NIH SAVE update 2023-08-23

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BA.2.86

See: Jesse Bloom: https://slides.com/jbloom/new_2nd_gen_ba2_variant
And: https://github.com/cov-lineages/pango-designation/issues/2183

Highlights:, emphasis

- i. BA.2.86: A novel SARS-CoV-2 variant with a very distinctive spike was discovered in Israel and Denmark last week. It is still very rarely sampled but found in 5 countries. It has been designated a WHO variant under monitoring.
 - ii. EG.5.1 is still the most rapidly expanding variant
- iii. XBC.1.6 still has a presence in Australia but is not expanding.

Sequences and Metadata



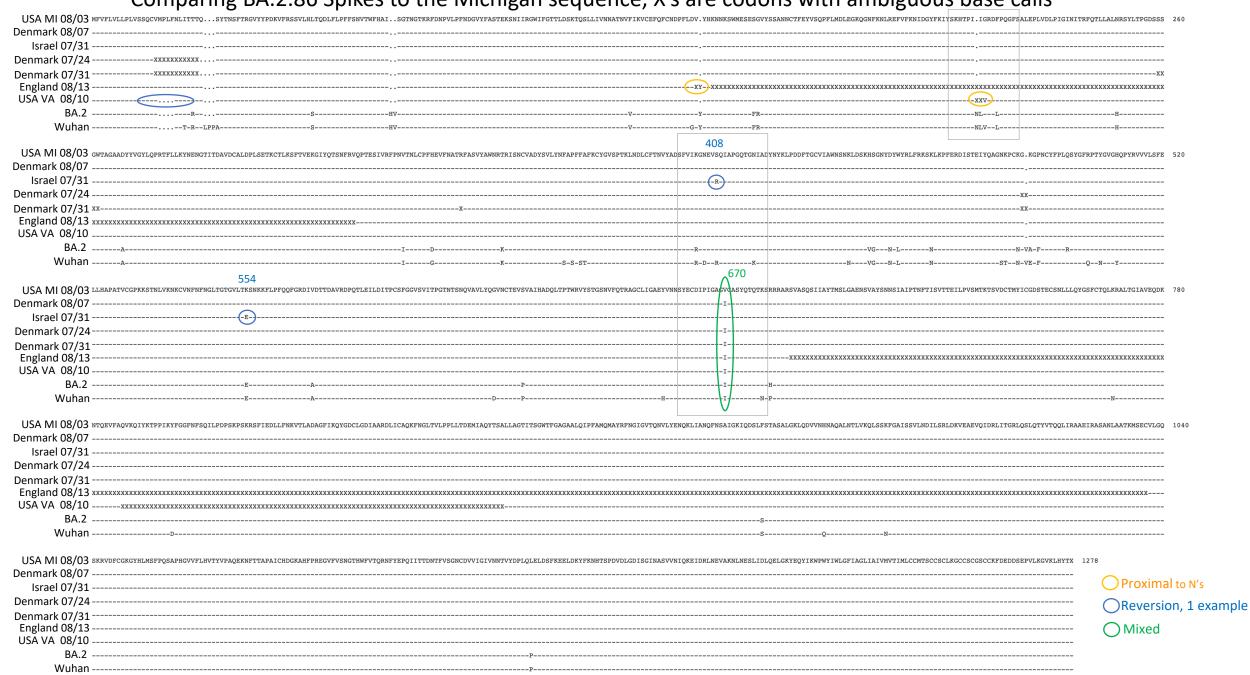
Figures are made from tools available at: cov.lanl.gov
We gratefully acknowledge the authors, originating and submitting laboratories
of the sequences from GISAID on which this research is based. The original data
are available from https://www.gisaid.org

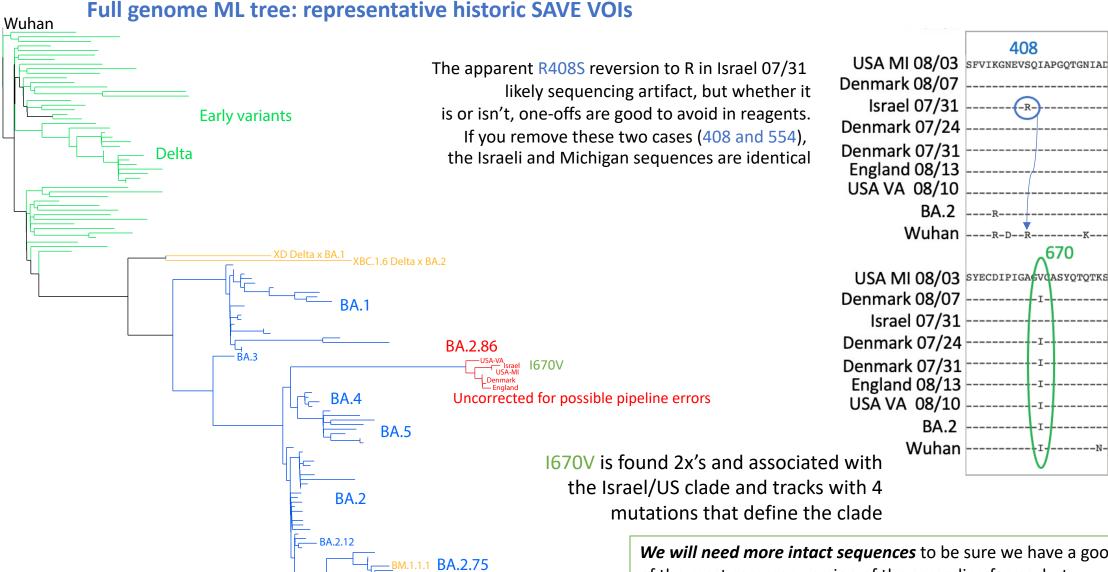


Considerations for Spike reagents and choice of natural isolates:

