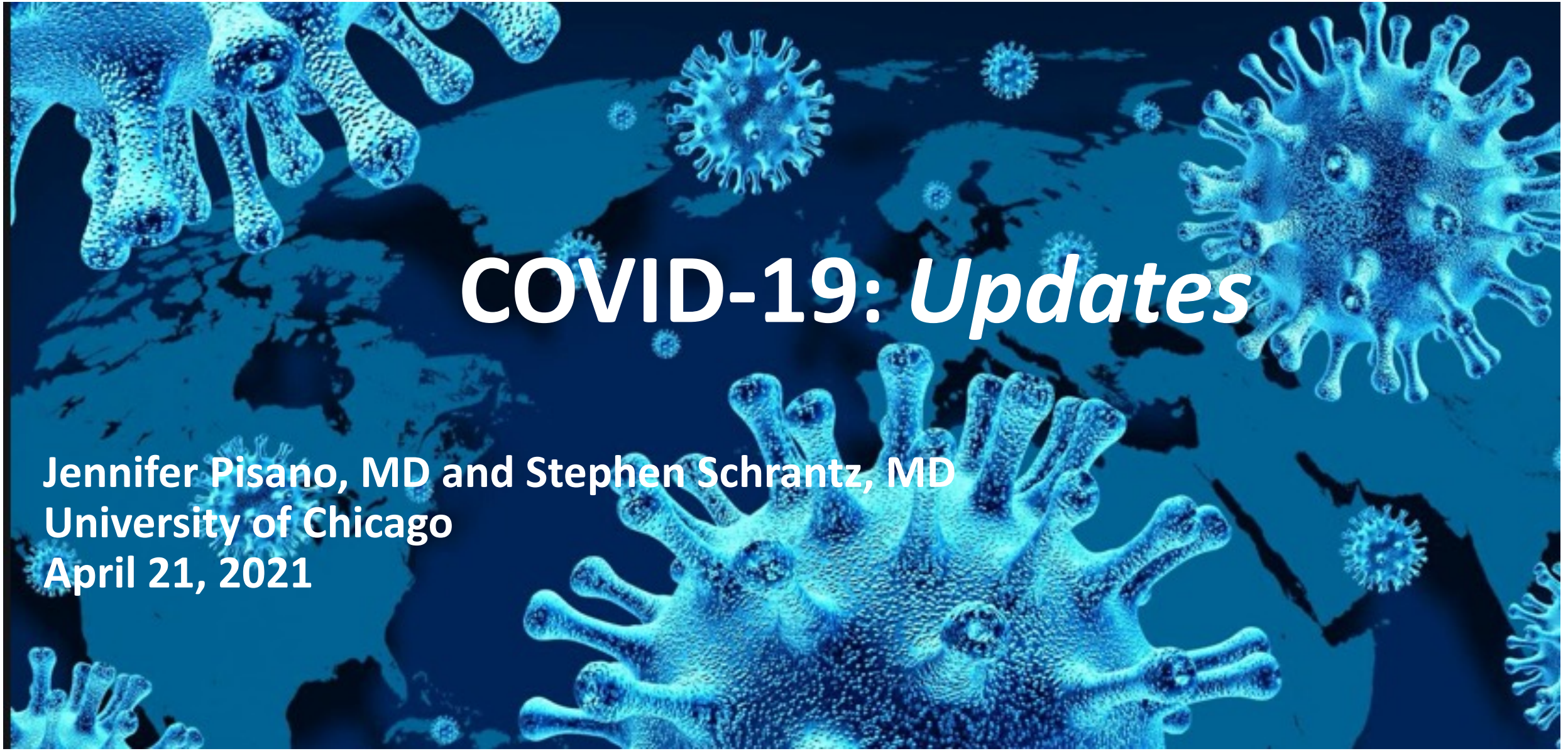

COVID-19: *Updates*

Jennifer Pisano, MD and Stephen Schrantz, MD
University of Chicago
April 21, 2021

