COVID-19 UPDATE:
SARS-CoV-2 VARIANTS AND COVID-19 VACCINES

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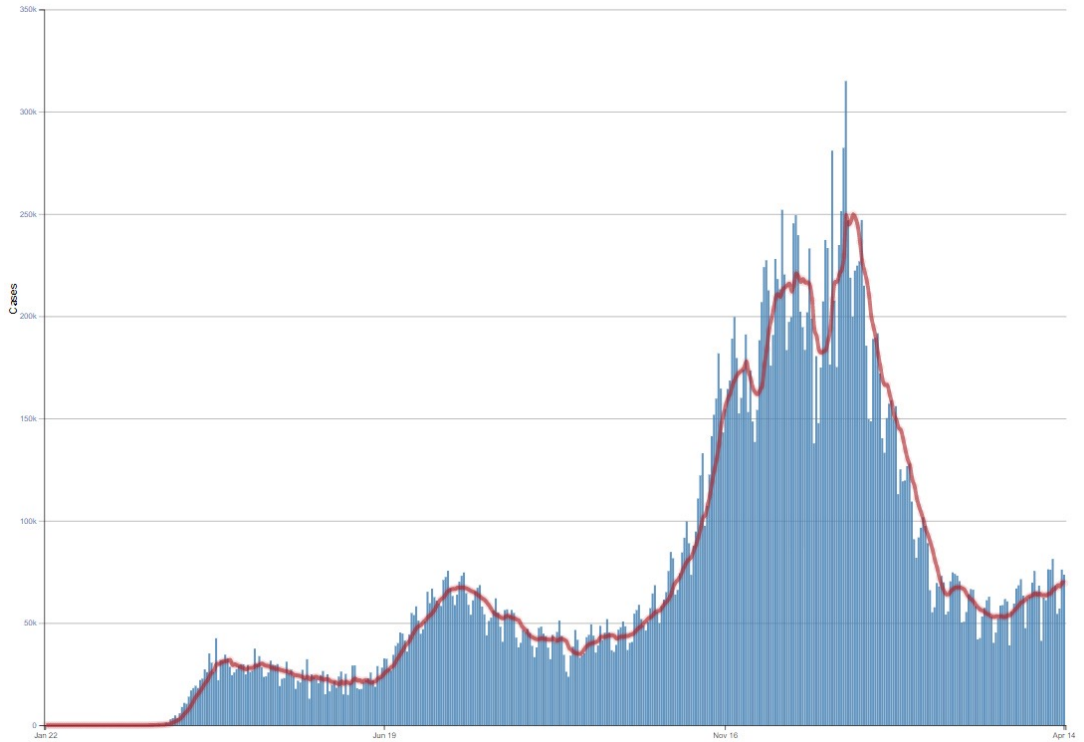
Some slides shown by Dr. Ralph Baric at UNC Symposium

CURRENT SARS-CoV-2 EPIDEMIOLOGY, US

- Number total cases, US = 31,000,000 (total deaths = 563,980)
- Number of people with one vaccine dose = 125,000,000 (37.9% US pop)
- Number of people fully vaccinated = 78,000,000 (23.6% US pop) – 3.7% increase from last week
- Average US hospitalizations (7d ave) = 5,507 (+4.5% change in 7d average)
- Average US deaths (7d ave) = 712 (+10.8% change since prior week)
- Driving factors for increased cases, hospitalizations, and deaths: 1) Elimination of mask requirements in some stated; 2) Increase in SARS-CoV-2 variants; 3) Spring Break
- Total infected or fully vaccinated = 109,000,000 (~33%)



https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days

IMPACT OF COVID-19, US 2020

Table. Number of Deaths for Leading Causes of Death, US, 2015-2020[a]

	No. of deaths by year					
Cause of death	2015	2016	2017	2018	2019	2020
Total deaths	2 712 630	2 744 248	2 813 503	2 839 205	2 854 838	3 358 814
Heart disease	633 842	635 260	647 457	655 381	659 041	690 882
Cancer	595 930	598 038	599 108	599 274	599 601	598 932
COVID-19[b]						345 323
Unintentional injuries	146 571	161 374	169 936	167 127	173 040	192 176
Stroke	140 323	142 142	146 383	147 810	150 005	159 050
Chronic lower respiratory diseases	155 041	154 596	160 201	159 486	156 979	151 637
Alzheimer disease	110 561	116 103	121 404	122 019	121 499	133 382
Diabetes	79 535	80 058	83 564	84 946	87 647	101 106
Influenza and pneumonia	57 062	51 537	55 672	59 120	49 783	53 495
Kidney disease	49 959	50 046	50 633	51 386	51 565	52 260
Suicide	44 193	44 965	47 173	48 344	47 511	44 834

[a] Leading causes are classified according to underlying cause and presented according to the number of deaths among US residents. For more information, see the article by Heron.[4] Source: National Center for Health Statistics. National Vital Statistics System: mortality statistics (http://www.cdc.gov/nchs/deaths.htm). Data for 2015-2019 are final; data for 2020 are provisional.

[b] Deaths with confirmed or presumed COVID-19, coded to *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code U07.1 as the underlying cause of death.

Ahmed FB, Anderson RN. JAMA, 31 March 2021

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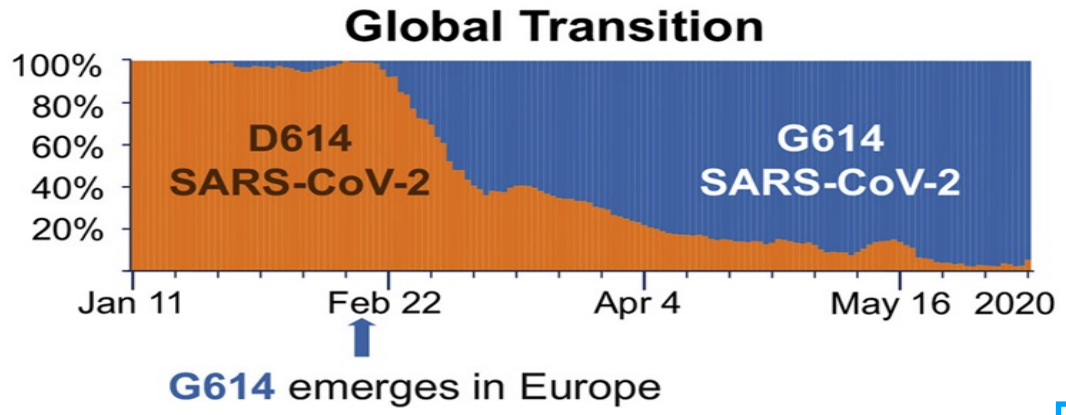
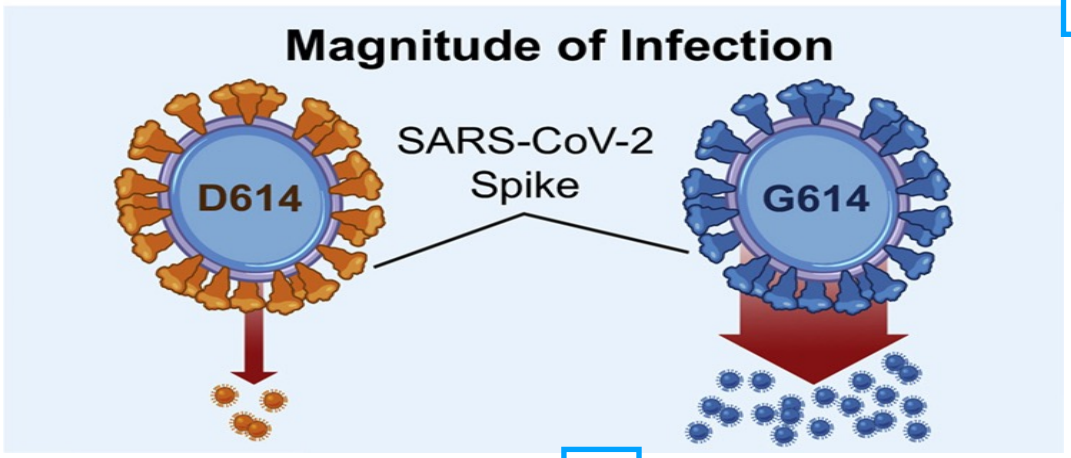




Hou et al., Science 2020 Nov 12:eabe8499.
Plante et al., Nature 2020; Baric NEJM 2020

NEW SARS-CoV2 Variants

D614G Rapidly Replaced the Ancestral Wuhan 2019 Strain Around the World

Replicates More Efficiently and to Higher Titer in Upper Airway Epithelial Cells

Significantly More Transmissible in Hamsters and Humans

~2 Fold More Sensitive to Neutralization as Compared to Original Wuhan Strain

RBD Structure-Open Position (Yurkovetskiy et al 2020)

							Transmission	Virulence	Escape
UK VOC 202012/01, B.1.1.7 with 7 amino acid substitutions	69-70 del	144-145 del	N501Y	A570D D614G	P681H T716I	S982A D1118H	↑	? (30%↑)	2X
South Africa VOC 501Y.V2, B.1.351 IC-0433 with 7 amino acid substitutions	D80A	242-245 del R246I	K417N E484K N501Y	D614G A701V			↑	+/-	~6-10 X
Isolate from travelers from Brazil, B.1.1.248 IC-0561 with 12 amino acid substitutions	L18F T20N P26S	D138Y R190S	K417T E484K N501Y	D614G H655Y		T1027I V1176F	↑	+	4X

Wu et al., 2021 bioRxiv **doi:** https://doi.org/10.1101/2021.01.25.427948

POSSIBLE IMPLICATIONS OF NEW SARS-CoV-2 VARIANTS, CDC

- **Ability to spread more quickly in people**. There is already evidence that one mutation, D614G, confers increased ability to spread more quickly than the wild-type[2] SARS-CoV-2. In the laboratory, 614G variants propagate more quickly in human respiratory epithelial cells, outcompeting 614D viruses. There also is epidemiologic evidence that the 614G variant spreads more quickly than viruses without the mutation.
- **Ability to cause either milder or more severe disease in people**. In January 2021, experts in the UK reported that B.1.1.7 variant may be associated with an increased risk of death compared to other variants. More studies are needed to confirm this finding.
- **Ability to evade detection by specific viral diagnostic tests**. Most commercial reverse-transcription polymerase chain reaction (RT-PCR)-based tests have multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets will still work.
- **Decreased susceptibility to therapeutic agents such as monoclonal antibodies.**
- **Ability to evade natural or vaccine-induced immunity**. Both vaccination against and natural infection with SARS-CoV-2 produce a "polyclonal" response that targets several parts of the spike protein. The virus would likely need to accumulate multiple mutations in the spike protein to evade immunity induced by vaccines or by natural infection. -
- Among these possibilities, the last—the ability to evade vaccine-induced immunity—would likely be the most concerning because once a large proportion of the population is vaccinated, there will be immune pressure that could favor and accelerate emergence of such variants by selecting for "escape mutants." There is no evidence that this is occurring, and most experts believe escape mutants are unlikely to emerge because of the nature of the virus.

