COVID-19: Current Concerns

RM Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

NewYork-Presbyterian

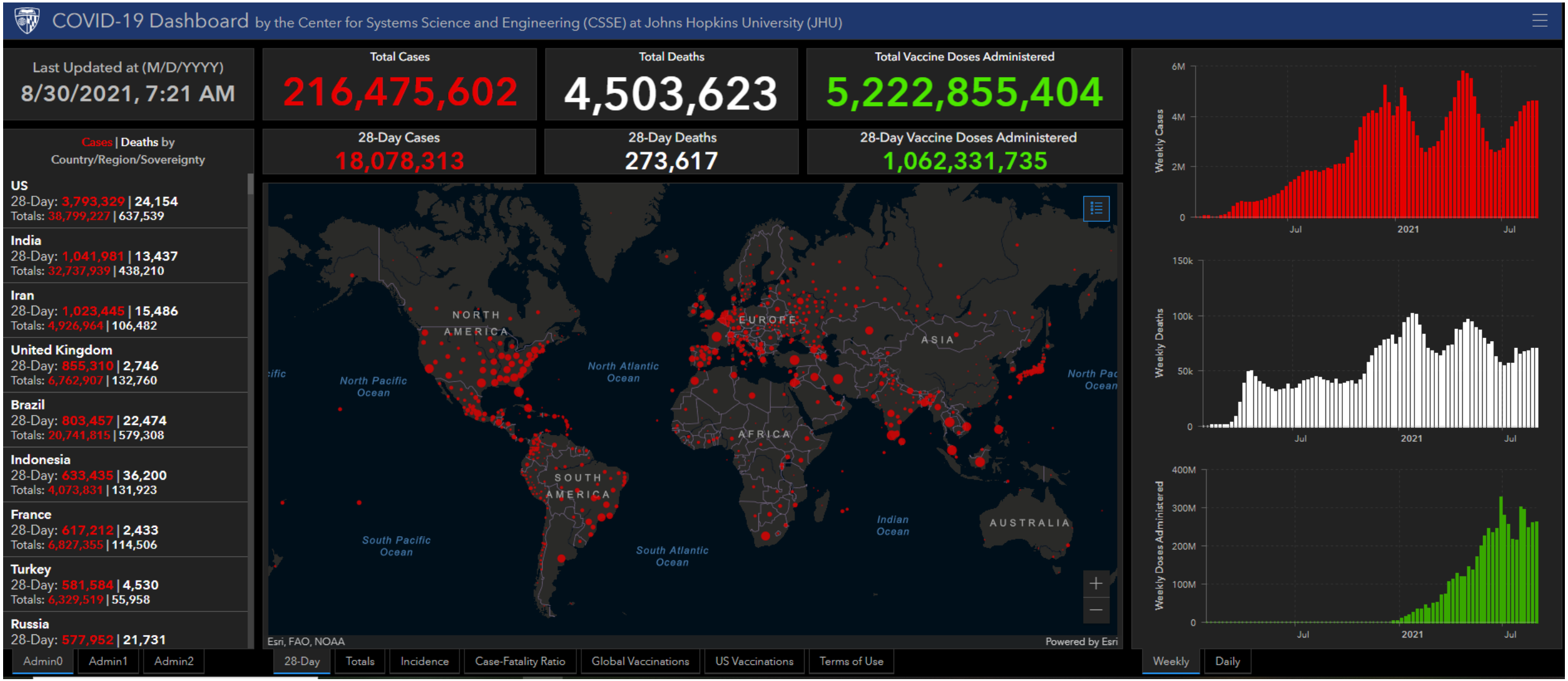
Weill Cornell Medicine

Disclosure Information

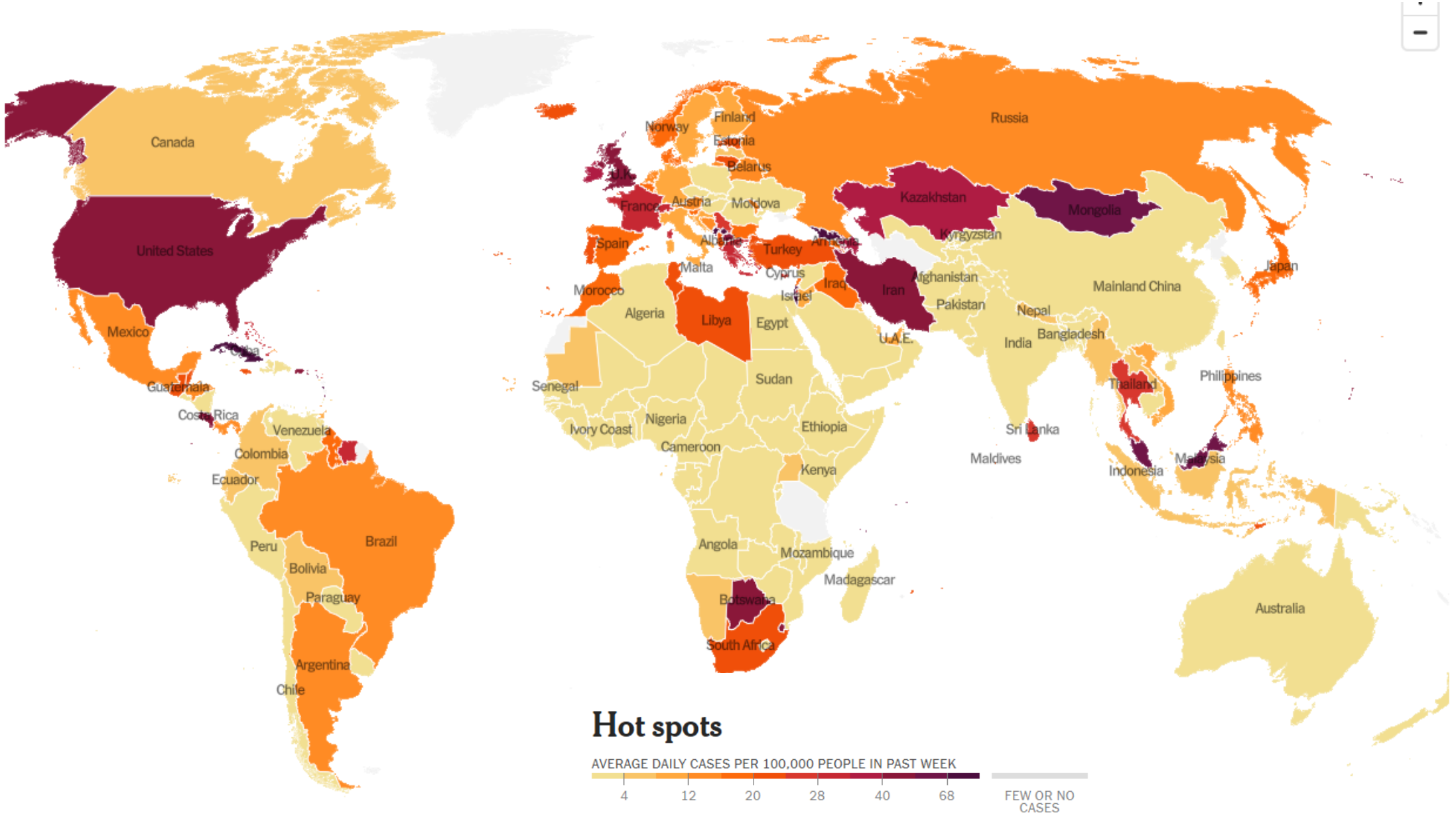
none

Epidemiology

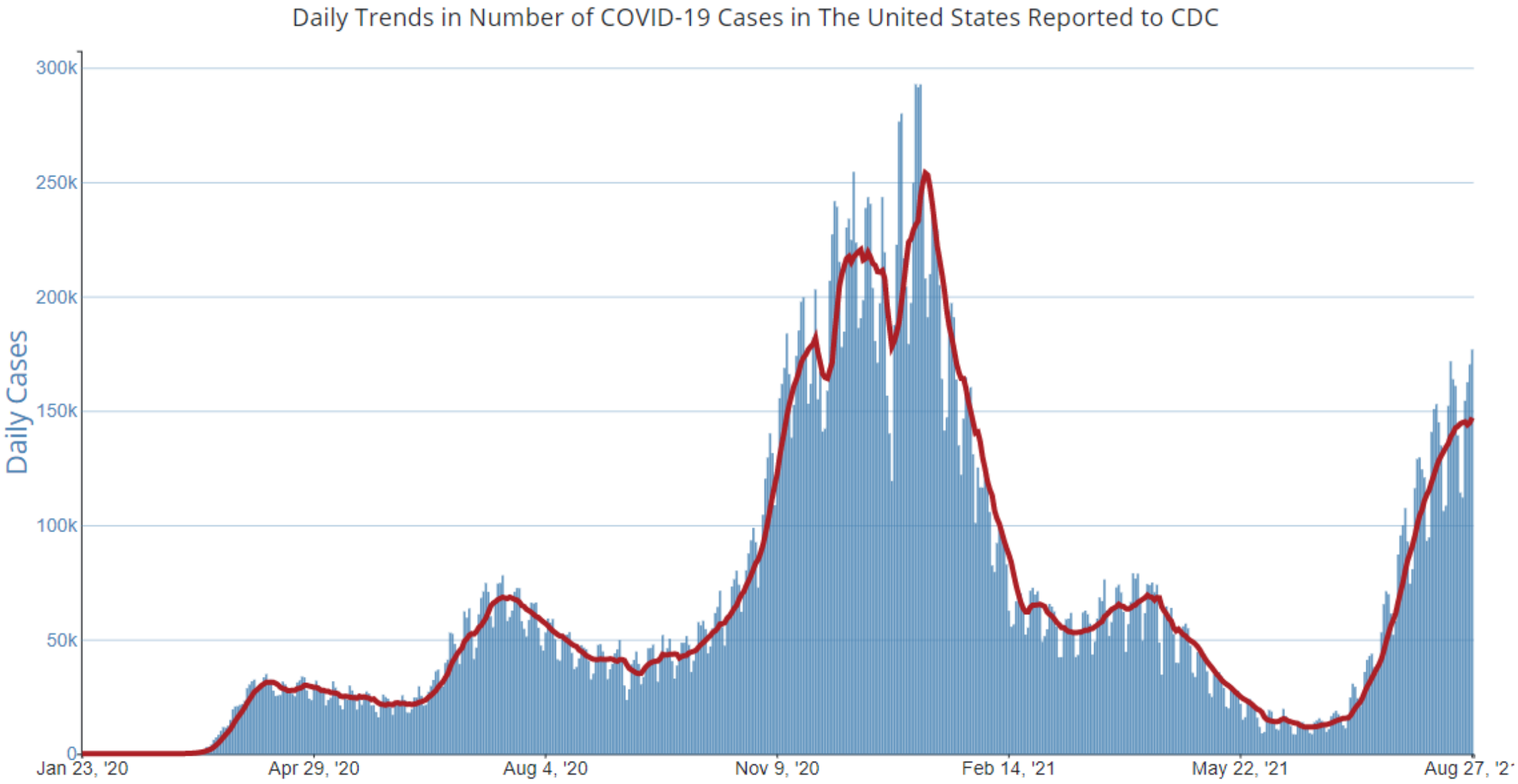