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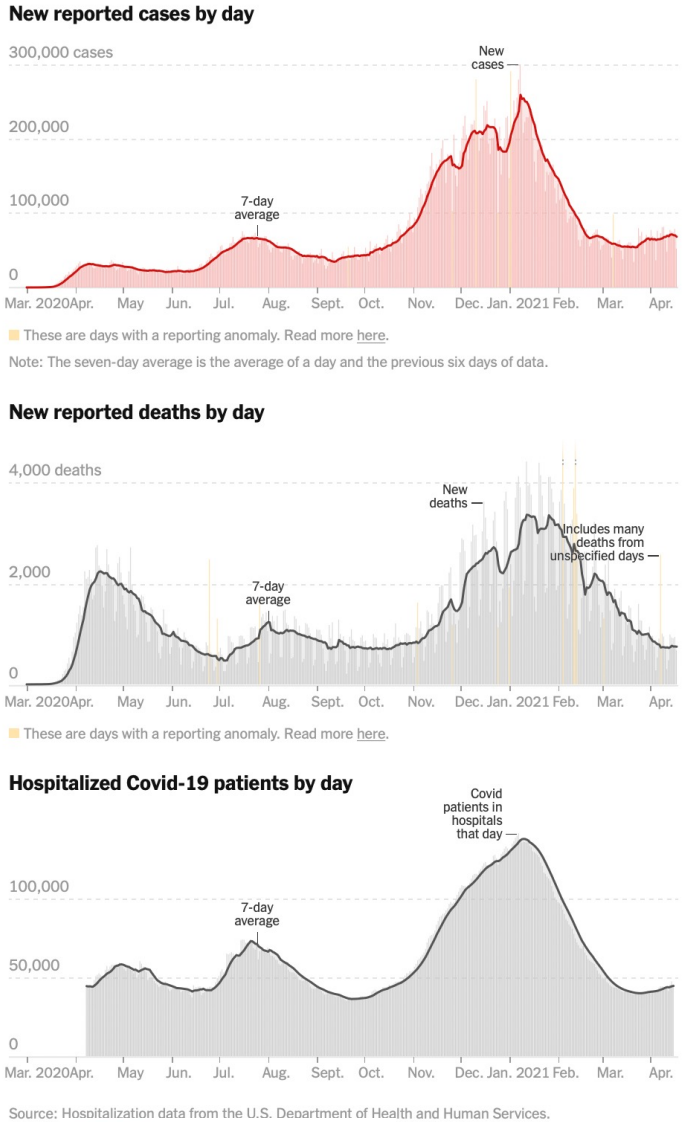
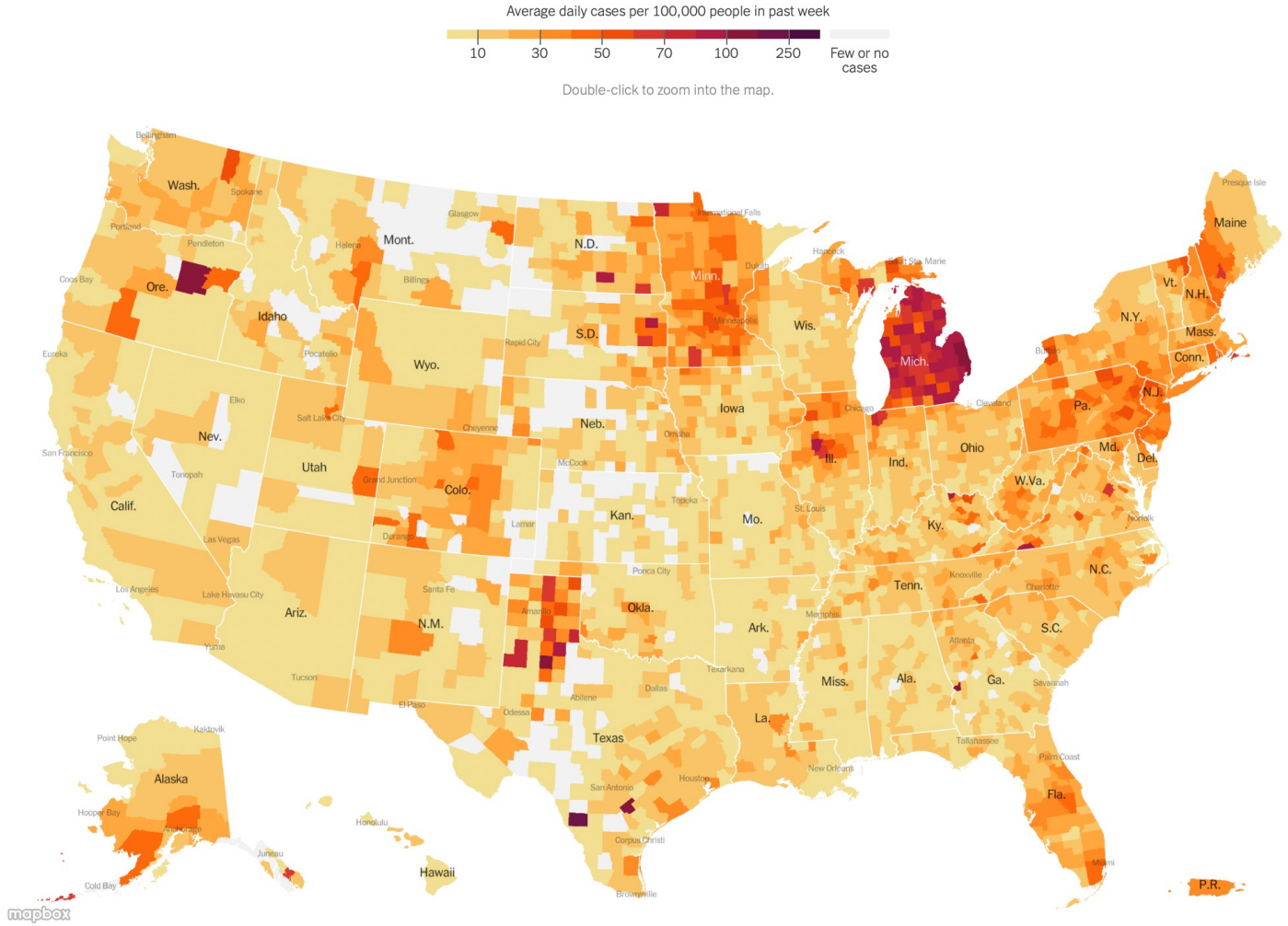
AT THE FOREFRONT
UChicago Medicine

Disclosures

- We have no relevant financial interests to disclose.

The Latest Trends





https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html?action=click&module=Top%20Stories&pgtype=Homepage

CHICAGO | COVID-19 Citywide Positivity Rate

Last updated April 19, 2021

Data for this dashboard is updated daily.

Select mode

Daily by Demographic | Weekly by ZIP | Positivity Rate

Select date range

3/1/2020 — 4/20/2021

About

Positivity rate is the percentage of COVID-19 PCR and antigen tests that come back positive, relative to the total number of tests performed. The positivity rate decreases if there are fewer cases of COVID-19 OR if the total number of tests increases and community transmission is stable.

Note: the positivity rate test counts do include multiple tests for the same person.

To account for reporting lag, all 7 day rolling averages are as of 4/16/2021

Reset to default

built by slalom

Current Positivity rate

Based on a 7 day rolling average

5.4% ▼

Prior wk.: 5.7%

Tests performed (3/1/2020 - 4/19/2021)

Cumulative tests

3,807,046

Daily tests (7 day rolling average)

13,788 ▼

Prior wk.: 14,160 (-3%)

Cases (3/1/2020 - 4/20/2021)

Cumulative cases

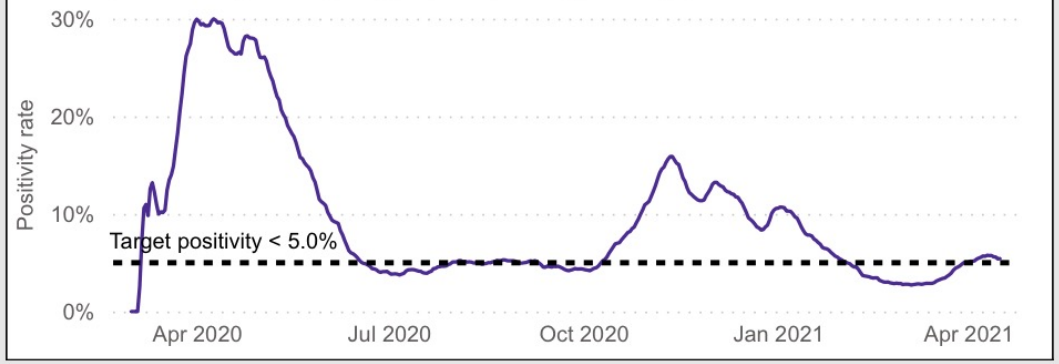
269,705

Daily cases (7 day rolling average)

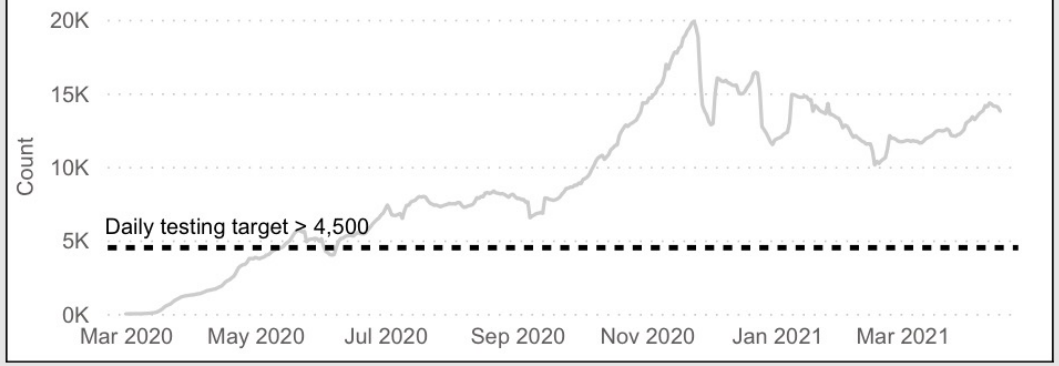
640 ▼

Prior wk.: 708 (-10%)