- Representative of the most common expanding form of an emerging lineage – it may not be the ancestral form, and not many variants can be tested so which do you choose?
- I emphasize variants that are both natural and most representative, as co-variation may impact phenotype.
- Often historically with newly divergent forms there have been issues with amplicon drop out, assembly... that needs some time to resolve.
- People want to order Spikes very quickly in a case like BA.2.86, so uncertainty has to be weighed against a best guess...

Comparing BA.2.86 Spikes to the Michigan sequence, X's are codons with ambiguous base calls





0.001

We will need more intact sequences to be sure we have a good call of the most common version of the spreading forms, but right now, I think the Michigan sequence or the August 7th Denmark Spike would be good choices for reagent design. They are intact in Spike only vary at I670V, so represent the Spike forms of the two clades.

Corrected:

hCoV-19/USA/MI-UM-10052670540/2023|EPI_ISL_18110065|2023-08-03

ins16MPLF, 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, R408S, D405N, K417N, N440K, V445H, G446S, N450D, L452W, N460K, S477N, T478K, N481K, V483-, E484K, F486P, Q498R, N501Y, Y505H, E554K, A570V, D614G, P621S, H655Y, I670V, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, P1143L

hCoV-19/Denmark/DCGC-647694/2023|EPI_ISL_18114953|2023-08-07

ins16MPLF, 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, R408S, D405N, 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

Phenotypic assessment of spike mutations in BA.2.86 (new highly mutated BA.2 variant: Jesse Bloom

https://slides.com/jbloom/new_2nd_gen_ba2_variant

Likely effects of mutations relative to BA.2

These are **only estimates** of mutation effects from deep mutational scanning experiments.

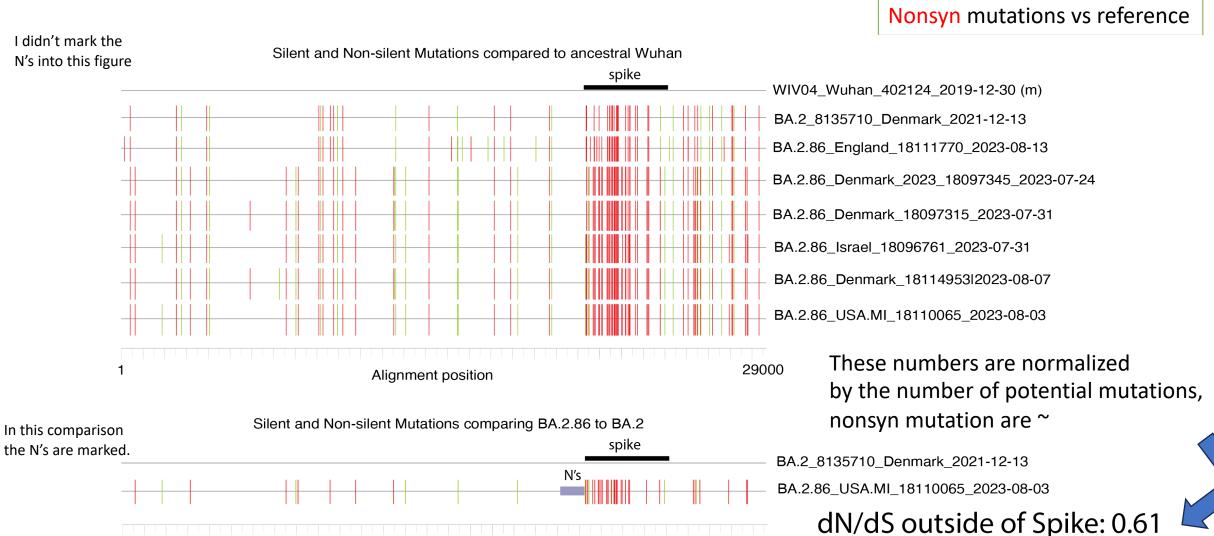
- **ins16MPFL**: antibody escape (NTD supersite)
- R21T
- S50L
- del69-70
- V127F
- **delY144**: antibody escape (NTD supersite)
- **F157S**: antibody escape (NTD supersite)
- **R158G**: antibody escape (NTD supersite)
- delN211
- L212I
- L216F
- **H245N**: antibody escape (NTD supersite)
- A264D: antibody escape (NTD supersite)
- I332V
- D339H
- **K356T**: antibody escape, adds N-glycosylation site
- **R403K**: improves ACE2 affinity, antibody escape

- V445H: antibody escape
- **G446S**: antibody escape
- **N450D**: antibody escape
- **L452W**: antibody escape
- N460K: improves ACE2 affinity, antibody escape
- N481K
- **delV483**: reduces ACE2 affinity, antibody escape
- A484K: antibody escape
- **F486P**: reduces ACE2 affinity, antibody escape
- **R493Q**: improves ACE2 affinity
- E554K
- A570V
- P621S
- 1670V*
- H681R
- S939F
- P1143L: increases spike-mediated entry in cell culture

Estimates of effects of mutations from RBD deep mutational scanning by Tyler Starr, full-spike deep mutational scanning of BA.2 and XBB.1.5 by Bernadeta Dadonaite (Bloom lab), the Bloom lab RBD escape calculator informed by data from Yunlong Cao, and definition of the NTD supersite by Matthew McCallum & David Veesler. Experiments were performed in various genetic backgrounds and so there could be unmodeled epistasis. The * indicates mutations only in some sequences of the new variant.

