

Fighting a Moving Target: SARS-CoV-2 Evolution and Viral Escape

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This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

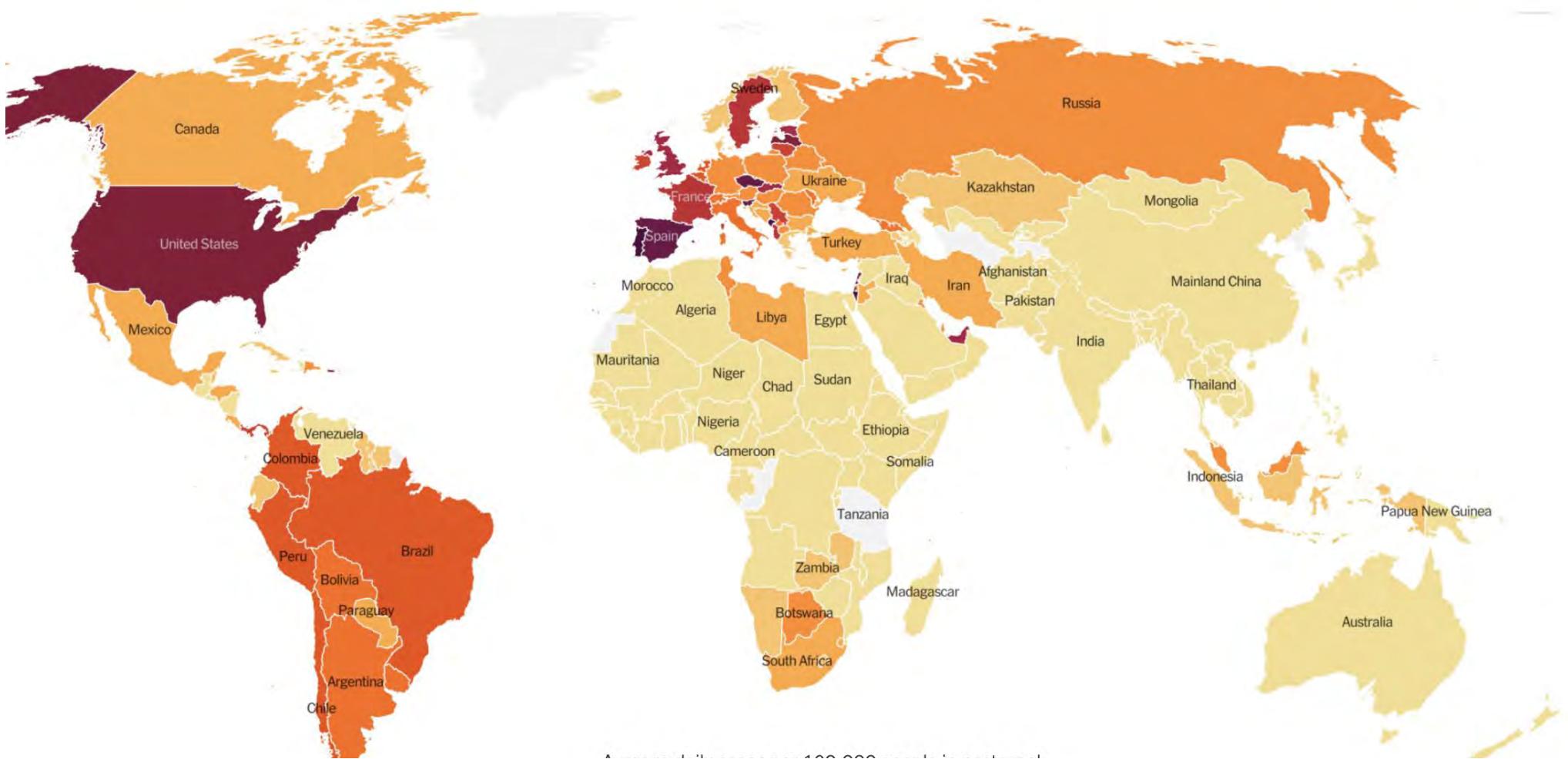
Overview

- Update on numbers in the United States
- Persistent infection and new variants
- Monoclonal antibodies and effect of new variants
- Where could these variants have come from?

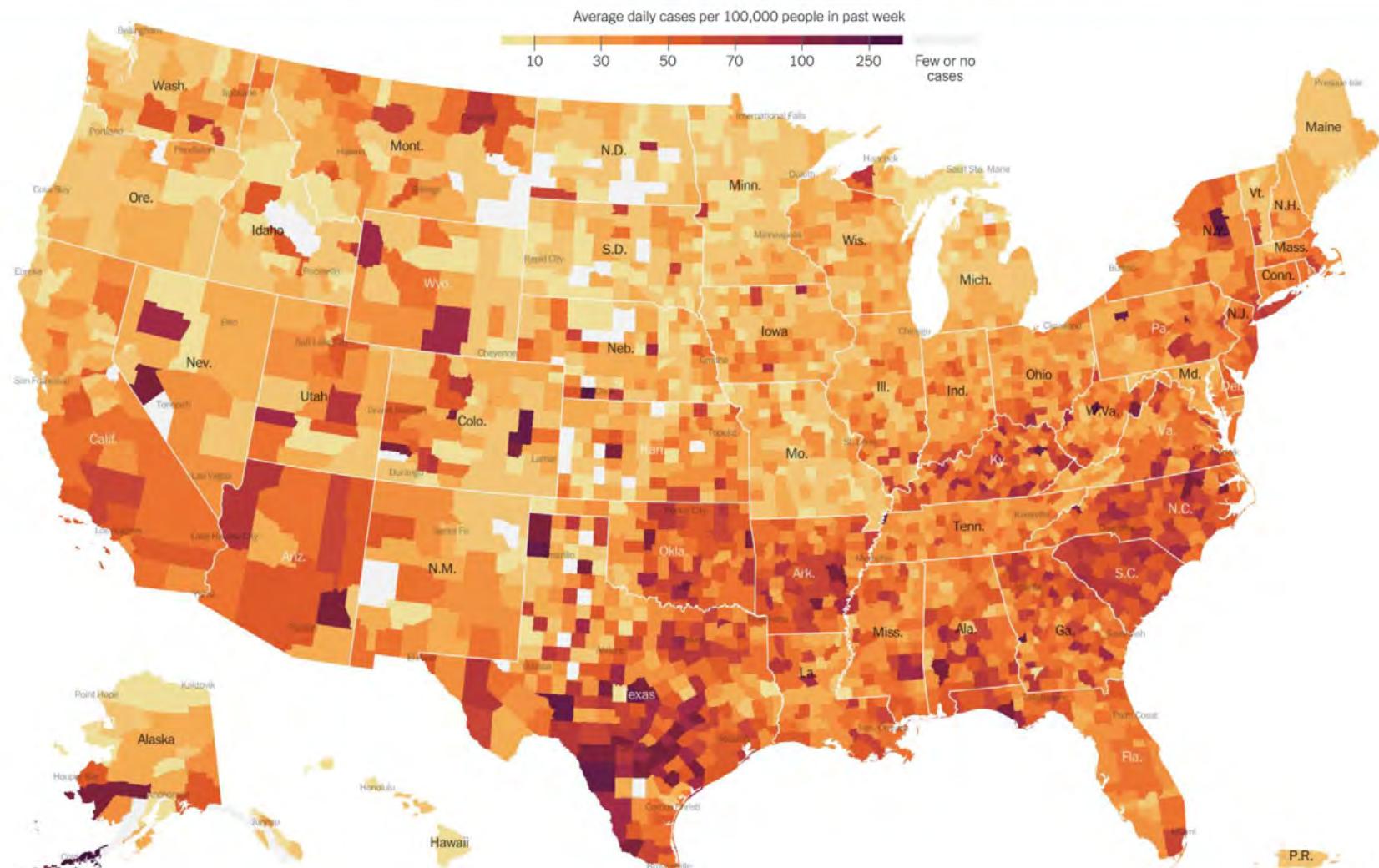
Definitions

- The virus: SARS-CoV-2
 - The disease: Coronavirus Disease 2019 (COVID-19)
-

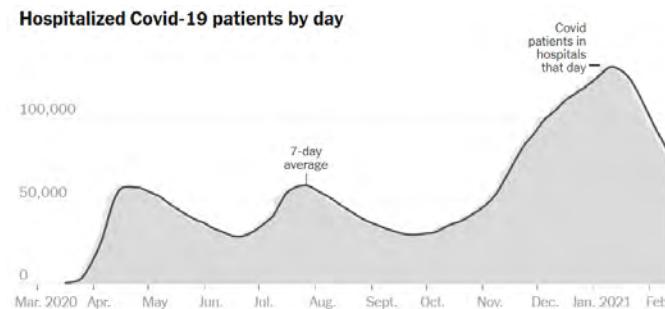
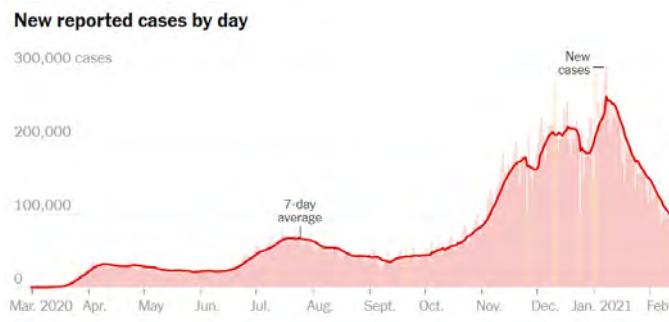
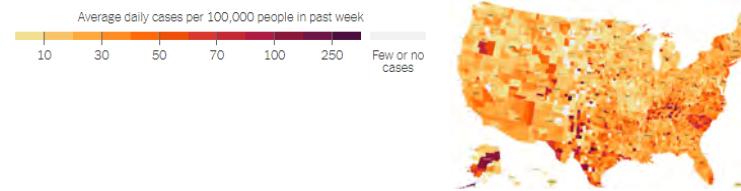
World: over 105 million cases and 2.2 million deaths



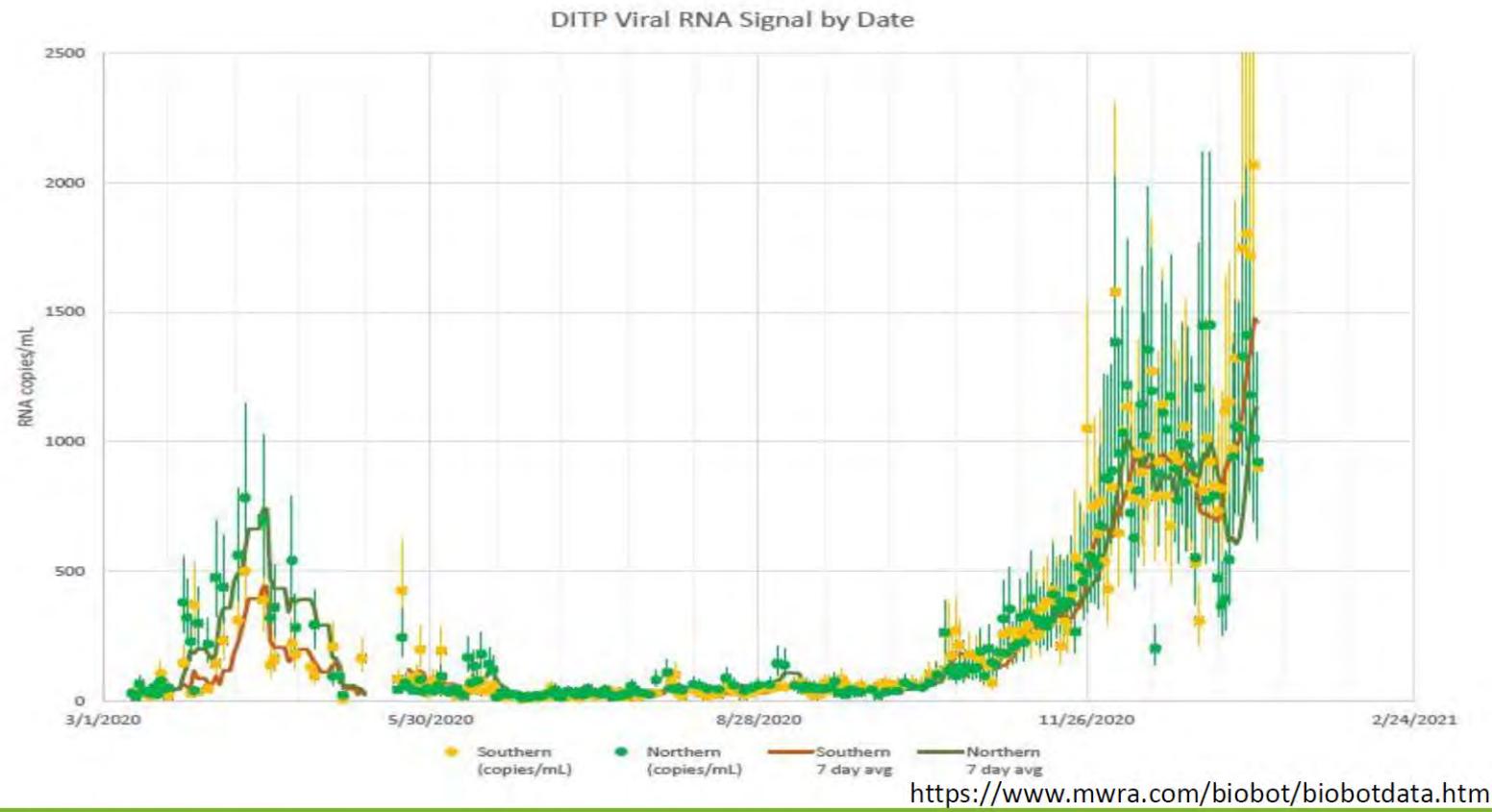
USA: over 27 million cases and 455,000 deaths