COVID-19: 8/30/21



https://coronavirus.jhu.edu/map.html



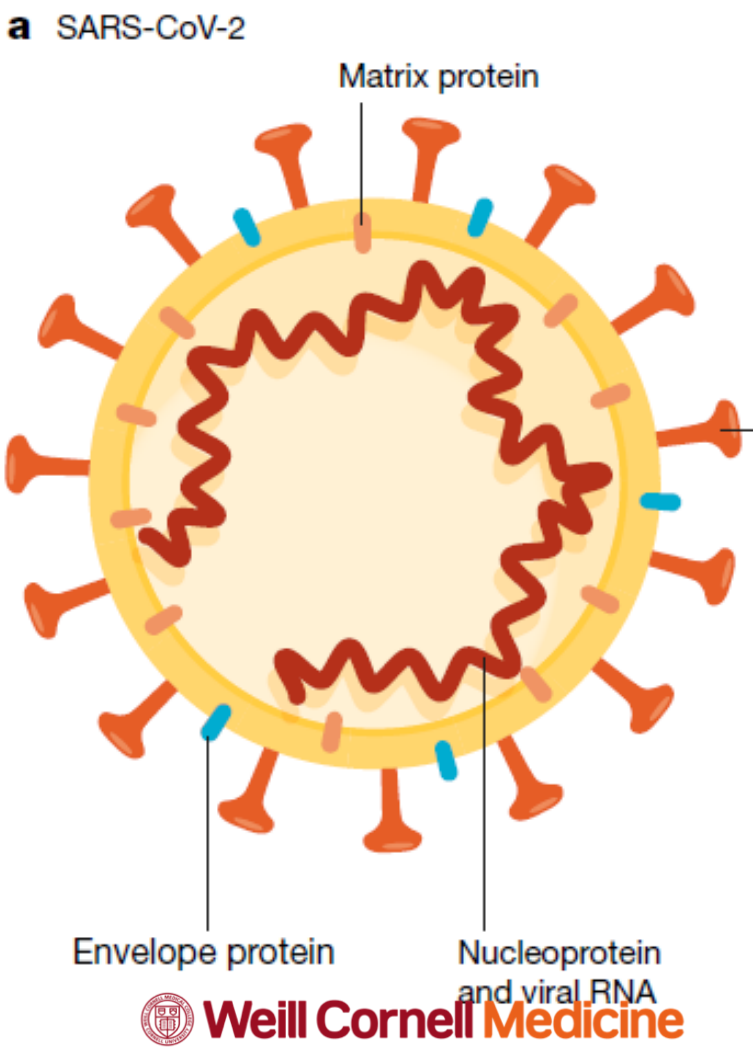
https://www.nytimes.com/interactive/2021/world/covid-cases.html (accessed 8/27/21)

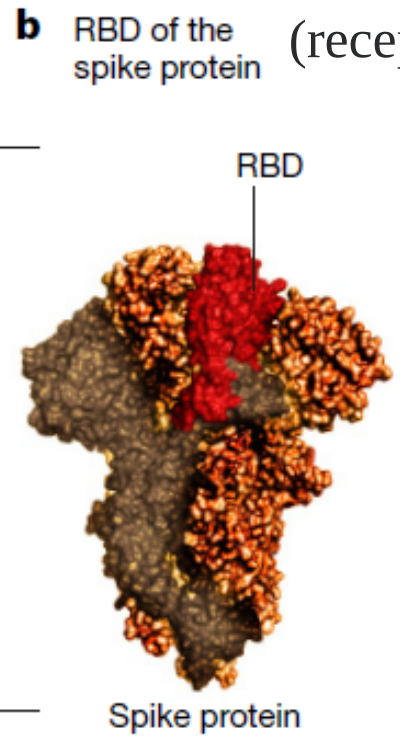


https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases (accessed 8/30/21)