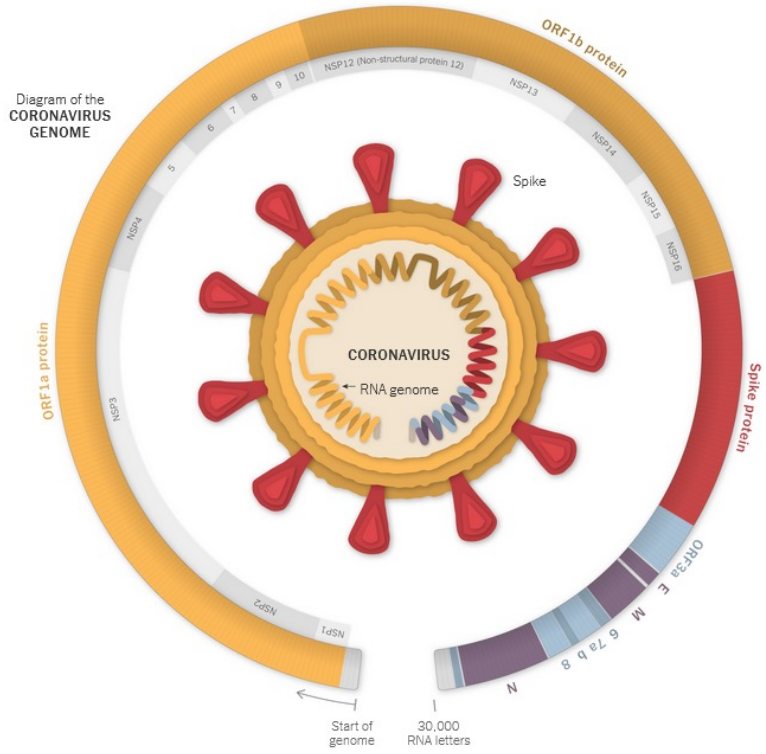
https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-emerging-variants.html?CDC_AA_ refVal=
https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fmore%2Fscience-and-research%2Fscientific-brief-emerging-variants.html

CORONAVIRUS VARIANTS AND MUTATIONS

Coronavirus Variants and Mutations

By Jonathan Corum and Carl Zimmer Updated March 22, 2021

Each coronavirus contains nearly 30,000 letters of RNA. This genetic information allows the virus to infect cells and hijack them to make new viruses.



As an infected cell builds new coronaviruses, it occasionally makes tiny copying errors called **mutations.** Scientists can track mutations as they are passed down through a **lineage,** which is a branch of the viral family tree.

A group of coronaviruses that share the same inherited set of distinctive mutations is called a **variant.** If enough mutations accumulate in a lineage, the viruses may evolve clear-cut differences in how they function. These lineages come to be known as **strains**. Covid-19 is caused by a coronavirus strain known as SARS-CoV-2.

Over the course of the pandemic, a number of variants of SARS-CoV-2 have arisen. Some of them are raising worries that they may draw out the pandemic or make vaccines less effective.

https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html?action=click&module=Top%20Stories&pgtype=Homepage

SARS-CoV-2 VARIANTS, CURRENT INFORMATION

News and updates

March 5	Scientists find the **E484K** mutation in a sample from Portland, Oregon.
Feb. 23	Added the **B.1.526** variant, which is spreading in New York City.
Feb. 23	Studies suggest that a variant discovered in **California** is more contagious.
Feb. 17	Maryland confirms its first case of the **P.1** variant.
Feb. 16	Massachusetts confirms its first case of the **B.1.351** variant.
Feb. 15	Added the **Q677** spike mutation, which was found in several lineages in the U.S.
Feb. 15	**B.1.351** is confirmed in a Connecticut resident hospitalized in New York City.
Feb. 13	Studies suggest **B.1.1.7** is likely more deadly than other circulating variants.
Feb. 11	Illinois and North Carolina confirm their first cases of the **B.1.351** variant.
Feb. 7	South Africa stops using AstraZeneca's vaccine against the **B.1.351** variant.
Feb. 7	The **B.1.1.7** variant is doubling every 10 days in the United States.

Variants of concern

Lineage	Variant name	Status
B.1.1.7	Variant of Concern 202012/01, or 501Y.V1	Emerged in Britain in December and thought to be roughly 50 percent more infectious.
B.1.351	501Y.V2	Emerged in South Africa in December. Reduces the effectiveness of some vaccines.
P.1	501Y.V3	Emerged in Brazil in late 2020. Has mutations similar to B.1.351.
B.1.427, B.1.429	CAL.20C	Common in California and thought to be about 20 percent more infectious. Carries the L452R mutation.

Variants of interest

Lineage	Variant name	Status
B.1.525	—	Spreading in New York. Carries some of the same mutations as B.1.1.7.
B.1.526	—	Spreading in New York. One version carries the E484K mutation, another carries S477N.

Mutations that may help the coronavirus spread

Lineage	Mutation	Status
B.1	D614G	Appeared in early 2020 and spread around the world.
Several	N501Y	A defining mutation in several lineages, including B.1.1.7, B.1.351 and P.1. Helps the virus bind more tightly to human cells.
Several	E484K or "Eek"	Appears in several lineages. May help the virus avoid some kinds of antibodies.
Several	K417	Appears in several lineages, including B.1.351 and P.1. May help the virus bind more tightly to cells.
Several	L452R	Increasingly common in California, but not yet shown to be more infectious.
Several	Q677	Found in seven U.S. lineages, but not yet shown to be more infectious.

https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html?action=click&module=Top%20Stories&pgtype=Homepage

COVID-19 VARIANTS IN US, CDC

Key Points:

- Genetic variants of SARS-CoV-2 have been emerging and circulating around the world throughout the COVID-19 pandemic.
- Viral mutations and variants in the United States are routinely monitored through sequence-based surveillance, laboratory studies, and epidemiological investigations.
- A US government interagency group developed a Variant Classification scheme that defines three classes of SARS-CoV-2 variants:
  - Variant of Interest
  - Variant of Concern
  - Variant of High Consequence
- **The B.1.1.7, B.1.351, P.1, B.1.427, and B.1.429 variants circulating in the United States are classified as variants of concern**
- **Viruses constantly change through mutation**. A variant has one or more mutations that differentiate it from other variants in circulation. As expected, multiple variants of SARS-CoV-2 have been documented in the United States and globally throughout this pandemic. To inform local outbreak investigations and understand national trends, scientists compare genetic differences between viruses to identify variants and how they are related to each other

- There are currently five VOCs in the United States:
- **B.1.1.7**: This variant was first identified in the US in December 2020. It was initially detected in the **UK**.
- **B.1.351**: This variant was first identified in the US at the end of January 2021. It was initially detected in **South Africa** in December 2020.
- **P.1**: This variant was first detected in the US in January 2021. P.1 was initially identified in travelers from **Brazil**, who were tested during routine screening at an airport in Japan, in early January.
- **B.1.427 and B.1.429**: These two variants were first identified in **California** in February 2021 and were classified as VOCs in March 2021.

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

VARIANTS OF INTEREST, CDC

- Variants of interest: A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.
- Possible attributes of a variant of interest: 1) Specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape; 2) Evidence that demonstrates it is the cause of an increased proportion of cases or unique outbreak clusters; 3) Limited prevalence or expansion in the US or in other countries

Name (Pango lineage)	Substitution	Name (Nextstrain[a])	First Detected	BEI Reference Isolate[b]	Predicted Attributes
B.1.526	**Spike:** (L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*) **ORF1a:** L3201P, T265I, Δ3675/3677 **ORF1b:** P314L, Q1011H **ORF3a:** P42L, Q57H **ORF8:** T11I **5'UTR:** R81C	20C	New York/November 2020		• Potential reduction in neutralization by monoclonal antibody treatments • Potential reduction in neutralization by convalescent and post-vaccination sera
B.1.525	**Spike:** A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L **ORF1b:** P314F **ORF1a:** T2007I **M:** I82T **N:** A12G, T205I **5'UTR:** R81C	20C	New York/December 2020		• Potential reduction in neutralization by monoclonal antibody treatments • Potential reduction in neutralization by convalescent and post-vaccination sera
P.2	**Spike:** E484K, D614G, V1176F **ORF1a:** L3468V, L3930F **ORF1b:** P314L **N:** A119S, R203K, G204R, M234I **5'UTR:** R81C	20J	Brazil/April 2020		• Potential reduction in neutralization by monoclonal antibody treatments • Potential reduction in neutralization by convalescent and post-vaccination sera

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

VARIANTS OF CONCERN, CDC

- Variants of concern: A variant for which there is evidence of an increase in transmissibility, more severe disease (increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.
- Possible attributes of a variant of concern (In addition to the possible attributes of a variant of interest): 1) Evidence of impact on diagnostics, treatments, and vaccines (widespread interference with diagnostic test targets; evidence of substantially increased resistance to one or more class of therapies; evidence of significant decreased neutralization by antibodies generated during previous infection or vaccination; evidence of reduced vaccine-induced protection from severe disease); 2) Evidence of increased transmissibility; 3) Evidence of increased disease severity

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

Name (Pango lineage)	Spike Protein Substitutions	Name (Nextstrain[a])	First Detected	BEI Reference Isolate[b]	Known Attributes
B.1.1.7	Δ69/70 Δ144Y (E484K*) (S494P*) N501Y A570D D614G P681H	20I/501Y.V1	United Kingdom	NR-54000	- ~50% increased transmission [5] - Likely increased severity based on hospitalizations and case fatality rates [6] - Minimal impact on neutralization by EUA monoclonal antibody therapeutics [7,14] - Minimal impact on neutralization by convalescent and post-vaccination sera [8,9,10,11,12,13,19]
P.1	K417N/T E484K N501Y D614G	20J/501Y.V3	Japan/ Brazil	NR-54982	- Moderate impact on neutralization by EUA monoclonal antibody therapeutics [7,14] - Reduced neutralization by convalescent and post-vaccination sera [15]
B.1.351	K417N E484K N501Y D614G	20H/501.V2	South Africa	NR-54009	- ~50% increased transmission[16] - Moderate impact on neutralization by EUA monoclonal antibody therapeutics [7,14] - Moderate reduction on neutralization by convalescent and post-vaccination sera [8,12,18,19,20]
B.1.427	L452R D614G	20C/S:452R	US-California		- ~20% increased transmissibility [21] - Significant impact on neutralization by some, but not all, EUA therapeutics - Moderate reduction in neutralization using convalescent and post-vaccination sera [21]
B.1.429	S13I W152C L452R D614G	20C/S:452R	US-California		- ~20% increased transmissibility [21] - Significant impact on neutralization by some, but not all, EUA therapeutics - Moderate reduction in neutralization using convalescent and post-vaccination sera [21]

VARIANTS OF HIGH CONSEQUENCE, CDC

- A variant of high consequence has clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants.
- Possible attributes of a variant of high consequence (In addition to the possible attributes of a variant of concern) - Impact on Medical Countermeasures (MCM): 1) demonstrated failure of diagnostics; 2) evidence to suggest a significant reduction in vaccine effectiveness, a disproportionately high number of vaccine breakthrough cases, or very low vaccine-induced protection against severe disease; 3) significantly reduced susceptibility to multiple Emergency Use Authorization (EUA) or approved therapeutics; 4) more severe clinical disease and increased hospitalizations
- A variant of high consequence would require notification to WHO under the International Health Regulations, reporting to CDC, an announcement of strategies to prevent or contain transmission, and recommendations to update treatments and vaccines.
- Currently there are no SARS-CoV-2 variants that rise to the level of high consequence.