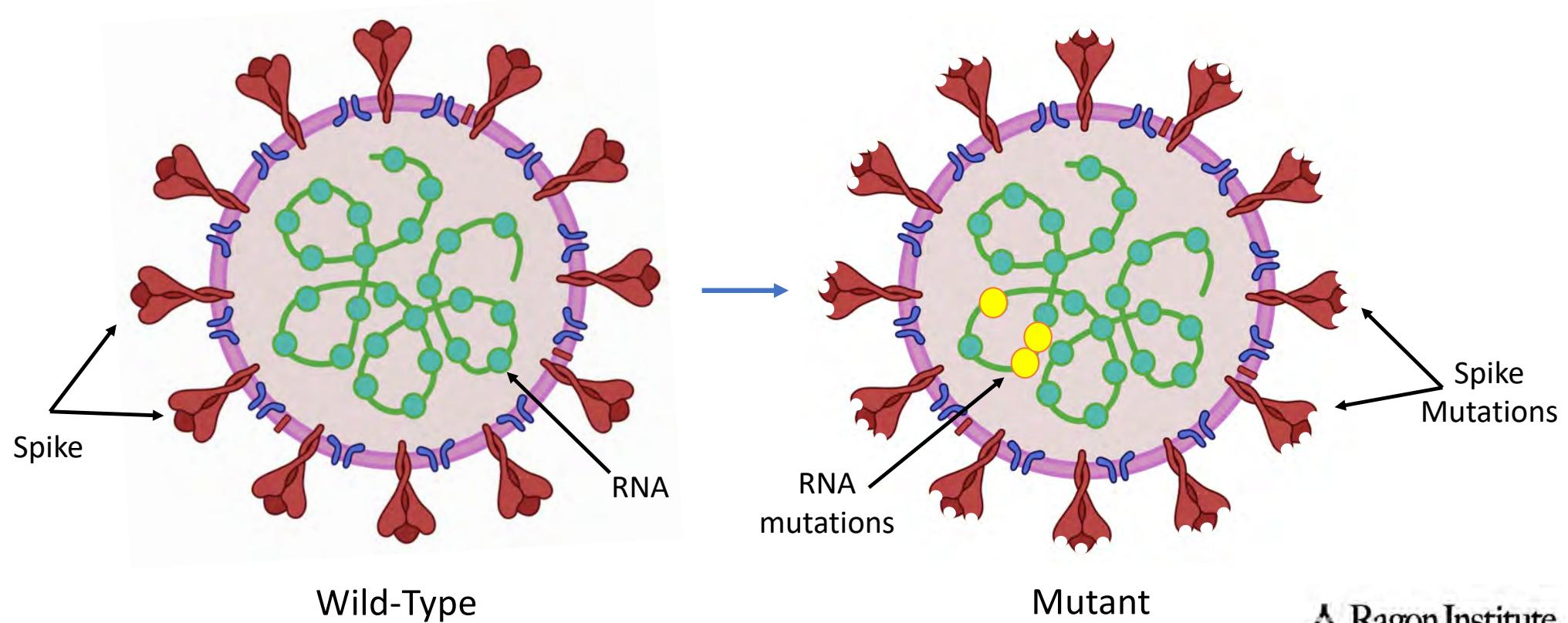
US COVID-19: 27,695,000



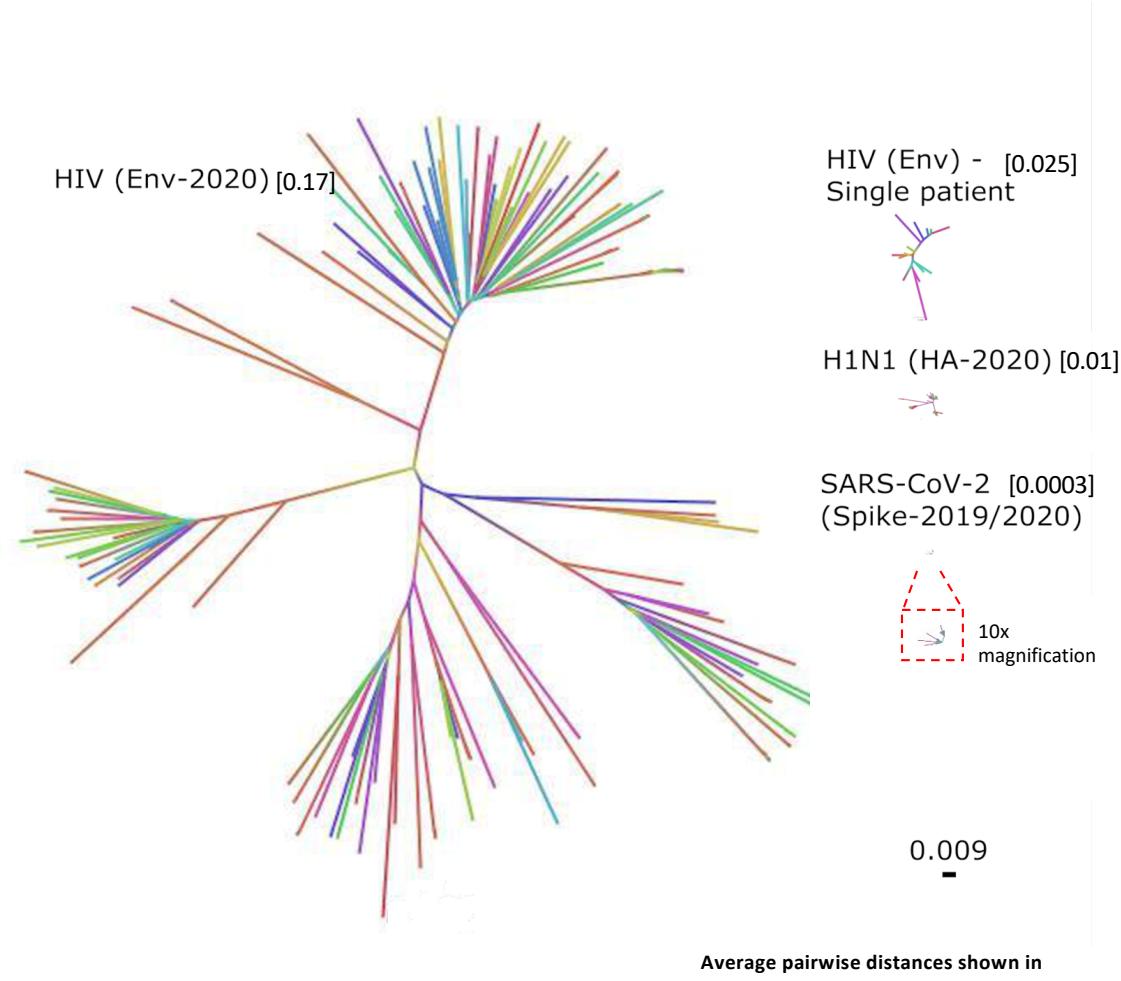
Wastewater COVID-19 Tracking



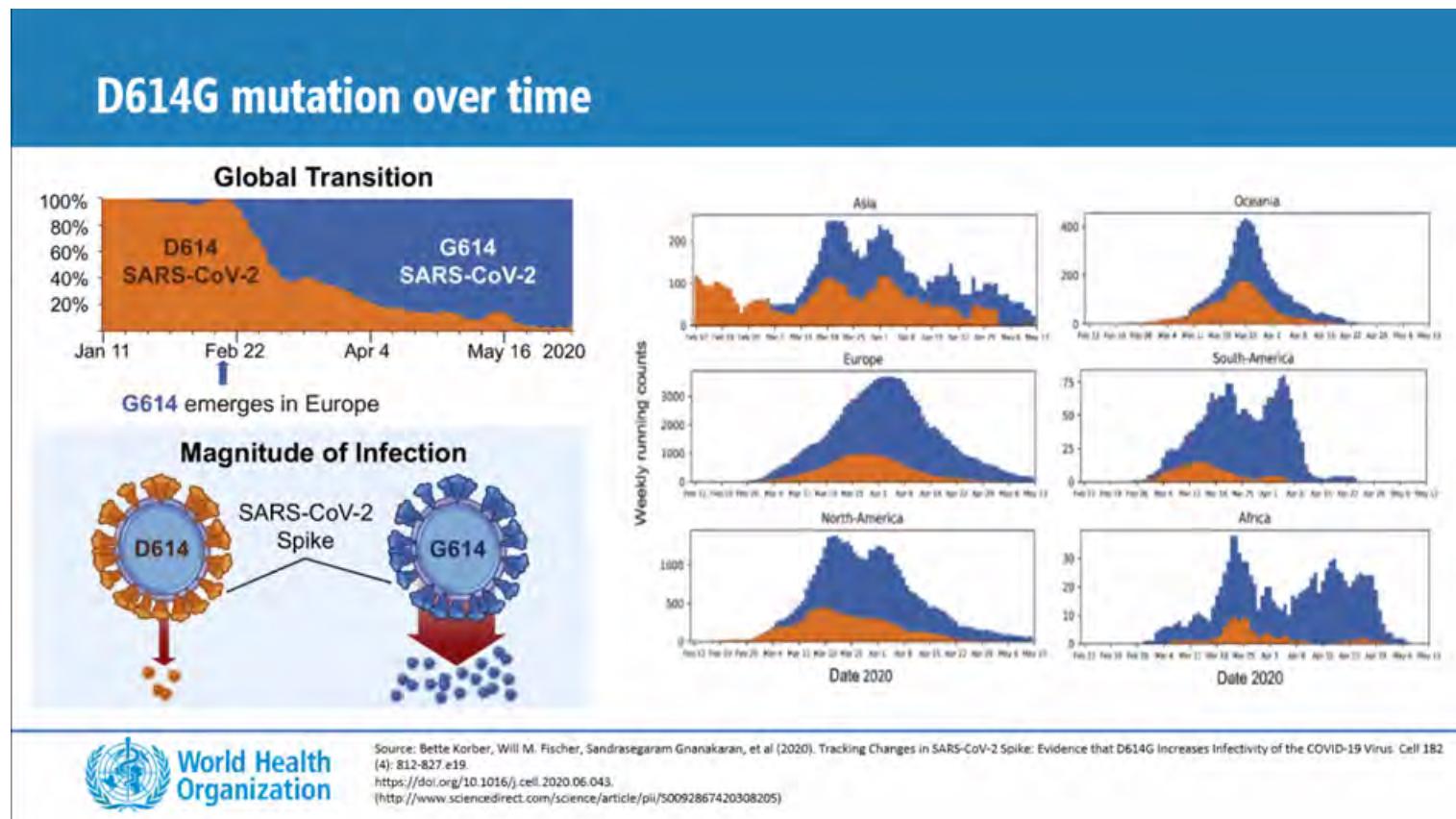
How Worried Should We Be About Mutations?



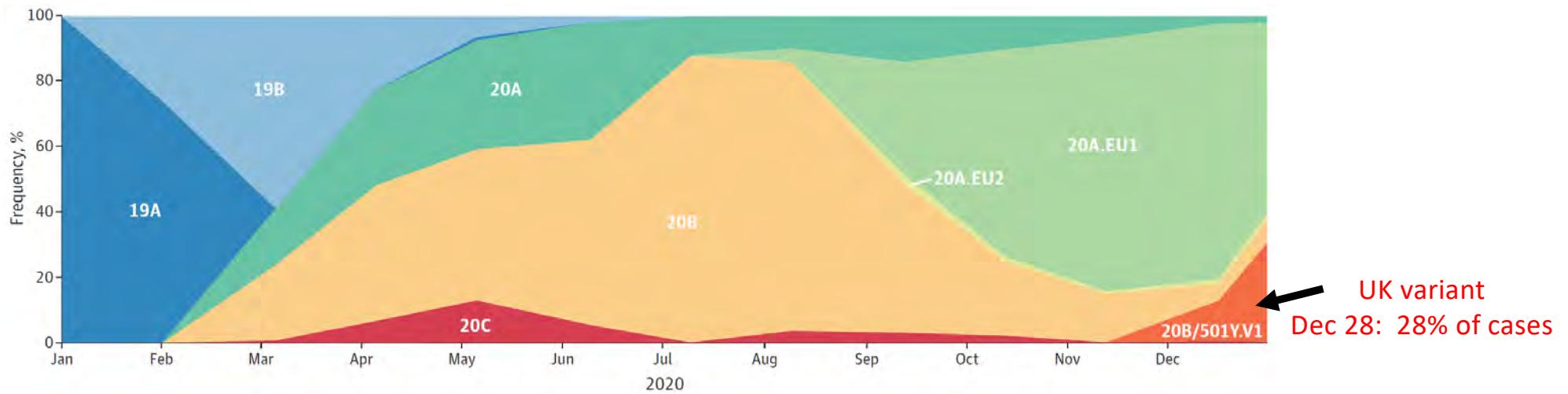
SARS-CoV-2 viral evolution in perspective



New variants have emerged previously

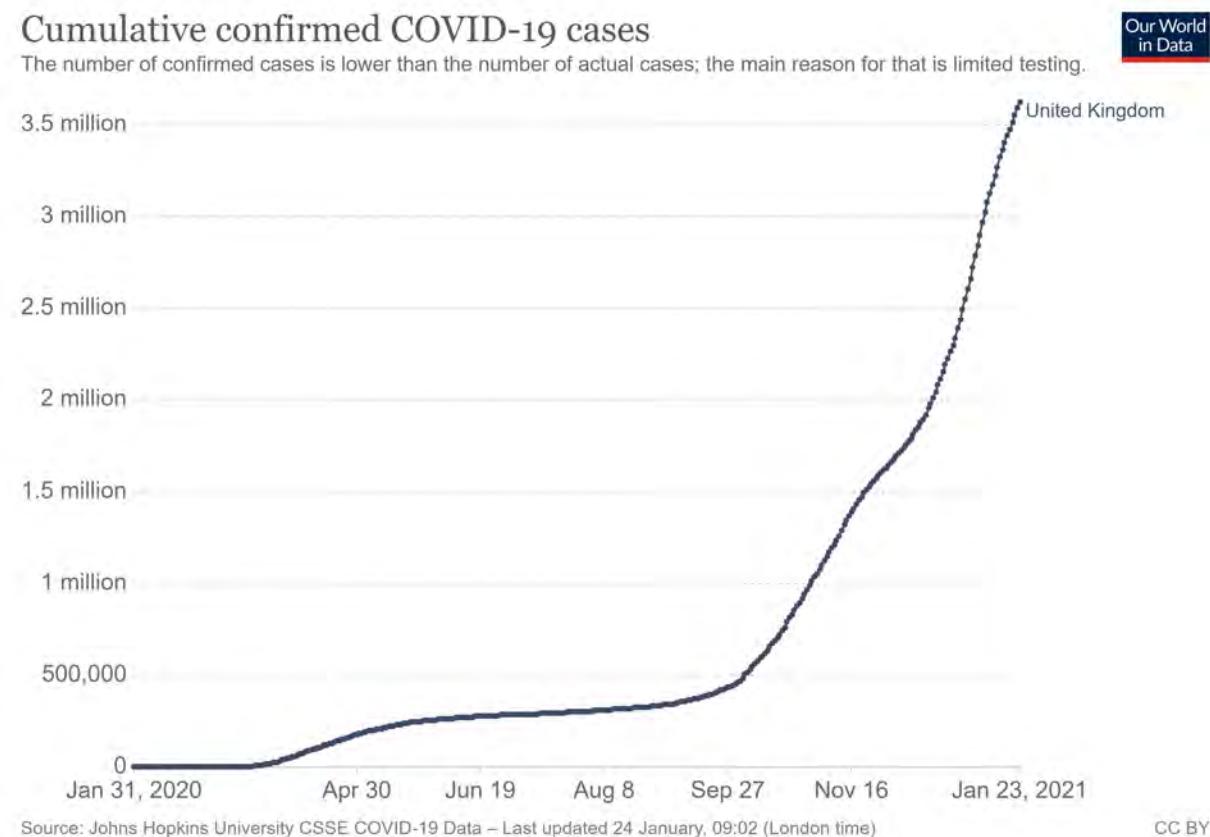


How much is SARS-CoV-2 changing over time? Data from England

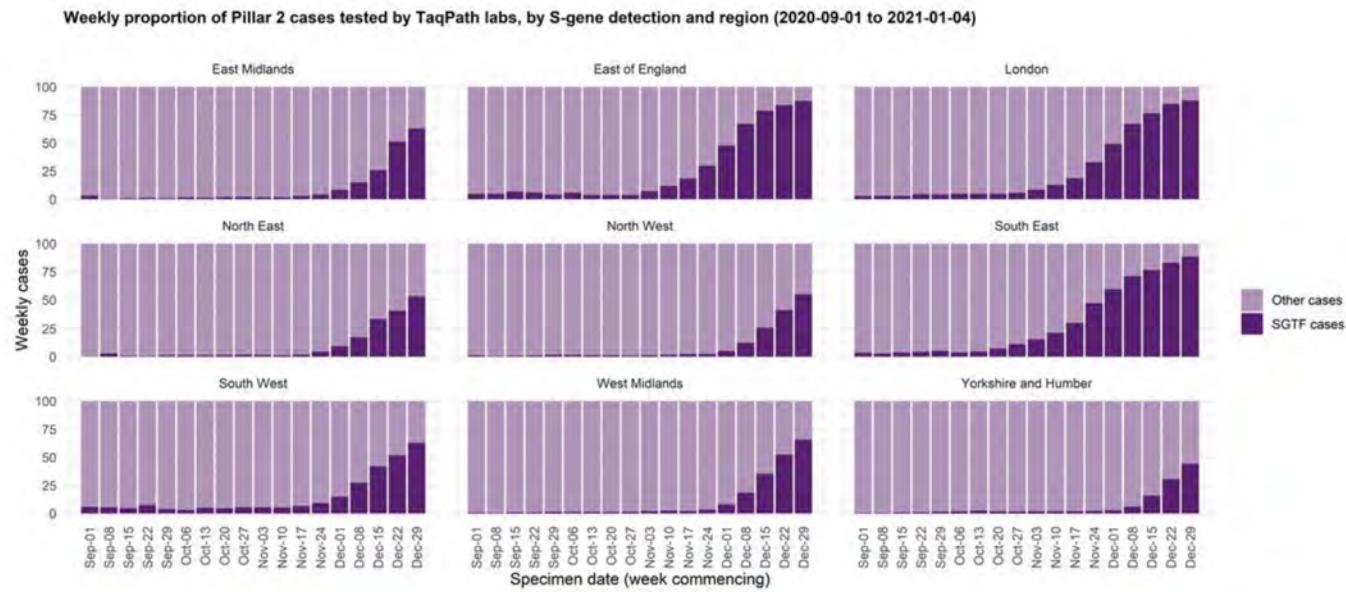
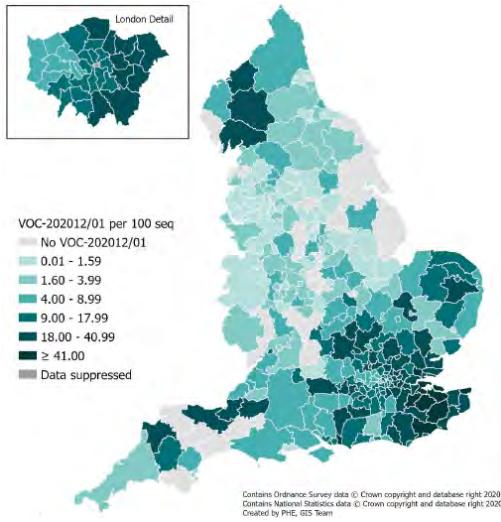


Lauring, JAMA 2021

How rapidly did SARS-CoV-2 spread in England?