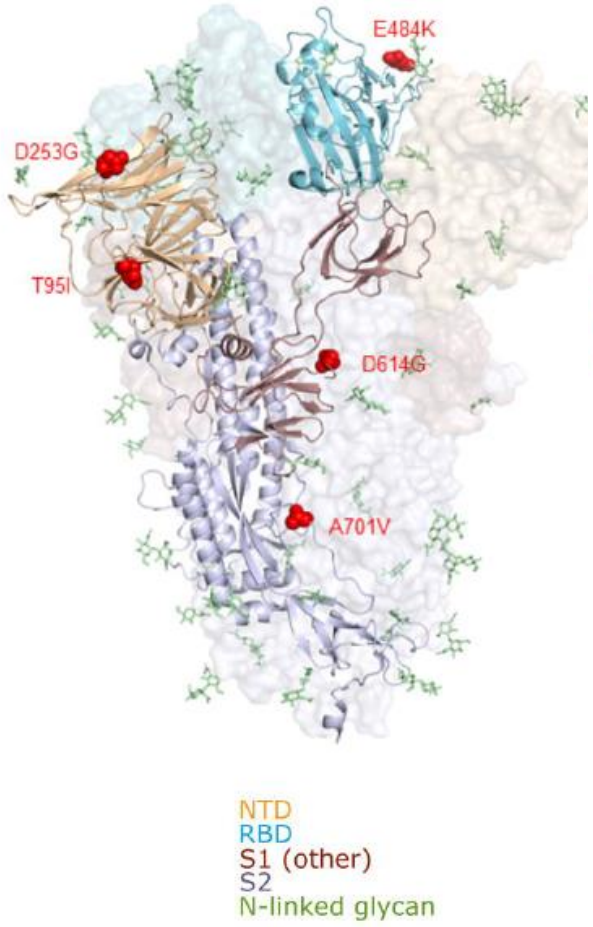
Variants

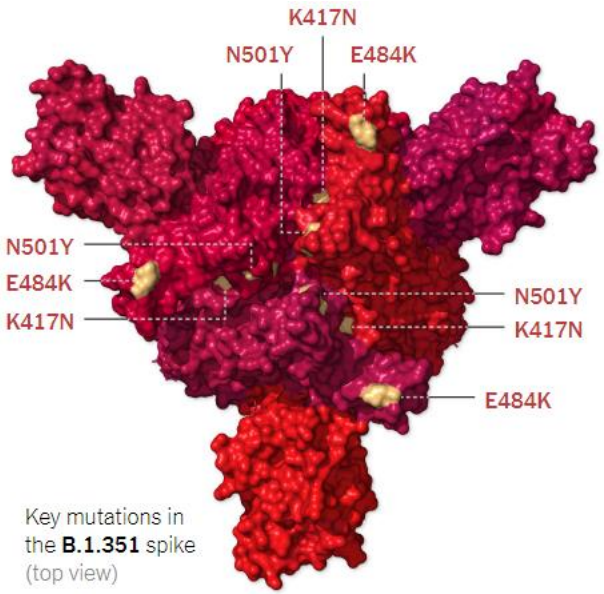
COVID-19 Structure





(receptor binding domain)





Krammer Nature 2020;586:516-527 and Annavajhala Nature (epub 8/24/21)

New WHO Variant Nomenclature

New name	Pangolin lineage	Earliest documented sample
Alpha	B.1.1.7	United Kingdom, Sep 2020
Beta	B.1.351	South Africa, May 2020
Gamma	P.1	Brazil, Nov 2020
Delta	B.1.617.2	India, Oct 2020
Epsilon	B.1.427/B.1.429	California/US, March 2020
Zeta	P.2	Brazil, April 2020
Eta	B.1.525	Multiple countries, Dec 2020
Theta	P.3	Philippines, Jan 2021
Iota	B.1.526	New York/US, Nov 2020
Kappa	B.1.617.1	India, Oct 2020

variants of concern

Adapted from https://www.who.int/en/activities/tracking-SARS-CoV-2-variants

COVID-19 Variants

- US government SARS-CoV-2 Interagency Group (SIG) developed a variant classification scheme that defines three classes:

  - **Variant of interest (VOI):** Has genetic markers associated with changes to receptor binding, ↓neutralization by antibodies, ↓efficacy of treatments, potential diagnostic impact, or predicted ↑transmissibility or disease severity.
    - e.g. eta, iota, kappa

  - **Variant of concern (VOC):** Evidence of ↑transmissibility, ↑severe disease (hospitalizations/deaths), significant ↓neutralization by antibodies, ↓ effectiveness of treatments or vaccines, or diagnostic detection failures.
    - e.g. alpha, beta, gamma, delta

  - **Variant of high consequence (VOHC):** Clear evidence that prevention measures or medical countermeasures (MCMs) have significantly ↓ effectiveness relative to previously circulating variants.
    - e.g. none

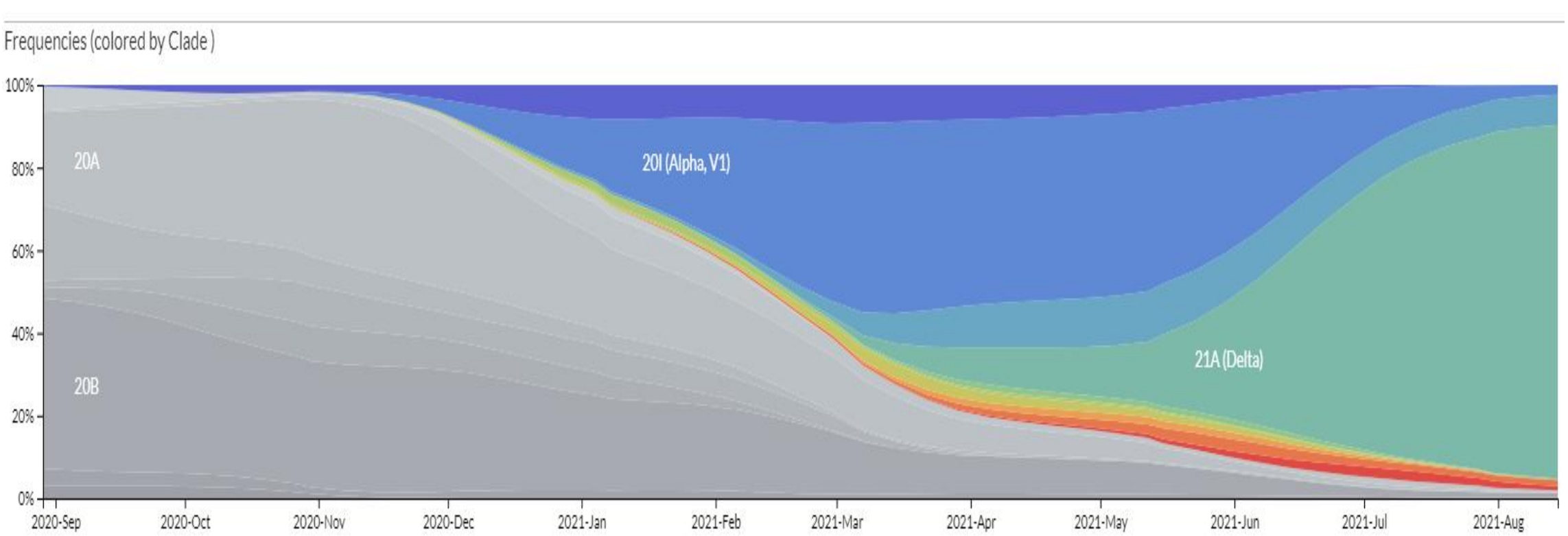
https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