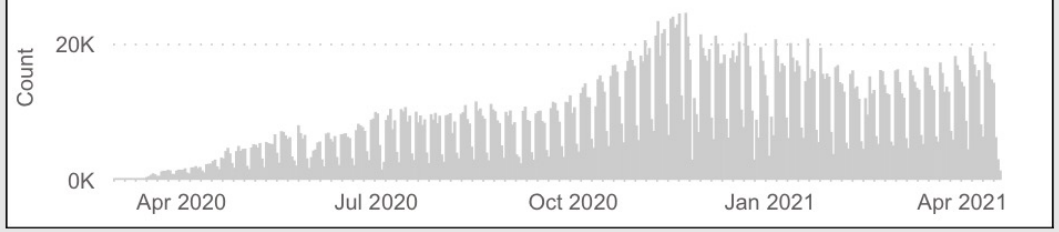
Positivity rate and positivity target (7 day rolling average)



Tests performed and testing target (7 day rolling average)



Daily tests performed



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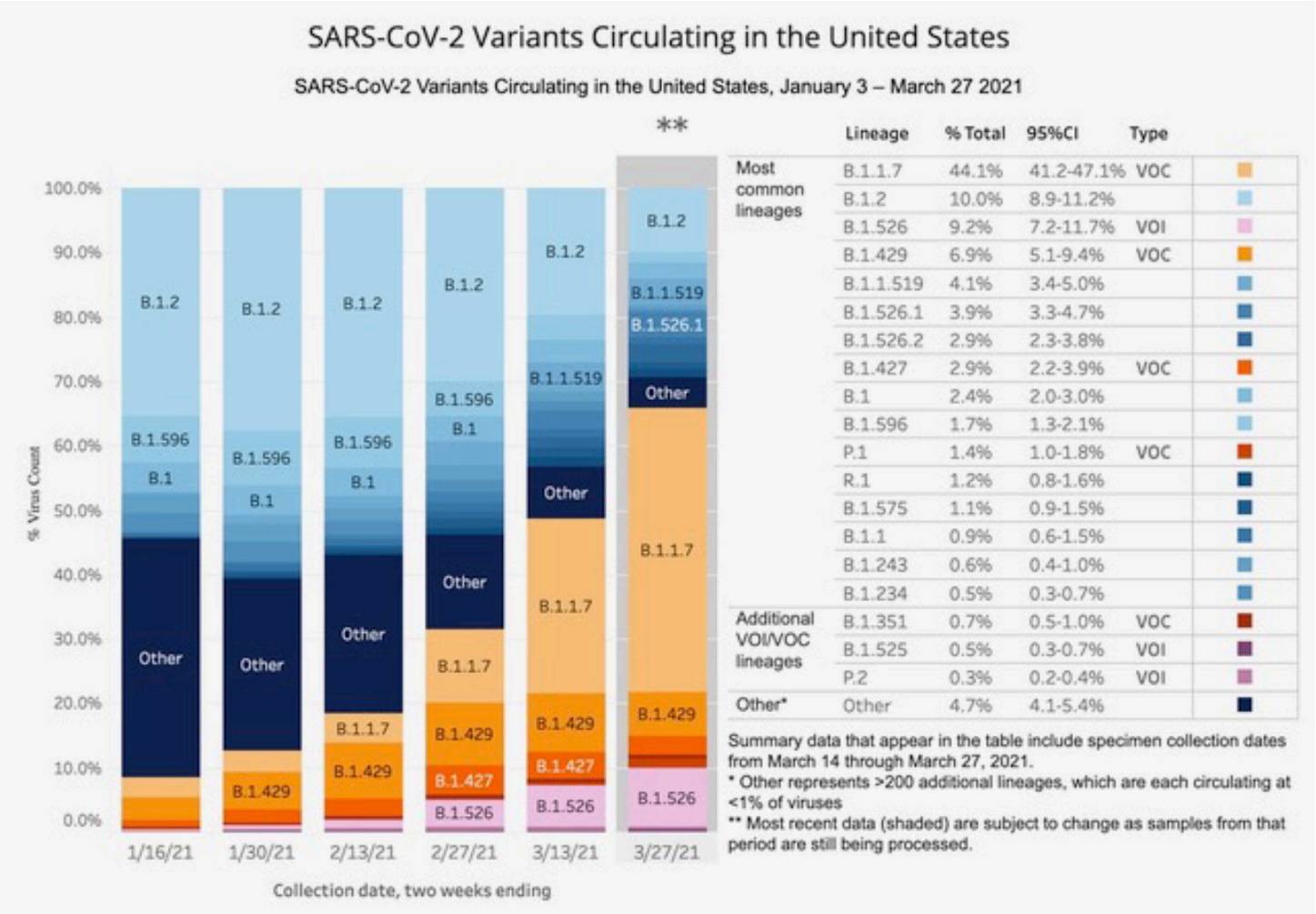

More Contagious Virus Variant Is Now Dominant in U.S., C.D.C. Chief Says

The B.1.1.7 variant, first identified in Britain, is now the source of most new coronavirus infections in the United States, the director of the Centers for Disease Control and Prevention said.

B.1.1.7, the first variant to come to widespread attention, is about 60% more contagious and 67% more deadly than the original form of the coronavirus, according to the most recent estimates.

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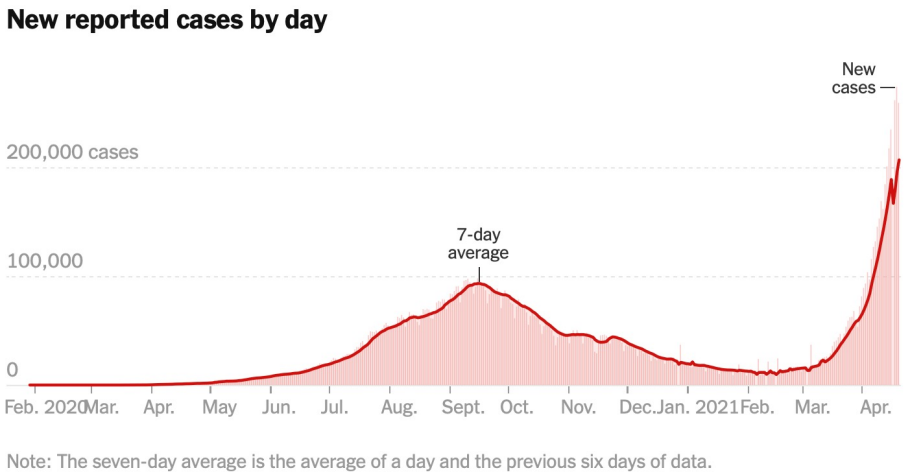
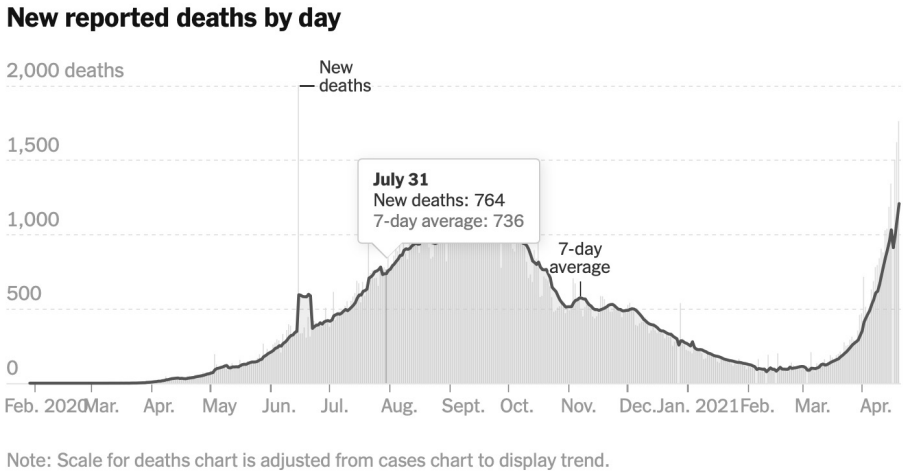
https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html

What's going on in India!?