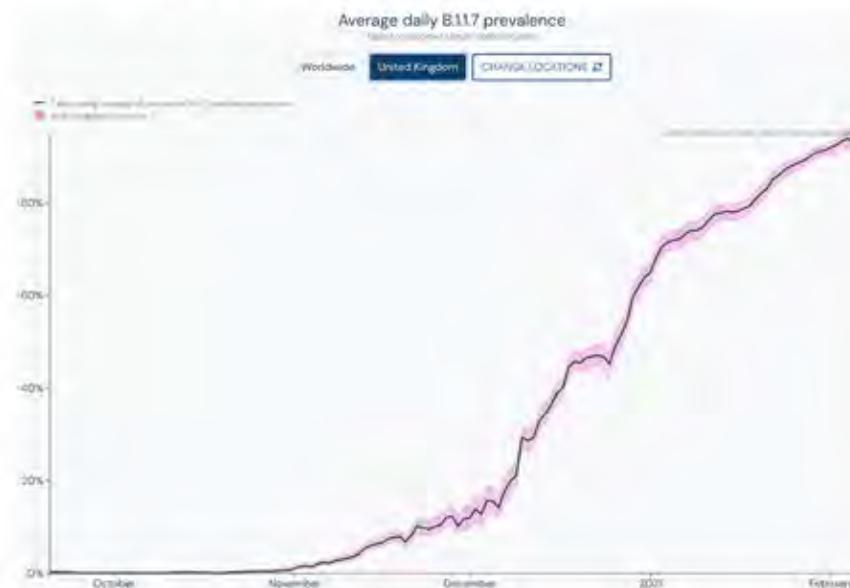


Trajectory of B.1.1.7 variant spread across the UK



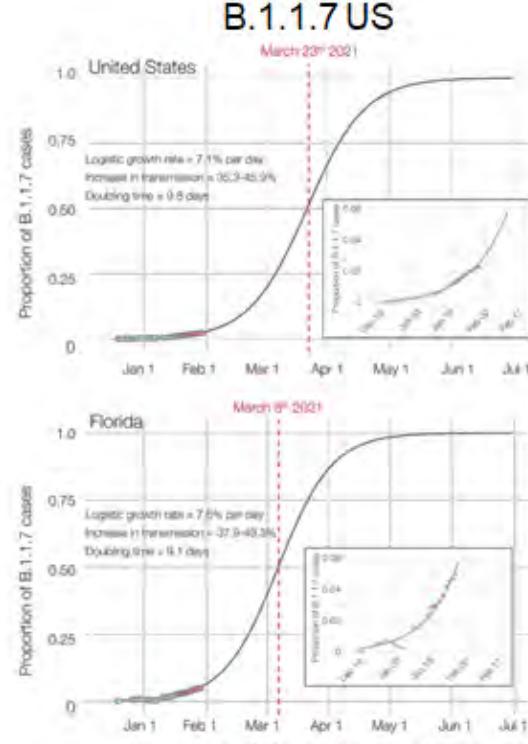
B.1.1.7 is spreading world-wide

B.1.1.7 UK



Outbreak.info

B.1.1.7 US



How much more transmissible is B.1.1.7 (UK variant)?

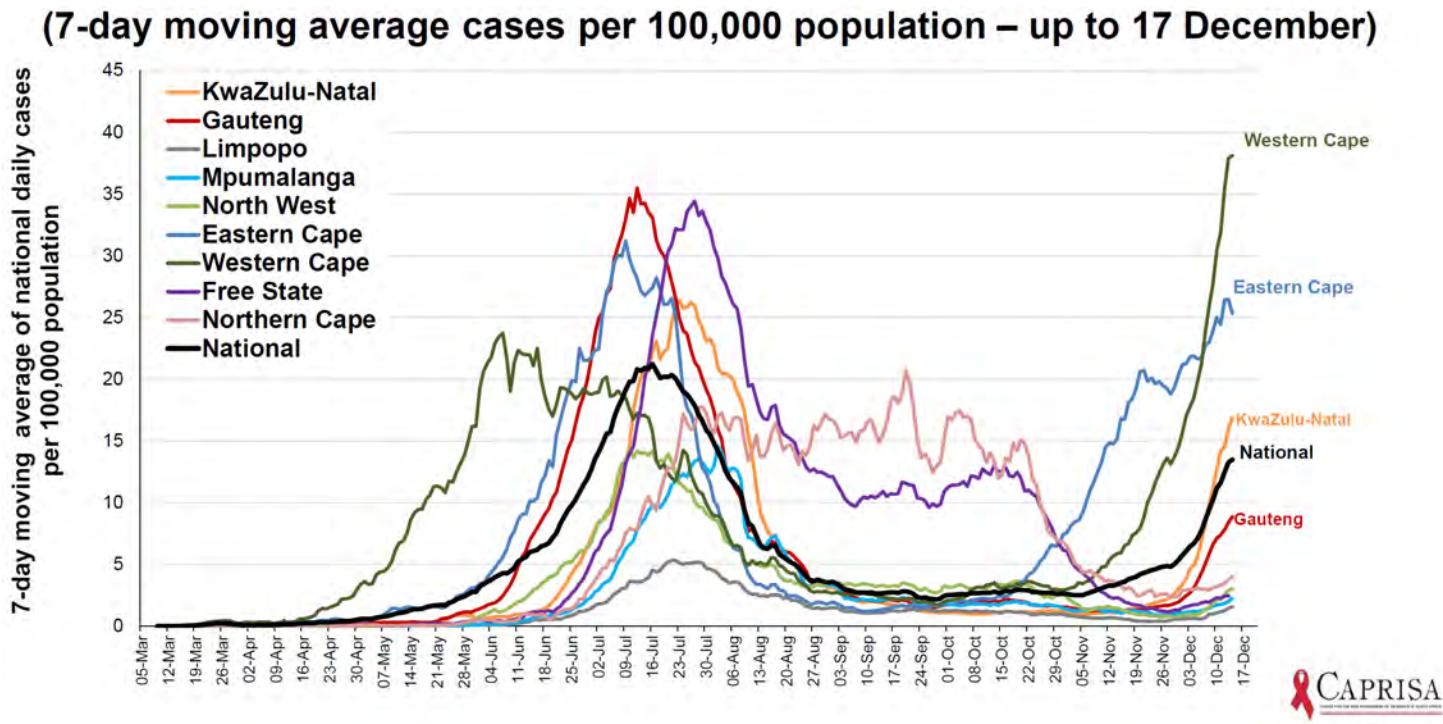
Attack rates: contacts becoming cases, England

Breakdown by contact characteristics using genomic sequencing data

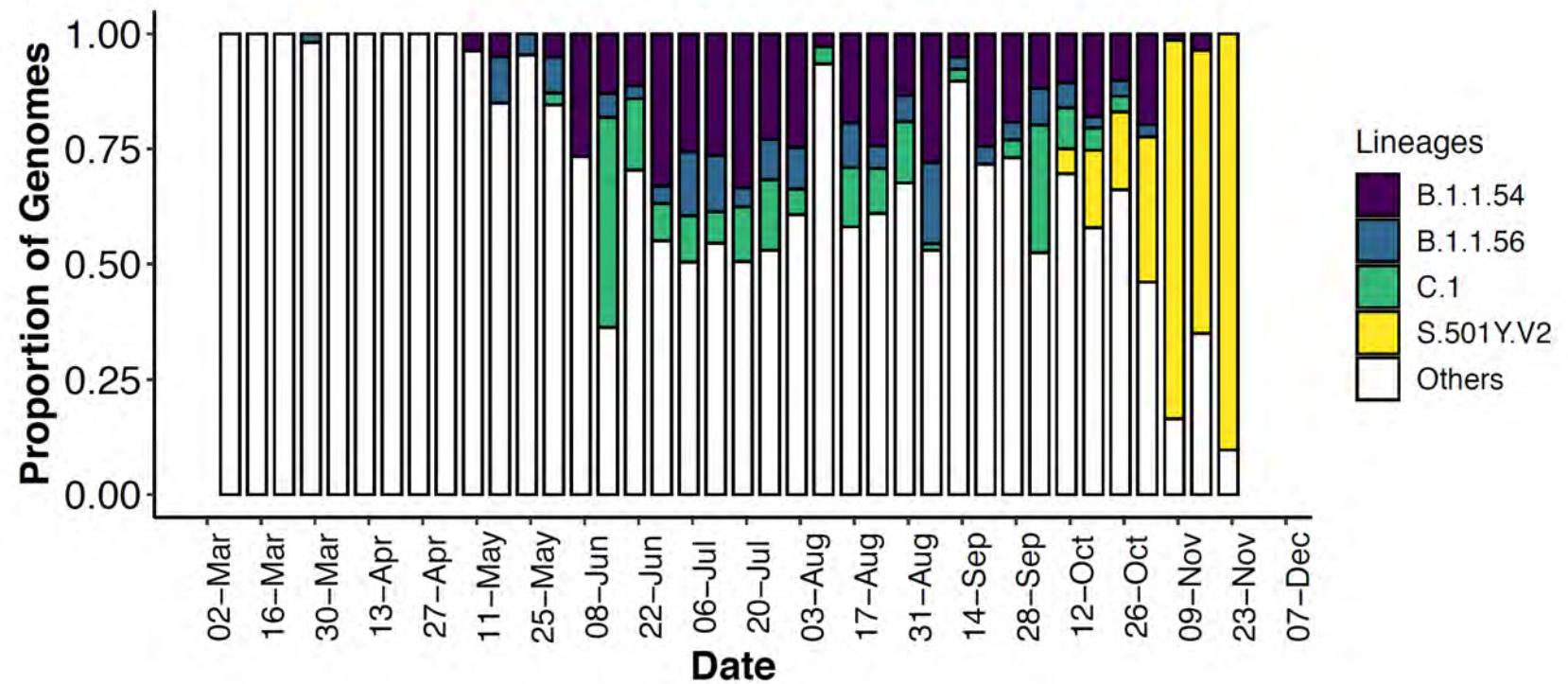
- Estimated AR for VOC 202012/01 are 10%-70% higher than estimated AR for wild type virus in most regions and age groups, excepting the East Midlands (small numbers)

Characteristic of contact		All contacts	Contacts of people with VOC 202012/01		Contacts of people with wild type (not VOC 202012/01)		Contacts of people without sequencing		
		Total contacts	All contacts	Contacts that became cases	%	All contacts	Contacts that became cases	%	%
Region of residence	All	956,519	9,228	1,361	14.7	11,269	1,246	11.0	12.7
	East Midlands	60,153	150	15	10.0	1,008	112	11.6	11.2
	East of England	154,144	1,869	263	14.1	1,199	153	12.8	13.5
	London	281,461	3,507	505	14.4	1,844	192	10.7	13.1
	North East	28,450	235	29	12.3	738	79	10.7	11.8
	North West	71,002	400	65	16.2	2,182	223	10.2	11.7
	South East	186,311	2,419	377	15.6	1,155	107	9.3	13.5
	South West	41,465	230	43	18.7	380	50	13.2	11.8
	West Midlands	78,112	299	47	15.7	1,388	155	11.2	11.6
	Yorkshire and Humber	53,192	109	16	14.7	1,339	158	11.8	10.6
Level of contact*	Direct	875,237	8,399	1,299	15.5	10,088	1,193	11.8	13.2
	Close	79,867	829	62	7.5	863	49	5.2	6.9
	0 – 9	135,998	1,345	121	9.0	1,536	93	6.1	7.2
	10 – 19	172,506	1,659	196	11.8	1,943	186	9.6	10.4
	20 – 29	111,391	1,020	167	16.4	1,352	192	14.2	15.1
	30 – 39	111,712	1,145	229	20.0	1,361	175	12.9	16.7
	40 – 49	126,005	1,241	263	21.2	1,448	199	13.7	16.8
	50 – 59	101,501	953	190	19.9	1,236	181	14.6	17.1
	60 – 69	44,985	366	74	20.2	610	92	15.1	17.7
	70 – 79	17,817	142	34	23.9	198	38	19.2	18.1
	80+	7,429	53	11	20.8	93	14	15.1	17.7
Source: PHE		Not known	127,175	1,304	76	5.8	1,492	74	5.0

How extensive was the surge in South Africa?



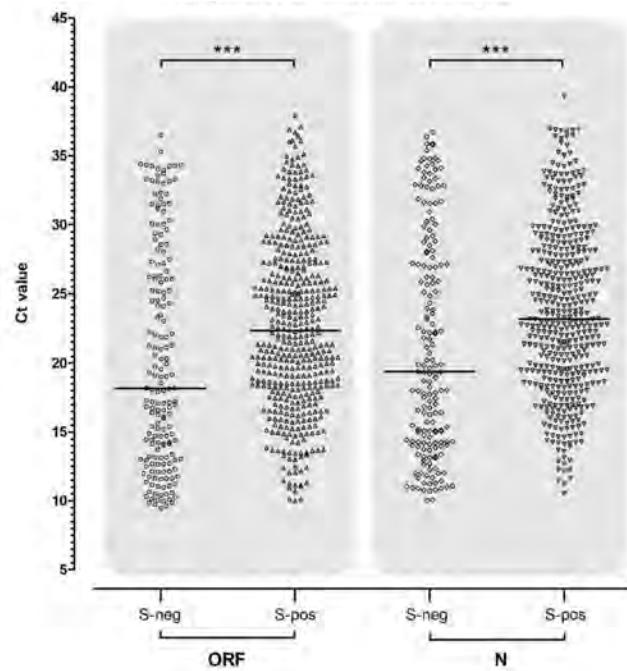
How quickly did B.1.351 (501Y.v2) spread in South Africa?