Variants of Concern (VOC)

	Alpha (B.1.1.7)	Beta (B1.351)	Gamma (P.1)	Delta (B.1.617.2)
# of spike mutations	10-13	10	11	> 12
Receptor binding domain mutations	N501Y	K417N E484K N501Y	K417N E484K N501Y	E484K L452R
Transmissibility	↑ 50%	↑ 50%		↑ 60% vs. alpha ↑ 2X from original
Disease severity	? ↑ risk of death	no effect	may cause severe disease in those with prior COVID	? ↑
Monoclonal Abs	No effect	↓ susceptibility to BAM + ETE	↓ susceptibility to BAM + ETE	potential ↓ susceptibility (?)
Vaccines (U.S.)	No effect	No effect	No effect	Modest ↓ effect

1
2

SARS-CoV-2 Variants: Global (8/21)



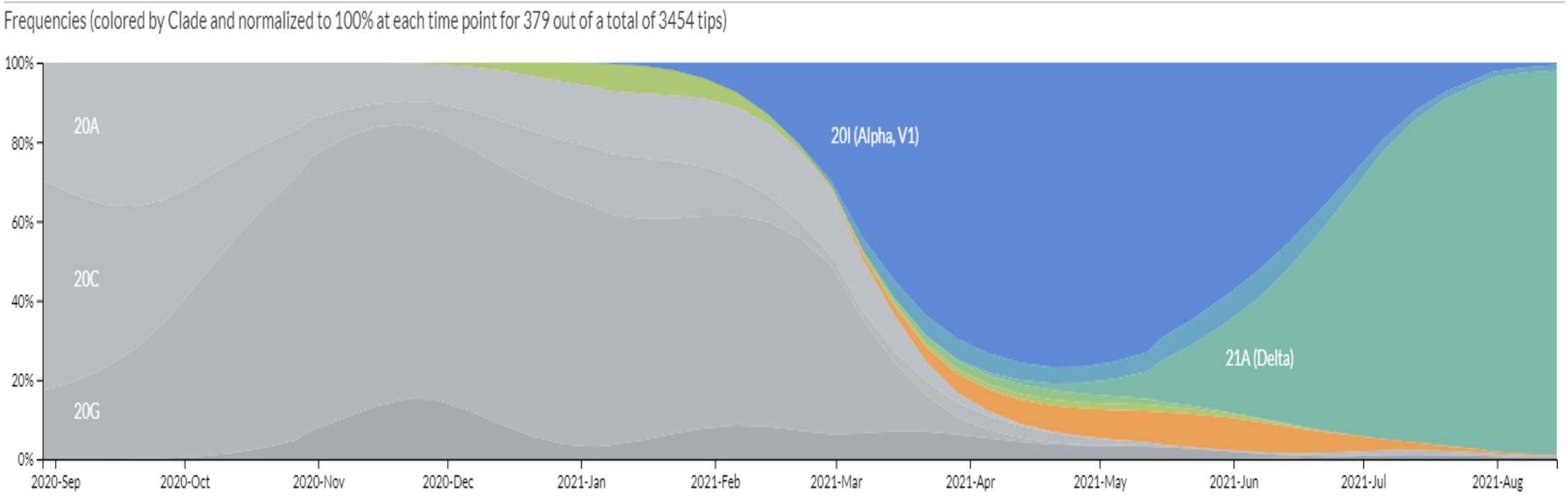
2%
alpha
7%
gamma

86%
delta

nextstrain.org

1
3

SARS-CoV-2 Variants: U.S. (8/21)



97%
delta

nextstrain.org

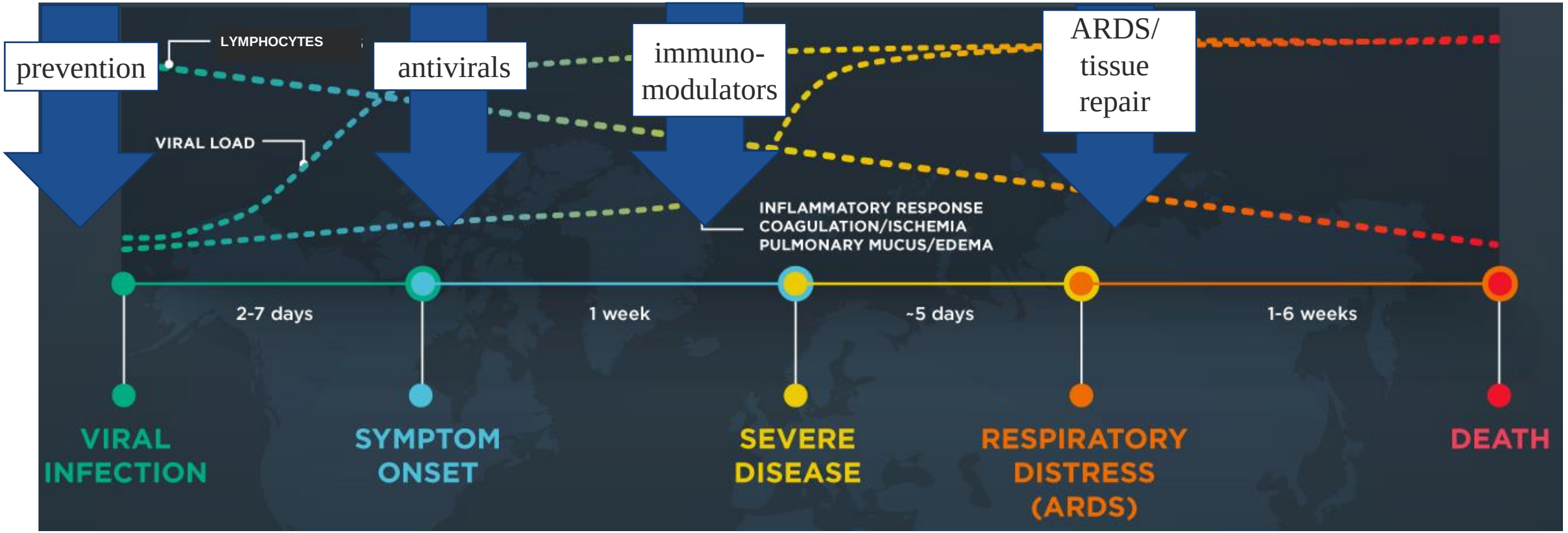
COVID-19 Delta Variant

- **Highly transmissible -- more than 2x as transmissible as previous variants**
- **Might cause more severe illness**
  - Pts with Delta more likely to be hospitalized than pts with alpha or wild-type viruses (Canada/Scotland).
  - Vast majority of hospitalizations and deaths in unvaccinated people.
- **Unvaccinated people remain the greatest concern**
  - More likely to get infected and transmit the virus.
  - Fully vaccinated people get COVID-19 infections less often.
  - ALL people infected with the Delta variant can transmit the virus to others.
- **Vaccinated people appear to spread the virus for a shorter time**
  - For prior variants, lower amounts of viral RNA were found in samples taken from fully vaccinated people with COVID-19 infection than from unvaccinated people.
  - For people with Delta, similar amounts of viral RNA have been found among both unvaccinated and fully vaccinated people.
  - Viral RNA may ↓faster in fully vaccinated people.
    - Transmit for less time.
- **Vaccines in the US are highly effective, including against the Delta variant**