- Unclear what is driving the huge surge
- New variant B1617 has been described – contains the L452R mutation, similar to CA variant B1427 – may make it easier to transmit
- Also has a E484Q – leading to people referring to this strain as a "double mutant"
- Unclear how this will be affected by current vaccinations

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https://theconversation.com/q-a-indian-coronavirus-variant-what-is-it-and-what-effect-will-it-have-159269

CDC, FDA Recommend Pausing Use of Janssen COVID-19 Vaccine After Reports of Rare Blood Clots

- According to a joint statement, the CDC and FDA are currently reviewing data involving these 6 cases in which cerebral venous sinus thrombosis (CVST) occurred in combination with thrombocytopenia among women 18 to 48 years of age. In all 6 cases, symptoms developed 6 to 13 days after vaccination.
- FDA reported that 1 of these cases was fatal, while another patient is in critical condition. As of April 12, more than 6.8 million doses of the Janssen COVID-19 vaccine were administered
- The CDC's Advisory Committee on Immunization Practices held a meeting on April 14 to review the cases and concluded more data was needed
- Pause will likely be lifted this week with new warning regarding risks and possibly limitations regarding who receives vaccine
- What will this do for those who are vaccine hesitant?

Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination

- Further evidence is accumulating that suggests a rare link between Adenoviral vectored vaccines and the occurrence of thrombotic thrombocytopenia with similar MOA found in HIT
- Recent case report: patient with cerebral venous sinus thrombosis had received the Ad26.COV2.S vaccine 14 days before symptom onset. The screening test for antibodies against platelet factor 4 (PF4)–heparin by latex-enhanced immunoassay was negative. However, the result of ELISA for antibodies against PF4–polyanion was strongly positive. Heparin was switched to argatroban. She also received intravenous immune globulin for 2 days. This treatment was followed by an increase in the platelet count from 30,000 to 145,000 during a 5-day period.
- Vaccine-induced immune thrombotic thrombocytopenia in studies of clots from the AZ vaccine were associated with IgG antibodies that recognize PF4 and activate platelets through their Fcγ receptors.
- Inhibition of platelet activation by intravenous immune globulin paralleled its efficacy in the treatment of autoimmune heparin-induced thrombocytopenia.
- One case of CVST was discovered in the J and J trial but was dismissed as not being related to vaccine. Experts are re-considering this.

https://www.nejm.org/doi/full/10.1056/NEJMc2105869?query=pfw&jwd=000000659072&jspc=IM

Cerebral venous sinus thrombosis (CVST)

General Population	COVID-19	Pregnancy	Oral Contraceptive Pill	Johnson & Johnson /Janssen Vaccine
				
3 to 15 per 1,000,000 / year	4.5 to 20 per 100,000 COVID-19 cases	10 to 12 per 100,000 deliveries	2.7 to 40 per 100,000 people	6 per 6,800,000 million vaccines
0.0003% - 0.0015%	0.0045% - 0.02%	0.01% - 0.012%	0.0027% - 0.04%	0.00009%
	↑ 14 – 66x increase	↑ 32 – 39x increase	↑ 8 – 132x increase	?

References:

Amoozegar, F. Fron Neurol, 2015. Jick. S. Contraception, 2006. Niksirat, A. J Pioneer Med Sci, 2014. Dentali, F. Blood, 2006. Abdalkader, M. J Stroke Cerebrovasc Dis, 2021. Siegler, J. Int J Stroke, 2020. FDA/CDC, 2021.

Rarity Reference: Odds of Lightning Striking: 1 in 500,000
0.0002%

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Credit: Dr. Jesse O'Shea

Vaccine Breakthrough Infections Remain Rare

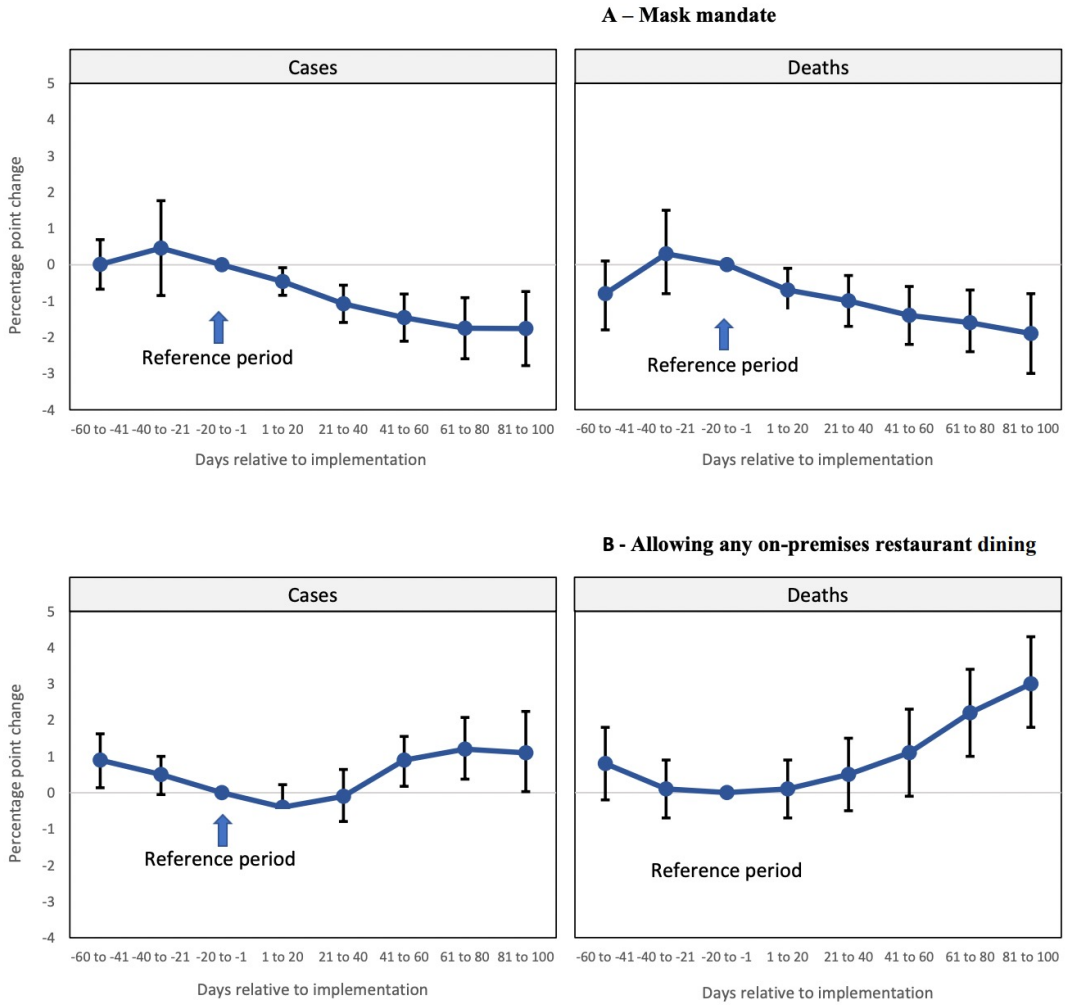
- *As of April 13, 2021 more than 75 million people in the US have been fully vaccinated against COVID-19*
- *In that time, CDC reports only 5,814 cases of vaccine breakthrough infection found in 43 states*
  - *1,695 (29%) of the vaccine breakthrough infections were reported as asymptomatic*
  - *396 (7%) people with breakthrough infections were known to be hospitalized and 74 (1%) died*
- *Current vaccines appear to effective against all circulating variants in the US*