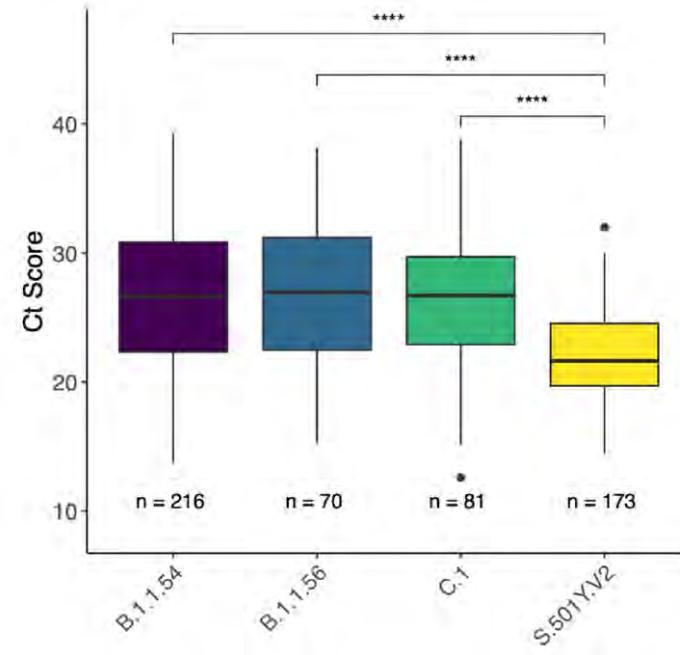
Lauring, JAMA 2021

How do the new variants affect transmission? Increase in viral load in the respiratory tract

B.1.1.7 (UK)



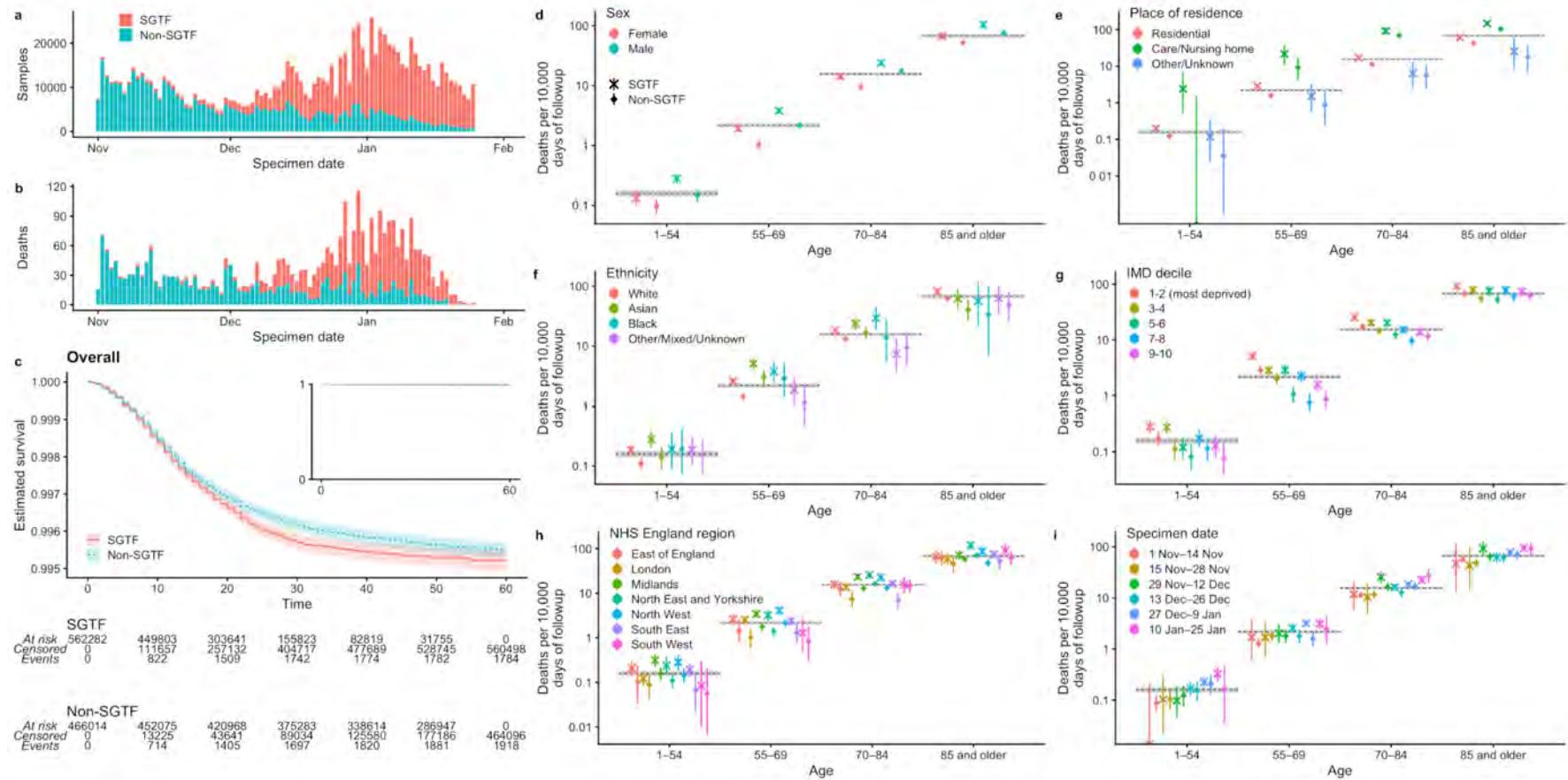
501Y.v2 (South Africa)



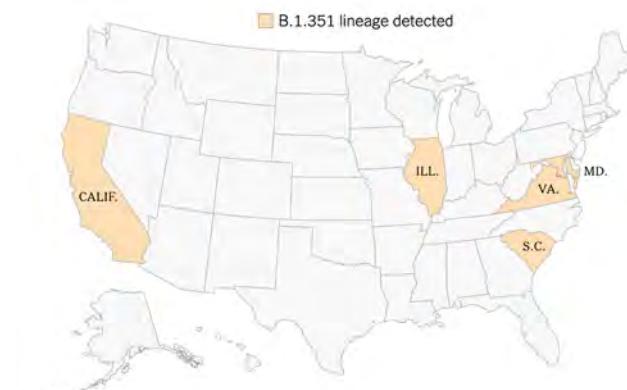
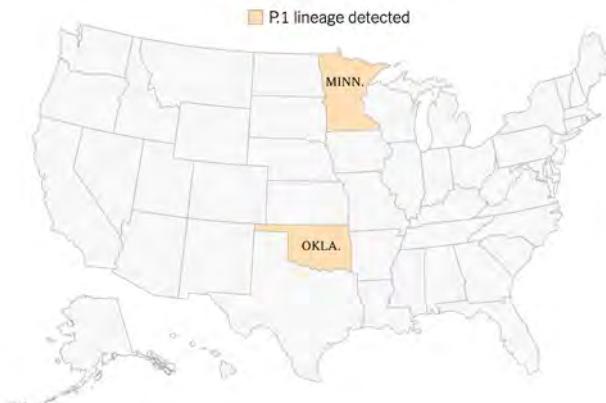
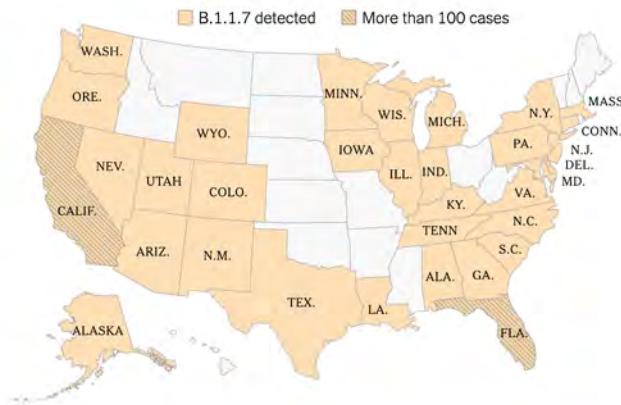
CAPRISA; Kidd, medRxiv 2021

Lower CT (cycle threshold) = higher viral load

B.1.1.7 associated with increased mortality

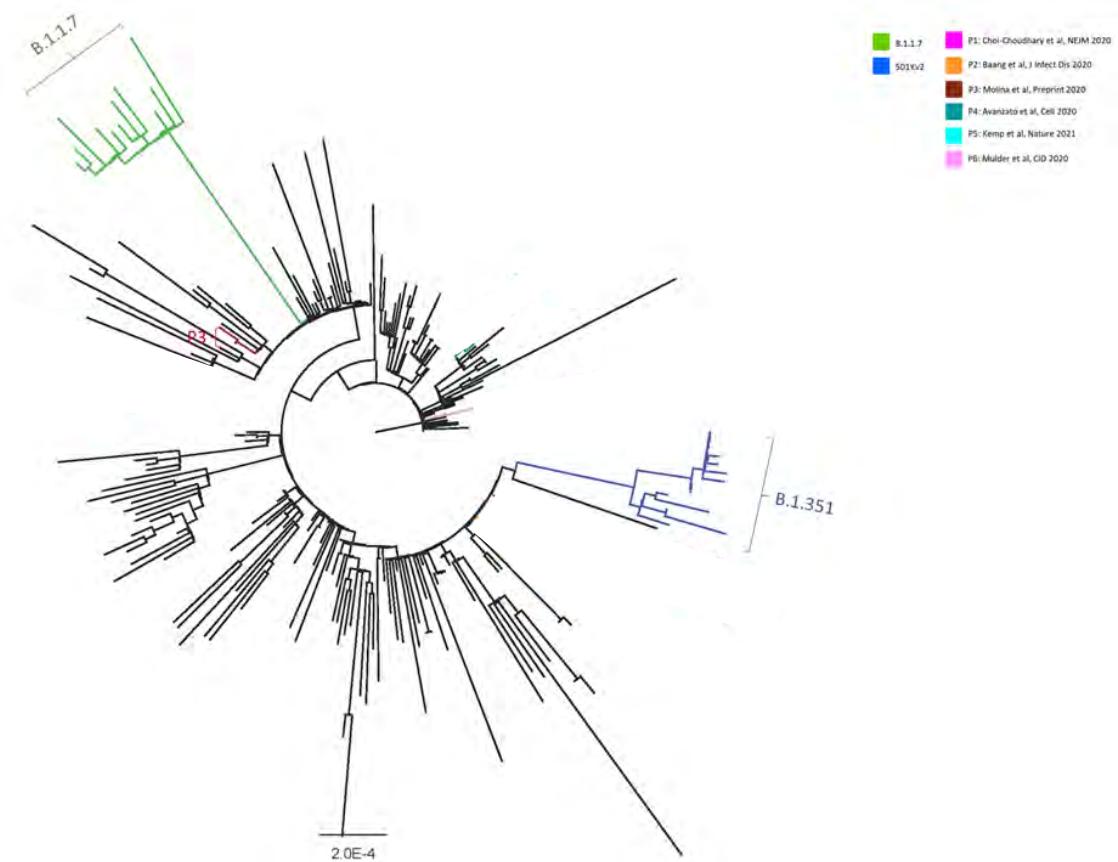


Variants of concern in the United States



New York Times

How did these mutations arise?



Uneven rate of SARS-CoV-2 sequencing globally

U.S. lags behind dozens of other countries in sequencing the coronavirus

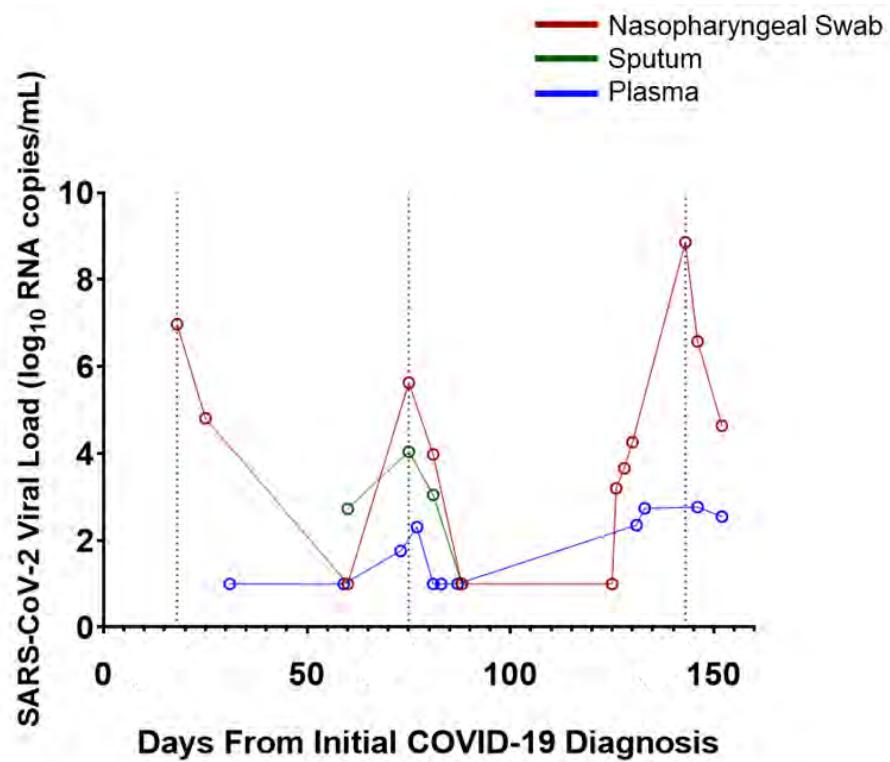
Share of coronavirus outbreak sequenced by countries with at least 100 reported cases

RANK	COUNTRY	REPORTED CASES	SAMPLES SEQUENCED	PERCENTAGE OF CASES SEQUENCED
1	Australia	28,238	16,537	58.6%
2	New Zealand	2,128	1,034	48.6
3	Taiwan	776	137	17.7
4	Denmark	144,047	16,790	11.7
5	Iceland	5,683	601	10.6
6	Gambia	3,791	360	9.5
7	Vietnam	1,421	113	8.0
8	Britain	2,116,609	157,439	7.4
9	Thailand	5,762	343	6.0
10	Japan	207,001	9,599	4.6
43	United States	18,229,260	51,212	0.3

Note: Timor-Leste has sequenced 58% of its 33 reported cases.