https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html

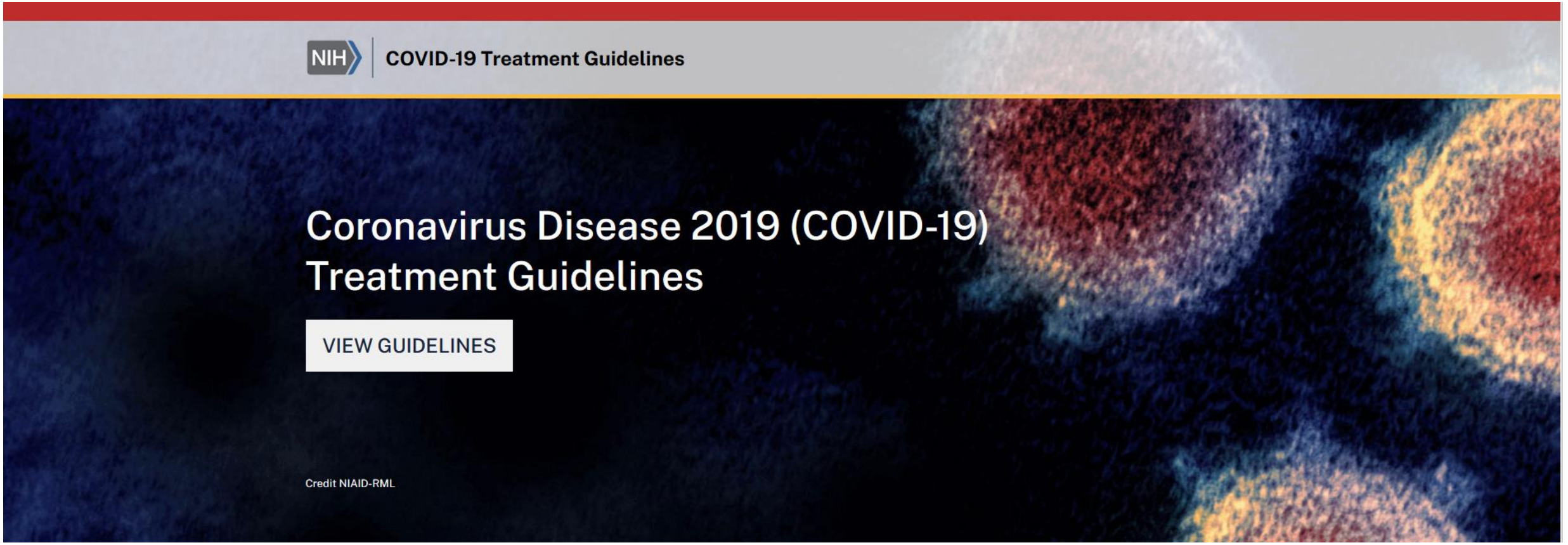
Treatment

COVID-19: Clinical Course and Interventions



Modified from: Biocentury

www.covid19treatmentguidelines.nih.gov



COVID-19 Treatment Guidelines Panel Members

Co-Chairs

Roy M. Gulick, MD	Weill Cornell Medicine, New York, NY
H. Clifford Lane, MD	National Institutes of Health, Bethesda, MD
Henry Masur, MD	National Institutes of Health, Bethesda, MD

COVID-19 Treatment

- For inpatients with COVID-19:
  - 1 FDA-approved drug: **remdesivir**
  - 3 drugs demonstrated to ↓ mortality: **dexamethasone, tocilizumab,** and **bariticinib**
  - EUAs for **baricitinib** and **convalescent plasma**

- For outpatients with COVID-19: no approved therapies
  - 3 **monoclonal antibodies** demonstrated to ↓ disease progression (available by EUAs)
    - **bamlanivimab + etesivimab (BAM + ETE)**
    - **casirivimab + imdevimab (CAS + IMD)**
    - **sotrovimab (SOT)**

- Additional candidate treatments: antivirals, immunomodulators, antithrombotics, ARDS and cellular therapies

NIH COVID-19 Inpatient Treatment Guidelines (8/25/21)

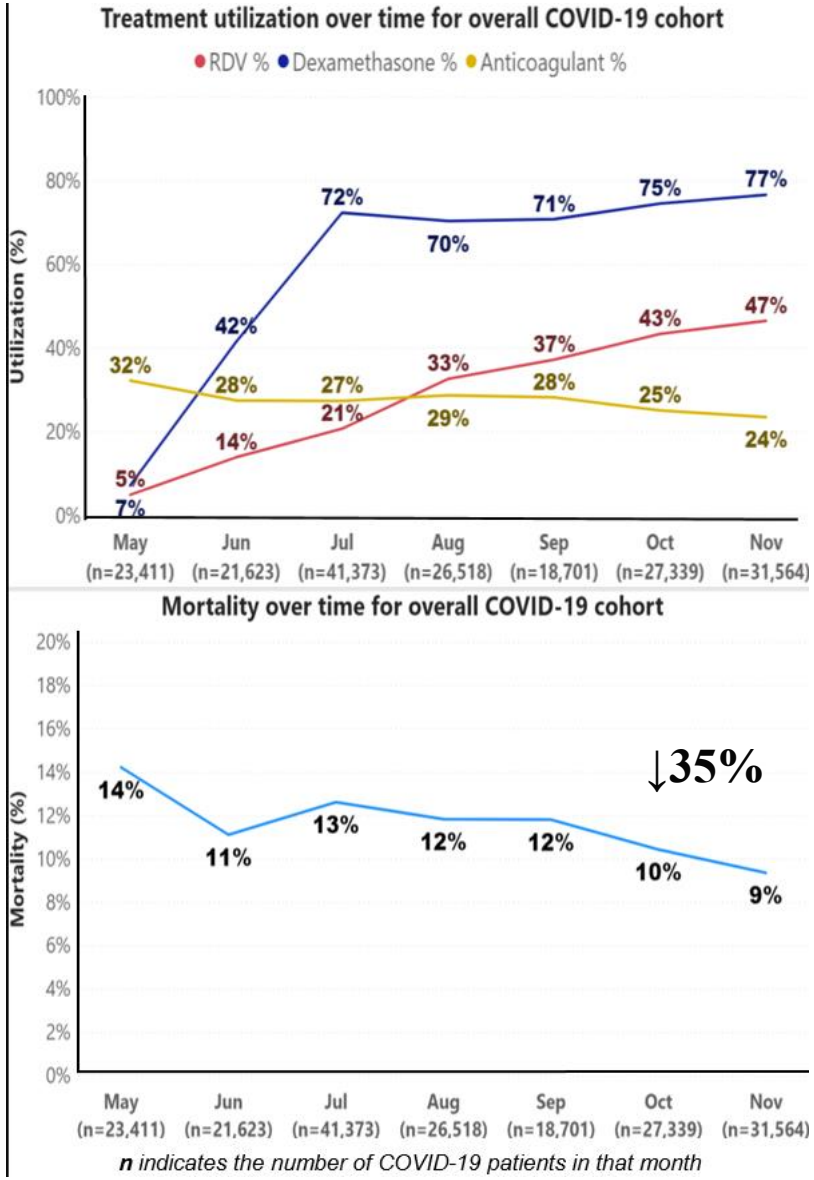
www.covid19treatmentguidelines.nih.gov

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

COVID-19 Treatment Over Time

- Retrospective Cohort Study from the Premiere
- Health Database
- Hospitalized pts with COVID-19 -- 5/20-11/20
- 190,529 pts / 823 U.S. hospitals
  - Mean age 64
  - 53% men
  - 64% W, 19% B
  - 65% Medicare/Medicaid
  - >20% with significant comorbidities
    - (chronic pulm disease, obesity, HTN)
- Treatment trends
  - Dexamethasone 7%→77%
  - RDV 5%→47%
  - anticoagulants 32%→24%
  - tocilizumab 5%, sarilumab <1%, baricitinib <1%
- Length of stay -- median
  - hospital 6d→5d (↓17%)
  - ICU 5d→4d (↓20%)