Mutations are focused in Spike, and under positive selection in Spike

Syn mutation vs reference



Alignment position

non-Spike

Spike

Potential nonsyn

19124

2960

Potential syn 5365

838

Nonsyn

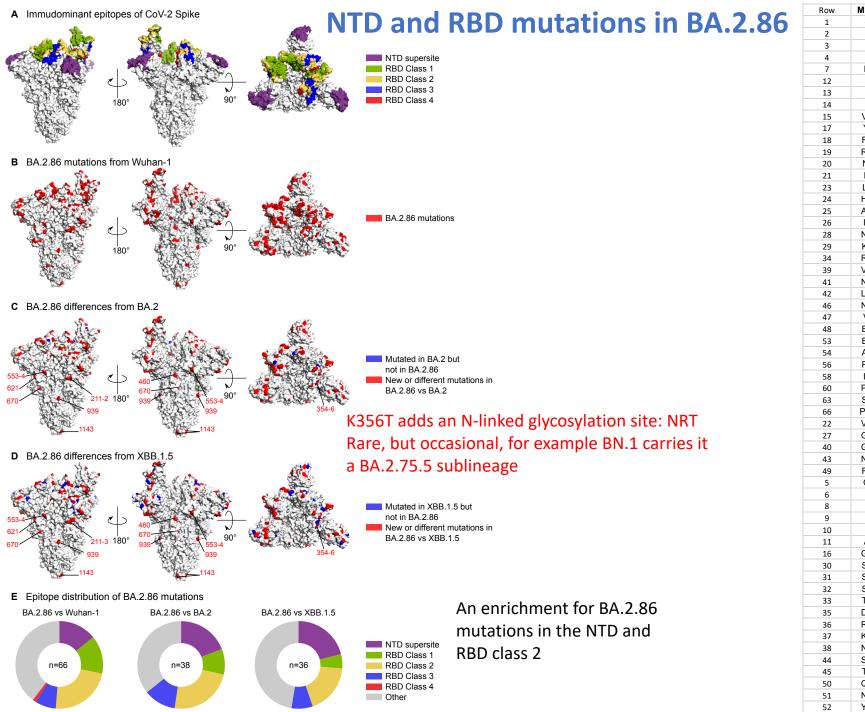
33.5

6.5

29000

SNAP: www.hiv.lanl.gov, Nei and Gojobori

dN/dS in Spike: 1.46



Row	Mutation	Epitope	Shared with BA.2	Shared with XBB.1.5	
1	-16M	NTD	No	No	
2	-16P	NTD	No	No	
3	-16L	NTD	No	No	
4	-16F	NTD	No	No	
7	R21T	-	No	No	
12	S50L	-	No	No	
13	H69-	-	No	No	
14	V70-	-	No	No	
15	V127F	-	No	No	
17	Y144-	NTD	No	No	
18	F157S	NTD	No	No	
19	R158G	NTD	No	No	
20	N211-	-	No	No	
21	L212I	-	No	No	
23	L216F		No	No	
24	H245O	NTD	No	No	
			No		
25	A264D	-		No	-
26	1332V		No	No	
28	N354O	Class3	No	No	-
29	K356T	Class3	No	No	
34	R403K	Class2, Class1	No	No	
39	V445H	Class2, Class3	No	No	
41	N450D	Class2	No	No	
42	L452W	Class2	No	No	
46	N481K	Class2	No	No	
47	V483-	Class2	No	No	
48	E484K	Class2, Class1	No	No	
53	E554K	-	No	No	
54	A570V	-	No	No	
56	P621S	-	No	No	
58	I670V	-	No	No	
60	P681R	-	No	No	
63	S939F	-	No	No	
66	P1143L	-	No	No	
22	V213G	-	Yes	No	
27	G339H	Class2, Class3	No	Yes	
40	G446S	Class2, Class3	No	Yes	
43	N460K	Class1	No	Yes	
49	F486P	Class2, Class1	No	Yes	
5	O17N	NTD	Yes	Yes	
6	T19I	NTD	Yes	Yes	-
8	L24-	-	Yes	Yes	
9	P25-	-	Yes	Yes	
10	P26-	-	Yes	Yes	-
11	A27S	-	Yes	Yes	
16	G142D	NTD	Yes	Yes	
30	S371F	Class4, Class2	Yes	Yes	
31	S373P	Class2	Yes	Yes	
32	S375F	-	Yes	Yes	
33	T376A	-	Yes	Yes	
35	D405N	Class2, Class1	Yes	Yes	
36	R408S	Class1	Yes	Yes	
37	K417N	Class2, Class1	Yes	Yes	
38	N440K	Class3	Yes	Yes	
44	S477N	Class1	Yes	Yes	
45	T478K	Class2	Yes	Yes	
			Yes	Yes	
	Q498R	Class2, Class1			
50	Q498R N501Y	Class2, Class1 Class2, Class1	Yes	.,	hitij '