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

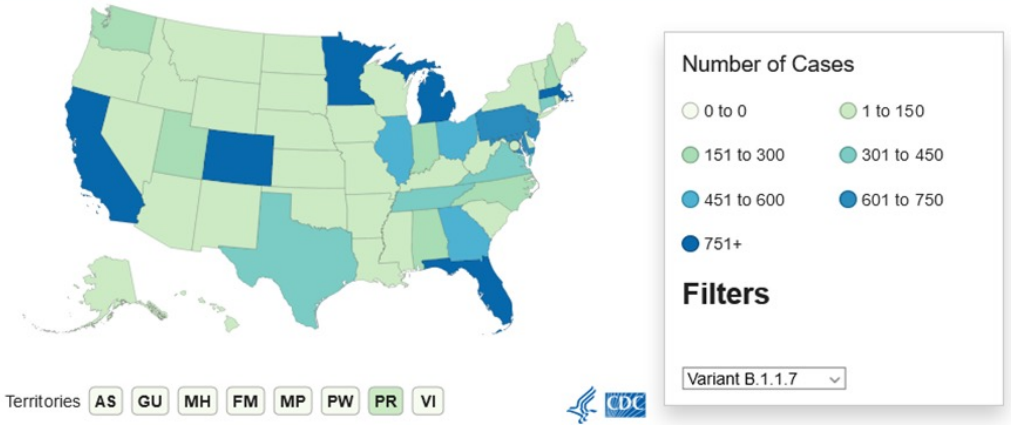
COVID-19 VARIANTS IN US, CDC

US COVID-19 Cases Caused by Variants

Updated Apr. 6, 2021 Languages Print

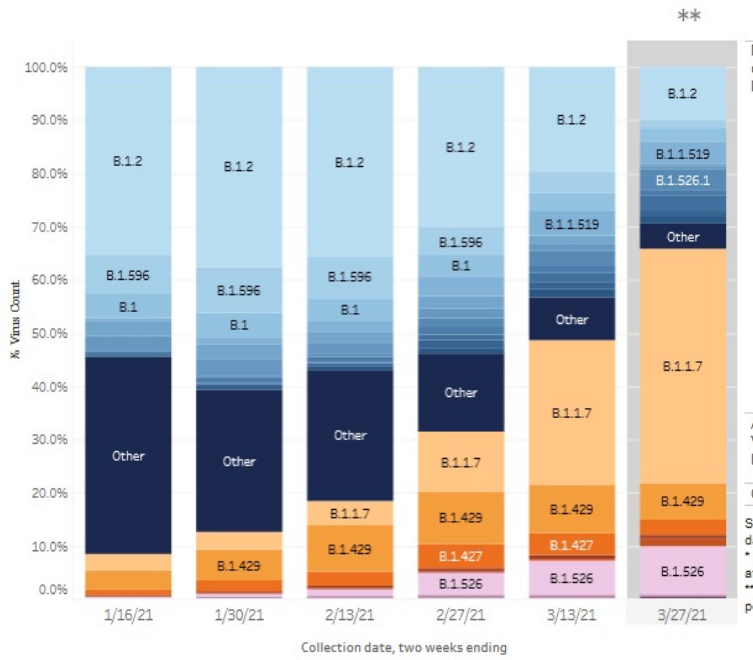
Variant	Reported Cases in US	Number of Jurisdictions Reporting
B.1.1.7	16,275	52
B.1.351	386	36
P.1	356	25

Cases of Variants of Concern in the United States*†



SARS-CoV-2 Variants Circulating in the United States

SARS-CoV-2 Variants Circulating in the United States, January 3 – March 27 2021



	Lineage	% Total	95%CI	Type
Most common lineages	B.1.1.7	44.1%	41.2-47.1%	VOC
	B.1.2	10.0%	8.9-11.2%	
	B.1.526	9.2%	7.2-11.7%	VOI
	B.1.429	6.9%	5.1-9.4%	VOC
	B.1.1.519	4.1%	3.4-5.0%	
	B.1.526.1	3.9%	3.3-4.7%	
	B.1.526.2	2.9%	2.3-3.8%	
	B.1.427	2.9%	2.2-3.9%	VOC
	B.1	2.4%	2.0-3.0%	
	B.1.596	1.7%	1.3-2.1%	
	P.1	1.4%	1.0-1.8%	VOC
	R.1	1.2%	0.8-1.6%	
	B.1.575	1.1%	0.9-1.5%	
	B.1.1	0.9%	0.6-1.5%	
	B.1.243	0.6%	0.4-1.0%	
	B.1.234	0.5%	0.3-0.7%	
Additional VOI/VOC lineages	B.1.351	0.7%	0.5-1.0%	VOC
	B.1.525	0.5%	0.3-0.7%	VOI
	P.2	0.3%	0.2-0.4%	VOI
Other*	Other	4.7%	4.1-5.4%	

Summary data that appear in the table include specimen collection dates from March 14 through March 27, 2021.
* Other represents >200 additional lineages, which are each circulating at <1% of viruses
** Most recent data (shaded) are subject to change as samples from that period are still being processed.

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html

COVID-19 VARIANTS IN NC, UNC-MC, 15 April 2021

- Holding steady around 75% variants of interest/concern (N=740 cases sequenced)
- B.1.1.7 and B.1.526 continue to dominate, but B.1.1.7 is about twice as prevalent this past week.
- Several samples show S:L5F, S:E484K, S:D614G, and S:DA701Y; similar to but not quite the B.1.526 from New York. Notably, these lack T95I and D253G but do have the ORF1a 3675-3677 deletion common in other VOCs (B.1.1.7, B.1.351, P.1). They show reduction but not complete loss of our ORF1a_del qPCR probe.

Strain	Clade	NC (CDC)	NC (UNC)	ref
B.1.1.7	20I:501Y.V1	178	140	2
B.1.351	20H/501Y.V2	29	23	3
B.1.427/429	20C	*	45	1
B.1.526	20C	*	78	4
B.1.525	20A	*	2	
P.1	20J/501Y.V3	0	4	6
P.2	20J	*	1	5
R.1	20B	*	6	7

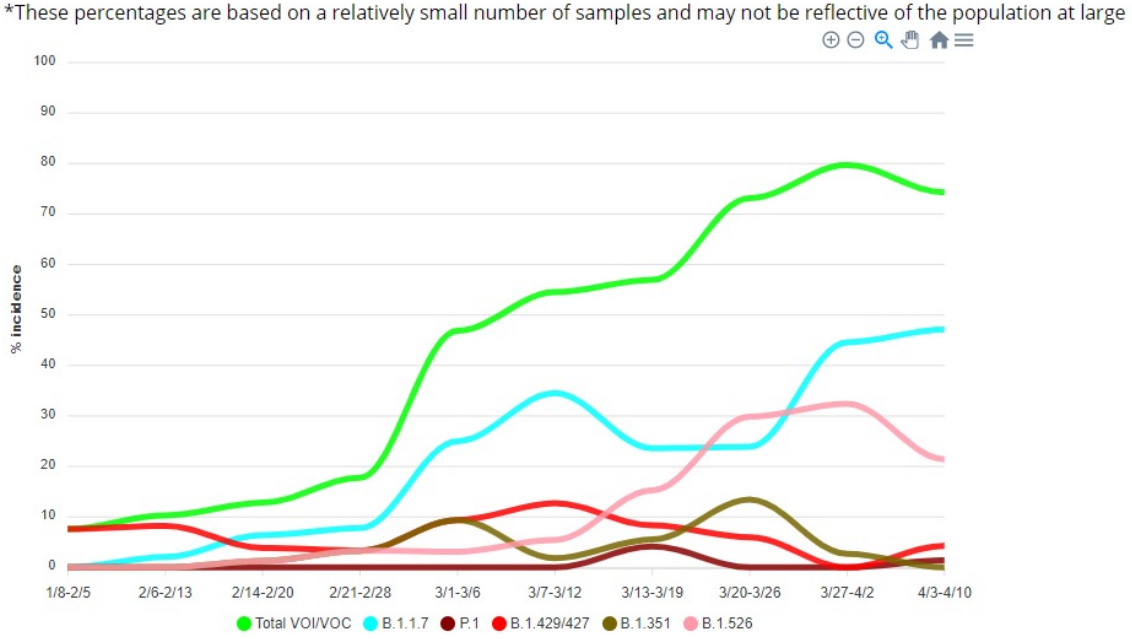
Mutation/Variant trends

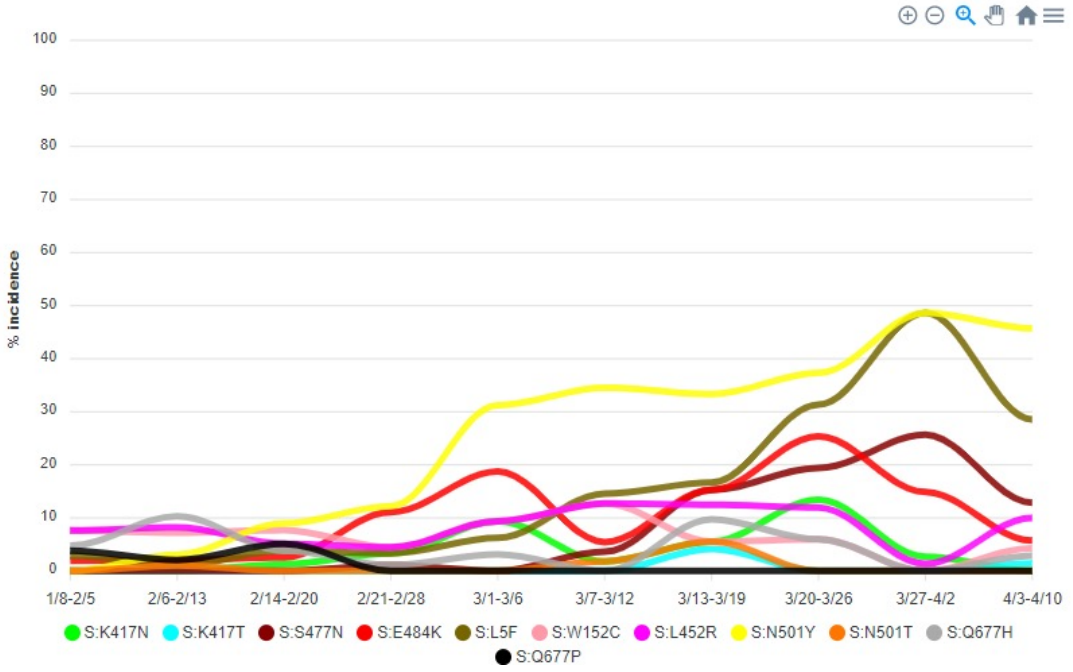
Pango lineage	All	UNCMC
B.1.1.7	140	133
B.1.351	23	23
B.1.427	6	6
B.1.429	39	32
B.1.525	2	1
B.1.526	78	77
P.1	4	1
P.2	1	1
Other	447	408
Total samples	740	682
VOI/VOC	293	274
VOI/VOC %	39.59%	40.18%

http://unc.cov2seq.org/

COVID-19 VARIANTS IN NC, UNC-MC, 2 April 2021

*These percentages are based on a relatively small number of samples and may not be reflective of the population at large





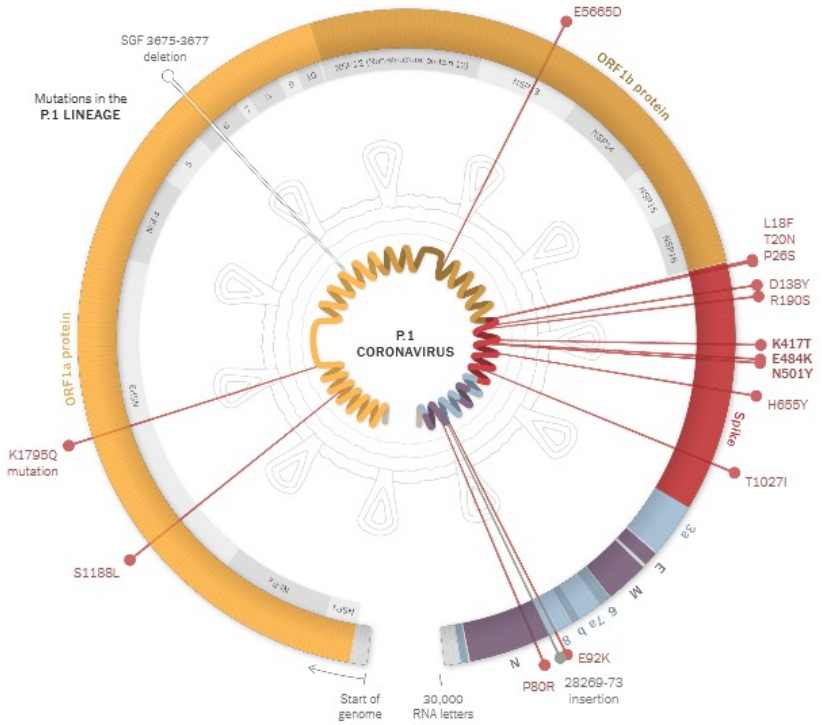
UNC SARS-CoV-2 Surveillance (cov2seq.org)

P.1 VARIANT

A variant known as **20J/501Y.V3** is from the **P.1** lineage, an offshoot of the larger **B.1.1.28** lineage.