Sources: GISAID Initiative, COVID-19 Genomics UK Consortium, Johns Hopkins University, Post reporting HARRY STEVENS/THE WASHINGTON POST

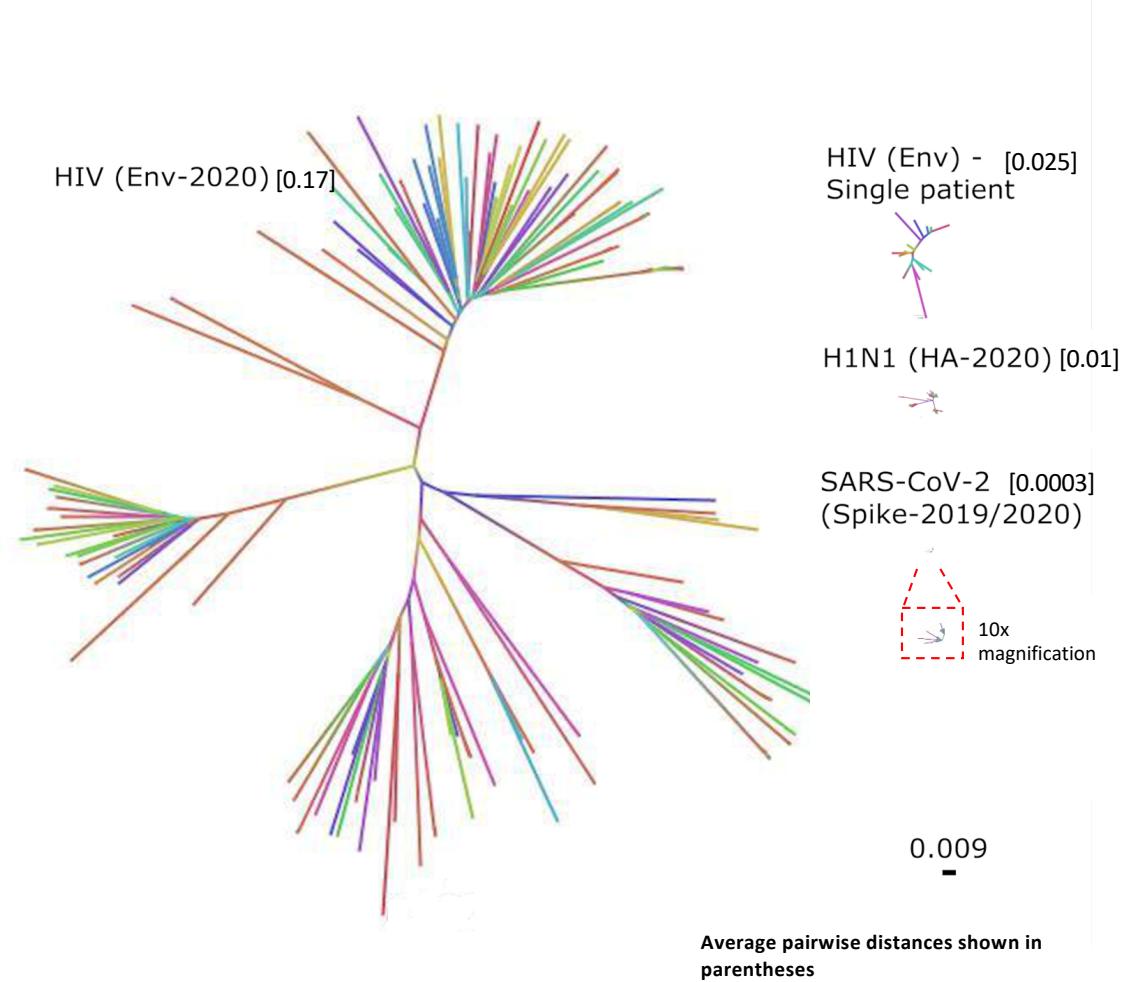
Where could these variants have come from: an unexpected case from Boston



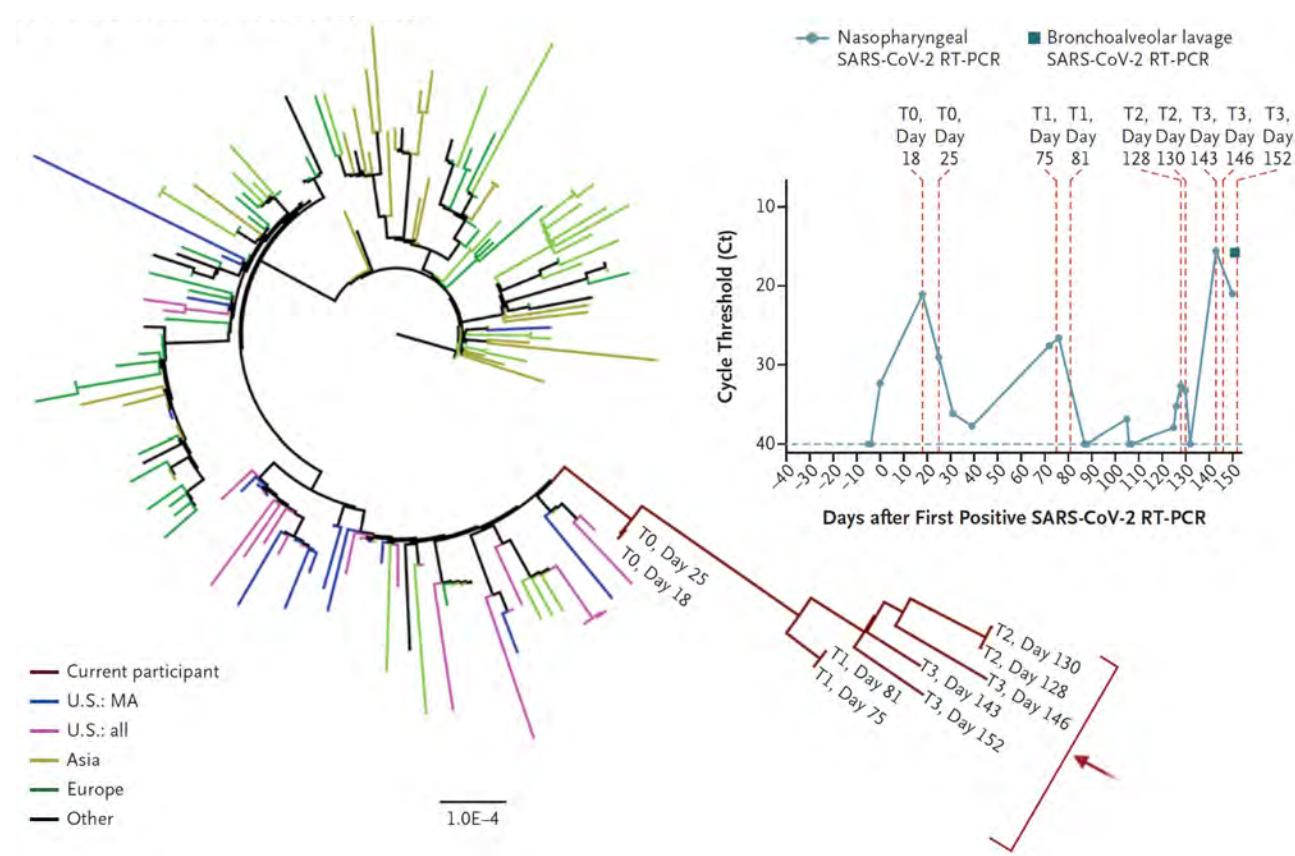
Key questions:

- Is this persistent COVID or reinfection?
- Are there signs of directed viral evolution and viral escape?
- Is this virus infectious?

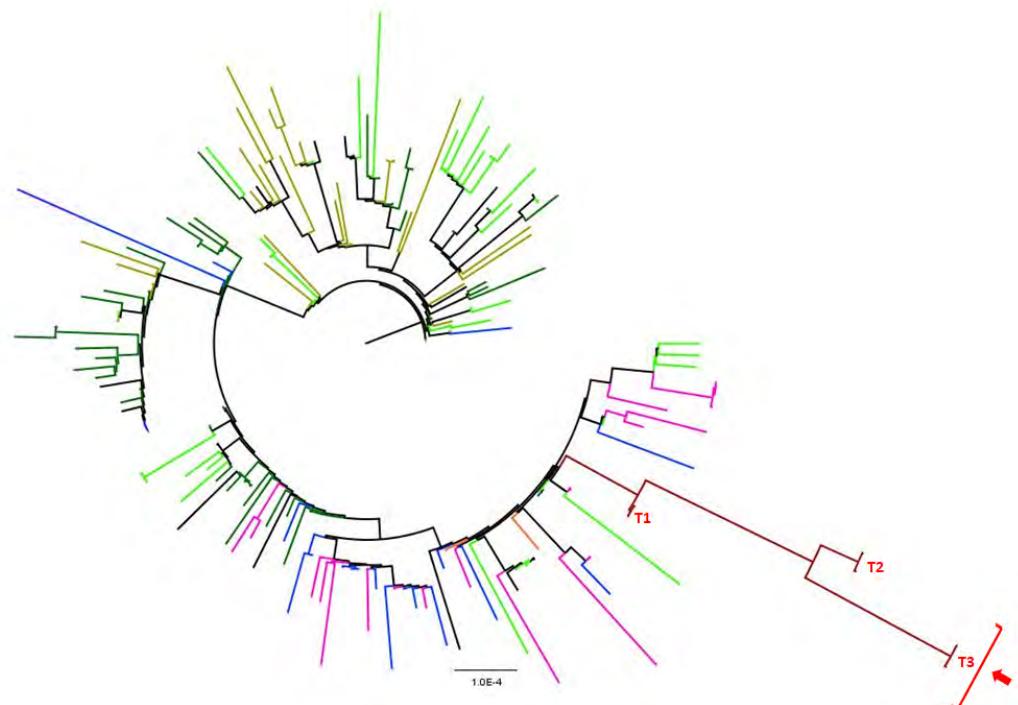
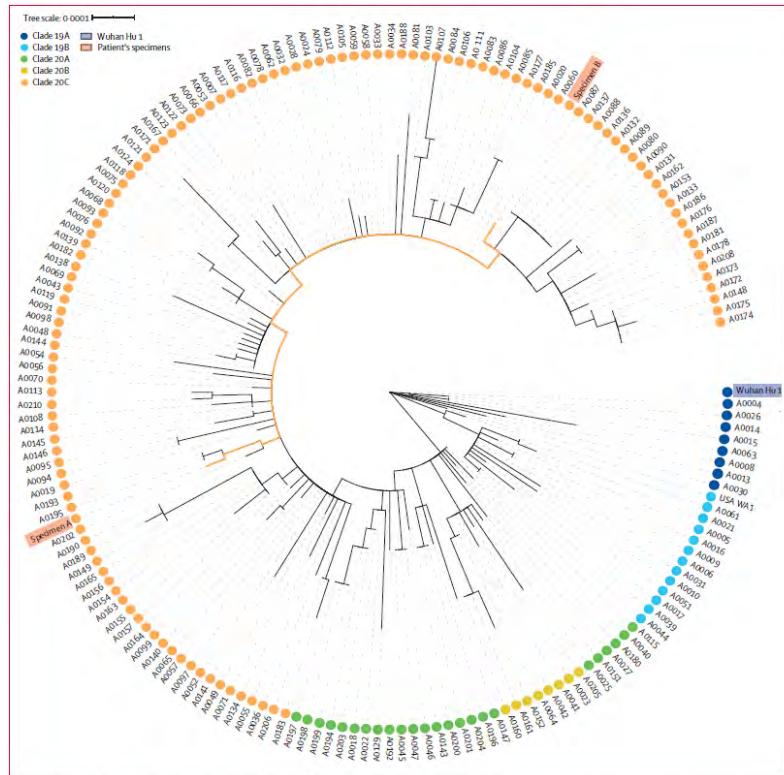
SARS-CoV-2 viral diversity in perspective



Phylogenetic evidence of viral persistence and evolution



Reinfection vs persistent infection



Persisting virus is infectious

Negative control



Positive control



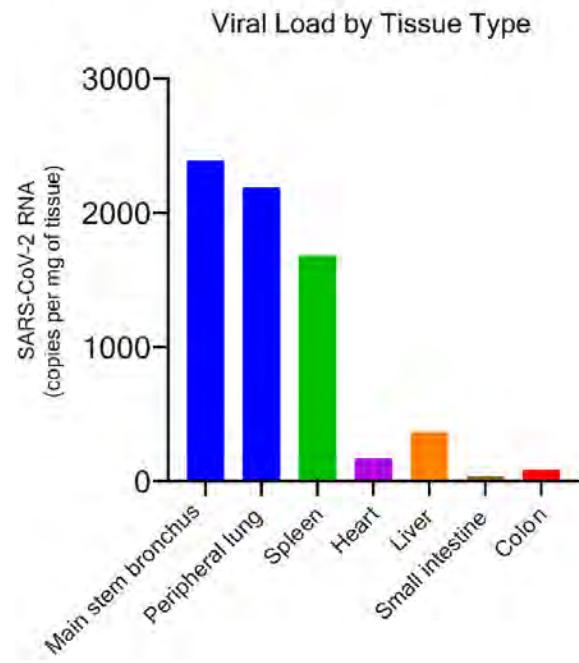
NP swab: Day 75



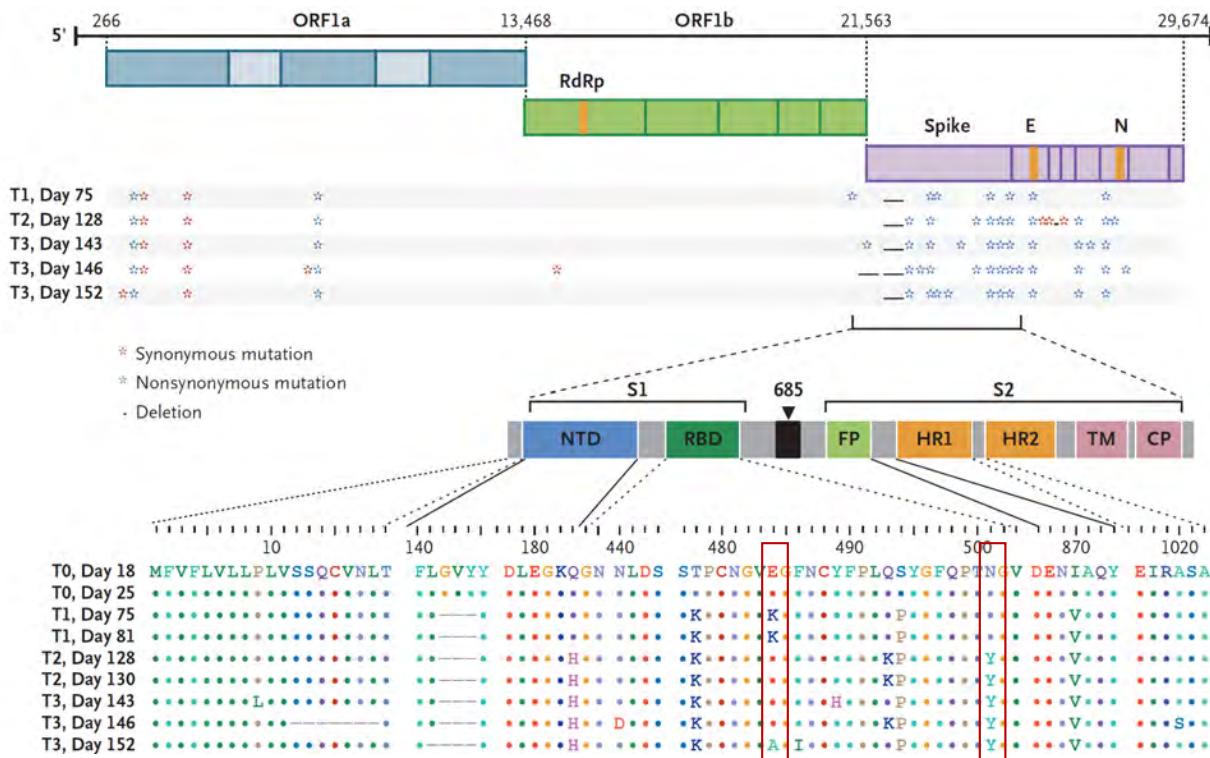
NP swab: Day 143



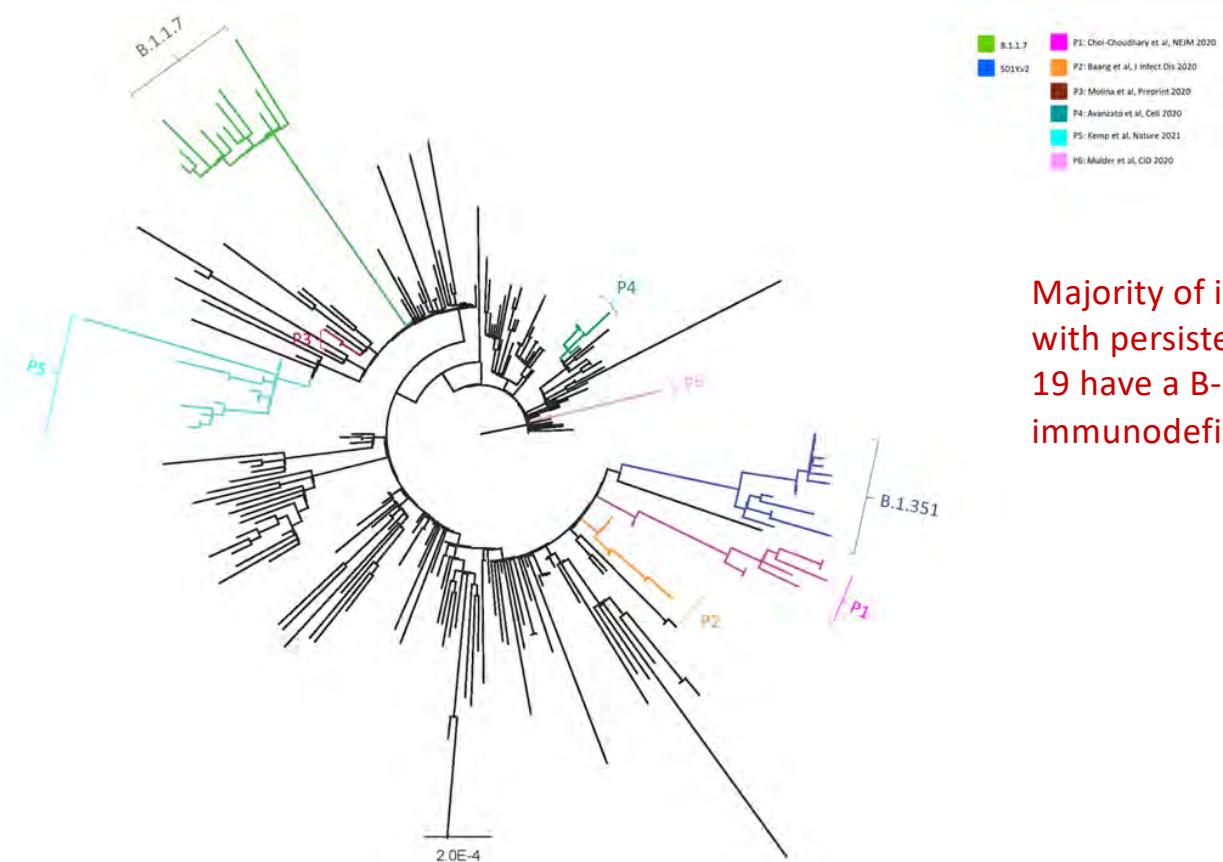
Disseminated SARS-CoV-2 across tissue types



