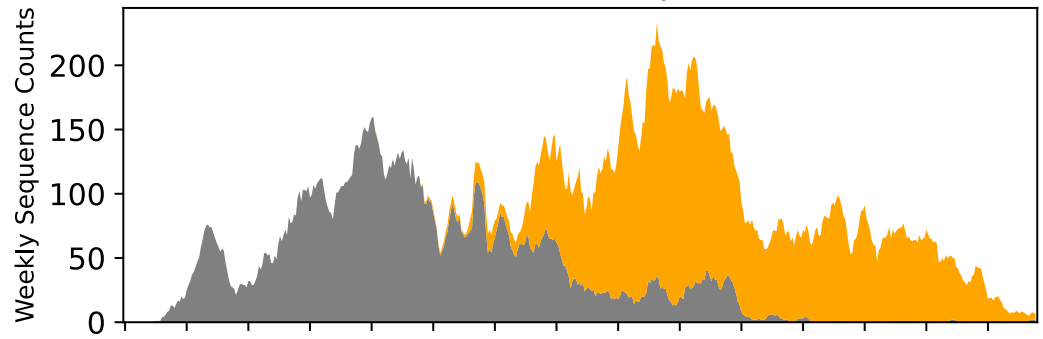
R346S
R346

Oceania: 4456 sequences
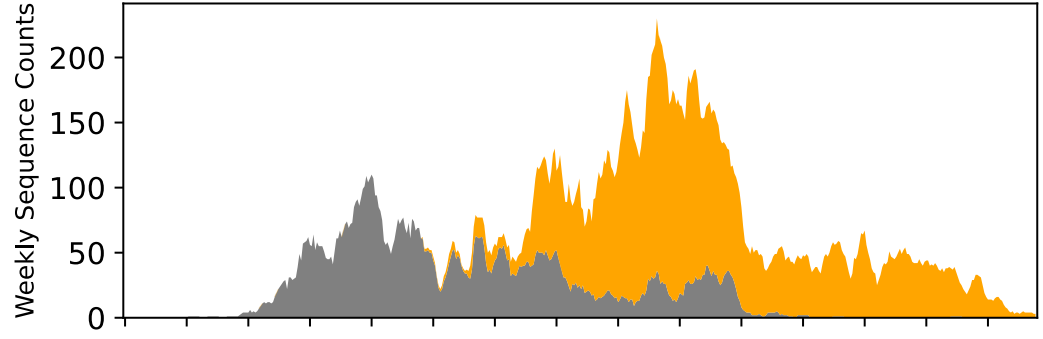
Oceania: 4456 sequences

XBC
R346

XBC
R346T

2022-08-01 to 2023-12-31
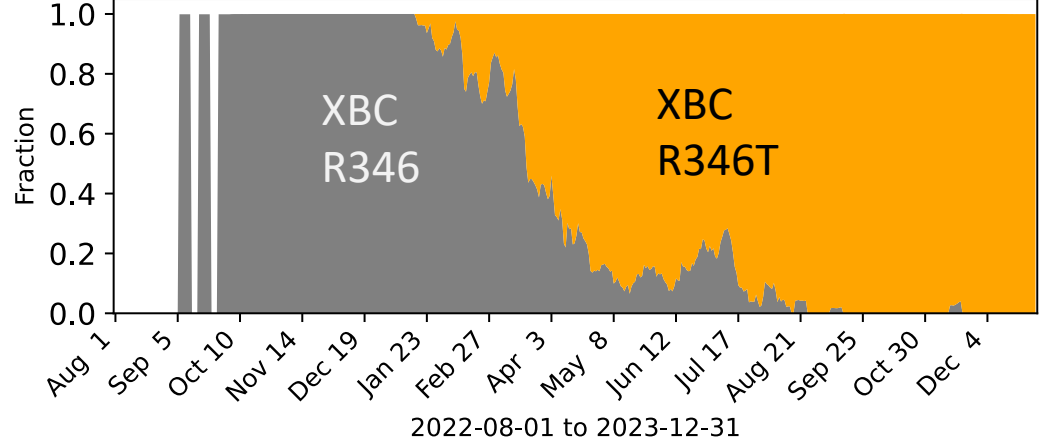
XBC.1.6
Global: 3248640 sequences

2022-08-01 to 2023-12-31
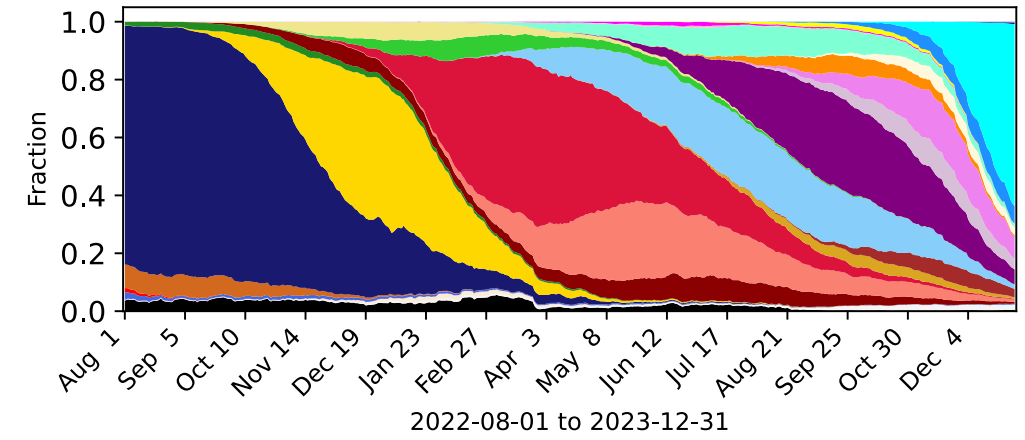
Oceania: 114225 sequences

XBC.1.6

2022-08-01 to 2023-12-31
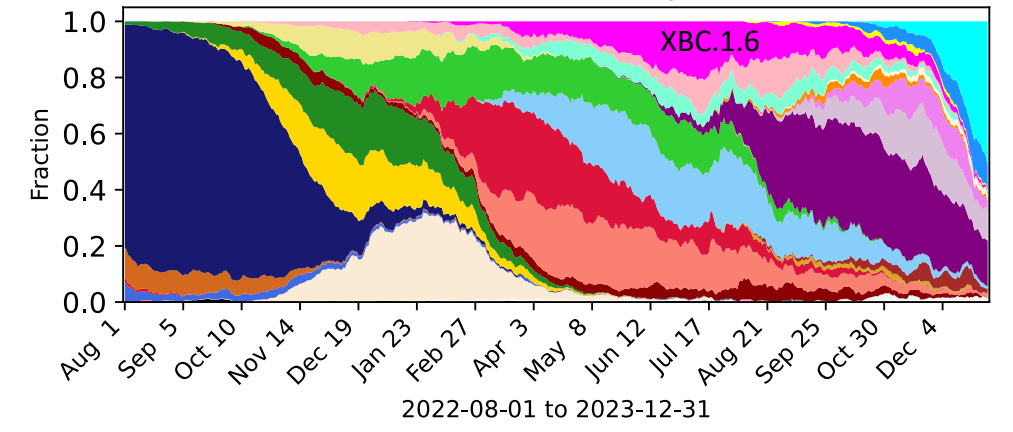
HIV-1 Nomenclature
and comparisons to SARS-CoV-2

HIV-1 nomenclature proposal

D L Robertson, J P Anderson, J A Bradac, J K Carr, B Foley, R K Funkhouser, F Gao, B H Hahn, M L Kalish, C Kuiken, G H Learn, T Leitner, F McCutchan, S Osmanov, M Peeters, D Pieniazek, M Salminen, P M Sharp, S Wolinsky, B Korber

HIV-1 Nomenclature Proposal

A Reference Guide to HIV-1 Classification

https://www.hiv.lanl.gov/content/sequence/HIV/COMPENDIUM/1999/6/nomenclature.pdf

Groups: The three distantly related "groups" of HIV-1 viruses that have been previously established are **M (for main), N (for non-M, non-O), and O (for outlier) (**[2]**)**. If new groups are discovered, they should be named by continuing through the alphabet: P, Q, R, etc.

• **Subtypes** will continue to refer to the distinctive lineages within group M, the group of viruses that dominates the AIDS pandemic. The subtype designations A to D, F to H, J, and the newly defined K ([3]) will be retained. As new subtypes are discovered, they will be named by continuing through the alphabet, so that there could eventually be a group M, subtype N virus (written M:N when a distinction is required).

• **Sub-subtype** designations will be used to describe distinctive lineages that are not genetically distant enough to justify designating a new subtype. For example, distinct lineages that form sister clades within subtype F have been named sub-subtypes F1 and F2.

• **Recombinant viruses that are epidemic strains will be called circulating recombinant forms (CRFs)** and numbered sequentially, with the first fully sequenced virus of a CRF serving as the prototype. There are currently four defined CRFs. For example, CRF02_AG (IbNg) refers to the second CRF that was defined; it is common in parts of Africa and contains regions that resemble A and G subtypes, with a prototype sequence called IbNg. Mosaic viruses with regions that resemble four or more subtypes will be called complex, and designated cpx.