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BA.2.86: loss of the proline P1143L may impact conserved S2 stem helix antibody epitope

Stem helix antibodies

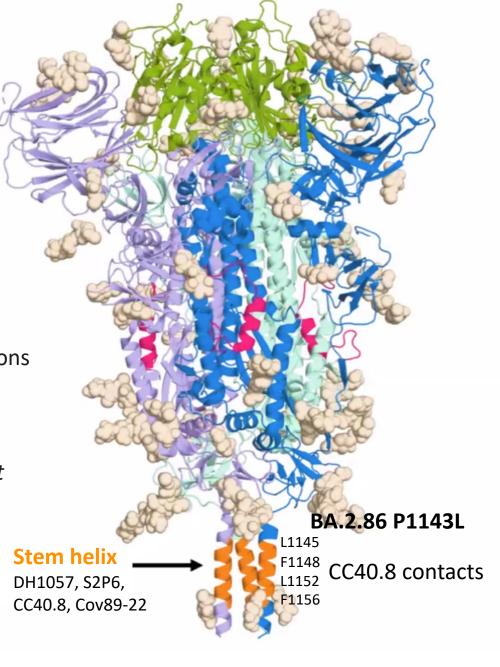
- rarely induced in natural infection, requires ACE2 binding for epitope exposure
- very broadly neutralizing across sarbecovirus clades and across SARS-CoV-2 VOCs
- Can protect against challenge in animals by inhibiting S-mediated membrane fusion

Also: Jesse Bloom points out deep mutational scanning shows mutations in P1143 and P1140 improve viral entry

(During the call Jesse noted he tested the stem helix antibodies CC67.105 and CC9.104 with Dennis Burton, and happily, they were not compromised by a mutation at 1143.)

Kapingidza... Mihai Azoitei bioRxiv

Engineered Immunogens to Expose Conserved Epitopes
Targeted by Broad Coronavirus Antibodies
doi: https://doi.org/10.1101/2023.02.27.530277



GISAID sampling: Jul 13 – August 13



In the last month, (Jul 21 – Aug 21), this is the number of sequences deposited in GISAID by continent:

- 24 African sequences
- 55 from South America
- 6557 from North America
- 4787 Asia
- 3531 from Europe
- 551 from Oceania

The Southern Hemisphere is currently only marginally sampled. It would be important to find ways so facilitate outreach to collaborate and improve this situation.

Denmark United Kingdom BA.2: 2 Jul13 – Aug 13 BA.2: 1 Sources of BA.2.86; CH.1: 5 BA.2.3.20: 1 EG.1: 6 BA.5: 1 Israel BQ.1: 4 In this slide the BA.2's EG.5: 36 **USA Michigan** CH.1: 13 XBB.1.16: 21 BA.2: 1 EG.1: 22 Data were not yet updated to be called BA.2: 1 EG.5: 181 XBB.1.22.1/FY: 1 CH.1: 9 EG.5: 13 FD.1.1: 1 BA.2.86, the "BA.2's" are actually XBB.1.5: 13 EG.1: 3 FE.1: 30 FE.1: 1 XBB.1.9: 11 EG.5: 59 FK.1: 5 the BA.2.86. FK.1: 1 XBB: 23 XBB.2.3: 12 FE.1: 3 XBB.1.16: 413 XBB.1.16: 27 XBB: 8 total: 107 XBB.1.22.1/FY: 22 XBB.1.22.1/FY: 1 XBB.1.16: 40 XBB.1.5: 108 Ancestral XBB.1.5: 23 XBB.1.9: 128 XBB.1.22.1/FY: 10 BA.1 BA.2 XBB.2.3: 123 XBB.1.9: 9 XBB.1.5: 27 BA.2.12.1/BG XBC.1.6: 3 BA.2.3.20 XBB.2.3: 13 XBB.1.9: 78 total: 1079 BA.2.75 BA.4/CS total: 89 XBB.2.3: 25 XBC.1.6: 1 CH.1 total: 264 D614G/Other Delta EG.1 EG.5 FD.1.1 FE.1 Other_Recombinants XBB XBB.1.16 XBB.1.22.1/FY XBB.1.5 XBB.1.9 XBB.2.3 XBC.1.6

Angola

South Africa

BA.2.86 metadata in GISAID and discovery

	/irus name	Accession ID	Collection date	Location	Additional host information	Sampling strategy
	nCoV-19/Israel/ICH-741198454/2023	EPI_ISL_18096761	7/31/23	Asia / Israel		
	nCoV-19/Denmark/DCGC-647646/2023	EPI_ISL_18097315	7/31/23	Europe / Denmark	n_infections=2,last_infection_date=2022-01-31	
	nCoV-19/Denmark/DCGC-647676/2023	EPI_ISL_18097345	7/24/23	Europe / Denmark	n_infections=2,last_infection_date=2022-01-10	
*	nCoV-19/Denmark/DCGC-647694/2023	EPI_ISL_18114953	8/7/23	Europe / Denmark	n_infections=2,last_infection_date=2022-03-21	
*	nCoV-19/USA/MI-UM-10052670540/2023	EPI_ISL_18110065	8/3/23	North America / USA / Michigan		Baseline surveillance
	nCoV-19/England/GSTT-YYBYBN4/2023	EPI_ISL_18111770	8/13/23	Europe / United Kingdom / England / London		
	nCoV-19/USA/VA-GBW-H20-330-6734/2023	EPI_ISL_18121060	8/10/23	North America / USA / Virginia / Loudoun County	Traveler from Japan	
_	nCoV-19/South Africa/NICD-N55999/2023	EPI_ISL_18125249	7/28/23	Africa / South Africa / Mpumalanga		Baseline Surveillance
	nCoV-19/South Africa/NICD-N55967/2023	EPI_ISL_18125259	7/24/23	Africa / South Africa / Gauteng		Baseline Surveillance

^{*}Currently proposed reference Spikes based on available data

SUPPLEMENTAL TABLE

Data Availability

Thank you!