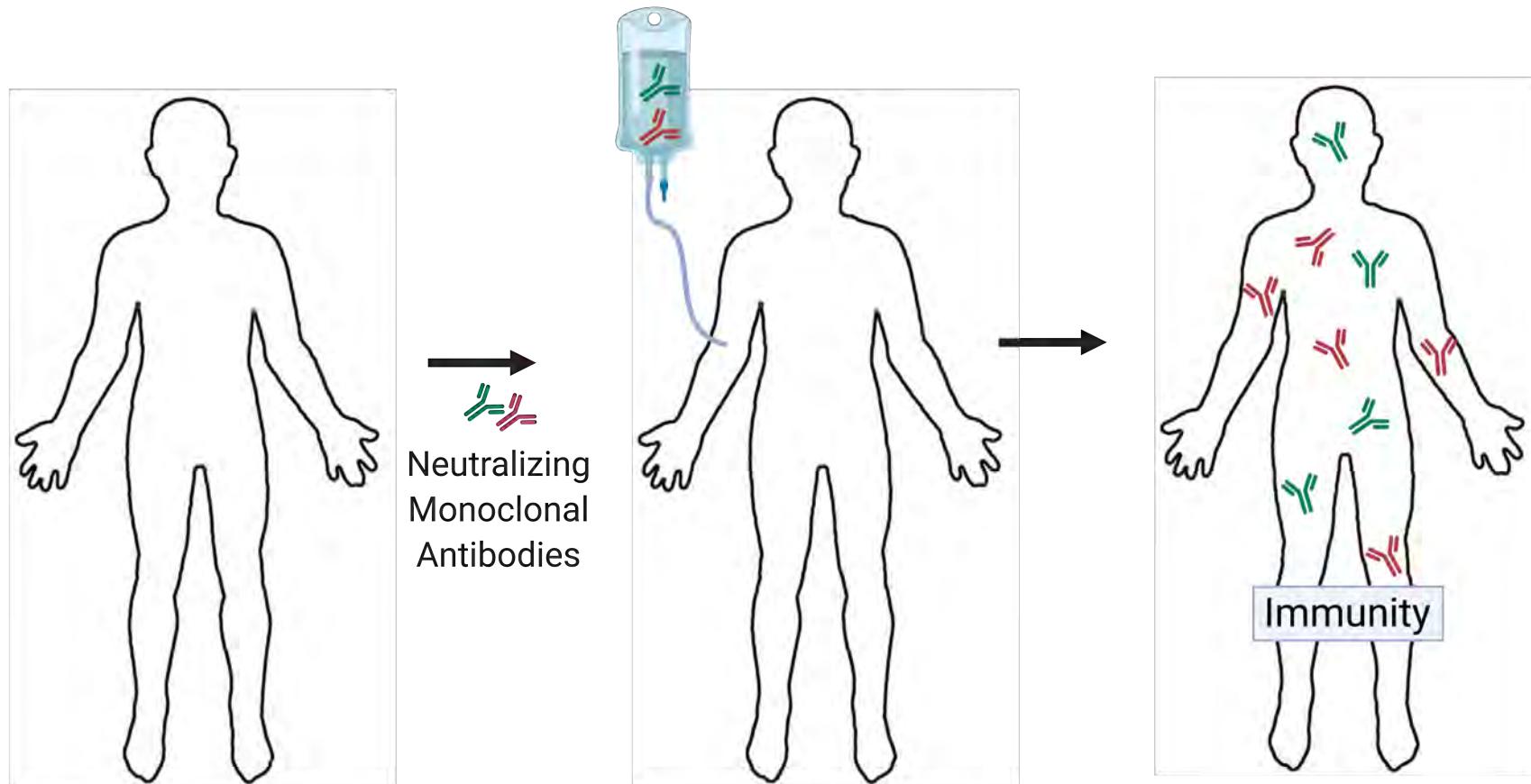
Directed viral evolution, especially in the spike and receptor binding domains



Could the evolutionary “jumps” have originated from an individual with persistent infection?

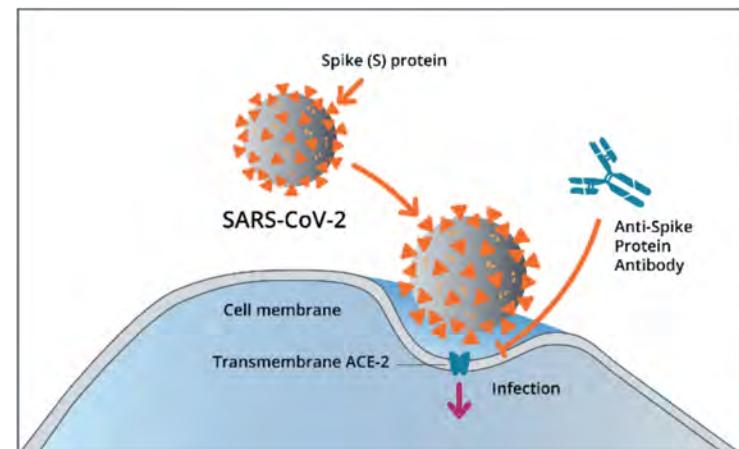


Do mutations affect efficacy of Bnabs to SARS-CoV-2?



Background on monoclonal antibodies (mAbs)

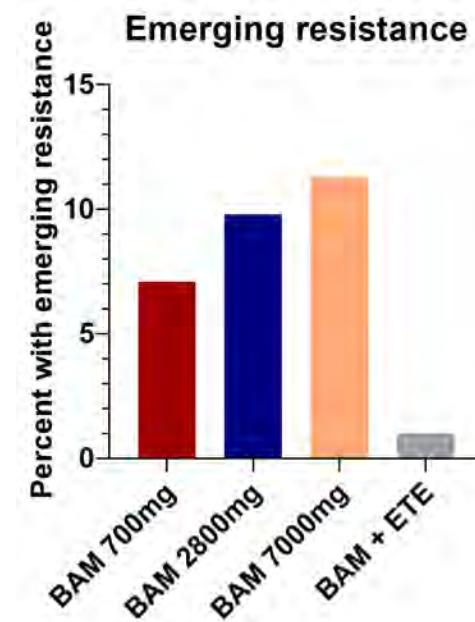
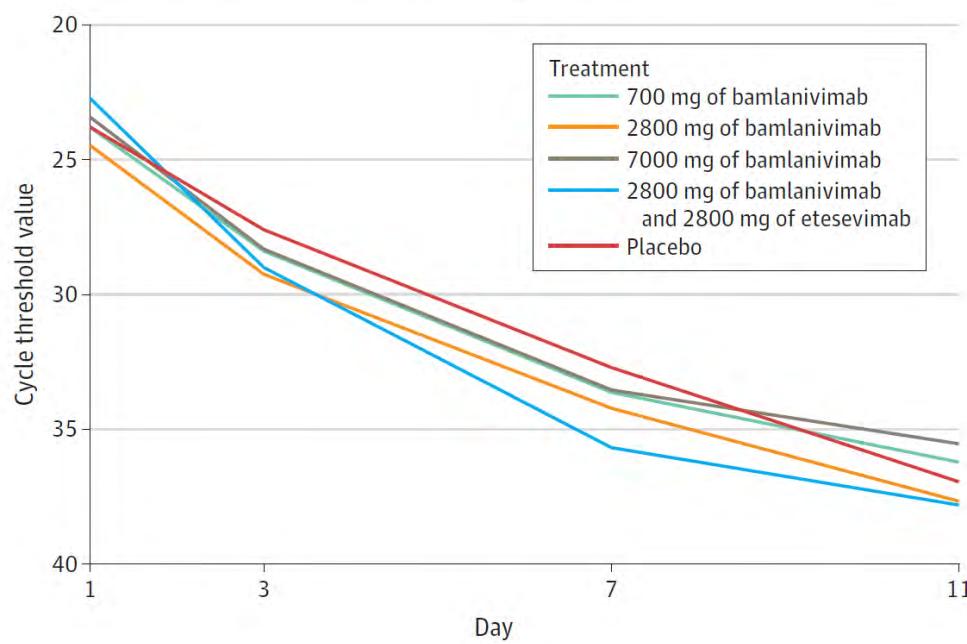
- Engineered humanized mAb has been efficacious for viral infections
- First mAb was palivizumab, developed in 1988 to treat RSV
- For COVID, mAbs have been developed to bind the spike protein to prevent ACE-2 binding
- Two mAb therapies with FDA EUA
 - Lilly LY-CoV555+LY-CoV016
(Bamlanivimab, Etesevimab)
 - Regeneron 10933+10987
(Casirivimab, Imdevimab)



One mAb is good, but two is better

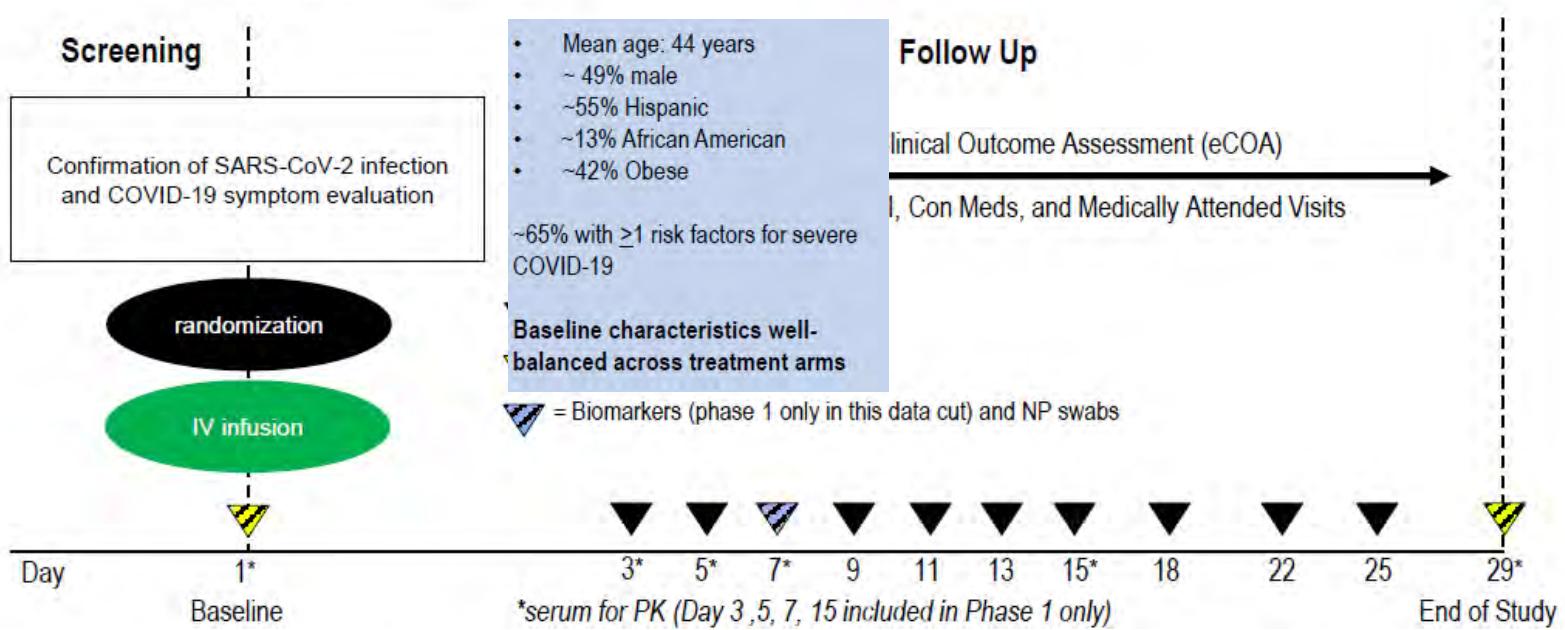
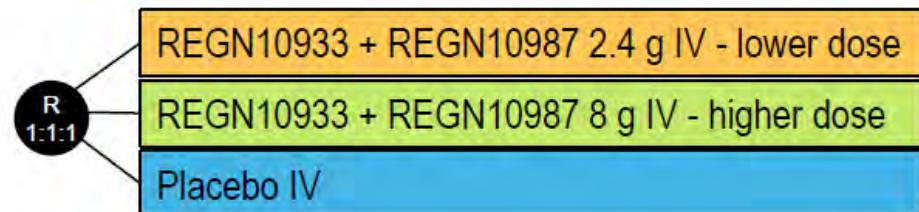
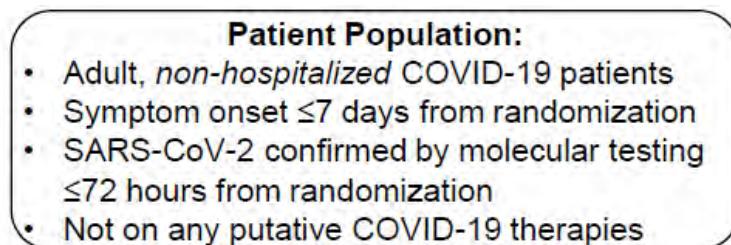
JAMA | Original Investigation

Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19 A Randomized Clinical Trial