HIV-1 Nomenclature Proposal, based on diversity circa 1999: Nine major clades, and 4 circulating recombinant forms
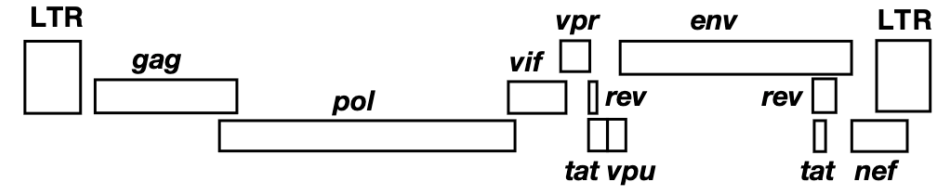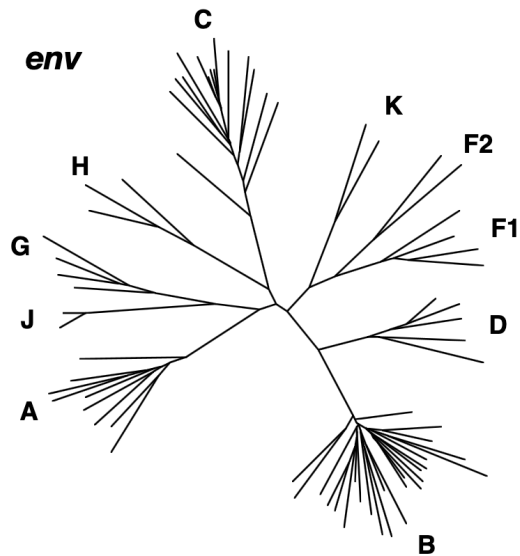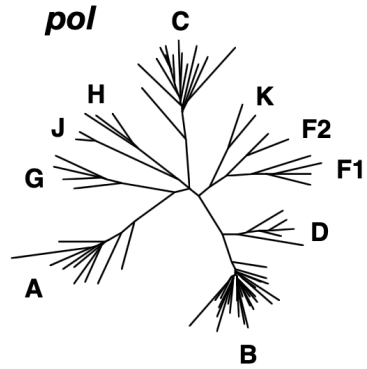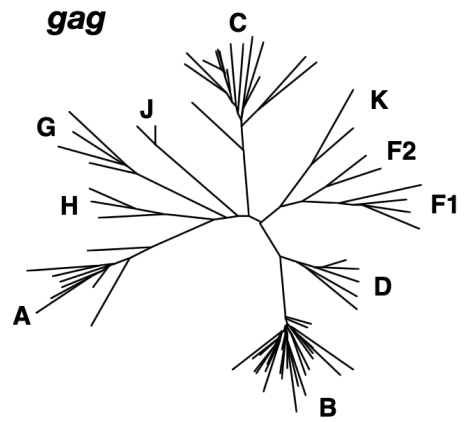
Brian Foley, HIV Database

HIV−1 M group

Pairwise Transitions and Transversions vs. F84 Distances
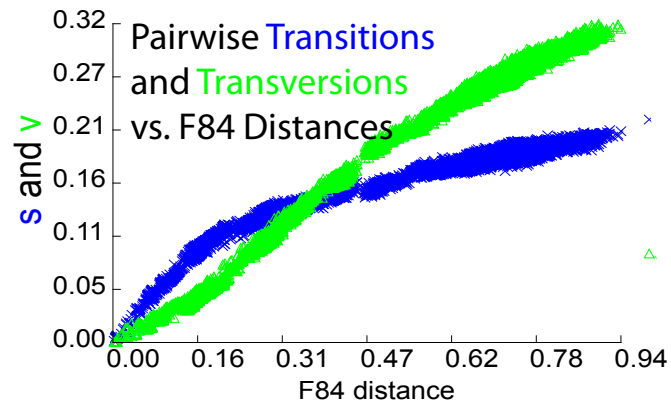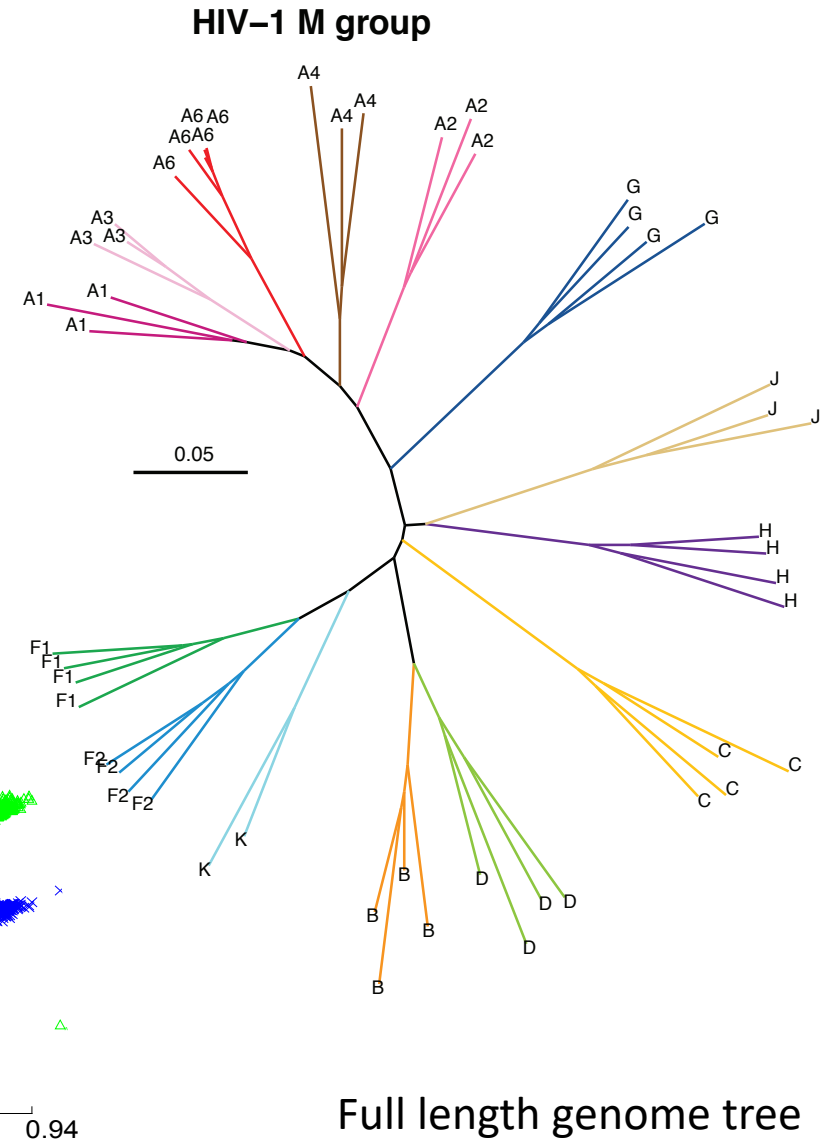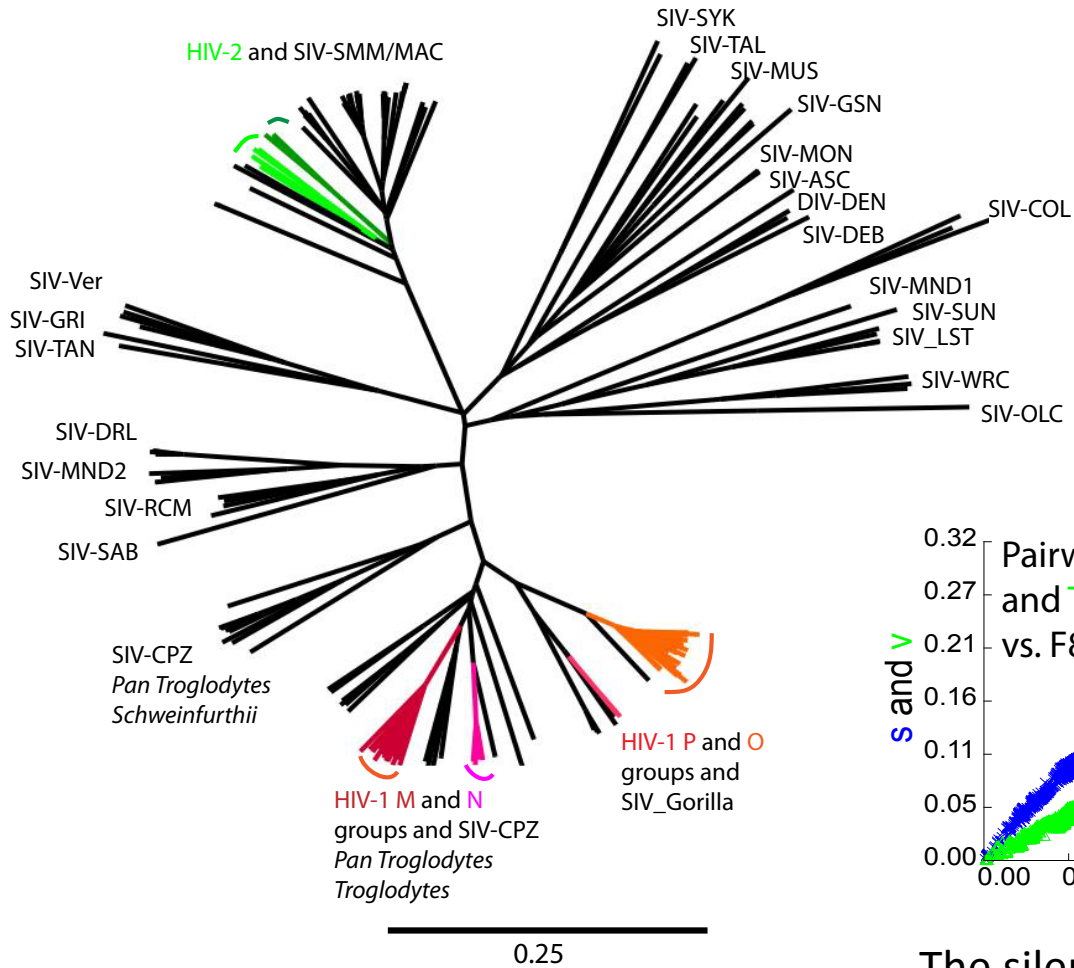
The silent transitions are essentially getting saturated