The variant was first reported in Japan, in four people who contracted P.1 on a trip to Brazil. The lineage emerged in late 2020 in Manaus, the largest city in Brazil's Amazon region. It quickly became the predominant variant there and in several other South American cities.

P.1 is a close relative of the B.1.351 lineage, and it has some of the same mutations on the coronavirus spike protein. It may be able to overcome the immunity developed after infection by other variants.



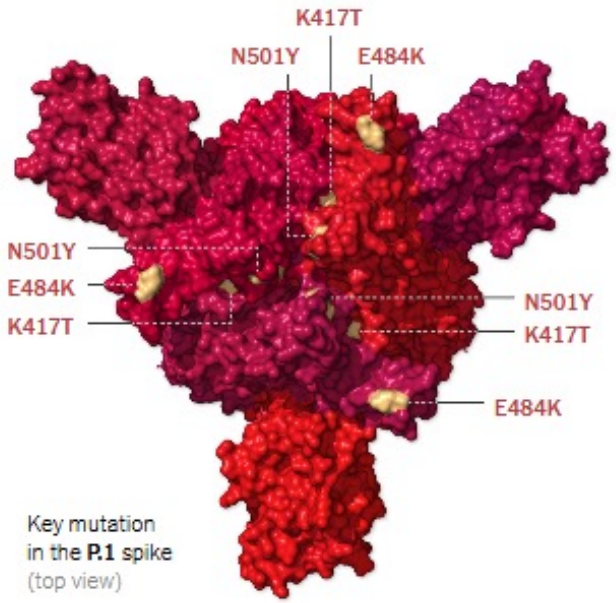
KEY MUTATIONS IN P.1

Key mutations in the spike protein are similar to those in the B.1.351 lineage, although they arose independently:

— **N501Y**, which helps the virus latch on more tightly to human cells. This mutation also appears in the B.1.1.7 and B.1.351 lineages.

— **K417T**, which is the same site as the K417N mutation in the B.1.351 lineage. It may also help the virus latch on tighter.

— **E484K**, which may help the virus evade some kinds of antibodies.



Key mutation in the **P.1** spike (top view)

https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html?action=click&module=Top%20Stories&pgtype=Homepage

INCREASED RESISTANCE OF SARS-CoV-2 VARIANTS BI.1.17 AND B.1.351 TO ANTIBODY NEUTRALIZATION

- Variants studied: UK, B.1.1.7; South Africa, B.1.351
- Concern: Described ease of transmission and extensive mutations in the spike protein.
- Results, B.1.1.7 demonstrated to be refractory to neutralization by most mAbs to the N-terminal domain (NTD) of spike and relatively resistant to a number of mAbs to the receptor-binding domain (RBD). It is modestly more resistant to convalescent plasma (~3 fold) and vaccinee sera (~2 fold)
- Results, B.1.351 demonstrated refractory to neutralization by most NTD mAbs but also by multiple individual mAbs to the receptor-binding motif on RBD, largely due to an E484K mutation, although some mAb combinations retain activity. Moreover, B.1.351 was markedly more resistant to neutralization by convalescent plasma (~11-33 fold) and vaccinee sera (~6.5-8.6 fold).

https://www.biorxiv.org/content/10.1101/2021.01.25.428137v2.full.pdf

IMPACT OF SARS-CoV-2 VARIANTS ON RESPONSE TO MABs

CASIRIVIMAB/IMDEVIMAB

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y[a]	no change[c]
B.1.351 (South Africa origin)	K417N, E484K, N501Y[b]	no change[c]
P.1 (Brazil origin)	K417T + E484K	no change[c]
B.1.427/B.1.429 (California origin)	L452R	no change[c]
B.1.526 (New York origin)[d]	E484K	no change[c]

BAMLANIVIMAB/ETESEVIMAB

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	>45[c]
P.1 (Brazil origin)	K417T + E484K + N501Y	>511[c]
B.1.427/B.1.429 (California origin)	L452R	7.4
B.1.526 (New York origin)[d]	E484K	17

While BAM/ETE has reduced activity against most of the variants, CAS/IMD activity against emerging variants is preserved. BAM alone seems to have significantly decreased activity (not pictured).

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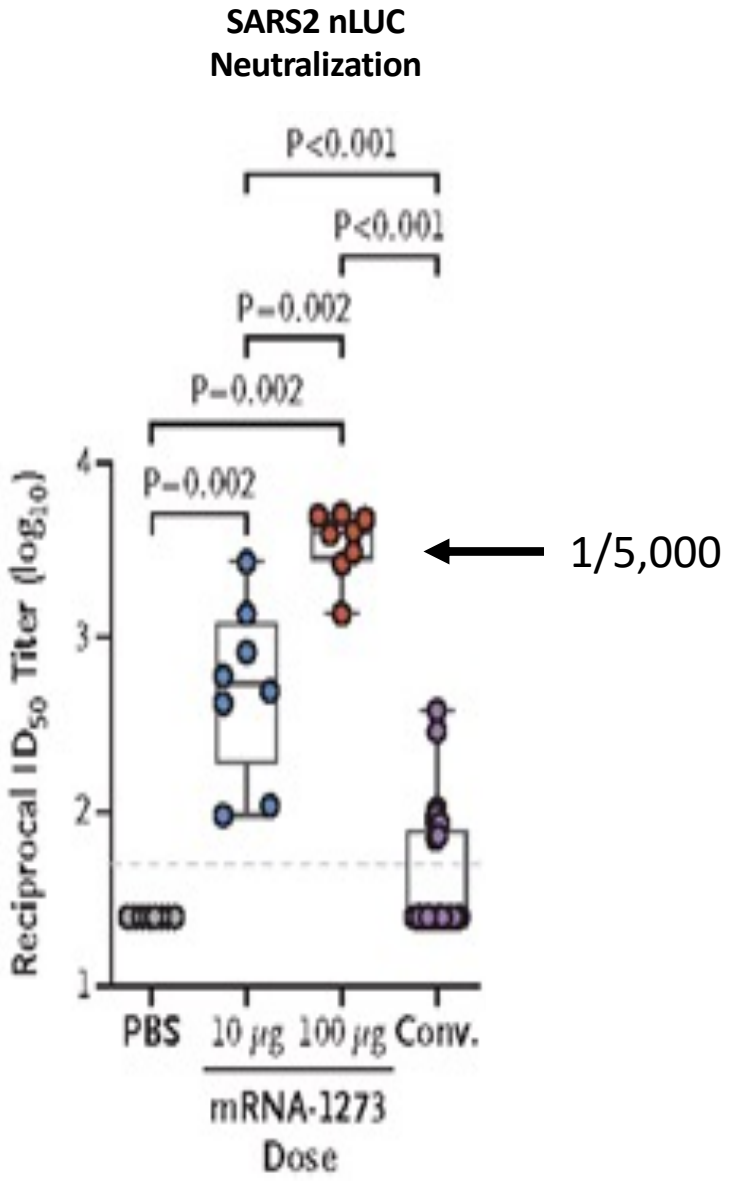
Vaccines

- **Pfizer and Moderna provide ~95% protection against SARS-CoV2 infection in humans**
  - S.A. Variant (~6-10 fold decrease in Ab binding)
  - Moderna and Pfizer are reformulating
- **Effect the performance of vaccines**
  - **<u>Novavax Vaccine: 89% effective</u>**
    - South Africa: 49% effective (>90% of breakthroughs were 501Y.V.2)
  - **<u>Astrazeneca Vaccine (67%)</u>**
    - Overall vaccine efficacy against mild-to-moderate COVID-19 in South Africa was 21.9% (95% CI -49.9 to 59.8)
    - Efficacy against B.1.351 was 10.4% (95% CI -76.8 to 54.8)
  - **<u>Killed Vaccines (~51%)</u>** **<u>Janssen Adenovirus Vaccines (?</u>**)
    - Variants? ~6 fold reduction in neutralization titers



Corbett et al., NEJM 2020

Vaccine Distribution: ACIP Ethical Principles

ACIP identified four ethical principles to guide the decision-making process if supply is limited:

Maximize benefits and minimize harms

Respect and care for people using the best available data to promote public health and minimize death and severe illness.

Mitigate health inequities

Reduce health disparities in the burden of COVID-19 disease and death, and make sure everyone has the opportunity to be as healthy as possible.

Promote justice

Treat affected groups, populations, and communities fairly. Remove unfair, unjust, and avoidable barriers to COVID-19 vaccination.

Promote transparency

Make a decision that is clear, understandable, and open for review. Allow and seek public participation in the creation and review of the decision processes.