GISAID Identifier: EPI SET 230823eb

doi: <u>10.55876/gis8.230823eb</u>

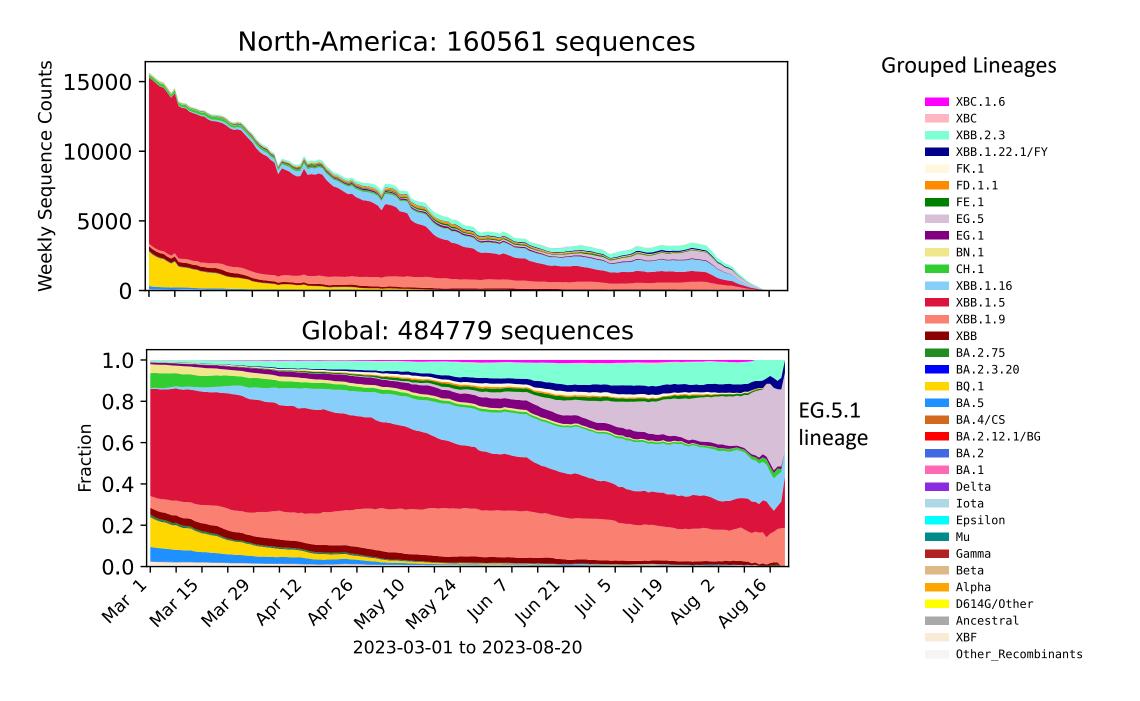
All genome sequences and associated metadata in this dataset are published in GISAID's EpiCoV database. To view the contributors of each individual sequence with details such as accession number, Virus name, Collection date, Originating Lab and Submitting Lab and the list of Authors, visit 10.55876/qis8.230823eb