Full length genome tree

Next Strain HIV database collaboration
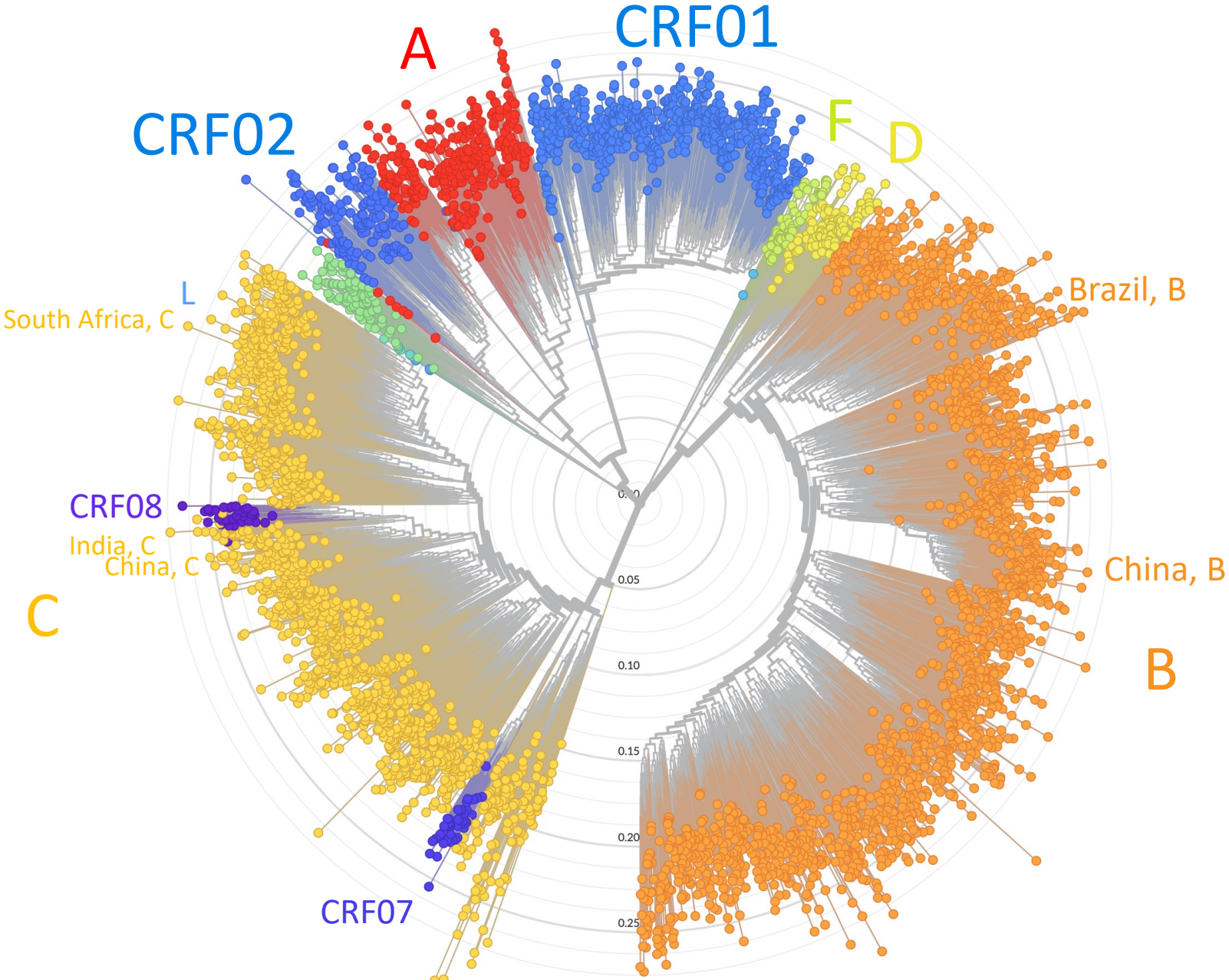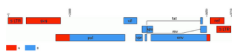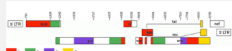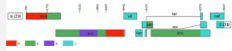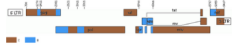
HIV Circulating Recombinant Forms (CRFs)
www.hiv.lanl.gov

There are 157 HIV-1 CRF's and one HIV-2 CRF

	Name	Reference strain	Subtypes	Corresponding author	Genome map	#Seqs in SeqDB (>5000, >100)
			HIV-1 CRFs			
⊞	CRF01_AE	CM240 (U54771)	A, E	J.K. Carr		82,922
⊞	CRF02_AG	IbNG (L39106)	A, G	J.K. Carr		29,242
⊞	CRF03_A6B	Kal153 (AF193276)	A6, B	K. Liitsola		715
⊞	CRF04_cpx	94CY032 (AF049337)	A, G, H, K, U	D. Paraskevis		60
⊞	CRF05_DF	VI1310 (AF193253)	D, F	T. Laukkanen		58
⊞	CRF06_cpx	BFP90 (AF064699)	A, G, J, K	R. B. Oelrichs		3,398
⊞	CRF07_BC	97CN54 (AF286226)	B, C	R. Wagner		22,256
⊞	CRF08_BC	97CNGX-6F (AY008715)	B, C	F.E. McCutchan		4,572
⊞	CRF09_cpx	96GH2911 (AY093605)	A, G, U	F.E. McCutchan		253
⊞	CRF10_CD	TZBF061 (AF289548)	C, D	I.N. Koulinska		233
⊞	CRF11_cpx	GR17 (AF179368)	CRF01, A, G, J, U	M. Peeters		1,506
⊞	CRF12_BF	ARMA159 (AF385936)	B, F1	J.K. Carr		526
⊞	CRF13_cpx	96CM-1849 (AF460972)	CRF01, A, G, J, U	K. Wilbe		416
⊞	CRF14_BG	X397 (AF423756)	B, G	R. Najera		338
⊞	CRF15_01B	99TH.MU2079 (AF516184)	CRF01, B	F.E. McCutchan		57
⊞	CRF16_A2D	97KR004 (AF286239)	A2, D	U. Visawapoka		38
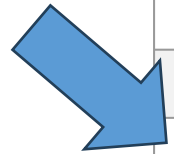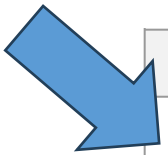
	CRF06_cpx	BFP90 (AF064699)	A, G, J, K	R. B. Oelrichs		3,398
	CRF07_BC	97CN54 (AF286226)	B, C	R. Wagner		22,256
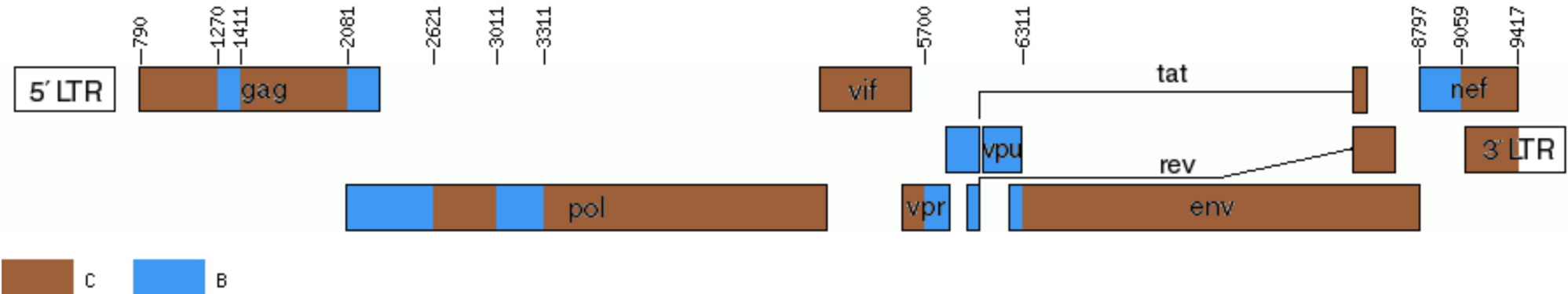
A description of this CRF was published by Su et al. 2000 but no sequences were deposited. A patent of the CN54 sequence was recorded with accession numbers AX149771 and AX149647. Two other genomes sequenced by Rodenburg et al. 2001 are available: 97CN001 (AF286226) and 98CN009 (AF286230); however, 97CN001 is reportedly from the same blood sample as CN54. Feng et al. 2016 published an analysis of the orgin and breakpoints of CRF07_BC, CRF08_BC, and other BC-derived CRFs.
Breakpoints from Su et al. 2000 Figure 3 and text descriptions.

```
790  1269 C
1270 1410 B
1411 2080 C
2081 2620 B
2621 3010 C
3011 3310 B
3311 5699 C
5700 6310 B
6311 8796 C
8797 9058 B
9059 9417 C
```

	CRF08_BC	97CNGX-6F (AY008715)	B, C	F.E. McCutchan		4,572
	CRF09_cpx	96GH2911 (AY093605)	A, G, U	F.E. McCutchan		253