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations-process.html

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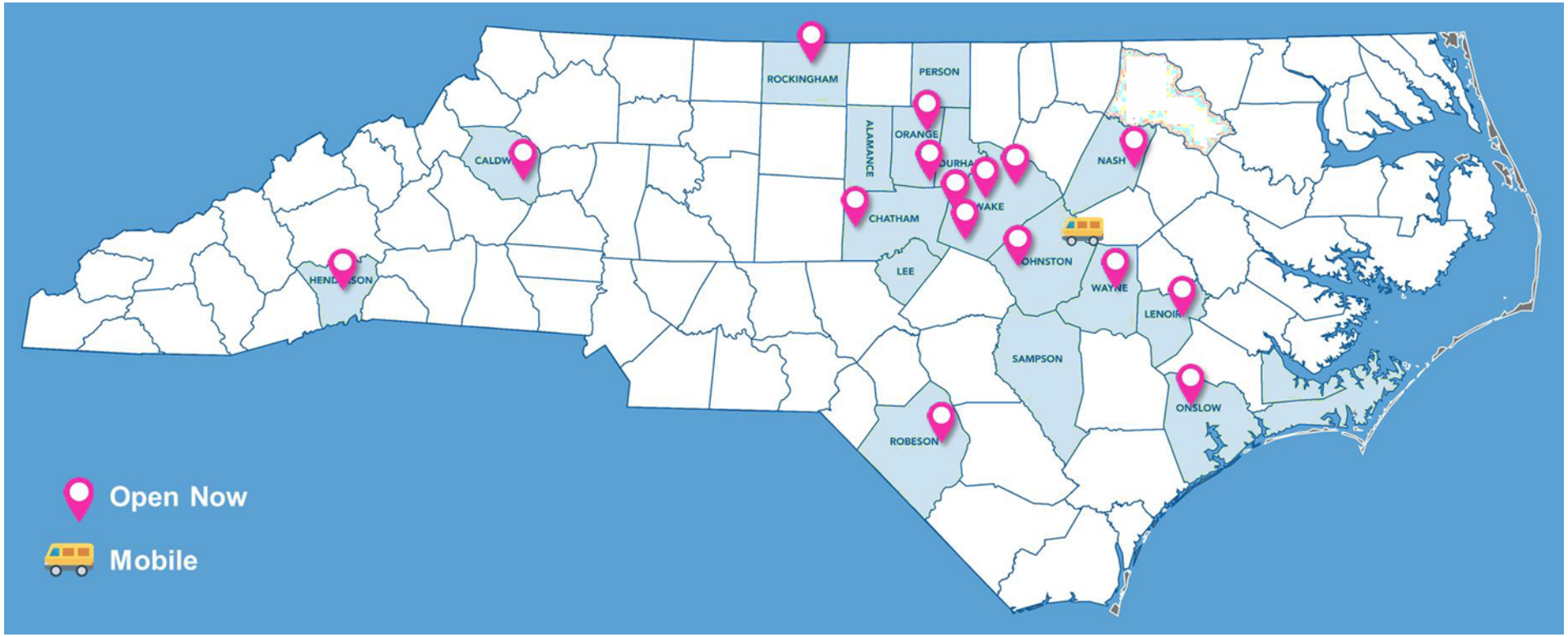
COVID-19 Vaccine Side-By-Side

	Pfizer/BioNTech	Moderna	Janssen/J&J
Type	**mRNA (virus genetic code)**	**mRNA (virus genetic code)**	**Recombinant adenovirus (Ad26) vector**
Antigen	Spike protein, 30 µg	Spike protein, 100 µg	Spike protein
Doses	**Two injections, 21 days apart**	**Two injections, 28 days apart**	**Single dose**
Study participants	~43,000	~30,000	~43,800
Age	**≥16 years**	**≥18 years**	**>18 years**
Effectiveness	**~95% against symptomatic COVID-19**	**~95% against symptomatic COVID-19**	**Effectiveness at preventing illness: ~77%, moderate-severe; 85%, severe, 100% hospitalizations and deaths**
Safety	**Grade 3 AEs ≥2%=fatigue, 3.8%; headache, 2%**	**Grade 3 AEs at ≥2%: local injection site reaction, 2.8%; injection site pain, 3.2%**	**No Grade 3 AEs ≥2%; Grade 3 AEs <2% include fatigue, 1.2%; myalgia, 1.4%; New reports, dizziness and syncope; Rare, clotting**
Preparation	Requires reconstitution (0.9% normal saline)	N/A	N/A
Long-term storage	-80 to -60 °C; protect from light	-25 to -15° C; protect from light	2° to 8° C; protect from light
Short-Term Storage	2° to 8° C up to 5 days, *or* Room temperature up to 2 hours	2° to 8° C up to 30 days, *or* Room temp (8° to 25° C) up to 12 hours	9° to 25° C up to 12 hours
Stability after 1st Puncture	6 hours, at room temperature	6 hours, at room temperature	6 hours, refrigeration; 2 hours, room temperature
Stability in Syringe	6 hours, at room temperature	6 hours, at room temperature	6 hours, refrigeration; 2 hours, room temperature
Administration Route	Intramuscular (IM)	Intramuscular (IM)	Intramuscular (IM)
Doses/Vial	5 doses (0.3 mL/dose)	10 doses (0.5 mL/dose)	5 doses/vial (0.5 mL/dose)

UNC HEALTH VACCINE SITES, NC



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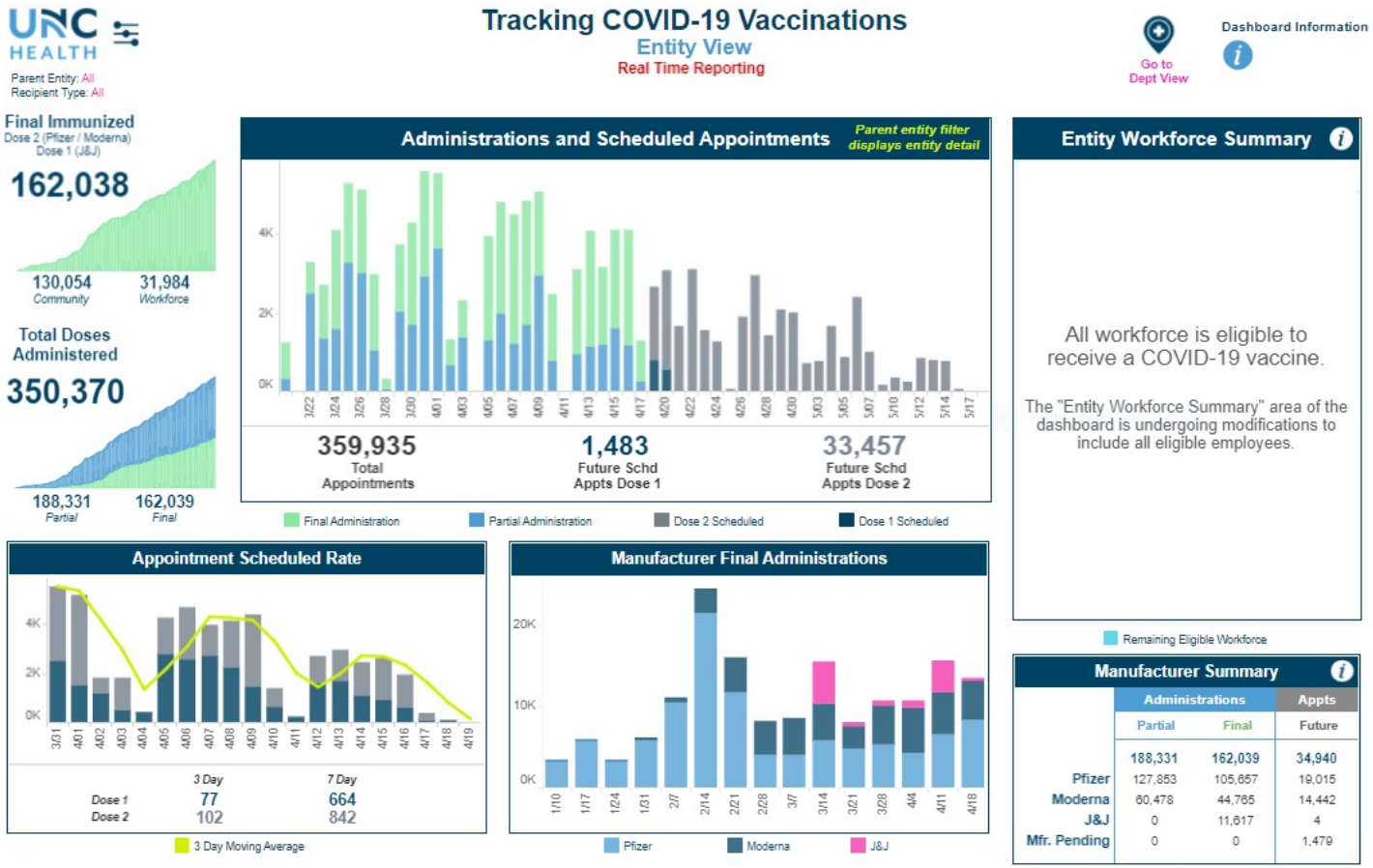
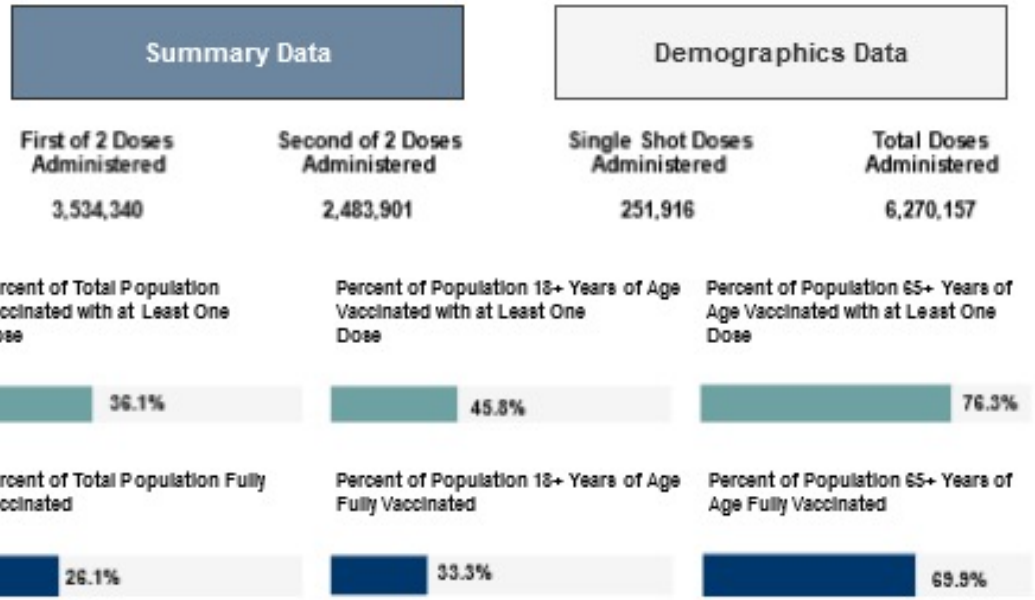
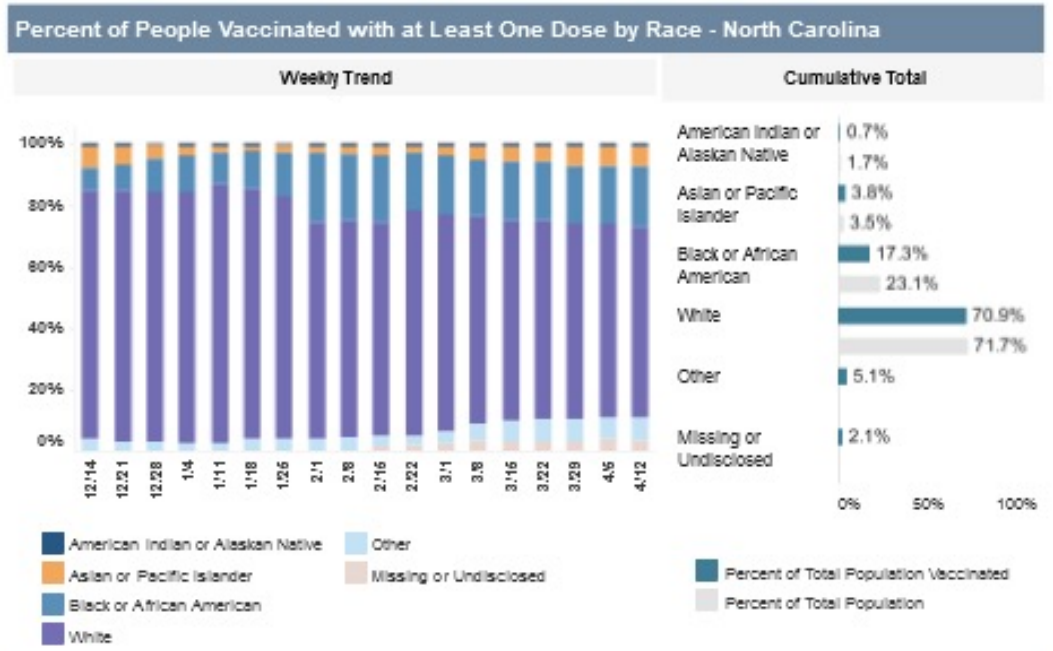
UNC HEALTH, COVID-19 VACCINE DASHBOARD