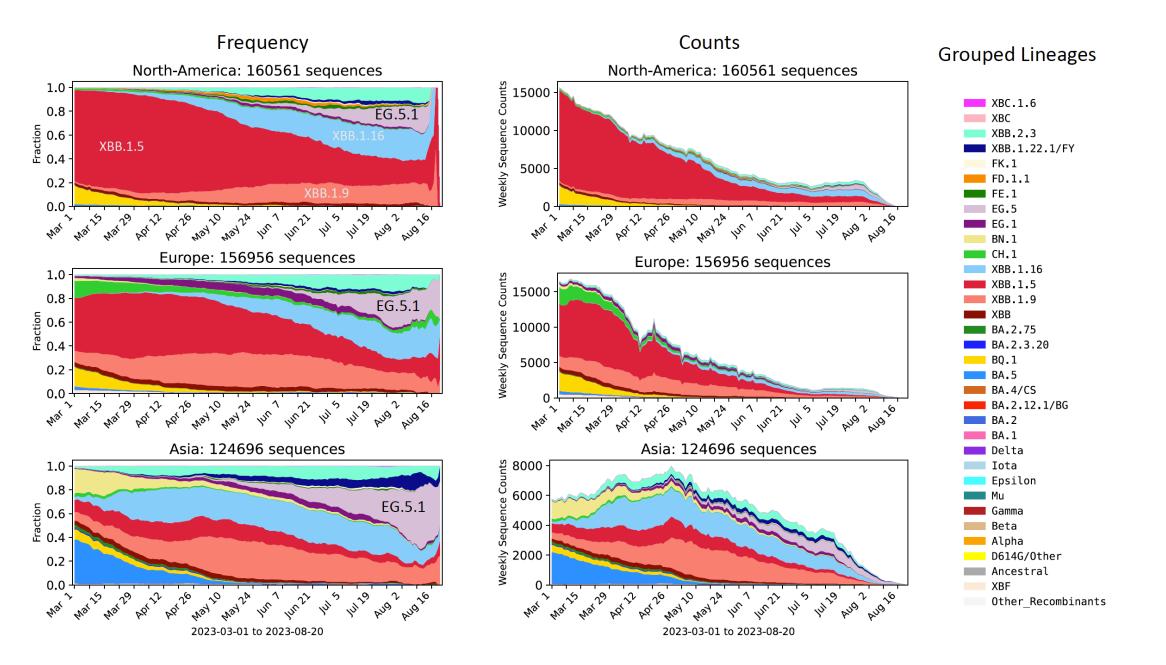
Data Snapshot

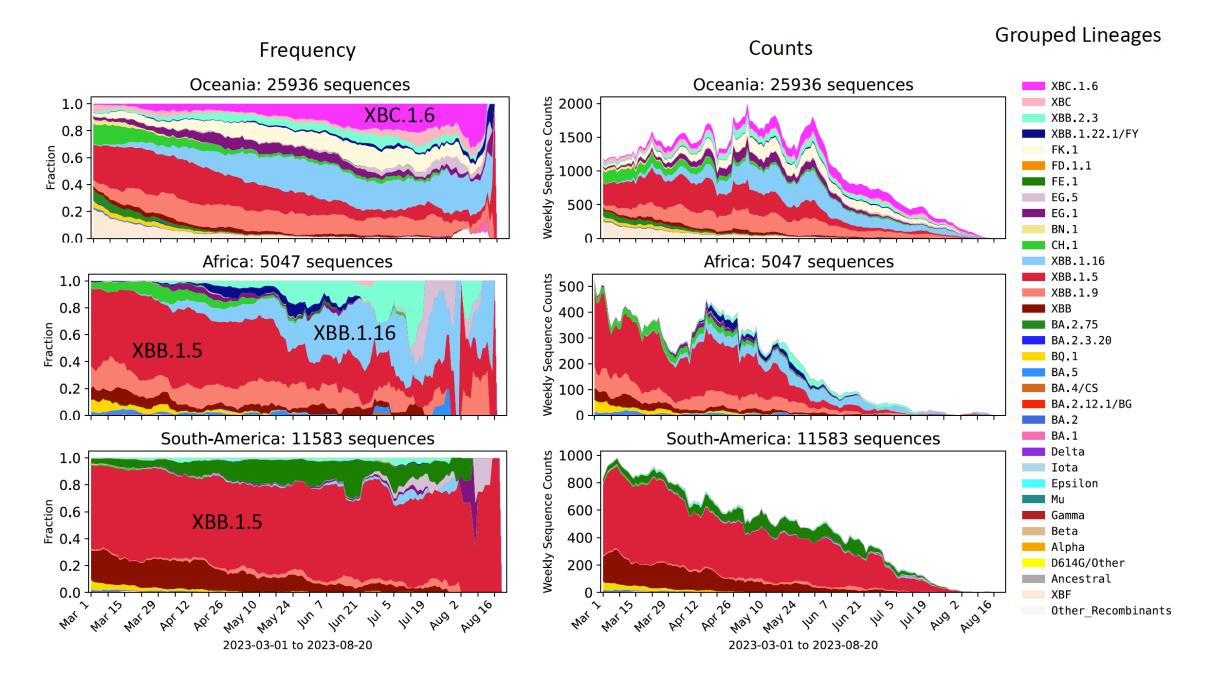
- EPI SET 230823eb is composed of 7 individual genome sequences.
- The collection dates range from 2023-07-24 to 2023-08-13;
- Data were collected in 4 countries and territories;
- All sequences in this dataset are compared relative to hCoV-19/Wuhan/WIV04/2019 (WIV04), the official reference sequence employed by GISAID (EPI ISL 402124). Learn more at https://gisaid.org/WIV04.

https://epicov.org/epi3/epi_set/230823eb?main=true

New-







Pango lineage designation in GISAID

EG.5 Isotonic Regression Results

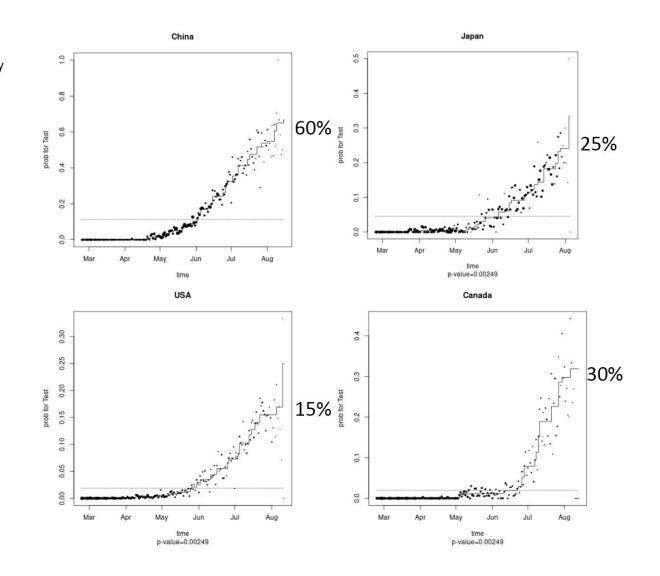
Test lineage(s): EG.5, EG.5.1 Background lineage(s): All