SARS-CoV-2 evolution

Will Fischer
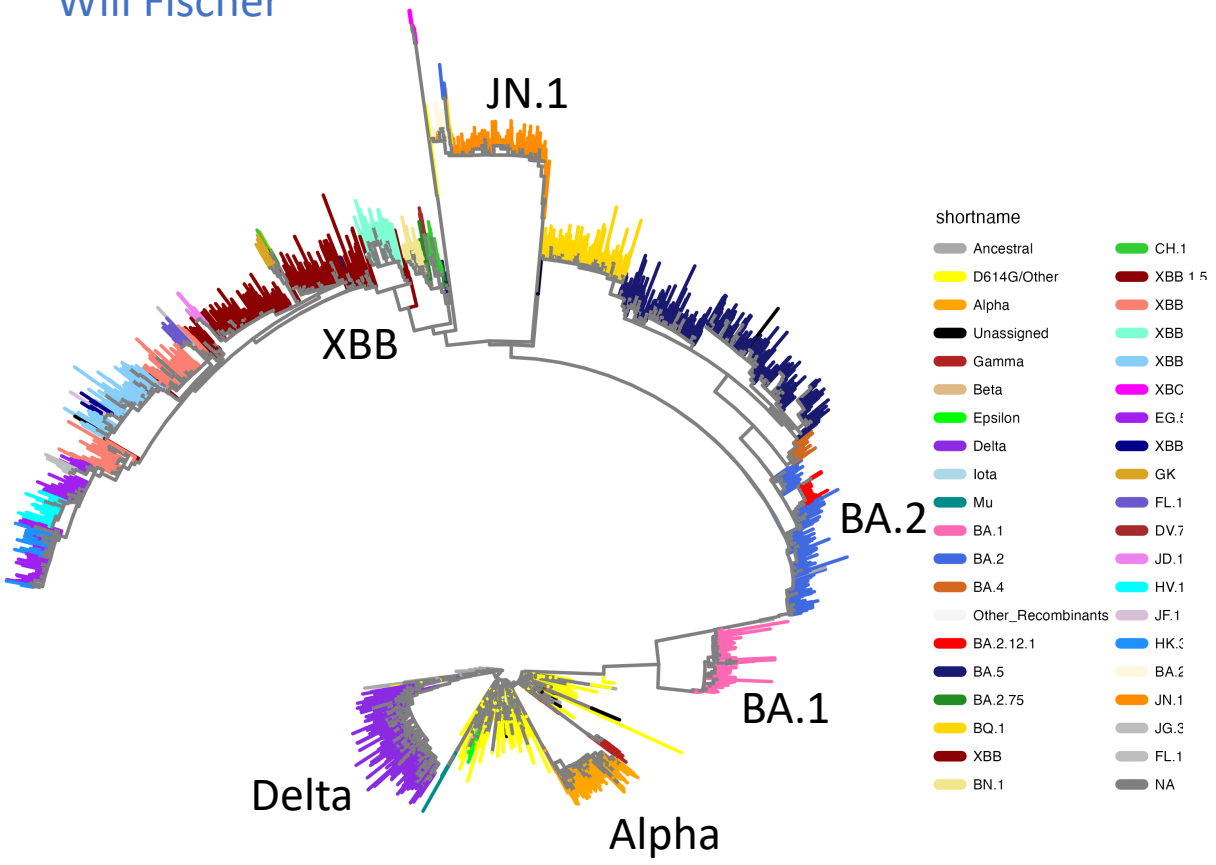
Time tracks quite sensibly

Full Length genome, ML tree, 100 randomly sampled sequences from the global GISAID collection per month.
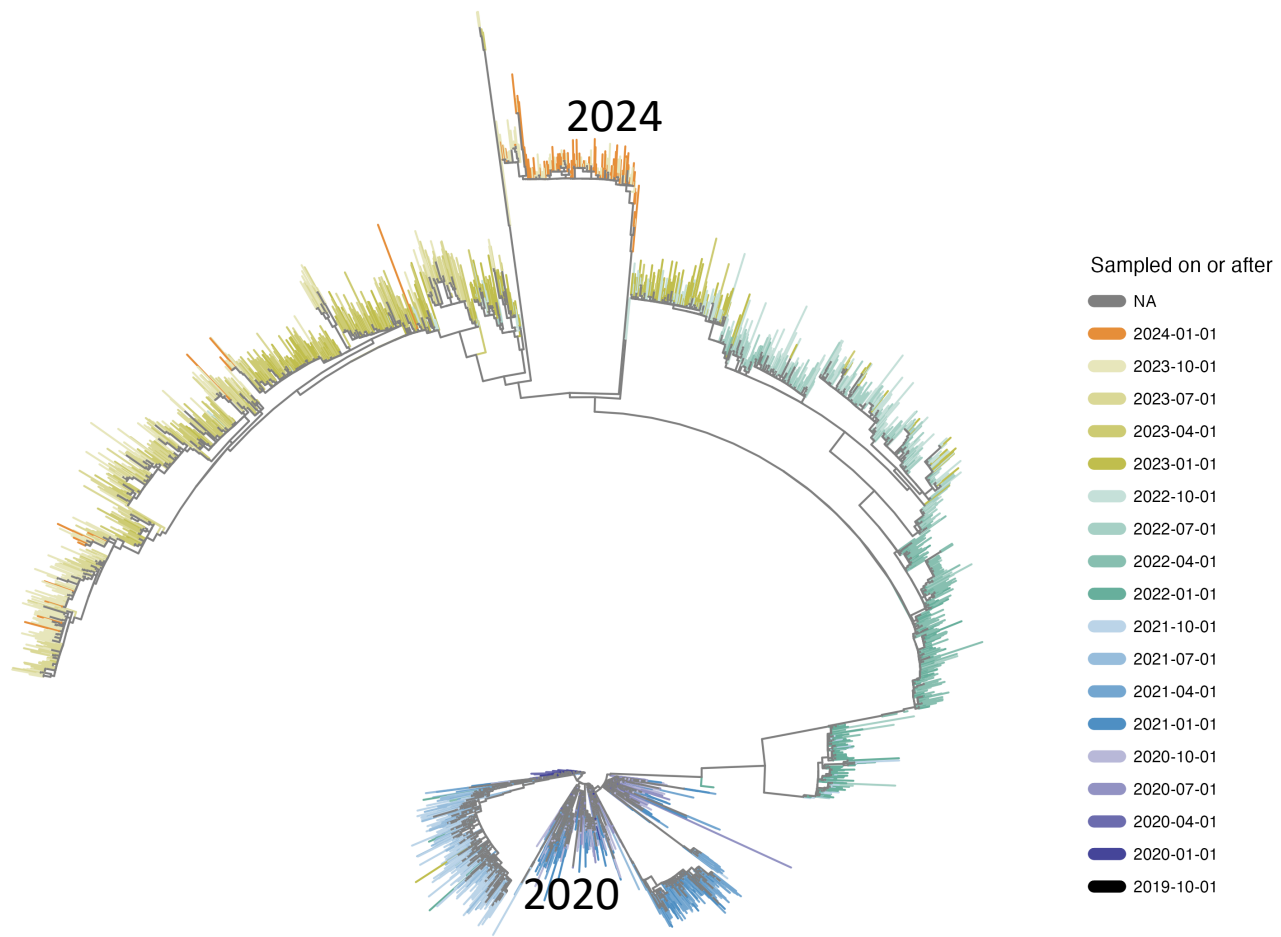
HIV-1 Phylogeny

Will Fischer

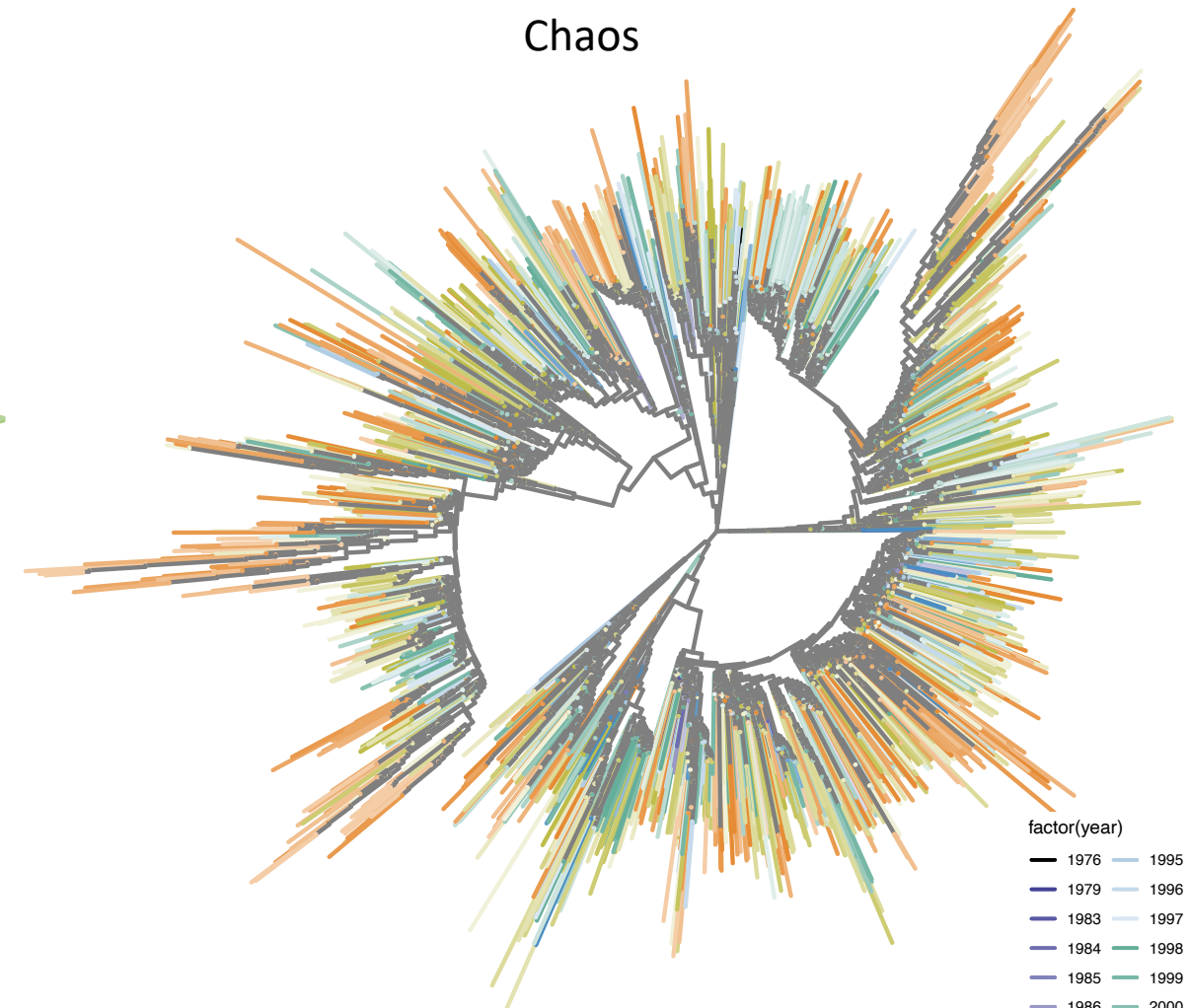100 randomly selected samples per month over the last 40 years