- ***99.992% of fully vaccinated people in the US protected from any COVID-19 disease***
- ***99.999% of fully vaccinated people in the US protected from hospitalization and death***

Masks Reduce Transmission

- *Consistent and correct use of masks can prevent SARS-CoV-2 transmission, which predominantly occurs through inhalation and other exposure to respiratory droplets from infected persons**. Mask use is particularly important because presymptomatic and asymptomatic spread is responsible for nearly 60% of COVID-19 cases**.*
- ***In a recent report, the CDC evaluated the association between state-issued mask mandates and allowing any on-premises restaurant dining and COVID-19 cases and deaths between March 1 and December 31, 2020**.*
- *State-issued mask mandates were associated with decreases in daily COVID-19 case growth rates and death growth rates within 20 days of implementation, ranging from 0.5 percentage points to 1.9 percentage points*

eFigure. Association of COVID-19 Cases and Death Daily Growth Rates[a] With Implementation of State Mask Mandates[b] and Allowing Any On-Premises Restaurant Dining[c], by Time After Implementation, United States



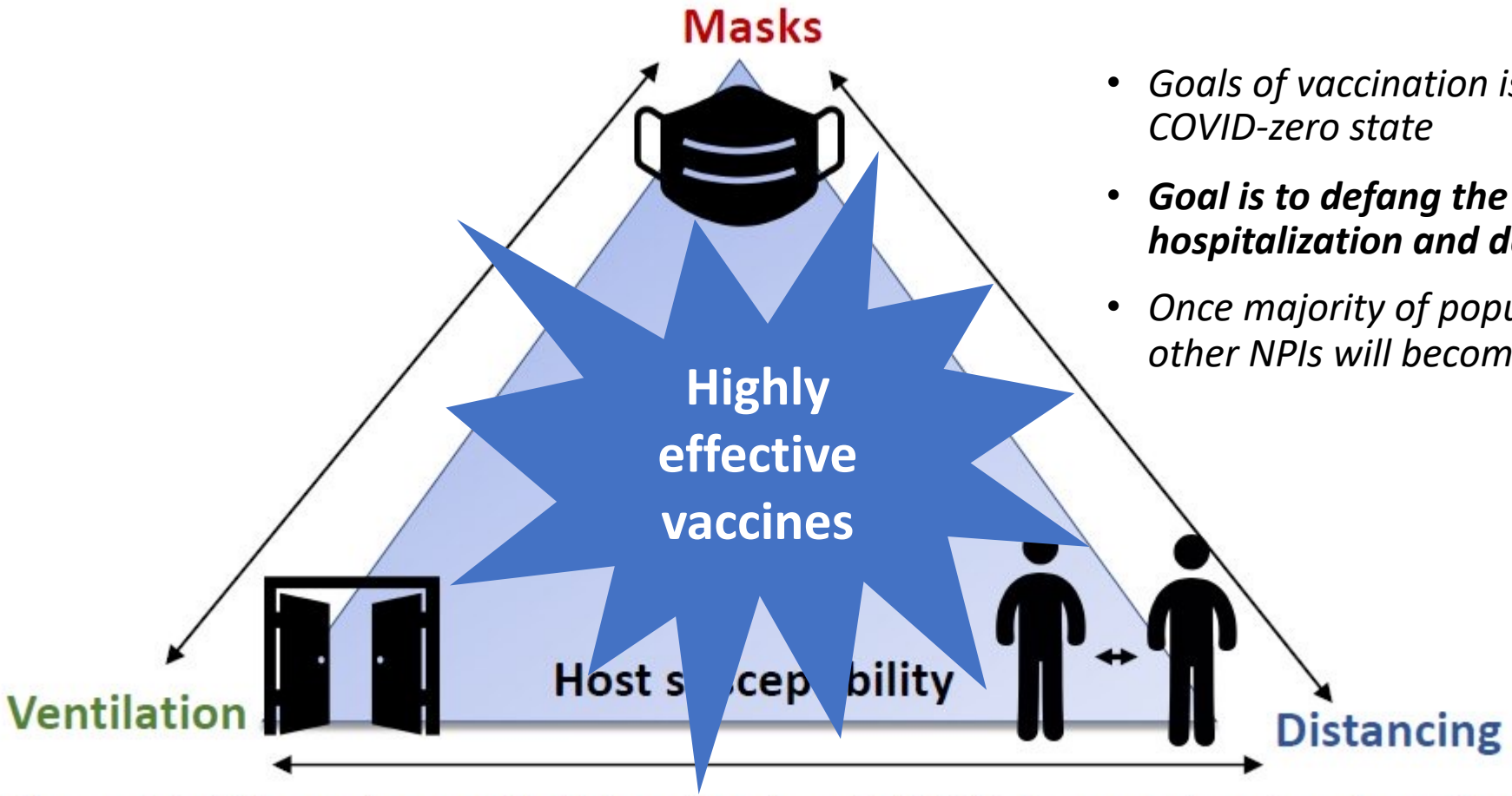
JAMA. Published online April 1, 2021. doi:10.1001/jama.2021.5455

Cleaning surfaces is not as important

- People can be infected with SARS-CoV-2 through contact with surfaces. However, based on available epidemiological data and studies of environmental transmission factors, surface transmission is not the main route by which SARS-CoV-2 spreads, and **the risk is considered to be low.**
- The principal mode by which people are infected with SARS-CoV-2 is through exposure to respiratory droplets carrying infectious virus.
- In most situations, cleaning surfaces using soap or detergent, and not disinfecting, is enough to reduce risk. Disinfection is recommended in indoor community settings where there has been a suspected or confirmed case of COVID-19 within the last 24 hours.
- The risk of fomite transmission can be reduced by **wearing masks consistently** and correctly, practicing hand hygiene, cleaning to maintain healthy facilities.

https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html

The Complementary Non-Pharmaceutical Interventions Triangle



- *Goals of vaccination is NOT to achieve COVID-zero state*
- ***Goal is to defang the virus, reducing hospitalization and death***
- *Once majority of population is vaccinated, other NPIs will become less important*

Legend: *Three points of the non-pharmaceutical interventions to combat COVID-19 are complementary. As one decreases, the other can compensate. So with less distancing, double masking (or higher fit/filtration masks) for adults keep them safe. With more ventilation (e.g. outdoors), the mask can be less fitted; Host susceptibility plays role in strength of NPI required*

Lancet Infect Dis. 2021 Feb 22;S1473-3099(20)30982-8.