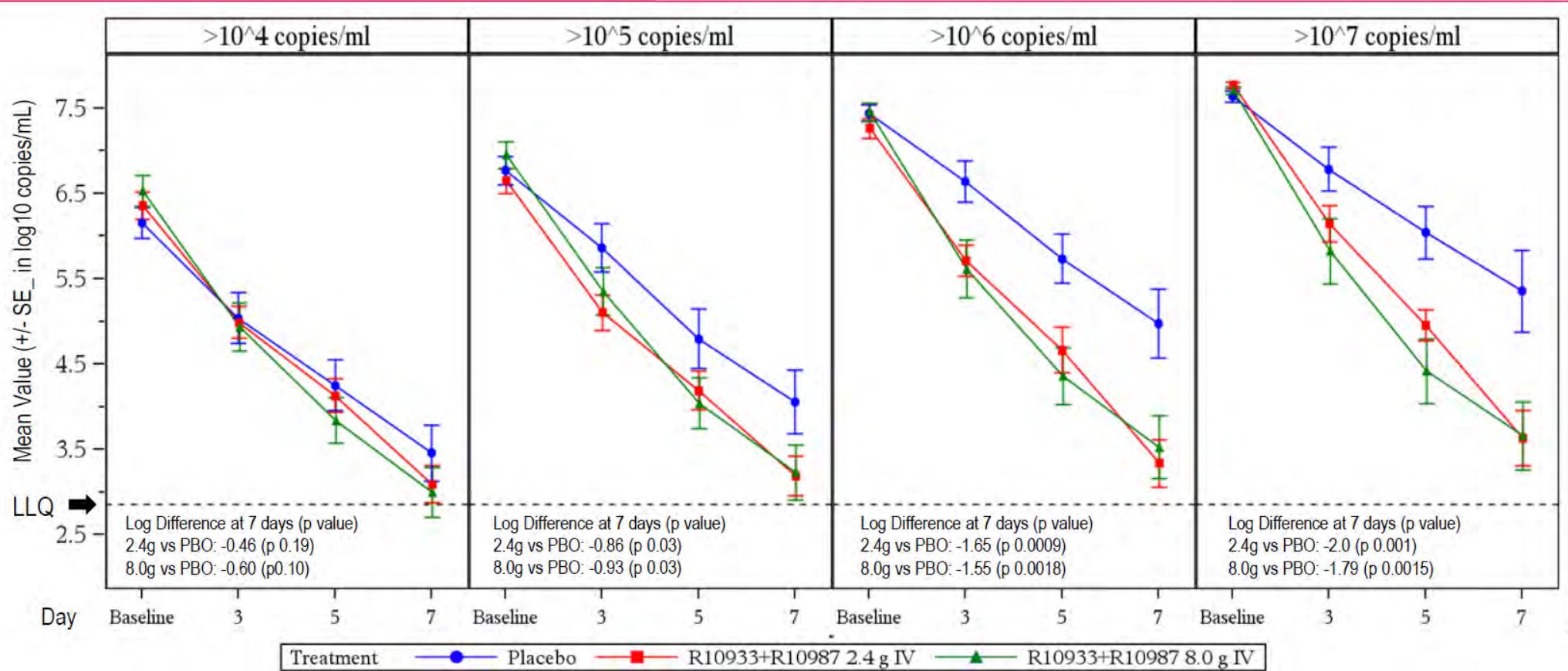


Gottlieb JAMA 2021

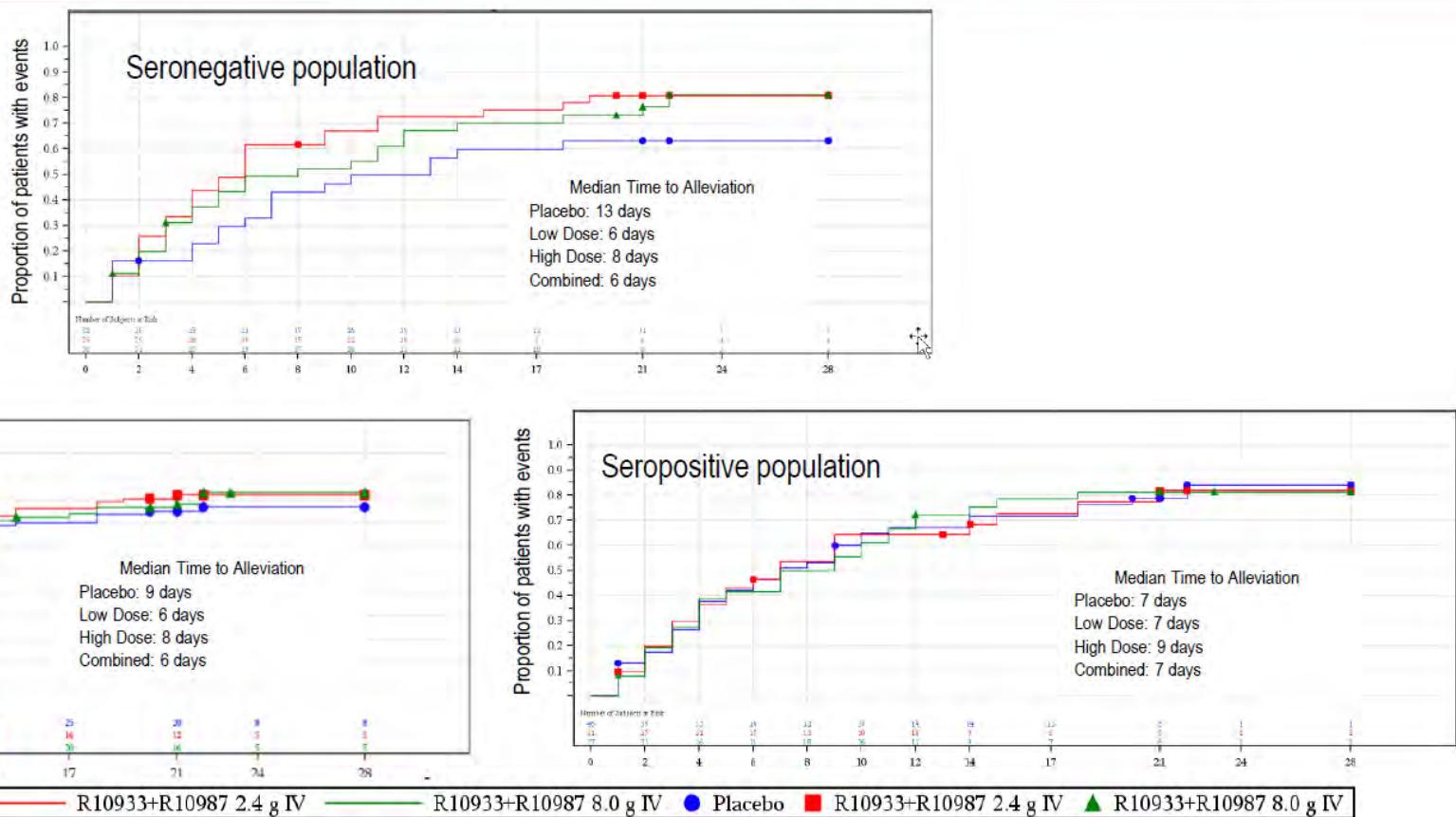
REGN mAb Data



REGN-COV2 PROVIDED GREATER REDUCTION IN VIRAL LOAD IN THOSE WITH HIGHER VIRAL LOAD AT BASELINE



TIME TO ALLEVIATION OF SYMPTOMS (GOING TO MILD OR ABSENT) IS FASTER IN TREATMENT GROUPS COMPARED TO PBO; EFFECT MOST PRONOUNCED IN SERONEGATIVE POPULATION



COVID-19-RELATED MEDICALLY ATTENDED VISITS ARE NUMERICALLY LOWER IN BOTH TREATMENT GROUPS (SERONEGATIVE POPULATION)

Regeneron Pharmaceuticals, Inc.
Protocol: R10933-10987-COV-2067 Phase 1/2

Page 1 of 3

Table 14.2.2.10-2 Proportion of Patients with ≥ 1 COVID-19 Related Medically-attended Visit through Day 29 by Baseline Serology Status
Full Analysis Set (FAS)

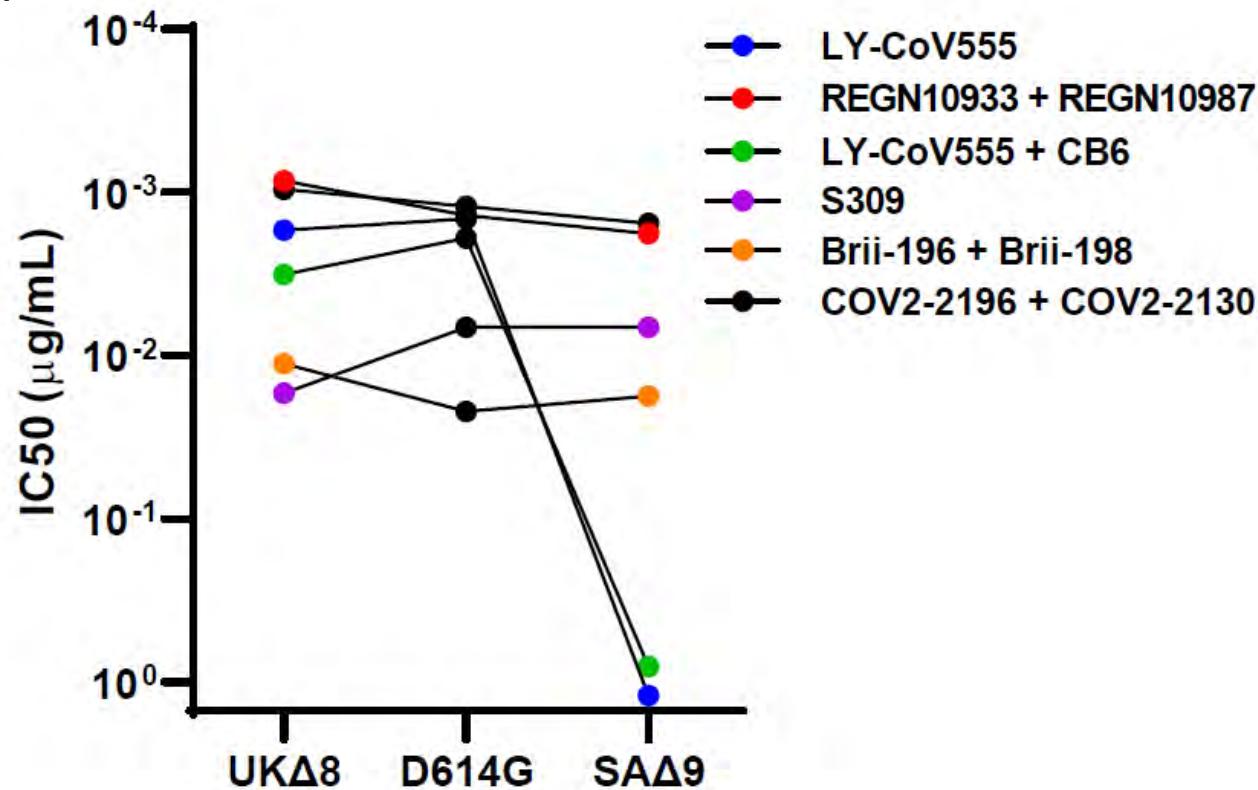
Baseline Serology Status: Negative

	Placebo (N=33) n/N1 (%)	R10933+R10987 2.4 g IV (N=41) n/N1 (%)	R10933+R10987 8.0 g IV (N=39) n/N1 (%)	R10933+R10987 Combined (N=80) n/N1 (%)
Patients with ≥ 1 COVID-19 Related Medically-attended Visit through Day 29	5/33 (15.2%)	2/41 (4.9%)	3/39 (7.7%)	5/80 (6.3%)
95% CI [1]	(-5.1%, 31.9%)	(-0.6%, 16.5%)	(1.6%, 20.9%)	(2.1%, 14.0%)
Proportion Difference vs Placebo	-10.3%	-7.5%	-8.9%	
95% CI [1]	(-32.4%, 12.6%)	(-30.2%, 15.9%)	(-28.7%, 11.3%)	
P-Value	0.1370	0.2723	0.1324	

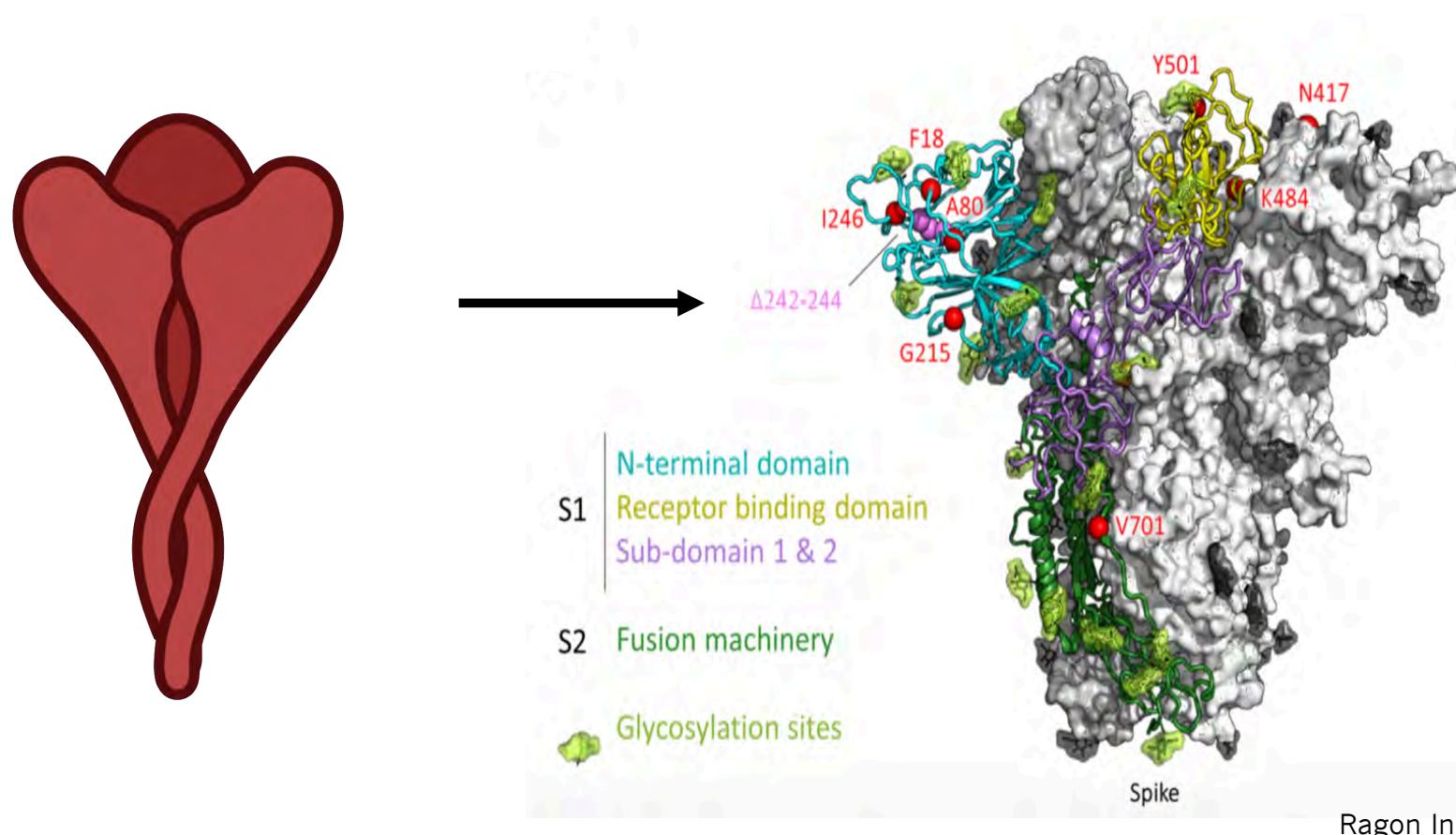
Do mutations affect efficacy of Bnabs to SARS-CoV-2?