Chaos

A1/D A1 A6

CRF01

B

factor(Subtype)

01_AE	63_02A6
0107	89_BF1
01B	A1
01BC	A1C
02_AG	A1CD
0209	A1D
02A	A6
02A1	B
02B	BC
02G	BF1
06_cpx	C
07_BC	CD
08_BC	D
106_cpx	F1
11_cpx	F2
111_01C	G
12_BF	Other
35_A1D	NA

By Subype/CRF

0.1

By Year

factor(year)

1976	1995	2009
1979	1996	2010
1983	1997	2011
1984	1998	2012
1985	1999	2013
1986	2000	2014
1987	2001	2015
1988	2002	2016
1989	2003	2017
1990	2004	2018
1991	2005	2019
1992	2006	2020
1993	2007	NA
1994	2008	

Variation in SARS-CoV-2 Spike (vs the Wuhan variant) vs HIV-1 Env (vs the global consensus)
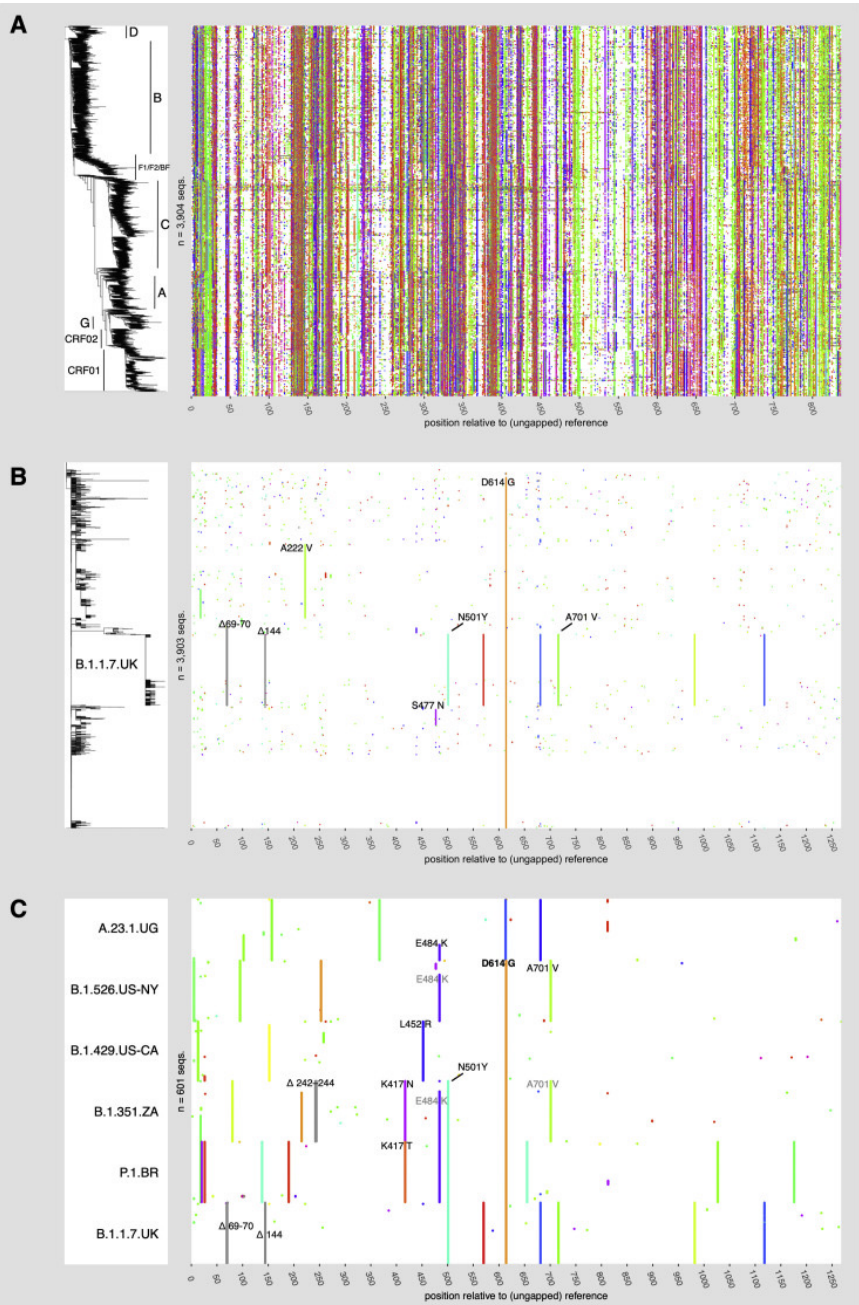
The current selective sweep: GISAID's global sample in the last 30 days

COV Variant Visualizer

2024-03-01-2024-04-04 Human SPIKE
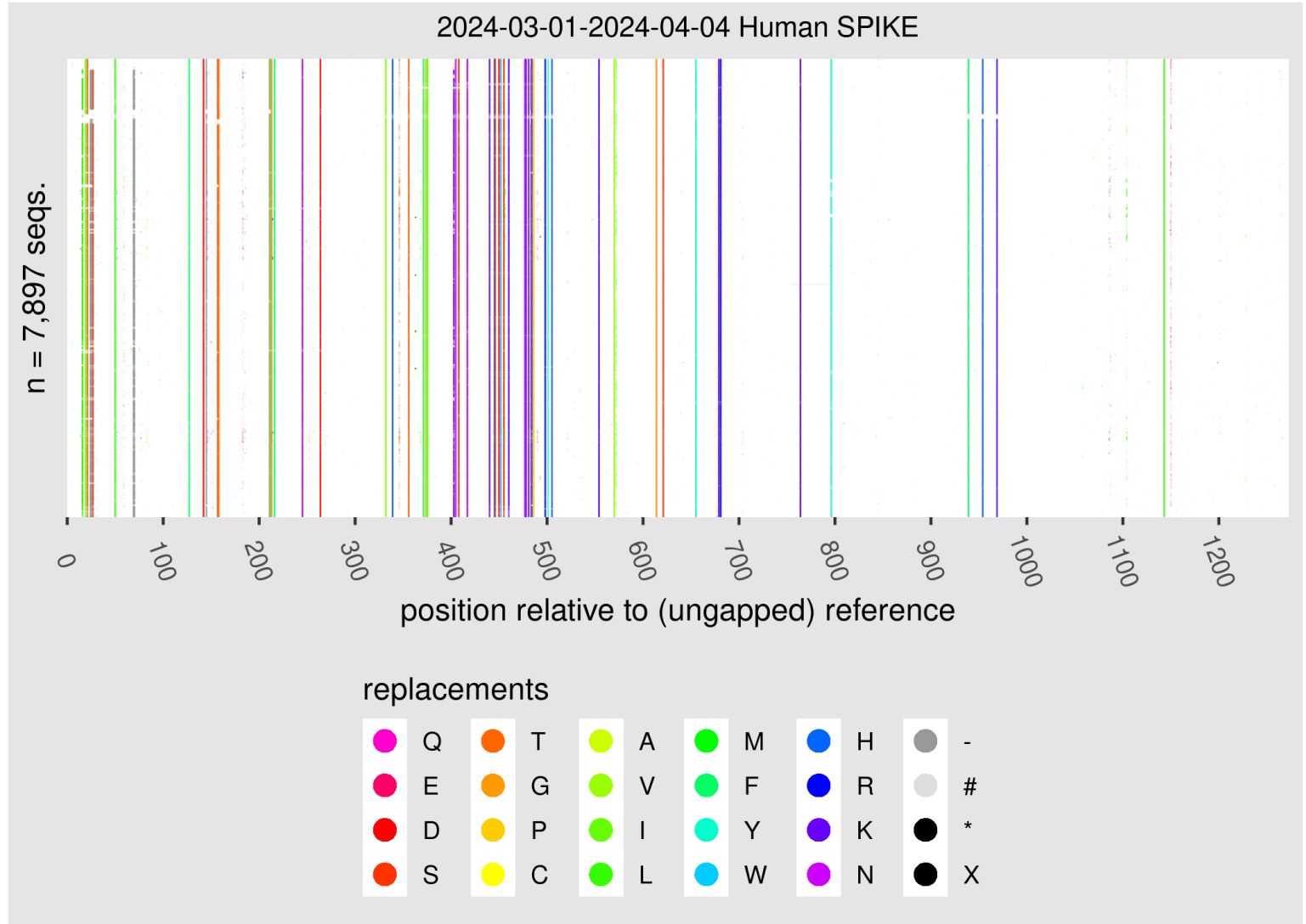
SARS-CoV-2: Last 534 sampled in GISAID since March 12: almost a complete selective sweep for JN.1
(Retrieving the 500 most recently sampled: March 12 was the most recent date to have >= 500 today, April 7)