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab

Alternative monoclonal antibody therapies authorized to treat patients with COVID-19 remain available

Casirivimab/Indevimab
Bamlanivimab/etesevimab

Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions

FDA

Variant Lineage	Key Substitutions Tested	Fold Reduction in Susceptibility		
		Bam	Bam + Ete	REGEN-COV
B.1.1.7 (UK Origin)	N501Y	No change	No change	No change [a]
B.1.351 (South Africa Origin)	E484K	>2,360	>45 [c]	No change [a]
P.1 (Brazil Origin)	E484K	>2,360	>511 [d]	No change [b]
B.1.427/B.1.429 (California Origin)	L452R	>1,020	7.4	No change
B.1.526 (New York Origin)	E484K	>2,360	17	No change

a - Pseudovirus expressing the entire variant spike protein was tested.
b - Also tested K417T
c - Also tested K417N and N501Y
d - Also tested K417T and N501Y
No change: <2-fold reduction in susceptibility for REGN-COV, <5-fold reduction for Bam and Bam+Ete
Red: No activity observed at the highest concentration tested.

https://www.fda.gov/media/146905/download

mAB updates – Casirivimab/Indevimab soon to be EUA approved for prevention?

Media & Investor Release

Roche

Phase III prevention trial showed subcutaneous administration of investigational antibody cocktail casirivimab and imdevimab reduced risk of symptomatic COVID-19 infections by 81%

- **Among individuals who still experienced symptomatic infections, those who received casirivimab and imdevimab were able to clear the virus faster and had much shorter symptom duration**
- **In a cohort of recently-infected asymptomatic patients, casirivimab and imdevimab reduced the overall risk of progressing to symptomatic COVID-19 by 31%**
- **Detailed results will be shared with regulatory authorities including the EMA and the FDA**

- Double-blind, placebo controlled trial assessed the effect of C/I on individuals without SARS-CoV-2 antibodies or any COVID-19 symptoms who lived in the same household as an individual who tested positive to SARS-CoV-2 within in the prior 4 days
- N=1,505 people who were not infected with SARS-CoV-2 at baseline and received one dose of C/I (1200mg SC) or placebo

	Casirivimab and imdevimab (1,200 mg subcutaneous dose)	Placebo
	n=753	n=752
Proportion of subjects with symptomatic SARS-CoV-2 infections through day 29 (primary endpoint)		
Risk reduction	81% (p<0.0001)	
# of patients with events	11 (1.5%)	59 (7.8%)
Symptoms and viral load		
Total weeks with symptoms		
Reduction	93% (p<0.0001)	
Total # of weeks (cumulative for all individuals in each arm)	13	188
# of weeks with symptoms (mean) in symptomatic individuals	1.2	3.2
Total weeks with high viral load (>10^4 copies/mL)		
Reduction	90% (p<0.0001)	
Total # of weeks (cumulative for all individuals in each arm)	14	136
# of weeks with high viral load (mean) in qPCR positive subjects	0.4	1.3

*Individuals without any COVID-19 symptoms who lived in the same household as an individual who tested positive to SARS-CoV-2 within the prior four days. Based on the seronegative modified Full Analysis Set population, which includes all randomized subjects without evidence of current or prior SARS-CoV-2 infection (i.e., a negative RT-qPCR test and a negative antibody test) at randomization.

https://www.roche.com/dam/jcr:b857b6d0-5ad6-4d19-8939-de4d425253f3/en/12042021-mr-2069-phase-iii-data-of-casivrimib-and-imdevimab.pdf

C/I in asymptomatic, SARS CoV-2 + patients

- The C/I cocktail was also evaluated in 204 recently infected, asymptomatic patients randomized to receive one dose of C/I or placebo.
- In this cohort, C/I reduced the overall risk of progressing to symptomatic COVID-19 by 31%

- AEs occurred in 34% of REGEN-COV patients and 48% of placebo participants; serious AEs 0% vs 3% of placebo patients

- 0 REGEN-COV participants vs. 4 of placebo participants required ED visit/hospitalization during 29-day efficacy period.

https://www.roche.com/dam/jcr:b857b6d0-5ad6-4d19-8939-de4d425253f3/en/12042021-mr-2069-phase-iii-data-of-casivrimib-and-imdevimab.pdf

Table 2: Key results from phase III treatment cohort in asymptomatic infected individuals

	Casirivimab and imdevimab (single 1,200 mg dose)	Placebo
	n=100	n=104
Proportion of subjects with symptomatic SARS-CoV-2 infections through day 29 (primary endpoint)		
Risk reduction	31% (p=0.0380)	
# of patients with events (cumulative for all individuals in each arm)	29 (29%)	44 (42%)
Symptoms, viral load and COVID-19 related events		
Total weeks with symptoms		
Reduction	45% (p=0.0273)	
Total # of weeks (cumulative for all individuals in each arm)	90	170
Total weeks with high viral load (>10^4 copies/mL)		
Reduction	40% (p=0.001)	
Total # of weeks	48	82

Based on the seronegative modified Full Analysis Set population, which includes all randomized asymptomatic patients who were SARS-CoV-2 positive but had no evidence of prior infection (i.e., a positive RT-qPCR test and a negative antibody test) at randomization

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Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial

Sanjay Ramakrishnan, Dan V Nicolau Jr*, Beverly Langford, Mahdi Mahdi, Helen Jeffers, Christine Mwasuku, Karolina Krassowska, Robin Fox, Ian Binnian, Victoria Glover, Stephen Bright, Christopher Butler, Jennifer L Cane, Andreas Halner, Philippa C Matthews, Louise E Donnelly, Jodie L Simpson, Jonathan R Baker, Nabil T Fadai, Stefan Peterson, Thomas Bengtsson, Peter J Barnes, Richard E K Russell, Mona Bafadhel*

- Open-label, parallel-group, phase 2, randomized controlled trial of inhaled budesonide vs. usual care
- **Enrolled within 7 days of the onset of mild COVID-19 symptoms**
- Participants asked to take 2 inhalations BID until symptom resolution
- Primary endpoint:
  - COVID-19 related urgent care visits, including emergency department assessment or hospitalization, analyzed for the per-protocol and intention to treat (ITT) populations