Mozaffari CROI 2021 #397

NIH COVID-19 Outpatient Treatment Guidelines (8/25/21)

www.covid19treatmentguidelines.nih.gov

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Prevention

COVID-19 Prevention

- Handwashing, masks, social distancing, droplet precautions, PPE

- **Pre-Exposure (PrEP)**
  - 1 FDA-approved vaccine for COVID-19: **Pfizer (Comirnaty)**
  - 2 FDA EUAs for vaccines, **Moderna** and **J+J**
  - Additional dose of Pfizer/Moderna recommended for moderate/severe immunocompromised patients
  - Emerging data for monoclonal antibodies

- **Post-Exposure (PEP)**
  - 1 FDA EUA: **casirivimab** + **imdevimab** (CAS + IMD)

- Additional candidate preventatives: antivirals, antibodies, vaccines

Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3	
Nucleic acid (mRNA)	moderna	Enrolled	Enrolled	Weill Cornell Medicine
	BIONTECH Pfizer	Enrolled	Enrolled	FDA APPROVED
Viral vector	UNIVERSITY OF OXFORD AstraZeneca	Enrolled	Enrolled	
	Janssen Johnson & Johnson	Enrolled	Enrolled	
	Sputnik			
Protein subunit	NOVAVAX Creating Tomorrow's Vaccines Today	Enrolled	Enrolled	Weill Cornell Medicine
	gsk SANOFI	Ongoing	--	
Whole inactivated	Coronavac	Enrolled	Enrolled	
	Covaxin	Enrolled	Enrolled	

COVID-19 Vaccines: Phase 3 Results

Vaccine	Study Population
Pfizer/BIONTECH (BNT162b2) **FINAL ANALYSIS** Polack NEJM 2020;383:2603-2615 FDA approved 8/23/21 as COMIRNATY	**N= 43,548** **49% women** **9% Black** **28% Latino** **83% White** **42% >55 years old** **46% with comorbidities**

6-month data: **COVID-19 infections: 850 placebo/77 vax (91% efficacy)**
severe infections: 95 placebo/0 vax (100% efficacy)

COVID-19 Vaccines: Phase 3 Results

Vaccine	Study Population
Moderna mRNA-1273 **FINAL ANALYSIS** Baden NEJM 2020 (epub 12/30/20)	**N= 30,420** **47% women** **10% Black** **20% Latino** **79% White** **25% >65 years old** **22% with comorbidities**

6-month data: **COVID-19 infections: >900 total (90% efficacy)**
severe COVID-19: >100 total (95% efficacy)

COVID-19 Vaccines: Phase 3 Results

Vaccine (reference)	Sample size
Johnson & Johnson Ad26.COV2.S **TOP-LINE ANALYSIS** Sadoff NEJM 2021	**N=43,783 international** **45% women; 19% Black, 45% Latino, 59% White; 41% comorb**

8-month data (n=20): durable antibody and cellular responses
Barouch NEJM (epub 7/14/21)

COVID-19 Vaccines: Side Effects

- **Most common:** pain at injection site, fatigue, HA, myalgias
  - ↑ after vax #2; 1/4 had fever/chills after #2
- **Axillary / cervical lymphadenopathy**
- **Dermal filler inflammation**
- **Myocarditis / pericarditis:** rare (~1/100,000)
  - adolescent/young adults; more common in men
  - mild; most recover fully
- **Clotting events:** rare (<1/100,000)
  - more common in women <50 years old
  - cerebral venous sinus and splanchnic
- **Guillain-Barre syndrome:** rare (~1/125,000)
  - only with J+J, not mRNA vaccines
- **Anaphylaxis:** very rare (1/200,000-280,000)
  - related to PEG/polysorbate(?)
  - more common in women, 80-86% had history of allergies, 24% had history of anaphylaxis
  - most within 15 minutes (one outlier at 20 hours)

A 72 year-old who signed up to test Moderna's Covid vaccine was struck by lightning 28 days after getting a dose of the real vaccine (Pictures: Getty/AP)

A volunteer who signed up for Moderna's coronavirus vaccine trial was struck by lightning 28 days after receiving the injection.

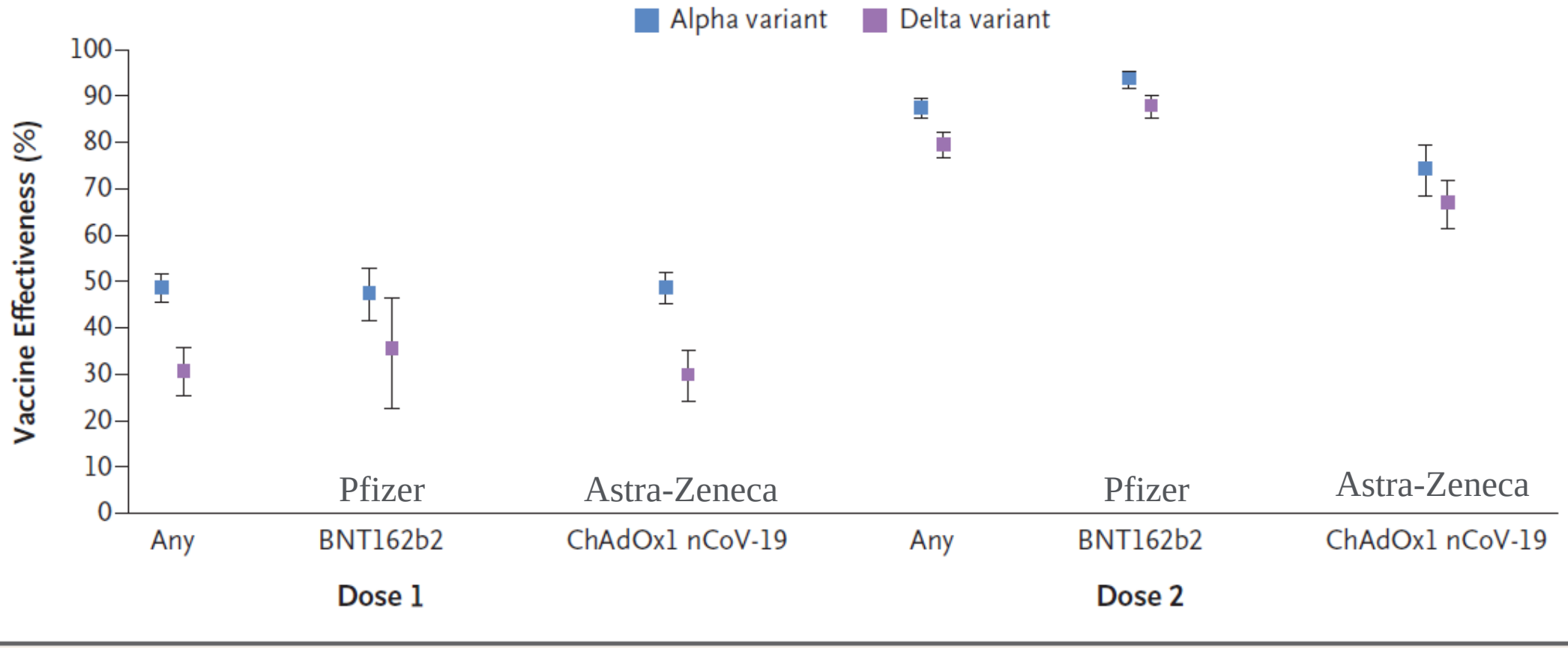


Figure 1. Vaccine Effectiveness against the Alpha and Delta Variants, According to Dose and Vaccine Type.