F456L

R346T
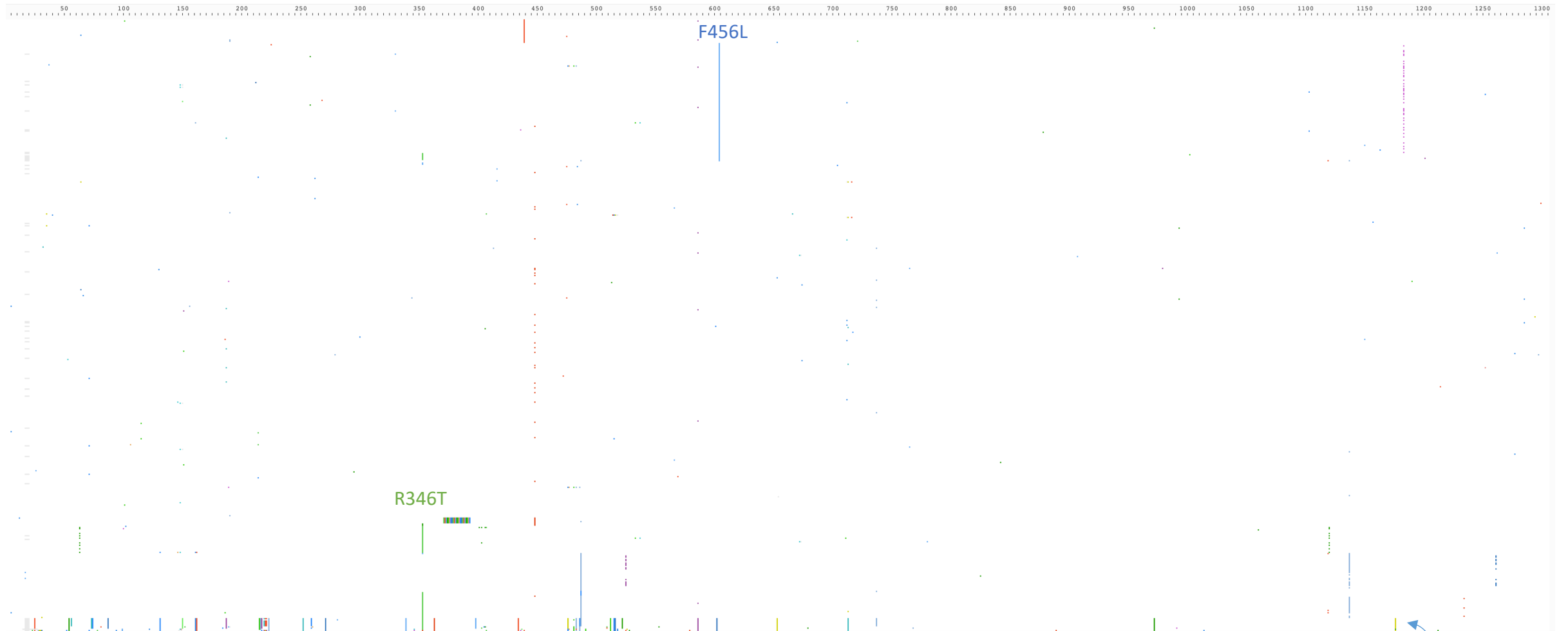
11 JG.3's

Within clades, HIV continues to diverge genetically and antigenically

HIV-1 Diversity is Increasing within Subtypes

Elena Giorgi

Phylogenetic analysis of within subtype Envs

- Showing clade C (confirmed in B and other clades too)

- ~1,380 Subtype C Envs sampled 1988-2021

- Includes 213 placebo Envs from HVTN 703 (AMP), HVTN 705 (Imbokodo), and HVTN 702 (Uhambo)

- Envs from HVTN trials sampled 2017-2021

Legend:
- 2006 or Earlier
- 2007–2014
- 2015 or Later
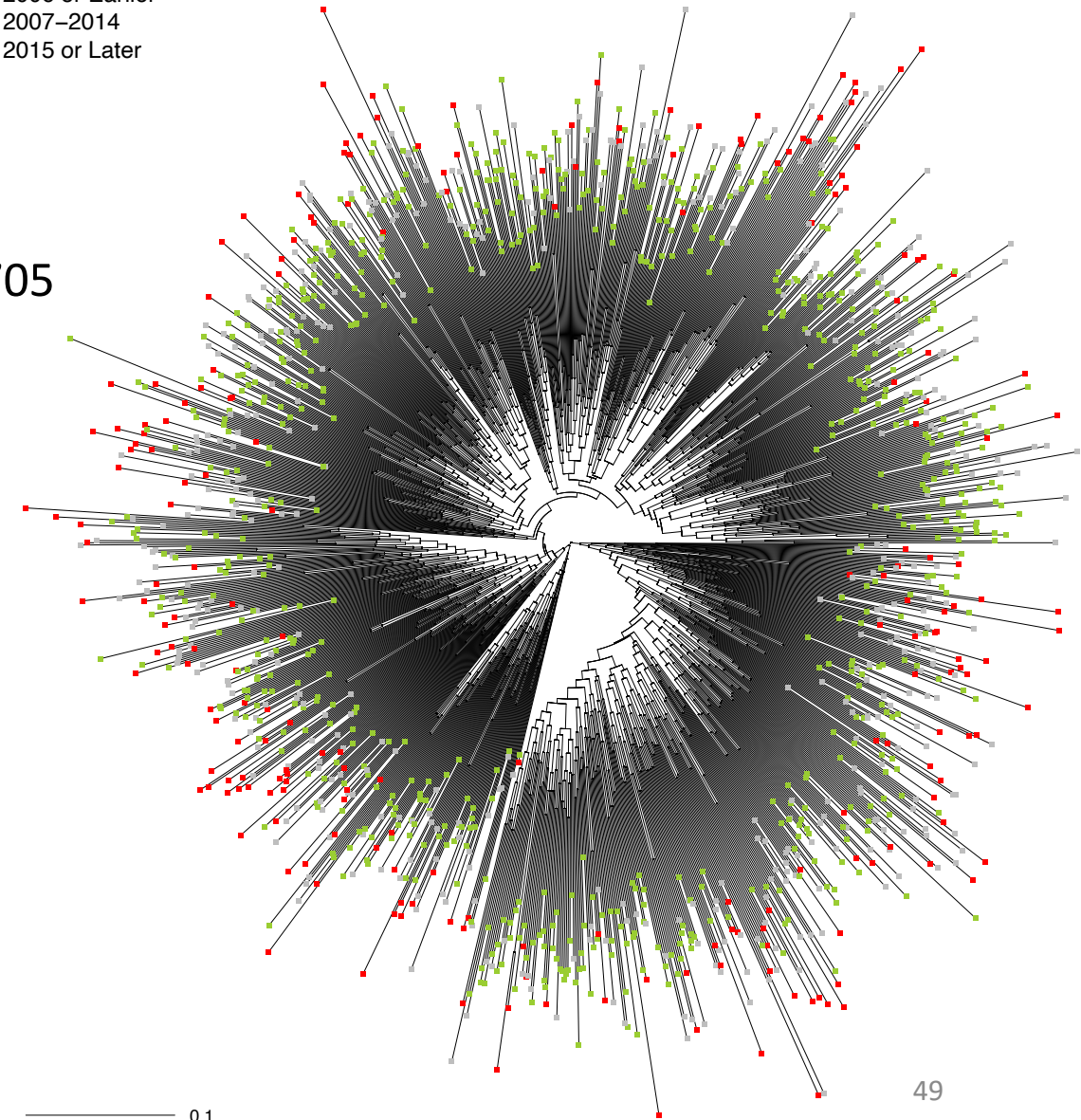
Branch lengths from midpoint tree root increase over time

P<2.2e-16
P=7.7e-8
P=6.3e-16

Tree Branch Lengths

2006 or Earlier   2007-2014   2015 or Later

0.1
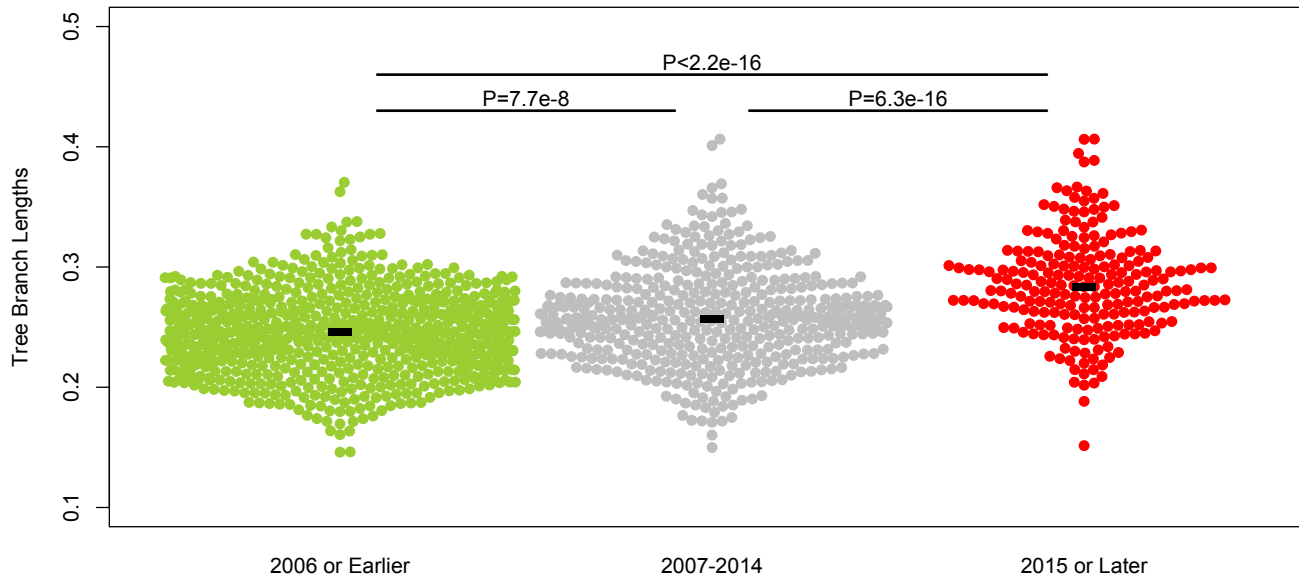
Increased Diversity Means Increased Resistance

Elena Giorgi

1. Higher diversity is correlated to higher bnAb and autologous sera resistance

- Rademeyer et al. (2016) first reported the increase in diversity in C Clade.