- N=146 participants assigned to usual care (n=73) or budesonide (n=73)
- Per-protocol population (n=139), **primary outcome occurred in 10/70 (14%) in usual care group vs. 1/69 (1%) in the budesonide group (95% CI 0.043 to 0.218, p=0.004)**
- For the ITT population, **primary outcome occurred in 11(15%) of usual care vs 2(3%) of patients in the budesonide group (95% CI, 0.033 to 0.213, p=0.009).**
- **NNT = 8**

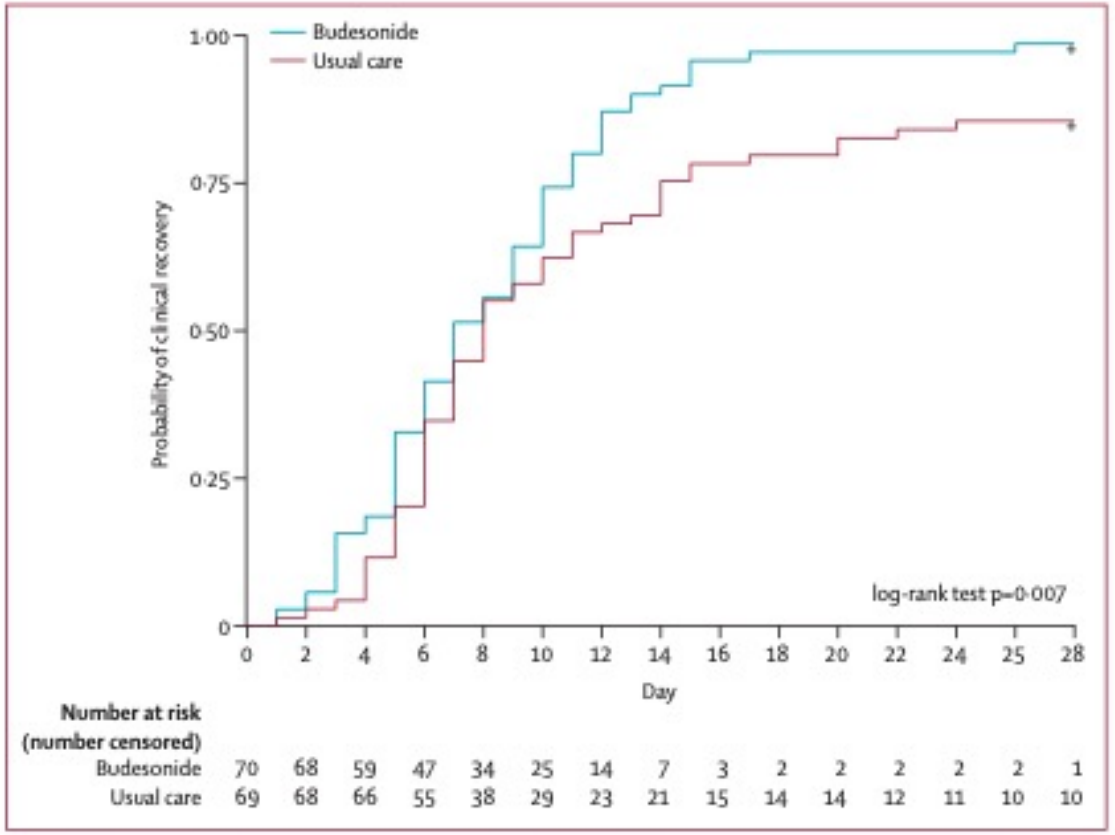


Figure 2: **Time to self-reported clinical recovery of per-protocol population using data censoring for primary outcome**

- Clinical recovery was 1 day shorter in budesonide group (7vs 8 days)
- Blood oxygen saturations and SARS-CoV-2 VL (cycle threshold) were not different between 2 groups
- Fewer participants in budesonide group had persistent symptoms at day 14 and 28 (27% [IQR 0-50] v 50% [15-71], p=0.025)

No NIH recommendation for ivermectin outside of a clinical trial

- Ivermectin is not approved by the FDA for the treatment of ANY viral infection at this time
- Ivermectin proposed MOA
  - In vitro studies show inhibition of the host importin alpha/beta-1 nuclear transport proteins - viruses use the proteins to enhance infection by suppressing the host's antiviral response
  - Ivermectin attachment may interfere with attachment of spike protein to the human cell membrane
  - Shown to inhibit replication of SARS-CoV-2 in cell culture
    - At concentrations that would require administration of doses up to 100-fold higher than those approved in humans
- **No clinical trials have reported convincing benefit**
- NIH guidelines: insufficient data to recommend for or against the use of ivermectin for treatment of COVID-19

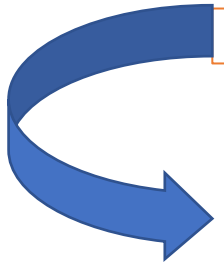
MERCK

February 4, 2021 11:45 am ET

KENILWORTH, N.J., Feb. 4, 2021 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today affirmed its position regarding use of ivermectin during the COVID-19 pandemic. Company scientists continue to carefully examine the findings of all available and emerging studies of ivermectin for the treatment of COVID-19 for evidence of efficacy and safety. It is important to note that, to-date, our analysis has identified:

- No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies;
- No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and;
- A concerning lack of safety data in the majority of studies.

We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information.



Great table outlining studies!