Assumption: Test lineages are increasing over time

Range of dates: 2023-02-23 - 2023-08-20

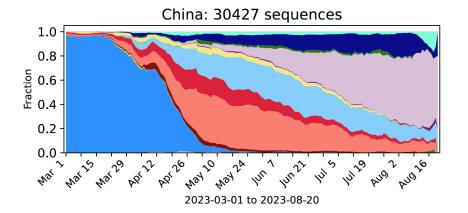
There were 10,978 sequences that matched your search term, It was significantly increasing in all 35 countries where it was found more than 10 times:

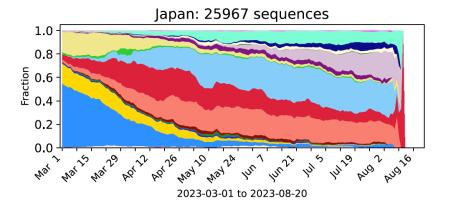
	# Test	# Others	Total	Test/Total (%)	# days	Time window	p-val
Australia	206	21748	21954	0.94	168	167	0.00249
Austria	85	16977	17062	0.50	146	165	0.00249
Belgium	17	3699	3716	0.46	146	165	0.00249
Canada	694	34587	35281	1.97	172	171	0.00249
Canary-Islands	14	461	475	2.95	156	166	0.00249
China	3402	27027	30429	11.18	174	173	0.00249
Colombia	29	1483	1512	1.92	146	148	0.00249
Costa-Rica	19	1273	1292	1.47	153	154	0.00249
Denmark	66	4742	4808	1.37	116	165	0.00249
Finland	13	2631	2644	0.49	150	160	0.00249
France	260	18277	18537	1.40	163	165	0.00249
Germany	136	17760	17896	0.76	156	160	0.00249
Guatemala	15	633	648	2.31	115	154	0.00249
Hong-Kong	74	632	706	10.48	149	163	0.00249
Iceland	28	460	488	5.74	137	166	0.00249
Indonesia	39	3738	3777	1.03	123	134	0.02239
Ireland	103	3209	3312	3.11	173	172	0.00249
Israel	106	3480	3586	2.96	149	172	0.00249
Italy	52	7039	7091	0.73	165	165	0.00249
Japan	1188	24803	25991	4.57	164	163	0.00249
Laos	23	146	169	13.61	69	103	0.10697
Luxembourg	60	2652	2712	2.21	144	150	0.00249
Malaysia	22	3310	3332	0.66	151	155	0.00249
Netherlands	35	4717	4752	0.74	165	173	0.00249
New-Zealand	20	3971	3991	0.50	144	145	0.00249
Portugal	102	1955	2057	4.96	136	146	0.00249
Puerto-Rico	16	2427	2443	0.65	146	154	0.00249
Singapore	197	7534	7731	2.55	156	160	0.00249
South-Korea	890	32292	33182	2.68	154	153	0.00249
Spain	246	15024	15270	1.61	174	173	0.00249
Sweden	91	7942	8033	1.13	168	167	0.00249
Taiwan	34	721	755	4.50	126	151	0.00249
Thailand	15	2524	2539	0.59	162	166	0.00249
USA	2263	118083	120346	1.88	170	169	0.00249
United-Kingdom	347	36006	36353	0.95	164	163	0.00249

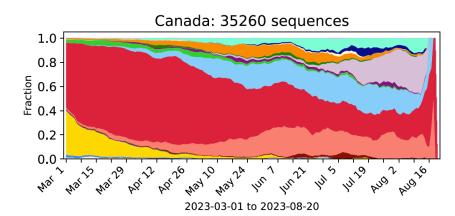


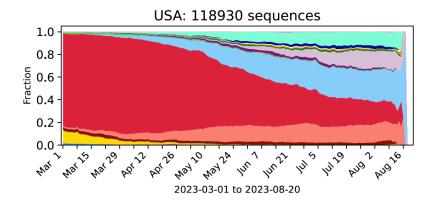
EG.5 and EG.5.1 in GISAID: the five or six most common forms

```
EG.5
            Alias of XBB.1.9.2.5,
                                  S:F456L
    EG.5.1
           Alias of XBB.1.9.2.5.1,
                                  S:Q52H
                                                                           Pango lineage
                                                                          designations not
                                                                           vet is GISAID
                                 Pct HD [Form as mutation string]
Lineage
              Count
                      Count
EG.5.1
                6068
                        4310
                              71.0%
                                       0 + [052H, F456L] (consensus)
EG.5.1
                6068
                        139
                               2.3%
                                       1 + [052H, H146K, F456L] - [H1460]
EG.5.1
                6068
                          87
                               1.4%
                                       1 + [052H, L455F, F456L]
                                                                            HK.3
EG.5.1
                6068
                               1.2%
                                       1 + [Q52H, F157L, F456L]
                          75
                                                                            EG.5.1.6
EG.5.1
                6068
                               1.0%
                                       1 + [Q52H, G257V, F456L]
                          61
                                                                            HK.1
                          37
EG.5.1
                               0.6%
                                        2 + [052H, F157L, L452R, F456L]
               6068
                                                                            HV.1
EG.5
                 550
                         268
                              48.7%
                                       0 + [F456L] (consensus)
EG.5
                 550
                               8.9%
                          49
                                       2 + [F456L, S704L, N1178D]
                                                                            EG.5.2.3
EG.5
                                                                            EG.5.2.1
                 550
                          42
                               7.6%
                                       1 + [F456L, S704L]
                                       2 + [H69 - , V70 - , F456L]
EG.5
                 550
                          23
                               4.2%
                                       2 + [L5F, F456L, S704L]
EG.5
                               3.1%
                 550
                          17
```