- As they evolve, clades become more resistant to sera neutralization from the same clade, as well as to bNAbs.

- Resistance signature motifs in the V2 apex and V3 glycan epitopes are increasing in frequency over time, either through drift or through bNAbs selection.
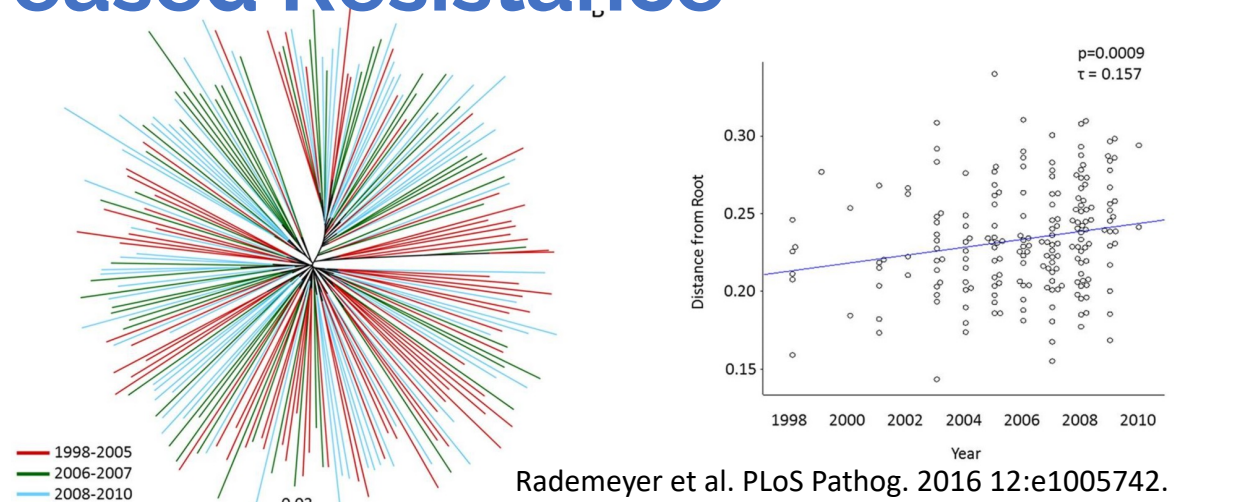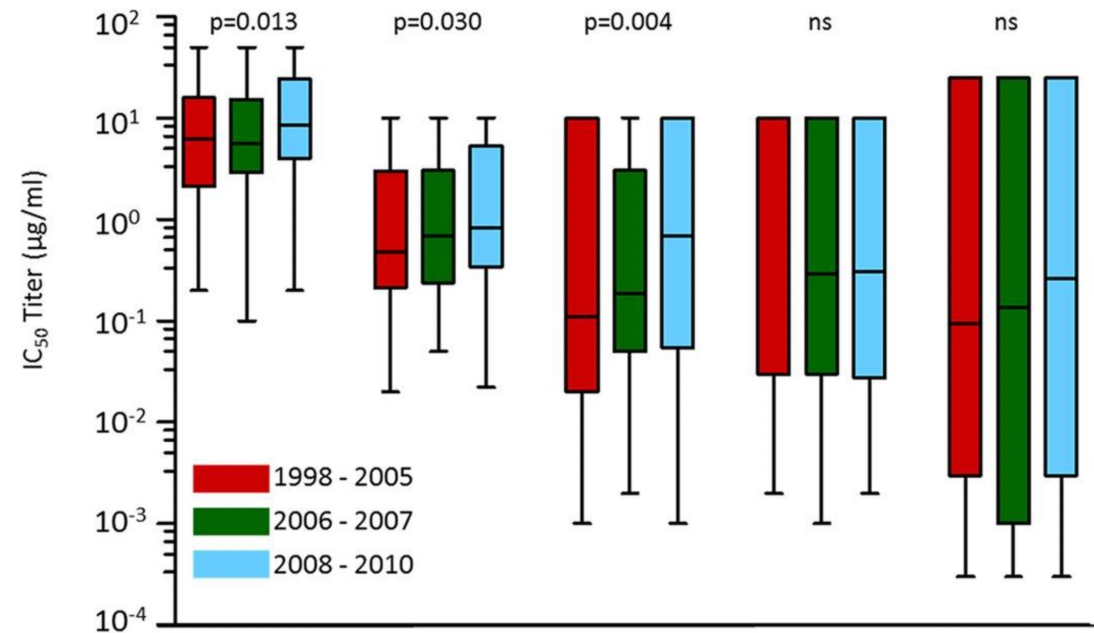
Rademeyer et al. PLoS Pathog. 2016 12:e1005742.

Hraber et al. J Virol. 2014 88:12623.

Rademeyer et al. PLoS Pathog. 2016 12:e1005742.

B clade bNAb Sensitivity of HVTN 704 Placebo Recent vs Historic

CD4bs bNAbs

VRC01, VRC01.23LS, 3BNC117-LS-J, VRC07-523.LS

N6.LS, N49-P9.6-FR-LS, 1-18

- Historic clade B
- HVTN 704 Set 1
- HVTN 704 Set 2
- AMP threshold IC_{80} = 1μg/ml

V2 apex bNAbs

PG9, PGDM1400, CAP256.V2.LS

V3 glycan bNAbs

10-1074-LS-J, PGT121

Interface & fusion peptide bNAbs

PGT151, LN02-ML85, VRC34.01

MPER bNAbs

10E8v4, 4E10, 2F5, DH511.2K3

Coverage (%)

IC_{80} (μg/ml)
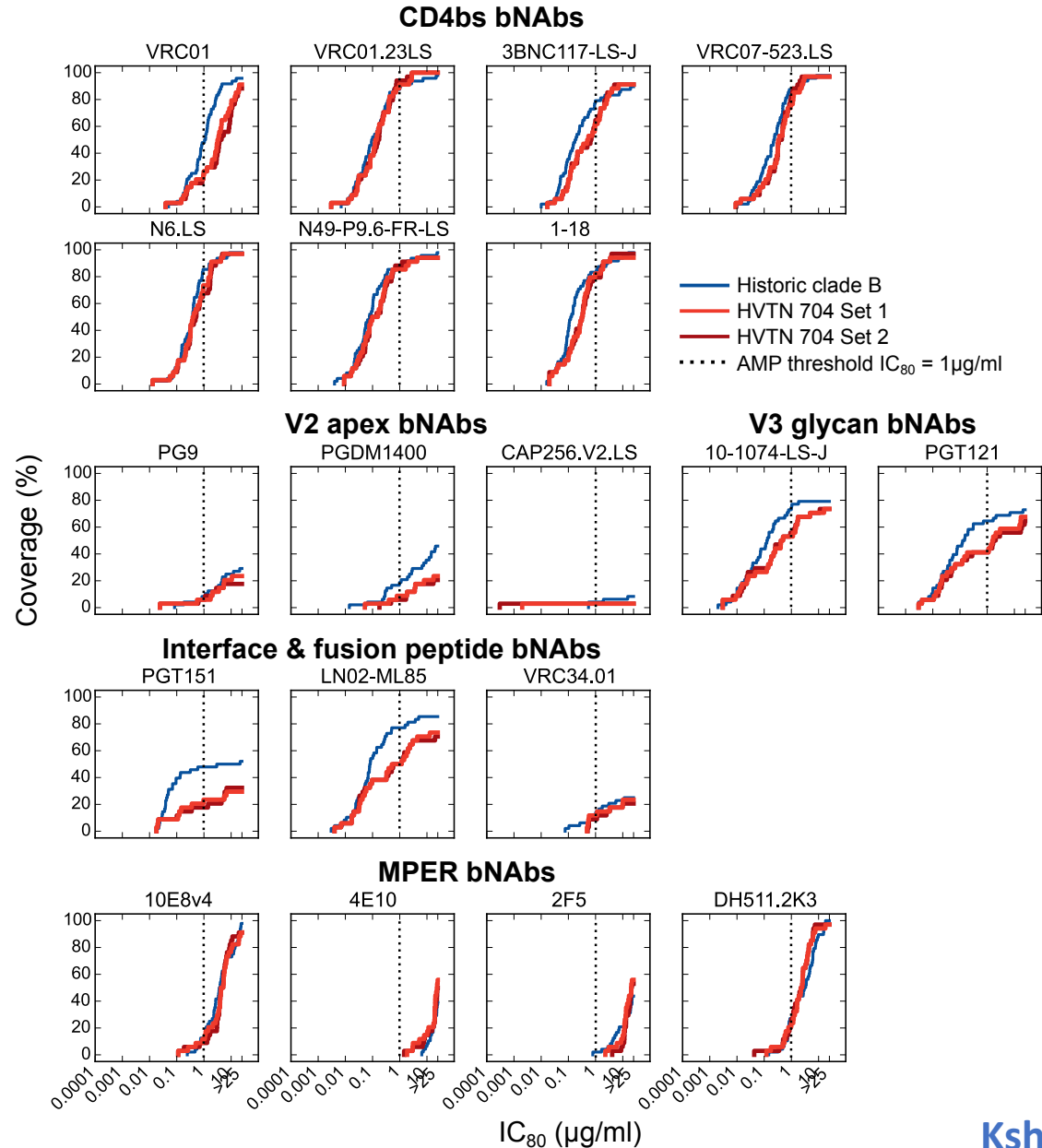
Some antibodies are holding their activity, Others are becoming less potent.