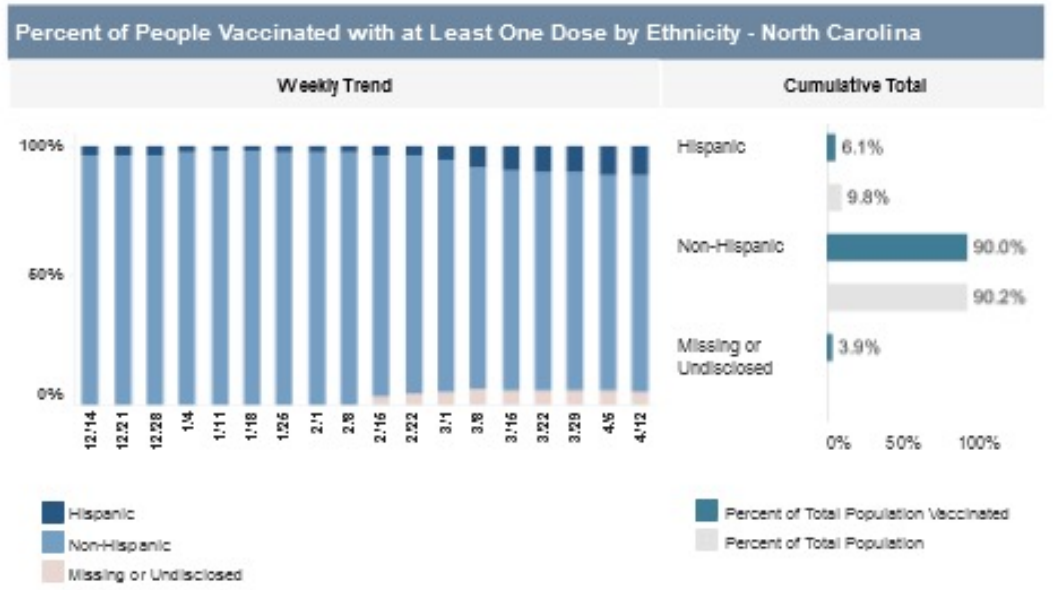


COVID-19 VACCINE ADMINISTRATION, NC



https://covid19.ncdhhs.gov/dashboard/vaccinations





Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)

Setting	Finding of xx% reduction in asymptomatic or infections including asymptomatic	Reference
Healthcare workers in England	**86%**	Hall SSRN, February 22, 2021
Healthcare workers in Israel	**75%**	Amit, Lancet, March 6, 2021
Patients in Mayo Clinic health system	**88.7%**	Pawlowski medRxiv, February 27, 2021
Israel Ministry of Health (nationwide) Israel general population (Pfizer)	**94%** **90%**	Pfizer press release, March 11, 2021 Dagan NEJM, February 24, 2021
Pre-surgical patients in Mayo Clinic system swabbed asymptomatically	**80%**	Tande Clin Inf Dis, March 10, 2021
Healthcare workers in Cambridge University Hospitals	**75%**	Weekes Authorea, February 24, 2021

Nasal viral load values are most important determinant of transmissibility (Lancet study); Nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid antigen tests after vaccination if want to test symptomatic)

VACCINE EFFICACY AGAINST ASYMPTOMATIC INFECTION: PFIZER VACCINE, ISRAEL

- Goal: Assess Pfizer vaccine effectiveness in persons vaccinated, 12/20/20-2/1/21
- Methods: Case-control (1:1 match to non-vaccinated controls); each group contained 596,618 persons
- Results: Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic Covid-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions.

Table 2. Estimated Vaccine Effectiveness against Covid-19 Outcomes during Three Time Periods.*

Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference
	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)
14 to 20 days after first dose	46 (40–51)	2.06 (1.70–2.40)	57 (50–63)	1.54 (1.28–1.80)	74 (56–86)	0.21 (0.13–0.29)	62 (39–80)	0.14 (0.07–0.21)	72 (19–100)	0.03 (0.01–0.07)
21 to 27 days after first dose	60 (53–66)	2.31 (1.96–2.69)	66 (57–73)	1.34 (1.09–1.62)	78 (61–91)	0.22 (0.13–0.31)	80 (59–94)	0.18 (0.10–0.27)	84 (44–100)	0.06 (0.02–0.11)
7 days after second dose to end of follow-up	92 (88–95)	8.58 (6.22–11.18)	94 (87–98)	4.61 (3.29–6.53)	87 (55–100)	0.22 (0.08–0.39)	92 (75–100)	0.32 (0.13–0.52)	NA	NA

* Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

Dagan N, et al. 24 February 2021

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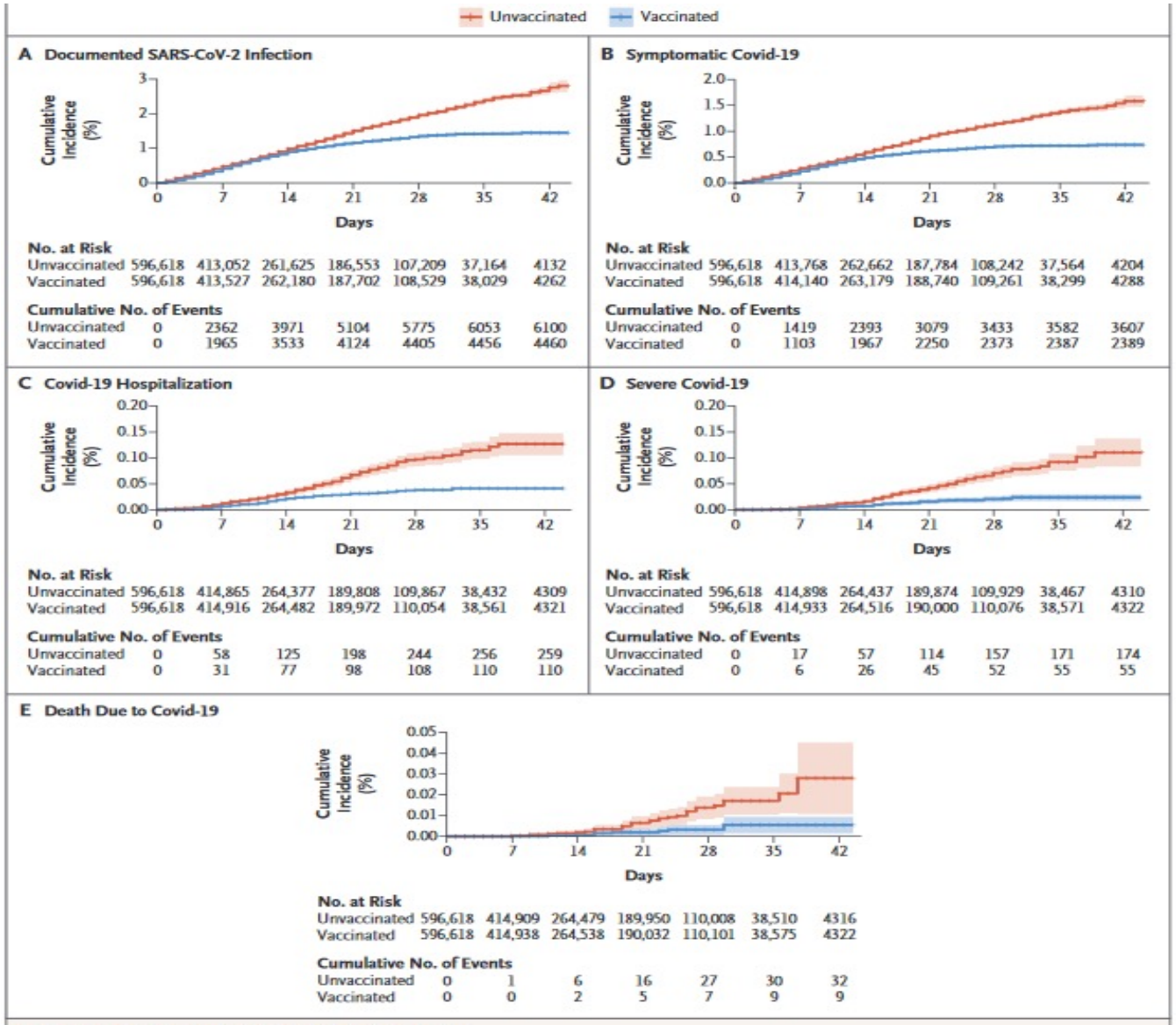

Figure 2. Cumulative Incidence of the Five Outcomes.

Cumulative incidence curves (1 minus the Kaplan–Meier risk) for the various outcomes are shown, starting from the day of administration of the first dose of vaccine. Shaded areas represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events are also shown for each outcome. Graphs in which all data are shown with a y axis scale from 0 to 100 (along with the data shown, as here, on an expanded y axis) are provided in Figure S8 in the Supplementary Appendix.

VACCINE EFFICACY AGAINST ASYMPTOMATIC INFECTION: PFIZER VACCINE, ISRAEL

Dagan N, et al. 24 February 2021

Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals

- Goal: Assess vaccine response after Pfizer vaccine in HCP s/p COVID-19
- Methods: Case-control analysis of 51 HCP; HCP tested 19-29 days after 1st dose
- Results:
  - Among those with a previous SARS-CoV-2 infection, vaccination increased anti-S titres more than 140-fold from peak prevaccine levels (figure)
  - This increase appears to be at least one order of magnitude greater than reported after a conventional prime-boost vaccine strategy in previously uninfected individuals.

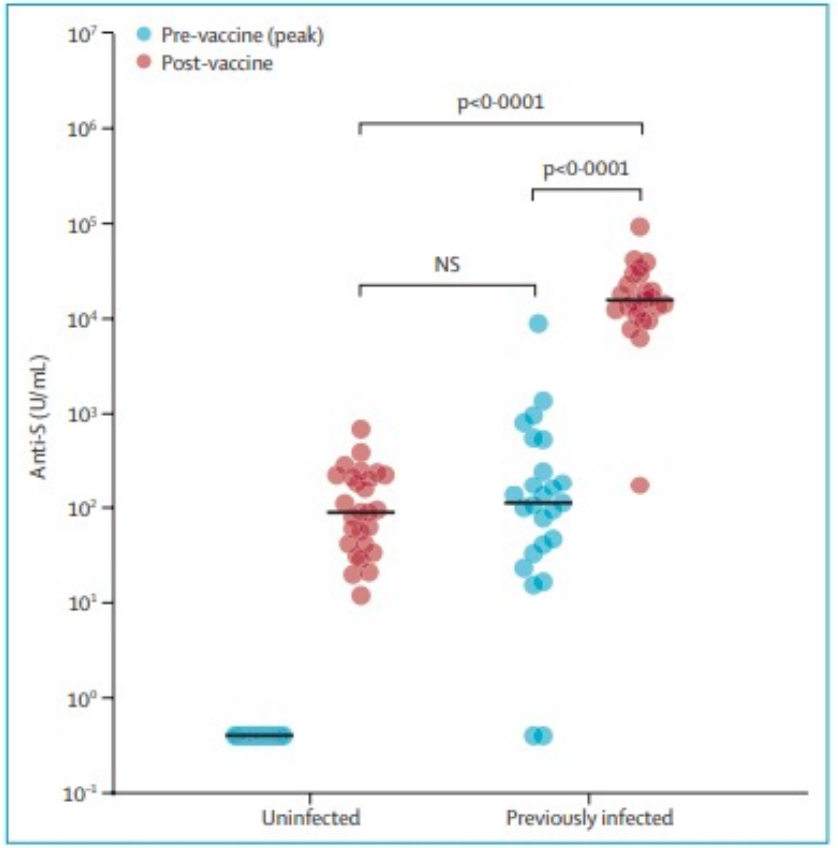

Figure: **Serological response to one dose of the BNT162b2 mRNA COVID-19 vaccine in individuals with and without laboratory-confirmed previous SARS-CoV-2 infection**

SARS-CoV-2 anti-S antibody titres in individuals with no previous infection are similar to titres in individuals who have had a mild SARS-CoV-2 infection. Anti-S titres in those with previous SARS-CoV-2 infection are more than 140-fold greater than at time of peak infection. Statistical analysis was by unpaired two-tailed *t* test. U=unit. NS=non-significant.