- Good news:
 - Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented symptomatic COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents
- Bad news:
 - Lilly's neutralizing antibody bamlanivimab (LY-CoV555) does not protect against the Brazilian (P.1) or South African (501.V2) strains
 - Convalescent sera from South African patients either do not neutralize the South African strain or do so only partially

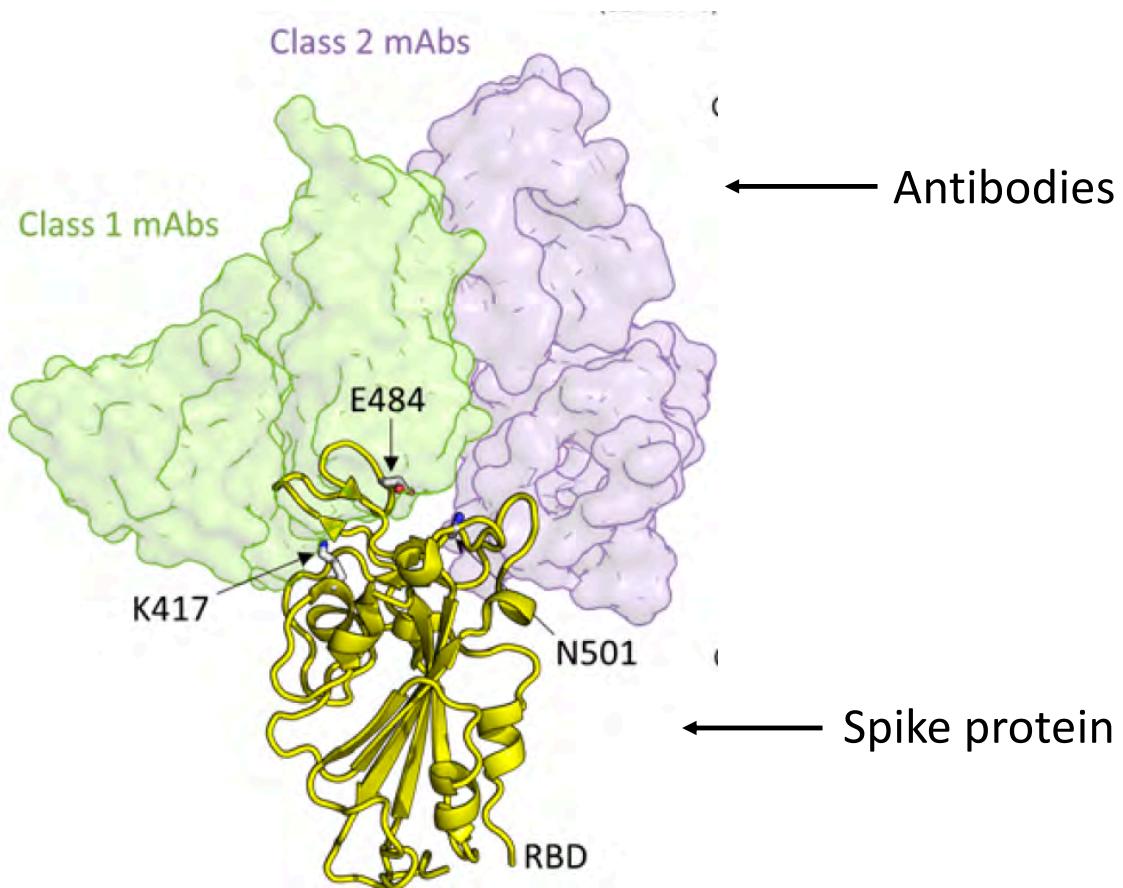
But not all mAb combination are created equal



Anatomy of the Spike Protein: B.1.351 (501Y.V2)



K417 and E484 are key sites of Ab binding



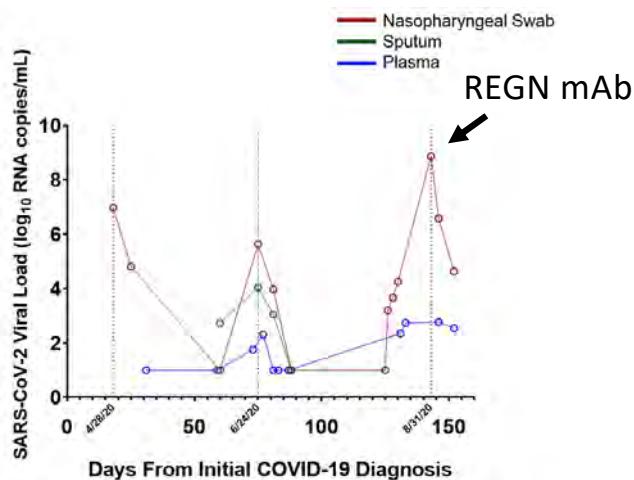
<https://doi.org/10.1101/2021.01.18.427166> doi: bioRxiv preprint, posted January 19, 2021. ;

Ragon Institute

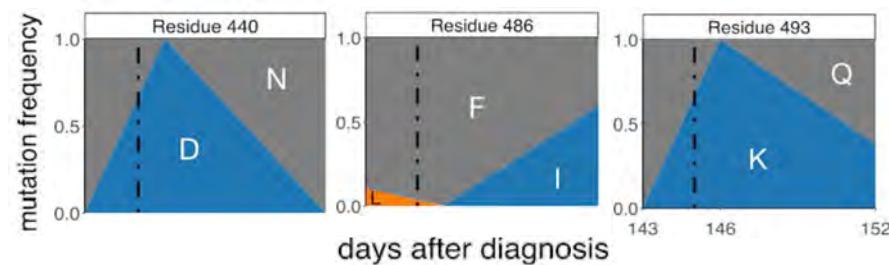
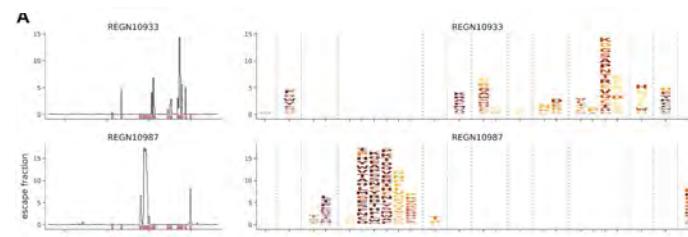
Regeneron mAbs have fewer overlapping escape sites

Escape mutants	REGN10989	REGN10987	REGN10933	REGN10934	REGN10933/10987
Wild-type	7.27×10^{-12}	3.65×10^{-11}	5.57×10^{-11}	5.99×10^{-11}	3.28×10^{-11}
K417E	2.49×10^{-11}	3.10×10^{-11}	8.33×10^{-9}	2.70×10^{-11}	4.15×10^{-11}
K444Q	2.47×10^{-11}	NC	7.81×10^{-11}	5.38×10^{-9}	1.23×10^{-10}
V445A	2.65×10^{-11}	NC	8.82×10^{-11}	1.42×10^{-10}	1.54×10^{-10}
N450D	4.10×10^{-11}	1.20×10^{-9}	7.60×10^{-11}	NC	1.88×10^{-10}
Y453F	2.77×10^{-11}	1.04×10^{-10}	NC	2.17×10^{-10}	1.15×10^{-10}
L455F	1.77×10^{-11}	3.87×10^{-11}	NC	4.34×10^{-11}	5.87×10^{-11}
E484K	NC	6.25×10^{-11}	1.13×10^{-9}	NC	6.19×10^{-11}
G485D	NC	2.34×10^{-11}	2.05×10^{-10}	4.47×10^{-11}	4.71×10^{-11}
F486V	NC	3.16×10^{-11}	NC	3.50×10^{-11}	8.8×10^{-11}
F490L	3.10×10^{-9}	3.56×10^{-11}	4.53×10^{-11}	1.94×10^{-9}	3.64×10^{-11}
F490S	2.23×10^{-10}	4.42×10^{-11}	6.63×10^{-11}	8.91×10^{-9}	3.4×10^{-11}
Q493K	NC	4.19×10^{-11}	NC	3.45×10^{-10}	3.24×10^{-11}

Rapid emergence of resistance to Regeneron mAbs in the immunocompromised patient

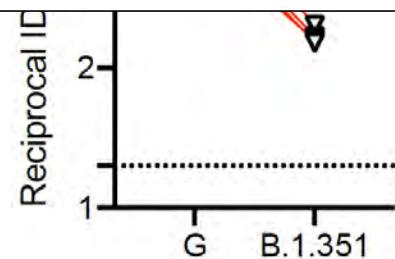
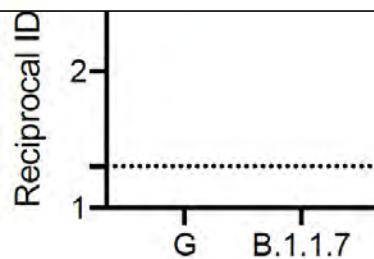


Prospective mapping of viral mutations that escape antibodies used to treat COVID-19

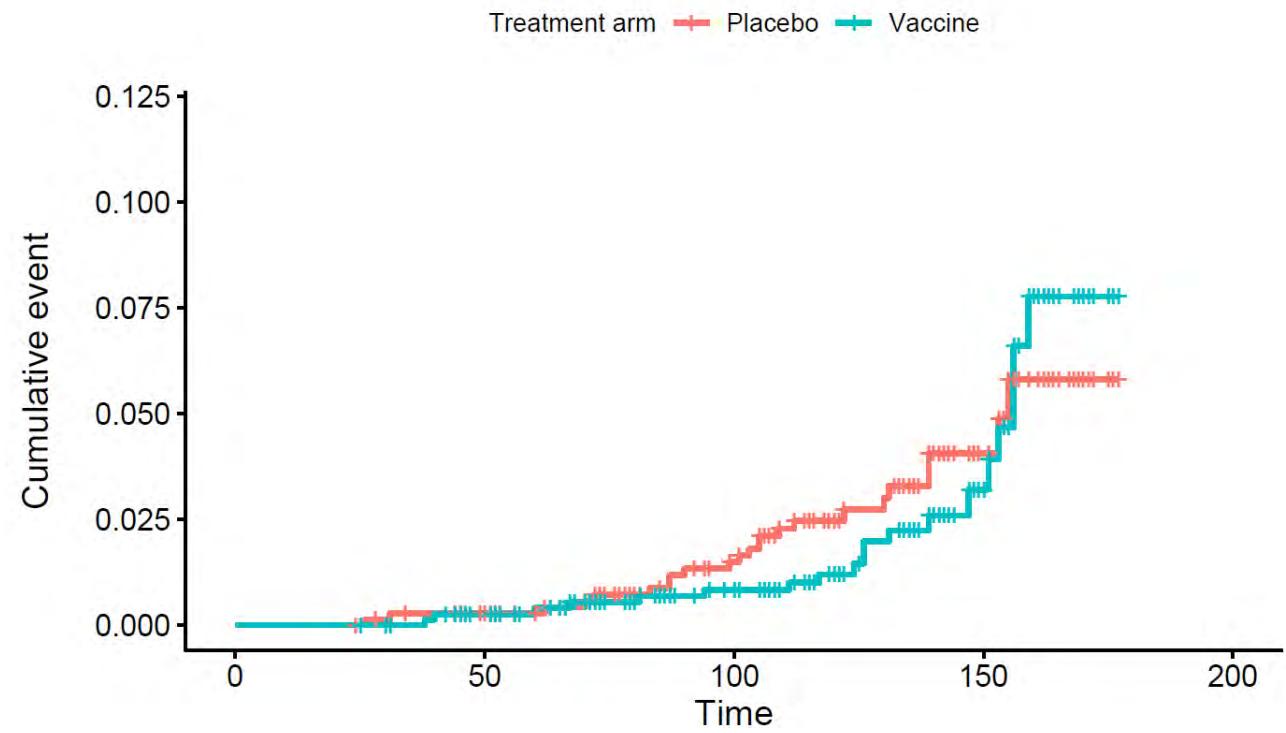
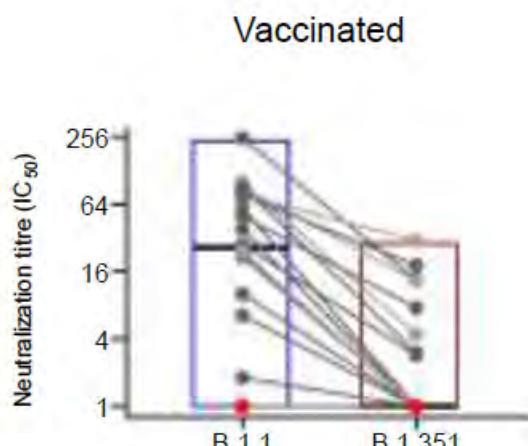


Will the new variants compromise vaccine efficacy?

Data from this sample set shows mRNA-1273 maintained activity against all circulating strain variants tested to date, and only the B.1.351 variant showed reduced neutralizing titers, as assessed from vaccinated human and NHP sera. Viral escape was not detected from any sample and neutralizing titers remained above those previously found to be protective in NHP challenge studies.



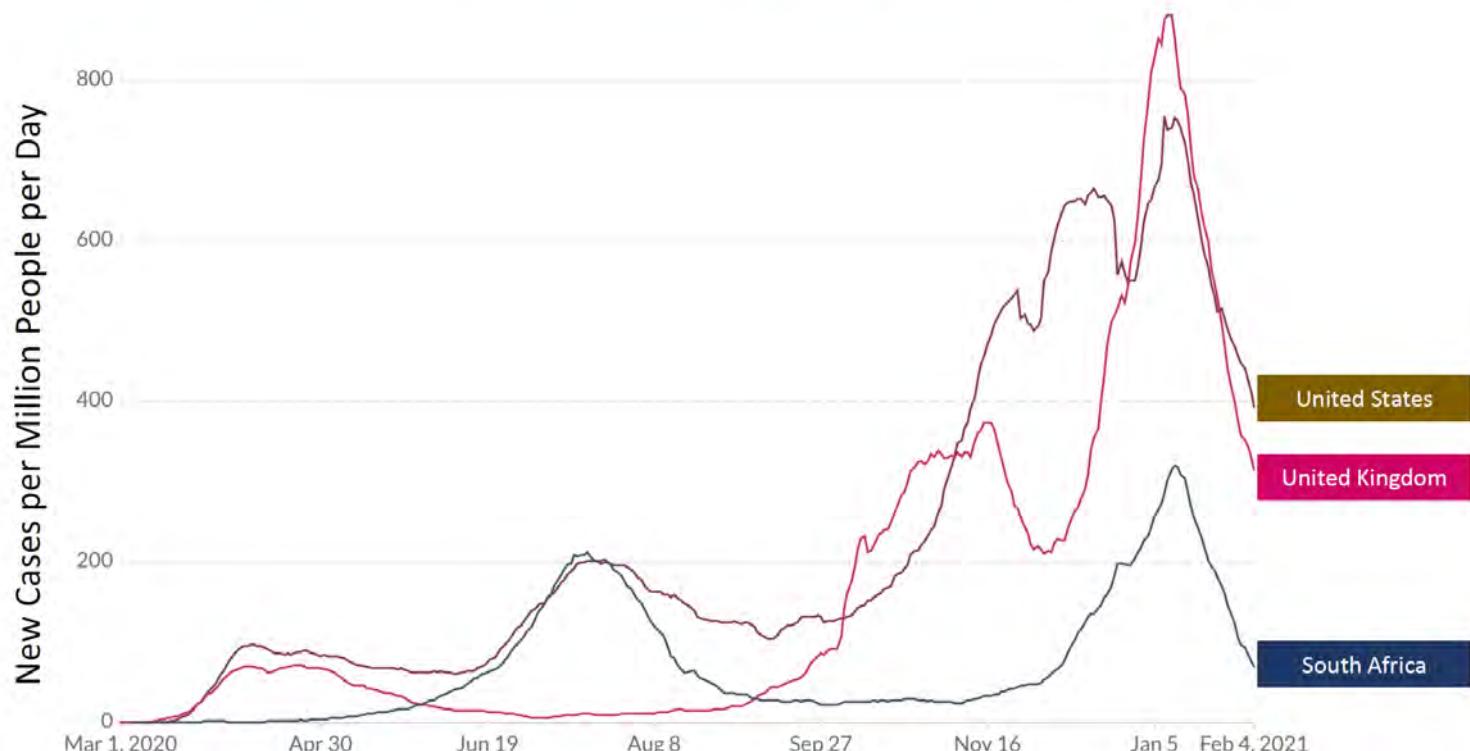
Concerns about other vaccines and new variants



Key Points

- Sudden emergence of novel SARS-CoV-2 variants with a large set of mutations suggests a “hidden” source of viral evolution in the community
 - Potential viral sequencing blind spots and a need to ramp up efforts
 - Immunosuppressed individuals (especially B-cell suppression) may cause persistent COVID and accelerated viral evolution with mAb resistance
- Novel variants have greater transmissibility, potentially from higher viral shedding and some evidence of more severe disease
- Novel variants (especially B.1.351 and P.1) are a threat to current monoclonal antibody treatments and vaccines

New Cases per Day – USA, UK, South Africa



ourworldindata.org



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