Very shift between the blue and red lines means that more antibody is required to neutralizing more viruses in the panels of more recently collected viruses.

Kshitij Wagh, David Monterioti, Mike Seaman

HIV-1 Global Diversity is Increasing

Elena Giorgi

CRFs, as well as A and F subtypes, are increasingly sampled in Europe, Asia, and South America

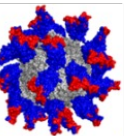https://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.html

52
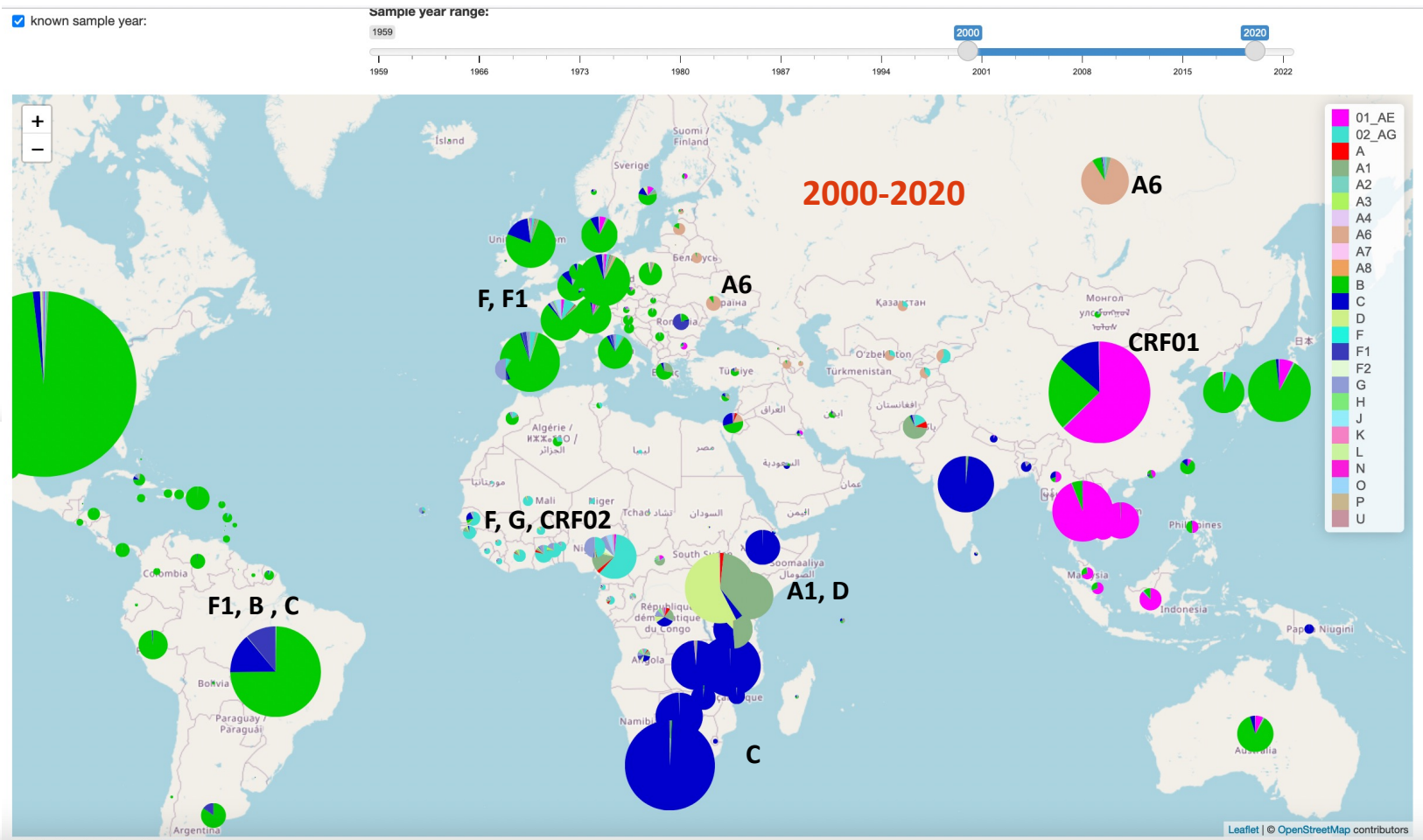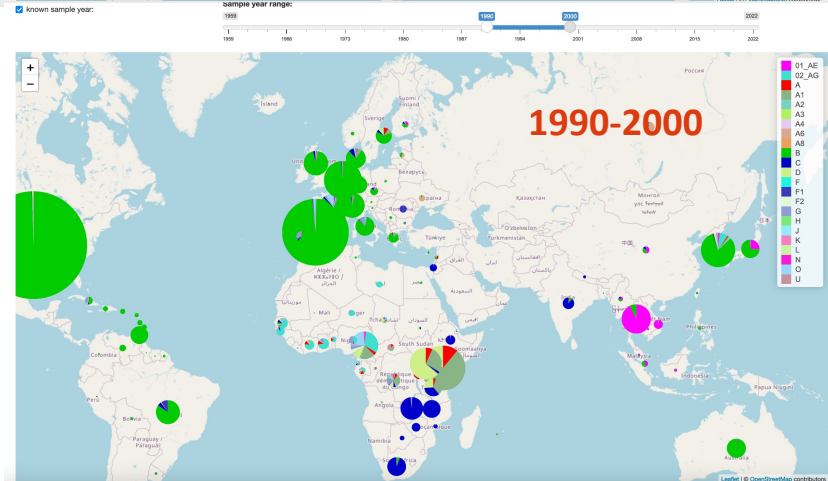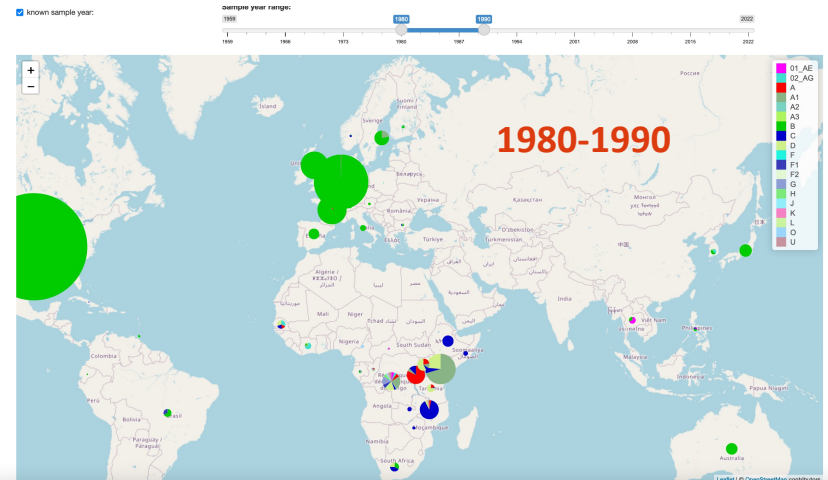
Conclusions

- **SARS CoV-2**
  - **Highly recurrent mutations that give rise to stable lineages cause phenotypic changes**
    - NAb immune evasion, greater stability, enhanced entry or ACE2 binding

  - **Prior convergence foreshadows mutations concentrated in newly emergent variants that achieve global dominance**

  - **Mutations that conferred immune evasion often had reduced ACE2 binding**
    - Potentially stabilize a "3-RBD-down" conformation inhibiting both RBD antibody and ACE2 binding
    - Could other mechanisms of entry be enabling such a pathway?

- **HIV-1**
  - **Vastly more diverse than SARS-CoV-2**
  - **CRFs are a major diversification mechanism**
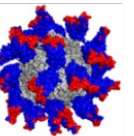 - **Within clade genetic and antigenic diversification is increasing**

Acknowledgements SARS-CoV-2:

- **James Theiler**, Will Fischer, Heyjin Yoon
    - https://cov.lanl.gov/

- GISAID and all who contribute: 16,584,800 SARS-CoV-2 viral sequence

- Pango designations from Cornelius Roemer: https://github.com/cov-lineages/pango-designation/blob/master/lineage_notes.txt

- Jesse Bloom and Bernadeta Dadonaite for sharing their rich data and helpful discussions
    - **Full-spike deep mutational scanning helps predict the evolutionary success of SARS-CoV-2 clades**
        - bioRxiv Dadonaite et al. 2023 Nov 14:2023.11.13.566961. doi: 10.1101/2023.11.13.566961

- Angie Hinrichs and Russ Corbett for generously providing current UShER Pango lineage designations.
    - **The ongoing evolution of UShER during the SARS-CoV-2 pandemic.**
        - Hinrichs A et al. Nat Genet. 2024 Jan;56(1):4-7. doi: 10.1038/s41588-023-01622-5
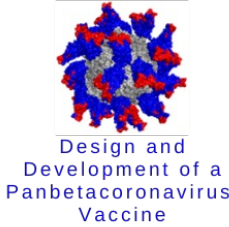
Design and Development of a Panbetacoronavirus Vaccine

Acknowledgements HIV-1:

Design and Development of a Panbetacoronavirus Vaccine

Acknowledgements