Shown is the effectiveness of one dose and two doses of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, or either vaccine ("any"), against symptomatic disease with the B.1.1.7 (alpha) or B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

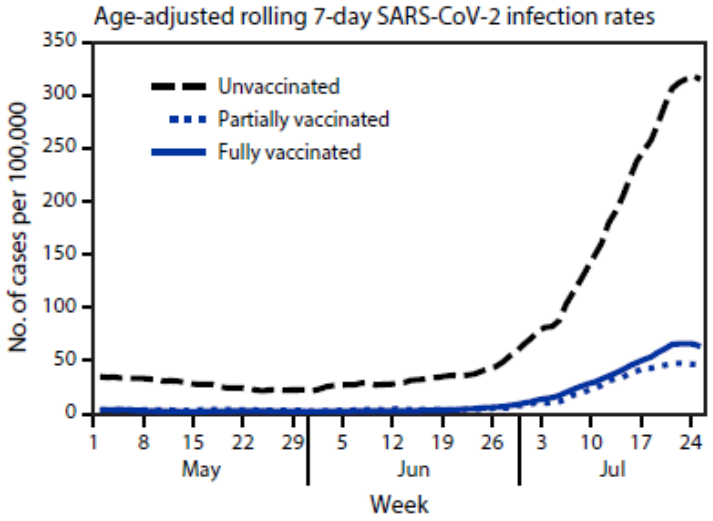
Bernal NEJM 2021:385:585-594

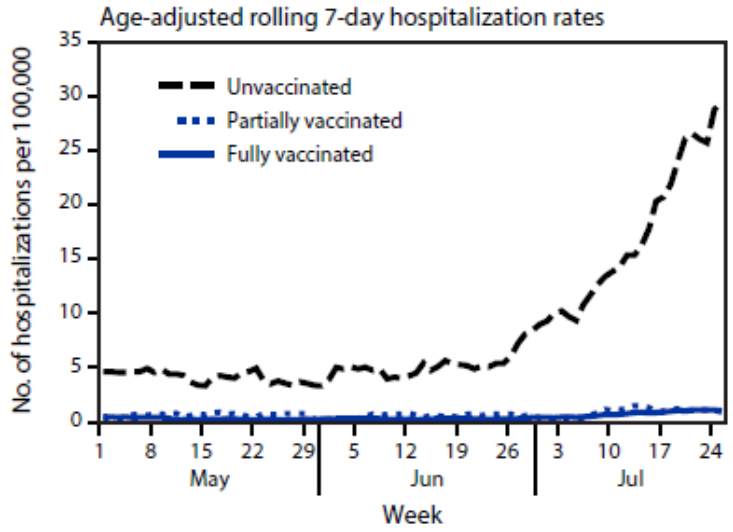
MMWR 8/24/21: Vaccine Effectiveness

- 8 cohorts of 4217 HCW, first responders, essential + frontline workers in 6 U.S. states: AZ, FL, MN, OR, TX, UT
- Followed from 12/20-8/21
- Tested weekly for SARS-CoV-2 X 35 weeks
- Assessed mRNA vaccines (Pfizer and Moderna) 14 days after 2nd dose
- Results:
  - Overall, **80%** effective in preventing SARS-CoV-2 infection (both symptomatic and asymptomatic) in fully vaccinated
    - 2 weeks-4 months after vax: 85% effective (95% CI 68, 93)
    - 4 months-7 months after vax: 80% effective (95% CI 34, 95)
    - After 7 months after vax: 73% effective (95% CI 49, 86)
    - Pre-delta / delta variant predominance: 91% / 66% effectiveness
- Conclusion: Sustained ↓ in infection risk with moderate reduction in effectiveness

MMWR 8/24/21: Breakthrough Infections (LA)

- Los Angeles Country Department of Public Health used COVID-19 surveillance and California Immunization Registry data
- 5/1/21→7/25/21; delta variant >87% of cases
- % fully vaccinated 27%→51%
- 43,127 reported SARS-CoV-2 infections in people ≥16 yo
  - 30,801 (71%) unvaccinated
  - 1,431 (3.3%) partially vaccinated
  - 10,895 (25%) fully-vaccinated
- Hospitalizations / ICU / mechanical ventilation / death
  - 7.6% / 1.5% / 0.5% / 0.6% unvaccinated
  - 6.2% / 1.0% / 0.3% / 0.5% partially vaccinated
  - 3.2% / 0.5% / 0.2% / 0.2% fully vaccinated
- Unvaxxed vs. fully vaxxed: infections ↑ 5X and hospitalizations ↑29X





Advisory Committee on Immunization Practices (ACIP) Recommendations

Following slides adapted from ACIP recommendations found at
https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

CDC/ACIP: Follow-Up Safety Assessment (3/29/21)

- 143 million vaccine doses administered in the US:
  - Pfizer-BioNTech: >72 million; Moderna: >67 million; Johnson & Johnson/Janssen: >3 million; unknown vaccines >141,000).

- **Passive and active surveillance systems monitored and reviewed**

- **Conclusions:**
  - No statistical signals for **multiple pre-specified outcomes** have been reported to date with >10 million doses administered across systems.
  - **Pregnancy and birth outcomes** following vaccination appear consistent with rates reported in the literature.
  - Data from passive systems suggest rates of all-cause **morbidity and mortality** NOT higher than expected.

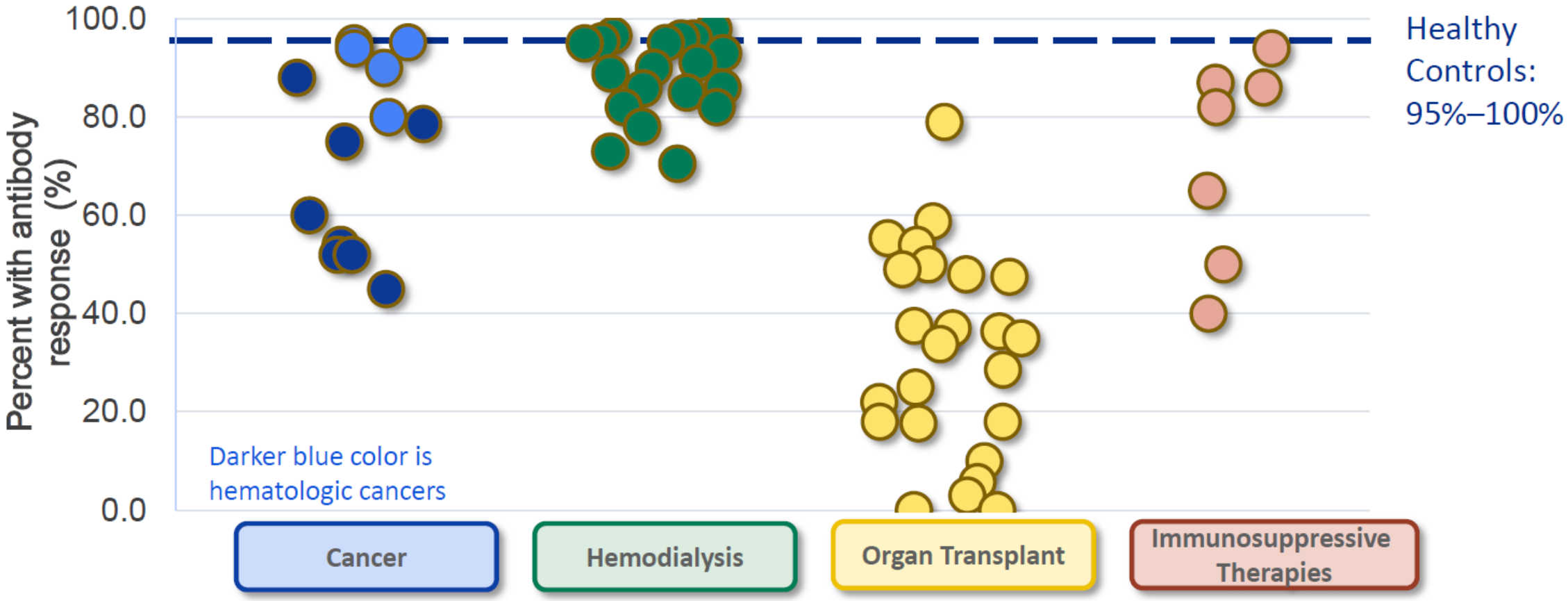
Recent CDC Update on Pregnancy Language 8/21