Manisty C, et al. Lancet 2021;25 February

COVID-19 VACCINES: SAFETY MONITORING

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

1. Text message check-ins from CDC (daily 1st week; weekly thru 6 weeks; then 3, 6, and 12 mo.)

Vaccine recipient completes web survey

Vaccine recipient

v-safe
after vaccination health checker

2. Clinically important event(s) reported

✓ Received medical care

Call center

3. A VAERS customer service representative conducts active telephone follow-up on a medically attended health impact event and takes a report if appropriate

CDC FDA

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CEREBRAL VENOUS SINUS THROMBOSIS (CVST)

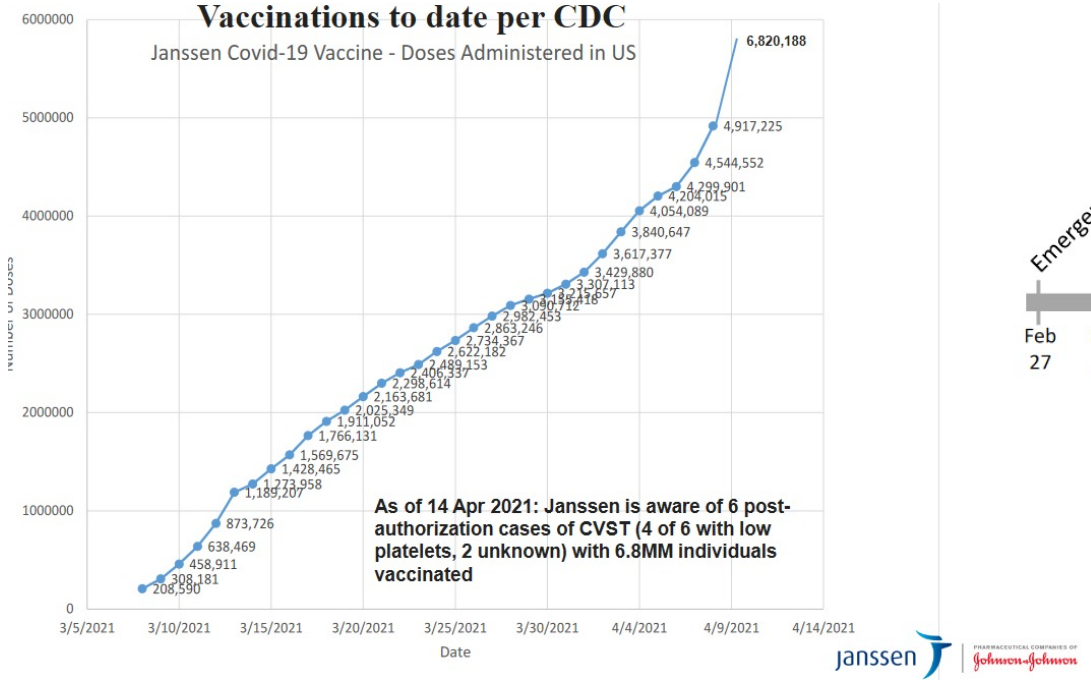
- Background epidemiology
  - Rare, 0.22–1.57 per 100,000, ~0.5-1% of all strokes
  - Median age 37 years
  - 8% of patients >65 years
  - Female:male ratio of 3:1
- Risk factors
  - Prothrombotic conditions (genetic or acquired)
  - Oral contraceptives
  - Pregnancy and the post-partum period
  - Malignancy
  - Infection
  - Mechanical precipitants (lumbar puncture)

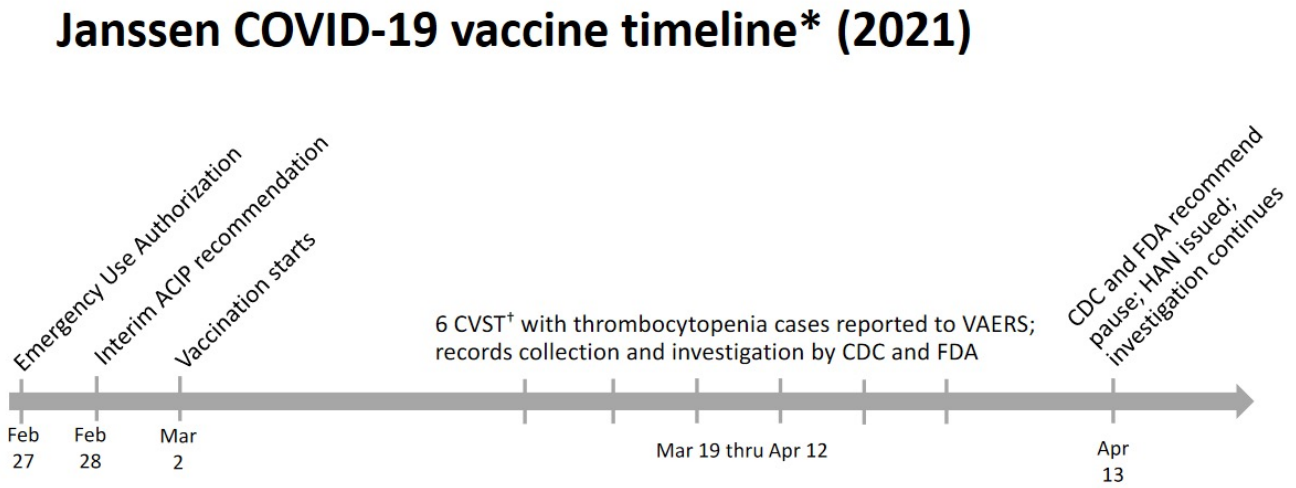
CVST signs and symptoms

- More common presentations
  - Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)
  - Focal syndrome (focal deficits, seizures, or both)
  - Encephalopathy (multifocal signs, mental status changes, stupor, or coma)
- Rare presentations
  - Cavernous sinus syndrome
  - Subarachnoid hemorrhage]
  - Cranial nerve palsies

CDC, ACIP, 14 April

JOHNSON & JOHNSON VACCINE, THROMBOTIC EVENTS



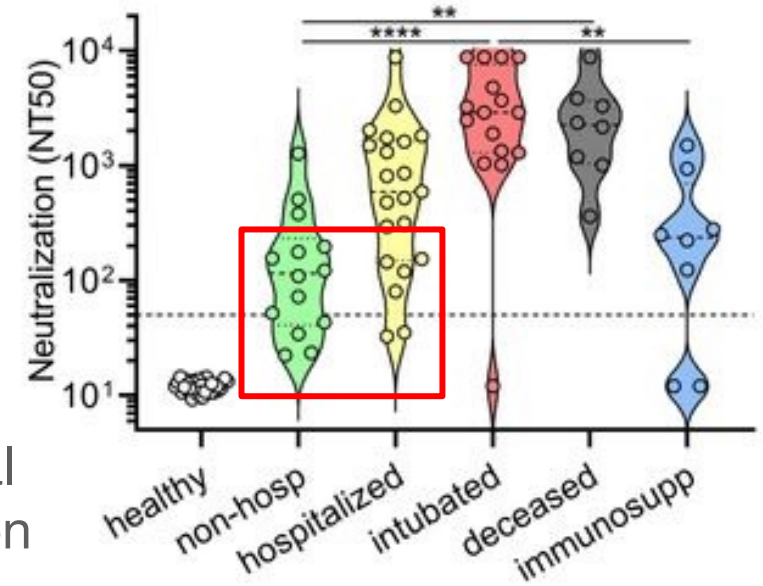


- J&J rate = 0.87 cases per million doses administered (no obvious risk factors but all were female)
- Pfizer = 0 reports, 97,9 doses administered
- Moderna = 3 reports, 84.7 million doses administered

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04/02-COVID-Janssen-508.pdf

Predictions

- **SARS-CoV2 Population Genetics is extremely large, globally**
  - **Perfect conditions to rapidly select for new variants: more transmissible**
  - **Selection will likely begin to change as vaccine, seroprevalence rates increase**
    - Promote the emergence of strains that are antigenically distinct (2-8 fold ↓ neutralization`)
    - May select for strains with increased virulence (UK B.1.1.7, B.1, South Africa B.1.351)

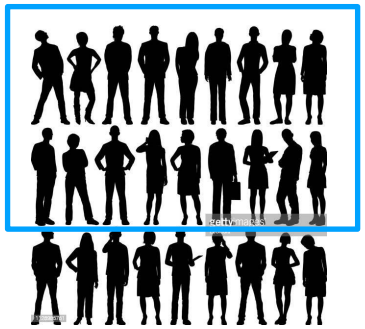


Natural Infection

~50-80% Asymptomatics Mild Infections

2-8 fold ↓

Reinfected



~200/8 == ~25

Early Stages Of VOC Emergence

NY: B.1.526 (27%)