Grouped Lineages



Fastest increasing forms of Spike sampled >60 times in the last 60 days globally, and a representative Pango lineage carrying that form

						Most in	eresting column is Relative differences, but Absolute (Abs) and counts are also of interest
Pango Global	Form	Form	Counts	Fractions	Dif	ferences	
Lineage Count	Count	Pct	Early/Later	Early/Later	Abs	Relative pva	HD [Form as mutation string relative to XBB.1.5]
v means variant							Sublineages of these XBB's
FE.1 31444	1402	4.5%	662/740	0.04319/0.04591	+0.2	7% +5.9% 3e-	1 +[F456L] Brazil. XBB.1.18.1, XBB.1.5, XBB.1.16, XBB.1.9
EG.5.1 31444	3047	9.7%	1155/1892	0.07536/0.11738	+4.2	0% +35.8% <1e	9 2 + [Q52H, F456L] XBB.1.9.2
EG.5.1v 31444	111	0.4%	43/68	0.00281/0.00422	+0.1	4% +33.5% 4e-	
XBB.1.16.6 31444	471	1.5%	176/295	0.01148/0.01830	+0.6	8% +37.3% 6e-	3 + [E180V, F456L, T478R] - [T478K] XBB.1.16
FL.1 31444	330	1.0%	53/277	0.00346/0.01719	+1.3	7% <mark>+79.9%</mark> <1e	9 3 +[F456L , T478R, A701V] - [T478K] XBB.1.9.1
							(33)23)2
XBB.2.3.3 31444	496	1.6%	229/267	0.01494/0.01657	+0.1	6% +9.8% 3e	1 6 + [K182N, D253G, P521S] - [G252V]
GE.1 31444	165	0.5%	56/109	0.00365/0.00676	+0.3	1% +46.0% 2e	4 8 +[N1851,F186-,D253G,T478R,P521S]-[G252V,T478K]
FY.3v 31444	94	0.3%	39/55	0.00254/0.00341	+0.0	9% +25.4% 2e	1 4 +[Y200C, I210T] XBB.1.22.1 sublineage
XBB.1.19.1v 31444	266	0.8%	97/169	0.00633/0.01049	+0.4	2% +39.6% 6e-	3 +[E554K] FL.10.1, FL.25
XBB.1.16v 31444	207	0.7%	96/111	0.00626/0.00689	+0.06%	+9.0% 5e-	5 + [E180V, K304N, T478R] - [T478K] XBB.1.16
XBB.1.16v 31444	187	0.6%	47/140	0.00307/0.00869	+0.56	% <mark>+64.7% </mark> ∢1e-	5 1 [D 1 0 0 0 7 0 D 0 D 5 2 1 T] _ [T 1 7 0 V]
FU.2v 31444	127	0.4%	45/82	0.00294/0.00509	+0.22	% +42.3% 3e-	6 + [E180V, T478R, T547I, E619Q] - [T478K] sublineages

Forms listed are both increasing and sampled >100 times in the last 60 days

Data: Take all non-ambiguous Spike sequences in the last 60 days. Divide that the number in half, and find the day where the split occurs. Count the number of every variant of Spike before and after the spilt, and see if the fraction is increasing. The Pango lineage is just the most common designation with that form of Spike.

XBC.1.6

Pango lineage designation in GISAID

Test lineage(s): XBC.1.6, XBC.1.6.1, XBC.1.6.2, XBC.1.6.3

Background lineage(s): All

Assumption: Test lineages are increasing over time

Range of dates: 2023-02-23 - 2023-08-21

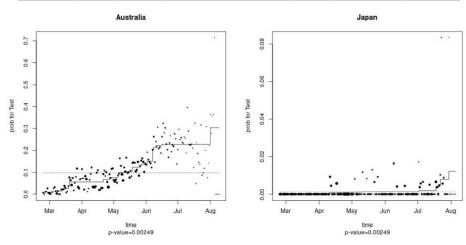
Hosts: include all

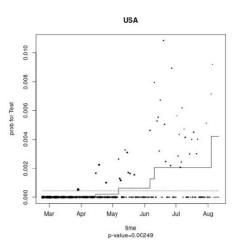
Download plots and data

Country level

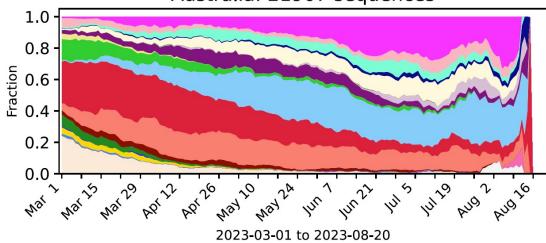
There were 2,278 sequences that matched your search term, the following summarizes the form in locations where it was found more than 10 times.

	# Test	# Others	Total	Test/Total (%)	# days	Time window	p-val
Australia	2138	19816	21954	9.74	168	167	0.00249
Japan	32	25959	25991	0.12	164	163	0.00249
USA	55	120291	120346	0.05	170	169	0.00249





Australia: 21907 sequences



California is state in the US in which XBC.1.6 was been sampled most, scattered samples: not increasing