- There is no evidence that any of the COVID-19 vaccines affect current or future fertility
  - COVID-19 vaccines do not cause infection in the pregnant person or the fetus
  - No safety signals in animal studies
  - Reassuring early safety data on mRNA COVID-19 vaccines during pregnancy
  - Early data suggest mRNA COVID-19 vaccines during pregnancy are effective

- **COVID-19 vaccination is recommended for all people aged 12 years and older, including people who are pregnant, lactating, trying to get pregnant now, or might become pregnant in the future**

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

Percent of subjects with antibody response after two mRNA COVID-19 vaccine doses by immunocompromising condition and study (n=63)



Studies that compared response after 1st and 2nd dose demonstrated less robust response after dose 1

Antibody measurement and threshold levels vary by study protocol

CDC ACIP 8/13/21

8/12/21: FDA amends the EUAs for Pfizer and Moderna to allow 3rd vaccine dose for IC pts

8/13/21: CDC recommends 3rd vaccine dose (Pfizer/Moderna) for moderate/severe IC pts

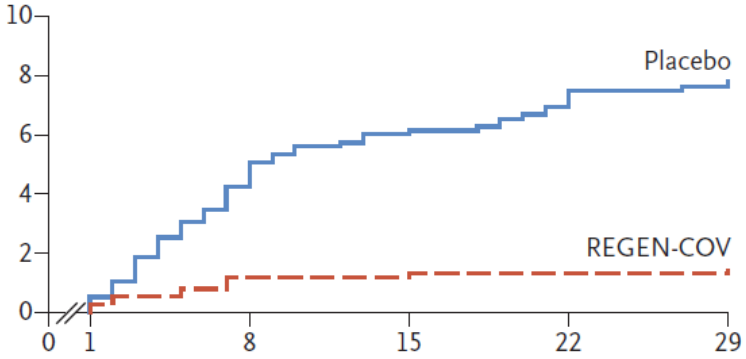
Moderately and severely immunocompromised people*

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge, Wiskott-Aldrich syndromes)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory

CDC ACIP 8/13/21

SQ Casirivimab/Imdevimab (C/I) for PEP

- Phase 3 randomized, pbo-controlled, study in household contacts with SARS-CoV-2 infection (N=1505 seronegative for SARS-CoV-2 Ab; 30% high-risk groups)
- Study Rx: C/I (1200 mg sq) or placebo
- Results
  - 1° endpoint: symptomatic COVID-19 by d28
    - 1.5% (11/753) C/I vs. 7.8% (59/752) pbo (RR 0.17; 95% CI, 0.09–0.33; p<0.001)
  - 2° endpoints:
    - symptomatic + asymptomatic infections: 4.8% C/I vs. 14.2% pbo (p<0.001)
    - VL >10,000 cps/ml (infected): 1.6% C/I vs. 11.3% pbo (p<0.001)
- Conclusion: C/I prevented (and abrogated) infection



O'Brien NEJM (epub 8/4/21)

NIH Guidelines (8/17/21) : Cas/Imd for PEP

- Recommend **casirivimab 600 mg + imdevimab 600 mg** SQ **(AI)** or IV **(BIII)** as PEP for people who are at **high risk for progression** to severe COVID-19 who have the following:

- ***Vaccination Status:***

    - **Not fully vaccinated** *OR* **fully vaccinated, but not expected to mount an adequate immune response** (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications)

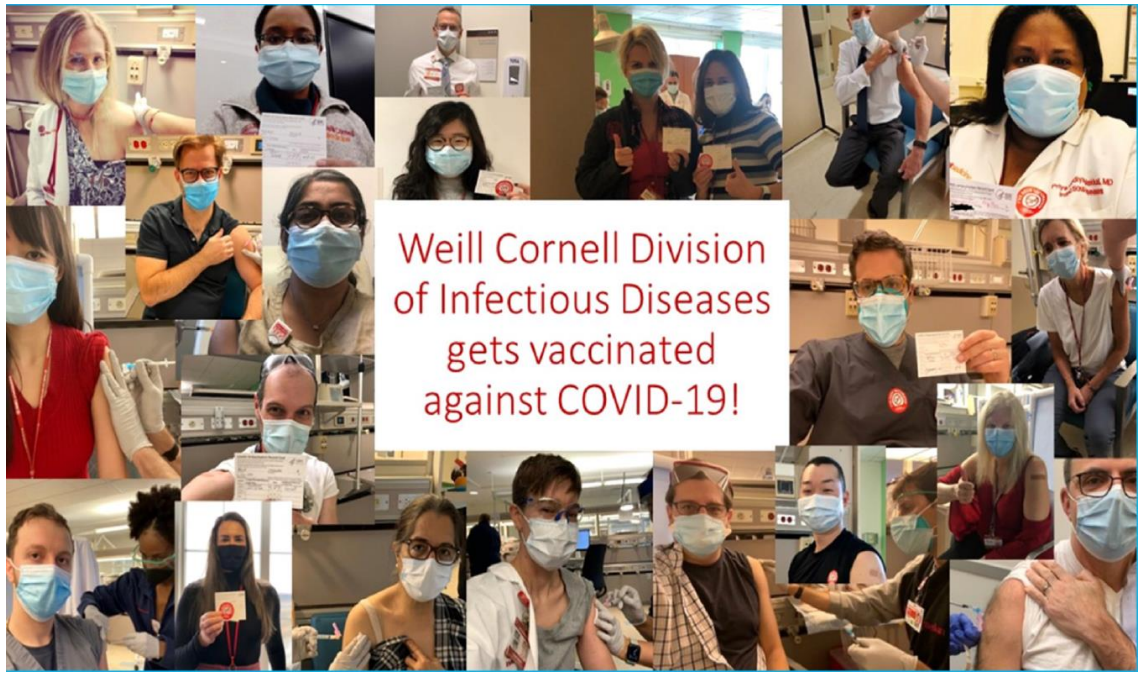
AND

- ***Exposure History:***

    - Had a **recent exposure** to an individual with SARS-CoV-2 infection; *OR*

    - At **high risk of exposure** to an individual with SARS-CoV-2 infection because of recent occurrence in other individuals in the **same institutional setting** (e.g., nursing homes, prisons)

Thanks to: Steve Chang, Rob DeSimone, Grant Ellsworth, Yoko Furuya, Raj Gandhi, Marshall Glesby, Kristie Marks, Susana Morales, Susana Naggie, Alice Pau, Laura Riley Matt Simon, Magadalena Sobieszczyk and Tim Wilkin for slides



rgulick@med.cornell.edu