E484K and S477N

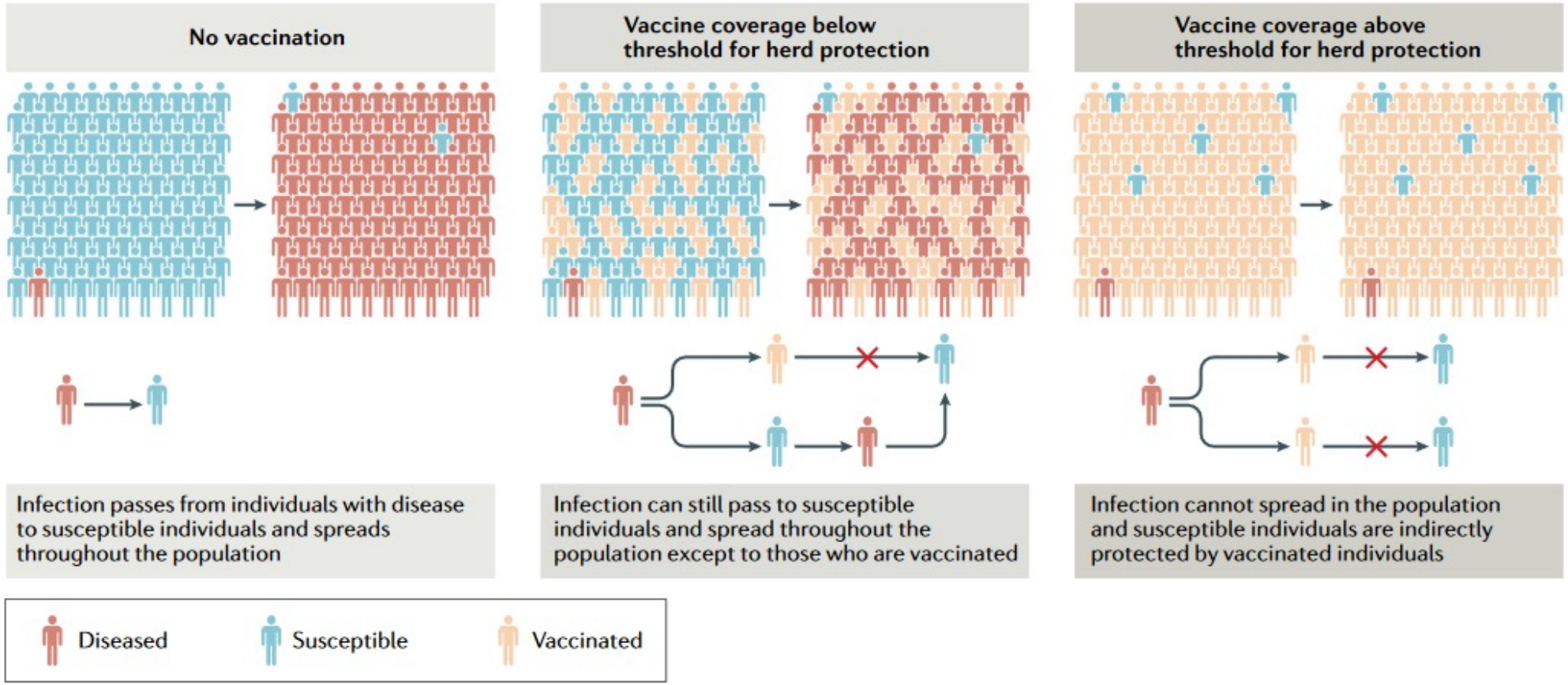
Eli Lily/Regeneron hmAB↓

Chen et al., 2020

PROJECTIONS FOR THE FUTURE

- **Known**
  - Estimated U.S. persons who have had COVID-19: Total infections, 31,000,000; symptomatic illness, 563,000 deaths (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html); current cases driven by transmission in young adults
  - SARS-CoV-2 variants of clinical importance described in US; UK variant now most common SARS-CoV-2 strain
  - Variants with increased transmissibility increasing worldwide in frequency
  - US surveillance for SARS-CoV-2 inadequate (i.e., only ~1% of SARS-CoV-2 positive tests sequenced; 10% in UK)
- **Likely**
  - Estimated US death toll of COVID-19: ~650,000 by 30 May
  - SARS-CoV-2 variants will rapidly spread in US
- **Unknown**
  - Rapidity of spread of SARS-CoV-2 variants; impact of variants on natural and vaccine induced immunity; impact of variants on effectiveness of mAb therapy
  - Rapidity of development of new mAbs and vaccines that “defeat” new variants
  - Impact of variants on future surges: Surges also depend on: 1) holiday travel/gatherings (Easter, July 4); 2) summer camps; 3) adherence to masking (esp. in vaccinated persons); 4) whether vaccine prevents SARS-CoV-2 infection and infectiousness

COMMUNITY PROTECTION (Herd Immunity)



Pollard AJ, Bijker EM. Nature Rev Immunol 2021;21:83-100

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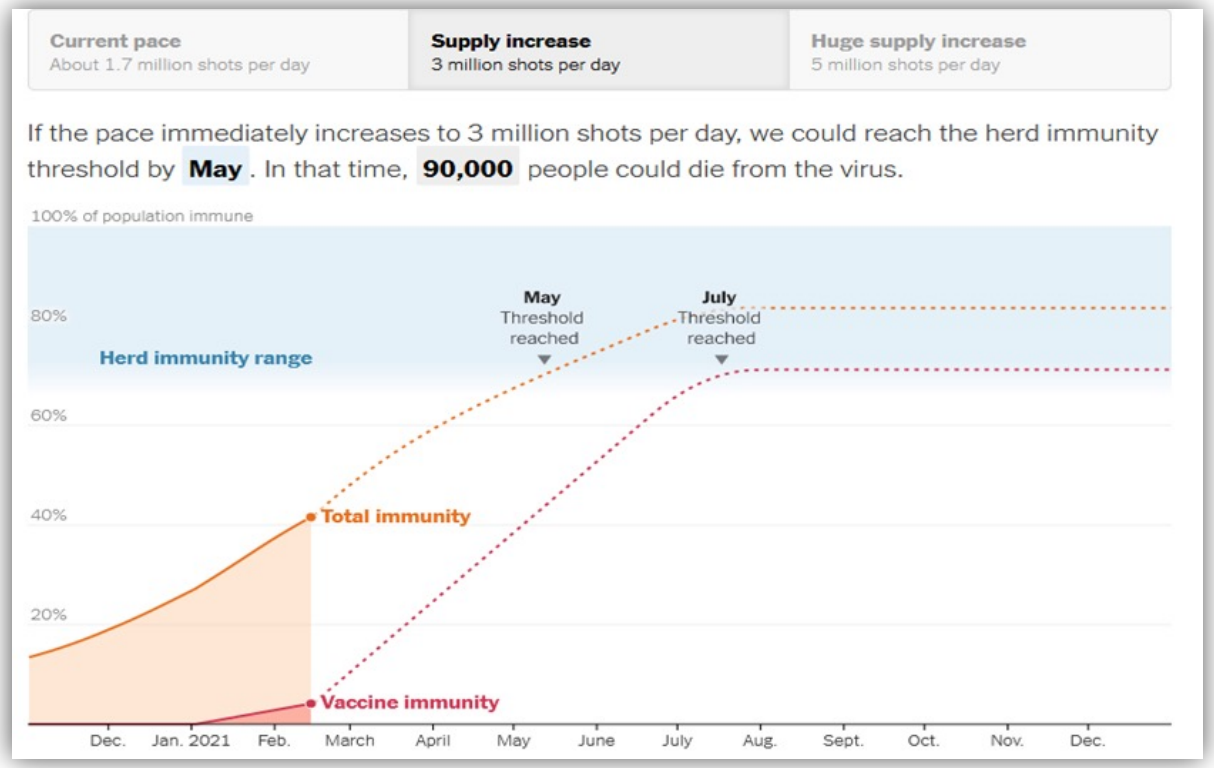
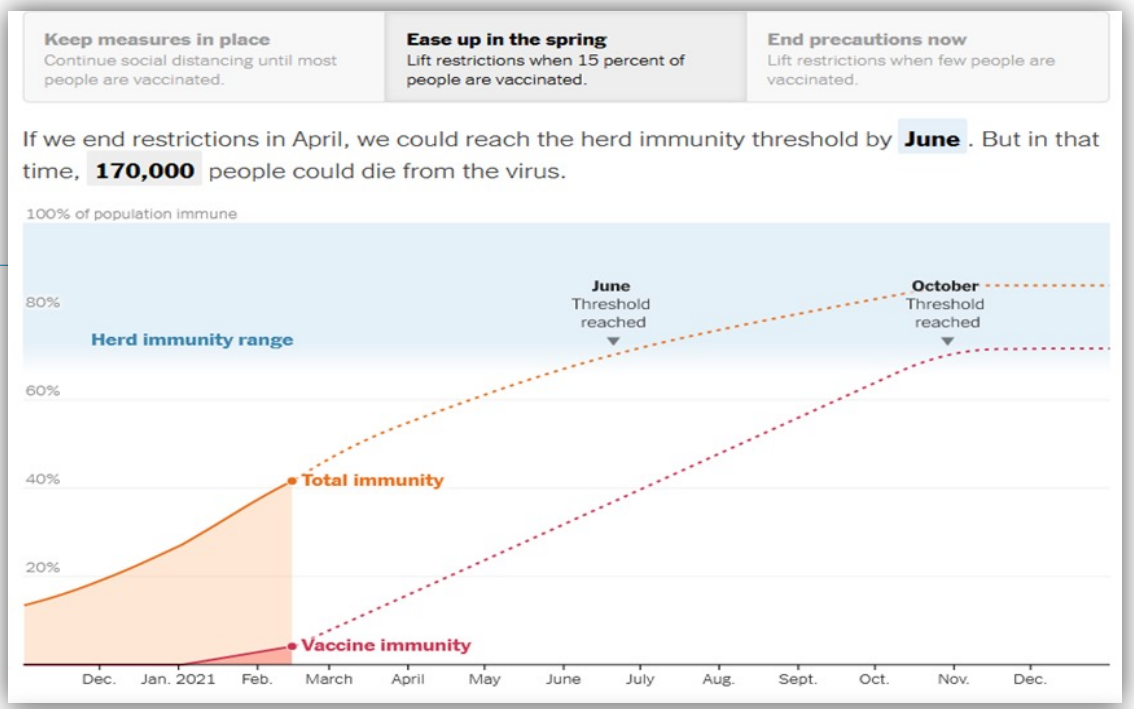
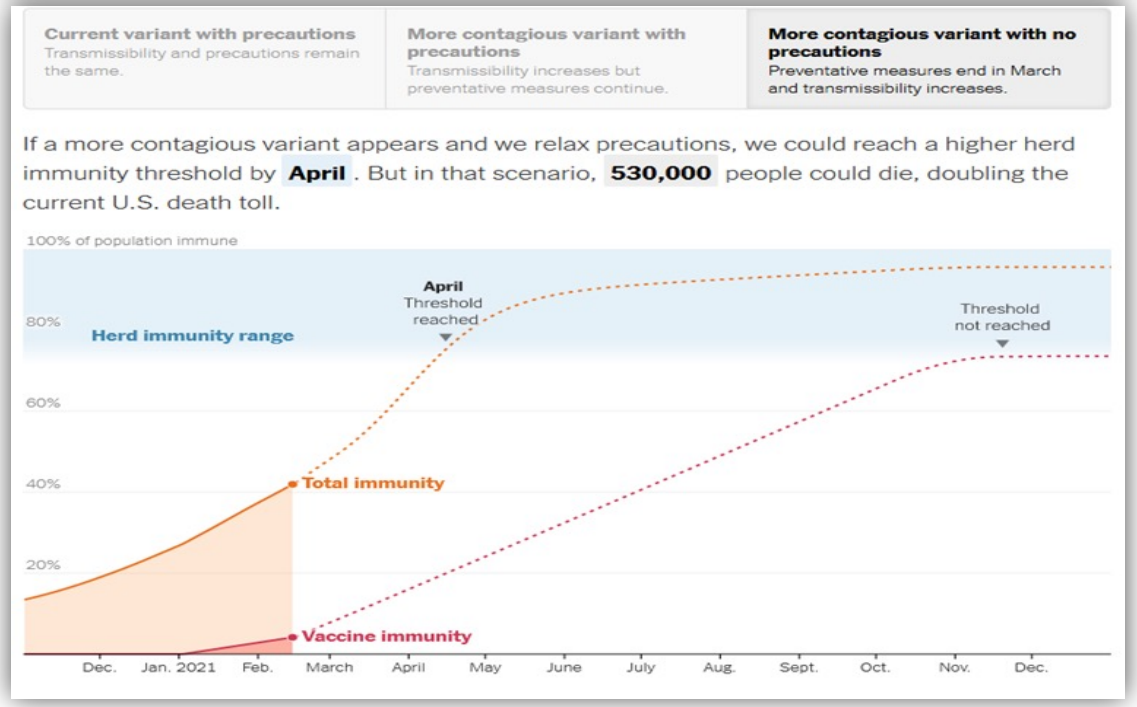
Path to Community Protection







Predictions: 1) continued but falling high cases counts (~200,000-500,000, last week in March); 2) Surge in cases in 2-6 wks followed by surge in hospitalizations and deaths (driven by Spring break, easing mitigation strategies, rapid doubling in US of UK variant)

https://www.nytimes.com/interactive/2021/02/20/us/us-herd-immunity-ovid.html