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/

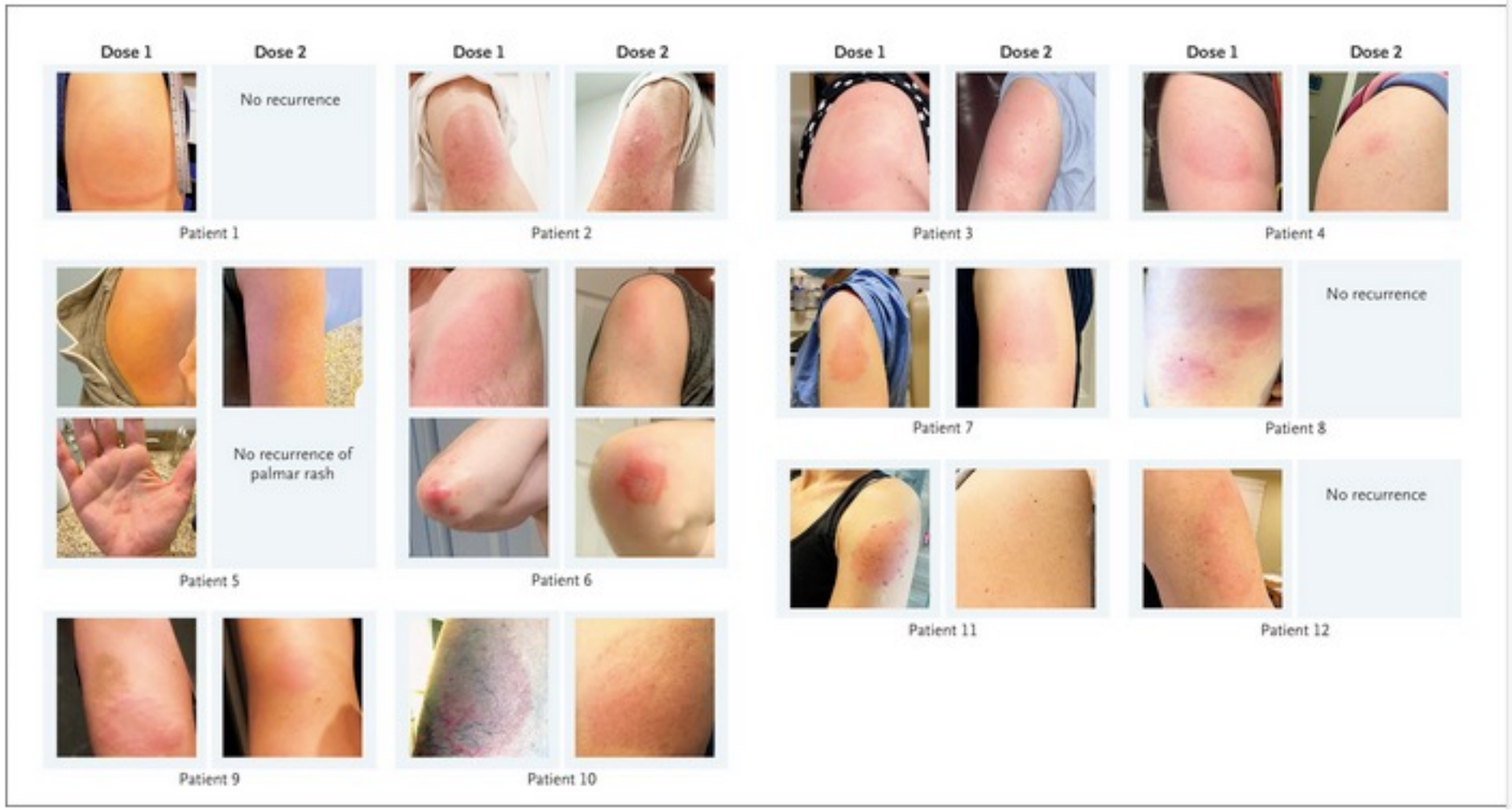
CORRESPONDENCE

Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2

April 1, 2021
N Engl J Med 2021; 384:1273-1277
DOI: 10.1056/NEJMc2102131

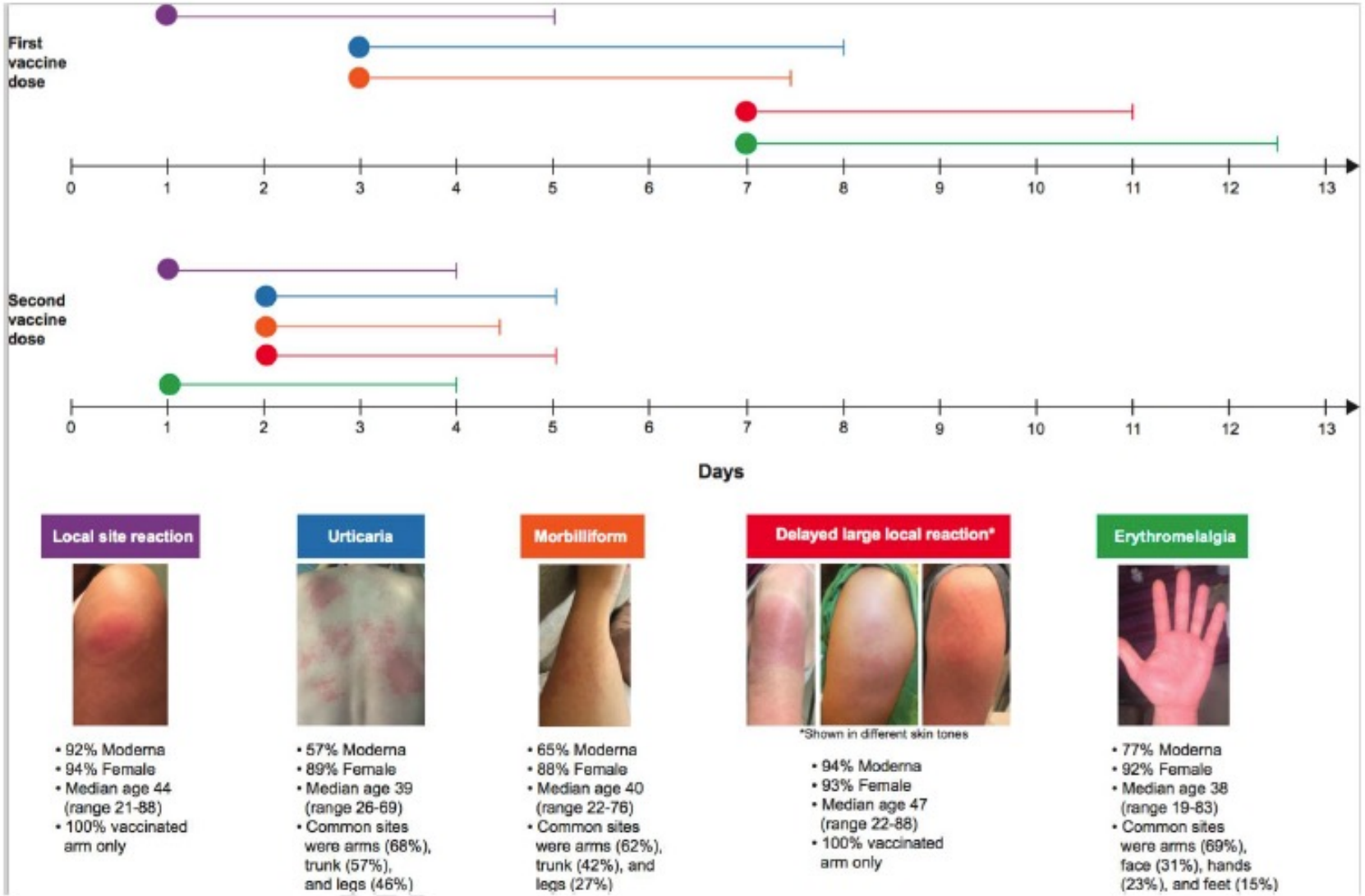
Blumenthal et al.

- mRNA-1273 (Moderna) vaccine trials reported delayed injection site reactions in 0.8% of patients after the first dose and 0.2% after the 2nd dose
- Case series of 12 patients
- Suspicion of delayed-type or T-cell mediated hypersensitivity reaction
- Not a contraindication to subsequent vaccination
- Variable recurrence



Hat tip: Keith So

Figure 1: Timeline representing the time to onset and duration of the top five most common dermatologic findings reported after the Moderna and Pfizer COVID-19 vaccines. Circles represent median time to onset of the cutaneous reaction and lines represent median duration of the cutaneous reaction. See Supplemental Table 1 for detailed information about timing of vaccine reactions.



McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, Desai SR, French LE, Lim HW, Thiers BH, Hruza GJ, Blumenthal K, Fox LP, Freeman EE, Cutaneous Reactions Reported after Moderna and Pfizer COVID-19 Vaccination: A Registry-Based Study of 414 Cases, Journal of the American Academy of Dermatology (2021), doi: https://doi.org/10.1016/j.jaad.2021.03.092.

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